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

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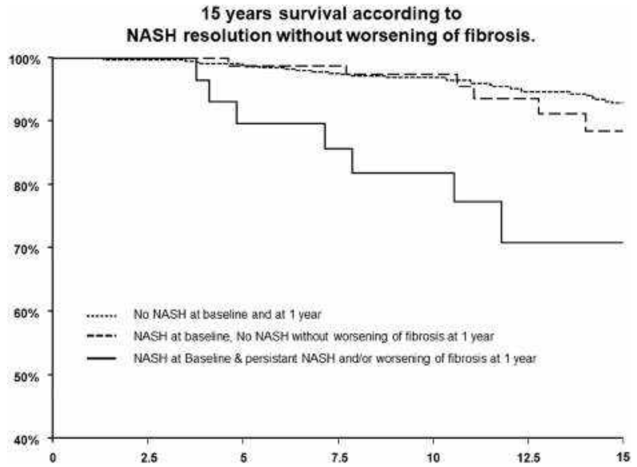
Background: Health agencies are waiting for studies with an extended follow-up evaluating whether *resolution of MASH without worsening of fibrosis* is associated with reduced risk of mortality. This study assessed the impact of histological evolution on long-term survival in MASH patients treated with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



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

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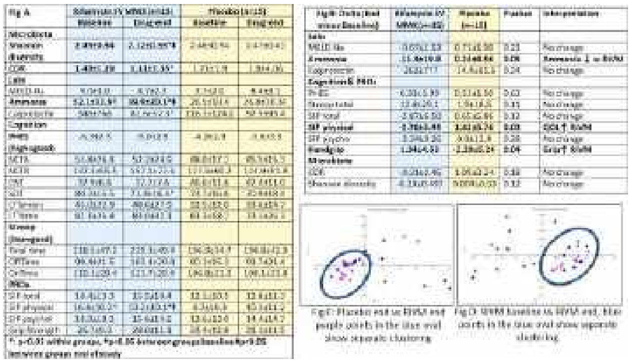
Background: Minimal hepatic encephalopathy (MHE) is associated with poor outcomes but treatment strategies are limited. Rifamycin SV MMX (RiVM) is a novel rifampin derivative which a non-absorbable antibiotic with maximal impact in the colon. Aim: Evaluate impact of RiVM on microbiome, safety & gut-brain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



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

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

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

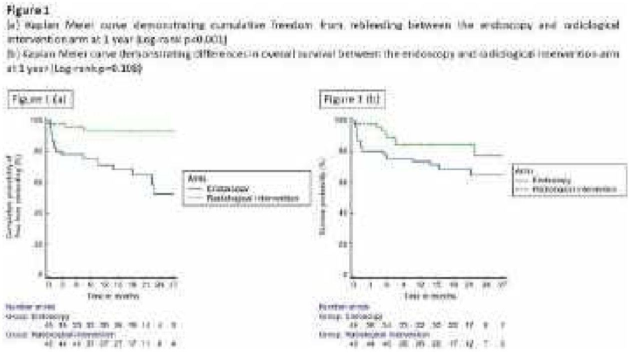

Figure 1

(a) Kaplan Meier curve demonstrating cumulative freedom from rebleeding between the endoscopy and radiological intervention arm at 1 year (Log-rank p<0.001)

(b) Kaplan Meier curve demonstrating differences in overall survival between the endoscopy and radiological intervention arm at 1 year (Log-rank p=0.108)

Disclosures: The following people have nothing to disclose: Sagnik Biswas, Manas Vaishnav, Shekhar Swaroop, Umang Arora, Arnav Aggarwal, Piyush Pathak, Abhinav Anand, Anshuman Elhence, Deepak Gunjan, Saurabh Kedia, Soumya Jagannath Mahapatra, Shivanand Gamanagatti, Dr Shalimar

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

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

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

Mohit Kumar Varshney[1]*, Manasa Alla*[2]*, Shasthry Sm*[1]*, Guresh Kumar*[3]*, Vinod Arora*[1] *and Shiv Kumar Sarin*[4]*, (1)Institute of Liver and Biliary Sciences, (2)Aig*

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Background: Long term reduction and alcohol abstinence have been known to reduce both short and long term mortality in patients with Alcohol associated Liver diseases (AaLD). Naltrexone, despite being known efficacy in Alcohol dependence, has not been tested in liver disease patients. We aimed to evaluate six and twelve month abstinence rates (and new onset decompensation events over 12 mo) after 12 weeks of Naltrexone (50 mg) compared with placebo in patients with underlying AaLD. **Methods:** 6 and 12 month abstinence rates were analyzed in AaLD patients given take home oral Naltrexone versus placebo; as part of 12 weeks double blind RCT at ILBS hospital, (NCT04391764). Consecutive AaLD patients with no recent decompensation (last 60 d) were given Naltrexone or placebo tablets if they fulfil DSM-5 criteria for AUD. Cirrhosis was confirmed with histology and imaging findings. Self report, family member's corroboration and blood Ethyl glucoronide testing were done to ascertain abstinence and lapses. Obsessive compulsive drinking scores (OCDS) and self reports of craving (Visual analogue scale-VAS) were used to measure craving at 6 and 12 months. All patients discontinued use of Naltrexone and placebo after the 12 weeks study period; as well as counselling as part of the study. Number of episodes of new onset decompensation was noted. As routine clinical practice all patients received Brief intervention counselling for AUD. **Results:** A total of 147 AaLD patients were screened for inclusion in the study, out of which 100 were included and 56 patients completed 12 months follow up and were analysed (28 in each group). Baseline clinical and alcohol use related parameters were comparable between the two groups. At 12 months, 7.1% (2/28) had new onset hepatic decompensation vs 14.2% (4/28) in the placebo group (aOR = 2.34, $p = 0.04$). There was significant improvement in CTP ($t = -3.94$, $p < 0.01$) and MELD scores ($t = -4.07$, $p < 0.01$) at 12 months; along with significant reduction in total Bilirubin ($t = 4.47$, $p < 0.01$), INR ($t = 0.37$, $p < 0.01$) and serum GGT levels ($t = 2.28$, $p = 0.03$). Among alcohol use related parameters proportion of patients abstinent at 12 months were higher in Naltrexone as compared to placebo ($x^2 = 0.37$, $p = 0.04$). There was reduction in number of lapses in the Naltrexone group ($p = 0.74$) at 12 months. Moreover craving measures including OCDS and VAS were also significantly lower in drug group as compared to placebo. Naltrexone group had lesser number of lapses per month at one year as compared to placebo (3.93 vs 6.50; $p = 0.26$). Both patients with new onset decompensation in Naltrexone continued alcohol consumption. Adverse events were comparable in both the groups (41.4 % vs 26 %; $p = 0.59$) and none required discontinuation of drug. **Conclusion:** This is the first placebo controlled RCT using Naltrexone in AaLD patients. It showed that it is a safe and effective drug for improving alcohol use related parameters and new onset decompensation at 6 and 12 months.

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6 | MOLECULAR SIGNATURES TO PREDICT RISK OF HEPATOCELLULAR CARCINOMA POST HEPATITIS C CURE

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Background: The emergence of direct-acting anti-HCV agents has led to a significant increase of patients who achieve sustained virologic response (SVR) but remain at risk of HCC development over a decade. HCC risk stratification post SVR is urgently needed. **Methods:** A hepatic transcriptome-based Prognostic Liver Signature for SVR (PLS-SVR) was identified in 85 patients who had curative resection/ablation for post-SVR HCC (derivation set), and independently validated in 39 HCC-naïve post-SVR patients (tissue validation set). Subsequently, a blood-based surrogate of PLS-SVR, Prognostic Liver Secretome signature for SVR (PLSec-SVR), was defined using our computational pipeline (TexSEC) for non-invasive HCC risk assessment. PLSec-SVR was validated in two independent cohorts of HCC-naïve (serum validation set 1; matched 41 cases and 123 controls) and HCC-experienced (serum validation set 2; cohort of 146 subjects) patients. In the serum validation sets, we assessed clinical utility of PLSec-SVR as an etiology-specific "plug-in" to refine HCC risk prediction with our previously reported etiology-agnostic PLSec-AFP score. **Results:** We defined a 170-gene PLS-SVR, including 133 high- and 37 low-risk genes, in the derivation set, where the 5-year de novo HCC recurrence rates were 66.1% and 6.3% in high- and low-risk patients, respectively (adjusted hazard ratio [aHR], 48.9; 95% confidence interval [CI], 11.3-194.8). In the tissue validation set, 25 (64%) patients were classified as high risk, which was significantly associated with incident HCC (aHR, 9.99; 95% CI, 1.11-1319.4). PLS-SVR was converted to a 6-protein PLSec-SVR. In serum validation set 1 and 2, PLSec-SVR identified 59 (36%) and 43 (29%) high-risk patients, respectively, and was independently associated with HCC risk (adjusted OR [aOR], 3.08; 95% CI 1.42-6.65 and aHR, 2.59; 95% CI, 1.55-4.32 in serum validation sets 1 and 2, respectively). Integration of PLSec-SVR with the etiology-agnostic PLSec-AFP improved prognostic capability as a "plug-in" module (aOR, 13.9; 95% CI, 3.82-50.5 and aHR, 14.2; 95% CI, 6.17-32.6 in serum validation sets 1 and 2, respectively). **Conclusion:** PLSec-SVR enables prediction of long-term risk of post-SVR HCC development and substantially improves the performance of the etiology-agnostic PLSec-AFP score to inform necessity of regular HCC screening.

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7 | RECOMPENSATION OF CHRONIC HEPATITIS C-RELATED DECOMPENSATED CIRRHOSIS FOLLOWING DIRECT-ACTING ANTIVIRAL THERAPY: REAL-WORLD DATA FROM THE PUNJAB HCV ELIMINATION MODEL★

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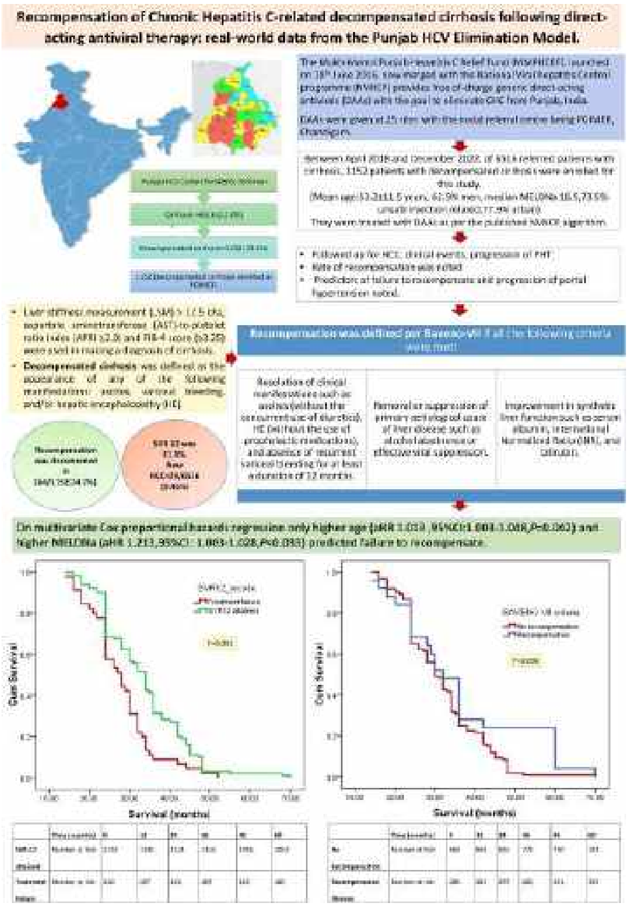
Background: Decentralized care, using free-of-charge generic direct-acting antiviral agents (DAAs) in patients with chronic hepatitis C (CHC) infection has resulted in cure rates of 91.6% in a large prospective multicentric population-based cohort from the state of Punjab, India. The rate of recompensation, as per BAVENO-VII criteria, in patients with decompensated CHC-related cirrhosis following DAAs, needs evaluation as part of public health policy to eliminate chronic hepatitis C in India. **Methods:** We evaluated patients with decompensated CHC-related cirrhosis treated at the PGIMER, Chandigarh and followed them up q6months for clinical events, viral, biochemical, endoscopic surveillance & imaging tests, and new evidence hepatocellular carcinoma (HCC). The diagnosis of cirrhosis was based on clinical evidence including AST-to-platelet ratio index (APRI e 2.0) and FIB-4 score (>3.25) or on liver stiffness measurement (LSM) e 12.5 kPa on Fibroscan. The rate of recompensation was noted. Progression of portal hypertension (PHT) was defined as the onset of varices needing treatment or PHT-related bleeding. Patients with HIV or HBV coinfection and HCC at presentation were excluded from analysis. **Results:** Between April 2018 and December 2022, of 6516 patients with cirrhosis who reported to the nodal centre, we enrolled 1152 with decompensated cirrhosis (mean age:53.2 ± 11.5 y, 62.9% men, median MELDNa 18.5,73.5%-unsafe injection related,77.9% urban). The decompensation events included ascites (1098, 95.3%), hepatic encephalopathy (191,16.6%), and history of variceal bleeding (284, 24.7%) at enrolment. SVR-12 was 81.8%, due to referral of difficult-to-treat cases to PGIMER. Resolution of ascites was noted in 993(86.2%), but diuretic withdrawal achieved in 280 (24.3%). Recompensation was documented in 284 (24.7%). On multivariate logistic regression only higher age (aHR 1.013 ,95%CI:1.003-1.048,*p* = 0.042) and higher MELDNa (aHR 1.213,95%CI: 1.003-1.028, *p* = 0.033) predicted failure to recompensate. Progression of PHT was noted in 158 patients: with rebleed in 45 (3.9%) during a follow-up period of 52 months (interquartile range, 18-68.5 mo). Treatment failure (OR 1.8, 95%CI:1.3-4.9, *p* = 0.002) and presence of HE (OR4.4, 95%CI:1.3-5.6, *p* = 0.044) were associated with progression of PHT. Of 145 patients who died, and 6 underwent liver transplantation. In follow up at 2 years. A decrease in MELDNa of e 3 occurred in 409(35.5%) and a final MELD score of < 10 was achieved in 31.7%. On surveillance, 29(0.45%) new cases of HCC were diagnosed during follow up. **Conclusion:** The Punjab HCV Model demonstrates that recompensation of cirrhosis is achievable in 24% of decompensated cirrhosis, but these patients should remain on HCC surveillance. Patients with cirrhosis should be followed up following virological cure for new decompensations and HCC, which should be integrated in public health-care policy for HCV elimination.



Recompensation of Chronic Hepatitis C-related decompensated cirrhosis following direct-acting antiviral therapy: real-world data from the Punjab HCV Elimination Model.

- Followed up for HCC, clinical events, progression of PHT
- Rate of recompensation was noted
- Predictors of failure to recompensate and progression of portal hypertension noted.

Recompensation was defined per Baveno-VII if all the following criteria were met!

Resolution of clinical manifestations such as ascites (without the concurrent use of diuretics), HE (without the use of prophylactic medications), and absence of recurrent variceal bleeding for at least a duration of 12 months.	Removal or suppression of primary aetiological cause of liver disease such as alcohol abstinence or effective viral suppression.	Improvement in synthetic liver function such as serum albumin, International Normalized Ratio (INR), and bilirubin.

On multivariate Cox proportional hazards regression only higher age (aHR 1.013 ,95%CI:1.003-1.048,P=0.042) and higher MELDNa (aHR 1.213,95%CI : 1.003-1.028,P=0.033) predicted failure to recompensate.

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

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

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

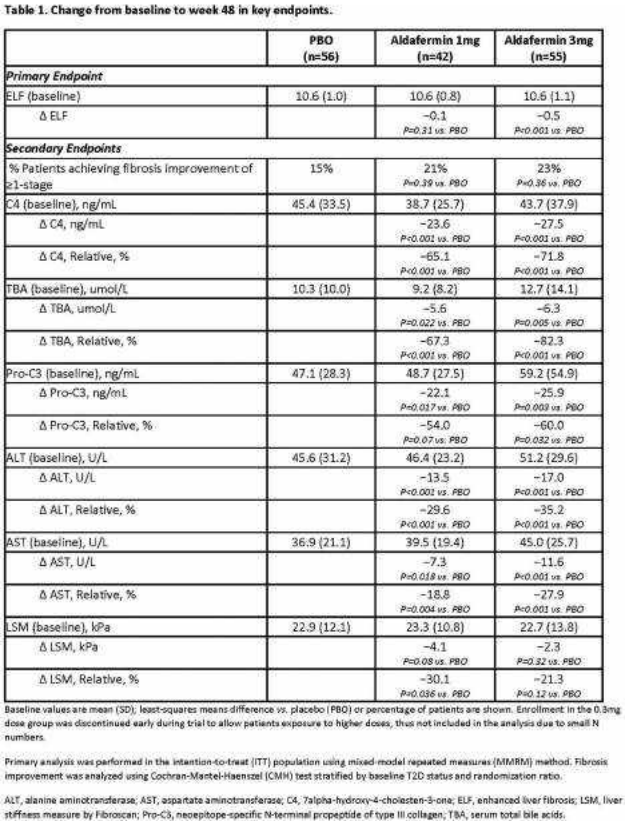

Table 1. Change from baseline to week 48 in key endpoints.

	PBO (n=56)	Aldafermin 1mg (n=42)	Aldafermin 3mg (n=55)
Primary Endpoint			
ELF (baseline)	10.6 (1.0)	10.6 (0.8)	10.6 (1.1)
Δ ELF		−0.1 *P=0.31 vs. PBO*	−0.5 *P<0.001 vs. PBO*
Secondary Endpoints			
% Patients achieving fibrosis improvement of ≥1-stage	15%	21% *P=0.39 vs. PBO*	23% *P=0.36 vs. PBO*
C4 (baseline), ng/mL	45.4 (33.5)	38.7 (25.7)	43.7 (37.9)
Δ C4, ng/mL		−23.6 *P<0.001 vs. PBO*	−27.5 *P<0.001 vs. PBO*
Δ C4, Relative, %		−65.1 *P<0.001 vs. PBO*	−71.8 *P<0.001 vs. PBO*
TBA (baseline), umol/L	10.3 (10.0)	9.2 (8.2)	12.7 (14.1)
Δ TBA, umol/L		−5.6 *P=0.022 vs. PBO*	−6.3 *P=0.005 vs. PBO*
Δ TBA, Relative, %		−67.3 *P<0.001 vs. PBO*	−82.3 *P<0.001 vs. PBO*
Pro-C3 (baseline), ng/mL	47.1 (28.3)	48.7 (27.5)	59.2 (54.9)
Δ Pro-C3, ng/mL		−22.1 *P=0.017 vs. PBO*	−25.9 *P=0.009 vs. PBO*
Δ Pro-C3, Relative, %		−54.0 *P=0.07 vs. PBO*	−60.0 *P=0.032 vs. PBO*
ALT (baseline), U/L	45.6 (31.2)	46.4 (23.2)	51.2 (29.6)
Δ ALT, U/L		−13.5 *P<0.001 vs. PBO*	−17.0 *P<0.001 vs. PBO*
Δ ALT, Relative, %		−29.6 *P<0.001 vs. PBO*	−35.2 *P<0.001 vs. PBO*
AST (baseline), U/L	36.9 (21.1)	39.5 (19.4)	45.0 (25.7)
Δ AST, U/L		−7.3 *P=0.018 vs. PBO*	−11.6 *P<0.001 vs. PBO*
Δ AST, Relative, %		−18.8 *P=0.004 vs. PBO*	−27.9 *P<0.001 vs. PBO*
LSM (baseline), kPa	22.9 (12.1)	23.3 (10.8)	22.7 (13.8)
Δ LSM, kPa		−4.1 *P=0.08 vs. PBO*	−2.3 *P=0.32 vs. PBO*
Δ LSM, Relative, %		−30.1 *P=0.036 vs. PBO*	−21.3 *P=0.12 vs. PBO*

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

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

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

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

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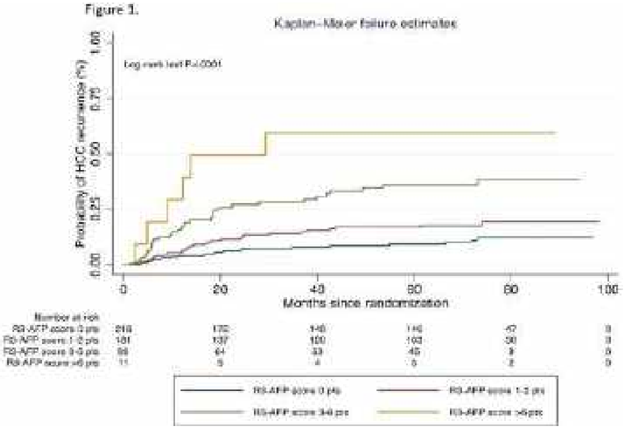
Background: Hepatocellular carcinoma (HCC) recurrence risk after liver transplantation (LT) has been evaluated with different prediction models following pathology explant analysis. The inclusion of alpha-feto protein (AFP) in these models, such as the novel R3-AFP score (1), have significantly improved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

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

15.3-22.6; n = 88 recurrences). The frequency distribution of the R3-AFP score was 42.6% low risk group (n = 216), 35.7% (n = 181) intermediate risk, 19.5% high risk group (n = 99), and 2.2% very high risk group (n = 11). The R3-AFP score correctly stratified HCC recurrence risk (Figure 1) (reference: low risk group): intermediate risk group SHR 1.80 (95% CI 1.02;3.18), high risk group SHR 4.20 (2.41;7.31), and very high risk group SHR 9.55 (3.66;24.92). Discrimination power for the R3_AFP model was 0.75 (95% CI 0.69;0.81) in the ITT population; lower in the mTOR group [Group A 0.75 (CI 0.69-0.81) when compared to Group B 0.67 (0.59-0.75); *p* = 0.048]. No significant differences were observed between expected and observed events across R3-AFP strata. **Conclusion:** The R3-AFP score has been validated in the ITT population of the SiLVER trial, a high-quality evidenced-based data, showing good performance. The model had lower discrimination of the risk of recurrence in exposed subjects with mTOR immunosuppression. This should lead to further hypothesis testing.

- Costentin C, et al. JHEP Rep. 2022 Feb 2;4 (5):100445. doi: 10.1016/j.jhepr.2022.100445.
- Geissler, EK; et al. Transplantation 100(1):p 116-125, January 2016. | DOI: 10.1097/TP.0000000000000965

Figure 1.



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10 | DISPARITIES IN ACCESS TO LIVER TRANSPLANTATION FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS-ASSOCIATED HEPATOCELLULAR CARCINOMA

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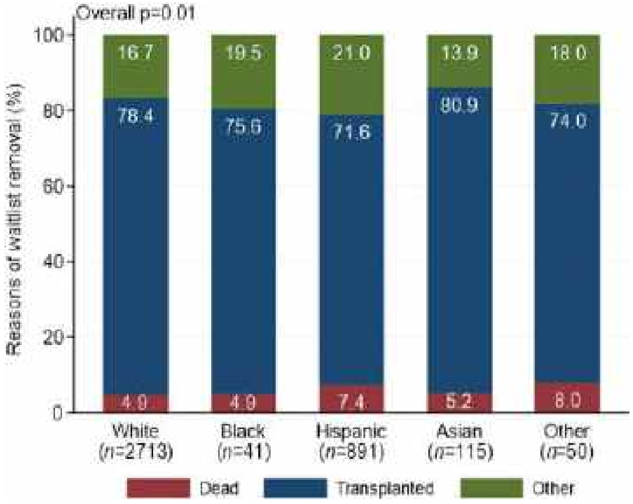
Background: Metabolic dysfunction-associated steatohepatitis (MASH) is the fastest-growing etiology of liver disease for patients with hepatocellular carcinoma (HCC) added to the liver transplantation (LT) waitlist in the US. Patients with MASH-HCC are disproportionately of Hispanic ethnicity, who have historically had poorer access to LT than non-Hispanic (NH) whites. However, it is unclear whether racial and ethnic minorities are waitlisted and transplanted for MASH-HCC at lower-than-expected rates. **Methods:** Adults with HCC waitlisted for LT between 1/2015 and 12/2021 were identified in the US Scientific Registry of Transplant Recipients standard analysis file. Patients were included if they (1) had a MASH diagnosis, or (2) had a diagnosis of cryptogenic/idiopathic cirrhosis and body mass index > 30 kg/m^2. Differences between groups were compared using Chi-square, Fisher's exact, or Kruskal Wallis tests as appropriate. Cox regression modeling was used to determine characteristics associated with having liver transplantation. A *p* value of < 0.05 was considered statistically significant. **Results:** Of the 3810 LT candidates, the majority (2713, 71.2%) were NH white. Only 49 (1.1%) were Black, 891 (23.4%) were Hispanic, and 115 (3.0%) were Asian. Most candidates went on to undergo LT, although the proportions of patients receiving LT were significantly different ($p = 0.001$; Figure 1). In pairwise comparisons, Hispanics underwent LT at significantly lower rates than NH whites ($p < 0.001$). Waitlist mortality rates were not significantly different among races/ethnicities ($p = 0.06$). Hispanics received LT at a significantly higher rates in the post-Median MELD at Transplant (MMAT) era (after 6/1/2019) than in the pre-MMAT era ($p = 0.02$). MMAT era did not impact the proportion of patients undergoing LT for other races/ethnicities (all $p > 0.05$). In multivariable Cox regression analysis, Hispanic (HR, 0.85; 95% CI, 0.77-0.95; $p = 0.002$) and Asian (HR, 0.79; 95% CI, 0.63-0.98; $p = 0.04$) patients were significantly less likely to receive LT than NH white patients. **Conclusion:** Hispanics and

Asians are less likely to receive LT for MASH-HCC than other races/ethnicities. A significantly greater proportion of Hispanic patients had LT in the post-MMAT era, likely reflecting efforts across the country to mitigate access disparities. The proportion of Black patients waitlisted for LT was also surprisingly low. Although there are encouraging trends, work is still needed to address disparities in access to LT for MASH-HCC.



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11 | IMPACT OF ACUTE KIDNEY INJURY RESPONSE ON SURVIVAL AND LIVER TRANSPLANT RATES IN HOSPITALIZED PATIENTS WITH CIRRHOSIS AWAITING LIVER TRANSPLANTATION: RESULTS FROM THE HRS-HARMONY CONSORTIUM

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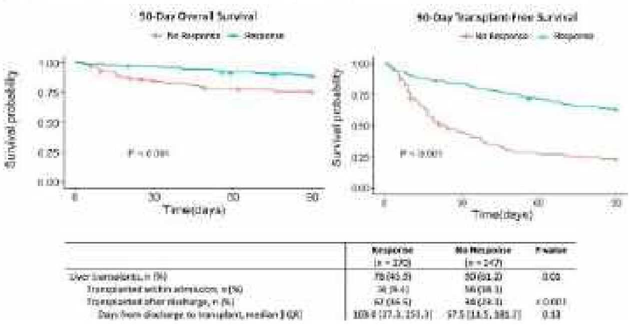
Background: Acute kidney injury (AKI) frequently complicates the course of hospitalized patients with cirrhosis and negatively impacts prognosis. Response to medical management in AKI is variable, depending on the etiology and severity of the injury. How AKI improvement or response affects liver transplant timing is less clear. We sought to assess the impact of AKI response to treatment on survival and liver transplantation (LT) for patients with cirrhosis waitlisted for LT. **Methods:** Retrospective study of consecutive patients with cirrhosis waitlisted for LT who had been hospitalized with AKI in 2019 at 11 U.S. transplant centers. The exposure of interest was AKI response to medical management (defined as a decrease in serum creatinine to within 0.3 mg/dL of baseline or regression of AKI stage) versus no response during hospitalization. The outcomes were 90-day rates of overall survival (with LT as a competing risk), transplant-free survival, and rates of LT with associated time to transplant, as well as resource utilization during hospitalization. We adjusted for confounders including age, sex, race, etiology of cirrhosis, study site and MELD-Na score at the time of admission. A sensitivity analysis was performed on the sub-population who received HRS vasoconstrictor therapy. **Results:** Of 2057 patients with AKI, 317 were waitlisted for LT and included in the study. 170 had AKI response to medical management (53.6%) and 147 with no response (46.4%). Compared to non-responders, responders had better 90-day overall survival (89.4% vs. 76.2%, aHR for 90-day mortality 0.34 [95% CI 0.18, 0.65, $p = 0.001$]), and better 90-day transplant-free survival (63.5% vs. 25.2%, aHR for 90-day risk of death or transplant 0.35 [95% CI 0.25, 0.50, $p < 0.001$]). The rate of LT was lower for responders compared to non-responders (45.9% vs. 61.2%, aHR 0.55 [95% CI 0.37, 0.84, $p = 0.005$]). The majority (79%) of LT in responders occurred after discharge, at a median of 103 days, while the majority (62%) of transplants in non-responders occurred during the same hospitalization, with the remainder occurring post-discharge at a median of 58 days. Compared to non-responders, responders had shorter hospital and ICU lengths-of-stay by a median of 10 and 6 days respectively, and smaller percentages of patients needing ICU, intubation, renal replacement therapy and pressor use. Sensitivity analysis within the sub-population that received HRS vasoconstrictor therapy ($n = 180$) yielded similar results. **Conclusion:** In patients with cirrhosis waitlisted for LT who are hospitalized with AKI, AKI response to therapy is associated with improved 90-day survival, despite a reduced LT rate and longer time to LT. As the newly approved vasoconstrictor terlipressin becomes more widely available in the U.S. for treatment of HRS-AKI, further research on how this therapy, which affects AKI response rates, impacts LT rate and timing, and potentially LT allocation, is warranted.

Figure 1. Survival and transplant rates by AKI response in patients with cirrhosis hospitalized for AKI



	Response (n = 170)	No Response (n = 147)	P value
Liver transplants, n (%)	78 (45.9)	90 (61.2)	0.01
Transplanted within admission, n (%)	16 (9.4)	56 (38.1)	
Transplanted after discharge, n (%)	62 (36.5)	34 (23.1)	< 0.001
Days from discharge to transplant, median [IQR]	103.0 [37.3, 151.3]	57.5 [14.5, 181.7]	0.13

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12 | SURGICAL BILIARY DIVERSION IS ASSOCIATED WITH AN INCREASED RISK OF LIVER TRANSPLANTATION OR DEATH IN ALAGILLE SYNDROME★

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Background: Alagille syndrome (ALGS) is an inherited liver disorder dominated by high γ-glutamyltransferase (GGT) cholestasis. Previous studies have demonstrated limited efficacy of surgical interruption of the enterohepatic circulation in ALGS, with varying degrees of improvement in pruritus and xanthomas. Utilizing the GALA database, we sought to evaluate whether surgical biliary diversion (SBD) alters the natural history of liver disease. **Methods:** Multicenter retrospective analysis of children with clinically and/or genetically confirmed ALGS. Laboratory data were collected preoperatively (−6 to 0 mo) and postoperatively (3 to 12 mo). Paired sample t-tests were used to compare continuous variables, and McNemar's tests were used to compare binominal variables pre-and postoperatively. Receiver operating characteristic (ROC) curves were used to determine the optimal laboratory threshold for predicting native liver survival (NLS) following SBD. Cox proportional hazards models were constructed to determine NLS in ALGS-SBD patients. **Results:** Of 1673 ALGS patients, 3.7% (n = 62; 54.8% male) underwent SBD from 26 centers. The median age of SBD was 2.5 years (IQR 1.8 – 4.4). Most ALGS patients underwent a partial external biliary diversion (54.8%, n = 34), followed by a partial internal biliary diversion in 19.4% (n = 12) and ileal exclusion in 12.9% (n = 8). 100% (n = 62) of patients reported pruritus at the time of SBD, and 51.4% (n = 18/35) reported xanthomas. ALGS-SBD patients had a 2.5-fold greater risk of liver transplantation (LT) or death (95% CI 1.6 – 3.9; $p < 0.01$). Following SBD, there were no significant differences in total bilirubin (TB) (8.8 vs. 9.1 mg/dL, $p = 0.51$), ALT (159.5 vs. 189.7 U/L, $p = 0.38$), GGT (495.0 vs. 459.5 U/L, $p = 0.21$) or cholesterol (493.0 vs. 414.6 mg/dL, $p = 0.21$). Availability of serum bile acids (SBA) was limited; however, in 10 patients with SBAs pre- and postoperatively, there was a significant reduction following SBD (257.2 vs. 97.7 μmol, $p = 0.05$). Among these patients, 80% achieved NLS. TB levels < 4.0 mg/dL following SBD were significantly associated with longer NLS ($p = 0.05$; AUC TB, 0.784; sensitivity, 94%; specificity, 52%). There were no significant improvements in pruritus (100% vs. 91.7%, $p = 0.25$) or xanthomas (51.4% vs. 45.1%, $p = 0.67$) after SBD. **Conclusion:** SBD in ALGS was associated with an increased risk of LT or death. SBD may be a marker for severe hepatic phenotype in ALGS. In contrast to PFIC, SBD does not appear to improve NLS in ALGS. However, in a subset of ALGS-SBD patients with SBA, higher rates of NLS were noted in those who experienced a substantial decrease in post-operative SBA levels. These findings also indicate that post-SBD TB levels can be used as a biomarker for NLS. In an era of ileal bile acid transporter (IBAT) inhibitors, SBD may become obsolete in ALGS.

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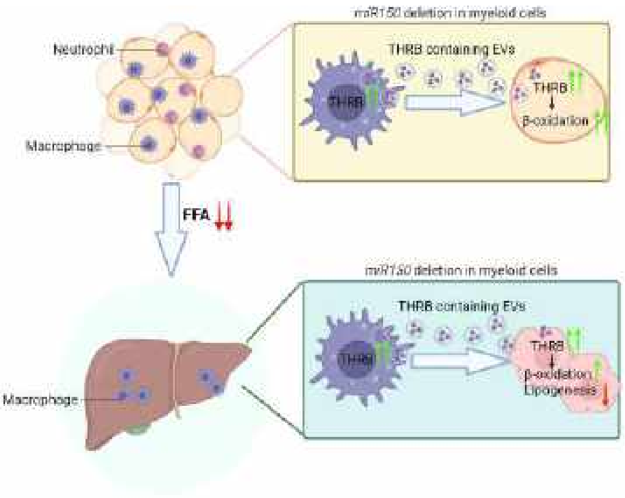
13 | MiR150 DEFICIENCY IN MACROPHAGES IMPROVES ALCOHOL INDUCED HEPATIC STEATOSIS VIA TRANSFERRING THYROID HORMONE RECEPTOR Β ENRICHED EVS TARGETING ADIPOSE TISSUE-LIVER AXIS: THYROID HORMONE RECEPTOR Β, A PROMISING THERAPEUTIC TARGET IN ALD

Jing Ma[1], Zhihong Yang[1], Nazmul Huda[1], Yanchao Jiang[1], Hui Gao[1], Il-Man Kim[2] and Suthat Liangpunsakul[3,4], (1)Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, in, (2)Department of Anatomy, Cell Biology and Physiology and Wells Center for Pediatric Research Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, IN, (3)Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, (4)Roudebush Veterans Administration Medical Center, Indianapolis, in

Background: The mechanisms of alcoholic hepatitis (AH) are complex and involve the cross talk between organ systems. MiR150, one of the most abundant microRNAs in immune cells, has been implicated in various liver diseases, but its role in AH pathogenesis remains unclear. We aimed to determine the role of the miR150-mediated immune cells-liver axis in AH pathogenesis. **Methods:** MiR150 levels were measured in serum (S) and liver (L) samples from healthy controls (HC, N = 15 for S, 5 for L), heavy drinkers (HD, N = 17 for S), and AH (N = 65 for S, 5 for L) patients. Correlations between miR150 levels, MELD scores, and serum transaminases were analyzed. Global *miR150* knockout mice ($miR150^{-/-}$) and myeloid cell-specific miR150 knockout mice ($miR150^{Lyz-/-}$) were generated to assess the function of *miR150* in a chronic plus binge alcohol feeding model. **Results:** Serum and hepatic miR150 level were significantly reduced in AH patients compared to HC. Serum miR150 level negatively correlated with serum AST, but not with MELD score. The level of hepatic miR150 was markedly reduced in mice fed with chronic plus binge alcohol model. Genetic deletion of *miR150* attenuated ethanol-induced liver injury and steatosis, as evidenced by the reduction of ALT, and hepatic triglyceride level. Fatty acid β-oxidation-associated proteins, including PPAR±, PGC1±, UCP2, CPT1A, and hormone sensitive lipase, were highly upregulated in both liver and WAT of ethanol-fed $miR150^{-/-}$ mice compared to WT mice. To understand how miR150 is involved in alcohol-induced steatosis, we observed a significant increase in the expression of the miR150 target gene, thyroid hormone receptor β (THRB), in the liver, WAT, and circulating extracellular vesicles (EVs). MiR150 deletion contributed to a significant increase in THRB in macrophages and macrophage-derived EVs. Ethanol fed myeloid cell-specific miR150 knockout mice also exhibited elevated THRB levels in the liver, WAT, and circulating EVs. The level of THRB was also increased in the serum EVs of AH patients compared with HC. Deletion of *miR150* in myeloid cells ameliorated ethanol-induced liver steatosis, with upregulated expression of PPAR±, UCP2, and CPT1A observed in both the liver and WAT. For the translational aspect of our results, we found that mice treated with THRB agonist, Resmetirom, significantly reduced ethanol-induced hepatic steatosis. The role of miR-150 and ALD pathogenesis is illustrated in the Figure. **Conclusion:** Macrophage-derived miR150 plays a crucial role in controlling the progression of steatosis through the release of THRB-containing EVs. MiR-150 and its target (THRB) may represent potential therapeutic targets for ALD.



MIR150 deletion in myeloid cells contributes to elevation in the release of THRB containing EVs from macrophages; which can be taken up by adipocytes. THRB leads to the promotion of FFA β-oxidation, reduction in circulation FFA level and a consequent improvement in hepatic steatosis. Macrophages derived THRB enriched EVs can also be internalized by hepatocytes, thereby promoting FFA β-oxidation, downregulating of hepatic lipogenesis, and amelioration of steatosis. MiR-150, notably its target, THRB, represent a potential therapeutic target for ALD.

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14 | HEPATITIS B VIRUS INFECTION OF PRIMARY AND PLURIPOTENT STEM CELL DERIVED MULTICELLULAR HEPATIC SPHEROIDS REVEALS COMPLEX INTRACELLULAR AND INTERCELLULAR INTERACTIONS AND HOST RESPONSES

Yaron Bram, Vasuretha Chandar and Robert E. Schwartz, Weill Cornell Medicine, NY

Background: Human pluripotent stem cell (PSC) derived hepatocyte-like cells and primary human hepatocytes applications for clinical or research uses is dependent on the ability to generate phenotypically and functionally relevant hepatocytes or hepatocyte-containing constructs. We have developed a scalable multi-well platform that enables the rapid generation of three-dimensional (3D) multicellular spheroids composed of primary and stem cell derived human liver parenchymal cell types including hepatocytes, liver sinusoidal endothelial cells (LSEC), stellate cells (HSC), and Kupffer cells. This 3D system is able to maintain hepatocellular function long-term and can be used to model the complex interactions and host responses between hepatocytes and nonparenchymal cells (LSEC, HSC, and Kupffer cells) during HBV Infection. **Methods:** Multicellular spheroids containing hepatocytes and nonparenchymal cells alone were generated from primary human liver tissue or from human PSCs. This robust human multicellular platform maintains hepatocellular and non-parenchymal cell differentiated function for greater that 6 weeks and allows for extended experiments. Given the longevity and stability of the platform we examined whether such a platform could be used to model the complex interactions and host responses between hepatocytes, LSEC, HSC, and Kupffer cells in vitro during HBV infection. **Results:** We generated multicellular spheroids and examined the acute and chronic changes due to HBV infection in multicellular spheroids. We found that multicellular spheroids maintain long-term infection in contrast to traditional hepatocyte-culture systems. Moreover, we found that metabolic perturbations led to impaired higher viral loads, hepatocyte injury, and macrophage and stellate cell activation. We evaluated the cross-talk between these different cell types early and late after HBV infection and found that in unexpectedly the presence of macrophages led to higher viral loads than when they were not present in the multicellular spheroids. We identified that Kupffer cell cytokine production is responsible for increased viral loads and neutralizing antibodies against IL-6 were able to mitigate this effect. **Conclusion:** Our work demonstrates that multicellular spheroids composed of primary and stem cell derived human liver parenchymal cell types including hepatocytes, LSEC, stellate cells, and Kupffer cells have stable function and can model complex disease phenotypes in vitro. Leveraging these technologies focused on HBV enabled studies of viral infection and can be leveraged in mechanistic studies of infection.
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f 15 | INHIBITION OF GUT BACTERIAL BILE SALT HYDROLASES (BSHS) ATTENUATES EARLY NON-ALCOHOLIC STEATOHEPATITIS (NASH) AND NASH WITH FIBROSIS

Yongtao Wang[1], Liz Jones[2], Yoojin Lee[1], Snehal Chaudhari[2], James C. Reed[3], Lawrence Zukerberg[4], Mozhdeh Sojoodi[5], Wenyu Lin[3], Min Xu[3], Eliana T. Epstein[3], Jonathan Eddy[1], Oizoshimoshiofu Dimowo[1], Alan C. Mullen[1], Georg M. Lauer[3], Kenneth K. Tanabe[5], A. Sloan Devlin[2] and Raymond T. Chung[3], (1)Division of Gastroenterology, Massachusetts General Hospital

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Background: Increased intestinal permeability is one of the multiple hits in the pathogenesis of non-alcoholic steatohepatitis (NASH). Bile salt hydrolase (BSH) is a gut bacterial enzyme that hydrolyzes conjugated bile acids (BAs) into unconjugated BAs. Our previous study reported that inhibition of BSH with a gut-restricted small molecule inhibitor, AAA-10, increased conjugated BAs and prevented the development of intestinal permeability and liver steatosis in an early onset, diet-induced rat steatosis model. This study sought to evaluate whether AAA-10 could treat pathogenic intestinal permeability and liver damage in models of early NASH and NASH with fibrosis. **Methods:** 8-week-old Wistar rats were fed a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) for either 3 or 6 weeks to develop early NASH or NASH with fibrosis, respectively. Rats were randomly assigned into two groups and gavaged twice daily with either 10 mg/kg of AAA-10 or control vehicle for 1 or 2 weeks. Molecular and histologic assessments on ileum and liver tissue were performed. RNA sequencing was performed to assess alteration of the global transcriptomic landscape of ileum and liver. *In vitro* human hepatic stellate cells (HSCs) and *ex vivo* human precision-cut liver slices (PCLS) were used to assess the effect of treatment with conjugated and/or unconjugated BAs. **Results:** Increased BSH activity and gut permeability were observed with liver fibrosis. After AAA-10 treatment, liver chemistry indices including ALT and AST improved. In both early NASH and NASH with fibrosis models, BSH inhibition reduced gut permeability by decreasing translocation of FITC-dextran and ileal expression of *occludin*, a tight junction protein upregulated and translocated to the membrane to compensate for disrupted tight junctions in NASH. BSH inhibition was associated with lowered liver collagen deposition, improved fibrosis score and reduced expression of pro-fibrogenic genes. Consistently, RNAseq analysis showed that the global transcriptomic signatures of intestinal function including absorption ability were restored after BSH inhibition, suggesting reduced intestinal permeability. Liver inflammatory and fibrogenic signatures were inhibited after AAA-10 treatment. BSH inhibition also enhanced 113 good prognosis genes and reduced 73 poor prognosis genes in the liver previously shown to be associated with progressive liver disease and HCC. Conjugated BA treatment attenuated TGF-β induced fibrogenic genes in *in vitro* human primary HSCs and TWNT4 cells and in *ex vivo* human PCLS; these changes were reversed by unconjugated BA treatment. **Conclusion:** BSH inhibition with AAA-10 treatment reduced gut permeability and alleviated liver fibrosis in rats with early NASH and NASH with fibrosis. These data suggest that inhibitors of gut bacterial BSHs could be developed as treatments for NASH and other diseases characterized by pathogenic intestinal permeability.

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16 | MODELLING PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS TYPE 1 USING PATIENT-SPECIFIC INDUCED PLURIPOTENT STEM CELLS

Rodrigo M. Florentino[1], Sriram Amirneni[1], Simon P. Horslen[2], Alejandro Soto-Gutierrez[1] and James E. Squires[3], (1)University of Pittsburgh, (2)UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, (3)UPMC, Pittsburgh, PA, United States

Background: Progressive familial intrahepatic cholestasis (PFIC) are a group of recessive disorders linked

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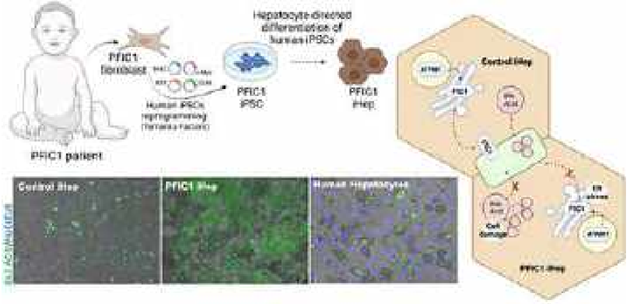
by the inability to appropriately excrete bile salts (BS) from hepatocytes. PFIC1 results from mutations in *ATP8B1* encoding FIC1, an apical membrane aminophospholipid translocase. FIC1 dysfunction is hypothesized to lead to BS retention via decreased farnesoid X receptor (FXR) activation. Unfortunately, a lack of reliable disease models has impeded scientific discovery and clinical advancement. We aim to explore how human induced pluripotent stem cells (hiPSCs) may be used to generate patient-specific liver tissue to model PFIC. **Methods:** Fibroblasts of 3 PFIC1 patients were reprogrammed into hiPSCs via nucleofection. hiPSC stemness was determined by qPCR and staining for pluripotency markers. Human induced hepatocytes (hiHeps) were then generated, carrying *ATP8B1* mutations. Hepatic differentiation was validated by comparison to primary human hepatocytes (hAH). Staining and Western Blot assessed FIC1 expression and localization. BA assays measured concentrations and investigated BA export. A luciferase assay enabled assessment of FXR activity, and a microarray was run to identify pathway specific alterations in gene expression. **Results:** We successfully generated PFIC1-hiPSCs, their stemness status comparable with commercially available hiPSC (OCT3/4 and Nanog positive nucleus > 95%) and differentiate these cells into hepatocyte-like cells. All generated hiHeps showed the expression of adult isoform of the HNF4a (> 90%positive nucleus) and albumin (> 70% positive cells) and no expression of the alpha fetoprotein. Additional mRNA levels of hepatocyte specific markers were comparable with hAH. Functionally, patient specific PFIC1 hiHeps exported less BA than healthy hiHeps and hAH hepatocytes (basal FXR activity: hiHeps control: 0.96 ± 0.06, PFIC1 hiHeps #1: 0.09 ± 0.05 and hAH: 1.37 ± 0.15). The luciferase assay demonstrated a reduction in FXR. Microarray showed increases in expression of ER stress related genes in the PFIC1 hiHeps, suggesting that the cells are compensating for the mutant FIC1 protein. **Conclusion:** PFIC1-specific hiHeps can recapitulate the dysfunctional activity of FIC1 and support the hypothesis that dysregulated FXR contributes to the PFIC1 phenotype. These findings represent a novel model for further interrogation to unlock a deeper understanding of PFIC1 pathophysiology and possible therapeutic targets.



Graphical abstract: Fibroblast from PFIC1 patient were reprogrammed to induced pluripotent stem cells (PFIC1 iPSC) and then differentiated into hepatocyte-like cells (PFIC1 iHep). Our analysis revealed an increase in the endoplasmic reticulum (ER) stress due the retention of the FIC1 protein in the ER and an inefficient exportation of bile acid into the biliary canaliculus leading to cellular damage.

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The following people have nothing to disclose: James E. Squires

Disclosure information not available at the time of publication: Rodrigo M. Florentino, Sriram Amirneni, Alejandro Soto-Gutierrez

17 | INTERACTION OF INNATE AND ADAPTIVE IMMUNITY DRIVES NLRP3 INFLAMMASOME ACTIVATION AND HEPATOCYTE APOPTOSIS IN MURINE LIVER INJURY FROM IMMUNE CHECKPOINT INHIBITORS

Layla Shojaie[1], Jacob Bogdanov[1], Helia Alavifard[1], Myra Ali[1], Simeon Mahov[2], Sue Murray[3], Gary C. Kanel[1], Zhang-Xu Liu[1], Akil Merchant[2], William Stohl[1] and Lily Dara[1], (1)Keck School of Medicine of USC, (2) Cedars-Sinai Medical Center, Los Angeles, CA, (3)Ionis Pharmaceuticals, Inc.

Background: Immune checkpoints (CTLA4 & PD1) are inhibitory pathways that block aberrant immune activity and maintain self-tolerance. Tumors co-opt these checkpoints to avoid immune destruction. Immune Checkpoint Inhibitors (ICIs) activate immune cells and restore their tumoricidal potential, making them highly efficacious cancer therapies. However, immunotolerant organs such as the liver depend on these tolerogenic mechanisms, and their disruption with ICI use can trigger the unintended side effect of hepatotoxicity termed immune mediated liver injury from checkpoint inhibitors (ILICI). Patients with severe ILICI discontinue ICIs and start steroids, to the detriment of their cancer. How liver cells are dying, and which cell death pathways are involved in ILICI is not known. Understanding how to uncouple ILICI from ICI anti-tumor activity is of paramount clinical importance. **Methods:** We developed a murine model to recapitulate human ILICI. CTLA4$^{+/-}$ mice were treated with combined anti-CTLA4 + anti-PDL1 or IgG1 + IgG2 for 14 days. We probed cell death subroutines: apoptosis, necroptosis, and pyroptosis. We tested two forms of antisense oligonucleotides to knockdown (KD) caspase-3 (C3) in a total liver (hepatocytes and NPCs) or in a hepatocyte-specific manner. We employed imaging mass cytometry (IMC), a powerful multiplex platform for immunophenotyping and spatial cell interaction analysis to study immune cross-talk in our model. **Results:** ICI treated mice had significant evidence of liver injury. We

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

detected cleaved caspase-3 (cC3), indicating apoptosis was occurring, as well as NLRP3 inflammasome activation, but no necroptosis. Total liver KD of C3 worsened liver injury, increased inflammasome activation, and triggered GSDMD-mediated pyroptosis. In contrast, hepatocyte-specific KD of C3 reduced liver injury and NLRP3 inflammasome activation. IMC-generated single-cell data for 77,692 cells was used to identify 22 unique phenotypic clusters. Spatial analysis revealed cC3+ hepatocytes highly interacted with macrophages and NLRP3^{hi} myeloid cells. We also observed zones of three-way interaction between cC3+ hepatocytes, CD8^{+} T-cells and macrophages. **Conclusion:** Our work is the first to identify hepatocyte apoptosis and NLRP3 inflammasome activation as drivers of ILICI. Our single-cell IMC data demonstrates macrophages and NLRP3^{hi} myeloid cells are among the nearest neighbors of cC3+ hepatocytes and contribute to injury. We report that the interplay between adaptive and innate immune cells is critical to hepatocyte apoptosis and ILICI.

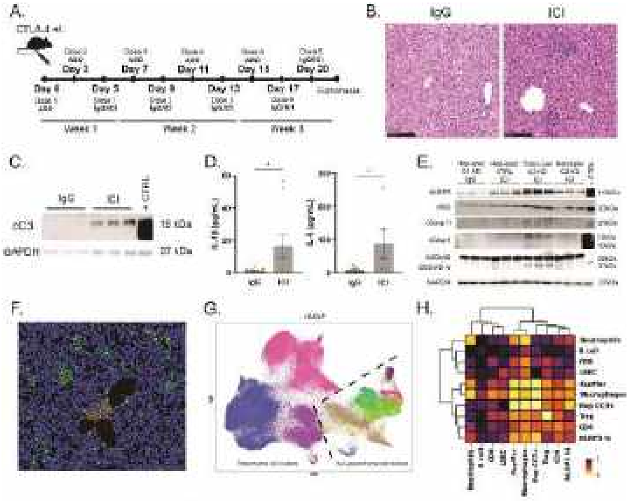

Figure 1. Innate and adaptive immune cells drive immune mediated liver injury from ICIs (ILICI) via activation of apoptosis and the NLRP3 inflammasome. (A) Murine ILICI injury model modified to include antisense oligonucleotide treatment. (B) Representative H&E, 20x magnification. (C) Immunoblot for cC3. (D) Cytokines. (E) Immunoblot for NLRP3 and downstream mediators of pyroptosis. (F) IMC region of interest pseudocolored according to cell phenotypic clusters. (G) Uniform manifold approximation and projection (UMAP) of all single-cells from IMC. (H) Heatmap depicting pairwise distance rank between clusters: 1- furthest distance pair, 0: closest.

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18 | RGS rs35197737 IN CHROMOSOME 1 IS ASSOCIATED WITH RISK OF STATIN INDUCED LIVER INJURY: RESULTS FROM THE DRUG INDUCED LIVER INJURY NETWORK (DILIN)

Tae-Hwi Schwantes-An[1], Marco A Abreu[1], Yi-Ju Li[2], Andrew Dellinger[2], Paola Nicoletti[3], Lily Dara[4], Victor J. Navarro, Md[5] and Naga P. Chalasani[6], (1)Indiana University School of Medicine, (2)Duke University, Durham, NC, (3)Mount Sinai, (4)University of Southern California, Los Angeles, CA, (5)Albert Einstein Medical Center, Doylestown, PA, (6)Indiana University Medical Center, Indianapolis, IN

Background: Statins may very rarely cause drug induced liver injury (DILI) but its pathogenesis is not well understood. Genetic factors may play a role in the pathogenesis of liver injury due to selected agents. In this study, we investigated genetic factors associated with statin DILI through a genome wide association study (GWAS). **Methods:** We conducted a GWAS of statin DILI. Statin DILI cases with definite, highly likely or probable causality scores were identified from Drug Induced Liver Injury Network (DILIN) studies between 2004 and 2022. Controls were statin treated patients with no DILI (statin controls) identified from Indiana Biobank (IB). Statin controls were defined as having ALT < 45 U/L and Alk $p < 125$ U/L during the 12 months preceding and 6 months following statin prescription and absence of ICD code 573.8 and K71. Imputed, QC passing variants from the cases and controls were combined then re-cleaned to adjust for any potential batch effects. We compared statin DILI cases to statin controls as primary GWAS then compared top three suggestive hits in 1) non-statin DILI from DILIN studies (DILI controls) and 2) not statin exposed individual's with no evidence for liver injury from Indiana Biobank (IB Controls). Association tests were conducted in cross ancestry group and EUR ancestry specific fashion while adjusting for age, sex, and several principal components. Logistic regression model with Firth correction was used. **Results:** There were 71 statin-DILI cases with definite, highly likely or probable causality and 552 statin controls. After QC, there were 5,483,580 variants available for GWAS. In both cross-ancestry and EUR ancestry specific analysis we observed 3 suggestive ($p < 5e^{-06}$) associations (Table 1). These associations were more prominent in EUR ancestry specific analyses. In the EUR comparison, rs35197737, variant in *RGS1* (regulator of G Protein signaling 1), showed a strong association with statin-DILI (OR = 5.03, (95% C.I. = 2.77- 9.13), $p = 1.14x10^{-07}$). On chromosome 10, rs75629598 in *FRMD4A* (FERM domain containing 4A) showed significant association with statin DILI (OR = 4.35 (95% CI: 2.33-8.12), $p = 3.97$ $x10^{-06}$). Lastly, rs7658630, intergenic variant, was associated with an increased risk (p-value = 2.68 $x10^{-07,}$ OR = 4.85, 95% CI: 2.66-8.85) for statin-DILI. The comparisons between statin DILI and DILI controls and between statin DILI and IB controls are also shown in Table 1. *RGS* rs35197737 showed genome-wide significant association with statin DILI in comparison to IB controls (OR: 5.74, 95% C.I. 3.29-10.00, $p = 7.22$ $x10^{-10}$) and strong association in comparison to DILI controls (OR:

4.11, 95%: 2.42-7.00, $p = 1.88 \times 10^{-07}$). **Conclusion:** rs35197737 in *RGS1* (Chr 1) appears to be a significant risk factor for statin DILI. Further studies to confirm this observation and to understand the mechanisms by which it contributes to statin DILI are warranted.

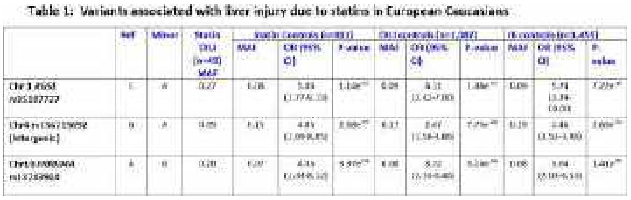

Table 1: Variants associated with liver injury due to statins in European Caucasians

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19 | EFFECTS OF MICROPLASTICS ON THE HEPATIC TRANSCRIPTOME

Ngozi Victoria Adiele[1], Frederick Ekuban[1], Abigail Ekuban[2], Jianzhu Luo[1], Jingjing Zhao[1], Julia Chariker[1], Eric C Rouchka[1], Timothy O'Toole[1] and Matthew Cave[1], (1)University of Louisville, Louisville, KY, (2) University of Louisville

Background: Pollution from plastics is an increasing health threat. Microplastics are small plastic pieces, which are formed by direct synthesis for industrial or consumer applications as well as by environmental plastic degradation. As plastic degradation is increased by UV light and "weathering", global warming has increased environmental microplastics. Polystyrene (PS) microplastics are ingested endocrine and metabolism disrupting chemicals, which have previously been associated with diabetes, obesity, NAFLD, gut dysbiosis, and increased intestinal permeability. PS in combination with polyethylene and polypropylene, makes up over 50% of environmental microplastics. Here, in order to better understand the hepatic effects of PS exposures, we performed mRNA-Seq in livers from a mouse PS exposure model. **Methods:** Chow diet-fed male C57Bl/6j were exposed to either 0.5 µm or 5 µm PS beads in water at 1µg/ml and controls were given water without PS beads for 12 weeks. Lipid analysis and mRNA-Seq was performed in whole liver abstracts and pathway enrichment analyses were performed using Ingenuity pathway analysis software (IPA). **Results:** Hepatic cholesterol was significantly increased by PS. Transcriptomics analysis revealed a size-dependent effect of PS bead exposures. The 0.5 µm exposures were associated with 278 unique differentially expressed genes (DEGs) in liver. Of these, *Steap4*, *Tnfaip3, and Ccl2* were the most up-regulated, while *Tpm2* and *Trib3* were the most down-regulated. 5 µm PS was associated with 44 unique DEGs. *Firre* was the most up-regulated gene, while *Slpi* and *Ctgf* were the most down-regulated. 5 DEGs (e.g., *Rev1*, *Brpf1*, *Ccnt2*, *Cavin2*, and *Pea15a*) were common to both exposure groups. 60 processes were enriched by 0.5 µm PS, and 6 were enriched by 5 µm PS. These processes included FXR/RXR Activation, Aryl Hydrocarbon Receptor Signaling, and LPS/IL-1 mediated inhibition of RXR. **Conclusion:** PS disrupted hepatic cholesterol metabolism. It was associated with hepatic transcriptional reprogramming in a PS bead size-dependent manner. Pathway enrichment analyses demonstrated a potential role for gut-derived signaling molecules (e.g., bile acids impacting FXR, indoles impacting AhR, and endotoxin impacting TLR4) in the metabolic toxicities associated with PS exposures. A confirmatory fecal/liver metabolomics analysis is currently ongoing.

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Disclosure information not available at the time of publication: Abigail Ekuban

20 | ACTIVATION OF TFEB PROTECTS AGAINST ACETAMINOPHEN-INDUCED LIVER INJURY IN MICE

Mengwei Niu, Xiaojuan Chao, Shaogui Wang, Hartmut Jaeschke, Hong-Min Ni and Wen-Xing Ding, University of Kansas Medical Center, Kansas City, KS

Background: Macroautophagy (referred to as autophagy hereafter) is a major intracellular lysosomal degradation pathway that is responsible for the degradation of misfolded/damaged proteins and organelles. Previous studies showed that autophagy protects against acetaminophen (APAP)-induced injury (AILI) via selective removal of damaged mitochondria and APAP protein adducts. The lysosome is a critical organelle sitting at the end stage of autophagy for autophagic degradation via fusion with autophagosomes.The goal of this study was to investigate the role and mechanisms of transcription factor EB (TFEB)-mediated lysosomal and mitochondria biogenesis in AILI. **Methods:** Wildtype mice, liver-specific TFEB knockout mice or mice with hepatic overexpression of TFEB using Adenovirus-Tfeb were treated with APAP for various time points. Serum alanine aminotransferase (ALT) levels, liver histology and TUNEL staining as well as RNA sequencing and western blot analysis were performed. A cell-based imaging high-throughput chemical screening for TFEB agonists using a stable GFP-TFEB AML12 cell line was also performed. **Results:** We showed that TFEB was impaired by APAP resulting in decreased lysosomal biogenesis in mouse livers, which was associated with levels of APAP-adducts and liver injury. Genetic loss-of and gain-of function of hepatic TFEB exacerbated or protected against AILI, respectively. Mechanistically, overexpression of TFEB increased clearance of APAP protein adducts and mitochondria biogenesis as well as SQSTM1/p62-dependent non-canonical nuclear factor erythroid 2-related factor 2 (NRF2) activation and hepatic glutathione biosynthesis to protect against AILI. Cell-based imaging high-throughput chemical screening identified a group of TFEB agonists. Among these agonists, salinomycin, an anticoccidial and antibacterial agent, activated TFEB and protected against AILI in mice. **Conclusion:** In conclusion, genetic and pharmacological activating TFEB promotes removal of APAP-adducts and damaged mitochondria with concurrent increased mitochondrial biogenesis, which may be a promising approach for improving recovery of AILI.

Disclosures: The following people have nothing to disclose: Mengwei Niu, Xiaojuan Chao, Shaogui Wang, Hartmut Jaeschke, Hong-Min Ni, Wen-Xing Ding

21 | MITOCHONDRIAL Ca2+ UNIPORTER (MCU) IN HEPATOCYTES BUT NOT IN KUPFFER CELLS PROMOTES LIVER INJURY INDUCED BY ACETAMINOPHEN (APAP)

Jiangting Hu, Anna-Liisa Nieminen, Judith A. Dent and John J. Lemasters, Medical University of South Carolina

Background: Iron-catalyzed formation of reactive oxygen species (ROS) increases after APAP overdose and triggers the mitochondrial permeability transition (MPT). Previous studies show that iron translocation from lysosomes into mitochondria by MCU in hepatocytes promotes the MPT after APAP. Kupffer cells are liver resident macrophages that are involved in uptake, processing, and export of iron. Here, our Aim was to investigate and compare the roles of MCU in hepatocytes and Kupffer cells in APAP hepatotoxicity. **Methods:** Hepatocyte specific MCU knockout mice (hsMCU KO) and Kupffer cell specific MCU knockout mice (ksMCU KO) were created by individual crosses of floxed MCU mice with Alb-Cre mice and Clec4f-Cre-tdTomato mice, respectively. MCU deficiency in hepatocytes and Kupffer cells was confirmed by Western blot or immunocytochemistry. hsMCU KO, ksMCU KO, and widetype (WT) mice were treated with 300 mg/kg APAP or vehicle. Liver injury was assessed by histology and serum ALT at 24 h. **Results:** Western blots confirmed the absence of MCU protein expression in isolated hepatocytes from hsMCU KO mice. MCU protein remained expressed in the kidneys of hsMCU KO mice. The absence of MCU protein expression in Kupffer cells of ksMCU KO mice was confirmed by immunocytochemistry. In hsMCU WT mice, overdose of APAP increased serum ALT (9398 U/L) and centrilobular necrosis (55%) at 24 h, indicating severe liver injury. By contrast in hsMCU KO mice, ALT and hepatic necrosis were decreased to 4104 U/L and 24%, respectively. However, ALT and hepatic necrosis between ksMCU KO and the corresponding WT mice at 24 h after overdose APAP were not significantly different. CYP2E1 expression in hsMCU KO mice was similar to WT mice, indicating the protection against APAP-induced hepatic injury in MCU deficient hepatocytes was not the result of decreased APAP metabolism by CYP2E1. **Conclusion:** The core protein of the mitochondrial calcium uniporter complex, MCU, specifically located in hepatocytes, but not in Kupffer cells, plays a central role in APAP-induced hepatotoxicity.

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Disclosure information not available at the time of publication: Anna-Liisa Nieminen

22 | IDENTIFICATION OF A REGULATORY VARIANT IN A LONG NONCODING RNA THAT INFLUENCES EXPRESSION OF EXOC3L4 AS A RISK FACTOR FOR CHOLESTATIC-MIXED DRUG-INDUCED LIVER INJURY

Paola Nicoletti[1], Song Zhenwei[2], Samreen Zafer[1], Andrew Dellinger[3], Yi-Ju Li[3], Huiman Barnhart[3], Naga P. Chalasani[4], Robert J. Fontana[5], Joseph Odin[1], Jose Serrano[6], Tae-Hwi Schwantes-An[7], Andrew Stolz[8], Guruprasad P. Aithal[9], Raul J. Andrade[10], Einar Stefan Bjornsson[11], Ann Daly[12], M I Lucena[13] and Paul B. Watkins[14], (1)Icahn School of Medicine at Mount Sinai, New York, NY, (2)University University of North Carolina at Chapel Hill, Research Triangle Park, NC, (3)Duke University, Durham, NC, (4)Indiana University Medical Center, Indianapolis, IN, (5)University of Michigan Medical Center, Ann Arbor, MI, (6)National Institute of Diabetes, Bethesda, MD, United States, (7)Indiana University School of Medicine, (8)University of Southern California, Los Angeles, CA, (9)Nottingham University Hospital NHS Trust and University of Nottingham, Nottingham, UK, (10)Universidad De Málaga,Málaga, Spain, (11)Landspitali University Hospital, Reykjavik, Iceland, (12)Newcastle University, Newcastle upon Tyne, UK, (13)Universidad De Málaga, Málaga, Spain, (14)University of North Carolina at Chapel Hill, Research Triangle Park, NC

Background: Genetic factors associated with DILI susceptibility have been observed to be largely drug specific. The aim of this study was to identify novel risk factors for Cholestatic-Mixed Drug Induced Liver Injury (CM-DILI). **Methods**: Genome-Wide Association (GWAS) and Transcriptome-Wide Association (TWAS) analyses were performed on 927 CM-DILI cases (R value < 5.0) and 10,397 population-based controls of European descent. Associations were confirmed in a validation cohort of 274 CM-DILI cases and 17,836 population-based controls. TWAS analysis was conducted by Fusion using summary statistics from the discovery European GWAS and multi tissues references designed by Context algorithm. CM-DILI cases were also compared to hepatocellular DILI cases. RNA knockdown and analysis of subsequent expression of candidate target genes were performed in three human liver cell lines (HepG2, Huh7, and PH5CH8). **Results**: A single nucleotide variant, rs11624069 (C) on chromosome 14, demonstrated a genome-wide significant association with CM-DILI risk in the discovery cohort (OR [95%CI] = 1.33 [1.20-1.46] $p = 9.3x10^{-9}$). The association was confirmed in the validation cohort (OR [95%CI] = 1.25 [1.06-1.48] $p = 0.009$). In contrast, hepatocellular DILI cases showed similar allele frequency as population controls. rs11624069 (C) was also overrepresented in Hispanic and African American CM-DILI cases compared to ethnically matched controls. Interestingly, rs11624069 has been associated with risk of Primary Biliary Cholangitis and elevation in serum cholestatic biomarkers in healthy populations. TWAS identified that rs11624069 (C) was colocalized with a cis eQTL signal conserved across tissues, increasing the expression of *RP11-736N17.8*, a long noncoding RNA ($p = 2.3x10^{-6}$). In the liver, rs11624069 (C) was associated with increased expression of *RP11-736N17.8* ($p = 7.0x10^{-10}$) and also, less strongly, of *EXOC3L4* ($p = 0.002$), a nearby gene selectively expressed in hepatocytes. Knockdown of *RP11-736N17.8* expression in the three liver cell lines was found to markedly reduce expression of *EXOC3L4*. **Conclusion**: GWAS identified a regulatory variant for *RP11-736N17.8,* a long noncoding RNA, which modulates expression of *EXOC3L4,* as a novel risk factor for CM-DILI due to multiple drugs. Since *EXOC3L4* is a component of the exocyst complex, which is involved in tracking of proteins to apical versus basolateral membranes, the association of rs11624069 (C) with CM-DILI may relate to altered membrane trafficking of transporters for bile constituents.

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Tae-Hwi Schwantes-An – Target RWE: Consultant, No, Yes;

Einar Stefan Bjornsson – Novo Nordisk: Consultant, No, No;

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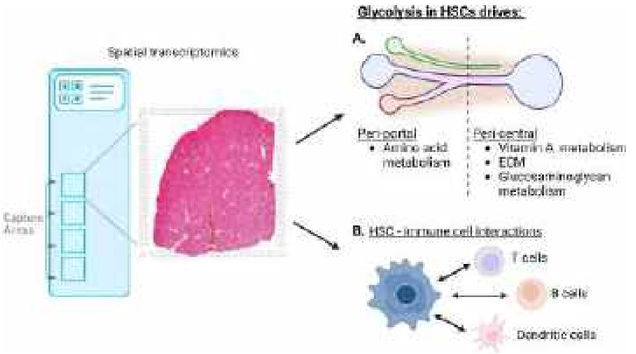
23 | HEPATIC STELLATE CELL-SPECIFIC GLYCOLYSIS REGULATES SPATIAL GENE ZONATION AND CELLULAR INTERACTIONS TO PROMOTE IN VIVO LIVER FIBROSIS

Leo Liu[1], Shalil Khanal[1] and Enis Kostallari[2], (1)Mayo Clinic, (2)Mayo Clinic, Rochester, MN

Background: Hepatic stellate cells (HSCs) are the main drivers of liver fibrosis. During The Liver Meeting 2022, we demonstrated that glycolysis deficiency selectively in HSCs attenuated liver fibrosis *in vivo*. The aim of the present study is to understand how HSC-specific glycolysis promotes liver fibrosis by altering signaling pathways and HSC interactions with the surrounding cell types in a spatial manner. **Methods:** Liver fibrosis was induced by carbon tetrachloride (CCl_4) administration in glycolysis-deficient mice, where hexokinase 2 (HK2) was deleted selectively in PDGFRβ$^+$ HSCs (HK2$^{\Delta HSC}$), and their HK2$^{fl/fl}$ littermate controls. 10X Genomics Visium platform was employed to examine spatial gene expression. Data were normalized using SCTransform and integrated using Harmony algorithm. Unsupervised clustering was performed using Louvain algorithm. In-house and public single cell RNA-seq data (GSE175939, GSE108097) were integrated for cell type deconvolution using RCTD algorithm. Differential co-localization analysis between cell types was performed using *Fisher's z* test. **Results:** RNA was collected and sequenced from each of the 55-μm spatial spots, each spot including several cells. Based on conserved gene expression, the spots were classified into 4 clusters (0-3) across the conditions. Clusters 0 and 3 expressed the peri-portal marker Cyp2f2, while clusters 1 and 2 expressed the peri-central marker Cyp2e1 as well as collagen 1±1 and 3±1 (adj. $p < 0.05$). Gene ontology analysis (Panther 2023) of differential gene expression showed that HSC-specific glycolysis regulated distinct pathways during liver fibrosis, such as amino acid metabolism in the peri-portal clusters and extracellular matrix, vitamine A and glucosaminoglycan-related pathways in the peri-central clusters (FDR < 0.02). These results suggest that glucosaminoglycan metabolism closely correlates to HSC activation and matrix deposition in the pericentral areas. In addition, a neighborhood analysis was performed to study how HSC-specific glycolysis regulates cell-to-cell interactions. CCl_4-mediated fibrosis was accompanied by an increased colocalization between HSCs and macrophages, T cells and dendritic cells ($p < 0.05$), which were significantly reduced when HK2 was selectively deleted in HSCs ($p < 0.05$). **Conclusion:** Our results suggest that HSC-specific glycolysis promotes liver fibrosis by regulating distinct metabolic pathways in peri-central versus peri-portal zones and facilitating the interaction between HSCs and immune cells *in vivo*.



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Disclosure information not available at the time of publication: Leo Liu

24 | EXTRACELLULAR MATRIX PROTEIN 1 ATTENUATES HEPATIC FIBROSIS BY INHIBITING PROTEASE-MEDIATED LATENT TGF-² 1 ACTIVATION

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Background: ECM1 depletion results in excessive latent TGF-β1 activation and lethal liver fibrosis in mice. In patients suffering from chronic liver diseases, ECM1 expression gradually decreases with increasing severity of fibrosis. We investigated the underlying mechanisms of how ECM1 contributes to tissue homeostasis in healthy livers and what changes occur during CLD progression. **Methods:** RNAseq of WT and ECM1-KO murine livers was performed to detect ECM1-KO-related changes in gene expression. Functional assays were performed using immortalised and primary hepatic stellate cells, WT and ECM1-KO mice, and liver tissue from patients suffering from CLD. **Results:** DESeq shows that expression of thrombospondins (TSPs), including TSP-1, matrix metalloproteinases, ADAMTS proteases, increased concomitantly with LTGF-β1 activation and fibrosis following ECM1-KO. In the LX-2 and phHSCs, ECM1 prevented TSP-1-, ADAMTS1-, MMP-2- and -9-mediated LTGF-β1 activation, as assessed by the concentration of active TGF-β in conditioned media through using the MFB-F11 TGF-β reporter cell line and the expression changes of hepatic fibrosis markers. IF staining for TGF-β1 LAP-D (R58) further demonstrated that protease-mediated LTGF-β1 activation is inhibited by the ECM1 in LX-2 HSCs. Co-IP analyses revealed that ECM1 interacts with all four of the tested LTGF-β1-activating proteases and, for MMP-2 and -9, binding occurred preferentially to their respective activated state. Next, in vitro interaction assays showed that ECM1 abrogates TSP-1- and ADAMTS1-mediated LTGF-β1 activation through an interaction with their respective KRFK or KTFR sequence. Further, ECM1 abolishes MMP-2/9-mediated LTGF-β1 activation through inhibiting their proteolytic activity. *In mice*, AAV-mediated overexpression of ECM1 in hepatocytes protected from KRFK-mediated LTGF-β1 activation and subsequent hepatic fibrosis. Importantly, KTFR injection was able to rescue the ECM1-KO phenotype and thus revert liver injury in mice affected by ECM1 depletion. We also found that in patients suffering from CLD, a loss ECM1 expression was accompanied by induction of TSP-1, ADAMTS1, MMP-2, and MMP-9, all of which mediate LTGF-β1 activation. **Conclusion:** ECM1 exerts its hepatoprotective effect through an inhibition of protease-mediated excessive LTGF-β1 activation by interacting with activating motifs and directly reducing proteolytic activity. During progression of CLD, ECM1 expression decreases and therewith liver tissue homeostasis is disturbed as protease-mediated LTGF-β1 activation becomes unhinged, resulting in increased active TGF-β1 bioavailability, elevated fibrogenic signaling, and ultimately the worsening of hepatic fibrosis. Our findings indicate that delivering ECM1 (or respective phenocopying peptides) to the liver when it is lost can serve as a novel yet safer TGF-β1 directed therapy.

Disclosures: The following people have nothing to disclose: Frederik Link, Yujia Li, Stefan Munker, Weiguo Fan, Zeribe Nwosu, Matthias Ebert, Honglei Weng, Sai Wang, Steven Dooley

25 | ER-ASSOCIATED PROTEIN DEGRADATION AS A POTENTIAL ANTI-FIBROTIC TARGET IN HEPATIC STELLATE CELLS

Jessica Maiers, Alexander Jackson, Reese A Baxter and Avishek Paul, Indiana University School of Medicine

Background: Liver injury activates hepatic stellate cells (HSCs) which drive fibrosis through secreting extracellular matrix proteins. Proteins destined for secretion are cotranslationally translocated into the endoplasmic reticulum (ER), folded, and exported for secretion. Activated HSCs exhibit increased protein translation leading to ER stress, which is sensed by ER membrane proteins Activating transcription factor 6 (ATF6±), Inositol-requiring enzyme 1 (IRE1±), and Protein kinase R-like ER kinase (PERK). These sensors initiate the Unfolded Protein Response (UPR) to relieve stress through processes including ER-associated degradation (ERAD): where misfolded proteins are targeted for proteasome degradation. The UPR is critical for HSC activation and fibrogenesis, but whether ERAD plays a key pro-fibrotic role is unknown. Publicly available RNAseq data revealed upregulation of ERAD components in cirrhotic livers, thus we hypothesized that ERAD is crucial for HSC activation and fibrogenesis. **Methods:** Primary human HSCs (hHSCs) were activated with TGFβ in combination with UPR inhibitors (Ceapin A7, 4µ8C, or GSK2656157 to inhibit ATF6±, IRE1±, or PERK respectively), or ERAD inhibitor Eeyarestatin 1 (EER1). ERAD components and HSC activation were analyzed by Western blot, qPCR, and microscopy. Immortalized hHSC (LX-2) cells were transfected with an siRNA targeting ERAD component SEL1L and analyzed for HSC activation. *In vivo*, C57BL/6J mice were fed a high fat diet for 8 weeks (D12102Ci) or control diet with biweekly injections of 2mg/kg EER1 or vehicle. Liver sections were analyzed for fibrosis by Western blot and Sirius red staining. **Results:** TGFβ increased ERAD components *ERdj4*, *ERdj5*, *HERPUD1*, and *HRD1*, while decreasing protein levels of ERAD substrate OS-9, indicative of increased ERAD activity ($p < 0.05$). IRE1± inhibition limited TGFβ induction of *ERdj4* and collagen deposition ($p < 0.05$), while PERK inhibition increased *HRD1*, *ERdj4*, and *ERdj5* levels, and TGFβ-induction of collagen deposition ($p < 0.05$), linking ERAD and HSC activation. ERAD inhibition decreased ±SMA and Collagen 1 protein levels in hHSCs treated with TGFβ, and knockdown of *SEL1L* decreased collagen I levels at 24h. Unexpectedly, disrupting ERAD increased collagen deposition at 48h in both hHSCs and LX-2 cells. Finally, *in vivo* studies revealed that ERAD inhibition limited diet induced fibrogenesis and HSC activation. **Conclusion:** ERAD components increased in activated HSCs, and ERAD inhibition limited fibrogenesis *in vivo*. *In vitro*, ERAD disruption limited HSC activation at earlier time points (24h), but increased fibrogenesis at later time points (48h). We hypothesize that prolonged ERAD inhibition induces protein trafficking and secretion to remove misfolded proteins from the ER *in vitro*, but that long term ERAD inhibition limits fibrogenesis *in vivo*. This work identifies ERAD as a possible therapeutic target for fibrosis and fibrogenesis.

Disclosures: The following people have nothing to disclose: Jessica Maiers

Disclosure information not available at the time of publication: Alexander Jackson, Reese A Baxter, Avishek Paul

26 | HEPATIC STELLATE CELL-DERIVED 12-HHTRE AUTOINDUCES LTB4R2 FOR CTNNB1-YAP1 HCC PROMOTION PATHWAY

Sonal Sinha[1], Keigo Machida[1], Meng Li[2], Audrey Kapelanski-Lamoureux[3], Alexander Rialdi[4], Ernesto Guccione[5] and Hidekatzu Tsukamoto[1], (1)University of Southern California, (2)USC Libraries Bioinformatics Service, University of Southern California, (3)Mcgill University, (4)Icahn School of Medicine at Mount Sinai

(ISMMS), (5)Icahn School of Medicine at Mount Sinai Hess Center for Science and Medicine

Background: A subpopulation of tumor-associated activated hepatic stellate cells (aHSC) is implicated in releasing an oxylipin, 12-hydroxyheptadecatrienoic acid (12-HHTrE) to render HCC promotion via its high-affinity receptor LTB4R2 and downstream activation of CTNNB1 and YAP1/TAZ in HCC cells, highlighting the novel tumor promoter role of LTB4R2 (Nature Comm 2023. PMID: 37156770). However, if or how aHSC regulate LTB4R2 expression in HCC is unknown. Aim: We aimed to test a hypothesis that LTB4R2 expression is auto-induced by aHSC-derived 12-HHTrE to provide a spatially-directed, positive forward loop for tumor promotion. **Methods:** *Scd2*$^{f/f}$*;Col1Cre* vs. *Scd2*$^{f/f}$ mice were injected with DEN and fed Western alcohol diet for 4-5 months to induce liver tumorigenesis. Huh7 cells were treated with conditioned media (CM) from LX2 cells with or without *SCD* or *CYP1B1* KD, 12-HHTrE or appropriate vehicle. Human *LTB4R2* promoter-first intron (-1517/+344) was cloned and its deletion-luciferase reporter constructs were generated for transfection analysis in Huh7 cells. Patient HCC tissues were analyzed by IHC and the LTB4R2 dependence of patient HCC organoid growth was examined by pharmacologic and genetic manipulations. **Results:** Liver tumorigenesis in *Scd2*$^{f/f}$ mice was associated with upregulation of LTB4R2 mRNA and protein, which were largely abrogated by conditional ablation of *Scd2* in aHSC in *Scd2*$^{f/f}$*;Col1Cre* mice with reduced liver concentration of 12-HHTrE and tumor burden, suggesting aHSC-SCD2-12-HHTrE regulation of LTB4R2. LX2 cells released 12-HHTrE in a manner dependent on SCD or CYP1B1 and CM from such cells induced LTB4R2 expression and LTB4R2-dependent CTNNB1/YAP1 activation in Huh7 cells. Direct 12-HHTrE treatment of Huh7 cells also caused LTB4R2 upregulation which was prevented by CTNNB1 KD. Using *LTB4R2* proximal promoter-first intron deletion-reporter constructs, 12-HHTrE-mediated stimulation was mapped to -492/-244 promoter and +258/+344 intronic regions and these activities were blunted by CTNNB1 KD. Bioinformatic analysis revealed CTNNB1 enrichment and multiple TCF sites within the first intron segment. Spatially directed LTB4R2 induction by CYP1B1-generated 12-HHTrE by aHSC was supported by the presence of CYP1B1+ aHSC surrounding LTB4R2+ HCC cells in patient HCC. Lastly, pharmacologic or genetic inhibition of LTB4R2 in patient HCC organoids significantly attenuated their growth. **Conclusion:** Our results suggest that 12-HHTrE released by aHSC in tumor microenvironment causes a CTNNB1-dependent, transcriptional upregulation of LTB4R2 in HCC to allow the 12-HHTrE-LTB4R2-CTNNB1-YAP1/TAZ tumor promotion pathway. CYP1B1-dependent 12-HHTrE release by aHSC may be considered as an upstream therapeutic target for HCC in this pathway.

Disclosures: Hidekatzu Tsukamoto – HepaTX: Consultant, No, No;

The following people have nothing to disclose: Sonal Sinha, Keigo Machida, Meng Li, Audrey Kapelanski-Lamoureux, Alexander Rialdi, Ernesto Guccione

27 | IDENTIFICATION OF ANTI-FIBROTIC microRNAs ENRICHED IN EXTRACELLULAR VESICLES DERIVED FROM BONE MARROW MESENCHYMAL STEM CELLS IN PATIENTS WITH DECOMPENSATED LIVER CIRRHOSIS

Daiki Kawamoto[1], Toshihiko Matsumoto[2], Naoki Yamamoto[2] and Taro Takami[1], (1)Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi, Japan, (2)Yamaguchi University Graduate School of Medicine

Background: We have been developing a liver regeneration therapy for decompensated liver cirrhosis (DLC) using cultured autologous bone marrow mesenchymal stem cells (BMSCs). Currently, we are conducting a clinical trial called "Self-contained liver cirrhosis regeneration therapy (jRCT2063200014)". In our clinical trial, hepatic arterial infusion of cultured autologous BMSCs has ameliorated liver function and fibrosis in patients with DLC. However, the mechanism of anti-fibrotic action of BMSCs remain to be fully determined. It was recently reported that extracellular vesicles derived from MSCs (MSC-EVs) exhibited antifibrotic properties. We therefore examined the effect of MSC-EVs on extracellular matrix (ECM) production by hepatic stellate cells, and identified anti-fibrotic microRNAs (miRNAs) enriched in MSC-EVs using BMSCs derived from patients with DLC in our clinical trial with aim of developing adequate quality standards for MSCs in liver regeneration therapy. **Methods:** Human hepatic stellate cells (HHSteCs) were treated with TGFβ for activation and subsequently treated with EVs isolated from the culture media of human BMSCs and ECM gene expression determined. We used a microarray to perform a comprehensive analysis of miRNA expression profiles and compared miRNA expression profiles in MSC-EVs derived from healthy individual's or patients with DLC in our clinical trial and HHSteCs. To identify the antifibrotic miRNAs enriched in MSC-EVs, each mimic of miRNAs that highly expressed in MSC-EVs and lowly expressed in HHSteCs was transfected into HHSteCs and ECM gene expression determined. **Results:** MSC-EVs inhibited expression of ECM genes (COL1A1, COL1A2, COL3A1 and ELN) by activated HHSteC ($p < 0.05$). Thirty-six miRNAs were extracted from the microarray data that showed normalized intensity of > 1,000 in both MSC-EVs of healthy individual's and that of patients with DLC in our clinical trial. Among these miRNAs, ten miRNAs highly expressed in MSC-EVs and lowly expressed in HHSteCs. Each miRNA mimic of the ten miRNAs was transfected into activated HHSteCs and we identified five miRNAs which suppress expression of any of ECM genes ($p < 0.05$). Furthermore, transfection of a combination of the five miRNAs into activated HHSteC resulted in a significant decrease in expression of COL1A1, COL1A2, COL3A1, and ELN ($p < 0.05$). **Conclusion:** This study identified five anti-fibrotic miRNAs enriched in MSC-EVs and provided insight into mechanisms of action of MSC-EVs in fibrosis regression. Hence, miRNAs in MSC-EVs may be potential biomarkers for functional assessment of MSCs in liver regeneration therapy.

Disclosures: The following people have nothing to disclose: Daiki Kawamoto, Toshihiko Matsumoto, Naoki Yamamoto, Taro Takami

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

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

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

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

Jing Zeng[1], Derrick Zhao[1], Andrew Fagan[2], Michael Fuchs[2], Puneet Puri[2], Brian C. Davis[2], Xuan Wang[1], Emily Gurley[1], Phillip B. Hylemon[1,3], Huiping Zhou[1,3] *and Jasmohan S. Bajaj[2,3], (1)Department of Microbiology and Immunology, Medical College of Virginia and Mcguire Veterans Affairs Medical Center, Virginia Commonwealth University, Richmond, VA, (2) Virginia Commonwealth University and Richmond VA Medical Center, (3)Stravitz-Sanyal Institute for Liver Disease & Metabolic Health, School of Medicine, Virginia Commonwealth University, Richmond, VA, USA*

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

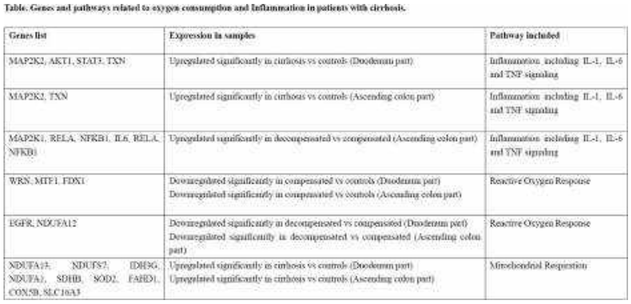

Table. Genes and pathways related to oxygen consumption and Inflammation in patients with cirrhosis.

Genes list	Expression in samples	Pathway included
MAP2K2, AKT1, STAT3, TXN	Upregulated significantly in cirrhosis vs controls (Duodenum part)	Inflammation including IL-1, IL-6 and TNF signaling
MAP2K2, TXN	Upregulated significantly in cirrhosis vs controls (Ascending colon part)	Inflammation including IL-1, IL-6 and TNF signaling
MAP2K1, RELA, NFKB1, IL6, RELA, NFKB1	Upregulated significantly in decompensated vs compensated (Ascending colon part)	Inflammation including IL-1, IL-6 and TNF signaling
WRN, MTF1, FDX1	Downregulated significantly in compensated vs controls (Duodenum part) Downregulated significantly in compensated vs controls (Ascending colon part)	Reactive Oxygen Response
EGFR, NDUFA12	Downregulated significantly in decompensated vs compensated (Duodenum part) Downregulated significantly in decompensated vs compensated (Ascending colon part)	Reactive Oxygen Response
NDUFA13, NDUFS7, IDH3G, NDUFA2, SDHB, SOD2, FAHD1, COX5B, SLC16A3	Upregulated significantly in cirrhosis vs controls (Duodenum part) Upregulated significantly in cirrhosis vs controls (Ascending colon part)	Mitochondrial Respiration

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Michael Fuchs

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

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

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

luminal antigens, especially endotoxins that translocate to the liver. This occurs because of (i) compromised gut barrier integrity due to epithelial tight junction (TJ) disruption; and (ii) qualitative/quantitative gut microbiota changes and increased production of pathogenic antigens. We have previously shown that ethanol consumption alters the liver methionine metabolic pathway causing a rise in intracellular S-adenosylhomocysteine (SAH) levels. While the levels of the key methyl donor, S-adenosylmethionine (SAM), is unchanged, the lowering of the SAM:SAH ratio impairs several methylation reactions leading to the generation of hallmark features of early alcohol-associated liver injury. We have further shown that treatment with betaine preserves the liver methylation potential to thereby prevent alcohol-induced liver damage. This study was undertaken to examine the effect of alcohol on intestinal methionine metabolic pathway and explore whether any functional detriment of these alterations could be prevented by betaine treatment. **Methods:** Adult male C57Bl/6 mice were fed the Lieber DeCarli control or ethanol diet for 6 weeks. At the end of the feeding regimen, blood, liver, cecal content and ileal segments were removed and analyzed. **Results:** We observed that while SAM levels were maintained in the ileal mucosa of the ethanol-fed mice, there was a significant rise in SAH levels which decreased the SAM:SAH ratio by ~2-fold ($p < 0.02$) compared with controls. All these changes were like those previously reported in the livers of ethanol-fed mice. Concomitant with the alterations in the crucial components of ileal methionine metabolic pathway that controls the cellular methylation potential, we observed disorganized localization of key members (occludin, claudin-1) of the multiprotein TJ complex by confocal microscopic analysis. Western blotting of the detergent insoluble fraction confirmed their loss in the ileal membrane fraction (where TJs are localized) of ethanol-fed mice compared with controls. The ethanol-induced TJ disruption was accompanied by systemic endotoxemia and ~2-, 8- and 3-fold enhanced hepatic expression of the respective mRNAs encoding the pro-inflammatory cytokines, TNF±, CCL2 and IL1β, respectively. Betaine supplementation not only prevented ethanol-induced TJ disruption and microbiota changes, but also mitigated systemic endotoxemia and liver inflammation. **Conclusion:** Taken together, our results indicate that alcohol-induced alterations in the intestinal epithelial methionine metabolic pathway and the resulting impairments in methylation reaction promotes gut leakiness and progressive liver injury. Betaine by preventing intestinal methylation defects and microbiota changes prevents the development of ALD.

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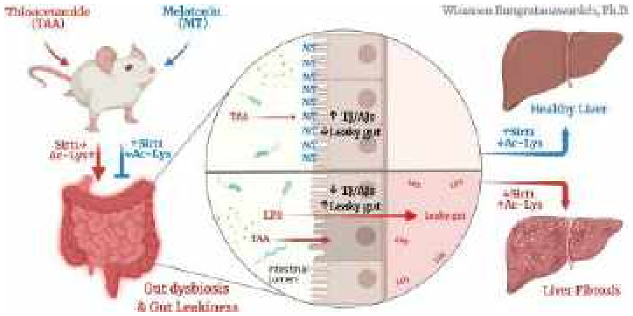
31 | NOVEL MECHANISMS UNDERLYING GUT LEAKINESS AND SYSTEMIC ENDOTOXEMIA IN PROMOTING LIVER FIBROSIS VIA THE GUT-LIVER AXIS AND THE MECHANISTIC PROTECTION OF MELATONIN

Wiramon Rungratanawanich, Karli LeFort and Byoung-Joon (B.J.) Song, Nih (NIAAA)

Background: Liver fibrosis is the consequence of chronic liver diseases that can progress to cirrhosis and liver failure. However, the role and mechanism of gut leakiness in liver fibrosis are poorly understood, and there is no FDA-approved drug to treat liver fibrosis. In this study, we aimed to investigate the causal role of protein acetylation and gut dysbiosis in promoting gut leakiness, endotoxemia, and liver fibrosis and the protection by melatonin (MT), a safe agent recognized by FDA, through the gut-liver axis. **Methods:** Young male Sprague-Dawley rats were divided into 12 groups (4 groups x 3 timepoints): Control (vehicle), MT (10 mg/kg/day, oral), TAA (200 mg/kg/dose twice a week, i.p.), and MT+TAA for 1, 2, or 4 weeks (n = 6-8/group). Histological analyses were determined by Picrosirius red, H&E, and TUNEL staining. Liver injury was evaluated by serum transaminases (ALT, AST) and markers for apoptosis and fibrosis. Gut dysbiosis was measured via 16S metagenomic sequencing and metabolomic analyses of cecum samples. Gut leakiness was assessed by serum endotoxin (LPS), while immunoblots and immunoprecipitation were performed to detect protein alterations. For additional mechanistic studies, similar experiments were performed in wild-type (WT) and gut- or liver-specific *Sirt1*-KO mice using TAA (200 mg/kg/dose twice a week, i.p.) for 5 weeks (n = 6-8/group). **Results:** TAA caused hyperacetylation (Ac-Lys) of gut and liver proteins via selective suppression of Sirtuin 1 (SIRT1) deacetylase along with gut dysbiosis, leading to gut leakiness, endotoxemia, and liver fibrosis, all of which were improved by MT. Gut tight and adherent junction proteins (TJ/AJs) were acetylated and degraded via ubiquitin-dependent proteolysis. Decreased TJ/AJs with increased intestinal deformation, enterocyte apoptosis, and serum endotoxin were observed as early as 1 week, while liver fibrosis and injury markers, hepatocyte apoptosis, and serum ALT and AST were markedly elevated 2 and 4 weeks after TAA exposure. TAA increased the abundance of pathogenic bacteria (Proteobacteria, Ruminococcaceae, etc.) but decreased the levels of short-chain fatty acids (Butyric, Propionic acids, etc.). Interestingly, TAA decreased only SIRT1 activity and protein levels, but not other six SIRT isoforms, and caused hyperacetylation of liver proteins related to inflammation (Ac-NFκB) and apoptosis (Ac-FOXO1). Pretreatment with

MT ameliorated all these changes at 1, 2, and 4 weeks. TAA-exposed gut- or liver-specific *Sirt1*-KO mice also showed markedly decreased gut TJ/AJs with greater enterocyte apoptosis, endotoxemia, liver fibrosis, and hyperacetylation of gut and liver proteins than those of WT mice. **Conclusion:** This study showed the novel mechanisms of the decreased SIRT1-mediated protein hyperacetylation along with gut dysbiosis in promoting gut leakiness and liver fibrosis and the protective role of melatonin through the gut-liver axis.



Disclosures: The following people have nothing to disclose: Wiramon Rungratanawanich, Karli LeFort, Byoung-Joon (B.J.) Song

32 | MICROBIAL MONOTHERAPY WITH LEUCONOSTOC SP. LB-P8 IMPROVES INFLAMMATION AND FIBROSIS IN MOUSE MODELS OF PRIMARY SCLEROSING CHOLANGITIS

Steven P. O'Hara[1], Kyoungsub Song[2], Seunghwan Choi[2], Carys A. Turner[1], Nicholas E. Pirius[1] and Nicholas F. LaRusso[3], (1)Mayo Clinic, (2)Liscure Bioscience, (3)Mayo Clinic, Rochester, MN

Background: PSC is an archetypical example of a disease with an impaired gut-liver axis and PSC patients with or without inflammatory bowel disease exhibit enteric microbial dysbiosis. Gut microbiota produce diverse metabolic products but how microbes influence PSC disease progression is unclear. By screening bacterial species (sp.) in a transwell gut-liver axis model, we identified novel *Leuconostoc sp*. (LB-P8) that may have anti-fibrotic properties via inhibition of TGF-β/SMAD signaling. Here we investigated whether oral dosing of LB-P8 improved inflammation and fibrosis in mouse models of PSC. **Methods:** We used two models: chronic feeding (7 weeks) of 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) and the Mdr2-/- mouse. Live culture or freeze-dried preparations of LB-P8 were orally gavaged daily for 4 weeks following disease onset. Peribiliary injury, inflammation, fibrosis, and cholangiocyte senescence were measured biochemically (ALT & ALP), and by histology, immunofluorescence, picrosirius red staining, hydroxyproline content, and qPCR. LB-P8-derived metabolites were analyzed using untargeted UPLC-MS/MS. Finally, RNA-seq was performed on hepatic stellate cells (HSCs) cultured in the presence or absence of LB-P8. **Results:** LB-P8 reduced DDC-fed and Mdr2-/- mouse model-induced elevations of serum ALT (~50 %), and ALP (20-50%). Fibrosis was reduced in live culture LB-P8 treated mice as evident by reduced picrosirius red staining (~50%), and hepatic hydroxyproline content. In Mdr2-/- mice, live culture LB-P8 treatment reduced hepatic mRNA expression of the fibrosis marker, Col1a1 (>50%), inflammatory markers, Tnf-± and Mcp-1 (~50%), and senescence markers, p16 and p21 (~80%). In DDC-fed mice, LB-P8 reduced macrophage number (F4/80; ~30%) and senescent cholangiocytes (p21 immunofluorescence) (~40%). Metabolomic profiling of LB-P8 cultures revealed increased detection of 38 metabolites involved in anti-fibrosis/inflammation compared to control and negative strains. RNA seq analysis of HSC further showed that LB-P8 decreased TGF-β, EMT, and integrin signaling pathways. **Conclusion:** LB-P8 ameliorates cholestatic liver disease progression likely by reducing cholangiocyte senescence, TGF-β-mediated fibroblast activation, and periportal accumulation of macrophages. These data suggest that LB-P8 targeting of the gut-liver axis is a potential novel therapeutic strategy for the treatment of PSC.

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Disclosure information not available at the time of publication: Kyoungsub Song, Seunghwan Choi, Carys A. Turner, Nicholas E. Pirius, Nicholas F. LaRusso

33 | GUT MICROBE-PRODUCED IMIDAZOLE PROPIONATE AGGRAVATED HEPATIC FIBROSIS BY BOOSTING HEPATOCELLULAR DEATH AND M1 MACROPHAGE POLARIZATION

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Background: Emerging evidence demonstrates microbial metabolites play pivotal roles in onset and progression of liver fibrosis and imidazole propionate (ImP) as a microbially produced histidine-derived metabolite was significantly increased in patients with chronic hepatitis B/cirrhosis compared to healthy controls. However, whether ImP is involved in hepatic fibrosis remains unclear. The present study aimed to explore the effects of ImP on hepatic fibrosis and its potential mechanisms. **Methods:** ImP (100μg) was administered i.p. twice daily for late 3 weeks in CCl_4-induced model (i.p. 9 weeks, twice weekly). Phosphorylated H2AX (γH2AX) DNA damage was detected by Western blot. M1 macrophage polarization was determined by gene expression of inducible nitric oxide synthase (iNOS), IL1β and IL6. **Results:** Although ImP administration alone did not cause liver fibrosis compared to controls, but it significantly exacerbated the progression of CCl_4-induced hepatic injury as documented by serum levels of ALT (452.5 ± 103.7 vs. 170.0 ± 27.5U/L, $p < 0.05$), AST (545.8 ± 102 vs. 237.0 ± 39.8U/L, $p < 0.05$). Collagen deposition was dramatically increased in CCl_4+ImP-treated compared to CCl_4-treated mice as indicated by Masson's staining and Sirius red staining. Gene expression of smooth muscle ±-actin (±-SMA) (3.35 ± 0.86 vs. 0.90 ± 0.09), procollagen 1±1 (COL1±1) (2.72 ± 0.58 vs. 1.00 ± 0.16) and procollagen 3±1 (COL3±1) (2.94 ± 0.78 vs. 0.98 ± 0.013, $p < 0.05$) was upregulated in CCl_4+ImP-treated mice. Additionally, liver showed more inflammation in CCl_4+ImP-treated mice, as demonstrated by enhanced infiltration of macrophages with CD11b immunofluorescence. To further analyze how ImP regulates macrophages *in vitro*, bone marrow-derived macrophages (BMDMs) were differentiated from WT mice. ImP increased expression of M1 polarization markers, iNOS (3.06 ± 0.45 vs. 1.03 ± 0.17, $p < 0.05$), IL1β (1.82 ± 0.09 vs. 0.98 ± 0.04, $p < 0.005$) and IL6 (3.17 ± 0.67 vs. 1.03 ± 0.19, $p < 0.05$) in BMDMs following LPS treatment. Furthermore, ImP elevated γH2AX protein in CCl_4-induced mouse liver and mRNA expression of iNOS in LPS-stimulated primary hepatocytes. Based on Hoechst staining, percentage of apoptotic primary hepatocytes in the LPS+ImP group was increased compared to LPS control. The supernatant of hepatocytes treated with LPS+ImP further potentiated proinflammatory polarization in BMDM than only LPS-stimulated hepatocytes, as evidenced by increased mRNA levels of iNOS. The supernatant of BMDM derived from hepatocytes treated by LPS+ImP further facilitated hepatic stellate cell (HSC) activation. **Conclusion:** Gut microbe-generated ImP potentiated fibrotic progression induced by CCl_4 intoxication in mice. Pronounced hepatocellular apoptosis, recruitment of inflammatory cells to damaged liver, release of pro-inflammatory cytokines (IL1β, IL6) may account for enhanced activation of HSCs into collagen type I-producing myofibroblast-like cells.

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Disclosure information not available at the time of publication: Fangyuan Chen

34 | INTESTINAL EPITHELIAL CELL OSTEOPONTIN PROTECTS FROM MASH BY CHANGING THE COMPOSITION OF THE GUT MICROBIOME AND BILE ACIDS

Hui Han[1], Sukanta Das[1], Xiaodong Ge[1], Zhuolun Song[1], Sai Santosh Babu Komakula[1,2], Ines Barahona[1], Romain Desert[1], Dipti Athavale[1], Wei Chen[1], Daniel Lantvit[1], Grace Guzman[1] and Natalia Nieto[1], (1)University of Illinois at Chicago, (2)University of Illinois at Chicago, Chicago, IL, United States

Background: osteopontin (OPN, encoded by *SPP1*) is involved in chronic liver disease. Previous studies reported that intestinal OPN regulates the gut microbiota, however the role of intestinal epithelial cell (IEC)-derived OPN in metabolic dysfunction-associated steatohepatitis (MASH) is unknown. **Methods:** we generated *Spp1* knock-in (*Spp1*$^{KI\ IEC}$) and knock-out (*Spp1*$^{\Delta IEC}$) mice in IECs and fed both genders with high fat, fructose, and cholesterol diet to induce MASH, or with isocaloric control diet, for 6 months. **Results:** immunohistochemistry revealed decreased OPN expression in IECs in WT mice with MASH compared to control diet. *Spp1*$^{\Delta IEC}$ showed worse hepatic inflammation (increased CD11b$^+$ cell infiltration and up-regulation of pro-inflammatory cytokines) than WT mice regardless of diet but developed more liver fibrosis and increased serum ALT than WT mice, when fed MASH-inducing diet. S*pp1*$^{\Delta IEC}$ mice displayed clutched IECs with condensed cytoplasm and pyknotic nuclei, increased TUNEL$^+$ IECs, downregulation of tight junction proteins, increased serum LPS and hepatic bacterial load, compared to WT mice, regardless of diet. Metagenomic analysis of gut microbiota revealed that *Spp1*$^{\Delta IEC}$ mice had enhanced β-diversity due to increased Deferribacteres and Verrucomicrobiota phyla. Multi-factor analysis revealed that 11 genera and 27 species were differentially upregulated in *Spp1*$^{\Delta IEC}$ mice, regardless of diet. Among them, Clostridium_XlVa, Parabacteroides and Dora regulate bile acid (BA) deconjugation and 7-dehydroxylation. Total BAs increased in portal serum and decreased in feces from *Spp1*$^{\Delta IEC}$ compared to WT mice with MASH, indicating less BA excretion. Both the MASH diet and the *Spp1*$^{\Delta IEC}$ genotype independently increased conjugated primary BAs, particularly taurocholic acid (TCA), in both genders. Unconjugated primary BAs decreased in MASH but were less affected in *Spp1*$^{\Delta IEC}$ mice. Secondary BAs were lower in serum, however taurodeoxycholic acid (TDCA) significantly increased in *Spp1*$^{\Delta IEC}$ mice, regardless of diet. The hepato-protective BA tauroursodeoxycholic acid (TUDCA), mildly increased in both genders, regardless of diet, but was less abundant than TCA and TDCA. Compared to WT mice, *Spp1*$^{KI\ IEC}$ mice were protected from MASH shown by reduced gut permeability, liver inflammation, and fibrosis. **Conclusion:** IEC-derived OPN protects against MASH by preserving gut permeability, changing the composition of the gut microbiome, and bile acids.

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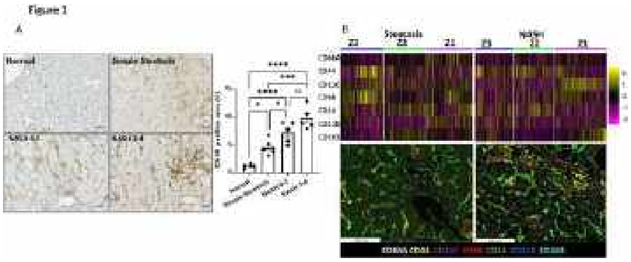
Disclosure information not available at the time of publication: Dipti Athavale, Wei Chen, Grace Guzman

35 | LIPID INDUCED ENDOTHELIAL INTERCELLULAR ADHESION MOLECULE 1 (ICAM1) PROMOTES METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Qianqian Guo[1], Mireille Khoury[1], Feda H Hamdan[2], Alexander Q. Wixom[2], Jose C. Villasboas[2] and Samar H. Ibrahim[2], (1)Mayo Clinic Rochester, Rochester, MN, (2)Mayo Clinic

Background: During metabolic dysfunction-associated steatohepatitis (MASH), liver sinusoidal endothelial cells (LSECs) acquire a pro-inflammatory phenotype characterized by increased adhesion molecules expression and myeloid cells-associated liver inflammation culminating in disease progression. However, the exact molecular mediators of this phenomenon are unclear. Herein, we aim to uncover the pathogenic role and the transcriptional regulation of intercellular adhesion molecule (ICAM1), an upregulated LSEC adhesion molecule in MASH and lipotoxicity. **Methods:** Chromatin immunoprecipitation (ChIP) assay was used to evaluate the enrichment at the *ICAM1* promoter of the active epigenetic mark, H3K27ac in primary human hepatic sinusoidal endothelial cells (HHSECs). HHSECs were seeded in a flow chamber, and primary human neutrophils were infused using a flow-based adhesion assay. Wild-type C57BL/6J mice were fed fat, fructose, and cholesterol (FFC) diet or choline-deficient high-fat diet (CDHFD) to induce MASH. Paraffin embedded liver sections from MASH patients or normal subjects were subjected to immunostaining and multiplex imaging using the CODEX (Co-detection by indexing) system. **Results:** Data mining of Assay for Transposase-Accessible Chromatin with sequencing (ATAC-seq) in LSECs from MASH and control mice identified open chromatin regions at the promoter region of *Icam1* that are significantly enriched in MASH mice. We validated the upregulation of ICAM1 expression in HHSECs with palmitate (PA) treatment. ChIP assay for H3K27ac showed H3K27ac enrichment is significantly induced by PA treatment at the ICAM1 promoter region. Using pharmacological and genetic inhibition approaches, we identified that ICAM1 upregulation in lipotoxicity is induced by glycogen synthase kinase 3 activation, and its downstream signaling pathway (JNK and c-Jun). Flow-based adhesion assay showed reduced neutrophil adhesion to PA treated HHSECs in the presence of ICAM1 Antibody (Ab). ICAM1 Ab-treated mice in both MASH models had reduced liver inflammation and fibrosis compared to controls, as assessed by decreased mRNA expressions of *Mcp1* and *Pdgfrb,* reduced immunostaining of the neutrophil marker myeloperoxidase (MPO), and reduction of infiltrated proinflammatory monocytes and neutrophils by flowcytometry. ICAM1 liver immunostaining was increased in patients with MASH and correlated with disease severity (Figure 1A). Bioinformatic analysis of the CODEX multiplexed liver tissue showed distinct zonal distribution of 7 myeloid cells in steatosis versus MASH with adherent myeloid cells to the sinusoidal endothelium (Figure 1B). **Conclusion:** Lipotoxic stress enhances the expression of LSECs ICAM1 via a c-Jun-associated histone modification. Inhibition of ICAM1 was salutary in murine MASH mainly secondary to reduced hepatic recruitment of proinflammatory myeloid cells and might serve as a potential therapeutic target for human MASH.



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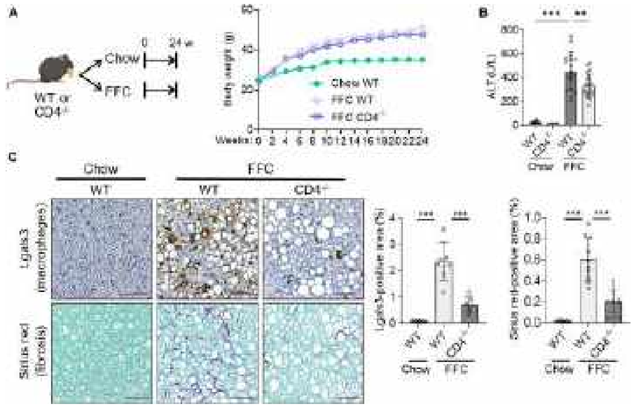
The following people have nothing to disclose: Qianqian Guo, Mireille Khoury, Feda H Hamdan, Alexander Q. Wixom, Jose C. Villasboas

f 36 | GENETIC ABLATION OF CD4 T CELLS IN MICE ATTENUATES LIVER INJURY, INFLAMMATION, AND FIBROSIS IN NONALCOHOLIC STEATOHEPATITIS★

Hyun Se Kim Lee, Lucia Valenzuela Perez, Rachel L. Bayer, Ivone Igreja E Sá, Ester Dohnalkova, Ece Janet Dinc, Qianqian Guo, Samar H. Ibrahim, Adebowale O. Bamidele and Petra Hirsova, Mayo Clinic

Background: Nonalcoholic steatohepatitis (NASH) is a progressive condition characterized by excessive inflammation, which may lead to fibrosis. To date, the contribution of T cells to NASH remains largely unexplored. Our unpublished data suggest that CD4 T cells with pathogenic Th1 phenotype accumulate in murine NASH livers. Therefore, we investigated the role of CD4 T lymphocytes in NASH development. **Methods:** Whole-body CD4 knockout ($CD4^{-/-}$) and wild-type (WT) mice were fed chow or NASH-inducing diet high in fat, fructose, and cholesterol (FFC) for 24 weeks. Insulin resistance and metabolic phenotype were evaluated at weeks 16 and 18, respectively. Liver injury, inflammation, and fibrosis, along with gut microbiome were evaluated after 24 weeks of feeding. **Results:** CD4 deletion in FFC-fed mice did not affect food intake, weight gain, lean and fat mass, insulin resistance, and metabolic profile (e.g., metabolic rate, energy expenditure) as assessed by CLAMS (Comprehensive Lab Animal Monitoring System). However, liver weight and liver injury (assessed by plasma alanine aminotransferase) were significantly reduced in FFC-fed $CD4^{-/-}$ mice compared to WT, despite no changes in liver steatosis (measured by triglyceride levels). Mouse intrahepatic leukocytes were isolated and subjected to immunoprofiling by mass cytometry (CyTOF) and flow sorting of monocyte-derived macrophages (MoMF). Transcriptomic analysis in isolated MoMF using NanoString technology revealed that scar-associated macrophage markers (Trem2 and CD9) were less abundant in FFC-fed $CD4^{-/-}$ mice. Concordantly, liver hydroxyproline assay and Sirius red staining demonstrated a striking reduction in hepatic collagen deposition in FFC-fed $CD4^{-/-}$ mice, suggesting that CD4 T cells are required for liver fibrogenesis in NASH. The decrease in inflammatory and fibrogenic response was further validated by IHC for galectin-3 (macrophage marker) and ±SMA (a marker for activated hepatic stellate cells). Finally, FFC-associated microbiota alterations, such as increases in bacterial genes linked with glycolysis, glucogenesis, and lysine biosynthesis, were not observed in FFC-fed $CD4^{-/-}$ mice. Also, the gut microbiota alpha diversity in FFC-fed $CD4^{-/-}$ mice resembled that of chow-fed controls, exhibiting similar Firmicutes/Bacteroidetes ratios. **Conclusion:** Genetic loss of CD4 T cells in a murine NASH model results in a reduction in liver injury, inflammation, and fibrosis, independent of the metabolic syndrome. Together, we allude that CD4 T cells contribute to NASH pathogenesis.



Disclosures: Samar H. Ibrahim – Alberio Pharam: Consultant, No, No; Mirum pharmaceutical: Consultant, No, No;

The following people have nothing to disclose: Hyun Se Kim Lee, Lucia Valenzuela Perez, Rachel L. Bayer, Ivone Igreja E Sá, Ester Dohnalkova, Ece Janet Dinc, Qianqian Guo, Adebowale O. Bamidele, Petra Hirsova

37 | INTESTINE SPECIFIC HIF-1α OVEREXPRESSION AMELIORATES WESTERN DIET-INDUCED MASLD AND METABOLIC PHENOTYPES

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Background: Intestine epithelial HIF-1± plays a critical role in the maintaining of gut barrier function. Disrupted gut barrier function contributes to the development of metabolic syndrome. The aim of this study is to determine whether pharmacological or genetic activation of intestinal HIF-1± ameliorates western diet-induced MASLD and metabolic syndrome. **Methods:** $Hif1\alpha^{LSL/LSL;VilERcre}$ and $Hif1\alpha^{LSL/LSL}$ mice were generated by crossing LSL-HIF1 dPA mice with villin-cre-ERT2 mice. The intestine *Hif1α* activation was induced by tamoxifen administration. Male adult $Hif1\alpha^{LSL/LSL}$ and $Hif1\alpha^{LSL/LSL;VilERcre}$ mice were fed with regular chow diet, high fructose (HFr) or high-fat (60%

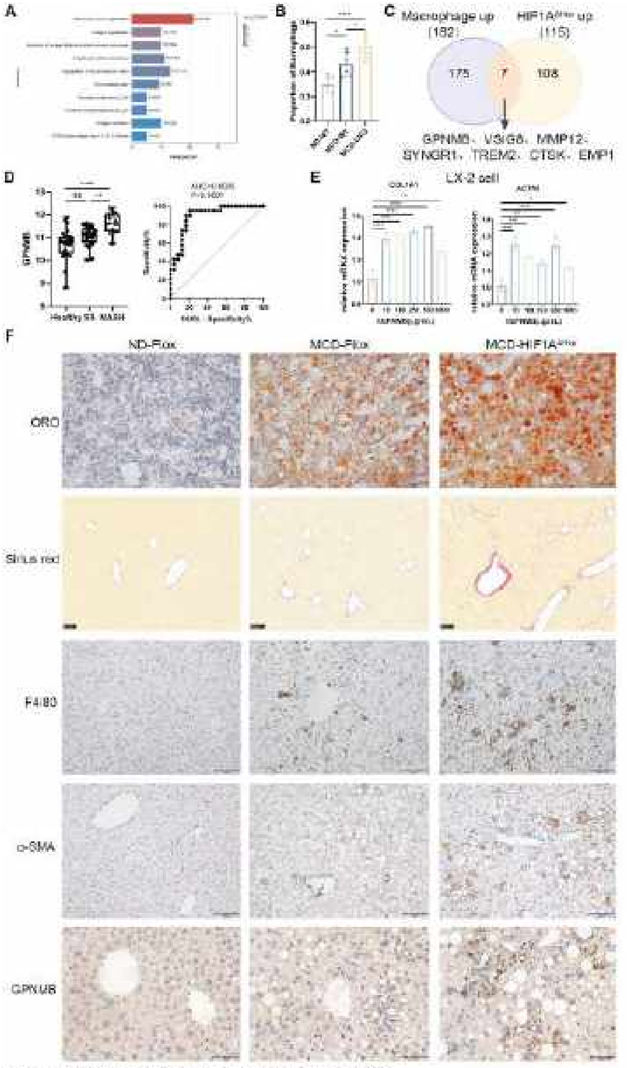
Kcal) high-fructose diet (HFHFr) for 8 weeks. High fructose diet was given via 30% fructose (w/v) in the drinking water *ad lib* for 8 weeks. Glucose and insulin tolerance test, and liver histology were evaluated. Ileum transcriptome was assessed by bulk RNA-seq. 8- to 10-week-old male HIF-1± luciferase reporter (ODD-luc) mice were fed with chow with or without 30% fructose (w/v) in the drinking water *ad lib* for 2 weeks and treated with dimethyloxalylglycine (DMOG), a pharmacological activator of HIF-1, at the dose of 8mg/mouse via IP injection every second day for 2 weeks. At the end of experiment, the luciferase activities of the entire GI tract were evaluated by bioluminescence imaging (BLI). Blood glucose level and cecal stool 16S rRNA sequencing were evaluated. **Results:** *Hif1α*$^{LSL/LSL;VilERcre}$ mice exhibited markedly improved glucose tolerance compared to *Hif1α*$^{LSL/LSL}$ mice in response to HFr diet. Intestine-specific *Hif1α*-overexpression led to markedly improved hepatic steatosis and a trend of decreased liver/body weight ratio without obvious alteration in the body weight when exposed to HFHFr diet. Of note, intestine-specific *Hif1α*-overexpression led to increased white adipose tissue (eWAT) weight and a trend of increased cecum/body weight ratio. DMOG treatment led to increased intestine HIF luciferase activity as shown by BLI and decreased blood glucose level associated with a remarkable alterations of gut microbiota composition in HFr diet fed ODD-luc mice. Ileum RNA-seq data analysis revealed that GO terms, including glycolytic process, pyruvate metabolic process, ATP generation from ADP were upregulated in *Hif1α*$^{LSL/LSL;VilERcre}$ mice. KEGG enrichment analysis further showed that glycolysis/gluconeogenesis was up in *Hif1α*$^{LSL/LSL;VilERcre}$ mice. **Conclusion:** Our data provide evidence that pharmacological or genetic activation of intestinal HIF-1± markedly ameliorate western diet-induced MASLD and metabolic phenotypes. RNA-seq data suggest that intestinal HIF-1± activation upregulates glycolysis, presumably leading to enhanced cell proliferation. Intestinal HIF-1± could be a promising therapeutic target for the treatment of MASLD and metabolic syndrome.

Disclosures: The following people have nothing to disclose: Ming Song, Manman Xu, Craig J. McClain

38 | HEPATOCYTE-SPECIFIC HIF-1α DELETION ACCELERATES NON-ALCOHOLIC STEATOHEPATITIS PROGRESSION TO LIVER FIBROSIS

Ziyong Zhang[1]*, Wenwen Li*[1]*, Jialin Liao*[2]*, Dongyan Zhang*[2]*, Yang Song*[2]*, Lushan Xiao*[1]*, Li Liu*[3] *and Xuejing Zou*[1]*, (1)Hepatology Unit and Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China, (2)Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China, (3)Big Data Center, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China;hepatology Unit and Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China*

Background: Non-alcoholic steatohepatitis (NASH) is prevalent, yet lacks for effective treatments to hinder rapid fibrosis progression, which is the main factor that limits patient prognosis. The role of Hypoxia-inducible factor 1± (HIF-1±) in NASH progression remains unclear. This study investigates the impact and mechanism of hepatocyte-specific HIF-1± deletion on NASH fibrosis, aiming to uncover a novel therapeutic target. **Methods:** Hepatocyte-specific HIF-1±-knockout mice were generated using the Cre-Lox system and non-alcoholic steatohepatitis (NASH) models were established via a methionine choline-deficient (MCD) diet or Gubra-Amylin NASH (GAN) diet. During the study, mouse food intake and weight changes were monitored, and biochemical indices were evaluated. Liver specimens were obtained for weighing, quantitative measurements of TC and TG, histopathological examination via H&E staining, Oil Red O staining, Sirius Red staining, and immunohistochemical staining. RNA-seq, histological techniques, flow cytometry, and co-culture experiments were employed to screen for and characterize the expression and functionality of GPMNB-positive macrophages. **Results:** Hepatocyte-specific HIF-1± knockout mice, compared with the Flox control group, demonstrated significantly exacerbated hepatic steatosis and increased formation of fatty granulomas when subjected to MCD and GAN diet-induced NASH models. However, knockout mice exhibited no significant difference in physiological parameters such as weight change and serum biochemistry under normal dietary conditions, compared to wild-type mice. HIF-1±-knockout mice characterized an earlier onset of hepatic fibrosis, accompanied by significantly upregulated mRNA expression of fibrosis-related genes. Recruitment of GPNMB$^+$ macrophages was observed in the HIF-1±-depleted liver. Single-cell sequencing data of the liver tissues indicated that GPNMB was predominantly expressed in macrophages. Furthermore, the GPNMB protein stimulated hepatic stellate cell activation, suggesting that GPNMB$^+$ macrophages might hasten the progression of NASH to liver fibrosis. **Conclusion:** Hepatocyte-specific HIF-1± deficiency accelerates NASH progression to liver fibrosis through the recruitment of GPNMB$^+$ macrophages. Targeting GPNMB might provide a promising strategy to curb fibrosis progression and benefit NASH prognosis.



HIF-1α Deletion in Hepatocytes Fast-Tracks NASH to Fibrosis.
A. Reactome enrichment of differential genes in Flox and HIF1A$^{\Delta Hep}$ mice liver under an MCD diet, highlighting fibrosis in HIF1A$^{\Delta Hep}$ NASH mice liver transcriptome.
B. Macrophage recruitment demonstrated by Cibersort analysis following hepatocyte-specific HIF-1α knockout.
C. Intersection of upregulated macrophage genes from the GSE199565 dataset and in HIF1A$^{\Delta Hep}$ mice represented in a Venn diagram.
D. GPNMB expression across health conditions in GSE89632 dataset with AUC demonstrating predictive power for distinguishing between healthy and NASH individuals.
E. PCR quantification of ACTA2 and COL1A1 mRNA levels in LX2 cells after 48 hours of recombinant human GPNMB protein stimulation.
F. Histological analyses of the liver in normal diet, MCD-fed Flox, and MCD-fed HIF1A$^{\Delta Hep}$ mice, including Oil Red O staining, Sirius red staining, and immunohistochemical staining of F4/80, α-SMA, and GPNMB.

Disclosures: The following people have nothing to disclose: Ziyong Zhang, Wenwen Li, Jialin Liao, Dongyan Zhang, Yang Song, Lushan Xiao, Li Liu, Xuejing Zou

39 | ROLE OF AUTOPHAGY IN HEPATIC ACETYLOME REGULATION

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Background: Liver acetylome is a set of protein acetylation's whose level reflects cellular metabolic health and is directly linked to intracellular pathways. However, to date, little is known about the cellular pathways that maintain the hepatic acetylome levels. Here, we show that macroautophagy hereafter referred to as autophagy, an intracellular lysosomal degradative pathway, regulates the hepatic acetylome. **Methods:** Various mouse models of autophagy deficient and autophagy activated conditions were used to dissect the role of autophagy in hepatic acetylome regulation. Wild type (WT) mice were injected with chloroquine (60mg/Kg, i.p) for 6 consecutive days to inhibit autophagy. Total liver lysate and subcellular fractions were analyzed by immunoblotting for acetylated lysine. Liver sections were immunostained for acetyl-Lysine. Hepatic level of acetyl-CoA, CoA and Histone H3 acetylation, and quantitative PCR of various enzymes involved in acetyl-CoA regulation were examined. For rescue experiments, acetyl-CoA was administered intraperitoneally (10mg/kg body weight) for eight consecutive days. Liver sections were subjected to H&E staining and serum ALT was examined as a measure of liver injury. **Results:** Examination of total acetylome (nuclear, cytosolic, mitochondrial, membrane) in autophagy-deficient or autophagy-defective liver exhibited remarkably lower levels compared to normal liver. The lower hepatic acetylome was independent of the cellular injury that is commonly seen in autophagy-deficient conditions. In contrast, autophagy activation by fasting or rapamycin treatment increased the level of hepatic acetylome. Moreover, mechanistic studies showed that hepatic autophagy function is essential to maintaining levels of acetyl-CoA, a central intermediate metabolite needed for acetylation of proteins. Autophagy impairment significantly reduced hepatic acetyl-CoA production through transcriptional downregulation of key enzymes involved in the acetyl-CoA synthesis, including *Acly, AceCS1, AceCS2, Mcd,* and *Pdha1*. Notably, replenishing hepatic acetyl-CoA rescued the lowered hepatic acetylome and, interestingly, protected against liver injury in the autophagy-deficient liver. **Conclusion:** In conclusion, autophagy regulates the hepatic acetylome as an important mechanism for protecting liver against injury and causing liver damage.

Disclosures: The following people have nothing to disclose: Kamal Baral, Arissa Mercer

Disclosure information not available at the time of publication: Adriana Lopez, Gang Liu, Xiao-Ming Yin, Bilon Khambu

40 | SINGLE-CELL ANALYSES IDENTIFY ENRICHMENT OF Th1 CELLS IN MURINE NONALCOHOLIC STEATOHEPATITIS★

Lucía Valenzuela-Pérez, Hyun Se Kim Lee, Rachel L. Bayer, Adebowale O. Bamidele and Petra Hirsova, Mayo Clinic

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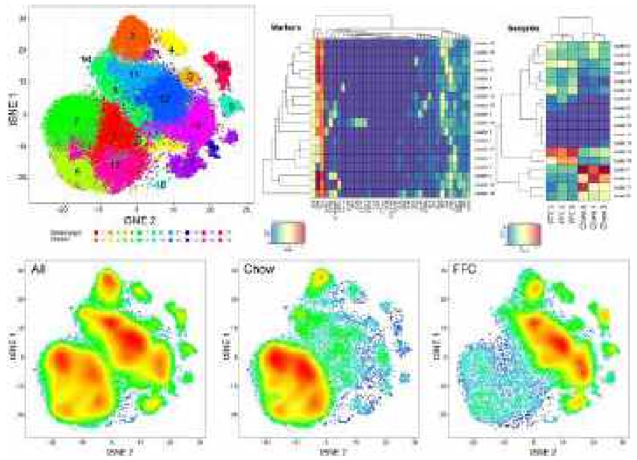
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Background: Nonalcoholic steatohepatitis (NASH) is a progressive disease characterized by liver inflammation. Emerging evidence implicates T cells in the disease pathogenesis. Our unpublished data show that CD4 T cells contribute to NASH development; however, hepatic CD4 T cell phenotypes and functions in NASH have not yet been systematically examined. **Methods:** C57BL/6J mice were fed with a chow or NASH-inducing diet high in fat, fructose, and cholesterol (FFC) for 24 weeks. Purified intrahepatic CD4 T cells were characterized by the cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq, which combines scRNA-seq with analysis of cell surface proteins), immunophenotyping by mass cytometry (CyTOF), NanoString targeted mRNA analysis (nCounter), and analyses of effector cytokines using flow cytometry following *ex vivo* stimulation (anti-CD3/CD28 with or without PMA/Ionomycin). **Results:** To better understand the role of CD4 T cell subsets in murine NASH, we leveraged two complementary approaches: an unbiased approach by CITE-seq and CyTOF with 44 well-established T cell markers. These two single-cell analyses revealed that hepatic CD4 T cells from chow and FFC diet-fed mice are highly heterogeneous as they separated into 15 and 18 unique clusters by CITE-seq and CyTOF, respectively. Livers from chow-fed mice had a distinct population of naïve T cells, while NASH livers were significantly enriched in T-bet$^+$ cells in various stages of activation, suggesting enrichment of Th1 cells. Interestingly, NASH livers were also enriched in Foxp3$^+$ cells as well as regulatory T cells (defined as Foxp3$^+$ CD25$^+$). To compensate for the depth of sequencing in CITE-seq, we profiled mRNA expression of select 750 immune-related genes in hepatic CD4 T using NanoString technology. A total of 207 genes were differentially expressed between chow liver and NASH-derived CD4 T cells. Top upregulated genes in NASH CD4 T cells included Ifng, Havcr2 (Tim3), and Pard3, confirming the enrichment of Th1 cells in NASH livers. To further validate the Th1 effector phenotype in NASH, hepatic CD4 T cells from chow and FFC-fed mice were re-stimulated *ex vivo*. Upon stimulation, NASH-derived CD4 T showed markedly increased expression of IFNγ, with minimal changes in IL17a, compared to chow liver CD4 T cells. Also, frequencies of TNF±$^+$ IFNγ$^+$ cells were significantly increased in NASH-derived CD4 T cells. **Conclusion:** These results indicate that IFNγ- and TNF±-producing Th1 cells are enriched in diet-induced murine NASH, likely promoting NASH pathogenesis.



Disclosures: The following people have nothing to disclose: Lucía Valenzuela-Pérez, Hyun Se Kim Lee, Rachel L. Bayer, Adebowale O. Bamidele, Petra Hirsova

41 | INTESTINAL ENDOGENOUS RETROVIRUSES PROMOTE ETHANOL-INDUCED LIVER DISEASE IN MICE★

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Background: Alcohol-associated liver disease (ALD) is a major public health problem worldwide, and gut microbial dysbiosis is an important contributor to ALD pathogenesis. Our previous study showed that patients with alcohol-associated hepatitis (AH) have increased proportions of mammalian viruses including retroviruses in the fecal virome. However, the role of the gut virome and in particular of endogenous retroviruses (ERVs) for ALD development is unknown. The aim of this study was to evaluate the contributions of ERVs to ALD onset and progression. **Methods:** We used transcriptomics for human duodenal biopsies. Gnotobiotic and genetically modified C57BL/6 mice were subjected to the chronic plus binge ethanol feeding model (NIAAA). **Results:** Three specific ERVs were upregulated in duodenal biopsies of patients with alcohol use disorder and ALD (n = 45) as compared with non-alcoholic controls (n = 15) as analyzed by RNAseq. Using the NIAAA model, we confirmed that chronic ethanol feeding of mice resulted in an increased abundance of ERVs in intestinal epithelial cells (IECs) of the small intestine and colon, but not in the liver. Ethanol treatment (50mM) induced the expression of ERVs in cultured small intestinal mouse organoids, which was blocked with the histone acetylation inhibitor A485, indicating that ethanol-mediated histone acetylation is involved in upregulation of ERVs. To further define the importance of ERVs in ethanol-induced liver disease, we colonized germ-free mice with stool from fecal retrovirus-positive and -negative AH patients. All patients were HIV negative. Germ-free mice transplanted with stool from fecal retrovirus-positive patients showed exacerbated ethanol-induced liver injury, steatosis, and inflammation. Oral treatment with antiretroviral medications (Emtricitabine, Tenofovir, Nevirapine) reduced ethanol-induced liver disease and intestinal ERV abundance in gnotobiotic mice colonized with stool from retrovirus-positive patients. Z- nucleic -binding protein 1 (*Zbp1*) is a sensor of ERVs and is known to trigger cell death in IECs and to induce gut barrier dysfunction. *Zbp1* was upregulated in the intestine of ethanol-fed mice and reduced following antiretroviral medications. To demonstrate that Zbp1 mediates the effect of ERVs in the intestine, we generated mice with an IEC specific deletion of Zbp1 ($Zbp1^{\Delta IEC}$). $Zbp1^{\Delta IEC}$ showed reduced ethanol-induced steatohepatitis as compared with floxed wildtype littermates. Deletion of *Zbp1* in hepatocytes or Kupffer cells did not affect ethanol-induced liver disease. **Conclusion:** Our results indicate that alcohol upregulates endogenous retroviral elements in the intestine of mice and humans. Reducing gut ERVs or deletion of intestinal *Zbp1* in mice protects against ethanol-induced liver disease, indicating that the ERV-Zbp1 axis could be a potential therapeutic strategy for ALD.

Disclosures: Bernd Schnabl – Nterica Bio: Executive role , No, No; Ferring Pharmaceuticals and Research Institute; Takeda; Gelesis: Consultant, No, Yes; Mabwell Therapeutics; Ambys Medicines; Surrozen: Consultant, No, No; Synlogic Operating Company; Axial Biotherapeutics; Prodigy Biotech: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; CymaBay Therapeutics; Intercept Pharmaceuticals; ChromoLogic: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Noemi Cabre, Marcos F. Fondevila, Xinlian Zhang, Yanhan Wang, Cristina Llorente

f 42 | EXPLORING THE ROLE OF X-BINDING PROTEIN-1 (XBP1) IN THE GUT- LIVER AXIS DURING ALCOHOL-RELATED LIVER DISEASE (ARLD)

Carlos Sanz-García[1,2], Raquel Benedé-Ubieto[3], Marina S Mazariegos[3], Kang Zheng[3], Alejandro H. Gutierrez[1], Javier Vaquero[4], Rafael Bañares[5], Eduardo Martinez-Naves[3], Rubén Francés[6], Esther Caparrós[6,7], Santiago Canals[6], Yulia Nevzorova[8] and Francisco Javier Cubero[8], (1)Complutense University School of Medicine, (2)Complutense School of Medicine, Madrid, Spain, (3)Ucm, (4)Centro De Investigación Biomédica En Red De Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain, (5)Centro De Investigación Biomédica En Red De Enfermedades Hepáticas y Digestivas (CIBEREHD), (6)Umh, (7) Miguel Hernández University, Spain, (8)Instituto De Investigación Sanitaria Gregorio Marañón (IiSGM)

Background: In the context of alcohol-related liver disease (ArLD), changes in the homeostasis of the gut-liver axis have become a focus of major attention in the past few years. The transcription factor X-Binding protein-1 (XBP1) is a major regulator of UPR, mediating adaptation to ER stress. In the present study, we aimed to analyze the function of XBP1 in the gut (intestinal epithelial cells, IECs), and in the liver (hepatocytes) in promoting ArLD. **Methods:** Eight- to 13-week-old female and male mice with specific deletion of XBP1 in IECs ($XBP1^{\Delta IEC}$), XBP1 in Hepatocytes ($XBP1^{\Delta HEPA}$), and XBP1-floxed wildtype ($XBP1^{f/f}$) mice were subjected different experimental models of ArLD: (i) Lieber-DeCarli control and ethanol diet for 8 weeks plus a multiple PBS or EtOH gavage, respectively, and (ii) DUAL diet, a preclinical model of non-alcoholic fatty fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH) characterized by the development of metabolic syndrome. Upon sacrifice, organs were extracted, and markers of liver damage, histopathological examination and techniques of Biochemistry and Molecular Biology were performed. Finally, antibiotic treatment (Abx) was performed as a therapeutic approach. **Results:** Serum markers of liver damage (e.g.: AST, ALT) were statistically increased in $XBP1^{\Delta IEC}$ compared with $XBP1^{f/f}$ after both preclinical models, and associated with significantly higher cell death. Concomitantly, H&E staining of $XBP1^{\Delta IEC}$ livers displayed macrovesicular ballooning accompanied by significantly elevated markers of inflammation including TNFa, IL-6, MCP-1, TLR2/4, liver fibrosis (Sirius red and collagen I deposition), and signs of bacterial translocation into the liver (LPS, LTA and bacterial DNA). Furthermore, the content of intrahepatic triglycerides revealed significantly increased lipid deposition in $XBP1^{\Delta IEC}$ compared with $XBP1^{f/f}$ after both types of preclinical models. Presence of autophagic vacuoles, decreased lysozyme granules and dilation of the Golgi cisterns associated with loss of Paneth cells and increased gut permeability (Mucin-2, ZO-1) was characteristic of $XBP1^{\Delta IEC}$ compared with $XBP1^{f/f}$ ilea, after both models of ArLD. Microbiota analysis revealed significantly increased abundance of *Lachnospiraceae*, *Muribaculaceae* and *Romboutsia* in in $XBP1^{\Delta IEC}$ mice. Abx therapeutics reversed the inflammatory phenotype of DUAL-ArLD with reduced liver injury, steatosis and fibrosis. **Conclusion:** Our results clearly suggest that loss of XBP1 in IECs trigger significant inflammation in the gut-liver axis, opening a novel therapeutic avenue for research in the context of ER stress and ArLD.

Disclosures: The following people have nothing to disclose: Carlos Sanz-García, Alejandro H. Gutierrez, Rubén Francés, Esther Caparrós

Disclosure information not available at the time of publication: Raquel Benedé-Ubieto, Marina S Mazariegos, Kang Zheng, Javier Vaquero, Rafael Bañares, Eduardo Martinez-Naves, Santiago Canals, Yulia Nevzorova, Francisco Javier Cubero

43 | TARGETING IL-17RA IN HEPATOCYTES AS A NOVEL THERAPEUTICAL APPROACH FOR AALD USING GALNAC DELIVERY SYSTEM

Raquel Weber[1], Vivian Zhang[1], Leon Lin[2], Alvaro Eguileor Gine[3], Sadatsugu Sakane[3,4], Souradipta Ganguly[3], Debanjan Dhar[3], Meghna Pulacode[1], Mira Sadek[2], David A. Brenner[3] and Tatiana Kisseleva[3], (1) University of California San Diego, (2)UCSD, (3) University of California, San Diego School of Medicine, (4)University of California, San Diego

Background: IL-17 signaling is implicated in the pathogenesis of alcohol-associated liver disease (AALD) leading to steatosis, fibrosis and hepatocellular carcinoma (HCC). We recently demonstrated that the specific deletion of IL-17RA in hepatocytes protects from steatosis, fibrosis and HCC in high fat diet plus ethanol (HFD+EtOH)-fed in MUP uPA mice (model that express urokinase-type plasminogen activator driven by a hepatocyte promoter for major urinary protein). As an alternative approach, the conjugation of antisense oligonucleotides to N-acetylgalactosamine (GalNAc) has been shown to efficiently target the liver via high-affinity binding to the asialoglycoprotein receptor expressed at the surface of hepatocytes. We hypothesize that the suppression of IL-17RA with GalNAc-IL-17RA siRNA therapeutical dosing in hepatocytes is sufficient to ameliorate AALD-induced steatosis, fibrosis, and HCC in mice. As a novel therapeutic approach, here we aim to treat AALD by selectively blocking IL-17RA in hepatocytes using GalNAc siRNA delivery system. **Methods:** MUP uPA mice were fed with HFD +EtOH or HFD only (Pair-fed) for 18 weeks. From week 9 to week 18, the mice were weekly treated, subcutaneously, with 10mg/kg of GalNAc siRNA IL17-RA or Control. The liver function, and the extent of steatosis, fibrosis and HCC were measured after 18 weeks. **Results:** The therapeutical dosing of GalNAc siRNA decreased the mRNA levels of IL-17RA by 60% in total liver, the downregulation of IL17-RA protein levels was also confirmed by western blot. Despite the number of tumors were not changed between groups, the tumors sizes were remarkably reduced (5x) in mice treated with GalNAc siIL-17RA. Interestingly, the therapeutically treatment in AALD mice also suppressed steatosis and fibrosis by 50%. In corroboration with our previous findings using an IL-17RA hepatocyte specific KO mice, we saw downregulation of target genes involved in ER stress-related and *de novo lipogenesis* (*Caspase 2, Srepb1, Srebp2, Dhcr7, Acca, Fasn*). In addition to these, the serum levels of ALT were decreased by 50% on GalNAc siIL-17RA treated mice in comparison to control, indicating an improvement of the liver function. **Conclusion:** Downregulation of IL-17RA in hepatocytes using GalNAc siRNA therapeutical approach, suppressed steatosis, fibrosis and remarkably reduced HCC growth in AALD mouse model. Targeting IL-17RA therapeutically using GalNAc, delivery system may become an efficient alternative to treat AALD.

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Disclosure information not available at the time of publication: Vivian Zhang, Leon Lin, Alvaro Eguileor Gine, Meghna Pulacode, Mira Sadek, David A. Brenner, Tatiana Kisseleva

44 | ALCOHOL CONSUMPTION ACCELERATES HEPATIC MICROPLASTIC ACCUMULATION VIA IMPAIRED INTESTINAL MUCOSAL BARRIER

Su-Min Baek, Tae-Un Kim, Jae-Hyuk Yim, Woo Jun Kim and Jin-Kyu Park, Kyungpook National University

Background: Microplastic (MP) is defined as the plastics size less than < 5mm. MP accumulates in humans via ingestion. Therefore, the gut-liver axis may be a important to prevent MP accumulation. However, many of the studies focus on the marine organisms and its biological effect and distribution pattern remain to be elucidated in mammals. Therefore,

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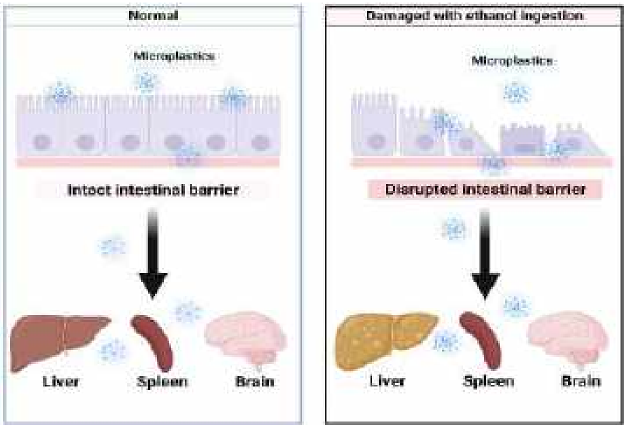
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

the present study investigates the role of gut-liver axis in protection of hepatic MP accumulation. **Methods:** During the experiment, mice were divided into control, control + MP, EtOH, and EtOH + MP groups. EtOH groups were ingested Lieber-deCarli ethanol diet for 5 weeks. Polystyrene (PS)-MP groups were orally administered at a dose of 0.1mg/kg 5 times a week. Since PS-MPs were tagged with immunofluorescent dye, the distribution pattern of MPs was analyzed with immunofluorescence assay. Liver injury was assessed with histopathology, serum ALT, AST, and TG assay, Oil-Red-O staining, and hepatic TG assay. Caco-2 was also used to analyze the MP distribution pattern under the similar condition as *in vivo*. **Results:** EtOH + MP group showed the higher hepatic steatosis and inflammatory lesions than other groups. Moreover, EtOH + MP group showed significant higher MP accumulation than control + MP group, indicating that MP accumulation was affected by hepatic damage. To explore the mechanism, MP accumulation pattern in the intestines was next investigated since gut-liver axis is one of the key mechanisms in alcoholic liver disease. EtOH + MP group exhibited significant intestinal damages such as epithelial necrosis, vacuolar degeneration, disintegration and detachment, and fusion of villi. However, control + MP group showed intact intestinal structure. Similar with the histopathological patterns, EtOH + MP group showed a remarkably higher MPs accumulation pattern in the intestines than in control + MP group. In confocal images, MPs penetrated into the lamina propria through the damaged intestinal epithelium in EtOH + MP group while only few MPs penetrated in control + MP group, which was characterized by intact intestinal epithelial structure. Ethanol ingestion disrupted the intestinal mucosal barrier, and the PS-MP accumulation was remarkably increased. **Conclusion:** The result suggests that ethanol aggravates PS-MPs accumulation in the liver via disrupted intestinal mucosal barrier, and the gut-liver axis could be a novel therapeutic target in prevention of PS-MPs accumulation in the body.


Normal
Microplastics
Intact intestinal barrier
Liver
Spleen
Brain
Damaged with ethanol ingestion
Microplastics
Disrupted intestinal barrier
Liver
Spleen
Brain

Disclosures: The following people have nothing to disclose: Su-Min Baek, Tae-Un Kim, Jae-Hyuk Yim, Woo Jun Kim, Jin-Kyu Park

f 45 I CHRONIC ETHANOL INSULT INCREASES HSD17beta13 ON HEPATOCELLULAR LIPID DROPLETS VIA A LOSS OF AN ASSOCIATED SEGREGASE p97/VCP TO PROMOTE HEPATIC STEATOSIS

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Background: Chronic EtOH insult is known to lead to an accumulation of lipid droplets (LDs) in hepatocytes resulting in hepatic steatosis. Our previous study reported that EtOH resulted in a 10-fold reduction of the LD-associated segregase VCP/p97, a protein implicated in LD protein clearance. Concomitant with this decrease was a 6-fold increase in the association of the hydroxysteroid enzyme HSD17β13 known to play an important role in hepatic steatosis. From these findings we predict that this alteration in the LD-proteome can lead to a disruption of LD catabolism and hepatocellular steatosis in vivo. The GOAL of this current study was to experimentally reduce hepatocellular VCP levels via a targeted knock out in mice to test the effects on LD-associated HSD17β13 levels and hepatic steatosis. **Methods:** A hepatocyte specific knockout of VCP was used along with histology, immunofluorescence microscopy, western blot analysis in combination with transient knockdown and manipulation of cultured hepatocytes. **Results:** The liver-specific knockout of VCP resulted in a dramatic > 10-fold increase in liver triglycerides and hepatic LDs in just 7days on a normal chow diet. Importantly, 13-day KO mice displayed livers with a 5-fold increase in HSD17β13. Parallel studies using primary isolated mouse hepatocytes showed that acute inhibition of VCP activity with either the drug DBeQ, or siRNA mediated knockdown, resulted in an elevation of HSD17β13 levels and a 5-fold increase in LD content. We have found that HSD17β13 is a mono-ubiquitinated protein predicted to be removed from the LD surface to the proteosome by VCP. Surprisingly, treatment of hepatoctyes with the proteasome inhibitor MG132 had no effect on HSD17β13 levels while inhibition of lysosome function with chloroquine resulted in a 6-fold increase of HSD17β13. In support of this finding IF staining of these hepatocytes shows a marked colocalization of lysosomes with HSD17β13-associated LDs. **Conclusion:** This study suggests that a reduction in the levels of the VCP segregase by EtOH insult, or targeted KO, results in a substantial increase in the hepatocellular levels, and LD association of HSD17β13. Hepatocytes without VCP are unable to target ubiquitylated HSD17β13 to the lysosome for degradation leading to hepatic steatosis. These findings provide new insights into the cellular mechanisms by which EtOH exposure disrupts normal hepatic lipid catabolism. Supported by R01AA020735 (to M.A.M. and C.A.C.).

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46 | GENERATION AND CHARACTERIZATION OF A HUMANIZED MOUSE MODEL OF ALCOHOL INDUCED STEATOSIS, INFLAMMATION AND FIBROSIS

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Background: Alcoholic associated liver disease (AALD) is a poorly characterized pathology characterized by steatosis, inflammation and fibrosis. The lack of an animal model which recapitulates key features of AALD has been a major limitation in understanding its etiology and in the development of effective therapies. To identify the cellular differences between the mouse and human liver responsible for the different injury response to alcohol we have generated humanized mice that can support human liver cells (parenchymal and non-parenchymal cells) along with human hematopoiesis [1]. **Methods:** In humanized and non-humanized mice (control mice having mouse liver and mouse hematopoiesis), we applied the NIAAA model of chronic and binge ethanol feeding (10-days ad libitum oral feeding with the Lieber-DeCarli ethanol liquid diet plus a single binge ethanol feeding 9 hours before the end of the experiment). This model was evaluated by: i) Serum ALT and bilirubin, ii) flow cytometry to define the immune cell composition in the liver and blood iii) H&E staining to assess steatosis, inflammation and ballooning iv) human/mouse aSMA and human Collagen-3 to asses mouse and human hepatic stellate cells activation and v) human CK8/18 to asses Mallory bodies formation. **Results:** We have seen that humanized mice had higher degree of steatosis, inflammation and ALT levels than non-humanized. In particular, the humanized mice had severe macrovesicular steatosis with Mallory bodies and ballooning whereas non humanized mice have minimal microvesicular steatosis. Also, humanized mice only have abnormal levels of bilirubin, mild to moderate fibrosis, severe peripheral lymphopenia. Of note, in the high degree steatotic areas of humanized mice, we observed human hepatic stellate cell activation between steatotic human hepatocytes, and human collagen. **Conclusion:** We have demonstrated that by fully humanizing mouse livers key features of AALD can be reproduced to a greater degree than they can in mouse only livers. This will be the first mouse alcohol model having high degree of macrovesicular steatosis in human hepatocytes, alcohol-driven fibrosis mediated by human hepatic stellate cells, and pathological immune responses driven by human Immune cells. This model will be a unique tool to study pathways leading to severe steatotic, fibrotic and inflammatory responses of ALD.

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47 | PRELIMINARY OFF-TREATMENT RESPONSES FOLLOWING 48 WEEKS OF VEBICORVIR, NUCLEOS(T)IDE REVERSE TRANSCRIPTASE INHIBITOR, AND AB-729 COMBINATION IN VIROLOGICALLY SUPPRESSED PATIENTS WITH HEPATITIS B E ANTIGEN NEGATIVE CHRONIC HEPATITIS B: ANALYSIS FROM AN OPEN-LABEL PHASE 2 STUDY

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Background: This open-label study assessed the safety and efficacy of vebicorvir (VBR)+AB-729+nucleos(t)ide reverse transcriptase inhibitor (NrtI) in virologically suppressed (VS) patients (pts) with hepatitis B e antigen (eAg) negative chronic hepatitis B infection (NCT04820686). VBR is a 1st-generation core inhibitor and AB-729 is a single trigger GalNAc-siRNA targeting all HBV RNA transcripts. Initial end of treatment (EOT) responses were previously described. Here, we report additional EOT data and preliminary off-treatment responses. **Methods:** Sixty-five VS eAg negative pts were randomized to receive VBR+AB-729+NrtI ($n = 32$), VBR+NrtI ($n = 16$), or AB-729+NrtI ($n = 17$) for 48 weeks (wks). VBR 300 mg was given orally once daily and AB-729 as a 60 mg subcutaneous injection every 8 wks. Based on Wk 48 lab results, pts with ALT < 2x upper limit of normal + HBV DNA < lower limit of quantification (LLOQ) + hepatitis B surface antigen (sAg) < 100 IU/mL could discontinue all treatment and enter follow-up. Patients not meeting this criterion continued NrtI alone during follow-up. Virologic markers included sAg (Abbott Architect; LLOQ = 0.05 IU/mL) and HBV DNA (Cobas TaqMan; LLOQ = 20 IU/mL). Safety was assessed by adverse events (AEs) and lab parameters. **Results:** Baseline characteristics were similar across treatments. Treatments were well tolerated with 9% (3/32), 6% (1/16), and 6% (1/17) of pts discontinuing treatment due to an AE in the VBR+AB-729+NrtI, VBR+NrtI, and AB-729+NrtI arms, respectively. AEs on treatment were generally Grade 1/2 and reported in 81% (26/32), 75% (12/16), and 71% (12/17) of pts in the VBR+AB-729+NrtI, VBR+NrtI, and AB-729+NrtI arms, respectively. There was a single serious AE (COVID-19 pneumonia in a VBR+AB-729+NrtI recipient). At time of analysis, while no pts had HBsAg seroconversion, 16/26, 0/15, and 8/10 pts with available Wk 48 data met criteria to stop all treatment in the VBR+AB-729+NrtI, VBR+NrtI, and AB-729+NrtI arms, respectively. Of these, 12 pts who received VBR+AB-729+NrtI and 7 who received AB-729+NrtI discontinued all treatment. 8 wks after discontinuing all treatment, continued suppression of sAg < 100 IU/mL was observed in 89% (8/9) and 83% (5/6) of pts with available data receiving VBR+AB-729+NrtI and AB-729+NrtI, respectively (Table). **Conclusion:** Treatments were well tolerated. Available data indicate that adding VBR to AB-729+NrtI does not result in significantly greater on- or post-treatment improvements in markers of active HBV infection vs AB-729+NrtI.

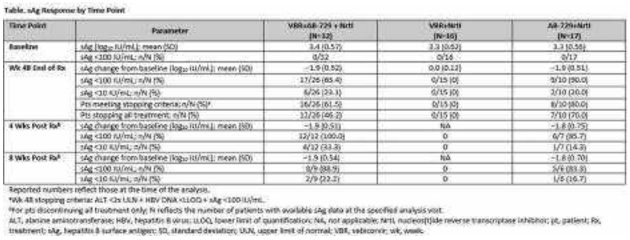

Table. sAg Response by Time Point

Time Point	Parameter	VBR+AB-729 + NrtI (N=32)	VBR+NrtI (N=16)	AB-729+NrtI (N=17)
Baseline	sAg (log$_{10}$ IU/mL); mean (SD)	3.4 (0.57)	3.3 (0.52)	3.3 (0.58)
	sAg <100 IU/mL; n/N (%)	0/32	0/16	0/17
Wk 48 End of Rx	sAg change from baseline (log$_{10}$ IU/mL); mean (SD)	−1.9 (0.52)	0.0 (0.12)	−1.9 (0.51)
	sAg <100 IU/mL; n/N (%)	17/26 (65.4)	0/15 (0)	9/10 (90.0)
	sAg <10 IU/mL; n/N (%)	6/26 (23.1)	0/15 (0)	2/10 (20.0)
	Pts meeting stopping criteria; n/N (%)[a]	16/26 (61.5)	0/15 (0)	8/10 (80.0)
	Pts stopping all treatment; n/N (%)	12/26 (46.2)	0/15 (0)	7/10 (70.0)
4 Wks Post Rx[b]	sAg change from baseline (log$_{10}$ IU/mL); mean (SD)	−1.9 (0.51)	NA	−1.8 (0.75)
	sAg <100 IU/mL; n/N (%)	12/12 (100.0)	0	6/7 (85.7)
	sAg <10 IU/mL; n/N (%)	4/12 (33.3)	0	1/7 (14.3)
8 Wks Post Rx[b]	sAg change from baseline (log$_{10}$ IU/mL); mean (SD)	−1.9 (0.54)	NA	−1.8 (0.70)
	sAg <100 IU/mL; n/N (%)	8/9 (88.9)	0	5/6 (83.3)
	sAg <10 IU/mL; n/N (%)	2/9 (22.2)	0	1/6 (16.7)

Reported numbers reflect those at the time of the analysis.

[a] Wk 48 stopping criteria: ALT <2x ULN + HBV DNA <LLOQ + sAg <100 IU/mL.

[b] For pts discontinuing all treatment only; N reflects the number of patients with available sAg data at the specified analysis visit.

ALT, alanine aminotransferase; HBV, hepatitis B virus; LLOQ, lower limit of quantification; NA, not applicable; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pt, patient; Rx, treatment; sAg, hepatitis B surface antigen; SD, standard deviation; ULN, upper limit of normal; VBR, vebicorvir; wk, week.

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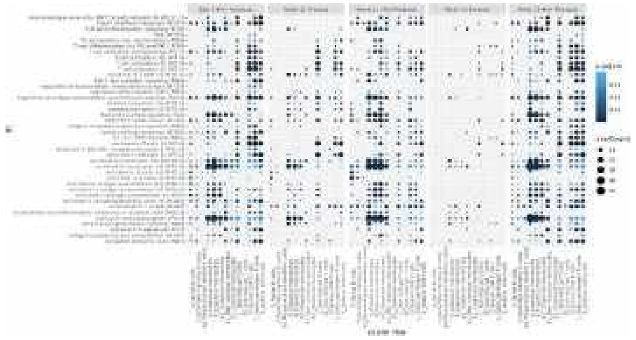
48 | PERIPHERAL SINGLE CELL GENE EXPRESSION CHANGES IN RESPONSE TO TOLL-LIKE RECEPTOR 8 AGONIST TREATMENT IN CHRONIC HEPATITIS B PATIENTS

Jeffrey Wallin[1], Circe McDonald[1], Bryan Downie[1], Leonard Anang Sowah[1], Mario Cortese[1] and Florian Wimmers[2], (1)Gilead Sciences, Inc., (2)University of Tuebingen

Background: Selgantolimod (SLGN) is an oral selective small molecule TLR8 agonist with antiviral potential that has been shown to be safe and well-tolerated in individual's with chronic hepatitis B (CHB). SLGN stimulates a robust pharmacodynamic response as measured by the detection of TLR8 pathway cytokines such as interleukin (IL)-12p40 and IL-1RA. We further characterized the molecular impact of SLGN treatment in peripheral blood mononuclear cells (PBMCs) using single cell profiling technologies. **Methods**: Viremic chronic hepatitis B (CHB) patients received once weekly 3 mg SLGN for 24 weeks. Blood samples were collected before and 4 hours post dosing at baseline, week 11 and week 23 for four participants. PBMCs were isolated and gene expression was evaluated using the 10X single cell RNA-seq protocol. Analysis was performed using the Seurat R package with cell type identification performed with SingleR. Differences in gene expression between baseline and on- treatment timepoints were determined by a non-parametric Wilcoxon rank sum text. **Results**: Seventeen cell clusters were identified by single cell gene expression analysis. Pathway-level analysis using blood transcriptional modules (BTM) indicated type I interferon modulation at on treatment time-points across multiple cell types ($FDR < 0.01$). Particularly, interferon stimulated genes, such as *IFI144L, STAT1, and MX1* were upregulated after SLGN treatment in several clusters, including those annotated as B, T, and NK cells. Furthermore, we observed modulation of TLR and inflammatory signaling associated with classical and non-classical monocytes. Of the many differentially expressed genes (DEGs) identified in the classical monocyte cluster ($FDR < 0.05$), *MECP2* and *FKBP5*, among others, were upregulated at all 4 hr postdose timepoints. Their gene products have been reported to act as regulator of chromatin structure and gene expression in immune cells (MECP2), and to be involved in the downregulation of excess interferon responses (FKBP5). Further, in the non-classical monocyte cluster, we observed DEGs at the same on-treatment timepoints, with overall lower fold change differences as compared to classical monocytes (mean log2 fold change 0.66 compared to 0.49). Of interest, different kinetics for DEGs were observed for naïve T cells in comparison to baseline. While several hundred DEGs were observed at 4hr post first administration of SLGN in the naïve T-cell cluster, including *STAT3* and NFkB pathway-related genes, subsequent on-treatment timepoints demonstrated overall fewer DEGs. **Conclusion**: Single cell PBMC analysis from SLGN-treated CHB viremic patients identified substantive changes in gene expression in multiple cell types. These findings provide greater insight into the cellular changes following SLGN treatment, and may inform complementary mechanisms for a HBV cure combination strategy.



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49 | PEGYLATED INTERFERON REDUCES RELAPSES FOLLOWING BEPIROVIRSEN TREATMENT IN PARTICIPANTS WITH CHRONIC HEPATITIS B VIRUS INFECTION ON NUCLEOS(T)IDE ANALOGUES: END OF STUDY RESULTS FROM THE PHASE 2b B-TOGETHER STUDY

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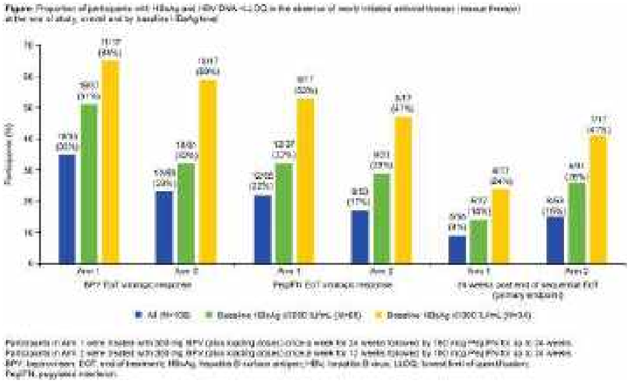
Background: In the Phase 2b B-Clear study (209668), bepirovirsen (BPV; an antisense oligonucleotide) 300 mg for 24 weeks (wks) achieved sustained HBsAg and HBV DNA loss (< lower limit of quantification [LLOQ] for 24 wks off BPV therapy) in 9% of participants (pts) who remained on nucleos[t]ide analogs (NA); end of BPV response rates were higher (26%), but some pts relapsed during follow-up. Response was higher in pts with lower baseline HBsAg (d 3000 vs d 1000 IU/mL: 12% vs 16%). The B-Together study assessed if sequential therapy with BPV and pegylated interferon (PegIFN) can improve on the BPV efficacy rates observed in B-Clear. **Methods:** B-Together was a Phase 2b, multicenter, randomized, open-label study. Patients on stable NA therapy were eligible if they had HBsAg > 100 IU/mL, HBV DNA < 90 IU/mL, ALT d 2x upper limit of normal and no contraindication to receive PegIFN. Pts were randomized 1:1 to receive BPV 300 mg once weekly (QW; plus loading dose on Days 4 and 11) for 24 (Arm 1) or 12 (Arm 2) wks. Post BPV end, eligibility was assessed to receive up to 24 wks of PegIFN 180 mcg QW, with 24 (Arm 1) or 36 (Arm 2) wks follow-up post PegIFN end. Pts continued NA therapy throughout the study. Primary endpoint: proportion of pts with HBsAg and HBV DNA < LLOQ for 24 wks after planned end of sequential treatment, in the absence of newly initiated antiviral therapy (rescue therapy). Safety was assessed by adverse event (AE) monitoring. **Results:** The study enrolled 108 pts (n: Arm 1 = 55; Arm 2 = 53). Baseline characteristics were similar between arms and to those in B-Clear. The primary endpoint was achieved by 5 (9%) pts in Arm 1 and 8 (15%) pts in Arm 2 (Figure); all responders had baseline HBsAg d 3000 IU/mL. Only BPV responders benefited from Peg-IFN treatment, through prevention of relapse off-treatment (relapse rate B-Together vs B-Clear: Arm 1: 58% vs 63%; Arm 2: 0% vs 75%). The proportion of pts experiencing AEs was similar in both arms (Arm 1: 52 [95%]; Arm 2: 52 [98%]). Serious AEs were reported in 8 (7%) of pts (during BPV: 5 [5%]; during PegIFN: 0; follow-up period: 3 [3%]). BPV did not appear to adversely influence the safety profile of subsequent PegIFN. **Conclusion:** Sequential therapy with BPV and PegIFN results in an improved off-treatment response vs BPV alone (B-Clear), which appears to be driven by prevention of relapse in BPV responders. There were no new safety signals of concern. Funding: GSK (study 209348).



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50 | A PHASE 2b, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, IMMUNOGENICITY AND TREATMENT REGIMENS OF VTP-300 COMBINED WITH LOW-DOSE NIVOLUMAB IN CHRONIC HEPATITIS B INFECTION

Henrik Sorensen[1], Tom Evans[1], Dereck Tait[1], Louise Bussey[1], Radka Kolenovska[1], Debalina Mukherjee[2], Sazlyna Lim[2], Wan Long Chuang[3], Man-Fung Yuen[4] and Anchalee Avihingsanon[5], (1)Vaccitech Plc, (2) Novotech, (3)Kaohsiung Medical University Hospital, Kaohsiung Medical University, (4)State Key Laboratory of Liver Research, the University of Hong Kong, Hong Kong, Hong Kong, China, (5)Chulalongkorn University

Background: New treatment concepts focus on enhancing rates of functional cure of chronic hepatitis B (HBV) with the aims of stopping nucleos(t)ide treatment (NA) with no risk of virological relapse or liver disease progression and further decreasing the risk of hepatocellular carcinoma (HCC). Induction of a CD8+ T cell response to HBV is likely a required mechanism to achieve a functional cure. VTP-300 is an antigen-specific investigational immunotherapy consisting of a Chimpanzee Adenovirus (ChAdOx1) prime and Modified Vaccinia Ankara virus (MVA) boost delivering antigens associated with hepatitis B infection. A Phase 1b/2a study in 54 patients previously showed VTP-300 had meaningful and durable hepatitis B surface antigen (HBsAg) responses as a monotherapy and in combination with low dose nivolumab (LDN). This study will examine different dose timing and boosting regimens to further optimize HBsAg level reductions. **Methods:** A Phase 2b trial is enrolling up to 120 patients (40 patients in each of 3 groups) with CHB, on antivirals for at least six months before screening with a HBV-DNA viral load of d 1000 IU/mL and HBsAg e 10 IU/mL and d 4,000 IU/mL). Group 1, ChAdOx1-HBV (2 x 10*10 viral particles) followed by MVA-HBV (1 x 10*8 pfu) and LDN (0.3 mg/kg IV) at D29; Group 2, ChAdOx1-HBV (2 x 10*10 viral particles) followed by MVA-HBV (1 x 10*8 pfu) and LDN (0.3 mg/kg IV) at D29 followed by MVA-HBV (1 x 10*8 pfu) and LDN at D85; Group 3, ChAdOx1-HBV (2 x 10*10 viral particles) followed by MVA-HBV (1 x 10*8 pfu) at D29 followed by LDN at D36 followed by MVA-HBV (1 x 10*8 pfu) at D85 (only if HBsAg is e 10IU/mL. The primary endpoint is the percentage of participants with a greater than 1 log HBsAg reduction at 6 months after initiation of therapy. HBV specific T cell responses are assessed using genotype C and D HBV peptides spanning the HBV immunogen in an IFNg ELISpot assay during the one-year follow-up period. **Results:** As of 22 May 2023, 51 participants have been enrolled in HBV003 and efficacy and safety data continue to accrue. At the 2023 AASLD meeting, we expect to report on at least 50 participants who will have reached D113, showing the effects of a second MVA-HBV booster on HBsAg levels and the impact of a LDN administration at D36 rather than at the time of MVA-HBV administration. In addition, at least 40 participants are expected to have reached the D169 timepoint when they will be evaluated for NA discontinuation. We expect recruitment to be complete by December 2023 with final results available early 2025. **Conclusion:** VTP-300 is a novel antigen-specific investigational immunotherapy which has shown (in a Phase 1b/2a study) meaningful and durable HBsAg reductions in patients with HBV as a monotherapy and in combination with LDN. Evaluating the addition and

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

timing of PD-1 inhibitor administration and a second boost of MVA-HBV is critical to optimizing the regimen of VTP-300 which may be a critical component of a functional cure regimen.

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51 | INTRAHEPATIC CHANGES IN VIRAL AND IMMUNE MARKERS FOLLOWING TREATMENT WITH JNJ-73763989 (JNJ-3989) AND NUCLEOS(T)IDE ANALOGS (NAS), IN PATIENTS WITH CHRONIC HEPATITIS B (CHB): INSIGHT WEEK 40 (W40) INTERIM RESULTS

Pietro Lampertico[1,2], Tarik Asselah[3], Edward J. Gane[4], Scott K. Fung[5], Patrick T. Kennedy[6], Thomas Vanwolleghem[7], Ewa Janczewska[8], Julian Schulze Zur Wiesch[9], Mark S Sulkowski[10], Hans Wils[11], Daniele Filippo Colombo[11], Koen Van Den Berge[11], Hinrich W.H. Gohlmann[11], Jeroen Aerssens[11], John Jezorwski[12], Zacharias Anastasiou[13], Thierry Verbinnen[11], Thomas N. Kakuda[14], Marianne Tuefferd[11], Carine Guinard-Azadian[11], Oliver Lenz[11], Kim Thys[11] and Michal Biermer[11], (1)Division of Gastroenterology and Hepatology, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, (2) CRC "a. M. and a. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, (3)Université De Paris-Cité, Inserm UMR1149, Department of Hepatology, AP-HP Hôpital Beaujon, Clichy, France, (4) Auckland Clinical Studies, (5)Toronto Liver Centre, *Toronto, on, Canada, (6)Blizard Institute, Barts and the London SMD, Qmul, (7)Erasmus University Medical Center, (8)ID Clinic, Myslowice, Poland, (9)University Medical Center Hamburg – Eppendorf, (10)Johns Hopkins University School of Medicine, Division of Infectious Diseases, (11)Janssen Pharmaceutica NV, Beerse, Belgium, (12)Janssen Research & Development, LLC, Titusville, NJ, USA, (13)Janssen-Cilag Pharmaceutical, Pefki, Greece, (14)Janssen Research & Development, LLC, Brisbane, CA, USA*

Background: Treatment of CHB with JNJ-3989 and NA ± JNJ-6379 has shown profound reductions in serum hepatitis B viral (HBV) markers. The INSIGHT study aims to assess intrahepatic changes in virological and immunological markers with JNJ-3989 based treatment in CHB patients. **Methods:** INSIGHT is a phase 2 multicenter study in CHB patients who are hepatitis B e-antigen positive (HBeAg+) and not currently treated (NCT; Group 1) or HBeAg-negative (HBeAg-) and virologically suppressed (VS) by NA (Group 2). Patients received 48 weeks of JNJ-3989 + NA (± JNJ-6379 withdrawn from study). Paired percutaneous core liver biopsies and fine needle aspiration biopsies (FNABs) were collected using standardized procedures at baseline and week 40 to investigate changes in intrahepatic viral and immune markers. **Results:** Levels of viral serum markers were higher for participants in Group 1 versus Group 2 at BL. JNJ-3989 treatment resulted in a mean (SE) hepatitis B surface antigen (HBsAg) change from BL of -3.78 (0.481) $\log_{10}$ IU/mL for Group 1 and -2.40 (0.160) for Group 2 at Week 40. One out of nine (11.1%) patients in Group 1 reached HBsAg seroclearance at W40. The estimated mean percentage of HBsAg positive hepatocytes decreased by W40 in both groups while the mean percentage of HBcAg+ cells decreased only in Group 1 (Table). In Group 1, the percentage of HBV RNA+ hepatocytes declined from min 90.2 to max 100% at BL to 4.4-28.4% at W40 (n = 4 patients in each group with samples profiled at BL and W40) and in Group 2 from 8.6-31.6% at BL to 5.6-15% at W40 (n = 4 pairs). The percentage of cccDNA–/HBV RNA– cells increased during JNJ-3989 treatment in both groups, from 0-1.2% at BL in Group 1 and 31.3-64.8% in Group 2; to 48.1-68.9% in Group 1 (n = 4 pairs) and 51.1-66.7% in Group 2 (n = 4 pairs) at W40. Profiling of FNABs identified enrichment in early activated CD8+ T cells by W40 in Group 1 and depletion of CD8+ exhausted T cells, CD8 + effector memory T cells, and CD8+ memory stem cells in Group 2. **Conclusion:** Treatment of CHB patients with JNJ-3989 resulted in reduction of HBsAg + hepatocytes at week 40 with an increased fraction of non- infected hepatocytes. Changes during treatment were seen in intrahepatic CD8+ T cells (increase of early activated CD8+ T cells in Group1 and depletion of exhausted T cells in Group 2), suggesting that JNJ-3989 + NA treatment combination leads to activation of intrahepatic adaptive immunity.

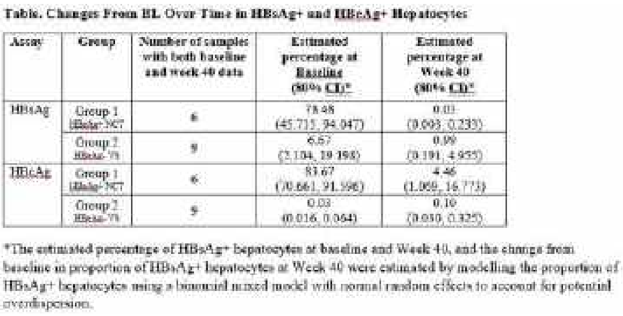

Table. Changes From BL Over Time in HBsAg+ and HBcAg+ Hepatocytes

Assay	Group	Number of samples with both baseline and week 40 data	Estimated percentage at Baseline (80% CI)*	Estimated percentage at Week 40 (80% CI)*
HBsAg	Group 1 HBeAg+ NCT	6	78.48 (45.715, 94.047)	0.03 (0.003, 0.233)
	Group 2 HBeAg- VS	9	6.67 (2.104, 19.198)	0.99 (0.191, 4.955)
HBcAg	Group 1 HBeAg+ NCT	6	83.67 (70.661, 91.598)	4.46 (1.069, 16.773)
	Group 2 HBeAg- VS	9	0.03 (0.016, 0.064)	0.10 (0.030, 0.325)

*The estimated percentage of HBsAg+ hepatocytes at baseline and Week 40, and the change from baseline in proportion of HBsAg+ hepatocytes at Week 40 were estimated by modelling the proportion of HBsAg+ hepatocytes using a binomial mixed model with normal random effects to account for potential overdispersion.

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52 | LONG TERM HBsAg REDUCTION BY A NASAL ADMINISTRATIVE THERAPEUTIC VACCINE CONTAINING HBsAg AND HBCAG MIXED WITH MUCOADHESIVE CVP IN PATIENTS WITH CHRONIC HBV INFECTION: THE RESULTS OF 48 MONTHS FOLLOW UP

Osamu Yoshida[1], Kana Shiraishi[1], Yusuke Imai[1], Takahiro Sanada[2], Kyoko Tsukiyama-Kohara[3], Takashi Miyazaki[4], Taizo Kamishita[4], Teruki Miyake[1], Yoshio Tokumoto[1], Julio Cesar Aguilar[5], Gerardo Enrique Guillen[5], Michinori Kohara[2] and Yoichi Hiasa[1], (1)Ehime University, (2)Tokyo Metropolitan Institute of Medical Science, (3)Kagoshima University, (4)Toko Yakuhin Kogyo CO., Ltd., (5)Cigb

Background: We reported the HBsAg reduction by a nasal administrative therapeutic vaccine containing HBsAg/HBcAg mixed with mucoadhesive excipient carboxy-vinyl polymer (CVP-NASVAC) in chronically HBV infected patients. This study was aimed to assess the long-term efficacy of CVP-NASVAC at 48 months after the first 10 doses. **Methods:** CHB patients were enrolled in an open-label clinical trial at Ehime University Hospital, Japan, after receiving written consent, and permission from institutional review board (CRB#18EC003), and registration to the clinical trial authority of Japan jRCT (#jRCTs061180100). CVP-NASVAC was administrated for 10 times, once in every 2 weeks, some patients received additional 10 doses at least 12 months interval. We analyzed the data at 48 months after the first 10 doses of CVP-NASVAC. **Results:** Seventy-two patients enrolled in this study, and sixty-one participants completed 48 months follow-up and analyzed data. Twenty-five participants continued NAs during the study. Forty participants received additional 10 doses of CVP-NASVAC. At 48 months after the first 10 doses, 85.2% (n = 52/61) patients showed HBsAg reduction from the baseline, and the mean HBsAg reduction was -40.3% (-0.4352 Log IU/mL). Notably, eight participants lost HBsAg. CVP-NASVAC induced anti-HBs in 70.5% (43/61) patients. HBcAg specific CTL were increased after the CVP-NASVAC treatment. Three out of nine patients lost HBeAg during 48 months follow-up. HBcrAg reduction was observed all the twenty-four participants who were detected HBcrAg at the baseline. **Conclusion:** CVP-NASVAC displayed a long term HBsAg reduction and loss. CVP-NASVAC could be a novel immune therapy for HBsAg reduction and elimination in HBV infected patients.

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53 | HEALTHCARE ACCESS THROUGH FACILITATED TELEMEDICINE FOR UNDERSERVED POPULATIONS: A STEPPED WEDGE CLUSTER RANDOMIZED CONTROLLED TRIAL OF HEPATITIS C VIRUS TREATMENT AMONG PERSONS WITH OPIOID USE DISORDER

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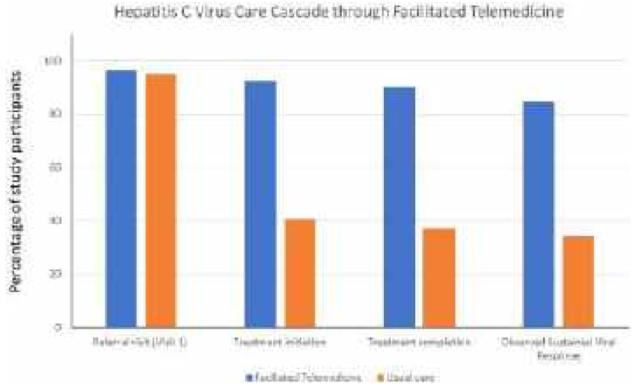
Background: Telemedicine removes geographic and temporal obstacles to healthcare access. Few randomized trials have evaluated telemedicine effectiveness for underserved populations. We compared sustained virological response (SVR12) rates for hepatitis C virus (HCV) infection among persons with opioid use disorder through facilitated telemedicine (FTM) versus offsite liver specialist referral (usual care or UC). **Methods:** We conducted a prospective, cluster randomized trial utilizing the stepped wedge design to compare SVR12 rates between FTM onsite in opioid treatment programs (OTPs) to UC. Between 3/1/17 and 2/29/20, we enrolled 602 participants at 12 OTPs throughout New York State. All OTPs began with UC and every 9 months, 4 sites, randomly selected, transited from UC to FTM during 3 steps. We followed participants for two years to assess for reinfection. Participant inclusion criteria required six months enrollment in the OTP and active insurance. Multiple imputation was used to handle missing data (5.8% missingness). To estimate the intervention effect, we used a robust, non-parametric, within-period, cluster-level method. To assess for heterogeneity of treatment effects, we utilized generalized linear mixed effects models. **Results:** A total of 602 participants (FTM [n = 290] and UC [n = 312]) with mean age of 48.1 ± 13.0 years, 61.3% male, 30.7% Hispanic, 49.2% African American or other races, 28.1% with anxiety/depression, and 23% with cirrhosis. In FTM, 268/290 (92.4%) participants initiated treatment while 126/312 (40.4%) UC participants initiated treatment. The overall SVR12 was 90.7% in FTM compared to 35.2% in referral. The period specific intervention effect, computed as the difference between the SVR12 rate cluster-period summaries for FTM and UC is 0.596 ($p < 0.0001$, 95% CI: (.237, .955)). We did not identify heterogeneity of treatment for fibrosis, urban/rural, or mental health (anxiety/depression) conditions. We found that drug use decreased significantly ($p = < 0.0001$) among cured participants, regardless of intervention arm between the first and SVR12 visits. Minimal (n = 13) reinfections occurred, resulting in an HCV reinfection incidence of 2.42 per 100 person-years of observation. Participants reported very high healthcare delivery satisfaction, equivalent between arms. **Conclusion:** HCV treatment through FTM integrated into OTPs results in significantly higher SVR12 compared with offsite referral. Drug use also declined significantly, and the response was durable with minimal HCV reinfections over two years. FTM integrates HCV management into OTPs, increasing access of underserved populations to high-quality HCV care with high patient satisfaction. FTM should be considered an approach to expand healthcare access as part of HCV elimination approaches.



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54 | LONG-TERM RISK OF LIVER-RELATED AND NON-LIVER-RELATED DEATH AFTER DIRECT-ACTING ANTIVIRAL-MEDIATED SUSTAINED VIROLOGIC RESPONSE IN HEPATITIS C VIRUS PATIENTS

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Background: Direct-acting antiviral (DAA) treatment enables almost all patients with hepatitis C virus (HCV), including those with decompensated cirrhosis to achieve sustained virologic response (SVR), and improves prognosis in SVR patients. However, factors associated with long-term prognosis after SVR are unclear. The aim of this study is to clarify the risk factors for long-term prognosis according to liver-related and non-liver-related death. **Methods:** This prospective study included 3,238 HCV patients who started DAA treatment between September 2014 and June 2021 and achieved SVR in Japanese hospitals. Patients who developed hepatocellular carcinoma (HCC) before SVR were excluded. SVR was defined as serum HCV-RNA undetectable at 24 weeks after the end of treatment. The start of the observation period was the time of SVR confirmation. Factors associated with liver-related and non-liver related death after SVR were examined by Cox proportional hazard analysis. Liver-related death was defined as death from HCC, liver failure and varix rupture. **Results:** The median age was 69 years, 43% of patients were male, 9% of patients had a history of HCC and 18% of patients had liver cirrhosis. During the median follow-up of 50.4 months from SVR, 24 patients died of liver-related causes, and 103 patients died of non-liver-related causes. Among the 24 patients who died of liver-related causes, 20 patients died of HCC, three died of liver failure and one died of varix rapture. Among the 103 patients who died of non-liver-related causes, the most common causes of death were malignant tumors other than HCC (20 patients), cerebrovascular and cardiovascular events (14 patients) and infections (12 patients). The proportion of patients who died of liver-related causes was significantly higher in patients with a history of HCC than in those without (46% vs. 11%, $p < 0.001$). Annual liver-related mortality at 3/4/5 years after SVR was 1.5/1.3/3.6% in patients with a history of HCC. Liver-related and non-liver-related mortality at 5 years were 1.1% and 4.4%, respectively. In the multivariate analysis, older age ($p = 0.008$), history of HCC ($p = 0.002$) and lower albumin level at SVR ($p = 0.014$) were significantly associated with liver-related mortality after SVR, and older age ($p < 0.001$), male sex ($p = 0.006$) and lower albumin level at SVR ($p < 0.001$) were significantly associated with non-liver-related mortality after SVR. **Conclusion:** Approximately 80% of deaths in SVR patients were non-liver-related cause, and older age, male sex and lower albumin level at SVR were significantly associated with non-liver-related death. In patients with a history of HCC, the risk of liver-related death persists over the long term after SVR.

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55 | CHARACTERIZING LINKAGE TO HEPATITIS C VIRUS CARE DURING AND FOLLOWING PREGNANCY: IDENTIFYING MISSED OPPORTUNITIES FOR TESTING AND TREATMENT

Andrew Bryan Mendlowitz[1,2,3], Jennifer A. Flemming[2,4], Tatyana Kushner[5], William W. L. Wong[2,3,6], Zoe R Greenwald[2,7,8], Jeff Kwong[2,7,9], Camelia Capraru[1], Jordan J. Feld[1] and Mia Biondi[1,10], (1)Toronto Centre for Liver Disease/Viral Hepatitis Care Network (VIRCAN), University Health Network, Toronto, Canada, (2)Ices, (3)University Health Network, (4)Queen's University, (5)Icahn School of Medicine at Mount Sinai, New York, NY, (6)University of Waterloo, Waterloo, Canada, (7)University of Toronto, (8)St. Michael's Hospital, (9)Public Health Ontario, (10)School of Nursing, York University, Toronto, Canada

Background: With the ongoing opioid epidemic, hepatitis C virus (HCV) prevalence in women of childbearing potential has increased in North America.

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As pregnancy may be the only time many women interact with the healthcare system, it presents an opportune time for HCV screening and linkage to care. Poor postpartum follow-up may justify treatment in pregnancy, but there is currently little known about the cascade of care for women of childbearing potential with HCV in pregnancy or postpartum. **Methods:** We performed a population-based retrospective cohort study linking pregnancies between 2008 and 2020 to HCV testing records (spanning 1999 to 2020) and health administrative data in Ontario, Canada. Pregnancies were identified using algorithms that detected pregnancy loss < 20 weeks, induced abortion, prenatal ultrasound, livebirths, and stillbirths ≥ 20 weeks. We determined whether individual's tested positive for HCV antibody (Ab+), were RNA tested, RNA+, and/or initiated treatment. Kaplan Meier methods were used to model time from Ab+ to subsequent RNA test, and from first RNA+ record to treatment. Missed opportunities for engagement in HCV care were defined as pregnancies that occurred following Ab+ prior to subsequent RNA test, and following first RNA+ record prior to treatment initiation. **Results:** We identified 13,432 individual's with HCV Ab+ and/or RNA test(s) and ≥ 1 pregnancy record (corresponding to 28,761 pregnancies). Of these, 2,868 (21.4%) had their earliest Ab+ test record during a pregnancy. Of individual's ever Ab+,11,668 (86.9%) received RNA testing and 2,668 (22.9%) had their earliest RNA test during a pregnancy. Of the 4,945 individual's ever RNA+ without spontaneous clearance, 2,057 (41.6%) initiated treatment. Time to RNA test from Ab+ record improved from 47.5 (95% CI:41.7-53.7) weeks prior to 2012 to 5.7 (95% CI:5.2-6.8) weeks after 2018. Time to treatment from RNA+ improved from 15.1 (95% CI:14.1-16.2) years prior to 2012 to 1.9 (95% CI:1.6-2.2) years after 2018. Of those with their earliest Ab+ test (N = 9,527), 1,956 (20.1%) had ≥ 1 pregnancy before a subsequent RNA test. Treatment occurred in the minority with a RNA+ record. Following those from their first RNA+ (N = 4,936), 2,266 (45.9%) had ≥ 1 pregnancy before initiating treatment (Figure). There were 1,767 individual's never linked to an RNA test corresponding to an average of 1.6 missed pregnancies per person. Considering the 2,212 missed pregnancies among those RNA+ with no treatment record (assuming clearance of 40% and 5% vertical transmission rates), we estimate 195 infected infants may have been a consequence of these missed opportunities for engagement. **Conclusion:** We observed significant gaps in follow-up testing after initial Ab+ test, and in treatment following an RNA+ result. It will be critical to enhance linkage after HCV diagnosis during or before pregnancy to reduce transmission, particularly following adoption of universal HCV screening in pregnancy.

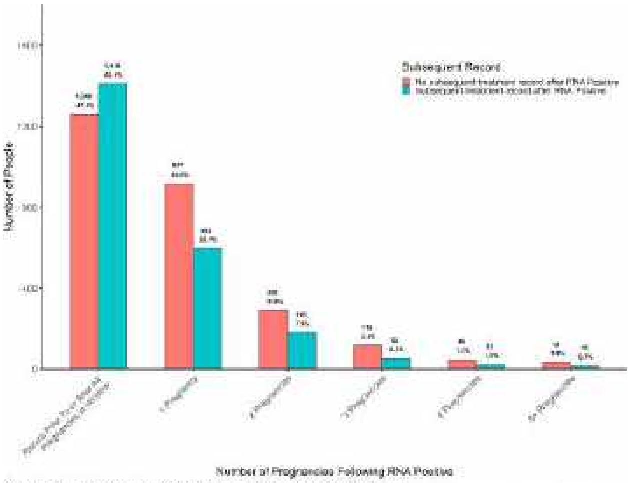

Figure: Potential missed opportunities for engagement in HCV treatment following RNA positive test.
Annotation above each bar indicates the number and percentage of total individuals for subsequent treatment record and no treatment record groups.

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56 | ONGOING EXPERIENCE OF IMPLEMENTING "THE TORONTO PROTOCOL": AN ULTRA-SHORT COURSE GLECAPRIVER/ PIBRENTASVIR WITH EZETIMIBE FOR SOLID ORGAN TRANSPLANTATION FROM HCV-INFECTED DONORS TO HCV-UNINFECTED RECIPIENTS

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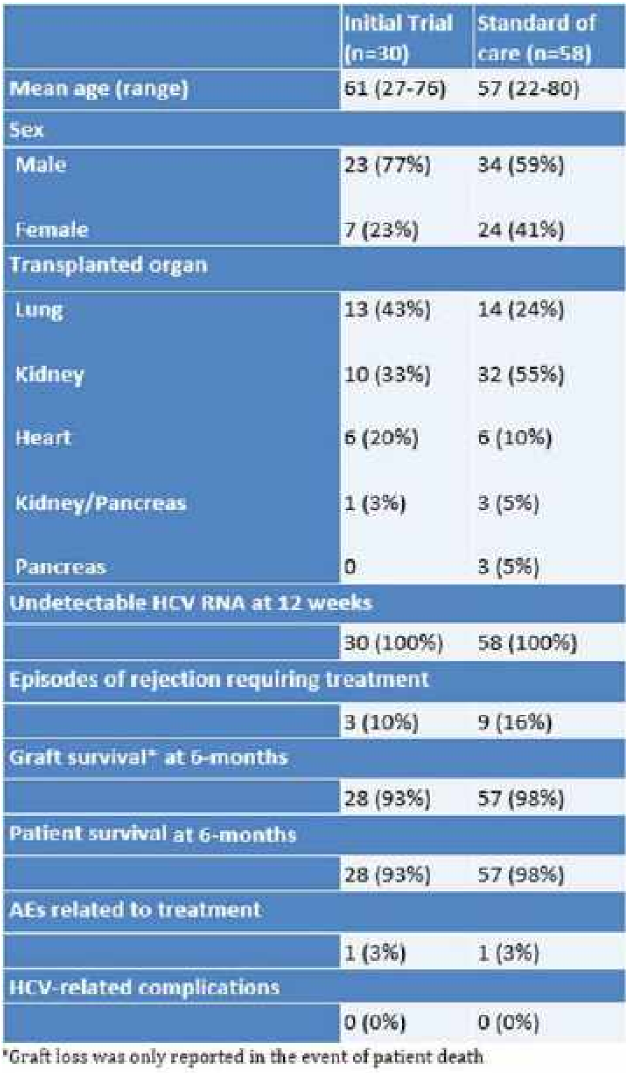
Background: The ongoing overdose crisis has led to an increase in transplantation of organs from HCV-infected donors (D+) to uninfected recipients (R-). We previously showed that an ultra-short course (1 d pre and 7 d post) of glecaprevir/pibrentasvir (G/P) combined with ezetimibe (E) prevented chronic infection in non-liver solid organ recipients. We report our results for 2 cohorts: extended follow-up for patients in the original study (n = 30), as well as outcomes since adoption of the “Toronto Protocol” as standard of care (SOC) (n = 58). **Methods**: All D+/R- organ recipients who received the Toronto Protocol with G/P+E x1 dose pre- and daily for 7 days post-transplant were followed to last HCV RNA result or patient death. The primary endpoint was establishment of chronic HCV infection, defined as positive HCV RNA 12 weeks post-transplant or need for retreatment. Additional outcomes include graft rejection and patient survival. **Results**: Since adoption of the protocol as standard of care, 58 patients received D+/R- organ transplants from 42 donors. The SOC cohort included 34 (59%) males and 24 (41%) females. The mean age was 57 years (range 22-80), with 32 kidney, 14 lung, 6 heart, 3 pancreas, and 3 kidney-pancreas organ transplants. All non-kidney and 26 (81%) of kidney transplants completed the full treatment regimen before hospital discharge with no dose reductions or treatment discontinuation. All patients had undetectable HCV RNA 2 weeks post-transplant and at last follow-up; median 65 weeks (range 2-171 weeks). 27 (46%) patients developed HCV antibodies that persisted post-treatment. There were 3 deaths unrelated to HCV treatment reported at 11, 188, and 286 days post-transplant and 10 episodes of biopsy-proven rejection, all after completion of HCV therapy. The initial trial included 30 recipients from 18 donors. With extended follow-up to 220 weeks (median 186 weeks; IQR 56-317), no patients developed chronic HCV infection or relapsed. The 6- month patient survival rate was 93%. There was no graft loss, but 14 (24%) patients died from 7 to 178 weeks post-transplant with no HCV-related deaths. In total, 88 organ recipients have completed the G/P+E protocol with no virological breakthrough or need for retreatment and no HCV-related complications. **Conclusion**: An ultra-short regimen of G/P+E prevented chronic HCV infection in all D+/R- transplant recipients and was well tolerated, allowing the majority to complete treatment before hospital discharge. These results support the current AASLD/IDSA guidance recommendation to initiate treatment promptly after transplantation.



	Initial Trial (n=30)	Standard of care (n=58)
Mean age (range)	61 (27-76)	57 (22-80)
Sex		
Male	23 (77%)	34 (59%)
Female	7 (23%)	24 (41%)
Transplanted organ		
Lung	13 (43%)	14 (24%)
Kidney	10 (33%)	32 (55%)
Heart	6 (20%)	6 (10%)
Kidney/Pancreas	1 (3%)	3 (5%)
Pancreas	0	3 (5%)
Undetectable HCV RNA at 12 weeks		
	30 (100%)	58 (100%)
Episodes of rejection requiring treatment		
	3 (10%)	9 (16%)
Graft survival* at 6-months		
	28 (93%)	57 (98%)
Patient survival at 6-months		
	28 (93%)	57 (98%)
AEs related to treatment		
	1 (3%)	1 (3%)
HCV-related complications		
	0 (0%)	0 (0%)

*Graft loss was only reported in the event of patient death

Table 1. Demographic and outcome data for the initial trial and standard of care (SOC) D+/R- patient cohorts at UHN receiving the Toronto Protocol treatment regimen.

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and manages the funds), No, No; Gilead: Consultant, No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GSK: Consultant, No, No; Janssen: Consultant, No, No; Janssen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Wesam Aleyadeh

Disclosure information not available at the time of publication: Marcelo Cypel, Rhonda Allan, June Wang, Dipika Munyal, Atul Humar

57 | ESTABLISHING A PHARMACIST-LED HEPATITIS C TREATMENT CLINIC WITHIN A LARGE HEALTHCARE SYSTEM

Kenneth John Barga[1], Anthony Michaels[1,2], Adam Hanje[1,2], Ruchi Bhatia[1,2], Pamella Kibbe[1,2] and Gretchen Calhoun[1,2], (1)Ohiohealth Comprehensive Liver Program, (2)Ohio Gastroenterology Group

Background: Hepatitis C Virus (HCV) is a blood-borne viral pathogen resulting in hepatic inflammation that – if left untreated – may lead to advanced liver disease, hepatocellular carcinoma, and death. With the advent of improved treatment modalities, several national, state, and local governing bodies have called for HCV eradication. In March of 2023, the United States Presidential Administration announced plans to start a National Hepatitis C Elimination Program. This five-year plan, budgeted to start in the Fiscal Year 2024, will focus on access to diagnostic testing and HCV treatment along with comprehensive public health efforts. From a state level, HCV remains prevalent in Ohio with the ongoing opioid epidemic. To help improve access to HCV treatment, the Ohio Department of Health created the Hepatitis Surveillance Program and Hepatitis Prevention Initiative. Despite this, OhioHealth – a large healthcare system of 15 hospitals and affiliate organizations in Central Ohio – did not have ambulatory hepatology services until January of 2023. During the inception of the OhioHealth Comprehensive Liver Program, clinicians developed a pharmacist-led, referral-based viral hepatitis clinic to expand access to HCV treatment throughout Ohio. This quality improvement project under a collaborative practice agreement looks to evaluate the program's success while also spreading best practices. **Methods:** This project assessed all patients referred to the OhioHealth Viral Hepatitis Clinic since the program's inception in January 2023. Data was collected via manual, retrospective chart review. Descriptive statistics were performed to assess the data. **Results:** Since January of 2023, 70 adult (average age: 46.8 y), HCV-infected patients have followed with the program. Of these 70 patients, 81.4% were white and 57.1% were female. The most common means of viral acquisition was intravenous drug exposure (62.9%). Most were treatment-naïve (91.4%), genotype 1a (48.6%) and non-cirrhotic (74.3%). Two patients (2.9%) had HBV coinfections while none had concurrent HIV. Most patients received either an 8- or 12-week course of treatment (85.7%). Patients initiated treatment within an average of 8.9 days of their first pharmacist visit. Patients were not required to visit with the pharmacist while on-treatment; however, they will complete 12-week post-treatment assessments. **Conclusion:** This pharmacist-led, referral-based viral hepatitis clinic has been very successful and well received thus far in our large healthcare network with the goal of achieving HCV elimination. All outcomes data will be available and presented at AASLD's Liver Meeting in November of 2023.

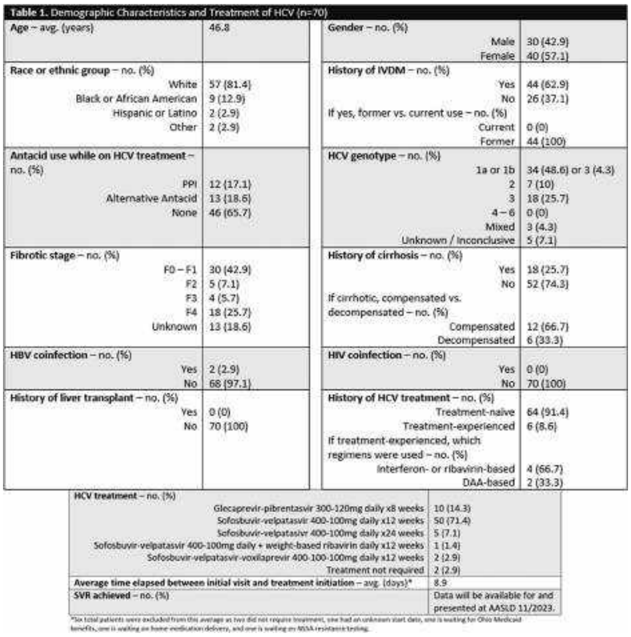

Table 1. Demographic Characteristics and Treatment of HCV (n=70)

Age – avg. (years)	46.8	**Gender** – no. (%)	
		Male	30 (42.9)
		Female	40 (57.1)
Race or ethnic group – no. (%)		**History of IVDM** – no. (%)	
White	57 (81.4)	Yes	44 (62.9)
Black or African American	9 (12.9)	No	26 (37.1)
Hispanic or Latino	2 (2.9)	If yes, former vs. current use – no. (%)	
Other	2 (2.9)	Current	0 (0)
		Former	44 (100)
Antacid use while on HCV treatment – no. (%)		**HCV genotype** – no. (%)	
PPI	12 (17.1)	1a or 1b	34 (48.6) or 3 (4.3)
Alternative Antacid	13 (18.6)	2	7 (10)
None	46 (65.7)	3	18 (25.7)
		4 – 6	0 (0)
		Mixed	3 (4.3)
		Unknown / Inconclusive	5 (7.1)
Fibrotic stage – no. (%)		**History of cirrhosis** – no. (%)	
F0 – F1	30 (42.9)	Yes	18 (25.7)
F2	5 (7.1)	No	52 (74.3)
F3	4 (5.7)	If cirrhotic, compensated vs. decompensated – no. (%)	
F4	18 (25.7)		
Unknown	13 (18.6)	Compensated	12 (66.7)
		Decompensated	6 (33.3)
HBV coinfection – no. (%)		**HIV coinfection** – no. (%)	
Yes	2 (2.9)	Yes	0 (0)
No	68 (97.1)	No	70 (100)
History of liver transplant – no. (%)		**History of HCV treatment** – no. (%)	
Yes	0 (0)	Treatment-naive	64 (91.4)
No	70 (100)	Treatment-experienced	6 (8.6)
		If treatment-experienced, which regimens were used – no. (%)	
		Interferon- or ribavirin-based	4 (66.7)
		DAA-based	2 (33.3)
HCV treatment – no. (%)			
Glecaprevir-pibrentasvir 300-120mg daily x8 weeks	10 (14.3)		
Sofosbuvir-velpatasvir 400-100mg daily x12 weeks	50 (71.4)		
Sofosbuvir-velpatasivr 400-100mg daily x24 weeks	5 (7.1)		
Sofosbuvir-velpatasvir 400-100mg daily + weight-based ribavirin daily x12 weeks	1 (1.4)		
Sofosbuvir-velpatasvir-voxilaprevir 400-100-100mg daily x12 weeks	2 (2.9)		
Treatment not required	2 (2.9)		
Average time elapsed between initial visit and treatment initiation – avg. (days)*	8.9		
SVR achieved – no. (%)	Data will be available for and presented at AASLD 11/2023.		

*Six total patients were excluded from this average as two did not require treatment, one had an unknown start date, one is waiting for Ohio Medicaid benefits, one is waiting on home medication delivery, and one is waiting on NS5A resistance testing.

Disclosures: The following people have nothing to disclose: Kenneth John Barga

Disclosure information not available at the time of publication: Anthony Michaels, Adam Hanje, Ruchi Bhatia, Pamella Kibbe, Gretchen Calhoun

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

58 | LOW ANTIVIRAL TREATMENT RATE FOR PATIENTS WITH HEPATITIS C (HCV)-RELATED HEPATOCELLULAR CARCINOMA (HCC)– A REAL-WORLD NATIONWIDE U.S. STUDY

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Background: All-oral interferon-free direct-acting antiviral agents (DAAs) for treatment and cure of hepatitis C virus (HCV) became available in 2013-2014. Our primary objective is to determine the proportion of patients with HCV-related HCC who received DAA after 2014 and factors associated with treatment receipt. We also evaluated DAA treatment impact on the overall survival in this population as a secondary outcome. **Methods:** This retrospective study identified patients with HCV-related HCC from 2015-2021 using Optum's Clinformatics® Data Mart (CDM) Database – a large, national, de-identified, adjudicated claims database of medically insured patients. Adults with HCV-related HCC and at least 6 months of insurance coverage, but without prior liver transplant, hepatitis B, D or HIV co-infection were included. **Results:** We identified and analyzed 3,922 patients with HCV-related HCC. Of these, 922 (23.5%) received DAA. Treatment rates were higher for patients with cirrhosis (both compensated and decompensated), those who received care from gastroenterology (GI) or infectious disease (ID) with or without oncology specialists (Figure 1A). Compared to untreated patients, the DAA-treated group was also younger (65.2 ± 7.5 vs. 66.4 ± 7.5 y, $p < 0.001$). In multivariable logistic regression, younger age (aHR 0.98, 95%CI: 0.97-0.99, $p < 0.001$), being seen by a GI/ID physician (aHR 3.06, 95%CI: 2.13-4.51, $p < 0.001$), having cirrhosis (compensated: aHR 1.60, 95%CI 1.18-2.21; $p = 0.003$; decompensated: aHR 1.45, 95%CI 1.07-1.98, $p = 0.02$) were associated with higher odds of receiving DAA treatment, but not sex or race/ethnicity. DAA treated patients had significantly higher 5-year survival compared to untreated patients (47.2% vs. 35.2%, $p < 0.001$, Figure 1B). Following adjustment for age, sex, race/ethnicity, Charlson Comorbidity Index, HCC treatment, receiving DAA treatment remained significantly associated with lower mortality (aHR:0.61, 95%CI: 0.53-0.69, $p < 0.001$). **Conclusion:** Although those who received DAA treatment had a significantly better 5-year survival, DAA treatment remains underutilized even in the sickest of patients with HCV who are insured as less than one in four patients were treated. Seeing GI/ID specialist was associated with 3 times higher odds of receiving DAA therapy in patients with HCV-related HCC, highlighting the needs for a multidisciplinary approach to care for this population.

Figure 1A. Treatment rates among HCV-related HCC patients in the total cohort by sex, cirrhosis, race, and care provider

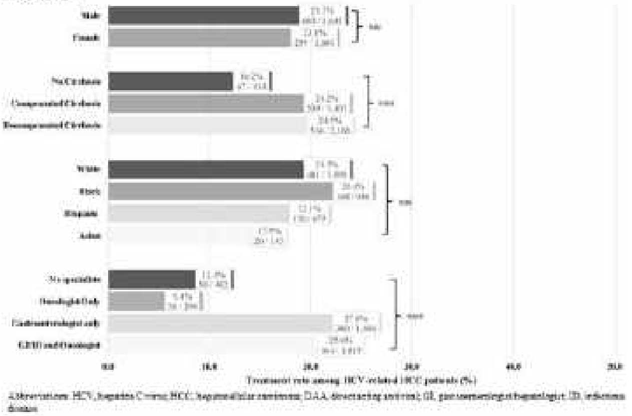
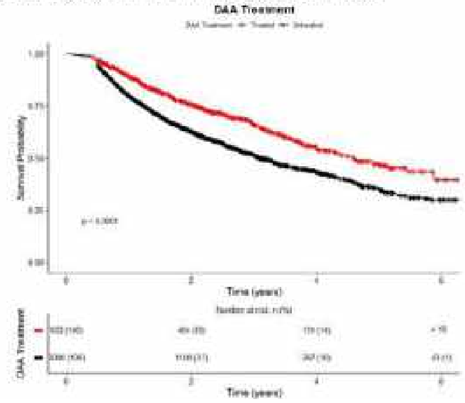


Figure 1B. Survival of patients with HCV-related HCC by DAA treatment status



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59 | IMMEDIATE POSTPARTUM CESSATION OF TENOFOVIR IN HIGHLY VIREMIC PREGNANT MOTHERS WITH CHRONIC HEPATITIS B INFECTION: MATERNAL AND INFANT OUTCOMES

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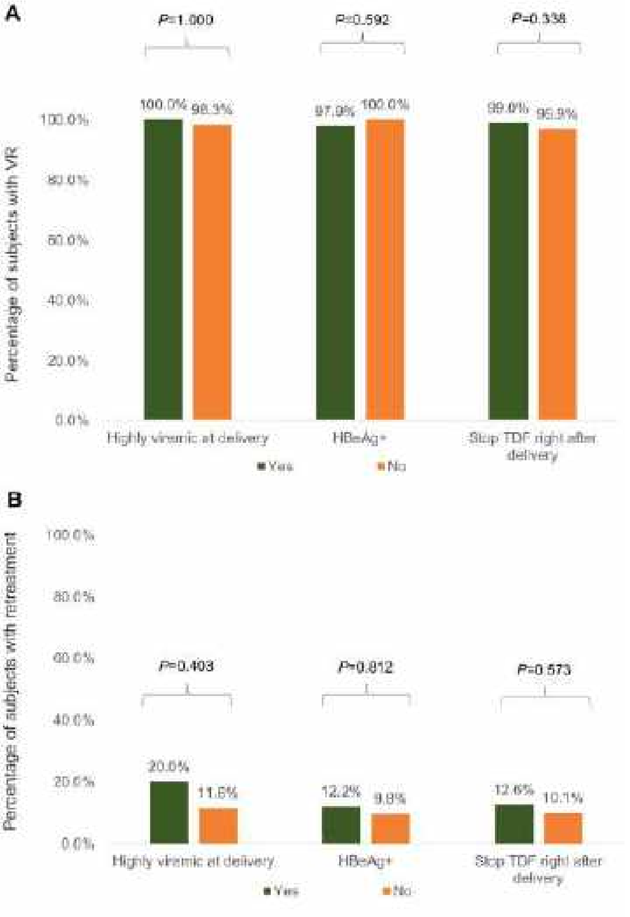
Background: Antiviral prophylaxis with tenofovir disoproxil fumarate (TDF) during pregnancy is the current standard of care to prevent mother-to-child transmission (MTCT) of chronic hepatitis B (CHB) infection in highly viremic mothers. We investigated the maternal and fetal outcomes in a large Chinese cohort of TDF-treated CHB pregnant subjects. **Methods:** In this prospective study, consecutive treatment-naïve non-cirrhotic highly viremic (defined as hepatitis B virus [HBV] DNA e 200,000 IU/mL) CHB mothers were treated with TDF at 24-28 weeks of pregnancy. In accordance with Chinese CHB guidelines, TDF was stopped right after delivery, or e 4 weeks postpartum. Serum HBV DNA and alanine aminotransferase (ALT) were monitored every 6-8 weeks to determine virological relapse (VR, defined as HBV DNA e 2 log increase from treatment cessation). Retreatment was indicated for VR + ALT above upper limit of normal. Infants were given HBV vaccine within 12 hours of birth, 1 and 6 months, in addition to HBV immunoglobulins. Serum hepatitis B surface antigen (HBsAg), antibody to HBV core (anti-HBc) and antibody to HBsAg (anti-HBs, lower limit of detection 10 IU/L) were checked in infants at 6 months. **Results:** A total of 330 eligible subjects were recruited (median age 30 [interquartile range IQR 28-32], 81.8% HBeAg+). At baseline, the median ALT was 17 (13-24) U/L and median HBV DNA was 7.82 (6.91-8.20) log IU/mL. At delivery, 6.2% remained highly viremic. TDF was stopped right after delivery in 66.4%, and e 1 month in 33.6%. Among 293 with full follow-up data, VR was observed in 98.3% and 11.8% were retreated. Timing of TDF cessation, HBeAg status and DNA levels at delivery did not alter the risk of VR (Figure A) or retreatment (Figure B). Among 299 livebirths who had full serological profile at 6 months, 0% were HBsAg+, 23.1% were anti-HBc+, and 98.7% were anti-HBs+ (32.8% > 1000 IU/L). On multivariate analysis, age (odds ratio [OR] 0.884, 95% CI 0.792-0.988), baseline ALT (OR 1.071, 95% CI 1.026-1.119), and infant anti-HBs > 1000 IU/L (OR 0.364, 95% CI 0.133-0.996) were independently associated with retreatment. Infant anti-HBs > 1000 IU/L (OR 7.203, 95% CI 3.913-13.200) and birth weight (OR 0.422, 95% CI 0.195-0.912) were independently associated with infant anti-HBc+. **Conclusion:** Prophylactic TDF and neonatal immunization were highly effective to prevent MTCT of HBV in highly viremic mothers. Cessation of prophylactic TDF right after delivery showed similar rates of VR or retreatment compared to stopping TDF e 4 weeks postpartum. Figure legend: Risk of A) VR and B) retreatment stratified by clinical parameters with respect to whether they were highly viremic at delivery, HBeAg status, and whether tenofovir was stopped at delivery vs stopped e 4 weeks postpartum.



VR: virological relapse: defined as HBV DNA >2 log increase following treatment cessation
Highly viremic: defined as HBV DNA >200,000 IU/mL
HBeAg: hepatitis B e antigen
TDF: tenofovir disoproxil fumarate

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Disclosure information not available at the time of publication: Mary Tang, Jingyi Yang, Chen Bang Chow, Om Tang, Tao Lyu, Juan Wu, Qingjuan Huang, Haibo Huang, Ka Shing Cheung

60 | LIVER STIFFNESS MEASUREMENT TO DETECT SEVERE FIBROSIS AND CIRRHOSIS IN PATIENTS WITH CHRONIC HEPATITIS D INFECTION

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Background: Hepatitis D virus (HDV) infection is associated with accelerated progression of liver disease to cirrhosis. Liver biopsy (LB) remains the gold standard procedure for fibrosis staging in HDV chronic hepatitis. Transient elastography (TE), which has transformed the management of hepatitis B and C infection has not been evaluated in large populations of HDV-infected patients. We investigated TE (FibroScan) performance for the diagnosis of HDV-induced liver fibrosis. **Methods:** HDV RNA-positive patients from a national cohort were investigated by TE, performed within 6 months from LB. Hepatic fibrosis stages were assessed using the Metavir score (F0-4). TE diagnostic performance in identifying cirrhosis (F4), severe fibrosis (F3) and significant fibrosis (F2) was compared to that of non-invasive fibrosis tests, such as the AST to platelet ratio index (APRI), the fibrosis-4 score (FIB-4) and the Delta-4 fibrosis score (D4FS). AUROC and Youden indexes were used to establish optimal cut-offs values. **Results:** Valid liver stiffness measurements (LSM) from 230 patients were analyzed (median age 36 [30-44] yrs, median BMI 24.0 [21.6-27.5] kg/m^2). Histologic fibrosis stage prevalence was 20.4% for F0F1, 27.0% for F2, 18.7% for F3 and 33.9% for F4. TE displayed excellent diagnostic accuracy for the detection of cirrhosis (AUROC of 0.88), superior to that of APRI (0.76), FIB-4 (0.79) and D4FS (0.86) ($p = 0.007$). TE was also superior for detecting severe fibrosis: AUROC of 0.85, compared to 0.72 for

APRI and 0.76 for FIB-4 ($p = 0.003$). Its performance was not better for detecting significant fibrosis (AUROC of 0.81 compared to 0.72 for APRI and 0.72 for FIB-4, $p = 0.39$). At the optimized cut-off value of 11.1 kPa for cirrhosis diagnosis, TE showed 81% sensitivity, 81% specificity, PPV of 68.5% and a NPV of 89%; 81% of the patients being correctly classified. At the optimized cut-off value of 10.4 kPa for determining severe fibrosis, TE sensitivity was 70.2%, specificity 83.5%, PPV 82.5% and NPV 71.7%, with 76.5% of correctly classified patients. At both cut-off values, PPV remained unchanged after exclusion of patients with ALT > 5N. **Conclusion:** In this large real-life cohort of HDV-patients, TE showed good diagnostic performance for determining severe fibrosis and cirrhosis, superior to that of APRI, FIB-4 and D4FS. The high probability of severe fibrosis, when LSM > 10.4 kPa, and cirrhosis, when LSM e 11.1 kPa, justifies rapid treatment. In case of LSM d 10.4kPa, LB is still recommended.

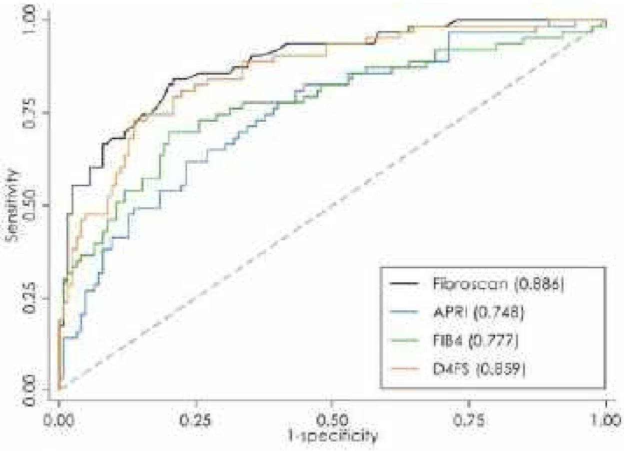

Figure 1:Transient elastography ROC curve compared to curves of serum markers for cirrhosis in CHD patients

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The following people have nothing to disclose: Richard Layese, Louis D'Alteroche, Nathalie Ganne-Carrié, Christiane Stern, Antonio Saviano, Vincent Leroy, Francoise Roudot-Thoraval

f 61 | AN OPEN-LABEL ROLLOVER STUDY FOLLOWING A RANDOMIZED TRIAL FOR CHRONIC HEPATITIS B WITH HIGH SERUM VIRAL LOAD BUT MILD ELEVATED AMINOTRANSFERASE

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Background: This study extends the follow-up of participants who completed a randomized placebo-controlled trial evaluating the safety and efficacy of tenofovir disoproxil fumarate (TDF) in reducing the risk of histological progression in patients with chronic hepatitis B (CHB) characterized by high viral load and minimally raised serum alanine aminotransferase (ALT) levels. We report herein the outcomes of patients who received three years of open-label TDF treatment after completing a randomized trial **Methods:** This open-label study enrolled participants who had completed a three-year trial of TDF vs. placebo for CHB patients with serum HBV DNA exceeding 2000 IU/mL and ALT levels between one to two times the upper limit of normal (ULN). Exclusion criteria included malignancy, cirrhosis, hepatic insufficiency, renal failure, pregnancy, or viral coinfections. Upon completing the randomized trial, eligible patients were all rolled over to receive three years of open-label TDF treatment, followed by a liver biopsy to evaluate histological changes. The severity of fibrosis was evaluated using the Ishak scoring system, and necroinflammation was assessed using the Knodell system (ClinicalTrials.gov Identifier: NCT02463019). **Results:** A total of 146 patients (median age of 47 y, IQR: 41-57 y, 80.8% male) were enrolled in the study. At baseline, 18.5% (n = 27) of patients were HBeAg-positive, and 47.9% (n = 70) had undetectable HBV DNA. Moderate to severe liver fibrosis or cirrhosis (Ishak e 3 points) was present in 33.3% (n = 42) of patients. During the 3-year period, 23 patients withdrew from the study, including 5 who developed hepatocellular carcinoma (3 initially assigned to placebo, 2 to TDF). Among the remaining 123 patients with paired liver biopsies, severity of liver fibrosis significantly improved after 3 years of open-label TDF treatment ($p < 0.0001$, Stuart-Maxwell test), with the proportion of patients with an Ishak score of liver fibrosis e 3 points

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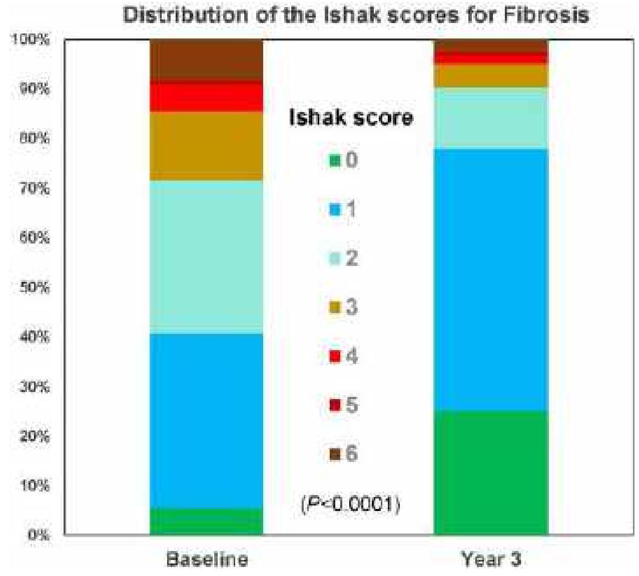
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

decreasing to 9.8% (12 patients, Figure 1). Furthermore, viral remission (defined as undetectable HBV DNA) and ALT normalization were achieved in 82.2% and 69.0% of patients, respectively. There were no serious adverse events attributable to the study medication. **Conclusion:** In this open-label rollover study following a three-year randomized trial, we found that continued use of TDF in CHB patients with high viral load and mild ALT elevation led to significant improvement in liver fibrosis.



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62 | HEPATOCELLULAR CARCINOMA RISK IN SUB-SAHARAN AFRICAN AND AFRO-SURINAMESE INDIVIDUALS LIVING WITH CHRONIC HEPATITIS B IN EUROPE: AN INTERNATIONAL MULTICENTER RETROSPECTIVE COHORT STUDY

Lesley Ann Patmore[1], Kirsi Van Eekhout[2], Maria Buti[3], Ozgur Mustafa Koc[4], K Agarwal[5], Rob J. De Knegt[1], Harry L. A. Janssen[6,7], Marc Van Der Valk[2], Faydra Ione Lieveld[8], Matthijs Kramer[4], Joep De Bruijne[8], Mark Claassen[9], Colette Smit[10], Robert A. De Man[11], Bart Takkenberg[2], Ivana Carey[12] and Milan J. Sonneveld[1], (1)Erasmus MC, University Medical Center, (2) Amsterdam University Medical Center, Amsterdam, Netherlands, (3)Hospital Universitari Vall d'Hebron, Department of Medicine of the UAB (Universitat Autònoma de Barcelona), Spain, (4)Maastricht University Medical Center, (5)King's College Hospital, (6)Erasmus MC, University Medical Center Rotterdam, (7)Toronto General Hospital Research Institute, (8) Utrecht Umc, (9)Rijnstate Hospital Arnhem, (10)HIV Monitoring Foundation, (11)Erasmus MC, University Medical Center, Rotterdam, Netherlands, (12)Institute of Liver Studies, Kings College Hospital, London, United Kingdom

Background: Cross-sectional studies have identified individual's from sub-Saharan Africa with (SSA) chronic hepatitis B (CHB) as a potential risk group for hepatocellular carcinoma (HCC) and advocate enrolment in an HCC surveillance program even in the absence of cirrhosis. However, the incidence of HCC and performance of HCC risk scores in this population are unknown. **Methods:** We conducted an international multicenter retrospective cohort study of all consecutive hepatitis B virus (HBV) mono-infected individual's with SSA or Afro-Surinamese (AS) ethnicity managed at sites in the Netherlands, the United Kingdom and Spain. We assessed the 5 and 10 year cumulative incidence of HCC in the overall study population and according to baseline fibrosis grade and HBV DNA levels. We also studied potential other predictors of HCC development using Cox regression. Finally, we assessed the performance of the (m)PAGE-B score for stratifying HCC risk. **Results:** We analyzed 1473 individual's; the majority of whom were male (59.7%) with a median age of 38 years (interquartile range [IQR] 29-46) at enrolment. At baseline 12.7% had advanced fibrosis (METAVIR e F3 based on biopsy or FibroScan). During a median follow-up of 8 years (IQR 3.9 – 11.4) 34 individual's developed HCC. The 5 and 10 year cumulative incidence of HCC was 1% (95% confidence interval [CI] 0.99 – 1.01) and 2.5% (95% CI 2.39–2.41), with no difference observed across ethnicities ($p = 0.238$). Among individual's without advanced fibrosis at baseline, the 5 and 10 year cumulative incidence of HCC was 0% and 0.7%, compared to 7.1% and 12.1% among individual's with advanced fibrosis ($p < 0.001$). The 5 and 10 year cumulative HCC incidence was 0.7% and 1% for individual's with a baseline HBV DNA < 2,000 IU/mL compared to 1.3% and 3.6% among individual's with HBV DNA at baseline > 2,000 IU/mL ($p = 0.031$). In addition to baseline fibrosis grade and HBV DNA levels, univariate analysis revealed that older age (hazard ratio [HR] 1.07, 95% CI 1.04–1.10 $p < 0.001$), male sex (HR 2.59, 95% CI 1.13–5.94 $p = 0.025$), platelet count (HR 0.98, 95% CI 0.97–0.98 $p < 0.001$), and albumin (HR 0.89, 95% CI

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

0.83–0.94 $p < 0.001$) were significantly associated with HCC development. The 10 year cumulative incidence of HCC was 0.5% among individual's with a low PAGE-B score (n = 771, 52.3% of cohort), compared to 2.9% in the intermediate risk group (n = 569, 38.6% of cohort) and 15.9% in the high risk group (n = 85, 5.8% of cohort; $p < 0.001$). Similar results were obtained for the modified PAGE-B score. **Conclusion:** This unique international multicenter cohort of SSA and AS individual's with CHB shows a limited 5 and 10 year cumulative risk of HCC. The risk of HCC was negligible for individual's without advanced fibrosis at baseline, and among individual's with low baseline (m)PAGE-B scores. Based on these findings, the majority of these patients can potentially be excluded from HCC surveillance based on absence of advanced fibrosis and/or low HCC risk scores.

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Harry L. A. Janssen – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GlaxoSmithKline: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Janssen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Vir Biotechnology Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Aligos: Consultant, No, No; Gilead Sciences: Consultant, No, No; GlaxoSmithKline: Consultant, No, No; Janssen: Consultant, No, No; Roche: Consultant, No, No; Vir Biotechnology Inc.: Consultant, No, No; Precision Biosciences: Consultant, No, No;

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63 | CONTINUED TREATMENT OF EARLY VIROLOGIC NON-RESPONDER OR PARTIAL RESPONDERS WITH BULEVIRTIDE MONOTHERAPY FOR CHRONIC HEPATITIS D LEADS TO IMPROVEMENT IN VIROLOGIC AND BIOCHEMICAL RESPONSES: RESULTS FROM AN INTEGRATED ANALYSIS AT WEEK 96

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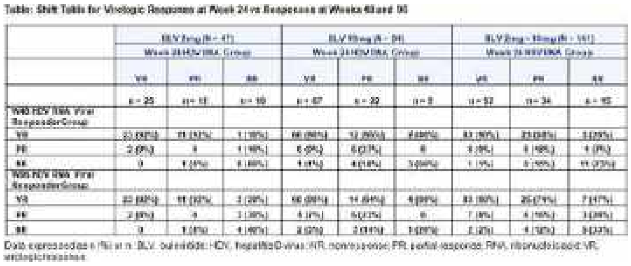
Background: Bulevirtide (BLV), a novel hepatitis delta virus (HDV) entry inhibitor, is approved in Europe for treatment of chronic hepatitis D (CHD). In clinical studies, virologic response (VR) was defined as undetectable HDV RNA or e 2-$\log_{10}$ IU/mL decline from baseline (BL). Optimal BLV monotherapy duration for CHD is unknown; it is also unclear whether continued therapy will benefit patients (pts) with early virologic nonresponse (NR) or partial response (PR). This integrated analysis evaluated continued BLV monotherapy in pts without VR after 24W. **Methods:** Results from pts who completed BLV monotherapy for 96W in the Phase 3 (MYR301; NCT03852719) and Phase 2 (MYR204; NCT03852433) studies were included. NR and PR were defined as HDV RNA declines of < 1 $\log_{10}$ IU/mL and e 1 but < 2 $\log_{10}$ IU/mL, respectively. Rates of biochemical response (alanine aminotransferase [ALT] within normal limits [WNL]) were compared. **Results:** 141 CHD pts (47 BLV 2mg; 94 BLV 10mg) were evaluated. At BL 67% were male, 87% White, 43% had cirrhosis, 40% received concomitant nucleos(t)ide analogues, and 50% had prior interferon exposure. Mean (SD) HDV RNA was 5.2 (1.3) $\log_{10}$ IU/mL; median (Q1, Q3) ALT was 94 (64, 136) U/L. At W24, 92/141 (65%) pts had VR (53 [58%] with ALT WNL), 34/141 (24%) had PR (19 [56%] with ALT WNL), and 15/141 (11%) had NR (2 [13%] with ALT WNL) (Table). 49 pts had NR or PR at W24. Of the 34 PR pts at W24, 25 (74%) had VR, and 24 (71%) had ALT WNL by W96. Of the 15 NR pts at W24, 7 (47%) had VR and 3 (20%) had PR by W96. A higher proportion of NR at W24 achieved VR at W96 among those receiving BLV 10mg (4/5, 80%) vs BLV 2mg (3/10, 30%). Among W24 NR or PR, the mean BL HDV RNA did not predict viral response at W96. Median (Q1, Q3) BL U/L ALT was higher in pts with NR (138 [112, 196]) vs VR (79 [53, 113]) and PR (95 [56, 150]) at W96. The mean (SD) $\log_{10}$ IU/mL HDV RNA change at W96 among VR/PR/NR was −3.6 (1.1), −1.4 (0.3), and −0.2 (0.7) for VR, PR, and NR at W96. Median (Q1, Q3) U/L ALT change at W96 among VR/PR/NR was −48 (−73, −12), −42 (−83, −6), and −67 (−102, −33), respectively. Among all NR at W96, ALT declined > 50% from BL in 7/11 (3/11 achieved ALT WNL). **Conclusion:** Of 49 pts without VR at W24, the majority with PR and nearly half with NR were able to achieve VR at W96. ALT improved in all viral-response groups including those with NR. These results provide evidence for continuing BLV therapy despite early (24W) suboptimal virologic responses.



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64 | TENOFOVIR VERSUS ENTECAVIR IN PREVENTING HCC AND DEATH: ANSWER FROM A LARGE INTEGRATED HEALTH PLAN POPULATION

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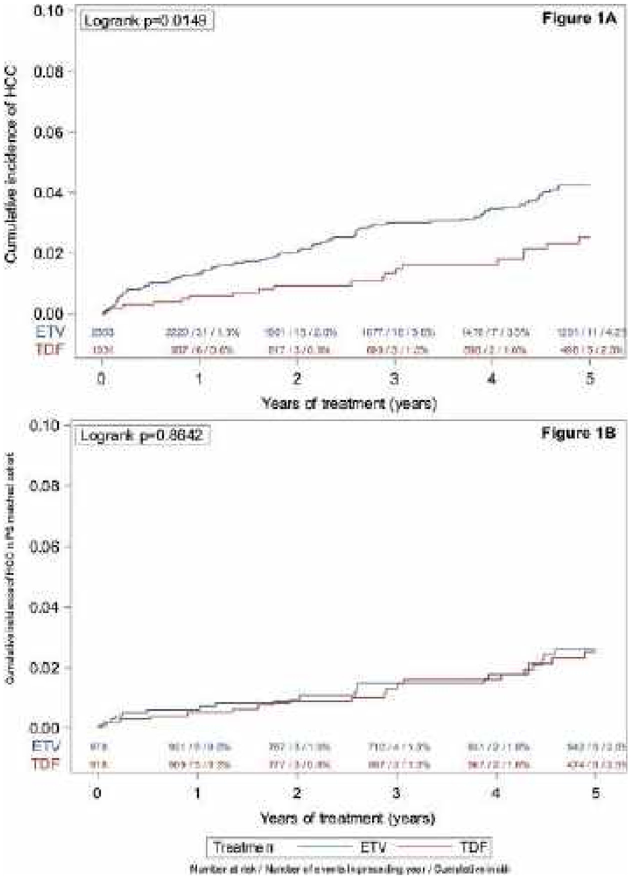
Background: Chronic hepatitis B (CHB) suppressive therapy with tenofovir disoproxil (TDF) or entecavir (ETV) has been shown to reduce the risk of hepatocellular carcinoma (HCC) and mortality. However, controversy exists regarding if one treatment is better than the other. **Methods:** All Kaiser Permanente Northern California adult (age > 17 y) patients with CHB undergoing suppressive treatment with either TDF or ETV for at least 1 year at any time between 1/1/2006 and 12/31/2021 and with > 90% adherence by prescription refill data were included. TDF treated patients were 1:1 propensity score (PS) matched to ETV treated patients on baseline age, sex, race/ethnicity, body-mass index (BMI), diabetes, hyperlipidemia, hypertension, alcohol abuse, HIV, cirrhosis, prior lamivudine treatment, creatinine, hepatitis B DNA and hepatitis B envelope antigen/antibody status. Outcomes of interest included HCC development and mortality and were compared in the overall TDF and ETV cohorts as well as in the PS matched cohorts **Results:** A total of 3384 treated HBV patients were included, 1031 (30%) TDF and 2353 (70%) ETV. Compared to ETV, TDF treated patients were younger (mean 48 vs. 52 y), more likely female (39% vs. 34%), thinner (BMI 24 vs. 25 kg/m^2), have less diabetes (10% vs. 14%), less hyperlipidemia (21% vs. 32%), less hypertension (21% vs. 31%), more HIV co-infection (4% vs. 0%), less cirrhosis (8% vs. 12%), more prior lamivudine treatment (16% vs. 7%), lower creatinine (0.88 vs. 0.96 mg/dL), lower DNA (6.0 vs. 6.3 million IU/mL) and more envelope antigen positivity (38% vs. 33%). 978 TDF patients were successfully PS matched to ETV patients and differences between groups resolved. Overall and compared to ETV, TDF was associated with reduced HCC (HR: 0.60, 95% CI: 0.4-0.9, $p = 0.02$; Figure 1A) and with reduced mortality (HR: 0.60, 95% CI: 0.4-0.9, $p < 0.01$). In PS matched and compared to ETV, TDF was *not* associated with reduced HCC (HR: 0.93, 95% CI: 0.4-2.0; $p = 0.85$; Figure 1B) *nor* with reduced mortality (HR: 0.71, 95% CI: 0.4-1.2, $p = 0.22$). **Conclusion:** When comparing overall TDF and ETV treated populations, TDF is better than ETV in HCC and mortality risk reduction. However, this result is likely related to provider treatment patterns where patients with additional risk factors for HCC and mortality are selected to receive ETV over TDF. When these additional risk factors are controlled for in PS matched cohorts, the advantage of TDF over ETV is not distinguishable.



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

65 | AN ADVANCED PRACTICE PROVIDER (APP) DRIVEN, WEIGHT INTERVENTION IN LIVER DISEASE (WILD) CLINICAL PATHWAY ACHIEVES MORE MEANING WEIGHT LOSS IN PATIENTS WITH MASLD COMPARED TO STANDARD OR CARE

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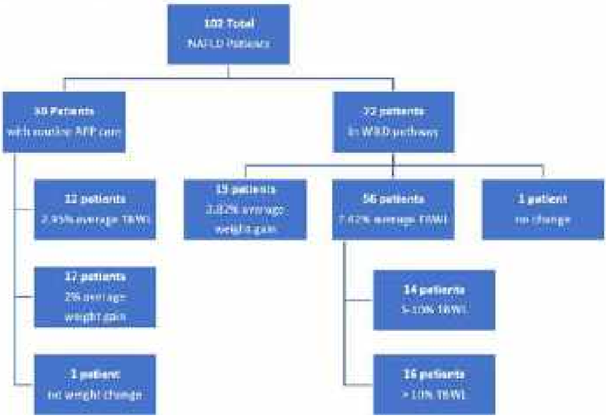
Background: As the prevalence of obesity and MASH continues to grow, novel treatment options are needed to prevent progression as there are currently no medications approved to treat MASH. Weight loss has been shown to be an effective treatment with a 5% weight loss reversing steatosis and a 10% weight loss reversing liver fibrosis. Clinical trials using lifestyle-based weight loss interventions in MASH have been shown to achieve > 5% total body weight loss (TBWL) in 30% of patients and > 10% TBWL in 10% of patients. It is unclear if the standard of care hepatology practice is sufficient to achieve these recommendations in the clinical setting or if a more dedicated intervention is needed. **Methods:** In 2018, our department developed the Weight Intervention in Liver Disease (WILD) clinical pathway, an intensive weight loss program embedded into our hepatology clinic. The program was supervised by a hepatologist board certified in obesity medicine and executed by three advanced practice providers (APP) with obesity certification. WILD provided lifestyle interventions for those with (1) MASLD (2) body mass index (BMI) > 27 with comorbidity or > 30 with or without comorbidity and (3) the willingness to participate. The patients were seen monthly to evaluate progress with nutrition, exercise, behavioral modifications, and weight loss medications. A retrospective chart review was completed to compare percent weight changes of WILD patients managed by APPs to those receiving standard of care in the APP hepatology practice. Patients were included if they had either participated in the WILD program for at least 6 months with a minimum of 2 visits or if they had achieved 10% body weight loss goal prior to the 6-month mark. Using electronic medical records, data collected included demographics, starting weight, maximum achieved weight loss and final recorded weight in the program. **Results:** Between October 2018 and May 2023, 72 patients participated in the WILD pathway and met criteria for the study. This was compared to 30 patients who received standard of care from October 2018 to June 2021. Of the 72 patients seen in the WILD pathway, 56 patients (77.8%) achieved weight loss with a median TBWL of 7.42%. Only 12 patients (40%) in the standard of care cohort achieved weight loss with a median TBWL of 2.95%. Of the 56 patients that lost weight in the WILD pathway, a total of 30 patients (53.6%) lost e 5-10% with 16 (28.5%) losing e 10%. In the standard of care cohort, only 4 patients (0.14%) lost e 5% TBWL and no patients with e 10% TBWL. **Conclusion:** A dedicated, intensive APP-directed weight intervention pathway embedded within a standard hepatology practice was more successful in helping patients achieve meaningful weight loss than standard hepatology APP-based care and published clinical trials for MASH. This data supports the development of APP driven weight loss interventions in GI and hepatology specialties to most effectively manage the massive clinical burden of MASH.

Figure 1. Comparison of TBWL between WILD pathway and routine APP care



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66 | INCORPORATING ADVANCE CARE PLANNING IN ADULTS WITH DECOMPENSATED CIRRHOSIS AT LIVER TRANSPLANT CENTERS: A NURSING-LED EDUCATIONAL INITIATIVE

Janet Gripshover[1,2], Rita D'Aoust[1], Deborah Baker[1] and Arpan Arun Patel[3], (1)Johns Hopkins University, (2) University of California Los Angeles, (3)Greater Los Angeles VA Healthcare System

Background: Clinician inexperience with advanced care planning (ACP) is a barrier to patient-centered care for adults with decompensated cirrhosis (DC) at liver transplant centers. Because transplant nurse coordinators are well-versed in DC prognoses and often develop marked therapeutic relationships with patients, these health care team members may be uniquely poised to promote ACP in the DC population.

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

Our aim was to pilot test an ACP educational program for transplant nurse coordinators. **Methods:** An ACP expert familiar with the liver transplant population (N.W.) conducted a 1-hour educational seminar, attended by liver transplant nurse coordinators (n = 8). Subject matter included the importance of ACP in the DC population as well as practical requirements for completing and documenting advanced directives (AD) at our medical center. Following the seminar, transplant coordinators were encouraged to bring up AD completion during intake appointments with pre-liver transplant patients. Three follow-up check-in meetings occurred at various intervals to help address barriers to workflow incorporation. Documentation of ACP conversations and AD completion rates in the 12 weeks before and after the intervention were compared using paired t-tests. A post- intervention survey was conducted to assess nurse coordinator engagement and perceptions on feasibility, applicability, and appropriateness of the intervention. **Results:** Prior to the intervention, 10 of 108 patients (9.3%) had any ACP documentation and 5 (4.6%) had a completed AD. After the intervention, 5 of 107 (4.7%) had any ACP documentation and 5 (4.7%) patients completed an AD, demonstrating no significant differences pre- and post- intervention (Δ ACP documentation: $p = 0.187$, Δ AD completion: $p = 0.998$). The most cited barrier by the transplant nurse coordinators was other responsibilities taking precedence (N = 3), as well as a perception that transplant social workers are better suited to perform this task (N = 5, open-ended responses). Regarding nurse coordinator engagement, acceptability scores received the highest mean scores of 4.0 out of 5.0 (SD 0.82), followed by feasibility (3.5, SD 0.65) and applicability (3.42, SD 0.57). **Conclusion:** This project demonstrates that an education intervention for health care providers alone may not be sufficient in improving ACP amongst patients with DC, and further work to reduce other ACP barriers such as operational constraints may be required.

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67 | HEPATITIS C MEDICATION ADHERENCE OUTCOMES FOR THE LOUISIANA MEDICAID SUBSCRIPTION-BASED MODEL AT SPECIALTY PHARMACY

Amanda Mooney and Claire Ozoral, Ochsner Health

Background: Prior to July 2019, Hepatitis C (HCV) treatment was limited in the state of Louisiana due to restrictive prior authorization (PA) criterion for Medicaid patients. Ochsner Specialty Pharmacy (OSP), a health-system integrated pharmacy within the largest non-profit health system in the state was unable to fill most Medicaid HCV prescriptions and instead had to assist most patients with enrollment in the manufacturer assistance program with an uncertain amount of refill follow-up and pharmacist contact. In July 2019, Louisiana entered a subscription-based contract which allowed Medicaid patients unrestricted access to authorized generic sofosbuvir-velpatasvir. Medicaid patients were now able fill their HCV treatment at OSP with close pharmacist follow up and contact. The primary outcome of this study was to determine the impact of specialty pharmacy on HCV medication adherence rates as determined by the proportion of days covered (PDC). Secondary outcome include the proportion of patients who achieve sustained virologic response (SVR), and time to treatment initiation. **Methods:** This retrospective review of Medicaid patients with a diagnosis of HCV was collected from the electronic medical record between the dates of January 1, 2019 through December 31, 2019. Medicaid patients were included in the study if they were prescribed a direct-acting antiviral (DAA) by an Ochsner provider and were DAA treatment naïve. Patients were excluded if they had advanced levels of fibrosis, a history of transplantation, and did not complete or were deceased prior to the end of treatment. **Results:** A total of 391 patients met all inclusion criteria (321 patients in the OSP group and 70 patients in the manufacturer group). For the primary outcome, patients in the OSP group saw a statistically significant increase in medication adherence as measured by PDC from 80.3% to 94% ($p < 0.05$). In addition, time to treatment initiation decreased from 94 days in the manufacturer group to only 20 days in the OSP group ($p < 0.05$). No significant difference was observed in SVR rates. **Conclusion:** The close follow up and clinical services provided by OSP led to increased rates of HCV medication adherence. In addition, the unrestricted access to HCV treatment led to much shorter times to treatment. This study demonstrates the importance the additional clinical services provided by health-system integrated specialty pharmacists have on HCV medication adherence.

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68 | SIX-YEAR FOLLOW-UP OF MANAGING PREDOMINANTLY HISPANIC PATIENTS WITH SIGNIFICANT STEATOSIS AT A PRIMARY CARE CLINIC

Anna Marie Hefner[1], Julian Diaz-Moreno[1], Fatma Barakat[1], Jose Santos[2], Cristobal Soto[2], Nabil Baig[1,2], Deanna Oliver[1,2] and Tarek I. Hassanein[1,2], (1)

Southern California Liver Centers, (2)Gateway Comprehensive Medical Group, APC

Background: The prevalence of obesity and metabolic syndrome is on the rise in the US particularly in Hispanic patients. Individual's with Nonalcoholic Fatty Liver Disease (NAFLD) are prone to progress to Nonalcoholic Steatohepatitis (NASH), which could lead to cirrhosis and liver cancer. Early identification of individual's at risk for developing NASH is critical. In 2017 we initiated and reported on a screening program for fatty liver and liver fibrosis using FibroScan® in a primary care practice (PCP) with predominantly Hispanic patients in Southern California "South Bay fatty liver cohort". This is a 6-year report on the disposition of the patients and follow-up in the primary care setting in contrast to those referred to a Hepatology practice. **Methods:** Between March, 2017 and June, 2017 958 adults (18 y and older) attending a primary care clinic, who had no known history of liver disease agreed to be screened and had an evaluable Fibroscan®. Pts were followed and managed per standard of care in the primary care setting including annual check-ups, FibroScan® assessments and referral to specialists if needed. **Results:** Of the 958 pts, 622 pts (64.9%) changed their health insurance carrier and had a change in their Primary Care practice during the COVID-19 pandemic, 6 pts (0.6%) were deceased, 109 pts (16.6%) were not able to be reached. The subjects of this analysis are 221 pts who returned for a 6-year follow-up. 68.2% were females; mean age was 56.0 ± 15.4 years and 86.4% Hispanic. ALT, AST, and Albumin were within normal range at baseline and 6-year follow-up. APRI was not applicable in this population and all had a score < = 0.1 at baseline and follow-up. Similarly, all had a Fib-4 Index < 1 at baseline and follow-up. Refer to table 1 for the 6-year change in BMI, FibroScan®, Hemoglobin A1C, and metabolic syndrome. **Conclusion:** In a pre-dominantly Hispanic community patient population with no known history of fatty liver disease attending a primary care clinic at baseline, 23% of patients continued to be followed up regularly. Over 6 years with annual follow-up visits, there was 1) a slight change in the fat infiltration and minimal change in liver stiffness measure by FibroScan®, 2) significant progression in the metabolic syndrome presentation and risk factors, and 3) significant changes in health insurance status and routine follow-up. This underscores the importance of implementing incentive programs for PCP based on patients outcomes in respect to the management of patients with NAFLD. In addition, these findings re-emphasize the need for educational programs to PCP on the nonalcoholic fatty liver disease spectrum, its consequences as well as the importance of close follow-up of patients at risk for metabolic syndrome and when to refer to liver specialists.

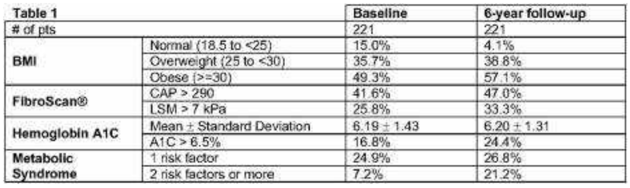

Table 1		Baseline	6-year follow-up
# of pts		221	221
BMI	Normal (18.5 to <25)	15.0%	4.1%
	Overweight (25 to <30)	35.7%	38.8%
	Obese (>=30)	49.3%	57.1%
FibroScan®	CAP > 290	41.6%	47.0%
	LSM > 7 kPa	25.8%	33.3%
Hemoglobin A1C	Mean ± Standard Deviation	6.19 ± 1.43	6.20 ± 1.31
	A1C > 6.5%	16.8%	24.4%
Metabolic Syndrome	1 risk factor	24.9%	26.8%
	2 risk factors or more	7.2%	21.2%

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The following people have nothing to disclose: Anna Marie Hefner, Julian Diaz-Moreno, Fatma Barakat, Jose Santos, Cristobal Soto, Nabil Baig, Deanna Oliver

69 | HIV COINFECTION INCREASES HBV-INDUCED HEPATIC FIBROGENESIS THROUGH A HIF-1α AND TGF-² 1 DEPENDENT PATHWAY

Min Xu[1], Charlotte Warner[1], Xiaoqiong Duan[2,3], Zhimeng Cheng[2], Andre Jeyarajan[1], Zachary Manickas-Hill[4], Tuo Shao[1], Yaontao Wang[2], Doseon Song[2], Shadi Salloum[1], Pei-Jer Chen[5], Xu Yu[4], Raymond T. Chung[2] and Wenyu Lin[2], (1) Massachusetts General Hospital and Harvard Medical School, (2)Massachusetts General Hospital, Harvard Medical School, (3)Institute of Blood Transfusion, Chinese Academy of Medical Sciences and Peking Union Medical College, (4)The Ragon Institute of

Massachusetts General Hospital, Massachusetts Institute of Technology and Harvard University, (5) National Taiwan University Hospital

Background: Approximately 4 million people worldwide are co-infected with chronic HBV (CHBV) and HIV due to shared transmission routes. The progression of CHBV to cirrhosis and hepatocellular carcinoma is accelerated by HIV coinfection compared to HBV monoinfection. The mechanisms underlying this accelerated natural history are not well characterized. HIV and its proteins, such as gp120, signal through CCR5 and CXCR4 on hepatocytes and hepatic stellate cells to promote cell growth and proliferation through hypoxia-inducible factor-1± (HIF-1±). We hypothesize that HIV and its proteins promote HBV-induced liver fibrosis in HIV/HBV coinfected cell culture models through HIF-1± and TGF-β1 signaling. **Methods:** Infectious HBV viral particles (HBVvp) were purified from the HBV supernatant (HBVsup) of HepAD38 cells. HIV NL4-3 strains viral particles (HIVvp) were isolated from HIV-infected U937 macrophage supernatant (HIVsup). The HBVvp, HBVsup, HIVvp or HIVsup were directly incubated (or infected) with LX-2 stellate cells, U937, and HBV-infected NTCP-HepG2 cells in mono or 3D spheroid coculture models. Cells were incubated with recombinant HIV proteins including gp120. HBV subgenomic constructs were transfected into NTCP HepG2 cells. We also evaluated the effects of inhibitors of HIF-1± and HIV gp120 in the HBV carrier mouse that were generated by hydrodynamic injection of pAAV/HBV1.2 plasmid though the tail vein into wild-type C57BL/6. The HIV/HBV replication, HIF-1±, and fibrotic gene expressions were monitored by qRT-PCR, ELISA, Western blot, and immunostaining. **Results:** HIV and HIV gp120, through engagement with CCR5 and CXCR4 coreceptors, activate AKT and ERK signaling and subsequently upregulate HIF-1± to increase HBV-induced TGF-β1 and profibrogenic gene expression in hepatocytes, HSCs and in the HBV carrier mouse. HIV gp120 exacerbates HBV X protein overexpression-induced HIF-1± expression and liver fibrogenesis through the TGF-β1 induced SMAD signaling pathway. Of note, HIF-1± siRNA transfection or the small molecule HIF-1a inhibitor acriflavine blocked HIV, HBV and the TGF-β1-induced fibrogenic response. HIV-induced upregulation of HIF-1± and profibrotic genes was abrogated by CCR5/CXCR4 inhibition. **Conclusion:** HIV and gp120 exacerbate HBV-induced liver fibrogenesis through upregulation of the HIF-1± and TGF-β1 pathway through CCR5/CXCR4. HIF-1± may be a novel target for antifibrotic therapeutic development in HBV/HIV coinfection.

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70 | SINGLE-CELL ANALYSIS OF LIVER FINE NEEDLE ASPIRATES REVEALS DIFFERENCES IN GENE EXPRESSION BETWEEN CHRONIC HBV-MONOINFECTED VERSUS HBV/HIV-COINFECTED ADULTS

Michael S. Wallace[1], Taonga Musonda[2], Hailey Patel[1], Christopher Oetheimer[3], Edford Sinkala[2,4], Paul Kelly[2,4,5], Owen Martin[1], Martin Feuerherd[1], Bright Nsokolo[2], Gilles Wandeler[6], Simutanyi Mwakamui[2], Debika Bhattacharya[7], Georg M. Lauer[1], Raymond T. Chung[3], Michael Vinikoor[2,8,9] and Nadia Alatrakchi[3], (1) Massachusetts General Hospital, Harvard Medical School, (2)University of Zambia, (3)Massachusetts General Hospital and Harvard Medical School, (4) University Teaching Hospital, Lusaka, (5)Queen Mary University of London, (6)University of Bern, (7) University of California, Los Angeles, (8)University of Alabama at Birmingham, (9)Centre for Infectious Disease Research in Zambia

Background: HIV infection accelerates the natural history of HBV-related liver disease. The mechanisms by which this occurs are incompletely understood due to limited access to comparable groups of people living with HBV with/without HIV and lack of access to the liver compartment. In the context of a unique HBV clinical cohort in Zambia, where 20% of people with chronic HBV infection have HIV coinfection, we collected liver cells with fine needle aspiration (FNA) and compared cell milieu and expression patterns by HIV infection status. **Methods:** Treatment-naïve adults with either HBV/HIV coinfection or antiviral treatment-eligible chronic HBV monoinfection were enrolled in an observational cohort in Lusaka, Zambia, and underwent liver FNAs. Liver cells were loaded into the HIVE device (Honeycomb Biotechnologies), which permits a field site to capture and stabilize the full spectrum of intrahepatic cells for subsequent analysis at a distant site via single-cell RNA sequencing. We analyzed the intrahepatic gene expression (in a total of 7,992 high-quality cells) in 12 participants, including 6 with HBV/HIV coinfection. **Results:** The median age of analyzed participants was 31 years (range: 20-45), 4 (33.3%) were female (2 in each group), and half had HIV coinfection. Participants with coinfection had a median peripheral CD4 count of 225 cells/mm^3 (range: 69-999). Overall, HBV/HIV coinfection was associated with increased frequencies of CD8+ T cells and decreased frequencies of neutrophils and B cells. S100, MHC-II, and interferon-stimulated genes (ISG) were recurring gene programs in the myeloid compartment, with distinct expression patterns in each cell type. Significant differences in gene expression by HIV status were seen across a range of immune cell types, and distinct expression patterns were detected within subpopulations. HBV/HIV coinfection was associated with increased expression of ISG and higher signaling of PD-1/PD-L1 in neutrophils, which was paralleled by increased PD-1 expression in CD8+ T cells. **Conclusion:** Through single-cell analysis of liver FNAs, we observed pre-treatment differences in the intrahepatic milieu between adults with HBV/HIV coinfection and HBV monoinfection. A higher basal level of innate immune ISG and PD-1/PD-L1 signaling suggests possible unique mechanisms by which HIV coinfection accelerates HBV-related liver disease. This work also demonstrates the feasibility of FNA-based single-cell sequencing from remote sites.

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71 | A RHESUS MACAQUE MODEL OF HIV/HBV CO-INFECTION

Sreya Biswas, Savannah Lutz, Lauren N Rust, Conor McMahon, Sofiya Yusova, Spandana Naldiga, Miranda Fischer, Jeremy Smedley, Jonah B. Sacha and Benjamin J. Burwitz, Oregon Health & Science University

Background: HBV and HIV are both major global health concerns as HBV infects 296 million people while HIV infects 38 million individual's worldwide. HIV/HBV co-infection is common due to similar routes of transmission, with an estimated 10% of HIV-infected individual's also infected with HBV. HIV/HBV co-infected individual's progress to chronic HBV infection more frequently and exhibit reduced HBV-specific T cell responses, with a higher probability of extensive liver fibrosis and hepatocellular carcinomas. Thus, a greater understanding of the interplay between HIV and HBV infections is urgently needed to design strategies to prevent accelerated liver disease. Rhesus macaques (RM) are a well-established non-human primate model for HIV research, and we discovered recently that antibody-mediated CD4$^+$ T cell depletion in RM leads to long-term, high-titer HBV replication. In this study, we investigated the potential of inducing natural CD4$^+$ T cell depletion via SHIV$_{\text{DH12 Clone 7}}$ infection and using it to establish HIV/HBV co-infection in RM. **Methods:** Animals were intravenously infected with SHIV$_{\text{DH12 Clone 7}}$ (5x10^3 TCID$_{50}$) and then three weeks later challenged with HBV (genotype D, 1x10^{9} virions, i.v). Weekly blood draws were taken to monitor HBV and SHIV infection, and track CD4^{+} T cells and HBV surface antigens (HBsAg). Liver biopsies were obtained every four weeks to quantify HBV replication in the liver by quantitative PCR. Serum chemistries were run weekly to monitor metabolic changes in the liver associated with co-infection. **Results:** Preliminary studies showed successful CD4^{+} T cell depletion in two RM following SHIV infection. However, one RM controlled SHIV infection (Mamu-B*08^{+}) and CD4^{+} T cells returned concurrent with clearance of HBV. The second RM exhibited SHIV ($>10^{5}$ copies/ml) and HBV ($>10^{4}$ copies/ml) chronic co-infection (>24 weeks). HBV infection was validated by the presence of HBsAg and HBV DNA in the serum and HBV RNA in the liver. Based on the preliminary results, we repeated the study with nine additional animals and found that four exhibited a similar trend of co-infection. **Conclusion:** These results indicate that SHIV-mediated CD4^{+} T cell depletion helps sustain HBV infection. Thus, we show for the first time an HIV/HBV co-infection model in RM that can be beneficial for studies investigating pathogenesis associated with co-infection; which will be critical for the further development of this model.

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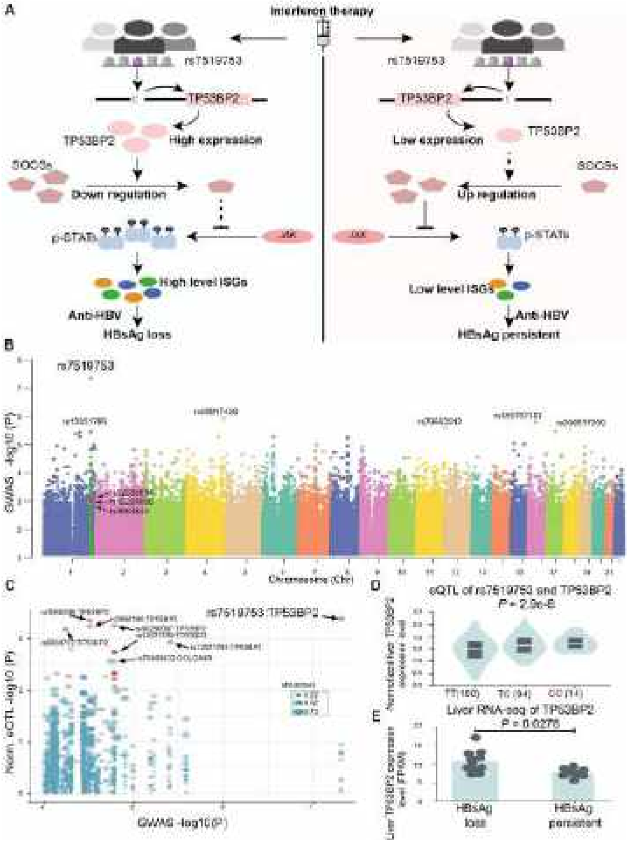
72 | TP53BP2 IS ASSOCIATED WITH HBsAg CLEARANCE IN PEGINTERFERON-ALFA-TREATED CHRONIC HEPATITIS B

Guiwen Guan[1], Xiangmei Chen[1] and Fengmin Lu[1,2], (1) Peking University, (2)Peking University People's Hospital

Background: Hepatitis B surface Antigen (HBsAg) loss occurs in a minor fraction of patients with Chronic Hepatitis B (CHB) under interferon therapy. Identifying the host factors critical for CHB cure can help recognize those who would benefit from interferon therapy. **Methods:** This study enrolled a total of 95 CHB patients, 48 achieved HBsAg loss under Peginterferon-alpha (Peg-IFN±) therapy while 47 did not. A Genome-Wide Association Study (GWAS) was conducted on these patients to pinpoint the host gene(s) contributing to HBsAg loss. We then validated the results in an additional cohort of 207 patients, 81 of whom achieved HBsAg loss. Expression Quantitative Trait Loci (eQTL) analyses, RNAseq analysis of liver biopsies from interferon-treated patients, and a series of in vivo and in vitro experiments using interferon treatment were then used to verify the functional involvement of the identified candidate gene. **Results:** The Single Nucleotide Polymorphism (SNP) rs7519753-C allele was found significantly associated with serum HBsAg loss in CHB patients undergoing Peg-IFN± treatment ($p = 4.85 * 10\text{-}8$, OR = 14.47). This association was consistently observed in the validation cohort, where the frequency of rs7519753-C genotype was significantly higher in the HBsAg loss group ($p = 0.008312$, OR = 1.64). RNA-seq analysis of liver biopsies from interferon-treated patients showed that the expression of TP53BP2 was significantly higher in the HBsAg loss group ($p < 0.05$). The population carrying the rs7519753 C allele had higher TP53BP2 expression in the liver ($p = 2.9 * 10\text{-}6$). Additional experiments demonstrated that TP53BP2 amplified the expression of Interferon-Stimulated Genes (ISGs) in the presence of interferon. Mechanistically, TP53BP2 could post-transcriptionally downregulate the expression of SOCS2, thus enhancing the antiviral activity of the JAK/STAT signaling pathway activated by interferon therapy. **Conclusion:** The SNP rs7519753-C allele correlates with a higher probability of serum HBsAg loss in CHB patients undergoing Peg-IFN± treatment and higher hepatic TP53BP2 expression. TP53BP2 can potentiate the hepatocyte response to IFN-± by inhibiting SOCS family gene expression. This suggests a pivotal role of TP53BP2 in predicting and enhancing interferon response in CHB patients.



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73 | CIRCULATING CLASSICAL MONOCYTE-DERIVED IL-1² PRODUCTION IS ASSOCIATED WITH THE REDUCTION OF SERUM HBsAg LEVELS IN CHRONIC HEPATITIS B

Satoshi Shigeno[1], Takahiro Kodama[2], Kazuhiro Murai[1], Akira Nishio[1], Hayato Hikita[1], Tomohide Tatsumi[1] and Tetsuo Takehara[2], (1)Osaka University, Graduate School of Medicine, (2)Osaka University Graduate School of Medicine

Background: Although nucleotide analogs (NA) prevent viral replication in chronic hepatitis B (CHB) patients, it rarely achieve HBsAg seroclearance. While the reduction of HBsAg levels is associated with HBsAg seroclearance, the factors regulating HBsAg levels are not well understood. To aim for "Functional Cure", we explored the host immunodynamics involved in the reduction of HBsAg levels. **Methods**: Among CHB patients (HBsAg > 1000 IU/mL before the NA treatment) treated with more than five years of NA treatment, we selected four patients whose HBsAg levels decreased below 100 IU/mL (declining group) and four patients whose HBsAg levels maintained above 1000 IU/mL (prolonged group). The peripheral blood mononuclear cells (PBMCs) from these patients, as well as three healthy controls, were sent for single-cell RNA sequencing (scRNAseq) targeting the 400 immune-related genes. PBMCs from additional 32 CHB patients (declining group: n = 24, prolonged group: n = 8) were used for the validation study. In vitro analysis was performed with HBV-expressing cell line HepG2/2.2.15. **Results**: The average duration of NA treatment for the eight CHB patients was 9.5 years, and there were no differences in clinical backgrounds including age, gender, type of NA treatment, or duration of treatment between the declining and prolonged groups. A total of 82,000 PBMCs were evaluated through scRNAseq and categorized into 10 immune cell clusters including $CD8^+$T cells, $CD4^+$T cells, NK cells, B cells, monocytes, and dendritic cells. Although the frequency of each cell population was not different between the declining and prolonged groups, analysis of the differentially expressed gene of each cluster revealed that the IL-1β expression levels of the $CD14^+CD16^-$ classical monocyte cluster were significantly higher in the declining group than those in the prolonged group. In the validation cohort, the IL-1β expression levels of the isolated circulating $CD14^+$ classical monocytes of the declining group were also significantly higher than those of the prolonged group. In vitro analysis, recombinant IL-1β treatment significantly decreased the HBsAg levels in the supernatant of HepG2/2.2.15 in a dose-dependent manner. **Conclusion**: In CHB patients, the differences in IL-1β production capacity in peripheral blood classical monocytes might be involved in the reduction of serum HBsAg levels during NA treatment.

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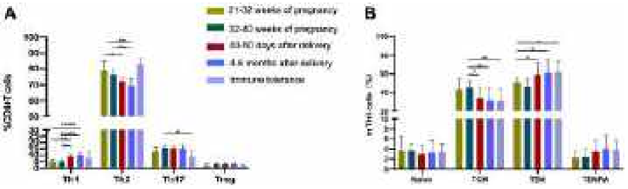
74 | DYNAMIC CHANGES OF T-CELL IMMUNITY IN WOMEN WITH CHRONIC HBV INFECTION DURING PREGNANCY AND POSTPARTUM AND ITS RELATIONSHIP WITH HBV INFECTION STATUS

Jinlin Hou[1], Yaohua Hao[1], Yunfei Gao[2], Yongyin Li[3], Yanchen Ma[1], Xiaoyi Liu[1], Meiting Huang[4], Xueru Yin[1] and Xuelian Zhang[1], (1)Nanfang Hospital, Southern Medical University, (2)Zengcheng Branch of Nanfang Hospital, Southern Medical University, (3)State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, (4)Huizhou Third People's Hospital

Background: The natural history and disease progression of hepatitis B virus (HBV) infection depend on the interaction between the immune system and the virus. Pregnancy, a special physiological process, can change the maternal immune status. For pregnant women with chronic HBV infection, it is still unclear how the maternal immune system changes during pregnancy and postpartum, and whether this change will lead to changes in HBV infection status and disease progression. In this study, we explored the dynamic changes of T-cell immunity in women with chronic HBV infection from pregnancy to postpartum and their correlation with virological markers and liver biochemical parameters. **Methods:** In this study, 24 HBeAg+ pregnant women with chronic HBV infection were enrolled and followed up from pregnancy to postpartum, and 12 HBeAg+ non-pregnant women in the stage of immunotolerance (IT) were included as control. We observed the dynamic changes of T cell phenotype and function, liver function, and virological markers during follow-up, and analyzed the correlation between parameters of T cell immunity and clinical laboratory. **Results:** By analyzing the dynamic change of T lymphocyte phenotype and function, we found that the frequency of Th1($CD4^+CXCR3^+CCR6^-$) subset was significantly lower during pregnancy than that after delivery($p = 0.000$). Conversely, the frequency of Th2 subset ($CD4^+CCR6^-CXCR3^-$) was significantly higher during pregnancy than that after delivery($p = 0.000$). However, Th17 ($CD4^+CXCR3^-CCR6^+$) frequency remained stable during pregnancy and postpartum ($p = 0.341$). In the analysis of differentiation stages of Th1 memory cells, we found that the central memory T cells (TCM) were dominant during pregnancy and effector memory T cells (TEM) were dominant after delivery. At 32-40 weeks of gestation, the ability of $CD4^+$T cells to secrete IL-17 was significantly higher than that of 40 days and 4-6 months after delivery ($p = 0.008$, $p = 0.009$). In addition, we found that Th1 frequency was negatively correlated with the level of HBeAg ($p = 0.045$, r = -0.442), and IL-17 was positively correlated with the level of ALT ($p = 0.043$, r = 0.647). **Conclusion:** T cell immunity experiences dynamic change from pregnancy to postpartum, with domination of anti-inflammatory reaction during pregnancy and domination of the pro-inflammatory reaction after delivery. Th1 subset is associated with immune clearance of HBV infection and liver inflammation.



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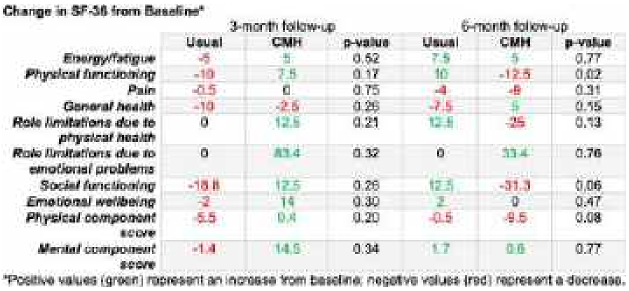
75 | THE CIRRHOSIS MEDICAL HOME: A PILOT RANDOMIZED TRIAL OF A COLLABORATIVE CARE MODEL FOR PATIENTS WITH DECOMPENSATED CIRRHOSIS

Eric S. Orman[1], Archita Parikh Desai[1], Noll Campbell[2], Nicole Fowler[1], Jake McCarty[1], Francis Pike[1], Naga P. Chalasani[3] and Malaz Boustani[1], (1)Indiana University, (2)Purdue University, (3)Indiana University Medical Center, Indianapolis, IN

Background: Patients with decompensated cirrhosis have poor quality of life and complex care needs that could be addressed with existing services; but the fragmented healthcare system does not provide the necessary coordination to best care for this population. Collaborative care models (CCM) can bridge this gap by providing coordinated, personalized care using care coordinators. In this pilot randomized trial, we developed and tested a CCM for cirrhosis: The Cirrhosis Medical Home (CMH). **Methods:** We randomized 40 hospitalized patients with decompensated cirrhosis and poor quality of life (SF-36 physical and/or mental component score < 40) to receive care through the CMH or usual care in a 1:1 ratio for 6 months following hospital discharge. In the CMH, a nurse coordinator, supported by an interdisciplinary clinical team, provides personalized protocol-driven care guided by dynamic feedback measures. Quality of life (SF-36) and mortality were compared at 3 and 6 months after enrollment. **Results:** The median age was 58, 70% were female, and 95% were White. 74% had Medicare or Medicaid insurance, 21% were employed, and 20% were discharged to a healthcare facility. The median MELD-Na was 24. Median baseline SF-36 domains ranged from 0 (role limitations) to 56 (emotional wellbeing), and median physical and mental component scores were 25.9 and 40, respectively. After 3 months, 13 patients (32.5%) died or enrolled in hospice (7 usual care and 6 CMH; p = 0.74), 4 (10%) underwent liver transplant (2 each), and 12 (30%) provided follow-up patient-reported outcomes (PROs). At 3 months, patients in the CMH had increases in all but one SF-36 domain; patients in usual care had decreases in all but two (Table). None of the differences were statistically significant. After 6 months, an additional 5 patients died (total 11 usual care and 7 CMH; 45% overall, $p = 0.20$), and 8 (20%) provided PROs. At 6 months, physical functioning increased in the usual care arm and decreased in the CMH arm ($p = 0.02$, Table). The remaining differences were not significant. **Conclusion:** Hospitalized patients with decompensated cirrhosis and poor quality of life have high short-term mortality, which may limit the impact of collaborative care interventions focused on improving PROs. Future transitional care interventions may have more impact by triaging those at lower risk of short-term mortality to interventions like the CMH while linking those at higher risk to high quality palliative care services.



Change in SF-36 from Baseline*

	3-month follow-up			6-month follow-up		
	Usual	CMH	p-value	Usual	CMH	p-value
Energy/fatigue	-5	5	0.52	7.5	5	0.77
Physical functioning	-10	7.5	0.17	10	-12.5	0.02
Pain	-0.5	0	0.75	-4	-8	0.31
General health	-10	-2.5	0.26	-7.5	5	0.15
Role limitations due to physical health	0	12.5	0.21	12.5	-25	0.13
Role limitations due to emotional problems	0	83.4	0.32	0	33.4	0.76
Social functioning	-18.8	12.5	0.26	12.5	-31.3	0.06
Emotional wellbeing	-2	14	0.30	2	0	0.47
Physical component score	-5.5	0.4	0.20	-0.5	-9.5	0.08
Mental component score	-1.4	14.5	0.34	1.7	0.6	0.77

*Positive values (green) represent an increase from baseline; negative values (red) represent a decrease.

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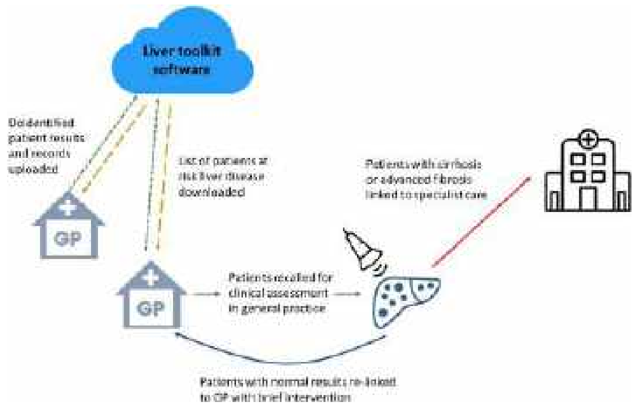
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

76 | THE LIVER TOOLKIT – AN INNOVATIVE INFORMATION TECHONOLOGY SOLUTION TO SCREEN PATIENTS IN GENERAL PRACTICE FOR UNDIAGNOSED CIRRHOSIS★

David S. Prince[1,2,3], Shakira Hoque[4], Christy Kim[4], Salim Maher[1,4], Nathan McGarry[4], Jane Miller[5], Phoebe Chomely[5], Janice Pritchard-Jones[1], Sally Spruce[1], Ken Liu[1,2], Simone I. Strasser[1], Brendan Goodger[5], Amany Zekry[4] and Geoffrey McCaughan[1,2], (1)Royal Prince Alfred Hospital, (2)Centenary Institute, (3)Liverpool Hospital, (4)St George Hospital, (5)Central and Eastern Sydney Primary Health Network

Background: Detecting patients with undiagnosed chronic liver disease is a public health challenge. Patients with advanced fibrosis or compensated cirrhosis have much better outcomes than those with decompensated disease and may be eligible for interventions to prevent disease progression **Methods:** A cloud-based software solution ('the liver toolkit') was developed to access primary care practice software to identify patients at risk of advanced chronic liver disease (ACLD). Clinical history and pathology results were extracted to calculate Aspartate aminotransferase to Platelet Ratio (APRI) and Fibrosis 4 (FIB-4) scores. Patients with elevated scores (APRI e 1.0 and FIB-4 e 3.25) or other risk factors of liver disease were recalled for assessment including transient elastography (TE) **Results:** Existing pathology results of more than 32,000 adults across nine general practices were assessed to identified 703 patients at high risk of ACLD (2.2% of the cohort). Patients with an existing diagnosis of cirrhosis were excluded. 179 patients (26%) were successfully recalled and 23 (13%) were identified to have advanced fibrosis or cirrhosis (Liver stiffness measure (LSM) e 10.0 kPa)(10% indeterminate results, 25% early fibrosis, 52% normal). In almost all cases the diagnosis of liver disease was new with the most common aetiology being non-alcoholic fatty liver disease (n = 20, 83%). The liver toolkit was better at detecting patients who required further assessment in secondary care than direct general practitioner referral to the team (22.9% vs 3.6%, *p* = 0.021). APRI e 1.0 and FIB-4 e 3.25 had a positive predictive value for detecting advanced fibrosis or cirrhosis of 20% and 24% respectively. Patients who did not attend recall had markers of more severe disease with a higher median APRI score (0.46 vs 0.57, *p* = 0.041). **Conclusion:** This novel information technology system successfully screened a large primary care cohort using existing pathology results to identity patients at increased risk of advanced chronic liver disease. More than one in five patients recalled were found to have liver disease needing ongoing specialist follow up.


Liver toolkit software
Deidentified patient results and records uploaded
List of patients at risk liver disease downloaded
Patients with cirrhosis or advanced fibrosis linked to specialist care
GP
GP
Patients recalled for clinical assessment in general practice
Patients with normal results re-linked to GP with brief intervention

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Disclosure information not available at the time of publication: Shakira Hoque, Christy Kim, Salim Maher, Nathan McGarry, Jane Miller, Phoebe Chomely, Janice Pritchard-Jones, Sally Spruce, Ken Liu, Simone I. Strasser, Brendan Goodger, Amany Zekry

77 | HEAR-MHE: POINT-OF-CARE ANALYSIS OF RECORDED SPEECH AS A NOVEL METHOD TO DETECT HEPATIC ENCEPHALOPATHY

Patricia Pringle Bloom[1], Caitlyn Fisher[1], Nazokat Otajonova[2], Luis Garrido-Treviño[3], Aran Farrell[2], Jessica Robin[4], Sumeet Asrani[3] and Anna Lok[5], (1) University of Michigan, (2)Baylor, (3)Baylor University Medical Center, Dallas, TX, (4)Winterlight Labs, (5) University of Michigan Medical Center

Background: Variation in speech may be an early sign of minimal hepatic encephalopathy (MHE) or future overt HE (OHE). Though a battery of tests is available for MHE assessment, these are cumbersome and rarely used in clinical practice. In a prospective study, we evaluated the ability of speech recorded at home or in the office to correlate with validated HE assessments in patients of diverse backgrounds. **Methods**: In a prospective study ("HE Audio Recording to Detect MHE" or HEAR-MHE), we enrolled 212 patients (169 cirrhosis and 43 non-cirrhosis controls) from two geographically disparate centers. Patients underwent psychometric HE score (PHES; validated test to diagnose MHE), animal naming test, and audio recording while reading a paragraph. Speech variables (acoustic, lexical, and syntactic) were automatically extracted from recordings via the Winterlight Labs Smartphone analysis platform, an app initially designed to characterize speech in dementia, and immediately transmitted data to the research team via a secure server. Patients with cirrhosis were in 3 non-overlapping categories: (1) prior OHE + HE treatment, (2) MHE with no prior OHE (diagnosed by PHES d -4), (3) no MHE or prior OHE. T-tests compared continuous

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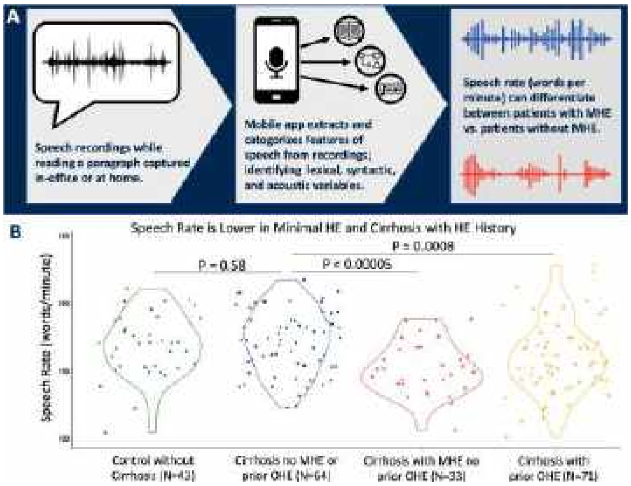
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

variables, Pearson correlation correlated continuous variables, and Vuong's test compared AUCs of different models. **Results:** Cirrhosis: median 63 years (IQR 55, 68), 52% male, median MELD 9 (IQR 7, 12), 39% alcohol and 33% fatty liver. Controls: median 55 years (IQR 42, 62), 56% male, and 58% had fatty liver disease and 16% viral hepatitis. Office Audio: Audio recordings were median 36 seconds (IQR 33, 41). Speech rate was significantly slower in patients with MHE (152 words/min) and history of OHE (155 words/min) as compared to either no MHE or controls (169 and 172 words/min; Figure). Prediction of MHE using speech rate was comparable to the animal naming test (AUC 0.73 vs 0.66, $p = 0.12$) Home Audio: Patients performed 43 audio recordings with personal Smartphone apps. 23/225 (10%) speech variables were significantly correlated (< 0.05) between home and office recordings, despite recordings on different days. Speech rate at home was highly correlated to that in the office ($r = 0.53$, $p < 0.01$) and PHES score in office ($r = 0.71$, $p < 0.01$). Speech rate findings were similar regardless of site ($p = 0.44$) or patient region of origin ($p = 0.30$), in the whole cohort or within patient sub-groups. **Conclusion:** Brief audio recordings through a Smartphone app either at home or office may help identify patients with MHE and perform as well as traditional HE tests. Speech data can be reliably obtained at home or in the office and is not adversely impacted by accent. Automated speech analysis through Smartphone apps is a promising novel method to identify high risk patients at risk for future complications of decompensated cirrhosis.



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Anna Lok – Abbott: Consultant, Yes, No; Chroma: Consultant, No, No; Enochian: Advisor, No, Yes; GlaxoSmithKline: Consultant, No, No; Roche: Consultant, Yes, No; TARGET: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; TARGET: Advisor, No, No; Virion: Consultant, No, No;
The following people have nothing to disclose: Nazokat Otajonova, Luis Garrido-Treviño, Sumeet Asrani
Disclosure information not available at the time of publication: Caitlyn Fisher, Aran Farrell, Jessica Robin

78 | PREOPERATIVE HEPATOLOGY AND PRIMARY CARE VISITS ARE ASSOCIATED WITH REDUCED POSTOPERATIVE MORTALITY IN PATIENTS WITH CIRRHOSIS UNDERGOING SURGERY: A VETERANS AFFAIRS PROPENSITY MATCHED STUDY

Bachir Ghandour[1], Elliot B. Tapper[2], Marina Serper[1,3,4,5] and Nadim Mahmud[1,4,5,6], (1)Hospital of the University of Pennsylvania, (2)University of Michigan, (3)University of Pennsylvania, Philadelphia, PA, United States, (4)Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, (5)University of Pennsylvania Perelman School of Medicine, (6) University of Pennsylvania

Background: Patients with cirrhosis have increased surgical risk compared to the general population. Preoperative optimization by nonsurgical clinicians improves postoperative outcomes after colectomy in studies of patients with major comorbidities, however, data specific to patients with cirrhosis and addressing more diverse surgeries are limited. This study aimed to assess the impact of preoperative primary care provider (PCP) and/or gastroenterology/hepatology (GI/Hep) visits on postoperative mortality in patients with cirrhosis undergoing surgery. **Methods:** This was a retrospective cohort study of patients with cirrhosis in the Veterans Health Administration who underwent surgery between 1/2008 and 12/2022. We compared patients with preoperative PCP and/or GI/Hep appointments in the 60 days prior to the surgery with a propensity score (PS) matched group without preoperative appointments. Groups were matched for baseline age, sex, race/ethnicity, liver disease etiology, surgery type (e.g. abdominal wall, major abdominal, orthopedic, etc.), Child-Turcotte-Pugh Score, MELD-Na, and medical comorbidities. We then used Cox regression (CR) and Fine and Gray competing risk (FGCR, transplant as competing event) regression to evaluate the association between preoperative outpatient visit type and postoperative mortality at 6 months. **Results:** We compared 1992 patients with cirrhosis who had preoperative PCP/

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

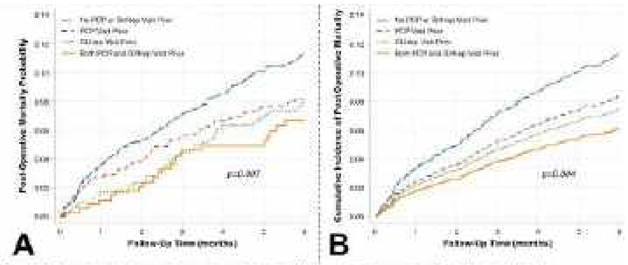

Figure 1: Association between Preoperative Outpatient Visits and Post-operative Mortality in (A) Kaplan-Meier and (B) Competing Risk Analyses in the Propensity Matched Cohort

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Nadim Mahmud – Grifols: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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

Neehar Dilip Parikh[1], *Patricia D. Jones*[2], *Reena J. Salgia*[3], *Irun Bhan*[4], *Lauren T. Grinspan*[5], *Janice Jou*[6], *Kali Zhou*[7], *Prasun Jalal*[8], *Giorgio A. Roccaro*[9], *Amol S. Rangnekar*[10], *Jihane N. Benhammou*[11], *Anna Mae Diehl*[12], *Neil Mehta*[13], *Joel P. Wedd*[14], *Ju Dong Yang*[15], *Amy K. Kim*[16], *Andres Duarte-Rojo*[17], *Omobonike Oloruntoba*[18], *Amit D. Tevar*[19], *Jennifer S. Au*[20], *Yamile Blain*[21], *Sanjana Rao*[22], *Felipe Furtado*[23], *Onofrio Catalano*[23], *Sara Lewis*[5], *Mishal Mendiratta-Lala*[24], *Kevin King*[25], *Lekha Sachdev*[26], *Edward Wolfgang Lee*[27], *Jill Bruno*[28], *Ihab Kamel*[29], *Celestina Tolosa*[29], *Karissa D Kao*[1], *Ihab Badawi*[30], *Eric Przybyszewski*[23], *Lisa Quirk*[31], *Piyush Nathani*[32], *Brandy Haydel*[33], *Nicole Wong*[6], *Robert Albertian*[34], *Ariana Chen*[1], *Fuad Zain Aloor*[8], *Ahmed Elkheshen*[8], *Charles Marvil*[9], *Aaron Issac*[9], *Joseph Clinton*[10], *Stephanie M Woo*[10], *Jung Yum*[27], *Erin Rieger*[35], *Alan Hutchison*[36], *Alan Turner*[28], *Manaf Alsudaney*[15], *Perla Hernandez*[15], *Ziyi Xu*[16], *Abdullah Khalid*[37], *Bethany Barrick*[37], *Bo Wang*[38], *Elliot B. Tapper*[24], *Wei Hao*[38] and *Amit G. Singal*[31], *(1)University of Michigan, (2)University of Miami Miller School of Medicine, (3)Henry Ford Health, (4)Massachusetts General Hospital and Harvard Medical School, (5)Icahn School of Medicine at Mount Sinai, (6)Oregon Health & Science University, (7)University of Southern California, Los Angeles, CA, (8)Baylor College of Medicine, (9)Emory University School of Medicine, (10)Medstar Georgetown University Hospital, (11)University of California, Los Angeles, Los Angeles, CA, (12)University of Chicago, (13)University of California, San Francisco, (14)Virginia Commonwealth University, (15)Cedars-Sinai Medical Center, Los Angeles, CA, (16)Johns Hopkins University School of Medicine, (17)Northwestern University Feinberg Scho, (18)Duke University, (19)University of Pittsburgh, (20)Scripps Clinic, (21)University of Miami, (22)University of Miami/Jackson Health System, (23)Massachusetts General Hospital, (24)University of Michigan Medical Center, (25)The David Geffen School of Medicine at UCLA, (26)Georgetown University, (27)University of California, Los Angeles, (28)Virginia Commonwealth University Health System, (29)Johns Hopkins University, (30)Henry Ford Health System, (31)University of Texas Southwestern Medical Center, (32)University of Texas Southwestern, (33)Mount Sinai Recanati/Miller Transplantation Institute, (34)University of Southern California, (35)Columbia University, New York, NY, (36)The University of Chicago, Chicago, IL, (37)Scripps Health, (38)University of Michigan School of Public Health*

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

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

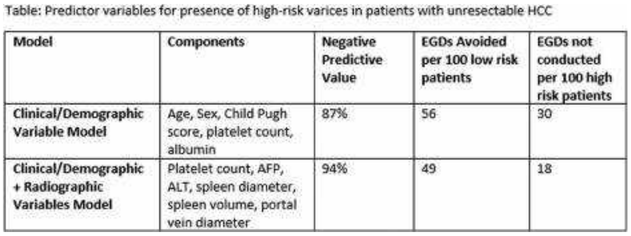

Table: Predictor variables for presence of high-risk varices in patients with unresectable HCC

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

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Anna Mae Diehl – Exelixis: Advisor, No, No; AstraZeneca: Advisor, No, No; Genentech: Advisor, No, No; Replimune: Advisor, No, No; Eisai Inc: Advisor, No, No;

Ju Dong Yang – AstraZeneca: Consultant, No, No; Eisai: Consultant, No, No; Exact Sciences: Consultant, No, No; Exelixis: Consultant, No, No; Fujifilm Medical Sciences: Consultant, No, No; Merck: Consultant, No, No;

Andres Duarte-Rojo – Echosens: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Mallinckrodt: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Axcella, Inc: Consultant, No, Yes; Axcella, Inc: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;

Amit G. Singal – Genentech: Consultant, No, No; AstraZeneca: Consultant, No, No; Bayer: Consultant, No, No; Eisai: Consultant, No, No; Exelixis: Consultant, No, No; Boston Scientific: Consultant, No, No; Gycotest: Consultant, No, No; Exact Sciences: Consultant, No, No; Roche: Consultant, No, No; FujiFilm Medical Sciences: Consultant, No, No; GRAIL, LLC: Consultant, Yes, No; Freenome: Consultant, No, No; Histosonics: Consultant, No, No;

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80 | DECISION-ANALYTIC MODEL TO PROJECT THE BENEFIT OF TERLIPRESSIN TREATMENT AMONG PATIENTS WITH ALCOHOL-RELATED CIRRHOSIS AND HRS

Khalid Mumtaz[1], Nikolaos T. Pyrsopoulos[2], Thomas M. Leventhal[3], Nyingi Kemmer[4], K. Gautham Reddy[5], Xingyue Huang[6] and Khurram Jamil[6], (1)The Ohio State University, Wexner Medical Center, (2)Rutgers University, Newark, NJ, (3)University of Minnesota, (4) Tampa General Hospital, (5)University of Chicago Medical Center, (6)Mallinckrodt Pharmaceuticals, Bridgewater, NJ

Background: Alcohol-related liver disease is a major cause of liver cirrhosis and has recently emerged as the most common indication for liver transplantation. Hepatorenal syndrome (HRS)—a rapidly progressive renal failure—is a fatal complication of decompensated cirrhosis with ascites. The FDA-approved vasopressin analogue, terlipressin (terli)—in combination with albumin—is recommended to treat patients (pts) with HRS-acute kidney injury (AKI). Terli also demonstrated efficacy in the subpopulation of pts with alcohol-related hepatitis. Based on the Premier Healthcare Database, the annualized estimate of HRS cases in 2021 was over 60,000 pts; approximately 60% of HRS cases were alcohol-related. In the pooled population of 3 Phase III North American, randomized, placebo (pbo)-controlled trials (NA RCTs) of terli in pts with HRS, cirrhosis had an alcohol-related etiology in 59.5% of pts. This study estimated the benefits of terli in adult pts with HRS and alcohol-related cirrhosis (AC) in real-world practice. **Methods:** A decision-analytic approach was used to create a model based on the US annual projection for HRS and AKI using data from the Premier Healthcare Database on the prevalence of an alcohol-related HRS diagnosis among hospitalized pts and the efficacy of terli vs pbo—including HRS reversal—reported in the 3 NA RCTs (OT-0401, REVERSE, and CONFIRM). Under the assumption that 80% of pts with HRS and AC would meet the FDA label criteria for terli (ie, pts with serum creatinine < 5 mg/dL, acute-on-chronic liver failure grade 0–2), the model projected additional responses (ie, HRS reversal), reduction in intensive care unit (ICU) stay duration, reduction in the need for renal replacement therapy (RRT), and an increase in transplant-free survival. **Results:** Using the estimate of 50,000 cases of HRS-AKI per year in the US, 60% of HRS-AKI cases with AC, and 80% of those pts meeting the label criteria, the model resulted in 24,000 pts with HRS-AKI and AC who would be eligible for terli treatment. The estimated outcomes are summarized in Table. **Conclusion:** Model estimates using terli (vs pbo) in pts with HRS and AC projected a substantial annual improvement in HRS reversal and remaining alive and transplant-free, and a reduction in RRT and duration of ICU stay. These projected benefits may result in improved outcomes and decreased cost of care among pts with HRS and AC who are treated with terli.

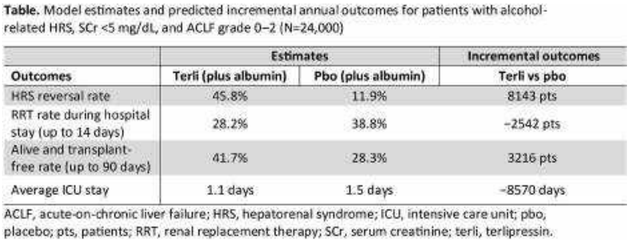

Table. Model estimates and predicted incremental annual outcomes for patients with alcohol-related HRS, SCr <5 mg/dL, and ACLF grade 0–2 (N=24,000)

	Estimates		Incremental outcomes
Outcomes	Terli (plus albumin)	Pbo (plus albumin)	Terli vs pbo
HRS reversal rate	45.8%	11.9%	8143 pts
RRT rate during hospital stay (up to 14 days)	28.2%	38.8%	−2542 pts
Alive and transplant-free rate (up to 90 days)	41.7%	28.3%	3216 pts
Average ICU stay	1.1 days	1.5 days	−8570 days

ACLF, acute-on-chronic liver failure; HRS, hepatorenal syndrome; ICU, intensive care unit; pbo, placebo; pts, patients; RRT, renal replacement therapy; SCr, serum creatinine; terli, terlipressin.

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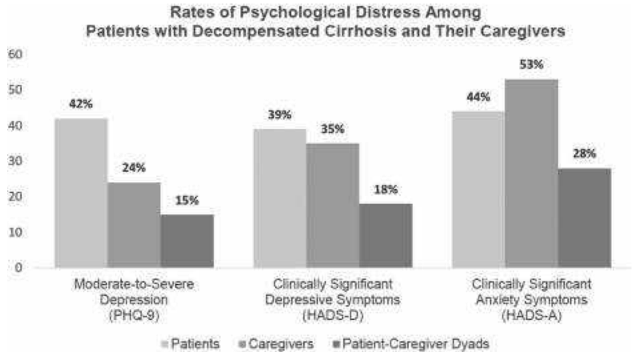
Xingyue Huang – Mallinckrodt Pharmaceuticals: Employee, Yes, No;
Khurram Jamil – Mallinckrodt Pharmaceuticals: Employee, Yes, No;
The following people have nothing to disclose: Khalid Mumtaz, Thomas M. Leventhal, Nyingi Kemmer, K. Gautham Reddy

81 | PSYCHOLOGICAL DISTRESS AMONG PATIENTS WITH DECOMPENSATED CIRRHOSIS AND THEIR FAMILY CAREGIVERS

Nneka Ufere[1], Lucinda Li[1], John Donlan[2], Teresa Indriolo[1], Joyce Zhou[1], Alyson Kaplan[3], Alan Noll[4], *Nathan Alhalel[5], Nancy Mason[1], Michaela Rowland[1], Kirsten Engel[1], Jennifer C. Lai[6], Maria Edelen[7], Chengbo Zeng[7], Kedie Pintro[1], Nora Horick[1] and Areej El-Jawahri[1], (1)Massachusetts General Hospital, (2)Harvard Medical School, (3)New York-Presbyterian/Weill Cornell Medical Center, (4)University of Pittsburgh Medical Center, (5)University of California, San Francisco, (6)University of California-San Francisco, San Francisco, CA, (7)Brigham and Women's Hospital*

Background: Patients with decompensated cirrhosis (DC) often experience high psychological symptom burden. Family caregivers of patients with DC are at risk for psychological distress. **Methods:** We conducted a cross-sectional study in which outpatients with DC and their caregivers completed assessments of depression severity (Patient Health Questionnaire 9, (PHQ-9) e 10 indicate moderate-to-severe depression; Hospital Anxiety and Depression Scale (HADS-D)), and anxiety symptoms (Hospital Anxiety and Depression Scale, HADS-A). Scores > 7 on HADS-A and HADS-D indicate clinically significant anxiety and depressive symptoms, respectively. Caregivers also completed the Zarit Burden Index 12 (ZBI-12 e 12 indicate caregiving burden and > 20 indicate high burden). To analyze patient-caregiver dyads, we used paired sample *t* tests and McNemar's tests for continuous and categorical variables, respectively. **Results:** Between July 2018 and September 2022 we prospectively enrolled 218 out of 330 (66%) patients with DC (mean age 57.5 [SD 10.2], median MELD-Na 16 [IQR 11-22]) and 127 caregivers (mean age 57.1 [SD 13.3], 63% spouses). Among patients, 42% had moderate-to-severe depression severity based on PHQ-9, and 39% and 44% had clinically significant depressive and anxiety symptoms based on HADS-D and HADS-A, respectively. Among caregivers, 67% screened positive for caregiving burden and 28% reported high caregiving burden. 24% had moderate-to-severe depression severity, and 35% and 53% had clinically significant depressive and anxiety symptoms, respectively. Among the 127 patient-caregiver dyads, patients reported significantly higher PHQ-9 ($M_{diff=}$ 3.0, $p < 0.001$) and HADS-D ($M_{diff=}$ 1.3, $p = 0.002$) scores compared to their caregivers. There was no difference between patients and caregivers on HADS-A (M_{diff} = -0.7, $p = 0.16$). Among patient-caregiver dyads, both patients and caregivers reported moderate-to-severe depression and clinically significant depressive and anxiety symptoms in 15%, 18%, and 28% of dyads, respectively. **Conclusion:** In this cohort study, patients with DC and their caregivers reported high rates of psychological distress and caregiving burden. Among patient-caregiver dyads, nearly 1 in 6 reported moderate-to-severe depression and over 1 in 4 reported clinically significant anxiety symptoms. These results underscore the critical need to develop supportive care interventions to reduce psychological distress in both patients with DC and their caregivers.



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82 | CRITICAL GAPS AND DISPARITIES IN GUIDELINE-RECOMMENDED ALBUMIN USE FOR SPONTANEOUS BACTERIAL PERITONITIS: A NATIONAL COHORT STUDY

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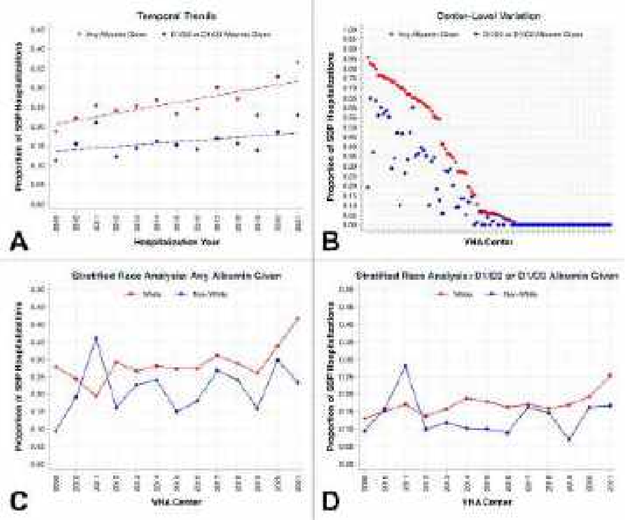
Background: Albumin reduces mortality in spontaneous bacterial peritonitis (SBP) and is recommended by national guidelines. However, gaps and potential disparities in standard of care are not well-studied in large cohorts. We investigated temporal trends, center-level variation, and racial disparities in guideline-recommended albumin use for patients hospitalized with SBP in a large national cohort of Veterans with cirrhosis (VOCAL). **Methods:** This was a retrospective cohort study of SBP hospitalizations from 2009-2021. SBP admission diagnosis was manually validated and defined as: an inpatient SBP diagnosis code in the presence of e 1 paracentesis and hospital stay > 2 days (positive predictive value 91%). Demographic and clinical variables including comorbidities, laboratory data, and liver disease severity were abstracted. Albumin administration was collected from inpatient (BCMA) tables; hospitalizations were classified as any albumin, guideline-recommended albumin (day 1+2 or day 1+3), no albumin. Temporal trends were evaluated using linear regression. Center-level variation was explored among the 92 centers with at least 10 SBP hospitalizations. Stratified analysis was performed by white vs. non-white race. **Results:** We identified 3742 SBP hospitalizations; 35% had Child Turcotte Pugh (CTP)-A cirrhosis, 57% CTP-B, and 8.6% CTP-C. The median MELD-Na on admission was 18 (IQR 23-33). Only 988 (26%) received any albumin; of whom 588 (60%) received guideline-recommended albumin. The proportion of patients receiving any albumin increased over time (beta 0.009, $p = 0.003$; Figure 1A); guideline-recommended albumin use numerically increased but was not statistically significant (beta 0.004, $p = 0.12$). There was substantial center-level variability in albumin administration (Figure 1B); 36 centers (39%) did not administer any albumin for patients hospitalized with SBP. Finally, we identified racial differences in albumin use (Figure 1C/D); white patients had a 7% higher probability of receiving any albumin versus non-white patients (beta 0.070, $p = 0.005$). **Conclusion:** A large proportion of VA patients hospitalized with SBP did not receive albumin. While utilization has increased over time, there is substantial center-level variability. Furthermore, white patients were consistently more likely than non-white patients to receive albumin. Additional research is needed to elucidate drivers of these observed disparities, and quality improvement efforts such as clinical decision support should prompt albumin use once SBP is diagnosed.



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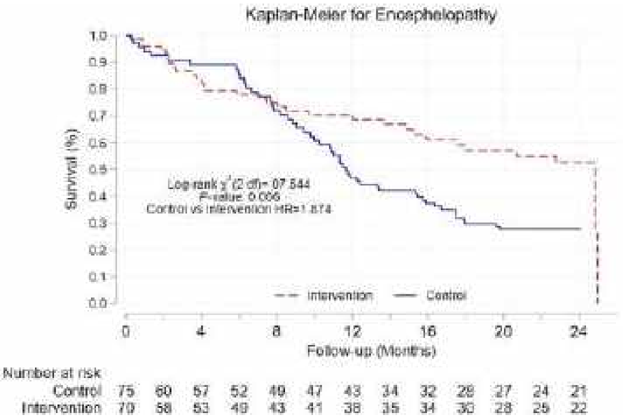
83 | NURSE CARE COORDINATION IN CHRONIC LIVER FAILURE REDUCES READMISSIONS FROM HEPATIC ENCEPHALOPATHY AND IMPROVES QUALITY OF CARE; RESULTS FROM THE MULTICENTRE RANDOMIZED CONTROLLED ALFIE TRIAL

Alan J Wigg[1,2], *Sumudu Narayana*[1], *Peter D Rose*[1], *Richard J Woodman*[2] *and ALFIE investigator group, (1) Southern Adelaide Local Health Network, (2)Flinders University*

Background: Emergency admissions related to chronic liver failure (CLF) are common, expensive and associated with frequent readmission. There are no multicenter randomized controlled trials (RCT) investigating models to reduce liver-related emergency admissions (LREA). The primary aim of the Australian Liver Failure (ALFIE) trial was, therefore, to assess the efficacy of a nurse coordination model of care to reduce LREAs. **Methods:** The study was a multicenter RCT occurring between 2018 and 2022. Patients were recruited following an inpatient admission with a CLF complication. The intervention at each site was a multifaceted care coordination model involving a nurse. Key components included intensive post-discharge monitoring (weekly phone calls for a minimum of 3 mo), rapid access to care pathway, enhanced patient and carer education and self-management support. The intervention was applied continuously for the duration of the trial. Secondary aims were to assess the effects of this model on other measures of hospital usage, mortality, patient-reported outcomes and quality of care. **Results:** 146 patients (75 Intervention group, 71 Control group) were recruited. The combined cohort had the following characteristics: mean age 54.9 years, 68% male, median MELD score 19.0 and median Child-Pugh score 9.0. The main causes of CLF were alcohol (68%), MAFLD (16%) and HCV (11%). The median (IQR) follow-up time for individual's in the Intervention and Control groups was 2.0 years. For the primary endpoint, LREA, there was a non-significant 11% reduction in LREA for the Intervention group vs. Control group (IRR 0.89, 95% CI 0.53-1.50, $p = 0.666$). Improvement trends were also seen for the Intervention group for ICU admissions (IRR = 0.62 $p = 0.491$), 7-day readmissions (IRR = 0.72, $p = 0.62$), and length of stay (IRR = 0.86, $p = 0.56$). The leading causes of LREAs were ascites (43%), encephalopathy (22%) and variceal bleeding (11%). There was an increased risk of LREA due to encephalopathy in the Control vs. Intervention group (Hazard ratio = 1.87, 95% CI = 1.18-2.96, $p = 0.007$); see Figure. There were no significant differences observed between groups for actuarial survival, or quality-of-life measures (CLDQ, EQ5D-5L utility, EQ-5D-VAS, QALY gains). All quality-of-care measures were improved in the Intervention group with significant improvement for HCC surveillance adherence ($p = 0.05$), performance of bone density ($p = < 0.001$) and vitamin D testing ($p = < 0.001$). **Conclusion:** This care coordination model showed benefits for CLF patients, particularly for reductions in LREA due to encephalopathy and improved quality of care. Further studies are needed to define this intervention model's optimal components, patient groups and settings. Further studies examining model cost-effectiveness and qualitative experiences of patients and care providers are in progress.



Disclosures: Alan J Wigg – Astra Zeneca: Speaking and Teaching, No, Yes;

The following people have nothing to disclose: Sumudu Narayana, Peter D Rose, Richard J Woodman

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

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

Background: AASLD and EASL guidelines recommend all people with cirrhosis undergo twice yearly screening for hepatocellular carcinoma (HCC) with hepatic imaging. However, patient, provider, and system level barriers impede ongoing surveillance efforts. This stepped-wedge hybrid effectiveness-implementation trial assessed the impacts of using a quality improvement playbook called Getting to Implementation (GTI) to support VA facilities to select, implement, and evaluate data-driven strategies to improve HCC surveillance. **Methods:** This hybrid type III (implementation-effectiveness) stepped-wedge cluster randomized design was conducted at 12 VA sites between October 2020 and April 2023. We used a multi-faceted facilitation strategy consisting of manualized GTI during a 12-month active implementation and six-month sustainment period. The primary implementation outcome was GTI completion and strategy implementation. The secondary clinical outcome was receipt of guideline-concordant HCC surveillance at baseline, post-intervention, and sustainment. Analysis involved a three-level, generalized linear mixed model. **Results:** Of 12 VA facilities, selected based on having low baseline HCC surveillance rates, 10 completed GTI with high fidelity. These 10 sites implemented a median of four implementation strategies while receiving an average of 19 ± 5 facilitation hours. HCC surveillance improved from 21% at baseline to 30% during intervention and remained elevated at 32% during sustainment. Sites receiving more facilitation ($r = 0.59$, $p = 0.048$) and sites implementing a greater variety of strategies had higher HCC surveillance improvement. Generalized linear mixed models indicated significant changes in HCC surveillance during both implementation (aOR = 1.306; 95% CI: [1.159, 1.472], $p < 0.0001$) and sustainment (aOR versus control = 1.511; 95% CI: [1.315, 1.73], p-value < 0.0001). Sustainment, a challenge for implementation trials, was significantly associated with improvement in HCC surveillance compared with active implementation (aOR = 1.168; 95% CI: [1.018, 1.340], p-value 0.0271). **Conclusion:** Data-driven strategies with facilitated quality improvement sustainably improved HCC surveillance in Veterans with cirrhosis receiving care in the lowest-performing VA facilities. Further research is needed to understand the heterogenous effects across sites, which may have been driven by differences in site baseline characteristics and facilitation and strategy implementation nuances.

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

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

Background: Providers at community hospitals often seek to transfer hospitalized patients with advanced liver disease to tertiary/quaternary care hospitals for further management due to lack of expertise in caring for these patients. However, it is possible to co-manage such patients at local hospitals by providing virtual consultation by tertiary care hepatologists via inpatient telehepatology (INP-TH) consultation. We aimed to describe demographics, liver disease severity, and related outcomes such as transfer rate, subsequent outpatient follow-up, readmission rate, and 30-day mortality. **Methods:** Indiana University Health (IUH) is a 16-hospital integrated health system with a single adult academic health center (AAHC) with concentrated hepatology expertise and a liver transplant program. We established a pilot INP-TH team led by a Hepatologist, an Advanced Practice Provider, and a Medical Assistant in July 2022 to co-manage hospitalized patients with advanced liver disease at an affiliated IUH community hospital. In this model, providers caring at the community IUH hospital request a telemedicine consultation from INP-TH team in lieu of a hospital transfer. American Well platform embedded with Cerner's electronic health record (EHR) with a patient facing Apple iPad was utilized for the current study. **Results:** A total of 81 INP-TH consultations were provided, with only 9 (11%) patients requiring a transfer to the AAHC. Of these 81 consultations, 66 consultations on 61 unique patients had outcomes data with greater than 30-day follow-up. The median age was 60 (range: 19-80) years with 65% having a diagnosis of cirrhosis. At the time of INP-TH consult, 80% had signs of liver decompensation with MELD 21 ± 7; 83% had MELD e 15. The more common etiologies of liver disease included alcohol associated liver disease (30%) and non-alcoholic fatty liver disease (29%). The duration of hospitalization was 9.2 ± 8.3 days with duration of stay 3.2 ± 3.9 days prior to INP-TH consultation. There were 20 (30%) patients requiring readmission. Thirty (45%) patients who were not transferred were seen in the outpatient setting at AAHC within 30 days. In 61 patients with 30-day post-discharge follow-up, there were 7 (11%) deaths (1 transferred and 6 non-transferred) with 61% deaths occurring inpatient. **Conclusion:** This proof-of-principle study shows that a telemedicine consultation service by tertiary care hepatologists is feasible to co-manage patients with advanced liver disease hospitalized to a community hospital within an integrated healthcare system. Hospital to hospital transfers can be dramatically minimized but a comprehensive evaluation of provider, patient, and caregiver with satisfaction surveys along with patient outcomes is necessary.

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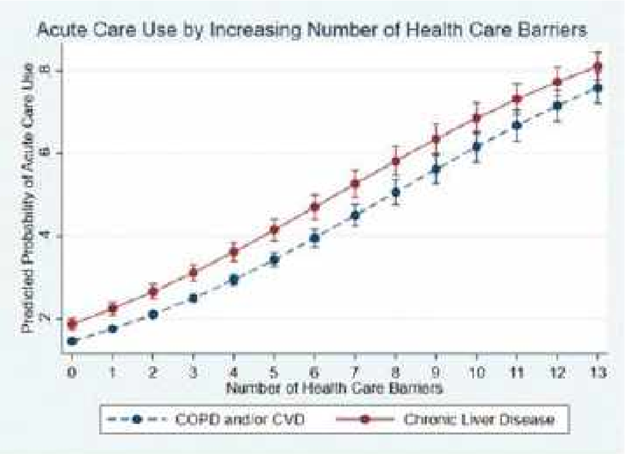
Disclosure information not available at the time of publication: Amber Rutues, Hollie Mayes

86 | ASSOCIATION OF HEALTH CARE BARRIERS AND ACUTE CARE USE AMONG ADULTS WITH CHRONIC LIVER DISEASE VS. OTHER CHRONIC DISEASES IN THE UNITED STATES

Carrie Wong and James Macinko, University of California, Los Angeles

Background: The relative prevalence of health care barriers for patients with CLD vs. those with non-CLD chronic diseases and the cumulative effect of these barriers on recurrent acute care use remains unknown. We aimed to assess the number of health care barriers and their association with acute care use by CLD vs. chronic obstructive pulmonary disease (COPD) and/or cardiovascular disease (CVD). **Methods:** We performed a pooled cross-sectional study using data from the National Health Interview Survey from 2011 to 2017 and applied weight adjustments to yield nationally representative estimates. In-person surveys provided self-reports on sociodemographic, health, and health care characteristics. Health care barriers (from organizational, financial, transportation domains) were measured as a count of all reported barriers (ranging from 0 to 13). Acute care use was defined as e 2 hospitalizations and/or emergency department visits in the past year. We performed descriptive statistics (χ^2, Wald test), multivariable regression analyses (negative binomial, logistic regression), and estimated predicted probabilities from these models. **Results:** The sample included 47,037 adults (5,062 CLD vs. 41,975 COPD/CVD) which provided weighted estimates for 43,264,685 persons (4,742,444 CLD vs. 38,522,241 COPD/CVD). The CLD group was younger (median age 55 vs. 62 years), had more Hispanics (17.5% vs. 8.6%), fair/poor health (41.4% vs. 33.3%), less than high school education (7.2% vs. 6.5%), poverty (20.1 vs. 15.3%), material hardship (29.5% vs. 21.5%), and public insurance (23.6% vs. 15.7%) than the COPD/CVD group ($p < 0.001$). The prevalence of health care barriers for CLD was 1.29 times greater compared to COPD/CVD after adjusting for age, sex, region, and year (incident rate ratio 1.29, 95% CI 1.22-1.37, $p < 0.001$). Adjusted odds of acute care use were 1.36 (95% CI 1.23-1.50, $p < 0.001$) times greater for CLD vs. COPD/CVD. Probability of acute care use increased with greater health care barriers (0.19-0.81 for CLD, 0.15-0.76 for COPD/CVD) and the differences between CLD and COPD/CVD were consistent across the distribution (Figure). **Conclusion:** Our findings from a national sample representative of over 43 million US adults revealed that those with CLD (vs. other common chronic conditions COPD/CVD) have a higher prevalence of health care barriers, which was in turn associated with increased probability of acute care use. These disparities in health care accessibility and utilization are attributable to both characteristics of US adults with CLD and their ability to access appropriate and timely medical care.



Data source: NHIS, 2011-2017. COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease. Predicted probabilities of acute care use were derived from a multivariable logistic regression model to predict acute care use by disease group (CLD vs. COPD/CVD) and included number of health care barriers, age, sex, US Census region, and year (n=47,023; population size=43,255,608).

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

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87 | FOUR-YEAR OVERALL SURVIVAL UPDATE FROM THE PHASE 3 HIMALAYA STUDY OF TREMELIMUMAB PLUS DURVALUMAB IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Background: In the primary analysis (data cut-off: 27 August 2021) of the phase 3 HIMALAYA study (NCT03298451) in unresectable hepatocellular carcinoma (uHCC), STRIDE (Single Tremelimumab Regular Interval Durvalumab) significantly improved overall survival (OS) and demonstrated a durable long-term survival benefit versus sorafenib; durvalumab monotherapy was noninferior to sorafenib (Abou-Alfa et al. *NEJM Evid* 2022). Here, we report an updated 4-year OS analysis of HIMALAYA. **Methods:** Participants with uHCC and no previous systemic treatment were randomized to STRIDE (tremelimumab 300 mg for one dose plus durvalumab 1500 mg every 4 weeks [Q4W]), durvalumab (1500 mg Q4W) or sorafenib (400 mg twice daily). Data-cut off was 23 January 2023 (STRIDE OS data maturity, 78%). OS and serious treatment-related adverse events (TRAEs) were assessed. In addition, baseline demographics and disease characteristics were assessed in long-term survivors (LTS; participants surviving e 36 mo beyond randomization). **Results:** Follow-up duration was approximately 4 years across treatment arms (Table). The OS HR versus sorafenib (0.78; 95% CI, 0.67–0.92) and estimated 36-month OS rate (30.7%) for STRIDE were consistent with the primary analysis. The 48-month OS rate remained higher for STRIDE (25.2%) versus sorafenib (15.1%). No new serious TRAEs occurred after the primary analysis for STRIDE (17.5%). Durvalumab OS noninferiority to sorafenib and safety was consistent with the primary analysis. Baseline demographics, clinical characteristics and subsequent therapies, including tremelimumab rechallenge, for LTS in the STRIDE arm were generally consistent with the full analysis set, suggesting that LTS were not from any particular subgroup. **Conclusion:** These data reinforce the sustained, long-term OS benefit of STRIDE versus sorafenib in a diverse uHCC population, demonstrating unprecedented 3- and 4-year OS rates and longest follow-up to date in phase 3 uHCC studies. STRIDE maintained a tolerable safety profile, with no new serious safety events. This abstract was originally presented at the 2023 World Congress on Gastrointestinal Cancer.

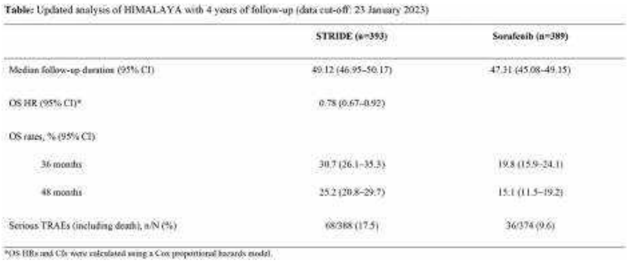

Table: Updated analysis of HIMALAYA with 4 years of follow-up (data cut-off: 23 January 2023)

	STRIDE (n=393)	Sorafenib (n=389)
Median follow-up duration (95% CI)	49.12 (46.95–50.17)	47.31 (45.08–49.15)
OS HR (95% CI)*	0.78 (0.67–0.92)	
OS rates, % (95% CI)		
36 months	30.7 (26.1–35.3)	19.8 (15.9–24.1)
48 months	25.2 (20.8–29.7)	15.1 (11.5–19.2)
Serious TRAEs (including death), n/N (%)	68/388 (17.5)	36/374 (9.6)

*OS HRs and CIs were calculated using a Cox proportional hazards model.

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88 | ANTICANCER EFFECTS OF VITAMIN K COMBINED WITH TRANSARTERIAL CHEMOEMBOLIZATION IN HEPATOCELLULAR CARCINOMA; A PROSPECTIVE, RANDOMIZED TRIAL.

Yoshimichi Haruna and Takayuki Yakushijin, Osaka General Medical Center

Background: We have previously reported that vitamin K dosing augments the anticancer effects of sorafenib by suppressing levels of des-γ-carboxy prothrombin (DCP), a known tumor growth and angiogenesis factor produced in HCC under sorafenib-induced ischemia. Herein, we aimed to establish whether vitamin K dosing could afford a similar anticancer effect when combined with transarterial chemoembolization (TACE), known to induce ischemic tumor necrosis in HCC. **Methods:** We performed a prospective, randomized, open-label trial, randomly assigning patients with unresectable HCC (1:1) to TACE + vitamin K or TACE alone groups. In the TACE + vitamin K group, patients received 45 mg of oral vitamin K2 daily from the day of TACE until day 28. Co-primary endpoints were objective response rate and progression-free survival (PFS); the secondary endpoint was safety. **Results:** No significant differences in baseline characteristics were observed between the TACE + vitamin K group ($n = 50$) and TACE alone group ($n = 51$). The TACE + vitamin K group exhibited a significantly higher objective response rate than the TACE alone group (96.0% *vs.* 82.4%, $p = 0.028$). The PFS was significantly longer in the TACE + vitamin K group than that in the TACE alone group (median time: 262 days [95% confidence interval (CI), 35.8–488.2 d] *vs.* 146 days [95% CI, 111.6–180.4 d]; $p = 0.013$, hazard ratio (HR): 0.55 [95% CI, 0.34–0.89]). Subgroup analysis revealed that vitamin K dosing prolonged PFS, particularly in females (HR of female and male: 0.25 *vs.* 0.72), patients within up-to-7 criteria (HR of within up-to-7 criteria and beyond: 0.44 *vs.* 1.21), or those with high baseline serum DCP levels (HR of DCPg 100 and < 100 mAU/mL: 0.38 *vs.* 0.65). The PFS was markedly prolonged in patients; male with their baseline DCPg 100 mAU/mL or female, and within up-to-7 criteria; who seem to be most favorable for TACE + vitamin K (median [95% CI] days: 712 [290.1–1133.9] *vs.* 141 [89.3–192.7], HR 0.11 [0.04–0.30], $p < 0.001$). Furthermore, we focused on the incidence of rapid and crucial recurrence defined as emergence of macroscopic vascular invasion (Vp4 or Vp3), multicentric intrahepatic recurrence (an increase > 10 nodules compared with the latest radiological image), massive infiltrative tumor growth, extrahepatic spread, or abrupt death due to rapid tumor progression, within 120 days after TACE. In the TACE + vitamin K group, 4 patients (8%) had 4 events of rapid and crucial recurrence, whereas 11 patients (22%) of the TACE alone group experienced 14 events of rapid and crucial recurrence. The rapid and crucial recurrence was observed more frequently in the TACE alone group than in the TACE + vitamin K group ($p = 0.049$). Regarding safety, there were no significant differences in the incidence of adverse events between the two groups. **Conclusion:** Compared with TACE alone, vitamin K dosing combined with TACE improved anticancer outcomes.

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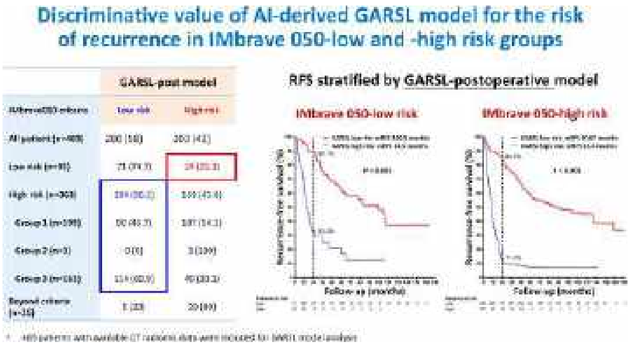
89 | COMPARISON OF RECURRENCE PREDICTION MODELS AND IMBRAVE 050 CRITERIA TO SELECT PATIENTS FOR ADJUVANT IMMUNOTHERAPY AFTER CURATIVE RESECTION OF HEPATOCELLULAR CARCINOMA

I-Cheng Lee[1,2], Hao-Cyuan Chu[2], Shinn-Ying Ho[2], Gar-Yang Chau[3], Ming-Chih Hou[1] and Yi-Hsiang Huang[1,2], (1)Taipei Veterans General Hospital, (2)National Yang Ming Chiao Tung University, (3)Taipei Veterans General Hospital Department Surgery

Background: The IMbrave 050 trial recently demonstrated positive results of the adjuvant atezolizumab plus bevacizumab therapy for hepatocellular carcinoma (HCC) patients at high-risk of recurrence after curative treatment. However, the IMbrave 050 criteria to define high-risk of recurrence might be suboptimal. The aim of this study was to compare the performance of current prediction models and IMbrave 050 criteria in predicting recurrence after curative resection for HCC. **Methods:** Consecutive 1444 HCC patients receiving curative resection were retrospectively enrolled, including 984 (68.1%) patients fulfilling IMbrave 050 high risk criteria. In the high risk group, patients were classified as group 1 (up to three tumors, with largest tumor > 5, n = 458), 2 (four or more tumors, with largest tumor d 5 cm, n = 15) and 3 (up to three tumors, with largest tumor d 5 cm with vascular invasion and/or poor tumor differentiation, n = 511) by IMbrave 050 definition. The performance of ERASL-post and an artificial intelligence (AI)-derived clinical-radiomic GARSL postoperative model were compared with IMbrave 050 criteria in predicting recurrence after resection. **Results:** Besides tumor size, tumor number and microvascular invasion, AFP level, ALBI grade and FIB-4 score were also independent predictors of early recurrence by multivariate analysis. The median RFS in patients with IMbrave low risk, and high risk groups 1, 2 and 3 were 80.0, 22.0, 16.2 and 49.6 months, respectively ($p < 0.001$). The median RFS in patients with ERASL low-, intermediate-, high-risk groups, and GARSL low-, high-risk groups were 69.1, 21.5, 5.0, 96.6 and 10 months, respectively. The area under the receiver operating characteristic curves (AUCs) of IMbrave 050 criteria, ERASL and GARSL models for predicting early recurrence of HCC within 2 years were 0.614, 0.674 and 0.857, respectively. In the IMbrave high risk group, 46.9% and 56.2% of patients were classified as low risk by ERASL and GARSL models, respectively. In the IMbrave low risk group, 0% and 25.3% of patients were classified as high risk by ERASL and GARSL models, respectively. **Conclusion:** The high risk patients defined by the IMbrave 050 criteria were heterogeneous and outcomes varied widely. Prediction models using more comprehensive prognostic factors, especially the AI-derived GARSL model, performed better to select high-risk candidates for adjuvant immunotherapy.



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90 | RECURR-NET, A MULTIPHASIC DEEP LEARNING MODEL, IS SUPERIOR TO MICROVASCULAR INVASION IN PREDICTING HEPATOCELLULAR CARCINOMA RECURRENCE AFTER CURATIVE SURGERY: RESULTS FROM INTERNAL VALIDATION AND EXTERNAL TESTING★

Rex Wan-Hin Hui[1], Keith Chiu[2], I-Cheng Lee[3], Chenlu Wang[4], Ho-Ming Cheng[1], Jianliang Lu[1], Xianhua Mao[1], Sarah Yu[1], Lok Ka Lam[1], Lung Yi Mak[5,6], Nam Hung Chia[2], Chin Cheung Cheung[7], Tan To Cheung[8,9], Yi-Hsiang Huang[3,10,11], Man-Fung Yuen[6], Philip Yu[4] and

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

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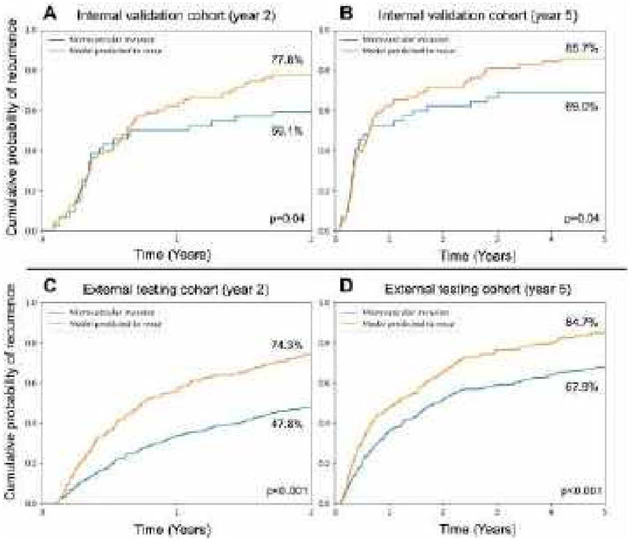
Background: Recurrence can occur in over 70% of hepatocellular carcinoma (HCC) patients within 5 years after curative resection. While histological microvascular invasion (MVI) predicts recurrence, it is ascertained from resected specimens and cannot provide pre-operative prognostication. We developed an artificial intelligence deep learning-based model using pre-operative computed tomography (CT) for predicting HCC recurrence. **Methods:** Chinese patients with resected histology-confirmed HCC were recruited from four centers in Hong Kong, and were randomly divided in an 8:2 ratio into training and internal validation groups. We developed Recurr-Net, a multi-phasic residual-network random survival forest deep learning model, incorporating pre-operative triphasic contrast CT images and clinical data (sex, age, comorbidities, blood tests) to predict HCC recurrence. The model was externally tested in an independent cohort from Taiwan. The area-under-curve (AUC), positive- and negative-predictive values (PPV/NPV) of the model was compared against MVI. Survival analysis was also performed. **Results:** This analysis included 1,254 patients (82.9% male, age at CT 62.2 +/-10.8 years, median follow-up 7.8 [5.8-10.0] years). 551 (43.9%), 140 (11.2%) and 563 (44.9%) patients were in the training, internal validation, and external testing cohorts respectively. The cumulative HCC recurrence rate at years 2 and 5 were 42.1% and 56.6% respectively. The model was trained for 42 epochs. In the internal validation cohort, Recurr-NET achieved an AUC of 0.823 (95%CI 0.684-0.842, PPV 0.778, NPV 0.753) and 0.801 (95%CI 0.632-0.815, PPV 0.857, NPV 0.547) for predicting recurrence at years 2 and 5, significantly outperforming the predictive value of MVI (year 2 AUC 0.564 [95%CI 0.484-0.653], PPV 0.591, NPV 0.554; year 5 AUC 0.527 [95%CI 0.437-0.624], PPV 0.690, NPV 0.365) (Both $p < 0.01$). In the external testing cohort, Recurr-NET achieved an AUC of 0.787 (95%CI 0.647-0.801, PPV 0.743, NPV 0.755) and 0.753 (95%CI 0.607-0.765, PPV 0.847, NPV 0.507) for predicting recurrence at years 2 and 5, significantly outperforming MVI (year 2 AUC 0.609, 95%CI 0.535-0.682, PPV 0.478, NPV 0.774; year 5 AUC 0.560, 95%CI 0.483-0.642, PPV 0.679, NPV 0.464) (Both $p < 0.05$). In both internal validation and external testing cohorts, Recurr-NET had significantly better discriminative ability than MVI for 2-year (Figures 1A & 1C; Validation: 77.8% vs 59.1%; External testing: 74.3% vs 47.8%) and 5-year recurrence risks (Figures 1B & 1D; Validation 85.7% vs 69.0%; External testing: 84.7% vs 67.9%) (Both $p < 0.001$). **Conclusion:** Recurr-NET was superior to MVI in predicting early and late HCC recurrence, and has potential to emerge as a novel tool for pre-operative prognostication of HCC outcomes. Funding: Health and Medical Research Fund, Hong Kong (Ref no: 07182346) and the General Research Fund, Research Grant Council (Ref no: 17100522).



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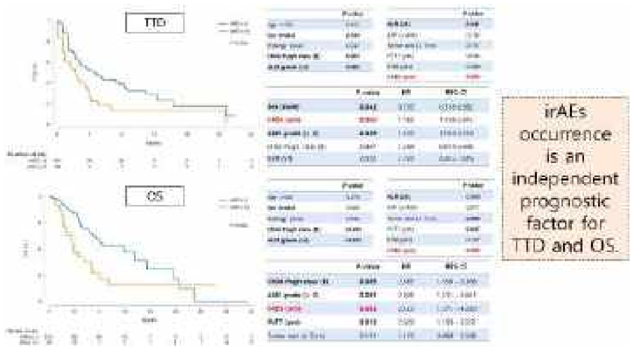
91 | ANALYSIS OF IMMUNE-RELATED ADVERSE EVENTS AND TIME-TO-TREATMENT DISCONTINUATION OF ATEZOLIZUMAB AND BEVACIZUMAB IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: A MULTICENTER COHORT STUDY

Heechul Nam[1], Ji Won Han[2], Soon Kyu Lee[1], Hyun Yang[1], Haelim Lee[1], Pil Soo Sung[3], Hee Yeon Kim[1], Myeong Jun Song[1], Jung Hyun Kwon[1], Chang Wook Kim[1], Si Hyun Bae[1], Jong Choi[3], Seung Kew Yoon[3] and Jeong Won Jang[3], (1)The Catholic University of Korea, (2)The Catholic University of Korea, Seoul, Korea, (3) Seoul St Mary's Hospital, the Catholic University of Korea, Seoul, Republic of Korea

Background: Pragmatic endpoints, such as time-to-treatment discontinuation (TTD), defined as the duration from starting a medication to the date of treatment discontinuation or death, have been proposed as a potential efficacy endpoint for real-world practice. This study aims to analyze the frequency and severity of immune-related adverse events (irAEs) and TTD in patients with hepatocellular carcinoma (HCC) receiving Atezolizumab and Bevacizumab (A+B) treatment. **Methods:** This retrospective, multi-center study included consecutive HCC patients who received A+B treatment from September 2020 to December 2022. The primary endpoint of the study was the assessment of TTD and overall survival (OS). The associations of factors on outcomes were analyzed using Cox proportional hazards regression and multivariable logistic regression models. **Results:** The study included 150 HCC patients with a median age of 64 years. 85.3% were male, and 69.3% had viral hepatitis etiology. 52% had portal vein tumor thrombus (PVTT). Overall, 34.0% patients experienced grade 3 or higher treatment-related adverse events, with 20.0% reported irAEs. The incidence rates of irAEs were hepatitis (9.3%), colitis (3.3%), severe fatigue (2.0%), pneumonitis (2.0%), cholangitis (1.3%), skin rash (1.3%), myositis (0.7%), asthma (0.7%), and anaphylactic shock (0.7%). The median OS was 13.6 months (95% CI, 8.0-20.6) and the median progression-free survival was 5.7 months (95% CI, 4.0-12.5), while the median TTD was 3.6 months (95% CI, 2.6-5.1). Occurrence of irAEs, female gender, ALBI grade e 2, Child-Pugh class B, and neutrophil-to-lymphocyte ratio (NLR) e 3 and were found to be significantly associated with poor TTD in the univariate analysis. In the multivariate analysis, occurrence of irAEs (HR, 1.765; 95% CI, 1.108-2.813, $p = 0.004$), ALBI grade e 2 (HR, 1.639; 95% CI, 1.054-2.550, $p = 0.028$) and female gender (HR, 1.687; 95% CI, 1.018-2.795, $p = 0.042$) were identified as the independent predictor of TTD. For OS, the univariate analysis showed that irAEs, ALBI grade e 2, Child-Pugh class B, NLR e 3, PVTT and tumor size (e 7cm) were found to be significant. The occurrence of irAEs (HR, 2.423; 95% CI, 1.371-4.280, $p = 0.002$), ALBI grade e 2 (HR, 2.926; 95% CI, 1.511-5.667, $p = 0.001$), Child-Pugh class B (HR, 2.685; 95% CI, 1.258-5.308, $p = 0.005$), and PVTT (HR, 2.029; 95% CI, 1.159-3.552, $p = 0.013$) were identified as the independent predictor of OS. **Conclusion:** In our multicenter retrospective cohort study, the combination therapy of A+B demonstrated significant efficacy. Our results highlight the importance of TTD as an important outcome measure, encompassing both disease progression and treatment discontinuation. We identified irAEs as an independent prognostic factor for A+B treatment. Thus, it is crucial to actively monitor and manage irAEs to optimize treatment outcomes.



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92 | MOLECULAR SIGNATURE OF PERIPHERAL CIRCULATING TUMOR CELLS IN CANCER PROGRESSION OF HEPATOCELLULAR CARCINOMA PATIENTS TREATED BY ATEZOLIZUMAB PLUS BEVACIZUMAB

Yosuke Murata[1,2], *Takuto Nosaka*[1], *Tatsushi Naito*[1], *Kazuto Takahashi*[1], *Yu Akazawa*[1], *Hidetaka Matsuda*[1], *Masahiro Ohtani*[1] *and Yasunari Nakamoto*[1], *(1) University of Fukui, (2)Sugita Genpaku Memorial Obama Municipal Hospital*

Background: The mechanisms leading to cancer progression of hepatocellular carcinoma (HCC) such as acquired resistance to immunotherapies and metastatic progression are not clear. Circulating tumor cells (CTCs) have been defined as cancer cells released into the blood circulation from primary tumor. CTCs have notable advantages in that they are noninvasive and real-time biomarker that provide information about metastatic process. CTC analysis has the potential to reveal the mechanism of disease progression and is expected to be applied clinical use such as treatment decision. We investigated the changes in CTC counts and gene expression related to cancer progression in patients with unresectable HCC treated by Atezolizumab plus Bevacizumab. **Methods:** We obtained 5mL of peripheral blood from 15 HCC patients treated with Atezolizumab plus Bevacizumab at baseline and response evaluation. Treatment response was assessed by modified RECIST. CTCs were isolated with RosetteSep^{TM} Human CD45 Depletion Cocktail and enriched cells were stained with monoclonal antibodies targeting the cell surface antigens including CD45, CD90, CD133, Pan-CK, EpCAM, and Vimentin. The cells were counted by flow cytometry using a FACSAria II. CD45 negative and Pan-CK positive cells were defined as CTCs. RNA was extracted from enriched cells and 373 genes related to cancer progression were investigated by next-generation sequencing (NGS) on Illumina Miseq and gene set enrichment analysis (GSEA) was performed. **Results:** Median CTC counts of PR/SD group decreased at response evaluation, compared with baseline (127 ± 43 vs. 58 ± 6, $p < 0.05$) and is lower compared with PD group at response evaluation (58 ± 6 vs. 153 ± 12, $p < 0.05$). In NGS analysis of 373 genes, 99 genes showed significant expression changes in clinical course. Unsupervised hierarchical clustering analysis with the changes of 99 genes expression levels classified into two clusters A and B. Patients in cluster A were responder with Atezolizumab plus Bevacizumab and showed 100.0% survival rate at 1-year, which was better than 50.0% survival rate in cluster B ($p = 0.06$). GSEA showed that the genes expression of apoptosis signaling pathway (FAS, BCL2) were significantly upregulated in responder group (cluster A). TGF-beta signaling pathway-related genes (TGF-β1, SMAD2) were upregulated in non-responder group (cluster B) in clinical course of Atezolizumab plus Bevacizumab ($p < 0.05$). **Conclusion:** In HCC patients treated by Atezolizumab plus Bevacizumab, the change of CTC counts was related to therapeutic effect. The gene expression analysis of CTCs showed that apoptosis signaling pathway-related genes were upregulated in responder group and the activation of TGF-beta signaling pathway may play an important role in resistance to Atezolizumab plus Bevacizumab. CTC in HCC patients treated by immunotherapy may be a notable biomarker that reveal molecular signature of cancer progression.

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93 | CLINICAL IMPACT OF CEUS ON INDETERMINATE LIVER NODULES ON MRI: SUB-ANALYSIS FROM A PROSPECTIVE MULTICENTER TRIAL

Yuko Kono[1], Fabio Piscaglia[2], Stephanie R Wilson[3], Alexandra Medellin[3], Shuchi K Rodgers[4], Paul S Sidhu[5], Aya Kamaya[6], David Fetzer[7], Virginia Planz[8], Annalisa Berzigotti[9], Lisa Finch[10], Corinne Wessner[11], Kristin Bradigan[11], John Eisenbrey[11], Flemming Forsberg[11] and Andrej Lyshchik[11], (1)University of California, San Diego, (2)University of Bologna, (3) University of Calgary, (4)Einstein Medical Center, (5) King's College Hospital, (6)Stanford University, (7) University of Texas, Southwestern Medical Center, (8) Vanderbilt University, (9)University of Bern, (10) Swedish Medical Center, (11)Thomas Jefferson University

Background: Contrast-enhanced ultrasound (CEUS) is a promising diagnostic technique for hepatocellular carcinoma (HCC) diagnosis. While EASL HCC guidelines endorse its use in cases of inconclusive CT or MRI based on non-focused studies, the diagnostic potential of CEUS for HCC is not currently recognized by AASLD guidelines. This study aimed to assess the clinical impact of CEUS specifically in cases where liver lesions were indeterminate on MRI. **Methods:** A prospective international multicenter validation study for CEUS LI-RADS (Liver Imaging Reporting And Data System) was conducted between January 2018 and August 2021. A total of 594 patients at risk for HCC were enrolled. CEUS was performed using intravenous administration of Lumason (Bracco Diagnostic) within 4 weeks of MRI, and the liver nodules were classified based on CEUS and MRI LI-RADS criteria. Tissue histology and CT/MRI imaging follow-up were used as the reference standard. **Results:** A total of 545 nodules reached a final diagnosis based on the reference standard. Among them, 75 nodules with indeterminate MRI characterization (LR-NC: non categorizable, and LR-3: intermediate probability of HCC) were selected for analysis. Reference standard used was follow up CT/MRI (54, 72%), biopsy (14, 18.7%), and explant histology (7, 9.3%). Among the nodules categorized as LR-NC on MRI (n = 21), one was CEUS LR-1, was determined to be benign, all 6 CEUS LR-5 were confirmed to be HCC and 2 LR-M were malignant resulting in a clinical impact in 42.9% (9/21). In the case of LR-3 on MRI (n = 54), there were a total of 14 HCCs, with 7 CEUS LR-4 (probable HCC) and 7 CEUS LR-5. CEUS LR-1 (n = 1) and LR-2 (n = 6), were all benign (100% NPV). PPV of CEUS LR-5 for HCC was 100%. There was one CEUS LR-TIV, and biopsy confirmed poorly differentiated HCC. However, in the case of one CEUS LR-M, the follow-up MRI revealed LR-2, suggesting a false positive CEUS result. When LR-NC and LR-3 lesions on MRI (n = 75) were combined, CEUS LR-1 (n = 2) and LR-2 (n = 6), nodules were all benign, CEUS LR-5 (n = 13) were all HCC. Two CEUS LR-M from LR-NC and one CEUS LR-TIV from LR-2 were malignant, resulting in a clinical impact in 32% (24/75). CEUS had one false positive LR-M case, which was benign on follow up MRI. **Conclusion:** CEUS LI-RADS demonstrated high clinical impact in liver nodules with indeterminate MRI characterization accurately, identifying both non-malignant lesions, HCC and other malignancy in 32% of patients. These findings highlight the significant clinical value of CEUS in the characterization and diagnosis of liver lesions, particularly in cases where MRI findings are inconclusive or indeterminate.

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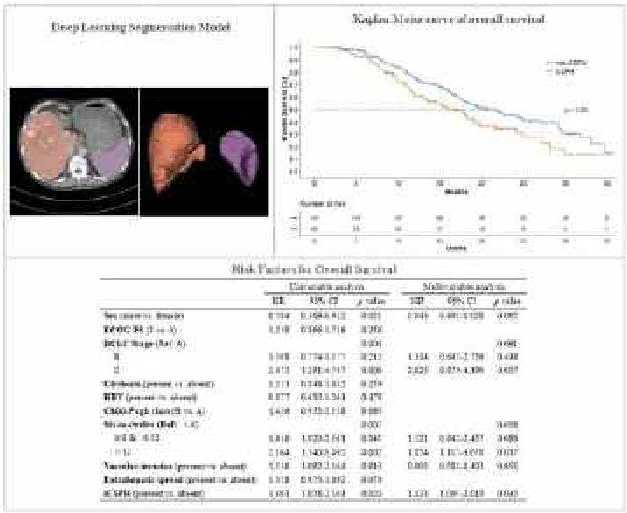
94 | CT-BASED DEEP LEARNING MODEL OF HEPATIC VENOUS PRESSURE GRADIENT FOR PREDICTING THE PROGNOSIS OF HEPATOCELLULAR CARCINOMA WITH TRANSARTERIAL CHEMOEMBOLIZATION (CHANCE-CHESS): A MULTICENTER COHORT STUDY

Yuqing Wang[1], Zhi-Cheng Jin[1], Qian Yu[1], Biao Luo[1], Chuan Liu[1], Jianjien Chen[1], Tao Pan[1], Li Chen[1], Haidong Zhu[1], Shenghong Ju[1], Xiaolong Qi[2] and Gaojun Teng[1], (1)Zhongda Hospital, Medical School, Southeast University, (2)Zhongda Hospital, Medical School, Nanjing, Jiangsu, China

Background: To evaluate the impact of CT-based deep learning model of hepatic venous pressure gradient (HVPG) on prognosis of hepatocellular carcinoma (HCC) patients treated with transarterial chemoembolization (TACE) and systemic therapy. **Methods:** A total of 261 consecutive HCC patients treated with TACE and systemic therapy, and had a contrast-enhanced abdominal CT as part of their pre-surgical work-up, were retrospectively collected between January 2010 and December 2021. A CT-based HVPG Score, whose computed formula was: 17.37-4.91*ln(Liver/Spleen volume ratio) +3.8[If presence of peri-hepatic ascites],was used to diagnose portal hypertension (image-based CSPH, iCSPH for short) with a cut-off value 11.606. The 3D liver and spleen volume were automate calculated by a deep learning segmentation model, and the presence of peri-hepatic ascites was diagnosed by two independent investigators in portal-venous phase CT. Overall survival (OS) as study endpoint was analyzed by Kaplan-Meier and Cox regression. **Results:** Among 261 patients, 80(30.7%) were diagnosed with iCSPH by CT-based HVPG Score. The median OS in iCSPH group was significantly shorter than non-iCSPH group (16.9 mo vs. 20.7 mo, $p = 0.022$). Multivariable analysis indicated that the presence of iCSPH was a negative prognostic factor for OS (adjusted hazard ratio [HR], 1.423, $p = 0.045$). **Conclusion:** The segmentation model shows good performance in liver and spleen segmentation in HCC patients, which may help non-invasive HVPG assessment and other CT imaging studies in HCC patients. CT-based HVPG Score was significantly associated with poor outcome and should be taken into consideration when managing HCC patients underwent TACE and systemic therapy.



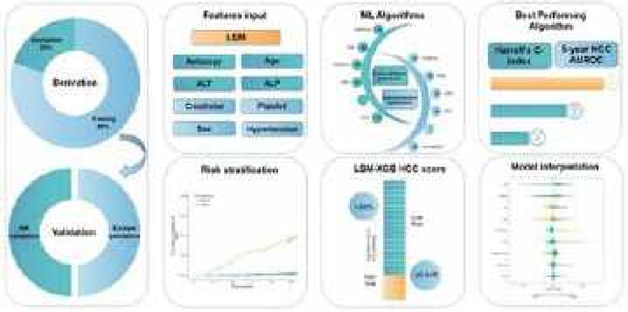
Disclosures: The following people have nothing to disclose: Yuqing Wang, Zhi-Cheng Jin, Qian Yu, Biao Luo, Chuan Liu, Jianjien Chen, Tao Pan, Li Chen, Haidong Zhu, Shenghong Ju, Xiaolong Qi, Gaojun Teng

95 | A LIVER STIFFNESS-BASED AETIOLOGY-INDEPENDENT MACHINE LEARNING ALGORITHM TO PREDICT HEPATOCELLULAR CARCINOMA

Huapeng Lin[1], Guanlin Li[1], Adèle Delamarre[2], Sang Hoon Ahn[3], Xinrong Zhang[1], Beom Kyung Kim[4], Lilian Yan Liang[1], Hye Won Lee[5], Grace Lai-Hung C Wong[6], Pong-Chi Yuen[7], Henry Lik Yuen Chan[8], Stephen Lam Chan[9], Vincent Wai-Sun Wong[10], Victor De Ledinghen[11], Seung Up Kim[3] and Terry Cheuk-Fung Yip[12], (1)The Chinese University of Hong Kong, (2) Ordeaux, (3)Yonsei University College of Medicine, Seoul, Republic of Korea, (4)Severance Hospital, Seoul, Republic of Korea, (5)Yonsei Liver Center, Severance Hospital, Seoul, South Korea, (6)Medical Data Analytics Centre (MDAC), the Chinese University of Hong Kong, (7)Hong Kong Baptist University, (8) Chinese University of Hong Kong, Hong Kong, China, (9)State Key Laboratory of Translational Oncology, Department of Clinical Oncology, Sir Yue-Kong Pao Center for Cancer, the Chinese University of Hong Kong, (10)The Chinese University of Hong Kong, Hong Kong, China, (11)University Hospital Bordeaux, (12)The Chinese University of Hong Kong, Hong Kong, 91, China

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

Background: The existing hepatocellular carcinoma (HCC) risk scores have modest accuracy and most are specific to chronic hepatitis B. In this study, we developed and validated a liver stiffness-based machine learning algorithm (ML) for prediction and risk stratification of HCC in various chronic liver diseases (CLDs). **Methods:** MLs were trained for prediction of HCC in 5155 adult patients with various CLDs in Korea and further tested in two prospective cohorts from Hong Kong (HK, N = 2732) and Europe (N = 2384). Model performance was assessed according to Harrell's C-index and time-dependent receiver operating characteristic (ROC) curve. **Results:** We developed the LSM-XGB HCC score, a liver stiffness-based ML HCC risk score, with liver stiffness measurement ranked as the most important among 9 clinical features (Figure). The Harrell's C-index of the LSM-XGB HCC score in HK and Europe validation cohorts were 0.89 (95% confidence interval [CI] 0.85-0.92) and 0.91 (95%CI 0.87-0.95), respectively. The area under ROC curves of the LSM-XGB HCC score for HCC in 5 years were e 0.89 in both validation cohorts. The performance of LSM-XGB HCC score was significantly better than existing HCC risk scores including aMAP score, Toronto HCC risk index, and seven hepatitis B related risk scores. Using a cutoff of 0.045, 82.7% and 89.0% of patients in HK and Europe validation cohorts were classified as low-risk for a possible exemption from HCC surveillance, respectively; the annual HCC incidence for low-risk group was 0.10%-0.19%. The high-risk group had an annual HCC incidence of 1.91% and 2.63% in the HK and Europe validation cohorts, respectively. **Conclusion:** The LSM-XGB HCC score is a useful machine learning-based tool for clinicians to stratify HCC risk in patients with CLDs.



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Disclosure information not available at the time of publication: Pong-Chi Yuen

96 | A DEEP LEARNING-BASED HEPATOCELLULAR CARCINOMA STAGING SYSTEM BY MULTI-PHASE COMPUTED TOMOGRAPHY

Chia-Shin Wei[1], Po-Chuan Wang[1], Hsinhan Tsai[1], Weichung Wang[1], Che Lin[1] and Tung-Hung Su[2], (1) National Taiwan University, (2)National Taiwan University Hospital

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer. The Barcelona Clinic Liver Cancer (BCLC) staging system is widely used to diagnose and manage HCC. However, currently, automated image-based staging algorithms are lacking. This study aims to automate the BCLC staging process

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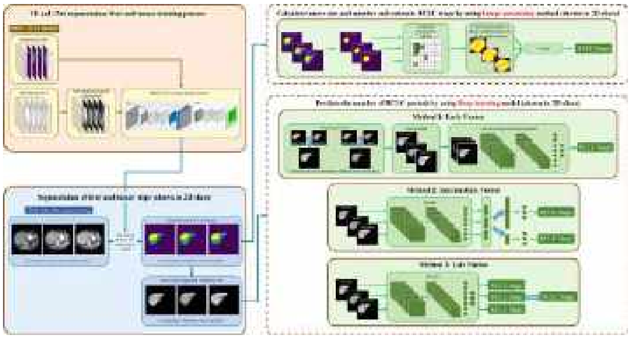
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

using deep learning techniques on multi-phase abdominal computed tomography (CT) images to enhance efficiency with good accuracy. **Methods:** This study utilizes two open datasets: Multimodality annotated HCC cases with and without advanced imaging segmentation (HCC-TACE-Seg) dataset and The Medical Segmentation Decathlon (MSD) Liver dataset. A novel two-stage deep learning pipeline for automatic BCLC staging was generated. We employ an automatic segmentation model in the proposed pipeline to locate the liver and possible lesions. Then, a 3D image classification model is applied to the liver to identify the lesions for BCLC staging. We adopt the nnU-Net as our segmentation model backbone. The segmentation model is trained and evaluated on the combined HCC-TACE-Seg and MSD datasets. For the BCLC staging model, we adopt the 3D ResNet as our model backbone and train on the HCC-TACE-Seg dataset. Furthermore, we proposed three inter-phase fusion techniques (early fusion, intermediate fusion, and late fusion) to utilize the information from the multi-phase CT images. **Results:** Our liver segmentation results were consistent with existing algorithms in accurately delineating the liver region (dice score 0.95), while liver tumor segmentation ranked above average among evaluated methods (dice score 0.64 vs. 0.54). We compared the multi-phase models with single-phase imaging for BCLC staging. Among the proposed multi-phase models, late fusion performed the best, and outperformed single-phase ones with an overall accuracy of 77.78% (vs. 68.89% in the pre-contrast phase and PV phase, 73.33% in A phase), demonstrating the importance of inclusion of different phases of CT images for accurate staging. The best prediction accuracy for BCLC stages A, B, and C were 93.33%, 73.33%, and 66.67% respectively. **Conclusion:** Our numerical experiments demonstrate that the multi-phase staging models outperform the single-phase one and image processing-based method with an accuracy of 77.78%. Overall, the proposed pipeline can aid the radiologist for the BCLC staging process in the future.

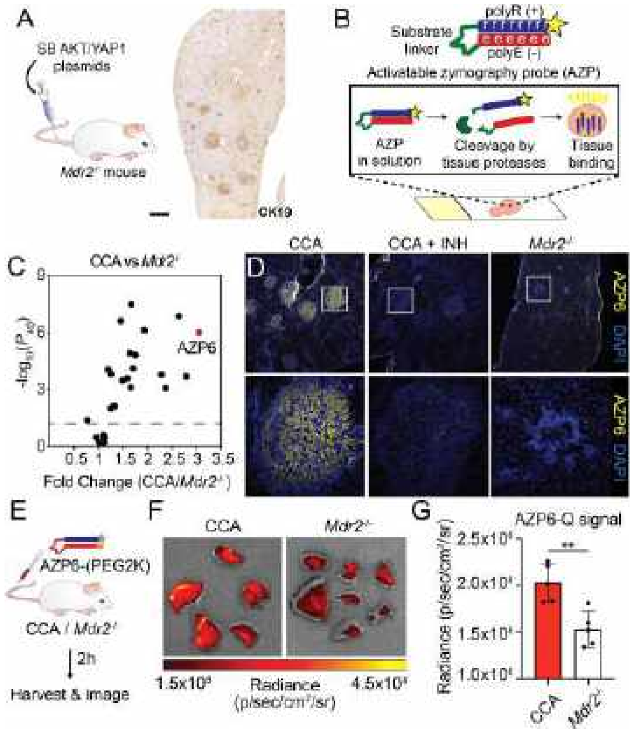


Disclosures: The following people have nothing to disclose: Chia-Shin Wei, Po-Chuan Wang, Hsinhan Tsai, Weichung Wang, Che Lin, Tung-Hung Su

97 | DETECTION OF CHOLANGIOCARCINOMA WITH PROTEASE ACTIVITY PROBES

Jesse Kirkpatrick[1,2], *Janvi Huria*[3], *Pinzhu Huang*[4], *Daniela Sia*[5], *Yury V. Popov*[4] *and Sangeeta Bhatia*[3,6], *(1)MIT, (2)Harvard-MIT, (3)Massachusetts Institute of Technology, (4)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (5)Icahn School of Medicine at Mount Sinai, New York, NY, (6)Howard Hughes Medical Institute*

Background: Patients with primary sclerosing cholangitis (PSC) are at a 400-fold increased risk of cholangiocarcinoma (CCA), and are thus recommended to undergo annual screening with magnetic resonance cholangiopancreatography (MRCP). Unfortunately, MRCP findings are nonspecific for CCA in the setting of biliary fibrosis and screening may not confer a survival benefit. We have previously developed a new class of diagnostic tools that detect dysregulated protease activity in the tumor microenvironment. In this work, we sought to leverage one such tool, activatable zymography probes (AZPs), which enable visualization of tumor-associated protease dysregulation *ex vivo* and *in vivo*. Because proteases have been shown to be dysregulated in CCA, we set out to develop a protease activity-based diagnostic for PSC-associated CCA. **Methods:** We induced CCA tumor formation in the *Mdr2*$^{-/-}$ mouse model of biliary fibrosis via hydrodynamic injection of plasmids encoding for AKT and YAP1, and the Sleeping Beauty (SB) transposase (Fig. 1A). We then synthesized a panel of 26 AZPs and applied them to fresh frozen liver tissue sections from tumor-bearing and *Mdr2*$^{-/-}$ mice (Fig. 1B). Finally, we administered PEGylated AZPs into tumor-bearing and *Mdr2*$^{-/-}$ mice and performed IVIS imaging to assess tumor uptake *in vivo* (Fig. 1E). **Results:** We found that 14 AZPs, most notably AZP6, exhibited significantly increased binding to CCA tumors ($p_{adj} < 0.05$, fold change > 1.5) relative to fibrotic bile ducts (Fig. 1C), which was abrogated by protease inhibitors (Fig. 1D, "INH"). We found that AZP6 bound significantly more strongly to cells with high expression of vimentin ($p < 0.01$) and low expression of cytokeratin 7 ($p < 0.001$), suggesting that AZP6 is cleaved by mesenchymal cells (not shown). To assess the generalizability of AZP6 across CCA models, we tested it on tissue sections from an FBXW7/AKT-mutant CCA model and found that it specifically labeled tumors in a pattern similar to that seen in the YAP1/AKT model (not shown). Finally, we found significantly increased fluorescence in explanted livers from mice with CCA after *in vivo* administration of AZP6 ($p < 0.01$) (Fig. 1F, G). **Conclusion:** AZPs detect and localize dysregulated protease activity *ex vivo* and *in vivo* in mouse models of CCA, without false positives from benign biliary fibrosis. Protease-activated diagnostics like AZPs, when used in conjunction with existing screening tools, may enable earlier and more accurate detection of CCA in PSC.



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Disclosure information not available at the time of publication: Janvi Huria, Pinzhu Huang, Sangeeta Bhatia

98 | A NOVEL 5-POINT SCORING SYSTEM FOR THE DIFFERENTIATION OF HCC FROM INTRAHEPATIC CCA IN LR-M PATIENTS

Rebekka J.S. Salzmann[1], Tudor Mocan[2,3], Cristiana Grapa[3], Lavinia Patricia Mocan[3], Bingduo Wang[1], Rares Craciun[3], Zeno Sparchez[3], Ingo G. Schmidt-Wolf[1], Christian P. Strassburg[1], Arnulf G. Willms[4], Veronika Lukacs-Kornek[1] and Miroslaw T. Kornek[1], (1) University Hospital Bonn, (2)Babes-Bolyai University, (3)Iuliu Haţieganu University of Medicine and Pharmacy, (4)German Armed Forces Central Hospital Hamburg

Background: Despite recent developments, it is still very difficult to differentiate hepatocellular carcinoma (HCC) from intrahepatic cholangiocarcinoma (iCCA). Clinically available methods such as CT, MRI, and contrast-enhanced ultrasound require the highest level of investigator experience to reliably differentiate between HCC and iCCA. Here, we used the surface analysis interferometric and fluorescence imaging methodology for small extracellular vesicles (small EVs) analysis in liver cancer category (LI-RADS) M (LR-M) patients. We evaluated their clinical performance and proposed a 5-point system using serological markers to distinguish HCC from iCCA. **Methods:** Small EVs from 24 patients' sera were isolated by size exclusion chromatography (SEC). Particle counts were measured by nanoparticle tracking analysis (NTA). Small EVs were captured on a microarray chip coated with CD9, CD63 and CD81 and surface stained with fluorescent labelled anti-CD133/2 antibody. Surface analysis of small EVs on a single particle level was performed with ExoView® R100 (NanoView Biosciences, Boston, USA). Data analysis was performed using ExoView® Analyzer 3.2. Additionally, thrombocytes, ALP, CRP were assessed. **Results:** 1) Whole sera particle concentrations isolated from iCCA and HCC differ significantly ($p = 0.0364$) with a mean particle concentration/mL ± SD of $1.8 \times 10^{15} \pm 1.4 \times 10^{15}$ in iCCA and $8.2 \times 10^{14} \pm 5.3 \times 10^{14}$ in HCC (AUROC 0.74, sensitivity and specificity 75% and 58.3%, respectively. 2) Individual small EV subpopulations as characterized by $CD9^+CD133/2^+$ and $CD81^+CD133/2^+$ were significantly elevated in iCCA ($CD9^+C133/2^+$: $p = 0.0315$, AUROC 0.74 and $CD81^+CD133/2^+$: $p = 0.0244$, AUROC 0.826). 3) Thrombocytes, ALP and CRP were elevated in iCCA compared to HCC. ($p = 0.0238$ and AUROC 0.76; $p = 0.0023$ and AUROC 0.85; $p = 0.0092$ and AUROC 0.88, respectively). 4) On an individual basis, each biomarker such as particles, small EVs, thrombocytes, ALP, and CRP did not achieve sensitivity or specificity greater than 80%. However, when each biomarker was converted into a binary categorical variable and a final score was calculated by assigning a point for each factor to the biomarker's cut-off value below it, samples could be scored from 0 to 5. Samples with a score of 3 to 5 were categorized as HCC and 0 to 2 points as iCCA, resulting in a diagnostic performance with a sensitivity of 100% and a specificity of 83.3%. **Conclusion:** Regarding the heterogeneity among liver cancer entities it was found that a combined consideration of biomarkers exceeds the diagnostic value of a single marker. Using a 5-point scoring system we were able to differentially diagnose 24 LR-M patients with HCC or iCCA with a sensitivity of 100 % and specificity of 83.3%. Our findings suppose that combining small EVs with serological biomarkers could improve the diagnostic performance of liquid biopsy markers in a clinical context.

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Disclosure information not available at the time of publication: Tudor Mocan, Cristiana Grapa, Lavinia

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Patricia Mocan, Bingduo Wang, Rares Craciun, Zeno Sparchez, Ingo G. Schmidt-Wolf, Christian P. Strassburg, Arnulf G. Willms

99 | HUMAN-CORRELATED GENETIC HCC MODELS IDENTIFY COMBINATION THERAPY FOR PRECISION MEDICINE

Miryam Müller[1], Stephanie May[1], Holly Hall[1], Timothy James Kendall[2], Lynn McGarry[1], Lauriane Blukacz[3], Sandro Nuciforo[3], Anastasia Georgakopoulou[1], Thomas Jamieson[1], Toshiyasu Suzuki[1], Kathryn Gilroy[1], Narisa Phinichkusolchit[1], Sandeep Dhayade[1], Jack Leslie[4], Júlia Huguet[5], Roger Esteban Fabro[5], Roser Pinyol[6], Matthew Hoare[7], Joep Sprangers[1], Gaurav Malviya[1], Agata Mrowinska[1], Emma Johnson[1], Misti Vanette McCain[8], John Halpin[1], Christos Kiourtis[1], Colin Nixon[1], Graeme Clark[1], William Clark[1], Robin Shaw[1], Ann Hedley[1], Tom Drake[1], Ee Hong Tan[1], Matt Neilson[1], Daniel J Murphy[1], David Lewis[1], Helen Reeves[8], Derek A. Mann[9], Karen Blyth[1], Josep M Llovet[10], Markus H. Heim[3], Leo M Carlin[1], Owen Sansom[1], Crispin Miller[1] and Thomas Bird[1,11], (1)Cancer Research UK Beatson Institute, Glasgow, UK., (2)The University of Edinburgh, (3) Department of Biomedicine, University of Basel, Basel, Switzerland, (4)Newcastle Fibrosis Research Group, Biosciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK, (5) Liver Cancer Translational Research Group, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Hospital Clínic, Universitat De Barcelona, Barcelona, Catalonia, Spain, (6)Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), (7)CRUK Cambridge Institute, Cambridge, UK, (8)The Newcastle University Centre for Cancer, Newcastle University, Newcastle upon Tyne, UK., (9)Newcastle University, UK, (10)Icahn School of Medicine at Mount Sinai, (11)MRC Centre for Inflammation Research, the Queen's Medical Research Institute, University of Edinburgh, UK

Background: Hepatocellular carcinoma (HCC) is a major cause of mortality worldwide. Providing precision medicine to patients is a key unmet need. Preclinical models, when accurately reflecting human disease, offer an opportunity to understand varying therapeutic responses between different patient groups. We aimed to develop a suite of genetically engineered mouse models (GEMMs), link them to human subtypes of HCC and integrate this with a cross-species organoid platform, to ultimately identify and test new therapies in human-relevant pre-clinical models. **Methods:** We developed a suite of 25 new GEMMs, modelled upon HCC-relevant mutations. We characterised these transcriptionally alongside classic non-genetic mouse models of HCC and used computational approaches to positionally align the mice to human HCC data. Integration of this data permitted the development of new cross-species molecular subclasses of HCC. We validated the subclasses histologically, performed organoid-based screening, and tested numerous therapeutic responses *in vivo*. **Results:** Our GEMMs exhibited many of the typical features of human HCC, including clonal origin, heterogeneity, histopathology, and disease progression, including metastasis. We classified four cross-species clusters (HuMo clusters) in the transcriptomic alignment using our specific algorithm. These HuMo clusters showed distinct characteristics including differentiation grade, degree of steatosis, and inflammatory profile. As proof of concept, we showed subtype specific responses to standard of care treatments within, and differing between, murine representative models of the clusters. Furthermore, the linked *in vivo* – *in vitro* approach identified a novel therapeutic candidate capable of priming immune-checkpoint inhibition (ICI) responses in previously ICI-resistant tumors. **Conclusion:** Our newly developed GEMMs show distinct subclass-specific features of human HCC. They present a platform for informing translational research and performing more in-depth mechanistical studies of HCC. We show that, by using multiple integrated resources, linking patient data with suitable preclinical *in vivo* and *in vitro* organoid models, we are able to propel therapeutic options forward towards precision medicine for HCC.

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100 | A POSITIVE FEEDBACK BETWEEN CHOLESTEROL SYNTHESIS AND THE PENTOSE PHOSPHATE PATHWAY RATHER THAN GLYCOLYSIS PROMOTES HEPATOCELLULAR CARCINOMA

Ningning Liu, Chinese Academy of Sciences and Guisheng Song, University of Minnesota

Background: Hepatic cholesterol accumulation and hypercholesterolemia are considered as the risk factors of hepatocellular carcinoma (HCC). However, the therapeutic effects of cholesterol lowering drugs for the treatment of HCC are controversial, indicating that the relationship between cholesterol metabolism and HCC is more complex than anticipated. **Methods:** FVB/NJ mice were hydrodynamically injected with c-Myc and *Sleeping Beauty* to induce HCC. UPLC-MS/MS was used to analyze metabolites of glycolysis and the pentose phosphate pathway (PPP). ^{14}C-acetate sodium and ^{3}H-thymidine were used to measure cholesterol synthesis and DNA synthesis, respectively. A dual-AAV8-based CRISPR/Cas9 was used to ablate the binding site of miR-206 within the 3’UTR (untranslated region) of its target genes. **Results:** Activation of cholesterol synthesis, glycolysis and the pentose phosphate pathway (PPP) was observed in HCC patients and c-Myc HCC mouse model. A positive feedback between cholesterol synthesis and the PPP was formed in tumors of c-Myc mice. Blocking the PPP prevented cholesterol synthesis and thereby development of HCC in c-Myc mice, while ablation of glycolysis did not affect cholesterol synthesis and failed to prevent c-Myc-induced HCC. Unexpectedly, *HMGCR* (3-hydroxy-3-methylglutaryl-CoA reductase) and *G6PD* (glucose-6-phosphate dehydrogenase), the rate-limiting enzymes of cholesterol synthesis and the PPP, were identified as direct targets of microRNA-206. By targeting *Hmgcr* and *G6pd*, microRNA-206 disrupted the positive feedback between cholesterol synthesis and the PPP, thereby inhibiting DNA synthesis and hepatocyte proliferation. Hydrodynamic injection (HDI) of microRNA-206 fully prevented HCC in c-Myc mice, while 100% of control mice dies of HCC. Disrupting the interaction of microRNA-206 with *Hmgcr* and *G6pd* restored cholesterol synthesis, the PPP and HCC growth in microRNA-206-treated c-Myc mice. **Conclusion:** This study identified a previously undescribed positive feedback loop between cholesterol synthesis and the PPP, which drives HCC development by providing substrate of DNA synthesis and energy for hepatocyte proliferation, while microRNA-206 prevents HCC by disrupting this loop. Cholesterol synthesis as a process rather than cholesterol itself is the major contributor of HCC, which at least in part explains the controversial findings of cholesterol-lowering drugs for the treatment of HCC.

Disclosures: The following people have nothing to disclose: Ningning Liu, Guisheng Song

101 | PHARMACOLOGICAL INHIBITION OF DISCOIDIN DOMAIN RECEPTOR TYROSINE KINASE 1 (DDR1) FOR HCC CHEMOPREVENTION AFTER HCV CURE

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Background: Active HCV infection has decreased with the introduction of direct-acting antivirals (DAAs). However, a subset of patients remains at risk for HCC development even after achieving a sustained virologic response (SVR). Chemopreventive measures post SVR are urgently needed to reduce incident HCC. **Methods:** We first validated our previously reported Prognostic Liver Signature (PLS) for association with post-SVR HCC risk in two independent cohorts of HCC-naïve ($n = 41$) and HCC-experienced ($n = 85$) patients with longitudinal observation up to 20 years. Post-SVR HCC risk driver genes were determined using multiscale embedded gene co-expression network analysis and based on association with time to HCC development. Candidate compounds targeting the HCC risk driver genes were tested for PLS modulation in a PLS-inducible cell culture system (cPLS) and ex vivo culture of clinical precision-cut liver slice (PCLS) for PLS modulation. HCC-preventive effect of the compound was assessed in two mouse models of HCC development: fibrosis/HCC induced by DEN + CCl4 and NASH HCC induced by genetic knockout of Pten and Scap genes (Pten/Scap-ko). **Results:** PLS was associated with long-term post-SVR HCC incidence in the HCC-naïve (adjusted hazard ratios [aHR], 5.02; 95% CI, 1.26-19.9) and HCC-experienced (aHR, 2.28; 95% CI, 1.01-5.15) patient cohorts. Among the PLS member genes, 19 putative key HCC risk driver genes were identified, including DDR1 as the most strongly associated with time to HCC development in multiple independent clinical cohorts. A comprehensive computational compound screening suggested a small molecule DDR inhibitor as a top candidate for reversal of high-risk PLS. A clinically developed DDR1 inhibitor, 7rh, significantly reversed high-risk PLS in the in vitro cPLS system and ex vivo PCLS culture. Further, 7rh diminished HCC development in the DEN + CCl4 mouse model accompanied by reversal of the high-risk pattern of PLS, whereas this effect was not observed in the Pten/Scap-ko mouse model. No notable toxicity was observed. **Conclusion:** Our pre-clinical study suggests that 7rh is a candidate post-SVR HCC chemoprevention agent with PLS as a companion biomarker to guide its indication and monitor the effect.

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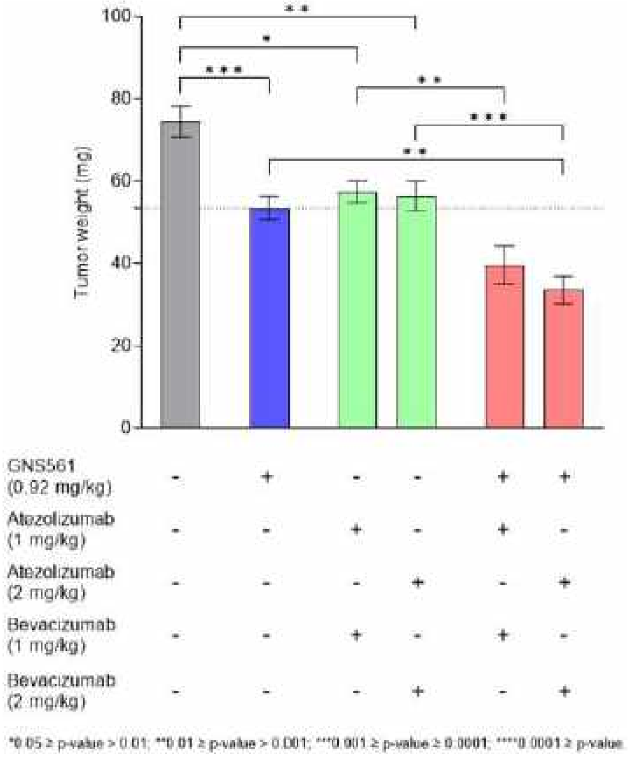
102 | EZURPIMTROSTAT AUTOPHAGY BLOCKER, A PALMITOYL-PROTEIN THIOESTERASE 1 (PPT1) INHIBITOR, AND ATEZOLIZUMAB/BEVACIZUMAB TRIPLE COMBINATION REGIMEN ENHANCES ANTITUMOR EFFICACY IN HEPATOCELLULAR CARCINOMA

Eloine Bestion[1], Soraya Mezouar[1], Antoine Rivière[1], Yan Wang[2], Arnaud Peyronnier[2], Christelle Ansaldi[1], Thomas Decaens[3], Gael Roth[3], Eric Raymond[1] and Philippe Halfon[1], (1)Genoscience Pharma, (2)Inovotion SAS, (3) Univ. Grenoble Alpes, Institute for Advanced Biosciences-Inserm U1209/ Cnrs Umr 5309, Clinique Universitaire d'Hépato-Gastroentérologie, CHU Grenoble Alpes

Background: Immune checkpoint therapies combination with anti-VEGF is the standard-of-care in first-line of hepatocellular carcinoma (HCC). However, only 30 % of patients present a response to first line therapy. Autophagy inhibitors were recently spotted out as a potential robust strategy to promote antigen presentation and therefore reinforce immune checkpoint inhibitors (ICIs) potency conducting to strong anti-tumoral response. Hereafter, we aimed to assess the efficacy of GNS561 (Ezurpimtrostat), an autophagy inhibitor targeting palmitoyl-protein thioesterase-1 (PPT-1) lysosomal enzyme, in combination with atezolizumab/bevacizumab in HCC in a chicken embryos model. **Methods:** Chorioallantoic membrane (CAM assay) model was used, inoculated with liver adenocarcinoma Hep3B cell line at day 9 (D9). Between D9 and D18, eggs were treated every two day with GNS561 alone (0.92 mg/kg), or in combination with atezolizumab/bevacizumab (at 1 mg/kg/1mg/kg (R1), or 2 mg/kg/2mg/kg (R2)). At D18, the upper portion of the CAM containing tumor is removed. The tumors are cut away from normal CAM tissue and weighed, and the number of dead embryos is counted. A one-way analysis of variance with post-tests is done. No cytotoxicity was reported. **Results:** All regimens induced a significant tumor growth regression compared to the control group, GNS561 alone having a more potent anti-tumoral effect ($p < 0.0004$) compared to both atezolizumab/bevacizumab regimens (R1, $p < 0.0147$; R2, $p < 0.0071$). Interestingly, atezolizumab/bevacizumab combination regimens exhibited no significant difference between the two tested dose-regimens. A triple combination regimen led to significantly improved anti-tumoral efficacy compared to the two atezolizumab/bevacizumab groups, for comparable dosing (R1, $p < 0.0076$, R2, $p < 0.0001$), spotlighting triple combination superior benefit. Results further pointed out GNS561 combination with atezolizumab/bevacizumab significant superior anti-tumor effect at the highest dose in comparison with GNS561 alone, reinforcing the interest of triple therapy ($p < 0.0030$). **Conclusion:** This study reports that GNS561 potentiates the anti-tumor effect of atezolizumab/bevacizumab combination emphasizing PPT1 inhibitors' therapeutic interest in combination with immunotherapy in HCC. This triple therapy is currently tested in the randomized phase 2 clinical trial ABE-LIVER, in first line setting in advanced HCC (NCT05448677).



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Disclosure information not available at the time of publication: Soraya Mezouar, Antoine Rivière, Yan Wang, Arnaud Peyronnier, Christelle Ansaldi, Thomas Decaens, Gael Roth, Eric Raymond

103 | PSMP INHIBITS HCC PROGRESSION BY REGULATING THE POLARIZATION OF TUMOR-ASSOCIATED MACROPHAGES THROUGH THE PI3K/AKT PATHWAY

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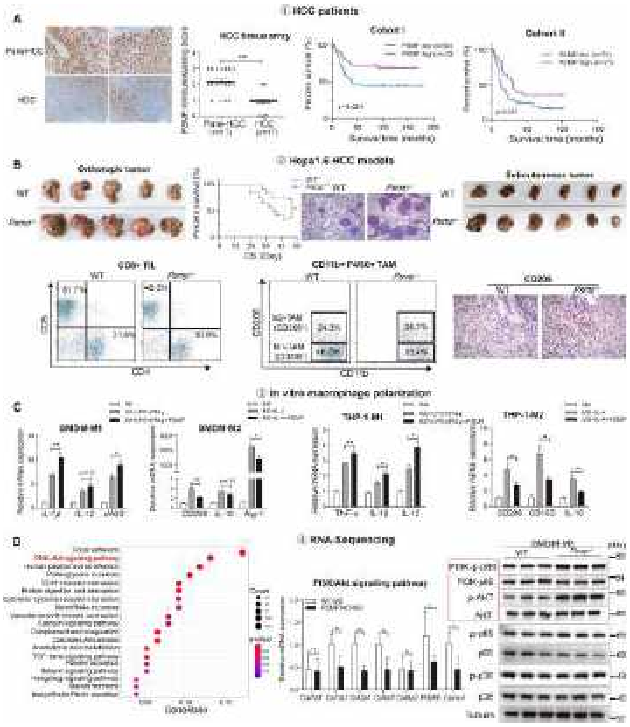
Background: Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and represents a major global health-care challenge. PC3

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

secreted microprotein (PSMP) is a novel chemotactic cytokine that can recruit peripheral blood monocytes and lymphocytes through its chemokine receptor CCR2. Our previous study found that PSMP is significantly highly expressed in human and mouse liver fibrosis/cirrhosis. PSMP promotes the progression of liver fibrosis by regulating the infiltration, activation and polarization of macrophages. However, the relationship between PSMP and the development and prognosis of HCC remains unclear. **Methods:** The expression of PSMP was detected in two independent HCC patients cohorts and its correlation with patients' prognosis was analyzed. *In vivo*: In PSMP knockout (*Psmp*$^{-/-}$) and wild-type (WT) mice, subcutaneous tumorigenesis models and liver orthotopic tumorigenesis models were established using two mouse HCC cell lines (Hepa1-6, H22); In nude mice, subcutaneous tumorigenesis models were established using two human HCC cell lines (Huh7, HepG2). The direct effects of PSMP on the polarization of macrophages (human THP-1 cell line and mouse bone marrow-derived macrophages (BMDMs) were studied *in vitro*. In addition, we performed RNA sequencing of BMDMs from *Psmp*$^{-/-}$ and WT mice. **Results:** Through the detection of clinical HCC patient samples, we found that PSMP is downregulated in human HCC tissues, and its expression level is positively correlated with the prognosis of HCC patients. *In vivo*, we found that genetic deletion of PSMP promotes subcutaneous and liver orthotopic tumor growth and metastasis in mice; Overexpression of PSMP inhibits the formation of subcutaneous tumors in nude mice. Mechanistically, the deletion of PSMP substantially suppresses the infiltration of CD8+ tumor-infiltrating lymphocytes (TILs) while promoting the infiltration and polarization of M2 tumor-associated macrophages (TAMs) within the liver. *In vitro,* we observed that PSMP possesses the capacity to induce M1-polarization and suppress M2-polarization of mouse BMDMs and human THP-1 cells. In addition, analysis of RNA sequencing results showed that PSMP may mediate the polarization of macrophages by regulating the PI3K/Akt signaling pathway. Then, we verified that PSMP mediates its inhibitory effect on M2-polarization of macrophages by suppressing the PI3K/Akt pathway through the inhibition of p85 and Akt phosphorylation. **Conclusion:** Collectively, PSMP may inhibit the M2 polarization of TAMs by downregulating PI3K/Akt pathway, and then promote the anti-tumor immune response of CD8+ T cells, and ultimately inhibit the progression of HCC. The results are expected to clarify the role and mechanism of PSMP in the liver tumor microenvironment for the first time, which has important theoretical significance, and may also provide new targets for the treatment of HCC, with potential application value.



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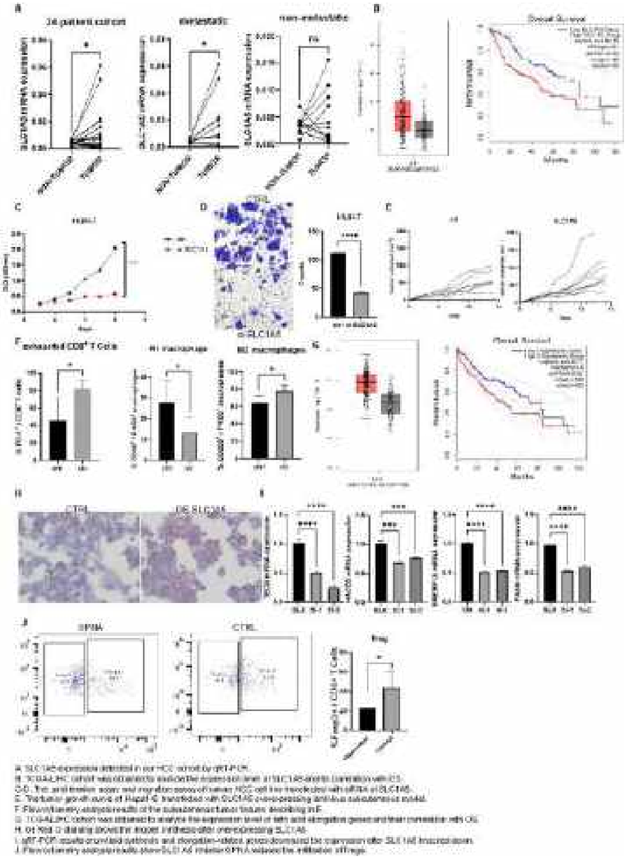
104 | SLC1A5 REGULATES LIPID METABOLISM AND FORMS AN IMMUNOSUPPRESSIVE TME IN HCC★

Jialin Liao[1], Wenwen Li[2], Ziyong Zhang[2], Xuejing Zou[2], Dehua Wu[1] and Dongyan Zhang[1], (1)Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China, (2) Hepatology Unit and Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China

Background: Tumor microenvironment(TME) reflects the intertwined crosstalk between cancer cells and tumor-infiltrating immune cells, affecting the efficiency of immunotherapy. Metabolic reprogramming, one of the major hallmarks of hepatocellular carcinoma(HCC), is unclear in the aspect of reshaping TME. In this study, we report the vital role of SLC1A5, the major glutamine transporter of tumor cells, in HCC progression and the formation of immunosuppressive TME. **Methods:** TCGA-LIHC cohort was obtained to analyze the expression level of SLC1A5 and its correlation with overall survival(OS) and SLC1A5 expression was further detected in our HCC cohort(metastatic vs non-metastatic patients) by qRT-PCR. The functions of SLC1A5 on HCC were investigated by gain-of-function and loss-of-function assays both *in vitro* and *in vivo*. Flow cytometry analysis, bioinformatics analysis, co-immunoprecipitation, qRT-PCR, Western blotting, and Oil Red O staining were performed to explore the mechanisms of SLC1A5 on HCC progression. **Results:** We found that the expression of SLC1A5 was significantly upregulated in HCC compared with non-tumor tissues among 2 cohorts. Metastatic patients in our cohort markedly upregulated SLC1A5 in the tumor than in the paired non-tumor tissues, while the paired specimens of non-metastatic patients presented identical levels of SLC1A5 expression. And high expression of SLC1A5 predicted poor OS. SLC1A5 overexpression potentiated cellular proliferation and migration, whereas its knock-down significantly attenuated them both *in vitro* and *in vivo.* Besides, SLC1A5-overexpression enhanced the infiltration of Tregs, drove CD8$^+$ T cells exhaustion and macrophage M2 polarization. Mechanistically, we found that SLC1A5 directly binds to lipid synthesis enzymes that engage in fatty acid elongation. SLC1A5 knockdown not only reduced lipid droplets but also decreased the expression of lipid synthesis and elongation-related genes, which is associated with poor survival. Finally, blocking SLC1A5 by GPNA effectively inhibits tumor growth and reduces Tregs infiltration. **Conclusion:** Our results reveal that SLC1A5 plays a pivotal role in the development of HCC by directly interacting with lipid metabolic enzymes to facilitate tumor cell proliferation and migration, thereby constructing an immunosuppressive TME. Hence, SLC1A5 may serve as a novel prognostic biomarker and therapeutic target in HCC, and SLC1A5 blockade holds the promise to counteract immunotherapy resistance.



Disclosures: The following people have nothing to disclose: Jialin Liao, Wenwen Li, Ziyong Zhang, Xuejing Zou, Dehua Wu, Dongyan Zhang

105 | REPROGRAMMING THE INTRAHEPATIC CHOLANGIOCARCINOMA IMMUNE MICROENVIRONMENT BY CHEMOTHERAPY AND CTLA-4 BLOCKADE ENHANCES ANTI-PD1 THERAPY

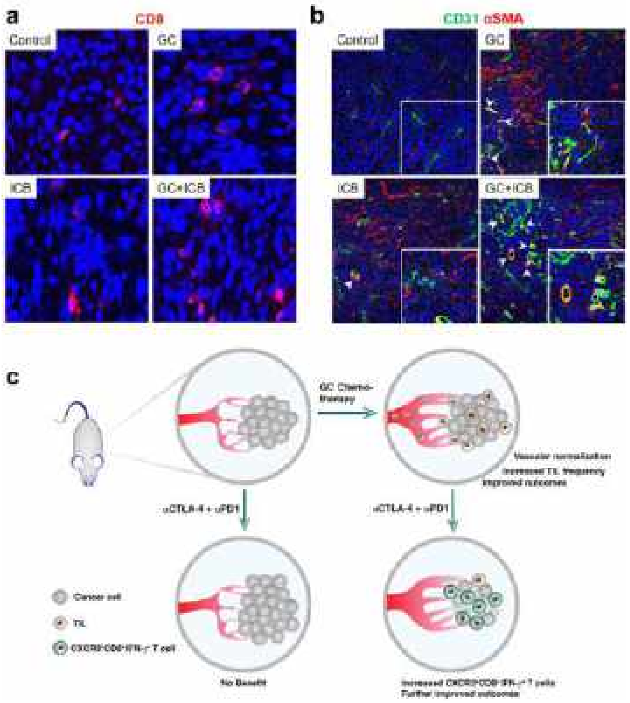
Jiang Chen[1,2], Zohreh Amoozgar[1], Xin Liu[1], Shuichi Aoki[1], Zelong Liu[1], Aya Matsui[1], Zhangya Pu[1], Stefan Halvorsen[1], Pin-Ji Lei[1], Won Jin Ho[3], Peigen Huang[1], Rakesh Jain[1], Nabeel M. Bardeesy[4] and Dan G. Duda[5], (1)Massachusetts General Hospital and Harvard Medical School, Boston, USA, (2)Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China, (3) Johns Hopkins School of Medicine, Baltimore, USA, (4) Department of Medicine, Division of Oncology, Massachusetts General Hospital, Boston, Harvard Medical School, Boston, USA, (5)Massachusetts General Hospital

Background: Intrahepatic cholangiocarcinoma (ICC) has limited therapeutic options and dismal prognosis. Anti-PD-L1 immunotherapy combined with gemcitabine/cisplatin chemotherapy has recently shown efficacy in biliary tract cancers, but responses are seen only in a minority of patients. Here, we studied the roles of anti-PD1 and anti-CTLA-4 immune checkpoint blockade (ICB) therapies when combined with gemcitabine/cisplatin and the mechanisms of treatment benefit in orthotopic murine ICC models. **Methods:** We evaluated the effects of the combined treatments on ICC vasculature and immune microenvironment using flow cytometry analysis, immunofluorescence, imaging mass cytometry, RNA-sequencing, qPCR, and in vivo T-cell depletion and CD8 + T-cell transfer using orthotopic ICC models and transgenic mice. **Results:** Combining gemcitabine/cisplatin with anti-PD1 and anti-CTLA-4 antibodies led to substantial survival benefits and reduction of morbidity in two aggressive ICC models, which were ICB-resistant. Gemcitabine/cisplatin treatment increased the frequency of tumor-infiltrating lymphocytes and normalized the ICC vessels, and when combined with dual CTLA-4/PD1 blockade, increased the number of activated CD8 + Cxcr3 + IFN-γ + T-cells. Depletion of CD8 + but not CD4 + T-cells compromised efficacy. Conversely, CD8 + T-cell transfer from Cxcr3 –/– versus Cxcr3 +/+ mice into Rag1 –/– immunodeficient mice restored the anti-tumor effect of gemcitabine/cisplatin/ICB combination therapy. Finally, rational scheduling of the ICBs using anti-CTLA-4 “priming” with chemotherapy followed by anti-PD1

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

therapy achieved equivalent efficacy with continuous dosing while reducing overall drug exposure. **Conclusion:** Gemcitabine/cisplatin chemotherapy normalizes vessel structure, increases activated T-cell infiltration, and enhances anti-PD1/CTLA-4 immunotherapy efficacy in aggressive murine ICC. This combination approach should be clinically tested to overcome resistance to current therapies in ICC patients.

Figure 1



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106 | HEPATOCYTE DELETION OF REGULATORY T CELLS BY ENCLYSIS IS INCREASED IN AUTOIMMUNE HEPATITIS COMPARED TO MASH AND CAN BE TOGGLED BY PPARA AGONISTS AND ANTAGONISTS★

Yiyu Fan[1], Zania Stamataki[1], Aekkachai Tuekprakhon[1], Rebecca Sinclair[1], Federica Pandolfini[2], Robert Bryce[1], Harriet Hill[1], Kulvinder Jennifer Gill[3], Gary Reynolds[3], Nicholas Barnes[4] and Omar Qureshi[5], (1)Institute of Immunology and Immunotherapy, University of Birmingham, (2)Cancer Research Horizons, UK, (3) Centre for Liver and Gastrointestinal Research, Nihr Birmingham Liver Biomedical Research Unit, University of Birmingham, (4)Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, (5)Celentyx Ltd, UK

Background: The liver is a tolerising organ, to prevent continuous immune activation following the portal influx of antigens from the gut. Regulatory T cells (Treg) dampen inflammation and are important to prevent liver injury. We discovered that hepatocytes engulf and delete live Treg cells by *enclysis*, which was distinct from known cell-in-cell structure processes and thus can be targeted specifically (PMID: 31693899). Understanding how enclysis is modulated will enable us to toggle Treg cell frequencies in the liver and dampen inflammation or boost immunity as required. We investigated the role of Peroxisome proliferator-activated receptor alpha (PPAR±) in the modulation of enclysis. **Methods:** FoxP3, Tbet and PPAR± were assessed in non-cirrhotic livers, AIH and MASH ($n = 30$) by immunohistochemistry (IHC). To test pharmacological inhibitors of enclysis in vitro, we set up a fluorescence-based high content assay using Huh-7 cells and Jurkat cells as models for hepatic epithelia and CD4+ T cells respectively, and tested titrations of Clofibric Acid, Fenofibrate, and GW6471. Cell-in-cell structures were quantified using custom rule-based algorithms in collaboration with Celentyx Ltd. Hits were validated in concentration-response assays using confocal microscopy. **Results:** Enclysis for Treg cells, but not Th1 cells, was reduced in AIH compared to MASH livers ($p = 0.0019$). PPAR± agonists Clofibric Acid ($p = 0.0156$) and Fenofibrate ($p = 0.0156$) reduced enclysis, and PPAR± antagonist GW6471 increased enclysis in vitro ($p = 0.02$). In non-cirrhotic livers, PPAR± was expressed in periportal hepatocytes and less in mid-lobular hepatocytes. MASH was similar, with high PPAR± in peri-fibrous regions and low in mid-lobular hepatocytes. Conversely, AIH liver explants showed reduced PPAR± in all hepatocytes, consistent with increased enclysis (Fig.1). **Conclusion:** The natural deletion of Treg cells by hepatocytes was increased in AIH compared to MASH, revealing enclysis as a new target for therapeutic intervention to dampen inflammation. The robust modulation of enclysis by PPAR± agonist and antagonist compounds suggests that enclysis can be toggled pharmacologically to control Treg cell frequencies specifically in the liver. The reduction of hepatocyte PPAR± expression in AIH compared to healthy livers and to MASH, proposes a role for aberrant PPAR± expression in the pathogenesis of AIH, which needs further investigation. Keywords: Enclysis, inflammation, regulatory T cells, fibrates, PPARalpha, fenofibrate, clofibrate, AIH, MASH

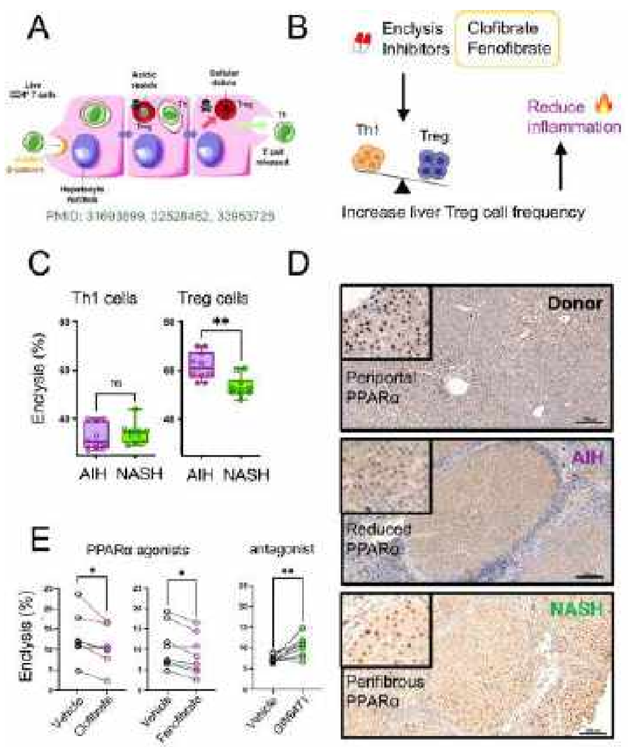


Figure 1. PPARα modulation toggles enclysis. A. Hepatocytes control Treg cell frequencies by enclysis. **B.** Enclysis inhibition aims to increase Treg cells and dampen inflammation. **C.** Enclysis was increased in AIH compared to NASH in end stage disease. **D.** PPARα expression was reduced in AIH explant livers compared to non-cirrhotic donors and to NASH patients, who had increased perifibrous but not mid-lobular PPARα. **E.** PPARα agonists clofibric acid (10μM) and fenofibrate (10μM) reduced enclysis and PPARα antagonist GW6471 (1.25uM) increased enclysis in vitro.

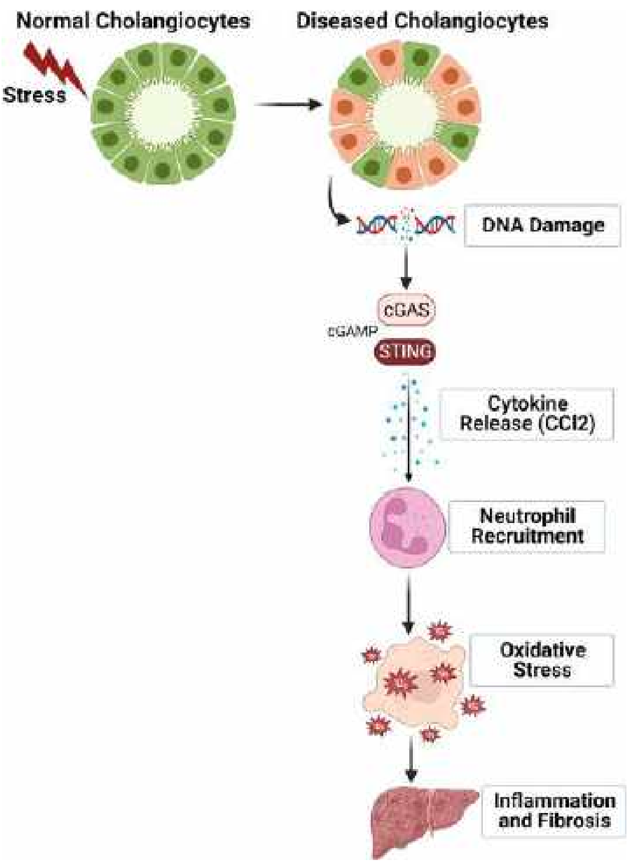
Peroxisome proliferator activated receptor alpha (PPARα), Regulatory T cells (Treg), autoimmune hepatitis (AIH), non-alcoholic steatohepatitis (NASH). $^*p<0.05$, $^{**}p<0.01$, Mann-Whitney test (C), Wilcoxon test (E).

Disclosures: The following people have nothing to disclose: Yiyu Fan, Zania Stamataki, Aekkachai Tuekprakhon, Rebecca Sinclair, Federica Pandolfini, Robert Bryce, Harriet Hill, Kulvinder Jennifer Gill, Gary Reynolds, Nicholas Barnes, Omar Qureshi

107 | CHOLANGIOCYTE-MEDIATED INFILTRATION OF NEUTROPHILS IN THE PERI-PORTAL REGION INDUCES OXIDATIVE STRESS IN PRIMARY SCLEROSING CHOLANGITIS

Abid Anwar[1,2], Jordan Young[3], Usman Yaqoob[4], Sofia Jerez[1], Robert C. Huebert[4] and Nidhi Jalan-Sakrikar[3], (1)Mayo Clinic, Rochester, MN, (2)University of Illinois College of Medicine, (3)Mayo Clinic, (4)Mayo Clinic Rochester, Rochester, MN

Background: Primary Sclerosing Cholangitis (PSC) manifests with fibrotic scarring of the intrahepatic and extrahepatic bile ducts due to an immune-mediated inflammatory response. The cyclic GMP–AMP synthase –stimulator of interferon genes (cGAS-STING) signaling pathway is a key mediator of inflammatory gene expression and cytokine release in response to cellular stress. The inflammatory milieu observed in PSC recruits immune cells, including neutrophils, to infiltrate the peri-portal region. Our goal is to investigate the mechanism of neutrophil homing to the biliary tree and the crosstalk between neutrophils and cholangiocytes. **Methods:** Immunofluorescence (IF) was performed on liver tissues from PSC patients and mouse models of PSC (3,5-Diethoxycarbonyl-1,4-Dihydrocollidine (DDC)-fed mice and Mdr2-/- mice) for markers of bile ducts and neutrophils (KRT19 and MPO). RT-PCR was employed on whole liver tissue for the neutrophil marker, MPO. Immunohistochemistry (IHC) for 8-hydroxy-2’ -deoxyguanosine (8-OHDG) was used to mark oxidative damage in liver tissues. Cholangiocyte-derived organoids (cholangioids) from wildtype and Mdr2-/- mice were analyzed for DNA damage using RT-PCR, western blotting, and immunostaining. cGAS-STING activation was evaluated by immunoblotting and IF. The NanoString NCounter assay was performed on mice liver tissues to investigate chemoattractants for neutrophils. Cholangiocytes isolated from mice injected with lipopolysaccharide (LPS) and H69 cells treated with LPS (to induce an inflammatory response) were analyzed for proinflammatory cytokines and components of the cGAS-STING pathway. **Results:** Increased presence of peri-portal neutrophils was observed from PSC patient and mouse liver tissues compared to controls (6.7 ± 1.74-fold, $p<0.0005$, n = 5). RT-PCR analysis from Mdr2-/- and DDC-fed mice tissues revealed increased gene expression of the neutrophil marker, MPO, compared to chow-fed mice (5-fold and 4.5-fold respectively, $p<0.05$). Congruently, oxidative stress was significantly increased in these liver tissues as shown by 8-OHDG staining. Immunostaining of Mdr2-/- cholangioids confirmed an increase in the DNA damage marker, 53BP1, compared to WT cholangioids. Downstream of DNA damage, we observe activation of the cGAS-STING pathway by immunoblotting for STING and IF for Phospho-STING in mouse models. Ncounter analysis revealed a ~30-fold upregulation of the chemokine, CCL2, in DDC-fed and Mdr2-/- mice liver tissues. This was further confirmed in primary cholangiocytes isolated from LPS-treated mice and H69 cells treated with LPS. **Conclusion:** Our findings suggest that activation of the cGAS-STING pathway in cholestatic liver disease triggers an immune response including peri-portal neutrophil infiltration. This infiltration propagates oxidative stress and perpetuates the biliary fibrosis and inflammation characteristics of PSC.



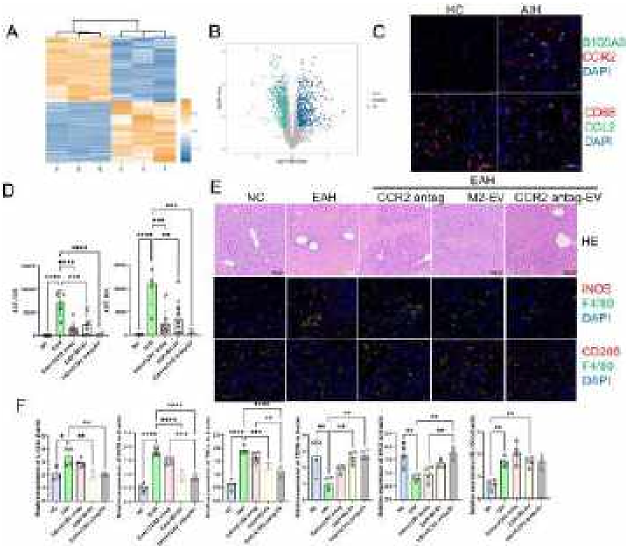
Disclosures: Robert C. Huebert – Miromatrix Medical: Advisor, No, No;
The following people have nothing to disclose: Abid Anwar, Jordan Young, Usman Yaqoob, Sofia Jerez, Nidhi Jalan-Sakrikar

108 | TARGETING OF INFLAMMATORY MONOCYTES VIA CCL2/CCR2 SIGNALING AS A THERAPEUTIC STRATEGY AGAINST AUTOIMMUNE HEPATITIS BY USING MACROPHAGE-DERIVED EXTRACELLULAR VESICLES

Xiaoli Fan[1], *Ruiqi Wu*[2], *Xiaoze Wang*[3] *and Li Yang*[1], *(1) West China Hospital, Sichuan University, (2)West China Hospital, Sichuan University, Chengdu, Sichuan, China., (3)West China Hospital*

Background: Autoimmune hepatitis is a serious chronic liver disease with immune disorders, histological lesions and liver dysfunction, with a gradually increasing prevalence. Yet the cellular and molecular mechanisms of immune dysregulation in AIH are poorly understood. **Methods:** Using proteomic analysis, we comprehensively profiled the differentially expressed proteins and signaling pathways of liver during human AIH. Then, monocytes and macrophage from blood and livers of AIH patients and controls were analyzed. The recruitment and polarization of monocyte-derived macrophages in AIH and the mechanism of CCL2/CCR2 axis activation were investigated by Concanavalin induced experimental AIH (EAH). The CCL2/CCR2 axis was blocked by CCL2 neutralizing antibody and CCR2 antagonist to determine its effect on AIH mice. Finally, M2 macrophage-derived extracellular vesicles (M2-EVs) were isolated and extracted as drug delivery tool of CCR2 antagonist, and its therapeutic effect on AIH mice was determined. **Results:** Proteomic analysis took expression ratio (FC) > 1.5 times and $p < 0.05$ as screening criteria, and a total of 1028 proteins were identified as increased or decreased. KEEG analysis suggested that differential expressed proteins were mainly associated with metabolic processes. The expression of mononuclear macrophage system marker proteins were increased in the liver tissue of AIH patients as revealed by proteomic analysis and immunohistochemistry. The proportion of classical monocytes in peripheral blood of AIH was increased, which was positively correlated with the levels of ALT and AST of AIH patients. The co-localization analysis of liver tissue suggested that CCL2 originated from Kupffer cells (KC), and the expression of CCR2 increased after circulating monocytes infiltrated liver. The expression of M1 marker in AIH liver tissue increased. AIH mouse models suggest mobilization of inflammatory monocytes on the bone marrow-liver axis and spleen-liver axis. Blocking-up of CCL2/CCR2 axis with CCL2 neutralizing antibody or CCR2 antagonist, respectively, alleviated liver injury in AIH mice, while recombinant CCL2 injection increased recruitment of inflammatory monocytes with bone marrow-liver axis and spleen-liver axis to liver, aggravating liver injury. CCR2 antagonist-M2-EV can target circulating mononuclear cells and activated mononuclear macrophages in the liver, respectively, to reduce liver injury in AIH mice. **Conclusion:** AIH mediates the recruitment of inflammatory monocytes from bone marrow and spleen to liver through the CCL2/CCR2 axis, which can be inhibited by different methods to reduce liver inflammatory injury in AIH mice. M2- EVs delivers CCR2 antagonists targeting activated pro-inflammatory monocytes and hepato-splenic mononuclear macrophage system in the circulating pool, indicating that CCR2 antagonists-EVs could be a potential agent for liver and monocyte targeted therapy for AIH.

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

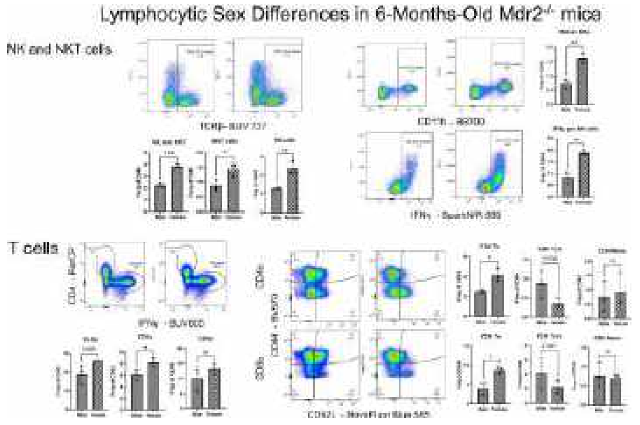


Disclosures: The following people have nothing to disclose: Xiaoli Fan, Ruiqi Wu, Xiaoze Wang, Li Yang

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

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

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



Disclosures: The following people have nothing to disclose: Grayson Way, Jing Zeng, Yun-Ling Tai,

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

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

Fanta Barrow, University of Minnesota

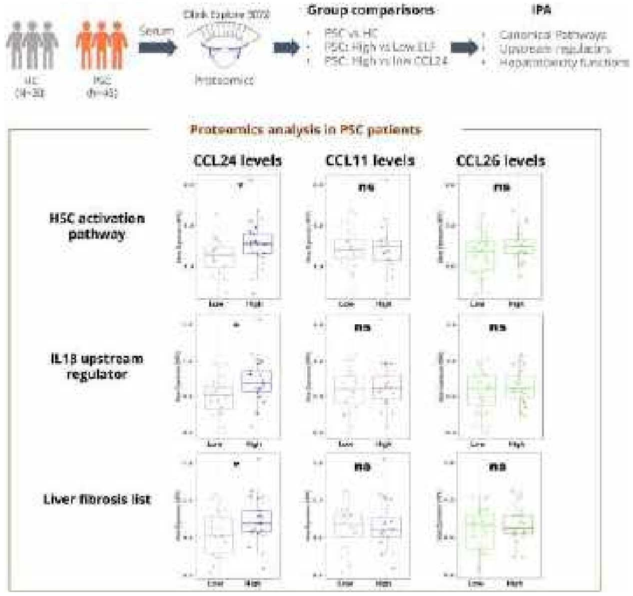
Background: Metabolic dysfunction associated steatohepatitis (MASH) involves immune mechanisms and the contribution of adaptive immunity to disease progression has been increasingly recognized. B cells, with their ability to modulate inflammation, are key players in inflammatory diseases. However, their precise role and underlying mechanisms in MASH pathogenesis remain unclear. Therefore, our research aims to investigate the mechanisms driving B cell activation and their pro-inflammatory activity in MASH. **Methods:** We established a mouse model of MASH by feeding mice a high-fat, high-carbohydrate diet to closely resemble human MASH. We focused on studying the secretome of B cells by employing Isoplexis single-cell B cell secretome analysis specifically on intrahepatic B cells from mice with MASH and healthy controls. To understand the phenotypic landscape of liver B cells during MASH, single-cell RNA sequencing was used to characterize their transcriptional profiles. Metabolic adaptations of B cells during MASH were explored using Seahorse XF assays and targeted metabolomics. To investigate the role of B cell antigen-specific responses in MASH, B cell receptor restricted mice fed the MASH-inducing diet were utilized. **Results:** Our investigation revealed a notable accumulation of pro-inflammatory B cells in the livers of MASH patients and mice fed a high-fat, high-carbohydrate diet. Single-cell B cell secretome analysis uncovered a proteomic landscape reflecting their pro-inflammatory function. Additionally, single-cell RNA sequencing identified a population of immature B cells that diminished during MASH, indicating altered maturation. We hypothesized that metabolic regulation might be involved due to these changes. Seahorse XF assays showed that B cells in MASH rely on increased oxidative phosphorylation (OXPHOS) rather than glycolysis for energy during immune activation. Importantly, we found that OXPHOS-dependent ATP production is fueled by pyruvate oxidation. Inhibiting pyruvate oxidation in MASH B cells completely abolished their pro-inflammatory potential, dependent on B cell receptor signaling. B cell receptor-restricted mice, recognizing an irrelevant antigen, displayed improved disease outcomes with enhanced fatty acid β-oxidation, decreased steatosis, and reduced fibrosis. Additionally, disease amelioration was accompanied by systemic decreases in IgG antibody isotypes, previously correlated with MASH severity in humans. **Conclusion:** Our study highlights the pro-inflammatory role of B cells in MASH, driven by metabolic adaptations and antigen-specific responses. Understanding the factors regulating B cell metabolism during inflammation could open avenues for selectively targeting their pathogenic activity in MASH.
Disclosures: The following people have nothing to disclose: Fanta Barrow

111 | SERUM PROTEOMICS REVEALS UNIQUE ASSOCIATION OF CCL24 WITH DISEASE-RELATED PATHWAYS AND SIGNATURES IN PRIMARY SCLEROSING CHOLANGITIS

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

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

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



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Raanan Greenman – Chemomab: Employee, Yes, No;
Revital Aricha – Chemomab: Employee, Yes, No;
John Lawler – Chemomab: Employee, Yes, No;
Massimo Pinzani – Chemomab: Consultant, Yes, No;
Adi Mor – Chemomab: Employee, Yes, No; Chemomab: Executive role , Yes, No;

The following people have nothing to disclose: Francesca Saffioti, Douglas Thorburn

112 | RUNX1 TRANSCRIPTION FACTOR MEDIATES THE TGF^{2} -STIMULATED INFLAMMATORY RESPONSE BY CHOLANGIOCYTES IN PRIMARY SCLEROSING CHOLANGITIS

Sayed Obaidullah Aseem[1], Jing Wang[2], Jing Zeng[3], Yunling Tai[4], Derrick Zhao[4], Grayson Way[2], Xuan Wang[4], Emily Gurley[4], Robert C. Huebert[5], Arun Sanyal[6], Phillip B. Hylemon[4] and Huiping Zhou[2], (1)Department of Internal Medicine and GI Division, Medical College of Virginia, Virginia Commonwealth University, Midlothian, VA, (2)Virginia Commonwealth University, (3)Department of Microbiology and Immunology, Medical College of Virginia and Mcguire Veterans Affairs Medical Center, Virginia Commonwealth University, Richmond, VA, United States, (4)Department of Microbiology and Immunology, Medical College of Virginia and Mcguire Veterans Affairs Medical Center, Virginia Commonwealth University, Richmond, VA, (5)Mayo Clinic Rochester, Rochester, MN, (6)Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

Background: Primary sclerosing cholangitis (PSC) is marked by inflammation and progressive biliary fibrosis, which can lead to cirrhosis and its complications. Cholangiocytes activated by transforming growth factor-β (TGF*β*) signal to immune cells and activate hepatic myofibroblasts to deposit the extracellular matrix. Our previous data suggest that TGFβ-mediated transcriptomic changes in cholangiocytes may occur through runt-related transcription factors (RUNX). However, studies of RUNX1 in hepatobiliary fibrosis have revealed conflicting findings because of unexplored mechanistic understanding in cholangiocytes, which is the focus of this study. **Methods:** Mouse large biliary epithelial cells (MLE) and PSC-derived cholangiocytes (PSC-C) were used to test the effects of RUNX inhibitors (Ro5-3335 and AI-10-104) and siRNA knockdown on TGFβ-mediated signaling. Multidrug resistance 2 deleted ($Mdr2^{-/-}$) mice (12 weeks, male and female) were treated with the RUNX inhibitor Ro5-3335 intraperitoneally at 50 mg/kg every other day for 3 weeks. **Results:** RUNX1 mRNA is significantly increased in TGFβ-treated cholangiocytes, $Mdr2^{-/-}$ mouse cholangiocytes and RNA-seq of PSC tissue (Log Fc 1.63) (GEO data set: GSE159676). RUNX inhibitors significantly reduced the expression of fibroinflammatory markers such as platelet-derived growth factor B (PDGFB) and interleukin 6 (IL-6) in TGFβ treated MLE. Ro5-3335, also reduced the basal expression of PDGFB and IL-6 in PSC-C. RUNX1 specific siRNA knockdown in PSC-C reduced the basal expression of IL-6. Conversely, the expression of anti-inflammatory and anti-fibrotic, peroxisome proliferator-activated receptor γ (PPARγ) was increased. Mdr2$^{-/-}$ mice treated with Ro5-3335 showed significant reductions in serum alanine transaminase and hepatic expression of inflammatory markers (Il-6, Tnfa, Il-1b, Nfkb) by 40-75% but not the anti-inflammatory cytokine, Il-10. In contrast, mRNA markers (Collagen, ±Smooth muscle actin) and picrosirius red histological staining of fibrosis did not show a significant reduction. **Conclusion:** RUNX1 has an essential role in TGFβ-mediated activation of the inflammatory response in cholangiocytes and Mdr2$^{-/-}$ mice. We are conducting longer *in vivo* experiments of RUNX inhibition to determine the effects on biliary fibrosis. Cholangiocyte-selective RUNX1 knockout mice will also be used for further investigation. Targeting RUNX1 may represent a novel therapeutic strategy in cholestatic liver disease.

Disclosures: Sayed Obaidullah Aseem – Parvus Therapeutics: Consultant, No, Yes;

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

The following people have nothing to disclose: Jing Zeng, Yunling Tai, Derrick Zhao, Grayson Way, Xuan Wang, Emily Gurley, Phillip B. Hylemon, Huiping Zhou

Disclosure information not available at the time of publication: Jing Wang

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

Kota Tsuruya[1], Akihide Kamiya[2], Yusuke Mishima[1], Yoshitaka Arase[1], Akira Honda[3] and Tatehiro Kagawa[1], (1)Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokai University School of Medicine, (2)Department of Molecular Life Sciences, Tokai University School of Medicine, (3)Joint

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

Research Center, Tokyo Medical University Ibaraki Medical Center

Background: Progressive familial intrahepatic cholestasis (PFIC) 3 is a life-threatening hereditary disease caused by adenosine triphosphate-binding cassette subfamily B member 4 (ABCB4) gene mutations. The murine bile acid composition is different from that of humans. Mice are less likely to develop cholestasis due to the predominance of hydrophilic bile acids such as muricholic acids, which are synthesized by enzymes including Cyp2c70. In this study we utilized Cyp2a12/Cyp2c70 double-knockout (DKO) mice which have human-like hydrophobic bile acid composition. We induced liver-specific Abcb4 deletion using adeno-associated virus (AAV)-mediated Cas9 and gRNA expression vectors in the DKO mice and investigated whether this mouse model would represent human PFIC3. **Methods:** We constructed an AAV vector containing SaCas9 under a liver-specific promoter. The DKO and wild type (WT) mice were infected with AAV containing SaCas9 and gRNAs against Abcb4. Liver injury, bile acid metabolism and gene expression were analyzed in 5 weeks after infection. **Results:** Abcb4 deficient DKO mice (Abcb4-DKO) showed a significant increase in the body-liver weight ratio compared with Abcb4 deficient WT mice (Abcb4-WT). Liver enzymes were significantly elevated in Abcb4-DKO compared with WT and Abcb4-WT; AST: 35.3 ± 31.5, 323.5 ± 173.7 and 740.2 ± 358.1, ALT: 33.5 ± 51.2, 393 ± 65.9 and 1284.8 ± 416.4, and ALP: 129.0 ± 53.2, 260 ± 63.3 and 614.8 ± 342.5 IU/L (mean ± SD), in WT, Abcb4-WT and Abcb4-DKO, respectively, suggesting the presence of severe liver injury in Abcb4-DKO. Serum total bile acid levels in Abcb4-DKO were also higher than Abcb4-WT (9.1 ± 6.1 vs. 5.8 ± 0.9 μmol/L). Abcb4-DKO showed more intense inflammatory cell infiltration in the portal region and scattered CK19 positive cells representing ductal reaction than Abcb4-WT. The mRNA expressions of mCol1a1 and mTimp-1 were significantly increased in Abcb4-DKO, indicating the progression of liver fibrosis. Analysis of bile acid composition in the liver demonstrated increase of TCDCA and decrease of TDCA in Abcb4-DKO. **Conclusion:** Abcb4 deficient mice with human-like bile acid composition showed severe liver inflammation compared with Abcb4 deficient WT mice, suggesting the importance of hydrophobic bile acid composition to induce liver injury. This mouse could be a useful tool for cholestasis research as a PFIC3 animal model.

Disclosures: Kota Tsuruya – Chugai Pharmaceutical Co., Ltd.: Speaking and Teaching, No, Yes; ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, No, Yes; Eisai Co., Ltd.: Speaking and Teaching, No, Yes; Kowa Company, Ltd.: Speaking and Teaching, No, Yes; AbbVie GK: Speaking and Teaching, No, Yes;

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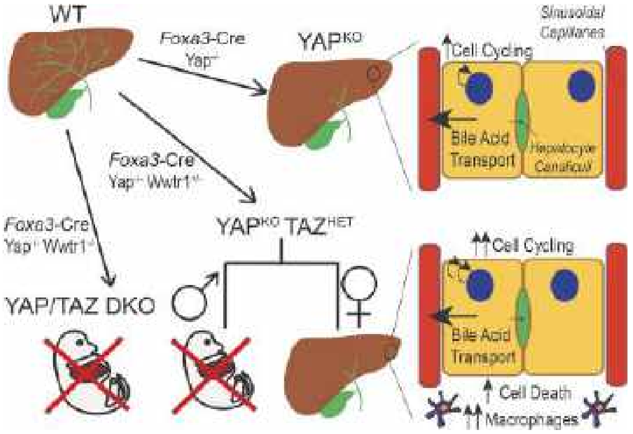
Tatehiro Kagawa – Chugai-pharma: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Sumitomo Pharma: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Mitsubishi Tanabe Pharma: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Eisai: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Abbvie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; EA pharma: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Otsuka Pharmaceutical: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Kyowa Kirin: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Teijin: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Japan Blood Products Organization: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Chugai-pharma: Speaking and Teaching, No, Yes; Sumitomo Pharma: Speaking and Teaching, No, Yes; Eisai: Speaking and Teaching, No, Yes; Abbvie: Speaking and Teaching, No, Yes; Gilead Sciences: Speaking and Teaching, No, Yes; Takeda Pharmaceutical Company: Speaking and Teaching, No, Yes; MSD: Speaking and Teaching, No, Yes; Kowa Company: Speaking and Teaching, No, Yes; EA pharma: Speaking and Teaching, No, Yes; Otsuka Pharmaceutical: Speaking and Teaching, No, Yes; Kyowa Kirin: Speaking and Teaching, No, Yes; AstraZeneca: Speaking and Teaching, No, Yes; Nobelpharma: Speaking and Teaching, No, Yes; Eli Lilly: Speaking and Teaching, No, Yes; Miyarisan: Speaking and Teaching, No, Yes; ASKA Pharmaceutical: Speaking and Teaching, No, Yes;

The following people have nothing to disclose: Akihide Kamiya, Yusuke Mishima, Akira Honda

114 | LOSS OF TAZ AFTER YAP DELETION SEVERELY IMPAIRS FOREGUT DEVELOPMENT AND WORSENS CHOLESTATIC HEPATOCELLULAR INJURY

Laura Molina[1], Adelya Gabdulkhakova[2], Yekaterina Krutsenko[3], Junjie Zhu[4], Silvia Liu[3], Minakshi Poddar[5], Sucha Singh[5], Xiaochao Ma[4] and Satdarshan (Paul) Monga[1,3], (1)University of Pittsburgh Medical Center, (2) University Hospital Heidelberg, (3)University of Pittsburgh School of Medicine, (4)University of Pittsburgh School of Pharmacy, (5)University of Pittsburgh

Background: We previously showed that loss of Yes-associated protein 1 (YAP) in early liver development (YAP^{KO}) leads to an Alagille syndrome-like phenotype, with failure of intrahepatic bile duct development, severe cholestasis, and chronic hepatocyte adaptations to reduce liver injury. TAZ, a paralog of YAP, was significantly upregulated in YAP^{KO} hepatocytes and interacted with TEAD transcription factors, suggesting possible compensatory activity. **Methods:** We deleted both *Yap1* and *Wwtr1* (which encodes TAZ) during early liver development using the *Foxa3* promoter to drive Cre expression, similar to YAP^{KO} mice, resulting in YAP/TAZ double knock out (DKO) and YAP^{KO} with TAZ heterozygosity (YAP^{KO} TAZ^{HET}). We evaluated these mice using immunohistochemistry, serum biochemistry, bile acid profiling, and RNA-sequencing. **Results:** DKO mice were embryonic lethal, but their livers were similar to YAP^{KO}, suggesting an extrahepatic cause of death. Male YAP^{KO} TAZ^{HET} mice were also embryonic lethal, with insufficient samples to determine the cause. However, YAP^{KO} TAZ^{HET}females survived and were phenotypically similar to YAP^{KO} mice, with increased bile acid hydrophilicity and similar global gene expression adaptations but worsened hepatocellular injury. TAZ heterozygosity in YAP^{KO} impacted expression of canonical YAP targets *Ctgf* and *Cyr61*, and we found changes in pathways regulating cell division and inflammatory signaling correlating with an increase in hepatocyte cell death, cell cycling, and macrophage recruitment. **Conclusion:** YAP loss (with or without TAZ loss) aborts biliary development. YAP and TAZ play a co-dependent critical role in foregut endoderm development outside the liver, but they are not essential for hepatocyte development. TAZ heterozygosity in YAP^{KO} had a subtle impact on cell cycling and inflammatory signaling in the setting of chronic injury, highlighting genes that are especially sensitive to TAZ regulation, and may exacerbate cholestatic liver injury.



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Disclosure information not available at the time of publication: Adelya Gabdulkhakova, Yekaterina Krutsenko, Junjie Zhu, Silvia Liu, Xiaochao Ma

115 | ELUCIDATING THE MECHANISMS OF KIF12-MEDIATED HIGH GGT CHOLESTASIS★

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Background: We and others have shown that rare bi-allelic loss-of-function mutations in Kinesin family member 12 (*KIF12*) cause pediatric high-GGT cholestasis as well as fibrosis, ductular reaction, and bile duct loss. KIF12 has putatively been defined as a microtubule-associated motor protein, but little is known about its function and even less about its role in the pathogenesis of cholestasis. **Methods:** We used Crispr-Cas9 technology to introduce a homozygous Arg219 premature termination mutation (Arg219*) reported in 6 patients into a human induced pluripotent stem cell (hiPSC) line. Wild-type and Arg219* hiPSCs were differentiated into cholangiocyte-like cells (iCCs) using a protocol that induces definitive endoderm followed by hepatic endoderm, hepatoblast, and finally iCCs. These iCCs were plated as monolayers, polarized on transwells, and cultured as 3D basolateral-out and apical-out organoids. Confocal microscopy was used to visualize protein markers and organelle localization. GGT activity and secretin response were performed. qPCR and bulk RNA sequencing were used to identify transcriptomic signatures. **Results:** iPSC differentiated cholangiocytes display stage specific markers in both wild-type and Arg219* cells. Arg219* cells showed no detectable defects in growth rate, actin cytoskeleton or iCCs maturation markers but demonstrated increased GGT activity. RNA sequencing between KIF12 mutant and wild-type iCCs identified differential expression in ~100 genes with gene ontology suggesting underrepresentation of proteins with extracellular signaling domains ($p = 2.5*10^{-8}$) in KIF12 mutant iCCs. Confocal microscopy demonstrated gross organelle localization defects with decreased mitochondrial footprint ($p = 1.8*10^{-5}$), decreased lysosomal distance to nucleus ($p < 2.2*10^{-16}$), and defects in cilia positioning in KIF12 mutant iCCs as compared to wild-type iCCs controls. To better understand cilia defects we performed 3D organoid culturing. Organoids also demonstrated mature cholangiocyte markers such as CK7 and CK19 as well as functional capability as demonstrated by secretin swelling protocol. Cilia were present on organoids but exhibited mislocalization to the basolateral membrane in Arg219* iCCs, independently of membrane polarization. **Conclusion:** Using iPSC differentiated cholangiocytes we have demonstrated that *KIF12* deficiency leads to increased GGT, transcriptional alterations with decreased extracellular signaling, and pronounced organelle mislocalization, possibly due to an impairment in organelle trafficking. This evidence implicates kinesins as critical mediators of cell homeostasis and provides new cellular and molecular insights into human cholestatic liver disease pathogenesis.

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Disclosure information not available at the time of publication: Nina Dashti-Gibson, Anubha Seth, Silvia M. Vilarinho

116 | EFFECTIVENESS AND SAFETY OF SECOND-LINE THERAPY IN PRIMARY BILIARY CHOLANGITIS (PBC): A PROSPECTIVE MULTICENTER REAL-WORLD COHORT

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Background: About 30% of patients with PBC have a suboptimal response to ursodeoxycholic acid (UDCA), leading to a worse prognosis. In the phase III POISE trial, response to obeticholic acid (OCA) was assessed by using the POISE score. Recently, complete biochemical normalization (normal ALP and bilirubin d 0.6 ULN) has been proposed as a new therapeutic aim in PBC, as it significantly improves liver-related and overall survival, but the effectiveness of second-line therapy for this new therapeutic target has not been evaluated. **Methods:** Prospective, multicentre real-world clinical practice study including PBC patients non-responders to UDCA according to Paris II criteria, from 25 hospitals from Spain and Portugal. All patients received OCA or OCA plus fibrates (19.25%), and the study evaluated the safety and effectiveness of treatment on biochemical and liver function scores, GLOBE-

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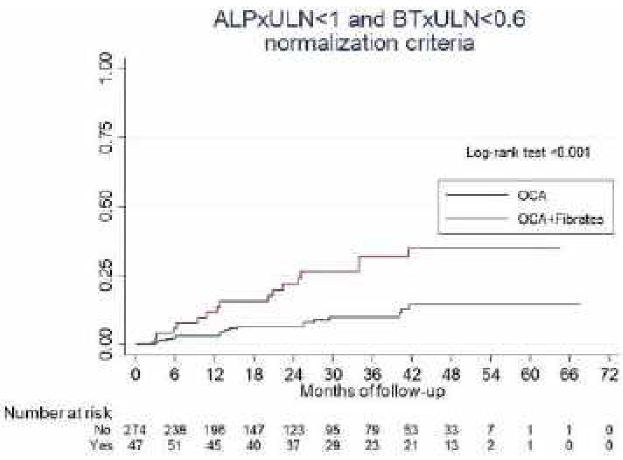
PBC and UK-PBC at 5 years. POISE response rates, biochemical complete response, incidence of decompensation, liver-related survival and safety were also assessed. **Results:** The study included 316 patients, with a median follow-up of 26.3 months (IQR: 13.3-43.3). ALP, GGT and aminotransferases decreased ($p < 0.01$), while serum albumin increased ($p < 0.01$) and bilirubin also decreased ($p = 0.013$). Globe-PBC and UK-PBC scores at 5 years improved ($p < 0.01$). At 12 months, 41.7% achieved a POISE response by intention-to-treat (ITT) analysis. Factors associated with POISE response in the univariate analysis were absence of cirrhosis, lower serum bilirubin and lower values of FIB-4, APRI, CPT, Globe and UK-PBC scores, as well as higher serum albumin, higher platelet count and triple therapy. After adjusting for sex, age, cirrhosis, albumin levels, bilirubin, platelet count and baseline OCA dose, triple therapy, serum albumin and bilirubin remained associated with POISE response. Triple therapy was more likely to achieve a complete biochemical response compared to dual therapy (fig. 1). Liver-related survival at 36 months was 97.3% (95% CI 94-98.8). OCA discontinuation occurred in 18.2% of patients. Decompensation, death and liver transplantation occurred in 19, 3 and 4 patients, respectively. Of the 72 patients with cirrhosis, 16 experienced decompensation, all of them with APRI e 0.75 (AUROC: 0.77, CI: 0.65-0.89). **Conclusion:** Second-line therapy with OCA or OCA plus fibrates showed long-term positive effects on liver biochemistry and liver function in patients with PBC non-responders to UDCA. Triple therapy was more effective than dual therapy in achieving a POISE response and a complete biochemical response. The treatment appears safe in the early stages of cirrhosis.



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The following people have nothing to disclose: Jose-Luis Montero, Marta Casado, Miguel Angel Simon, Javier Fuentes, Alvaro Diaz-Gonzalez, Isabel Conde, Isabel Garrido, Guilherme Macedo, Jose Antonio Presa, Sergio Rodriguez-Tajes, Ignasi Olivas, Eva Romero-Gonzalez, Sheila Gonzalez-Padilla, Desamparados Escudero-Garcia, Dario Lorga Gomes, Luis Santos, Antonio Olveria, Manuel Hernandez-Guerra, Manuel A. Santos, Armando S P Carvalho, Juan Uriz, Maria Luisa Gutierrez, Marta Quinones, Elia Perez, Javier Martinez, Agustin Albillos, Conrado Fernandez-Rodriguez

117 | A-LINK: UTILIZING A LEARNING HEALTH NETWORK MODEL FOR IMPROVING OUTCOMES IN AUTOIMMUNE HEPATITIS

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Background: A-LiNK (Autoimmune Liver disease Network for Kids) is a collaborative, multi-center learning health network uniting patients, parents, clinicians, researchers, and stakeholders to address gaps in care for children with Autoimmune Liver Disease. We seek to define predictors of optimal outcomes and determine current practices in Autoimmune Hepatitis (AIH). **Methods:** Patients aged 1-21 years old with AIH and e 1 year of follow-up were included in a retrospective registry, with clinical data collected at diagnosis and every 3 months for 1 year. The primary endpoints were biochemical remission rate (defined as normal serum AST and ALT based on

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age/sex) 6 months after diagnosis and predictors of non-remission. In an accompanying prospective cohort, patients with AIH had laboratory values, clinical findings, and patient-reported outcomes documented. Key outcomes were rates of biochemical and steroid-free remission. Statistical analysis for significance utilized Fischer's p test for dichotomous variables and Wilcoxon rank sum for continuous variables. **Results:** Seven A-LiNK centers included 116 patients with AIH in a retrospective cohort: 64% female, 71% white, and 17% African American. Within 1.5 months of diagnosis, 98% were treated with IV/oral corticosteroids, 14% budesonide, and 54% immunomodulators. Of 72 patients with 6-month biochemistries, 65% were in biochemical remission. Non-remission at 6 months was associated with being female; African American; low serum albumin and hematocrit; and elevated IgG, white blood cell count, and INR (all $p < 0.05$). Type of immunosuppression at induction was not associated with remission at 6 months. Prospectively, 4 A-LiNK centers enrolled 36 patients with AIH from March 2022-May 2023 with 61 visits. Participants had similar demographics as the retrospective cohort. The median age at enrollment was 16.4 years, with a median 3.8 years since diagnosis. Most patients were on immunosuppression: 42% prednisone, 25% budesonide, 61% azathioprine, 19% mycophenolate mofetil, and 6% tacrolimus. Only 3 patients were off immunosuppression. At initial visit, 11 (31%) endorsed fatigue and/or abdominal pain; 5 had steroid-associated complications, and 2 experienced complications of portal hypertension. Key outcomes of biochemical and steroid-free remission rates were reported monthly, shown in Figure 1. **Conclusion:** In a multi-center retrospective cohort, only 65% of patients with AIH achieved remission 6 months after diagnosis, with female and African American children less likely to enter remission. In a prospective prevalence study, only 61% were in remission and 33% were in steroid-free remission at a median of 3.8 years after diagnosis. These findings highlight the ongoing need for better pharmacological therapy and application of guideline-based care and is foundational for future implementation trials to improve biochemical and steroid-free remission rates in AIH.

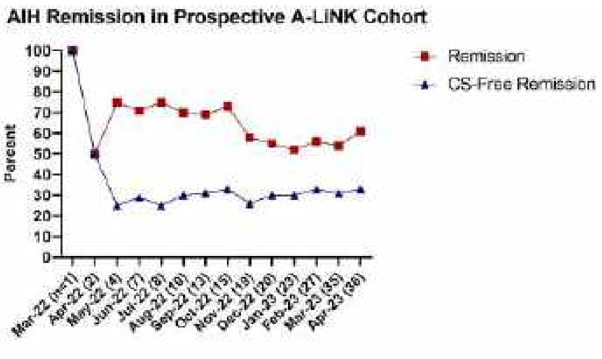

Figure 1: Remission rates in AIH. Enrollment began in March 2022 with patients of any age with a clinical diagnosis of AIH. Patients received care per provider/center practice. Running totals of patients enrolled were documented monthly, with biochemical remission and corticosteroid-free remission rates plotted for new and subsequent visits. For patients with multiple visits, monthly percentages were updated to reflect changes in remission status.

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118 | SPLEEN STIFFNESS MEASUREMENT BY TRANSIENT ELASTOGRAPHY WITH A SPLEEN-DEDICATED MODULE: A PROSPECTIVE PILOT FEASIBILITY STUDY IN A PEDIATRIC COHORT

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Background: Several studies in adults showed that spleen stiffness measurement (SSM) by vibration-controlled transient elastography (VCTE) can accurately assess clinically significant portal hypertension (HTN) and predict presence of esophageal varices. However, pediatric studies on SSM published thus far have used a liver-specific probe to measure the spleen making them difficult to interpret and possibly overestimating SSM, as the spleen is inherently a stiffer organ than the liver. The new dedicated spleen stiffness examination of the FibroScan® 630 uses a higher shear wave frequency (100 Hz v. 50 Hz) and can measure to a higher SSM (100 kPa v 75 kPa) compared to the liver-specific one. Given unique measurement challenges in children and lack of pediatric data, we aimed to conduct a feasibility study to assess SSM with the new spleen-dedicated examination in a cohort of pediatric patients. **Methods:** We conducted a prospective pilot study enrolling patients with chronic liver disease aged 5-30 years followed at Boston Children's Hospital. Subjects underwent SSM by VCTE with the spleen-dedicated examination on the M probe (FibroScan® 630) and liver stiffness measurement (LSM) by conventional VCTE. Laboratory data were collected if obtained within 1 month of SSM. **Results:** 152 patients (67% male) with median age 15 years [IQR 11, 18] were enrolled. Most common liver disorders were NAFLD (44%), viral hepatitis (10%), and biliary atresia (6%). Median weight was 68.8 kg [IQR 50, 88]. Laboratory data showed median [IQR] ALT 39 IU/L [20, 69], GGT 27 IU/L [17, 45], albumin 4.6 g/dL [20, 69], direct bilirubin 0.2 mg/dL [0.2, 0.2], INR 1.02 [0.94, 1.07], and platelet count 268 x10^9/L [211, 312, 13% < 150]. Thirteen percent of patients had a palpable spleen on exam. LSM was successfully obtained in 142 patients

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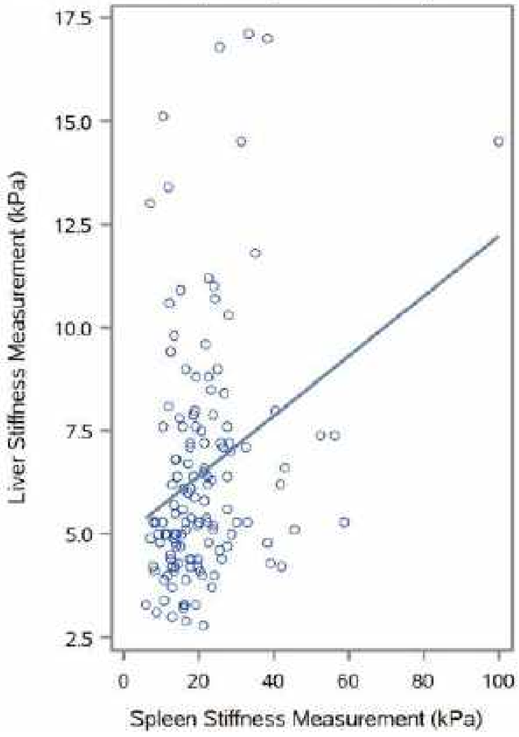
using a S1 (1%), M (77%) and XL probe (22%). Median LSM value was 5.5 kPa [IQR 4.7, 7.4] (15.5% LSM > 8.6 kPa); median CAP score was 239 [IQR 191, 291]. SSM was successfully obtained in 146 (96%) patients with an overall failure rate of 4% due to a high skin-to-capsule distance. Median SSM was 18.5 kPa [IQR 13.7, 25] and 11 (7.5%) patients had a SSM e 40. SSM significantly correlated with LSM ($p < 0.001$; Pearson coefficient 0.3) [Fig.], AST ($p < 0.001$), ALT ($p < 0.001$) and GGT ($p = 0.001$). **Conclusion:** This is the first study to show feasibility and extremely high success rate of the novel spleen-dedicated examination to measure SSM in children. With such spleen specific acquisition settings, feasibility and correlation to LSM, the novel spleen-dedicated SSM examination is a promising, more accurate tool to monitor for the evolution of portal HTN and its complications in children with liver disease.

Fig. Correlation between spleen stiffness measurement and liver stiffness measurement measured by vibration-controlled transient elastography with the new spleen-dedicated examination on the M probe (FibroScan® 630).



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119 | A PILOT STUDY OF MULTIPLEXED PROTEOMIC NEWBORN SCREENING FOR WILSON DISEASE IN WA STATE

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Background: Newborn Screening (NBS) is successful in identifying infants with fatal but treatable disorders enabling early intervention with favorable outcomes. Unfortunately, many congenital disorders in particular Wilson disease do not feature specific metabolic biomarkers nor analytical methods suitable for NBS even where highly effective preemptive treatments are available. In our recent study, we demonstrated that direct measurements of the ATP7B itself using multiplexed proteomic methods from dried blood spots can be highly diagnostic and utilized in population screening for Wilson disease. Through quantification of the extremely low abundance intracellular proteins in dried blood spots, patients with Wilson Disease are readily detected. **Methods:** A first-in-class proteomic-based in vitro diagnostic (IVD) reagent kit has been manufactured under the GMP facility for identification of the four new conditions (Wilson disease, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and Adenosine Deaminase deficiency (ADAD) in a single-run multiplex assay from DBS by LC-MS/MS. Within the assay range, linearity, accuracy, and precision were acceptable. A pilot study screening newborns in WA state for targeted conditions was initiated after IRB approval. Genetic sequencing of samples with peptide concentrations below tentative cutoffs is used for confirmation. **Results:** Kit validation shows consistent performance and inject-to-inject time is < 3 minutes. 19,100 newborns have been screened to date. Gender, ethnicity, birthweight and time of collections were included in the analysis. No differences in gender, ethnicity or birthweight are observed for ATP7B peptides. Two potential cases (one likely carrier and one uncertain) have been identified for Wilson disease to date. The first case carried one pathogenic variant, p.Gly626Ala and one likely benign variant, pLeu1015 = . ATP7B peptides were marginally below the cutoffs. The second case

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presented with two variants of uncertain significance, p. Pro610Leu and p.Arg1224Leu. ATP7P887 peptide was marginally below the cut off (71.0 pmol/L, cutoff = 75.7) while ATP7B1056 peptide was in the normal range. The overall rates of false positive were very low for all four conditions. **Conclusion:** This study highlights the use of novel IVD assay demonstrating the feasibility of LC-MS/MS proteomics for NBS of Wilson disease and other inborn errors of immunity.

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120 | THE SIGNIFICANT ASSOCIATION BETWEEN PNPLA3 G ALLELE AND ADVANCED FIBROSIS IN CHILDREN WITH NAFLD IS FURTHER INFLUENCED BY BMI AND type2 DIABETES★

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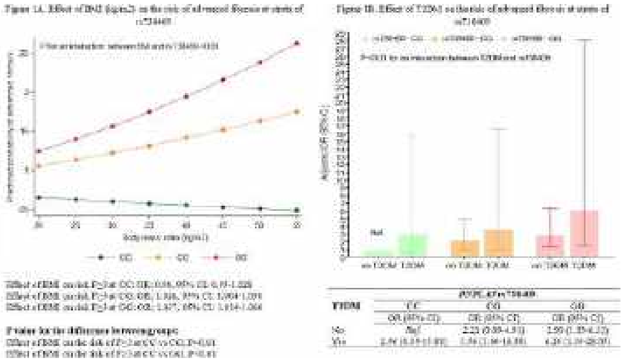
Background: *PNPLA3* rs738409 polymorphism, obesity, and type 2 diabetes mellitus (T2DM) are strongly associated with non-alcoholic fatty liver disease (NAFLD) and its severity in children. Whether *PNPLA3* rs738409-related predisposition to NAFLD severity is influenced by obesity and T2DM in children with NAFLD is not known. Therefore, we examined the relationship between *PNPLA3* rs738409, body mass index (BMI), T2DM, and the risk of advanced fibrosis in children with biopsy-proven NAFLD. **Methods:** 1,047 children between 2 and 18 years of age with biopsy-proven NAFLD enrolled into Non-Alcoholic Steatohepatitis Research Network prospective studies were analyzed. The primary study outcome was biopsy-confirmed advanced fibrosis (fibrosis stage e 3,). T2DM was defined as self-reported, or HbA1c levels e 6.5%, or fasting plasma glucose of e 126 mg/dl, or current use of glucose-lowering medications. Logistic regression models were used to examine associations of rs738409 (additive model of inheritance; CC, CG, or GG), T2DM, and BMI with advanced fibrosis, while controlling for race/ethnicity, sex, and hypertension. Multiplicative interaction terms between rs738409, T2DM, BMI, and age were included in all models. **Results:** The cohort consisted of 724 Hispanics (69%) and 261 non-Hispanic Whites (25%).The *PNPLA3* rs738409 variant was present at a frequency of 0.76. Among all children, rs738409 genotypes were distributed as follows: CC (n = 149, 14.3%), CG (n = 363, 34.6%), and GG (n = 535, 51.1%). The prevalence of advanced fibrosis was 13%. Out of 140 children with advanced fibrosis, 130 (93%) carried at least one *PNPLA3* G allele (CG; 44/130 (33.8%) or GG; 86/130 (66.2%)). The *PNPLA3* G allele was independently associated with a high risk of advanced fibrosis (OR: 1.55, 95% CI: 1.16-2.09). Compared with individual's with *PNPLA3* CC genotype, the risk of advanced fibrosis increased by 2.1-fold (95% CI: 1.0-4.3) for children with CG genotype and 2.8-fold (95% CI: 1.4-5.8) for children with GG genotype. BMI was independently associated with advanced fibrosis, with stronger effects seen in children with *PNPLA3* CG (OR: 1.03, 95% CI: 1.004-1.05) and GG (OR: 1.04, 95% CI: 1.014-1.06), compared with CC (OR: 0.99, 95% CI: 0.95-1.03) genotypes (*Figure 1A*), p for interaction < 0.01. T2DM was positively associated with the risk of advanced fibrosis, with stronger effects among children with CG (OR: 3.6, 95% CI: 1.0-16.6) and GG (OR: 6.2, 95% CI: 1.4-28.0) compared with CC (OR: 2.9, 95% CI: 0.5-15.8) genotypes (*Figure 1B*), p for an interaction < 0.01. **Conclusion:** *PNPLA3* G-allele, higher BMI and T2 DM are significantly associated with advanced fibrosis in children with NAFLD, The adverse relationship between *PNPLA3* G allele and advanced fibrosis is significantly worsened by higher BMI and type2 diabetes. This indicates aggressive attention to BMI and T2DM is particularly important in children with NAFLD carrying *PNPLA3* G-allele.



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121 | SERUM BILE ACIDS ARE ASSOCIATED WITH NATIVE LIVER SURVIVAL IN PATIENTS WITH ALAGILLE SYNDROME: RESULTS FROM THE GALA STUDY GROUP

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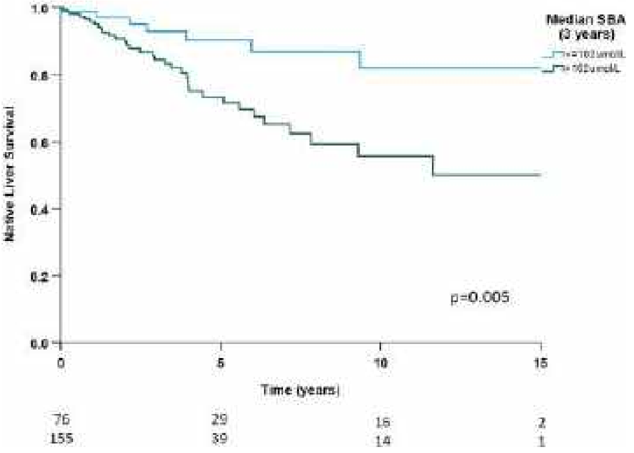
Background: Alagille syndrome (ALGS) is a rare, autosomal dominant multisystem disorder characterized by cholestasis and extrahepatic manifestations. Given the current era of ileal bile acid transporter (IBAT) inhibitor therapies that reduce serum bile acid (SBA) levels, the aim of this study was to determine whether SBA are a predictor of clinical outcomes in ALGS. **Methods:** Patients were ascertained from the GALA cohort, an international multicentre study including clinically and/or genetically diagnosed children with ALGS. Those with neonatal cholestasis and at least one SBA measurement during follow-up were eligible for inclusion. An established SBA threshold in progressive familial intrahepatic cholestasis (PFIC) (102 umol/L) was assessed as a time-dependent covariate in Cox regression analyses for native liver survival (NLS); liver transplantation and death as endpoints, overall and while adjusting for total bilirubin (TB) levels and stratified by geographical region. The association between median SBA in the first 3 years according to the PFIC threshold and NLS was also assessed. Patients who did not meet one of these endpoints were truncated at the time of biliary diversion, Kasai procedure, trial enrollment, or their last follow-up, up to a maximum of 18 years of age. **Results:** 570 patients from GALA were included, of whom 348 (61.1%) were male with a median year of birth of 2012 (IQR 2007-2015). Rates of NLS at 1, 5 and 18 years were 97.2%, 81.8%, and 53.6%, respectively. There is a moderate positive correlation between SBA and total bilirubin (Pearson correlation = 0.47, $p < 0.001$). The was a significant predictor of outcome (HR = 3.78, 95% CI 2.39-5.99, $p < 0.001$) and there was no significant difference in the impact of SBA between the first ($p = 0.32$). SBA remained a significant factor for NLS while adjusting for TB clearance at 1 year (HR = 2.00, 95% CI 1.10-3.65, $p = 0.02$), where clearance is defined as TB < 2 mg/dL. There was no significant interaction between the SBA threshold and clearance of TB. Furthermore, if median SBA in the first 3 years was above 102 umol/L, patients had lower NLS at 8 years of age (Figure, $p = 0.005$), including in those with favourable bilirubin trends (90.9% vs. 95.9, $p = 0.04$). **Conclusion:** SBA is an independent predictive factor for NLS in children with ALGS and neonatal cholestasis. Of note, SBA is also associated with NLS in children with ALGS who clear their bilirubin i.e. those with anicteric cholestasis. This is relevant in the context of IBAT inhibitors that promote a reduction in SBA and are currently indicated for pruritus but may also impact additional important clinical outcomes.



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122 | INDIVIDUAL PRURITUS AND BILE ACID RESPONSES OVER TIME WITH ODEVIXIBAT TREATMENT: POOLED DATA FROM THE PHASE 3 ASSERT AND ASSERT-EXT STUDIES IN PATIENTS WITH ALAGILLE SYNDROME

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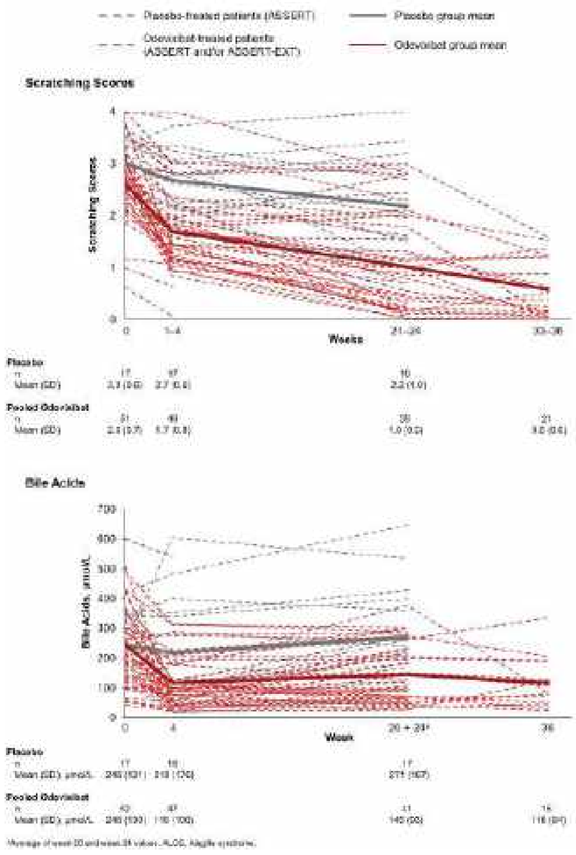
Background: Alagille syndrome (ALGS) is a rare, genetic, multisystem disorder in which cholestatic liver disease is common and that may include clinical manifestations of severe pruritus and elevated bile acids (BAs). The efficacy and safety of odevixibat, an ileal bile acid transporter inhibitor, were assessed in patients with ALGS in the phase 3 ASSERT and ASSERT-EXT trials. Using data from these studies, we analyzed the effects of odevixibat on pruritus and BAs over time. **Methods:** ASSERT (NCT04674761) was a randomized, placebo-controlled study that enrolled patients with ALGS who had a history of significant pruritus and elevated serum BAs. Patients were randomized 2:1 to odevixibat 120 μg/kg/day or placebo, respectively, and received treatment for 24 weeks. Patients who completed ASSERT could enter ASSERT-EXT (NCT05035030), an ongoing, 72-week open-label extension study in which all patients receive odevixibat 120 μg/kg/day. The primary endpoint in these studies was related to change in pruritus scores, evaluated using the PRUCISION observer-reported instrument (range, 0−4, with higher scores indicating worse symptoms). A secondary endpoint in both studies was change in serum BAs. Changes over time in scratching scores and BAs were analyzed in odevixibat-treated patients from ASSERT and/or ASSERT-EXT in a pooled analysis of data that spans from patients' first dose of odevixibat to a data cutoff date of September 9, 2022; data from patients who received placebo in ASSERT are presented for comparison. **Results:** At the data cutoff, 52 odevixibat-treated patients comprised the pooled population; 17 patients who received placebo in ASSERT subsequently received odevixibat in ASSERT-EXT. Odevixibat-treated patients had rapid reductions in mean scratching scores and BA levels that were sustained over time; responses in individual patients are shown in the Figure. At the data cutoff date, treatment-emergent adverse events (TEAEs) were reported in 83% (43 of 52) of odevixibat-treated patients and in 71% (12 of 17) of placebo-treated patients. The most common TEAEs during odevixibat treatment were diarrhea (29%; 6% with placebo) and pyrexia (21%; 24% with placebo). Drug-related TEAEs occurred in 29% of odevixibat-treated patients (15 of 52) and in 18% of placebo-treated patients (3 of 17). In the odevixibat-treated group, the only drug-related TEAEs occurring in > 1 patient were diarrhea (6 patients, 12%) and abdominal pain, upper abdominal pain, and vomiting (each in 2 patients, 4% each). No odevixibat-treated patients had TEAEs leading to treatment discontinuation as of the data cutoff date. **Conclusion:** In patients with ALGS, odevixibat treatment for up to 36 weeks resulted in improvements in pruritus and reduced BA levels; these changes occurred rapidly, with effects sustained over time. Most TEAEs with odevixibat were related to diarrhea and were mild or moderate in severity.

Figure. Scratching Scores (A) and Bile Acid Levels (B) From Individual Patients With ALGS Who Received Odevixibat in ASSERT and/or ASSERT-EXT or Placebo in ASSERT



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123 | SPATIAL TRANSCRIPTOMICS IDENTIFIES IMMUNE EXPANSION OF SCAR REGIONS AND REDUCED HEPATOCYTE ZONATION IN LIVERS FROM PATIENTS WITH BILIARY ATRESIA

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Background: Multiple metabolic and inflammatory pathways have been associated with patient outcome in biliary atresia (BA), however, the spatial relevance of these pathways among BA and non-BA disease controls has not been well defined. In the present study, we overcome this gap in knowledge and define the hepatic spatial transcriptome in pediatric cholestasis. **Methods:** VISIUM Spatial transcriptomics was performed on frozen liver tissue obtained at the time of pediatric liver transplantation from 4 groups: 1) BA patients < 2 years of age (BA1, n = 3), 2) BA patients > 2 years of age (BA2, n = 4), 3) non-BA cholestatic patients (nonBA, n = 4), and 4) non-diseased pediatric donor liver (NL, n = 3). Published single-cell datasets were used to infer cell-type composition of hepatocyte and scar regions. Standard statistical tools were used to integrate and identify differential gene expression (DE), and tissue composition within and between samples. Metabolic pathways were modeled from gene expression using the compass algorithm. **Results:** BA1 patients had higher direct bilirubin level at the time of sample collection with median of 20.4 mg/dL (IQR 11.7-NA) compared to BA2 and nonBA groups with medians of 2.0 mg/dL (IQR 0.6-2.2) and 4.8 mg/dL (IQR 1.3-11.7) respectively ($p = 0.004$). This was associated with an increase in bile acid synthesis pathways and a trend towards greater cholangiocyte signature (Figure 1) in BA1 compared to BA2. In contrast, BA2 had higher immune infiltration in scar regions (Figure 1A) and arginine and proline metabolism. BA1 scars were most unique with 662 DE genes, whereas BA2 and nonBA scars had fewer than 50 DE genes. More specific comparison among the scar signatures of BA patients demonstrated distinct scar-associated clusters involved in angiogenesis and T cell activation in BA1 versus enriched processes of translation and peptide metabolic processes in BA2. Both BA groups showed reduced hepatocyte zonation as demonstrated by lower portal hepatocyte gene signature than nonBA and NL groups (Figure 1B). **Conclusion:** We identify distinct spatial transcriptomes in children with cholestatic liver disease that differ by etiology and disease severity. BA patients requiring earlier transplant (BA1) exhibited a higher bile acid metabolic signature and greater heterogeneity within the scar region than older BA patients (BA2). These findings help identify aberrant immune-metabolic patterns that may contribute to disease progression in BA.

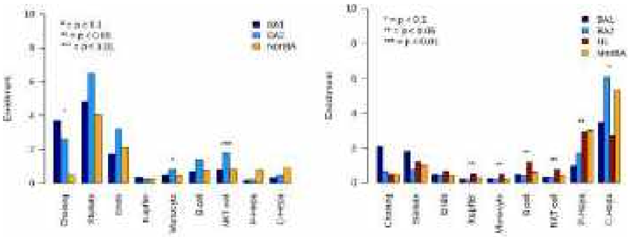

Figure 1. A. Enrichment for cell types in the scar region of diseased groups shows significantly increased NKT cell signature in BA2. **B.** Analysis within hepatocyte regions identified reduced peri-portal hepatocyte signature in BA groups whereas NL hepatocyte regions had increased expression of immune cell signatures.
C-Hepa – peri-central hepatocyte; Cholang – cholangiocyte; Endo – endothelial cell; NKT – natural killer T cells; P-Hepa – peri-portal hepatocyte.

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124 | STAT3 SIGNALING MEDIATES FXR AGONIST PROTECTION IN ACUTE CHOLANGIOPATHY MOUSE MODEL

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Background: Primary sclerosing cholangitis (PSC), a chronic cholangiopathy, results in cholestasis, inflammation, and stricturing of intrahepatic and extrahepatic bile ducts. Recently, we have shown that the transcription factor STAT3 mediated, in part, the protective role of the FXR agonist, GW4064, in parenteral nutrition

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

(PN)-associated cholestasis *(Ghosh* et al., *Hep comm 2023)*. The objective of this study is to determine the interaction of STAT3 and FXR agonists (IV GW4064 and obeticholic acid [OCA]) in a mouse model of acute cholangiopathy and *in vitro*. **Methods:** Acute DDC dietary mouse model (diethyl1,4-dihydro-2,4,6-trimethyl-3,5-pyridinedicarboxylate diet feeding x1 d) and cell culture were used. **Results:** DDC mice had increased AST, ALT, bilirubin, bile acids, ductular reaction and macrophage infiltration and reduced hepatocyte mRNA expression of *Abcb11, Abcg8, Nr0b2* (SHP), *Nr5a2* and *Abcc2* mRNA relative to chow fed mice; all of these were normalized by either FXR agonist treatment. Macrophage mRNA expression of pro-inflammatory (M1) and anti-inflammatory (M2) genes showed that FXR agonists led to upregulation of M2 (*Clec10a1*, *Msr1*, *Klf4*) and down regulation of M1 genes (*Cd68*, *Il-1b*, *Itgam, Cox1*) in DDC mice vs. controls. A significant increase in hepatic STAT3 phosphorylation and acetylation and binding of FXR to *Stat3* promoter, as well as decreased apoptosis markers by flow cytometry (FAS, caspase 8 and caspase 3), were present in FXR agonist/DDC mice compared to DDC mice. DDC mice showed elevated hepatic arachidonic acid (AA) levels (mass-spec) associated with apoptosis, both of which were ameliorated by FXR agonist treatment. AA incubation with Huh7 cells caused increased apoptosis (by Annexin V flow cytometry). In THP1 cells that were exposed to AA cocultured with Huh7 cells, treatment with GW4064 or OCA increased anti-inflammatory *Il-10* and *PPARA* mRNA in THP1 and *ABCB11*/BSEP mRNA in Huh7. In Huh7, AA suppressed the protective upregulation by OCA or GW4064 of BSEP and SHP, and when *STAT3* was knocked down by siRNA ,then the expression was further suppressed. Finally, in DDC mouse liver, increased binding of STAT3 to *Cpt1b* promoter with its increased expression (likely enhanced fatty acid oxidation) was induced by GW4064. **Conclusion:** In the DDC acute cholangiopathy model, FXR agonists are protective through STAT3 signaling, M1 to M2 macrophage polarization, and by inducing fatty acid oxidation, suggesting STAT3 as a potential therapeutic target in PSC.

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125 | SPATIALLY RESOLVED EXPANSION OF REGULATORY IMMUNE CELLS MAY PREDICT CLINICAL OUTCOMES IN PEDIATRIC ACUTE LIVER FAILURE

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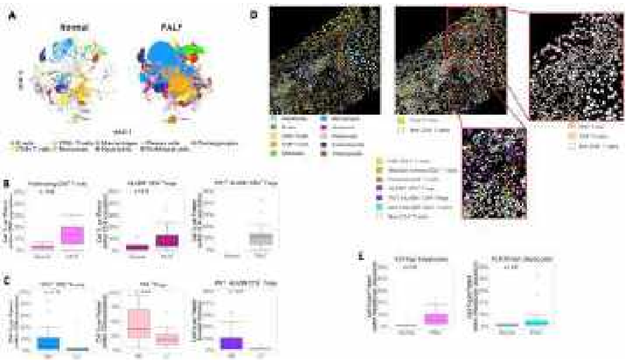
Background: Pediatric acute liver failure (PALF) remains a poorly-characterized disease entity that affects children of all ages. Emerging data supports an underlying immune-mediated process driving progression and severity. Up to 25% of patients will require liver transplantation (LT), yet there are no reliable indicators of disease trajectory to guide clinicians. **Methods:** A single center, retrospective cohort of 58 children was identified: 38 with PALF (25 who recovered (SR) and 13 who underwent LT) and 20 patients who underwent surveillance liver biopsy following LT, whose histologically normal liver tissue is indistinguishable from otherwise healthy liver biopsies. Imaging Mass Cytometry was performed on these specimens using a 25-marker panel. Post-processing using our informatics pipeline generated a spatially resolved, single-cell dataset. Results were stratified by disease, and sub-analyzed by PALF outcome (SR vs LT). **Results:** The study population resulted in 337,823 cells including 120,387 immune cells, which were identified based on lineage marker expression, making up 23 immune subpopulations. When comparing normal liver tissue and PALF, PALF patients had more immune cells overall ($p < 0.01$) – specifically macrophages ($p < 0.01$), monocytes ($p < 0.01$) and CD8+ T-cells ($p = 0.01$) (Fig 1A). No difference was observed between overall populations of CD4+ T-cells. When comparing immune populations between PALF and normal liver tissue, PALF demonstrated more proliferating CD8+T-cells ($p = 0.02$) and HLADR+CD4+T-cells ($p = 0.03$) than normal tissue (Fig 1B). In the CD4+ compartment, PD1+HLADR-CD4+Tregs were present in the PALF cohort that were absent in normal tissue. Within PALF, patients with SR demonstrated more CD4+ Tregs compared to LT ($p = 0.04$), specifically, PD1+HLADR-Tregs, as well as PD1+C8+T-cells (Fig 1C/D). When evaluating non-immune populations, PALF tissue demonstrated increased Ki67 and HLADR+ hepatocytes when compared to normal tissue ($p < 0.01$) (Fig 1E). **Conclusion:** Our spatially resolved single cell atlas of PALF has determined that PALF is associated with greater proliferative cell populations than normal liver tissue, and PD1+HLADR-CD4+Tregs and are unique to this disease entity. Hepatocyte proliferation as indicated by Ki67 and HLADR predominates PALF. Further, we have determined that favorable clinical outcomes are associated with expansion of regulatory cell populations. Our preliminary analysis has determined that a subset of regulatory and PD1+T cells are characteristic of patients who experience recovery, suggesting an important role for immune exhaustion mediating liver inflammation and injury in PALF. Future studies are needed to evaluate these cell populations as potential biomarkers and therapeutic targets.



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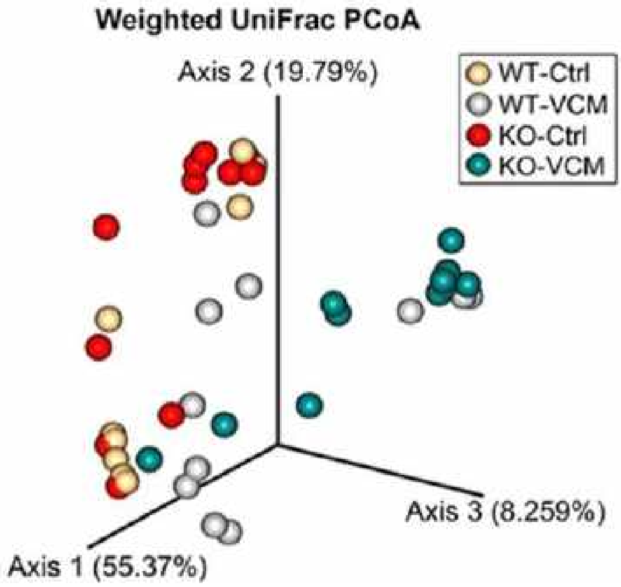
Disclosure information not available at the time of publication: Brittany Rocque, Sarah Bangerth, Carly Weaver, Arianna Barbetta, Tricia Saputera, Kambiz Etesami, George S. Yanni

f 126 | DEVELOPING A THERAPEUTIC MODEL FOR INTRAHEPATIC CHOLESTASIS BY MODULATING THE INTESTINAL MICROBIOME

Huey-Huey Chua[1], Shu-Hao Hsu[1], Yen-Hsuan Ni[1], Bang-Yu Liou[1], Ray Lin[1], Mei-Hwei Chang[2] and Huey-Ling Chen[1], (1)National Taiwan University College of Medicine, (2)National Taiwan University, College of Medicine

Background: The homeostasis of gut microbiota is pivotal to maintaining the physiological liver-gut axis. In cholestatic diseases, impaired bile flow changes the composition of gut bacteria and subsequently dysregulates the bile acids metabolisms. Beneficial roles of vancomycin (VCM) in treating patients with sclerosing cholangitis have been reported; yet the mechanism is not clear. The therapeutic values of the intestinal microbiome restoration in cholestatic disease are less explored. **Methods:** Adult male *Bsep (abcb11)* knockout mice with genetic variants in Plec demonstrated a more severe jaundiced phenotype named *Bsep-ko-JD (*KO). This intrahepatic cholestatic model treated with vancomycin (VCM) exhibited decreased serum bilirubin levels, improved liver bile acid profiles, and ameliorated damages in the biliary ductal structures. This study aims to explore the potential therapeutic gut microbe of the cholestatic liver disease model. **Results:** Using next generation sequencing to profile the intestinal microbiota, the weighted UniFrac principal co-ordinates analysis (PCoA) showed that VCM largely changed gut microbiota in the wild type (WT)-VCM and the KO mice compared to control (Ctrl). (Figure) Parabacteroides goldsteinii (PG) was the most abundant species in this intrahepatic cholestasis model. We treated the KO mice with 1*10^9 PG or phosphate buffered saline by intragastric gavage 3 times per week for a total of 4 weeks. Significant improvement in the PG-treated mice was noted as evidenced by decreased levels of serum bile acids, direct-bilirubin, alkaline phosphatase, as well as reduced levels of hepatic chenodeoxycholic acid, lithocholic acid, and lymphocyte infiltration in the liver. **Conclusion:** Our results suggested that the PG identified from a therapeutic model of intrahepatic cholestasis may modulate bile flow and/or bile acid metabolisms, and may direct future investigations of the treatment of cholestatic liver diseases.



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127 | BILIARY ATRESIA CANDIDATE GENE Pkd1l1 IS ESSENTIAL FOR MAINTENANCE OF BILIARY EPITHELIAL CELL INTERACTION AND INFLAMMATORY RESPONSE

Caroline Klindt-Morgan[1,2,3], David Lee[1], Dominick Hellen[1], Ashley Bennett[1], Kimberly Pachura[1], Paul A. Dawson[1] and Saul Karpen[1], (1)Children's Healthcare of Atlanta & Emory University School of Medicine, Atlanta, GA, (2)Emory University School of Medicine, (3) Heinrich Heine University Dusseldorf

Background: Biliary atresia (BA) is the most common reason for liver transplantation in infants, but its etiopathology is still not completely understood. A nationwide genomic study identified mutations in *PKD1L1* as a BA candidate gene. Liver-specific deletion of *Pkd1l1* in mice results in liver pathology analogous to changes seen in BA, but how *Pkd1l1*-deficient cholangiocytes differ from wild type cells is unknown. The aim of this study was to elucidate the role of Pkd1l1 in cell homeostasis using isolated biliary epithelial cells (BECs) and intrahepatic biliary organoids (ICOs). **Methods:** Intrahepatic BECs were isolated from 6–8-week-old male $Pkd1l1^{Fl/Fl}$ (control) and *Pkd1l1*-deficient *(KO)* mice by fluorescence-activated cell sorting. Two models were used: BEC Transwell cultures grown to polarized monolayers; and isolated BECs to generate ICOs in 3-D cultures. Cells were incubated with DMSO, CDCA (Chenodeoxycholic Acid, 100mM), UDCA (Ursodeoxycholic Acid, 100mM) and Lipopolysaccharides (LPS, 100 IU/ml) from 1 to 24 hours. Organoid formation was visualized using light microscopy. BECs and organoids were characterized by RT-qPCR for known reactive ductular genes and immunofluorescence (IF) to explore cell structure and tight junction integrity. **Results:** ICOs derived from KO mice were significantly smaller in size compared to control (average size 60204 mm^2 vs 2912 mm^2, 20-fold decrease; $p < 0.0001$). Tight junctions, as indicated by IF of markers such as beta-catenin, were disorganized in KO compared to control cells in both systems. After challenge with CDCA and LPS to induce a reactive biliary phenotype, ICOs demonstrated aberrant mRNA expression of several proinflammatory cytokines in KO versus control (e.g., *Ccl5 and Cxcl2* with 5-fold and 4-fold higher expression in KO compared to control cells respectively). A similar, pro-inflammatory phenotype has been observed in Transwell cultures with a basal increase of several markers (e.g, *Cxcl1*, with 9-fold increase in KO as compared to control). **Conclusion:** Our studies demonstrate that *Pkd1l1* is essential for the maintenance of normal BEC epithelial tight junctional structure and regulation of inflammatory response. This enhanced reactive ductular phenotype of KO cells mirrors features of human BA livers. These findings support the relevance of *Pkd1l1* KO as a mouse model of the cholangiopathy leading to the BA phenotype and a valuable tool for evaluation of possible therapies of this devastating disease.

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128 | CILIARY AND CELL STRUCTURE GENE VARIANTS CONTRIBUTE TO THE ETIOPATHOGENESIS OF BILIARY ATRESIA (BA): EXOME AND SNP ARRAY ANALYSIS OF > 1700 NORTH AMERICAN CHILDREN WITH BA

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

Background: Biliary atresia (BA) is the principal indication for liver transplantation in children, yet there is little information regarding its underlying etiology. Recent data strongly places BA as a developmental cholangiopathy suggesting that there are gene variant contributions that can be discovered using modern gene sequencing and analytical technologies. Exome analysis of a subset of BA patients with laterality features (BASM) identified causative variants in a ciliary gene, *PKD1L1*, supporting this approach; however, a larger dataset with multiple analytical approaches is needed to explore the likely multiple genetic contributors to BA. **Methods:** DNA was obtained from participants with BA enrolled in the NIH-supported NIDDK ChiLDReN consortium, a prospective study of cholestatic infants from 14 sites in North America. Exome sequencing and SNP microarray (Illumina 654k) were performed on participant DNA. Analyses were performed using heuristic filtering and artificial intelligence approaches that rely on evolutionary conservation, allele frequency, inheritance patterns, predicted protein impact and ClinVar annotation. Rare, protein-altering variants in genes identified by Gene Ontology (GO) pathway analyses were investigated. **Results:** 1751 BA participants (1564 BA and 187 BASM) underwent both exome and SNP array analysis. In both BA and BASM cases, rare protein-coding variants in several genes including *DNAH11*, *DNAH5*, *CCDC40*, *KMT2D* as well as *PKD1L1* were identified in expected inheritance patterns as previously reported to cause Mendelian human disease. Employing GO analytics for both BA and BASM subsets yielded several significant pathways (multiple test corrected p-values < 0.05) with variants in genes participating in crucial functions including: cell adhesion processes, microtubule processes and transport, ciliary assembly and structure. **Conclusion:** A combination of a large multi-center dataset and multiple methodologies has identified rare, presumably functionally relevant mutations in a number of genes known to cause human disease. Pathway approaches have identified a greater-than-expected number of variants in genes implicated in in ciliary, microtubule, and cell structural pathways. Taken together, these results provide a number of attractive BA candidate genes and pathways that can be explored and validated in suitable cell, organoid and animal-based models to better understand the genetic and mechanistic landscape of BA.

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129 | FAVOURABLE OUTCOMES OF PEDIATRIC LIVER TRANSPLANTATION FOR PRIMARY LIVER TUMORS- RETROSPECTIVE ANALYSIS OF A LARGE CANADIAN COHORT

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Background: Multimodal treatment for pediatric liver tumors, including indications for transplantation, has evolved over the last several decades. The main objective of this study was to describe the outcomes following liver transplantation (LT) for children with primary hepatic malignancies over 30 years at our center which has the largest pediatric LT program in Canada. **Methods:** Charts of patients transplanted at our center for primary hepatic tumors between January 1990 and December 2021 were included in our retrospective review. Demographic, operative, and outcome data were collected. Chi-square tests and univariate analyses were performed for survived vs non survived patients with hepatoblastoma. A *p* value of d 0.05 was considered significant. **Results:** A total of 37 patients underwent LT for primary hepatic malignancies during the study period: 31 hepatoblastoma (HB) and 6 non-HB (2 hepatocellular carcinoma (HCC), 2 undifferentiated embryonal sarcoma, 1 angiosarcoma and 1 multifocal infantile hemangioma). In HB patients with available data (14 females, median age at diagnosis 29.5 months; range 1-158), 2 (7.4%) were PRETEXT II, 8 (29.6%) and 16 (59.3%) were PRETEXT III and IV, respectively. Metastases at diagnosis were detected in 4 (13.3%) patients, all in the lungs. Of these, 1 patient had a residual lesion which was decreasing rapidly in size. All the patients received neo-adjuvant chemotherapy (median cycles- 6; range 2-10), while 14/25 had adjuvant chemotherapy. The median age at transplant was 34 months (range 6-160). One (3.2%) patient had salvage transplant secondary to incomplete tumor resection. Overall survival was 74.2% (23/31) with a median follow-up of 132 months (range 1-355). All deaths were secondary to disease recurrence (median 15 months after LT; range 1-78). The most common site of recurrence was lungs (62.5%). Higher median alpha-fetoprotein (AFP) prior to LT was associated with worse survival (160296 vs 848 µg/L; *p* 0.003). AFP decrease of > 95% from presentation was significantly associated with improved survival (*p* 0.024). Other factors such as tumor histology, AFP at diagnosis, PRETEXT/POSTEXT stage, metastasis at diagnosis, liver donor type and era of LT, or positive resection margin (R1) were not associated with differences in survival in our cohort. All the non-HB recipients were alive following LT at the last visit (median 9.5 months, range 1-51). None had extrahepatic disease at presentation. Recurrence of disease was noted in 2 patients (1 HCC and 1 angiosarcoma), each treated with surgical resection. **Conclusion:** The overall survival rate following liver transplant in HB patient is 74.2%, with tumor recurrence as the most important contributor of mortality. Lower AFP levels before LT and > 95% AFP decrease from presentation are associated with survival. LT in non-HB tumor has favorable outcomes in selected patients, even with post-transplant recurrence.

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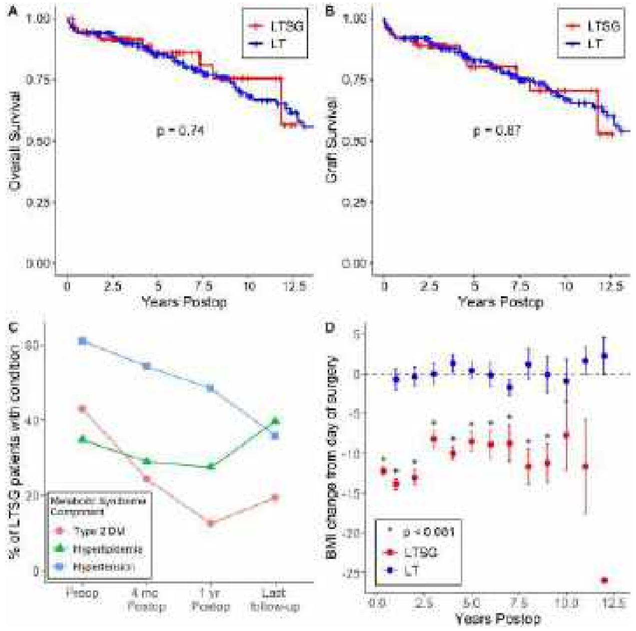
130 | SIMULTANEOUS LIVER TRANSPLANT AND SLEEVE GASTRECTOMY IS A SAFE SURGICAL OPTION THAT IMPROVES METABOLIC SYNDROME AND REDUCES ALLOGRAFT STEATOSIS

Ellen Larson[1], Samia Ellias[2], Nickie Francisco-Ziller[1], Michael D. Leise[1], Kymberly Watt[3], Dana Perry[1], Tayyab Diwan[1], Timucin Taner[1], Charles B. Rosen[1], Enrique F Elli[1], Caroline C Jadlowiec[4], Shennen A. Mao[1], Todd Kellogg[1] and Julie Heimbach[1], (1)Mayo Clinic, (2)Johns Hopkins, (3)Mayo Clinic, Rochester, MN, (4)Mayo Clinic Arizona, Phoenix, AZ

Background: The prevalence of obesity and metabolic syndrome (MS) is rising dramatically among liver transplant (LT) candidates, many of whom have NASH. Following LT, untreated MS often causes recurrent NAFLD and NASH. Several small case series describe bariatric surgery pre-, post-, or concurrently with LT as a treatment for MS. We reviewed our experience with LT and concurrent sleeve gastrectomy (LTSG) with aims to determine long-term safety, efficacy, and impact on progression of MS and liver disease after transplantation. **Methods:** A multi-center retrospective analysis of all patients undergoing LTSG using a single clinical protocol (n = 73) was performed. Follow-up duration was 4 to 153 months. Outcomes assessed included morbidity and mortality, graft loss, BMI, evolution of MS, and development of allograft steatosis on ultrasound and fibrosis on magnetic resonance elastography. A comparison cohort included all 185 patients with BMI > 30 who underwent LT-only for NASH transplanted during the same time period. **Results:** There was no significant difference in all-cause mortality or graft loss between LT and LTSG patients (Figure A, B). At last follow up, 20.3% and 23.4% of LTSG patients had steatosis and fibrosis, respectively, versus 40.4% and 37.3% of LT-only patients with steatosis and fibrosis respectively ($p = 0.01$ steatosis, $p = 0.12$ fibrosis). The prevalence of diabetes in LTSG patients decreased significantly from 42.2% at transplant to 20.3% at last follow up ($p = 0.01$), versus no significant change in diabetes prevalence in LT-only patients. The prevalence of hypertension in LTSG patients decreased from 61.1% to 35.8% ($p < 0.01$) and hyperlipidemia was not significantly changed (Figure C). LTSG patients, starting with an average BMI of 45.5, had significantly reduced BMI for at least 9 years following surgery (all $p < 0.001$). LT-only patients, with an average BMI of 34.0, had no significant change in BMI (Figure D). One LTSG patient (1.4%) had a gastric sleeve leak and one required hiatal hernia repair. None required revision. Severe gastric reflux occurred in 11.1% of LTSG patients; risk factors included male sex, pre-existing diabetes, and pre-existing GERD. **Conclusion:** LTSG is an excellent option for those with BMI > 40; it confers no increase in mortality or graft loss even when compared to a less obese cohort. LTSG reduces recurrence of steatosis and trends toward less fibrosis when compared to LT alone, and leads to sustained weight loss and resolution of diabetes and hypertension.



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131 I SINGLE CELL TRANSCRIPTIONAL T CELL DYNAMICS OF PEDIATRIC LIVER TRANSPLANT REJECTION

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Background: Conventional therapy for late T cell mediated acute cellular rejection (ACR) in liver transplant includes corticosteroids and anti-thymocyte globulin, has remained unchanged for six decades, and is not infrequently met with treatment failure. Here, we used single cell RNAseq with TCR V(D)J profiling to identify expanded (ie, alloreactive) T cell clones and their gene expression profiles in response to anti-rejection treatment. **Methods:** Single cell suspensions were generated from cryopreserved 16G liver biopsy tissue using cold active proteases. Whole cell and TCR libraries were constructed using 10X Chromium 5'v1.1 and 5'V(D)J TCR sequencing kits. Cells were clustered based on cell type specific gene expression profiles by unsupervised analysis in Seurat and TCR libraries were superimposed into the cell clusters. TCR clonotypes were defined as expanded if the CDR3±/ß sequences were expressed in >2 cells. Cellular communication between Kupffer cell (KC) and T cell populations was analyzed using CellPhoneDB. **Results:** Overall, 10,896 cells isolated from 30 biopsies obtained from 14 patients (5 normal or non-ACR allograft dysfunction, 9 ACR) were analyzed. Consistent with their role in mediating ACR, all expanded T cell clones were $CD8^+$ ($CD8_{EXP}$) according to transcriptional analysis and were significantly expanded in ACR biopsies ($p < 0.05$, Student's t-test). $CD8_{EXP}$ bore markers of activated tissue resident memory cells (Trm; *CD69*, *CXCR6*, *HLA-DR*, *GZMB*), and retained their clonotype identity and phenotype in subsequent biopsies from the same patients despite histologic ACR resolution. In contrast, $CD4^+$ T cells were only found in the unexpanded T cell pool and had a gene expression profile consistent with naïve T cells (*TCF7*, *CCR7*, *SELL*). CellPhoneDB analysis revealed differential crosstalk between KC and $CD8_{EXP}$ T cell populations, with activation of the CD2-CD58 proliferative pathway and downregulation of TGFß signaling. **Conclusion:** Despite 6-antigen HLA mismatches corresponding to a massive number of potential allogeneic epitopes, we uncovered a remarkably limited number of $CD8_{EXP}$ clones. Sequential biopsies demonstrated persistence of these clones up to several months, suggesting that the restricted clonal expansion is not due to sampling bias, but rather to a consistently focused allo-response. Transcriptomic analysis revealed differential gene expression and crosstalk between KC-T cell populations which may facilitate T cell retention in allograft liver tissue.
Disclosures: Anna L. Peters – Albireo: Consultant, No, Yes; Sanofi: Consultant, No, Yes;
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132 I ANONYMOUS LIVING LIVER DONATION IMPROVES ACCESS FOR MEDICALLY UNDERSERVED CHILDREN IN NEED OF LIVER TRANSPLANTATION: THE CANADIAN EXPERIENCE★

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

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Background: Since our first pediatric anonymous non-directed live donor liver transplant (Anon-LDLT) performed in April 2005, 62 children have undergone live donor liver transplant (LDLT) with an anonymous non-directed graft. Anon-LDLT organs being allocated as per our deceased donor liver transplant wait list. The objective of this study was to evaluate clinical outcomes, recipient characteristics and social determinants of health of pediatric recipients of Anon-LDLT in comparison to those who received a directed LDLT (Dir-LDLT). **Methods:** Retrospective analysis of all recipients of LDLT performed between January 2005 and March 2023. Demographic and clinical data included age, sex, race, ethnicity, single-parent households, primary diagnosis, recipient blood type, time on waiting list, post-LT intensive care unit (ICU) length of stay (LOS), time to extubation, and post-transplant comorbidities were assessed as covariates. A comparative analysis was conducted between children receiving Anon-LDLT versus Dir-LDLT. A *p* value of d 0.05 was considered significant. **Results:** A total of 236 (51% male, 62% white, 19.5% Asian, 7% Black, 3% indigenous) children (median age 11 mo) underwent LDLT. Biliary atresia (44%) and metabolic diseases (31%) were the commonest primary indications. Anon-LDLT was performed in 62 (26.2%) children, none of whom had any directed live liver donor options. Recipients of Anon-LDLT were more often non-white (55% vs 32%, $p = 0.001$), Black (13% vs 5%, $p = 0.043$) and Indigenous (8% vs 2%, $p = 0.018$) recipients in comparison to Dir-LDLT recipients. Anon-LDLT recipients were more frequently living in single parent households (18% vs 3%, $p < 0.001$) and to require interpreter assistance (11% vs 3%, $p = 0.010$) (Table), compared to children who received a Dir-LDLT. Out-of-province children were more likely to undergo Anon-LDLT (19/62, 31%) compared to Dir-LDLT (31/174, 18%, $p = 0.034$). Median time on the wait list was longer for Anon-LDLT (92 d) compared to Dir-LDLT (62 d) recipients ($p = 0.004$). Post-LT ICU LOS, time to extubation or other post-LT complications were not statistically different between groups. There were no cases of graft failure or re-transplantation in the Anon-LDLT recipients. **Conclusion**: This retrospective analysis of 62 children undergoing Anon-LDLT at a single institution confirms excellent patient and graft survival. Patients from Indigenous and Black communities, single parent and households where English is a second language, are more frequently the beneficiaries of Anon-LDLT grafts. Anon-LDLT, as utilized in this single center analysis, benefits medically underserved pediatric patients who otherwise have limited access to the advantages of LDLT.

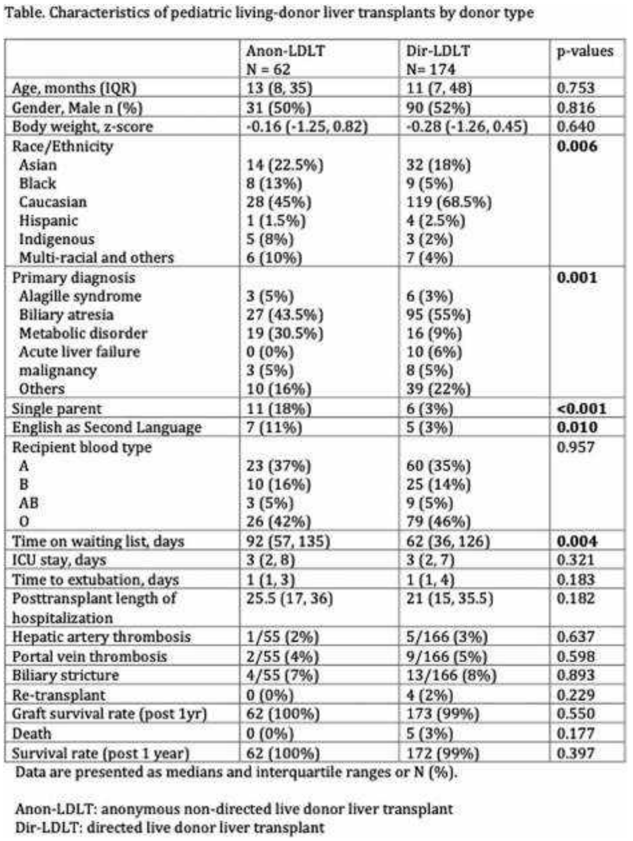

Table. Characteristics of pediatric living-donor liver transplants by donor type

	Anon-LDLT N = 62	Dir-LDLT N= 174	p-values
Age, months (IQR)	13 (8, 35)	11 (7, 48)	0.753
Gender, Male n (%)	31 (50%)	90 (52%)	0.816
Body weight, z-score	-0.16 (-1.25, 0.82)	-0.28 (-1.26, 0.45)	0.640
Race/Ethnicity			**0.006**
Asian	14 (22.5%)	32 (18%)	
Black	8 (13%)	9 (5%)	
Caucasian	28 (45%)	119 (68.5%)	
Hispanic	1 (1.5%)	4 (2.5%)	
Indigenous	5 (8%)	3 (2%)	
Multi-racial and others	6 (10%)	7 (4%)	
Primary diagnosis			**0.001**
Alagille syndrome	3 (5%)	6 (3%)	
Biliary atresia	27 (43.5%)	95 (55%)	
Metabolic disorder	19 (30.5%)	16 (9%)	
Acute liver failure	0 (0%)	10 (6%)	
malignancy	3 (5%)	8 (5%)	
Others	10 (16%)	39 (22%)	
Single parent	11 (18%)	6 (3%)	**<0.001**
English as Second Language	7 (11%)	5 (3%)	**0.010**
Recipient blood type			0.957
A	23 (37%)	60 (35%)	
B	10 (16%)	25 (14%)	
AB	3 (5%)	9 (5%)	
O	26 (42%)	79 (46%)	
Time on waiting list, days	92 (57, 135)	62 (36, 126)	**0.004**
ICU stay, days	3 (2, 8)	3 (2, 7)	0.321
Time to extubation, days	1 (1, 3)	1 (1, 4)	0.183
Posttransplant length of hospitalization	25.5 (17, 36)	21 (15, 35.5)	0.182
Hepatic artery thrombosis	1/55 (2%)	5/166 (3%)	0.637
Portal vein thrombosis	2/55 (4%)	9/166 (5%)	0.598
Biliary stricture	4/55 (7%)	13/166 (8%)	0.893
Re-transplant	0 (0%)	4 (2%)	0.229
Graft survival rate (post 1yr)	62 (100%)	173 (99%)	0.550
Death	0 (0%)	5 (3%)	0.177
Survival rate (post 1 year)	62 (100%)	172 (99%)	0.397

Data are presented as medians and interquartile ranges or N (%).

Anon-LDLT: anonymous non-directed live donor liver transplant
Dir-LDLT: directed live donor liver transplant

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The following people have nothing to disclose: Toshifumi Yodoshi, Krista Van Roestel, Anand Ghanekar, Mark Cattral, Blayne Sayed, Vicky Lee Ng

Disclosure information not available at the time of publication: Casey Ward, Tomisin John, Jennifer Stunguris, Maria DeAngelis, Julia Hensleyab, Yaron Avitzur, Robert H.J. Bandsma, Nicola Jones, Simon C. Ling, Mar Miserachs

133 | IMMUNE SYSTEM IN THE LIVER OF POST-TRANSPLANT ALLOIMMUNE HEPATITIS AND AUTOIMMUNE HEPATITIS PATIENTS TIPPED IN FAVOR OF NON-SUPPRESSIVE MECHANISMS

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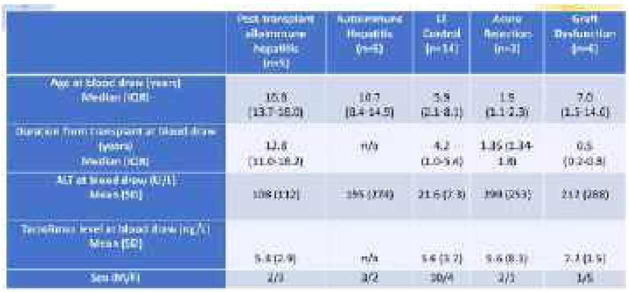
Background: Peripheral blood (PB) regulatory T cells (Tregs) in post-transplant alloimmune hepatitis (DAIH) & autoimmune hepatitis (AIH) have poor regulatory function, however little is known about intrahepatic (IH) Tregs in both diseases. As the human Treg compartment encompasses multiple subsets that delineate different developmental stages & their associated regulatory function, we used mass cytometry & unsupervised clustering algorithm Flow self-organizing map (FlowSOM) to interrogate the distribution of subsets within *ex-vivo* $CD25^{hi}CD127^{lo}/^{neg}FoxP3^{+}$ Treg in PB & liver (IH) of children with DAIH & non-transplanted children with AIH. **Methods:** Enriched $CD4^{+}$ T cells from peripheral blood mononuclear cells (PBMC) and intrahepatic lymphocytes (IHL) of children with DAIH (n = 5), AIH (n = 5), biopsy proven acute rejection (AR) (n = 3), liver transplanted children with graft dysfunction (n = 6), & liver transplanted children with normal graft function (LTC) (n = 14) were expanded in culture with Dyna beads CD3/CD28, rIL-2 & TGF-b for 5-days prior to FACS sorting of Tregs. For FACS sorting, Tregs were identified by high expression of CD25 & low expression of CD127. *Ex-vivo* sorted PB & IH Tregs were then stained for mass cytometry with metal-conjugated monoclonal antibodies (CD49D, CD4, CCR4, CD45RA, CD3, CD39, FoxP3, CD95, CD45RO, CD25, CD152, HLA-DR, CD127, CD73, NRP1, Helios, LAP, CD45). Cells were acquired using a CyTOF Helios mass cytometer. CyTOF data was time-based bead normalized using standard procedures. The data were then uploaded to OMIQ (Omiq.ai), manually gated using Gaussian parameters to resolve live, intact, single cells for further analysis. Expression levels were arcsinh transformed with a cofactor of 5 and compared across disease groups within the Treg population. Clustering was performed using FlowSOM & visualized using dimensionality reduction using UMAP. All statistical analyses were performed in GraphPad Prism v9 (Dotmatics). **Results:** Demographics reported in Table 1 below. 10 phenotypically distinct clusters were identified based on15 analyzed parameters within PB & IH Tregs of DAIH, AIH patients, as well as LTC subjects. IH Tregs of AIH patients were characterized by a higher CD45RA, & lower CCR4, Helios, FoxP3, CD25, CD73, CD39, CD45RO, & CD95 expression when compared with PB Tregs ($p < 0.001$). IH Tregs of DAIH patients were characterized by a higher expression of CD45RA, CCR4, CD25, CD73, CD95, & lower expression of FoxP3, Helios, CD39 compared to PB Tregs ($p < 0.001$). An important suppressive mechanism mediated by Treg involves the CD39/CD73 adenosine pathway. In humans, $CD39^{+}$ Tregs are implicated in the suppression of Th17 responses & the control of autoimmunity. **Conclusion:** The lower expression of FoxP3 & Helios in IH Tregs of patients with DAIH & AIH could suggest Treg destabilization. Further work is needed to determine if these IH Tregs have the potential to transdifferentiate into effector T cells.



	Post-transplant alloimmune hepatitis (n=5)	Autoimmune Hepatitis (n=5)	LT Control (n=14)	Acute Rejection (n=3)	Graft Dysfunction (n=6)
Age at blood draw (years) Median (IQR)	15.8 (13.7-18.0)	10.7 (8.4-14.5)	5.9 (2.1-8.1)	1.9 (1.1-2.3)	7.0 (1.5-14.0)
Duration from transplant at blood draw (years) Median (IQR)	12.8 (11.0-18.2)	n/a	4.2 (1.0-5.4)	1.35 (1.34-1.8)	0.5 (0.2-0.8)
ALT at blood draw (U/L) Mean (SD)	108 (112)	195 (274)	21.6 (7.3)	298 (253)	212 (288)
Tacrolimus level at blood draw (ng/L) Mean (SD)	5.4 (2.9)	n/a	5.6 (3.2)	5.6 (8.3)	7.7 (1.5)
Sex (M/F)	2/3	3/2	10/4	2/1	1/5

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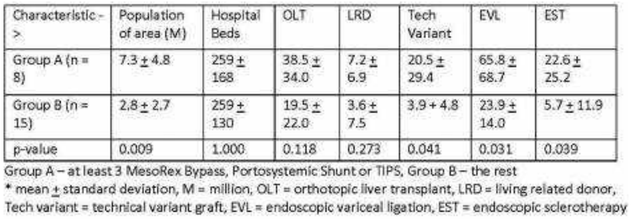
134 | CENTER-SPECIFIC DATA FROM THE INTERNATIONAL MULTICENTER PEDIATRIC PORTAL HYPERTENSION REGISTRY (IMPPHR) – INITIAL ANALYSES OF 23 INTERNATIONAL SITES

Tassos Grammatikopoulos[1], *Simon C. Ling*[2], *Jean Pappas Molleston*[3,4], *Catalina Jaramillo*[5,6], *Julio Rocha Pimenta*[7], *Rustam Yuldashev*[8], *Samar H. Ibrahim*[9], *Sakil Kulkarni*[10], *Pooja Reddy Spector*[11], *Amy Feldman*[12,13], *Mohit Kehar*[14], *Voytek Slowik*[15], *Kee Seang Chew*[16], *Anja Praprotnik Novak*[17], *Eyal Shteyer*[18], *Scott Elisofon*[19], *Alexis Gumm*[20], *Anita K Pai*[21], *Amal A. Aqul*[22], *Juan Cristóbal Gana*[23], *Rodrigo Vazquez Frias*[24], *Oanez Ackermann*[25], *Mathieu Duche*[25], *Sara Hassan*[26], *Mercedes Martinez*[27], *Chaitri Desai*[15], *Matjaz Homan*[17], *Katherine Sweeny*[19], *Saima Deen*[28], *Serpil Tutan*[28], *Uma Ramamurthy*[28], *Riccardo A. Superina*[29], *Jaime Bosch*[30], *Roberto De Franchis*[31] *and Benjamin L. Shneider*[28,32], *(1)King's College Hospital, (2)Division of Gastroenterology, Hepatology and Nutrition, the Hospital for Sick Children, Toronto, ON, Canada, (3)Indiana University School of Medicine, (4)Riley Hospital for Children, (5)University of Utah, (6) Primary Children's Hospital, (7)Hospital Das Clinicas - UFMG, (8)Republican Specialized Scientific Practical Medical Center of Pediatrics, (9)Mayo Clinic Rochester, Rochester, MN, (10)Washington University in St. Louis, (11)Columbia University, New York, NY, (12)Children's*

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

Hospital Colorado, (13)University of Colorado, (14) Children's Hospital of Eastern Ontario, (15)Children's Mercy Hospital, (16)University of Malaya, (17)University Medical Centre Ljubljana, (18)Shaare Zedek Medical Center, (19)Boston Children's Hospital and Harvard Medical School, Boston, MA, (20)Medical College of Wisconsin, (21)Vanderbilt University, (22)University of Texas Southwestern Medical Center, Dallas, Texas, (23)Pontificia Universidad Católica de Chile, (24) Hospital Infantil De México Federico Gómez, (25) Hôpital Bicêtre Université Paris-Saclay, (26)Mayo Clinic, (27)Newyork-Presbyterian, Department of Pediatrics, (28)Baylor College of Medicine, (29)Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, (30)Bern University Hospital, University of Bern, (31)University of Milan, (32)Texas Children's Hospital

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



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

Group A – at least 3 MesoRex Bypass, Portosystemic Shunt or TIPS, Group B – the rest

* mean ± standard deviation, M = million, OLT = orthotopic liver transplant, LRD = living related donor, Tech variant = technical variant graft, EVL = endoscopic variceal ligation, EST = endoscopic sclerotherapy

Disclosures: Tassos Grammatikopoulos – Albireo and AstraZeneca: Consultant, No, No;
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135 | PNPLA3 GENOTYPES ARE SIGNIFICANTLY ASSOCIATED WITH LIVER-RELATED OUTCOMES IN INDIVIDUALS WITH BIOPSY-PROVEN NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

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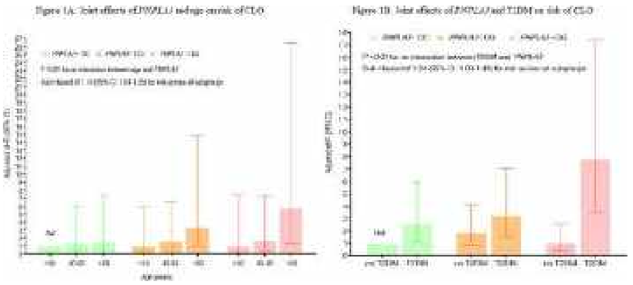
Background: The effect of *PNPLA3* rs738409 I148M variant (G allele) on the clinical course of adults with biopsy-proven nonalcoholic fatty liver disease (NAFLD) has not been prospectively investigated. We examined (1) the association between *PNPLA3* G allele and clinical outcomes and (2) how relationships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



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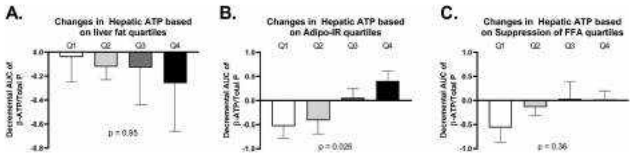
136 | ADIPOSE TISSUE INSULIN RESISTANCE AFFECTS LIVER MITOCHONDRIAL FUNCTION INDEPENDENTLY OF LIVER FAT ACCUMULATION★

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

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

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

provides a dynamic measurement of hepatic ATP consumption and re-synthesis as a surrogate marker of mitochondrial function. Hepatic ATP levels were estimated as β-ATP/total phosphorus. **Results:** A total of 37 patients were recruited (54 ± 11 years; 43% male/57% female; BMI: 34.4 ± 6.3 kg/m^2; NAFLD: 51%). No differences were found in basal hepatic ATP levels in patients with or without NAFLD ($p = 0.44$). Similarly, we did not observe any difference in basal hepatic ATP levels with increasing levels of adipose tissue IR ($p = 0.42$). After the OFC, no differences were observed in changes in hepatic ATP levels in patients with vs. without NAFLD ($p = 0.67$) or based on quartiles of liver fat (Figure 1A). However, changes in hepatic ATP levels after the OFC were significantly different among groups defined by quartiles of adipose tissue IR (Figure 1B-C). These differences were more pronounced when adipose tissue IR was measured during fasting (i.e., Adipo-IR) than the postprandial state. Patients on the highest quartile of adipose tissue IR showed no consumption of ATP after the OFC, but rather an overall increase in ATP levels over time. Adipo-IR significantly correlated with changes of hepatic ATP after the OFC (-0.52, $p = 0.001$). **Conclusion:** Patients with increased adipose tissue IR, particularly in the fasting state, showed an over-compensatory hepatic mitochondrial response, characterized by an increase in hepatic ATP levels after fructose consumption. This suggests that chronic elevated of fasting FFA lead a compensatory increase of hepatic mitochondrial oxidation capacity. At what point this compensation is overwhelmed leading to inflammation and lipotoxicity remains to be determined.



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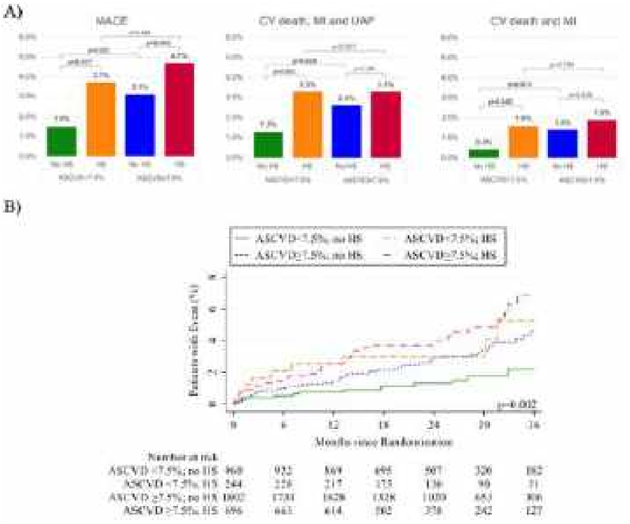
137 | HEPATIC STEATOSIS IS ASSOCIATED WITH INCREASED CARDIOVASCULAR EVENT RATE AMONG PEOPLE AT LOW 10-YEAR ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK

Julia Karady[1], Thomas Mayrhofer[1], Borek Foldyna[1], Michael T Lu[1], Nandini Mehyerson[1], Udo Hoffmann[1], Neha Pagidipati[2], Svati Shah[2], Pamela S Douglas[2], Maros Ferencik[1] and Kathleen E. Corey[3], (1) Massachusetts General Hospital, (2)Duke Clinical Research Institute, (3)Massachusetts General Hospital, Somerville, MA

Background: Hepatic steatosis (HS) and a 10-year atherosclerotic cardiovascular disease (ASCVD) risk of e 7.5% are associated with increased risk for future cardiovascular events. However, cardiovascular risk of patients with HS at ASCVD < 7.5% is not clearly understood. **Methods:** We studied adults with suspected stable angina and no history of coronary artery disease (CAD) who underwent coronary CT imaging in the PROMISE trial. HS, coronary artery calcium (CAC) score, obstructive CAD (stenosis e 50%) and vulnerable plaques (plaques with low attenuation, positive remodeling, and napkin-ring sign) were defined by using coronary CT datasets. Major adverse cardiovascular event (MACE) was defined as hospitalization for unstable angina, non-fatal myocardial infarction, and all-cause death. Multivariable Cox regression analysis adjusting for CAC, obstructive CAD and vulnerable plaques assessed whether HS independently predicts MACE among patients at < 7.5% ASCVD risk. **Results:** Among ASCVD < 7.5% risk patients, individual's with HS were younger (54.3 ± 5.2 vs 55.8 ± 5.2; $p < 0.001$), more likely to be males (40.2% [98/244] vs 27.1% [260/960]; $p < 0.001$), had more risk factors (mean number of risk factors: 2.06 ± 0.89 vs 1.93 ± 0.91; $p = 0.047$) and had higher triglycerides (138.0 vs 115.0 mg/dL, $p = 0.014$) and alanine transaminase (30.0 vs 19.0 mg/dL; $p < 0.001$) than those without HS. These features similarly differed among patients with ASCVD e 7.5% risk with and without HS. CAD characteristics, (CAC, obstructive CAD, vulnerable plaques) did not differ between HS vs no HS patients independent of ASCVD risk (all $p > 0.05$). Patients with HS had higher MACE rate in the ASCVD < 7.5% (1.5% [14/960] vs 3.75 [9/244]; $p = 0.027$) and ASCVD e 7.5% groups (3.1% [56/1,802] vs 4.7% [33/696]; $p = 0.043$) compared to patients without HS. Among patients without HS ASCVD e 7.5% had higher MACE rate compared to ASCVD < 7.5% (3.1% [56/1,802] vs 1.5% [14/960]; $p = 0.011$). In patients with HS MACE rates were similar (ASCVD e 7.5% vs < 7.5%: 4.7% [33/696] vs 3.7% [9/244], $p = 0.484$). The cumulative event rate was significantly lower for patients without HS and ASCVD <

7.5% compared to the other groups (*figure*). In patients with ASCVD $<7.5\%$, HS predicted MACE (aHR:2.34, 95%CI:1.01-5.43; $p = 0.048$), independent of CAD characteristics. **Conclusion:** Individual's with radiographic HS and $<7.5\%$ ASCVD risk have similar CAD severity and burden as patients without HS at $<7.5\%$ ASCVD but experience similar MACE rates as individual's at e 7.5% ASCVD risk.



A) Event rates across the four strata of patients with and without Hepatic Steatosis and ASCVD <7.5% vs ≥7.5%. **B)** Cumulative major adverse cardiovascular event rates across the four strata of patients with and without Hepatic Steatosis and ASCVD <7.5% vs ≥7.5%. ASCVD: Atherosclerotic cardiovascular disease; CV: Cardiovascular; HS: Hepatic steatosis; MI: Myocardial infarction; UAP: Unstable angina pectoris.

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138 | IDENTIFICATION OF THE ENVIRONMENTAL POLLUTANTS AND METABOLIC PATHWAYS ASSOCIATED WITH NONALCOHOLIC FATTY LIVER DISEASE SEVERITY

Niharika R. Samala[1], Matthew Ryan Smith[2], Christina Pinkston[3], Shesh N Rai[3], Young-Mi Go[2], Dean P. Jones[4], Naga P. Chalasani[5] and Matthew Cave[6], (1) Indiana University, Indianapolis, IN, (2)Emory University, (3)University of Cincinnati, (4)Emory University, Children's Healthcare of Atlanta, (5)Indiana University Medical Center, Indianapolis, IN, (6) University of Louisville, Louisville, KY

Background: Environmental pollutants are associated with disrupted hepatic metabolism and NAFLD. A pilot study ($n = 140$) presented at AASLD elucidated exposures and metabolic pathways associated with NAFLD severity. To confirm these findings, a larger cross-sectional multi-'omics study was performed in subjects with NAFLD. **Methods:** Exposomics and metabolomics (LC-MS^2 using HILIC & C18 columns & GC-MS^2) were performed in plasma samples from 341 prospectively enrolled NAFLD patients diagnosed by AASLD guidelines. Fibrosis severity was determined by liver stiffness measurement (LSM) and steatosis by controlled attenuation parameter (CAP). LSM $>$ 8.6kPa was considered to be clinically significant fibrosis (CSF). Exposome- and metabolome-wide association studies (EWAS & MWAS) were performed using the R package xMSPanda. Pathway enrichment analyses were performed using mummichog. **Results:** The NAFLD cohort (mean age $= 53 \pm 14$ y, mean BMI $= 35 \pm 7$ kg/m^2) was 60% female and 95% White. 48% had diabetes-2, 53% had dyslipidemia, and 60% had hypertension. Four environmental pollutants (ethyl-decanoate, ethyl-undecanoate, diethylthiophosphoric acid, and hydroxycitronellal) were significantly associated with CSF ($p < 0.05$, FDR < 0.20). At a less stringent threshold ($p < 0.05$, FDR > 0.20), 42 exposures were associated with CSF. These included environmental phenols confirming results from the pilot study. The MWAS of LSM revealed significant associations with 271 (HILIC) and 314 (C18) metabolic features ($p < 0.05$, FDR < 0.05). Thirty metabolic pathways were associated with fibrosis including: bile acids; glycosphingolipids; vitamin D3; hexose-phosphorylation; keratan-sulfate; N-glycan; pyrimidine, arginine-proline; and linoleate, confirming results from the pilot study. CAP was significantly associated with 35 (HILIC) and 17 (C18) metabolic features. Fifteen pathways were associated with hepatic steatosis, 8 of which were previously identified in the pilot study. **Conclusion:** Multiple environmental pollutants were associated with CSF, with several previously identified in the pilot cohort. Bile acid metabolism was the most significantly enriched pathway associated with liver fibrosis, and seven pathways were perturbed by both steatosis and fibrosis recapitulating results from the pilot study in this larger cohort. Reverse causality cannot be excluded. These findings suggests that pollutants have a significant impact on liver fibrosis in NALFD and warrant additional investigation.

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139 | HEPATIC LOBULAR INFLAMMATION IS THE MOST IMPACTED PROGNOSTIC FACTOR RATHER THAN FIBROSIS IN PATIENTS WITH BIOPSY-PROVEN MASLD: MULTI-CENTER STUDY★

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) captures patients at high risk of hepatic fibrosis and cardiovascular disease. However, limited information is available on the prognosis of MASLD. This study aimed to investigate the prognosis of patients with biopsy-proven MASLD and validate a group of fatty liver patients excluded from MASLD because of no metabolic abnormalities by a multi-center longitudinal cohort. We also investigate the most important histological finding associated with the prognosis of patients with MASLD. **Methods:** We enrolled 1,444 patients with fatty liver who underwent liver biopsy (age 57, female 55.1%, BMI 27.4). Patients were classified into the following three groups: the MASLD group (steatosis with metabolic abnormalities), the non-MASLD group (steatosis without metabolic abnormalities), or the Burnt-out group (no steatosis on biopsy). Cox proportional hazard analysis and Kaplan-Meier analysis were performed to identify the factor associated with the prognosis. Furthermore, decision-tree analysis was demonstrated to determine the most affected histological finding related to the prognosis of each group. **Results:** The prevalence of patients with MASLD, non-MASLD, and Burnt-out group was 92.1% (1,330/1,444) and 3.1% (45/1,444), 4.8% (69/1,444), respectively. During the 9,083 person-years of observation, 4.3 person-years of deaths occurred in all patients, and 84.2% (32/38) of the deceased patients were in the MASLD group in this study. As for the histopathological features, the MASLD group showed the highest prevalence of inflammation in grades 1-3 (95.2%). Whereas the Burnt-out group showed the highest prevalence of fibrosis stages 3 and 4 (35.3%). Compared to the MASLD group, the Burnt-out group was identified as an independent factor associated with prognosis in Cox proportional hazard analysis (RR 5.91, $p=0.0001$). On the other hand, it could not compare the statistical analysis with the other groups because of the absence of deaths in the non-MASLD group. Kaplan-Meier analysis revealed significant differences in prognosis among the three groups (Log-rank $p=0.0009$). Ten-year survival rate was 95.6% in MASLD, while no patient died in the non-MASLD group until the end of the follow-up period. Decision-tree analysis revealed hepatic fibrosis was the most affected histological finding associated with the prognosis in the Burnt-out group. In contrast, we identified hepatic inflammation as the most affected prognostic finding in the MASLD group. **Conclusion:** We showed MASLD was a major pathological condition related to the deaths and the prognosis of MASLD was worse than non-MASLD. Hepatic inflammation rather than fibrosis was the most affected prognostic histological finding in patients with MASLD. Thus, metabolic abnormalities may worsen the prognosis of patients with fatty liver. Inflammation may be responsible factor for the poor prognosis of MASLD.

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140 | ARTIFICIAL INTELLIGENCE TO MEASURE FIBROSIS CHANGE ON LIVER BIOPSY IN MAESTRO-MASH: A PHASE 3 SERIAL LIVER BIOPSY STUDY IN 966 PATIENTS WITH MASH TREATED WITH RESMETIROM OR PLACEBO

Stephen A Harrison[1], *Rebecca A. Taub*[2], *Ya-Yun Ren*[3], *Elaine Lay Khim Chng*[4] *and Dean Tai*[4], *(1)Pinnacle Clinical Research Center, San Antonio, TX, (2)Madrigal Pharmaceuticals, (3)Histoindex Pte Ltd, (4)Histoindex Pte Ltd, Singapore*

Background: MAESTRO-MASH (NCT03900429), an ongoing, randomized, double-blind, placebo-controlled Phase 3 serial liver biopsy study, achieved both primary endpoints on liver biopsy (MASH resolution and fibrosis reduction) at Week 52 with both resmetirom doses, including a e 1-stage reduction in fibrosis without worsening of MASH of 24%, 26% (mITT) at 80 and 100 mg resmetirom compared with placebo (14%). As an exploratory endpoint, artificial intelligence slide reading technologies were employed to measure the effect of resmetirom on fibrosis on serial liver biopsy using both continuous and quantitative scoring. **Methods:** Fibrosis was estimated as a continuous and categorical score using second harmonic generation (qFibrosis)/two photon excited fluorescence of 768 paired biopsy samples from MAESTRO-MASH. A separate unstained slide was analyzed for qFibrosis (normalized by tissue area and then corrected for qSteatosis (tissue area-steatosis area)). Relative changes in 184 fibrosis parameters were determined. **Results:** The analyses were based on a total of 768 slide pairs including a baseline and Week 52 slide that were received and met criteria for quality ($<10\%$ missing pairs; $<3\%$ excluded for quality). Based on a continuous qSteatosis score, the percent change from baseline in steatosis was 80 mg resmetirom, -36%; 100 mg resmetirom, -46%; placebo, -10%; $p<0.0001$ for both resmetirom doses. The continuous change from baseline in corrected qFibrosis score was 80 mg resmetirom, -22%; 100 mg resmetirom, -20%; placebo, 3%; $p < 0.0001$ for both resmetirom doses. The categorical qFibrosis stage aligned with the stage assigned by the central pathologists (F1, F2, F3) with the exception that qFibrosis estimated a high fraction (~20%) as F4 at baseline (F4 scored at baseline by the central pathologists were excluded from this study). Based on categorical change in qFibrosis score, there was a significant improvement in fibrosis stage (1-stage or 2-stage improvement) at 80 and 100 mg resmetirom relative to placebo, and less worsening of fibrosis in the resmetirom groups compared with placebo (Table). The percentage showing improvement in qFibrosis (e 1-stage) was higher than scored by the central pathologists and identified 90% of resmetirom responders determined by the central pathologists. Significant correlations were observed between reduction in qFibrosis and reduction in PDFF, ALT, AST, and ELF. **Conclusion:** Measurements of fibrosis change using qFibrosis on either a continuous or categorical scale demonstrated a clear improvement and less worsening in fibrosis among resmetirom-treated patients with MASH as compared with placebo-treated patients after 52 weeks.

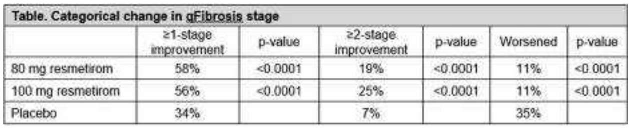

Table. Categorical change in qFibrosis stage

	≥1-stage improvement	p-value	≥2-stage improvement	p-value	Worsened	p-value
80 mg resmetirom	58%	<0.0001	19%	<0.0001	11%	<0.0001
100 mg resmetirom	56%	<0.0001	25%	<0.0001	11%	<0.0001
Placebo	34%		7%		35%	

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141 | TITLE: MAXIMIZING THE BENEFITS OF STATIN THERAPY FOR LIVER DISEASE PREVENTION: TARGETING PATIENTS WITH UNMET STATIN THERAPY NEEDS★

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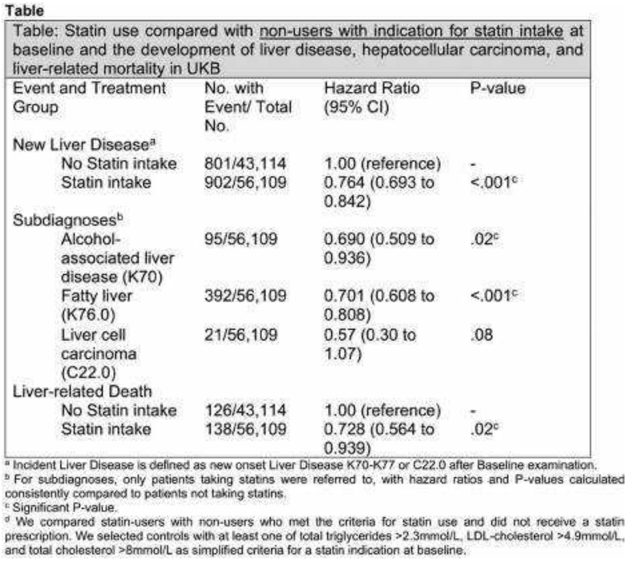
Background: Chronic liver diseases, such as non-alcoholic fatty liver disease (NAFLD) and viral hepatitis, contribute significantly to liver-related morbidity and mortality. Statins, commonly prescribed for dyslipidemia, have been suggested to possess hepatoprotective effects beyond their lipid-lowering properties. This study aims to assess the association between statin use and liver-related outcomes, including hepatocellular carcinoma incidence and liver-related mortality, utilizing data from the UK Biobank. **Methods:** Propensity score matching was employed to match patients without prior liver disease. Patients were matched according to the following criteria: Age, sex, BMI, ethnicity, diabetes mellitus with or without insulin or biguanide use, hypertension, ischemic heart disease, dyslipidemia, aspirin use, and number of medications taken. The study compared primary outcomes between 205,057 statin-users and non-users after matching using cox regression models as well as Fine and Grey models in R. We defined incident liver disease as the occurrence of any new diagnosis of K70-K77 after baseline. Hepatocellular carcinoma was identified using ICD-10 code C22.0, and liver-related death was determined based on deaths attributed to either K70-K77 or C22.0. **Results:** In the UK Biobank ($n=205{,}057$), statin-users exhibited a 15.4% reduced risk of developing new liver disease ($\mathrm{HR}_{\mathrm{UKB}}=0.846$, 95% CI, 0.782-0.915; $p=<0.001$), a 28.0% lower risk of liver-associated death ($\mathrm{HR}_{\mathrm{UKB}}=0.720$, 95% CI, 0.588-0.880; $p=0.001$) and a 42% lower risk of hepatocellular carcinoma development ($\mathrm{HR}_{\mathrm{UKB}}=0.580$, 95% CI, 0.350-0.963; $p=0.04$). When comparing statin-users to non-users with an indication for statin therapy but without a statin prescription, the risk reduction for new liver disease increased to 23.6% ($\mathrm{HR}_{\mathrm{UKB}}=0.764$, 95% CI, 0.693-0.842; $p=<0.001$). **Conclusion:** Our findings strongly suggest that the utilization of statins is linked to a notable reduction in liver-related outcomes, such as the incidence of hepatocellular carcinoma and liver-related mortality. Notably, these findings were even more pronounced when comparing individual's who were prescribed statins to non-users who were likely candidates for statin treatment. Our comprehensive analysis provides robust evidence that underscores the potential preventive benefits of statins on liver disease.



Table

Table: Statin use compared with non-users with indication for statin intake at baseline and the development of liver disease, hepatocellular carcinoma, and liver-related mortality in UKB

Event and Treatment Group	No. with Event/ Total No.	Hazard Ratio (95% CI)	P-value
New Liver Disease[a]			
No Statin intake	801/43,114	1.00 (reference)	-
Statin intake	902/56,109	0.764 (0.693 to 0.842)	<.001[c]
Subdiagnoses[b]			
Alcohol-associated liver disease (K70)	95/56,109	0.690 (0.509 to 0.936)	.02[c]
Fatty liver (K76.0)	392/56,109	0.701 (0.608 to 0.808)	<.001[c]
Liver cell carcinoma (C22.0)	21/56,109	0.57 (0.30 to 1.07)	.08
Liver-related Death			
No Statin intake	126/43,114	1.00 (reference)	-
Statin intake	138/56,109	0.728 (0.564 to 0.939)	.02[c]

[a] Incident Liver Disease is defined as new onset Liver Disease K70-K77 or C22.0 after Baseline examination.

[b] For subdiagnoses, only patients taking statins were referred to, with hazard ratios and P-values calculated consistently compared to patients not taking statins.

[c] Significant P-value.

[d] We compared statin-users with non-users who met the criteria for statin use and did not receive a statin prescription. We selected controls with at least one of total triglycerides >2.3mmol/L, LDL-cholesterol >4.9mmol/L, and total cholesterol >8mmol/L as simplified criteria for a statin indication at baseline.

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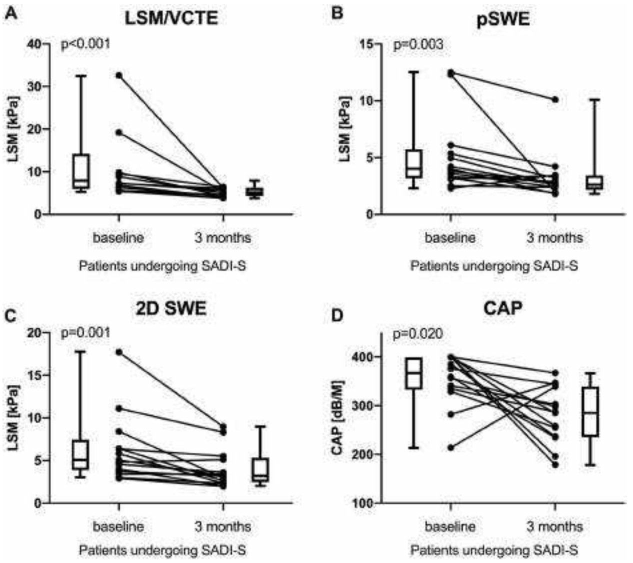
Disclosure information not available at the time of publication: Arunkumar Krishnan, Kirk J. Wangensteen, Inuk Zandvakili, Marijana Vujkovic

142 | SINGLE ANASTOMOSIS DOUDENO-ILEAL BYPASS WITH SLEEVE GASTRECTOMY ALLEVIATES LIVER STIFFNESS AND CONTROLLED ATTENUATION PARAMETER IN OBESE PATIENTS – COMPARISON OF 4 MODALITIES

Lukas Hartl[1], Larissa Nixdorf[2], Stefanie Ströhl[1], Moritz Felsenreich[2], Magdalena Mairinger[2], Julia Jedamzik[2], Paula Richwien[2], Mathias Jachs[1], Georg Semmler[1], Lorenz Balcar[1], Michael Schwarz[3], Christoph Bichler[2], Michael Trauner[4], Mattias Mandorfer[1], Thomas Reiberger[4], David Josef Maria Bauer[1,5] and Gerhard Prager[2], (1)Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria, (2)Department of General Surgery, Division of Visceral Surgery, Medical University of Vienna, Vienna, Austria, (3)Medical University of Vienna, (4)Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, (5)Department of Medicine IV – Gastroenterology and Hepatology, Klinik Ottakring, Vienna, Austria

Background: Obesity, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD) are becoming increasingly prevalent. Bariatric surgery, combining weight loss with metabolic improvements, may represent an effective treatment for these disease entities in obese patients with single anastomosis doudeno-ileal bypass with sleeve gastrectomy (SADI-S) representing a novel bariatric procedure. According to the recent guidance on non-invasive tests, liver stiffness measurement (LSM) assessed by vibration-controlled transient elastography (VCTE) or shear wave elastography (SWE) is recommended for risk stratification. **Methods:** Patients who underwent bariatric surgery at the Vienna General Hospital between 01/2021-12/2022 were included in this prospective study. LSM (via VCTE, as well as point SWE [pSWE] and 2D-SWE using the Siemens Sequoia Acuson system) and controlled attenuation parameter (CAP) assessment were performed before (baseline; BL) and three months after surgery (3M). Patients were stratified for the type of bariatric surgery. **Results:** Overall, 93 patients (SADI-S: 30.1% [n = 28], one anastomosis gastric bypass [OAGB]: 28.0% [n = 26]; Roux-en-Y gastric bypass [RYGB]: 29.0% [n = 27]; sleeve gastrectomy [SG]: 12.9% [n = 12]) with female predominance (68.8%) and a median age of 40.9 years were included. Patients with SADI-S had the highest median body mass index (BMI; 53.3 kg/m2). The median excess weight loss (EWL) after 3 months among all patients was 46.8% and did not differ between the different bariatric procedures. VCTE and CAP paired success rates were 76.8% (n = 43/56) and 83.9% (n = 47/56), while it was 98.2% (n = 55/56) for pSWE and 2D-SWE, respectively. After SADI-S and RYGB, VCTE significantly decreased (SADI-S: BL: 7.3 kPa vs. 3M: 4.8 kPa; $p < 0.001$/RYGB: BL: 5.5 kPa vs. 3M: 4.1 kPa; $p = 0.028$), while it remained unchanged after OAGB ($p = 0.391$) and SG ($p = 0.999$). Moreover, pSWE and 2D SWE LSM dropped significantly after SADI-S (pSWE: BL: 3.9 kPa vs. 3M: 2.7 kPa; $p = 0.002$/2D SWE: BL: 4.9 kPa vs. 3M: 3.2 kPa; $p < 0.001$), but not after other bariatric procedures. Interestingly, 19 patients (44.2%) showed no relevant decrease in LSM after bariatric surgery (< 10% decrease). Finally, there was a marked decline in CAP after SADI-S (BL: 367.5 dB/m vs. 3M: 286.0 dB/m; $p = 0.020$), OAGB (BL: 303.0 dB/m vs. 3M: 4.1 dB/m; $p = 0.019$) and RYGB (BL: 343.0 kPa vs. 3M: 277.0 dB/m; $p < 0.001$). **Conclusion:** LSM - as assessed by both VCTE and SWE - significantly decreased 3 months after bariatric surgery, particularly in patients undergoing SADI-S. We will continue to evaluate if the decrease in LSM and CAP are ‘just’ due to EWL or will translate into improved clinical outcomes.



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

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

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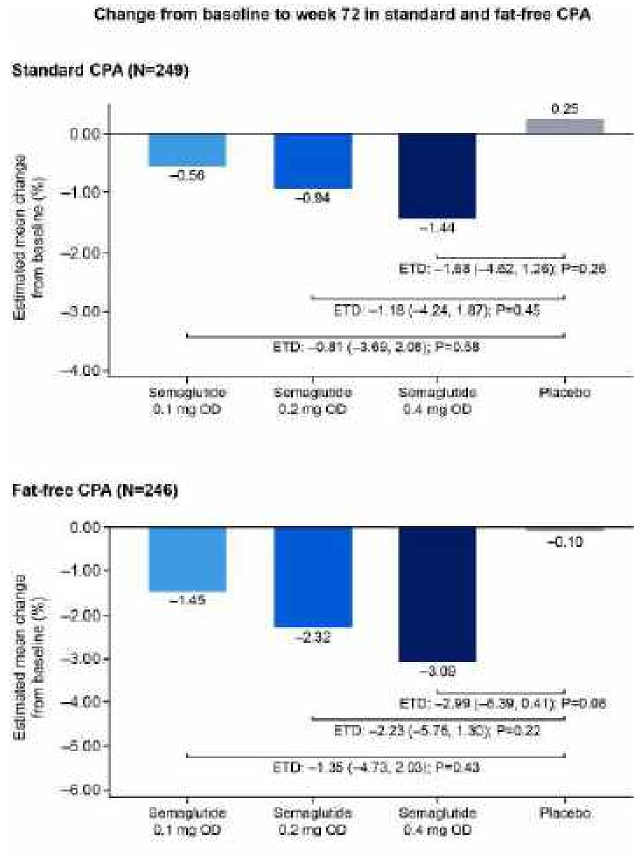
or at baseline and at week 72; digitized biopsy slides were evaluated. CPA was quantified by measuring collagen deposition as a proportion of either: 1) the total biopsy area (standard CPA) or 2) the non-steatotic biopsy area (i.e. normalized for fat: fat-free CPA = collagen area / [biopsy area – steatosis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



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

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

The following people have nothing to disclose: Vlad Ratziu

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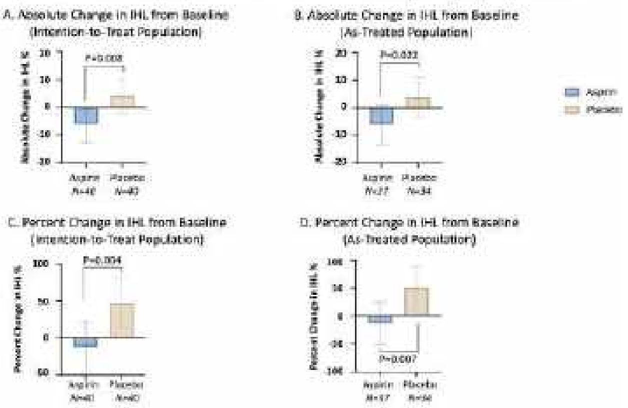
144 | DAILY ASPIRIN THERAPY FOR THE TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A RANDOMIZED CONTROLLED TRIAL

Robert M Wilechansky[1], Stefania Stoyanova[1], Alessandra Grossman[1], Laura E. Dichtel[1], Charles N. Serhan[2], Karen K. Miller[1], Kathleen E. Corey[1], Raymond T. Chung[3], Andrew T. Chan[1] and Tracey G. Simon[1], (1)Massachusetts General Hospital, (2) Brigham and Women's Hospital, (3)Massachusetts General Hospital, Boston, MA

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a chronic, progressive disease with substantial morbidity and mortality and no approved treatments. Observational studies have linked aspirin use to reduced prevalence and progression of MASLD. However, the efficacy and safety of aspirin for reducing hepatic steatosis, inflammation, and fibrosis in patients with MASLD are unknown. **Methods:** In a 6-month, randomized, double-blind, placebo-controlled trial, we assigned 80 adults aged 18-70 years with established MASLD (without cirrhosis) to receive daily aspirin 81mg daily or placebo in a 1:1 ratio. The primary endpoint was mean change in intrahepatic lipid content (IHL) by proton magnetic resonance spectroscopy (1H-MRS); secondary endpoints included mean changes in alanine aminotransferase (ALT), IHL by MRI proton density fat fraction (MRI-PDFF), and the combined inflammation and fibrosis cT1 score. Treatment effects were assessed from the intention-to-treat population. **Results:** Between September 2019 and November 2022, 80 participants were randomized, and 71 completed the trial. At baseline, mean age (47.9 ± 12.1), BMI (33.7 ± 6.0 kg/m^2), sex distribution (56.3% female), and IHL (37.6 ± 18.4%) did not differ between groups. Absolute IHL change at month 6 was -7.3% (95% CI: -14.3 to -0.3) with aspirin and 3.0% (95% CI: -4.4 to 10.5) with placebo ($p = 0.009$), yielding a relative IHL reduction of 10.3% with aspirin compared to placebo (95% CI: -17.9 to -2.8; $p = 0.011$). The percent change in IHL was -17.3% (95% CI: -30.3 to -3.7) with aspirin and 30.3% (95% CI: 5.4 to 56.1) with placebo ($p = 0.007$). Improvements in all prespecified secondary hepatic endpoints were observed in the aspirin group, including a reduction in mean cT1 score (-18.8, 95% CI: -50.7 to 13.0) vs. placebo (29.2, 95% CI: -2.3 to 60.7, $p = 0.011$). The mean absolute weight change did not differ between groups (0.1kg for aspirin vs. 0.4kg for placebo, $p = 0.80$), nor did the proportion of patients with e 3% weight loss (12.5% for aspirin vs. 10% for placebo, $p = 0.66$). The only drug-related adverse event in the aspirin group was heartburn in 1 participant. Adverse events led to discontinuation in 1 participant per group. **Conclusion:** In this 6-month trial in adults with MASLD, aspirin 81mg daily substantially reduced hepatic steatosis and markers of hepatic inflammation and fibrosis. These findings support larger, long-term trials assessing the effects of aspirin on MASLD histological and clinical endpoints.

Figure 1: Effect of Daily Aspirin versus Placebo on Intrahepatic Lipid (IHL) Content



Least-squares means are presented. Panels A and B show the absolute change in IHL percentage from baseline to month 6, derived from analysis of covariance models for the Intention-to-Treat (ITT) population (Panel A) and the As-Treated (AT) population (Panel B), as per the Methods. Panels C and D show the 6-month percent change in IHL percentage, derived from an analysis of covariance model for the ITT population (Panel C) and the AT population (Panel D). For Panels A and C, missing values at month 6 were imputed with multiple imputation. I-bars indicate 95% confidence intervals. IHL: Intrahepatic lipids.

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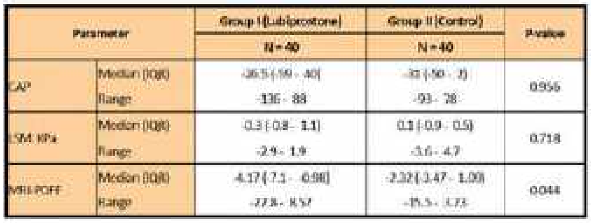
145 | LUBIPROSTONE REDUCES FAT CONTENT ON MRI-PDFF IN PATIENTS WITH MASLD

Mohamed El-Kassas, Endemic Medicine Department, Faculty of Medicine, Helwan University, Cairo, Egypt, Hongqun Liu, University of Calgary Cumming School of Medicine and Samuel S. Lee, University of Calgary

Background: Lubiprostone has been shown to improve intestinal permeability. We aimed to assess the safety and efficacy of lubiprostone in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** This randomised placebo-controlled trial was conducted in a specialized MASLD outpatient clinic at the National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt, and recruited patients with radiological evidence of MASLD. Eligible patients were randomly assigned to either lubiprostone 24 µg or placebo orally twice daily for 48 weeks. The primary endpoint was a change from baseline in fat quantification by MRI-PDFF. Safety was assessed clinically and by laboratory testing. This trial was registered at Clincaltrials.gov (NCT05768334). **Results:** Between November 2020 and February 2023, we screened 176 patients of whom 116 were eligible. 57 patients received lubiprostone (group 1) while 59 patients received placebo (group 2). In groups 1 and 2, MRI-PDFF was technically unfeasible in 3 and 1 patient; 12 and 18 subjects were lost to followup, respectively, and 4 patients discontinued lubiprostone, leaving 40 in each group for final analysis. A greater reduction in fat quantity by MRI-PDFF from baseline to 48 weeks was seen in the lubiprostone group vs. placebo group ($p = 0.04$; table 1) despite a statistically significant reduction in body weight in the control group compared to the lubiprostone group. However, no significant difference was found between both groups regarding liver stiffness measurement by Fibroscan or ALT levels. Severe diarrhea requiring treatment stoppage was encountered in one patient in the lubiprostone group. No other serious adverse events or mortality occurred. **Conclusion:** Lubiprostone was well tolerated and reduced liver MRI-PDFF fat content in patients with MASLD over 48 weeks. Lubiprostone appears promising to treat MASLD, and warrants larger studies to confirm efficacy.

Changes from baseline to week 48 in the two groups



Parameter		Group I (Lubiprostone)	Group II (Control)	P-value
		N = 40	N = 40	
CAP	Median (IQR)	-26.5 (-59 - 40)	-33 (-50 - 3)	0.956
	Range	-136 - 88	-93 - 78	
LSM KPa	Median (IQR)	0.3 (-0.8 - 1.1)	0.1 (-0.9 - 0.5)	0.718
	Range	-2.9 - 1.9	-3.6 - 4.7	
MRI-PDFF	Median (IQR)	-4.17 (-7.1 - -0.98)	-2.32 (-3.47 - 1.00)	0.044
	Range	-27.8 - 8.57	-15.5 - 3.73	

CAP, controlled attenuation parameter. LSM, liver stiffness measurement. IQR, inter-quartile range. Differences between the two groups analyzed by Mann-Whitney test.

Disclosures: The following people have nothing to disclose: Mohamed El-Kassas, Hongqun Liu, Samuel S. Lee

146 | RISK OF ADVERSE LIVER AND RENAL OUTCOMES AFTER INITIATION OF A SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITOR VS. GLP-1 RECEPTOR AGONISTS AND DIPEPTIDYL PEPTIDASE-4 INHIBITORS AMONG US ADULT PATIENTS WITH TYPE 2 DIABETES AND MASLD

Arunkumar Krishnan[1], Tinsay A. Woreta[2], Dipatsree Mukherjee[3], Shyam Thakkar[4], Shailendra Singh[4], William R. Hutson[4] and Saleh A Alqahtani[5,6], (1)Atrium Health Levine Cancer Institute, (2)Johns Hopkins Medicine, Baltimore, MD, (3)Apex Institute of Medical Sciences, (4)West Virginia University School of Medicine, (5)Johns Hopkins University School of Medicine, (6)King Faisal Specialist Hospital and Research Center

Background: The effects of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) on liver and renal outcomes in patients with type 2 diabetes mellitus (T2DM) were demonstrated in recent trials. However, the magnitude of benefits associated with underlying metabolic dysfunction-associated steatotic liver disease (MASLD) remains unclear. We aimed to explore the risk of adverse liver and renal outcomes in patients with MASLD and T2DM taking SGLT-2i vs. dipeptidyl peptidase-4 inhibitors (DPP-4i) and glucagon-like peptide-1 receptor agonists (GLP-1RA). **Methods:** We conducted a population-based, multicenter cohort study with consecutive patients diagnosed with MASLD (without cirrhosis) and T2DM using the TriNeTx dataset. Cohort entry was defined as the date of the first-ever prescription for one of the drugs of interest (SGLT-2i, GLP-1RA, or DPP-4i) during the study period. We used a lag of 6 months for all exposures to minimize protopathic bias. We performed a 1:1 propensity score matching (PSM) to reduce confounding effects. The primary outcomes were defined as the first incidence of cirrhosis, the composite outcome of hepatic decompensation events, and hepatocellular carcinoma (HCC). Secondary outcomes included composite outcome of chronic kidney disease (CKD), composite endpoint of a severe stage of CKD (stages 4-5), and need for hemodialysis. We conducted secondary mad sensitivity analyses to assess the robustness of our findings. The outcomes were estimated using a Cox proportional hazards model with hazard ratios (HR) and 95% confidence intervals (CI). **Results:** In this cohort, 47890 patients received SGLT-2i, and 45160 patients receiving DPP4i were included as controls. After PSM,

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

43758 patients were followed for a median of 1.9 years. For sensitivity analysis, 59205 were included in the GLP-1RA group. Compared with DPP4i use, SGLT-2i use was associated with a lower risk of incident cirrhosis (HR, 1.01), hepatic decompensation (HR 1.03), and HCC (HR 1.07). Similarly, secondary outcomes composite CKD, severe stages of CKD, and need for hemodialysis. The SGLT2i group was non-inferior to the GLP-1RA group in terms of liver outcomes: the incidence of cirrhosis (HR 1.0), hepatic decompensation (HR 0.99) and HCC(HR 0.89) was similar compared with the SGLT-2i group. Sensitivity analysis showed a similar magnitude to the primary and secondary analyses. **Conclusion:** In patients with MASLD and T2DM, SGLT-2i use was associated with significantly reduced risks of adverse liver and renal outcomes compared with DPP4i. SGLT-2i was not inferior to GLP1-RA for adverse liver outcomes but showed a significantly lower incidence.

Table 1. Adverse liver and renal outcomes between the Users of SGLT2 vs. DPP4i in patients with NAFLD and type 2 diabetes

Outcomes	SGLT2 (N=43738), n	DPP4i (N=43738), n	HR (95% CI)
Primary outcome			
Cirrhosis	2912	3215	0.92 (0.89-0.99)
Events of hepatic decompensations	2107	2547	0.90 (0.87-0.95)
Hepatocellular carcinoma	265	379	0.89 (0.78-0.85)
Secondary outcome			
Composite outcome of CKD *	5565	5943	0.98 (0.94-0.98)
Severe stage of CKD$	781	1079	0.72 (0.6 – 0.79)
Need for hemodialysis	166	275	0.60 (0.50-0.73)

Abbreviations: SGLT-2i, sodium-glucose cotransporter 2 inhibitors; DPP-4i, dipeptidyl peptidase-4 Inhibitors; CKD, chronic kidney diseases.
*Composite endpoint of CKD was defined as CKD progression from five stages (stages 1-5);
$Severe stage of chronic kidney disease was defined as CKD progression stages 4-5.

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147 | DEEP PHENOTYPING OF TM6SF2 TO CHARACTERIZE HEPATIC STEATOSIS, PLASMA LIPID TRAITS, AND METABOLIC RISK FACTORS USING A GENOME-FIRST APPROACH★

Helen Huang[1], *Cecilia Vitali*[1], *Michael C Phillips*[1], *Kate Townsend*[2], *David Zhang*[1], *Eleonora Scorletti*[2], *Nicholas J. Hand*[2], *Joseph Park*[1], *Kai M. Schneider*[3], *Daniel J. Rader*[2], *Carolin V. Schneider*[1] *and Regeneron Centre, (1)Perelman School of Medicine, University of Pennsylvania, (2)University of Pennsylvania, (3) University Hospital Rwth Aachen*

Background: An unbiased ‘genome-first’ approach has the potential to expand the understanding of common coding and predicted loss-of-function (pLOF) variants associated with non-alcoholic fatty liver disease (NAFLD). Utilizing this approach, we aimed to uncover the functionality of pathogenic variants in *TM6SF2*. **Methods:** We leveraged exome sequencing data from 44,297 patients in the Penn Medicine Biobank and interrogated 121 non-synonymous missense variants and 12 pLOF variants for associations with ICD-10 coded NAFLD, non-alcoholic steatohepatitis (NASH), and hepatocellular carcinoma (HCC). Significant variants were further analysed with serum parameters, liver fat scores, and imaging adjusted for age, sex, body mass index, principal components of ancestry, and carriage of *PNPLA3* rs738409:G. We replicated findings in the UK Biobank (UKB) and differences were statistically significant when $p < 0.05$. *In silico* prediction of the structure of *TM6SF2* was generated using ColabFold Alphfold2 notebook with MMseqs2. **Results:** E167K homozygotes are at an increased risk of ICD-diagnosed NAFLD ($p < 0.0001$, OR:4.8), NASH ($p < 0.0001$, OR:5.1), and HCC ($p = 0.001$, OR:1.77). Similarly, E167K heterozygotes exhibited a similar trend with NAFLD and NASH only. Additionally, L156P heterozygotes were at an increased risk of physician-diagnosed NAFLD ($p < 0.001$, OR:2.16) and NASH ($p < 0.0001$, OR:2.10). Only L156P homozygotes were at an increased risk for HCC (N = 2, $p < 0.0001$, OR:532.0). We successfully replicated associations with ICD-diagnosed NAFLD, NASH, and HCC in the UKB for both variants. Additional diagnoses on imaging, coupled with evidence of elevated CT-derived hepatic fat scores, in the PMBB strengthened these associations in E167K and L156P carriers ($p < 0.01$). Metabolomic analyses reveals lower circulating total cholesterol, triglycerides, fatty acids, and total choline in E167K and L156P carriers (Bonferroni-corrected, $p < 0.0001$). *In silico* predictions validate both mutations to cause structural disruptions on the EXPERA domain leading to loss of *TM6SF2* protein function. This hypothesis was strengthened when we interrogated pLOF variants and discovered a stop-gain truncation codon (W35X) associated with an increased risk of physician-diagnosed NAFLD ($p = 0.03$, OR:15.9), NASH ($p = 0.01$, OR:23.4) and elevated liver fat scores ($p < 0.001$) in the same directionality as E167K and L156P. **Conclusion:** We confirm that E167K and L156P induces a loss-of-function effect on the protein structure, thus leading to liver disease, and identified a stop-gain codon of potential therapeutic utility towards NAFLD.

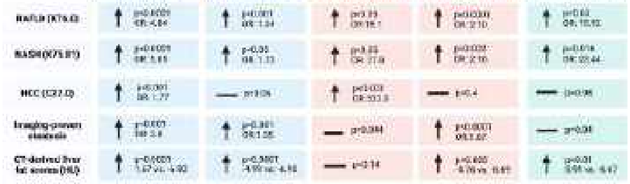

Figure 1. Multivariable regression analyses of E167K, L156P and W35X carriers in the PMBB associated with ICD-10 diagnoses, imaging reports, and liver fat scores on CT. [illegible]

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

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

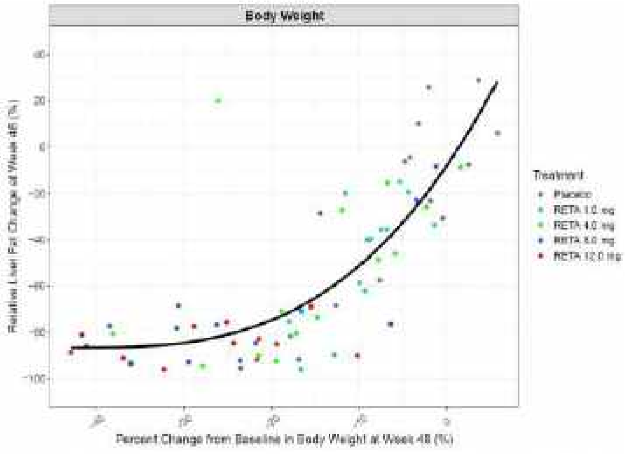

Figure 1 - Scatterplot and fitted power model curve between the relative liver fat reduction vs. percent changes in body weight at Week 48.

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

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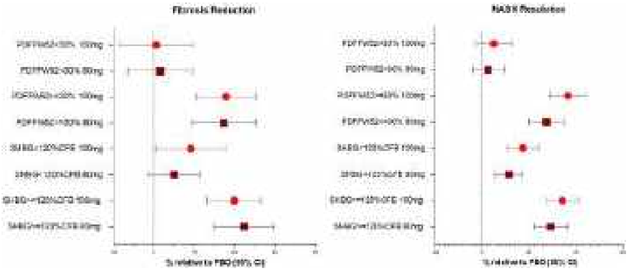
Background: MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed non-alcoholic steatohepatitis (NASH) and fibrosis. 966 patients with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80mg, resmetirom 100mg, or placebo administered once daily. Histologic endpoints were assessed after 52 weeks. Dual primary endpoints at Week 52 were achieved with both resmetirom 80mg and 100mg: NASH resolution with no worsening of fibrosis (NR) or e 1-stage reduction in fibrosis with no worsening of NAS (FR). **Methods:** Adults with e 3 metabolic risk factors, liver stiffness e 8.5 kPa, hepatic fat e 8%, biopsy-confirmed NASH with F1B-F3 fibrosis, and NAS e 4 were eligible to participate in MAESTRO-NASH. The relationship of non-invasive measures with histological response (NR and/or FR) in the resmetirom 80mg, resmetirom 100mg, and placebo groups was assessed. **Results:** Patients with biopsy-confirmed NASH with fibrosis had high metabolic risk including obesity (mean BMI = 36), type 2 diabetes (70%), hypertension (78%), and 10-year ASCVD risk score > 14. Baseline mean (SD) FibroScan VCTE was 13.3 (6.8), 13.6 (7.1), and 12.9 (5.6) kPa for the resmetirom 80mg, resmetirom 100mg, and placebo groups. Baseline ELF across all fibrosis groups was 9.8 (0.87). FIB-4 across all dose groups was 1.3. Median reduction in MRI-PDFF was 42% and 52% in the paired biopsy population at resmetirom 80mg and 100mg. Among patients treated with resmetirom 80mg or 100mg who achieved a e 30% reduction from baseline in MRI-PDFF, NR was observed in 28% and 38% and FR in 17% and 18% more patients than placebo. Among resmetirom-treated patients with a e 120% increase in SHBG (marker of drug exposure), NR was seen in 34% and 37% and FR in 22% and 20% more resmetirom 80mg and 100mg patients than placebo. A e 30% PDFF response was observed in 96%, 88%, and 92% of resmetirom 100mg NR, FR, and NR and/or FR responders. Half of the resmetirom e 30% PDFF responders without NR or FR showed e 2-point NAS reduction. On biopsy, NR correlated with FR ($r^2 = 0.30$). Additional correlates of NR and FR at resmetirom 100mg included reduction in PDFF ($r^2 = 0.39$, 0.23); ALT ($r^2 = 0.20$, 0.24); and liver volume ($r^2 = 0.25$, 0.18). Weaker correlations were observed with AST and FibroScan CAP. Correlations at resmetirom 80mg were similar. LDL-C lowering did not correlate with either NR or FR. Although MRE (kPa), Fibroscan VCTE, and ELF were reduced with resmetirom treatment, the reduction in these non-invasive measures did not correlate with NR or FR. **Conclusion:** Achievement of NASH resolution and fibrosis reduction was associated with a e 30% reduction from baseline in MRI-PDFF and e 120% increase in SHBG at both resmetirom doses (80 and 100mg). Additional analyses, including artificial intelligence (AI)-based assessments of histological response, are ongoing.



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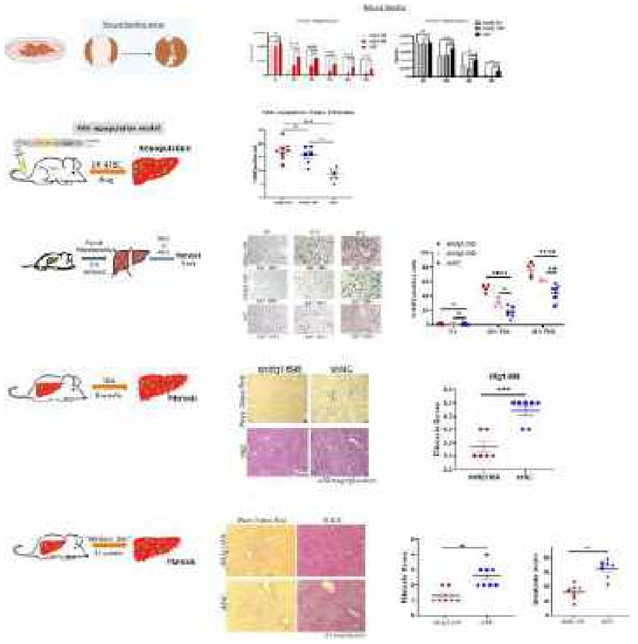
150 | ITFG1: A PROMISING TARGET FOR ENHANCED LIVER REGENERATION AND CHRONIC LIVER DISEASE TREATMENT

Viktoriia Iakovleva[1], Anna Potapova[1], Agnes Ong[1], Gao Rong[1], Yock Young Dan[2] and Torsten Wuestefeld[1,3], (1) Genome Institute of Singapore, (2)National University Health System (NUHS), (3)Nanyang Technological University

Background: The liver has a remarkable regenerative capacity. Nevertheless, under chronic liver-damaging conditions, this capacity becomes exhausted, allowing the accumulation of fibrotic tissue and leading to end-stage liver disease. Enhancing the endogenous regenerative capacity by targeting regeneration breaks is a novel therapeutic approach. We set up an in vivo functional genetic screen to identify such regeneration breaks. Integrin Alpha FG-GAP Repeat Containing 1 (ITFG1) was one of the top hits. We proofed that hepatocyte specific knockdown of Itfg1 enhances the endogenous regenerative capacity of the liver and counteracts chronic liver disease. **Methods:** We conducted an in vivo functional genetic RNAi screen in the thioacetamide (TAA) driven chronic liver disease model. Two independent shRNAs targeting Itfg1 were significantly enriched. We then tested the effect of Itfg1 knockdown on mouse and human hepatocyte proliferation in vitro. Furthermore, taking advantage of the FAH knockout mouse model, we tested for Itfg1 knockdown driven faster liver repopulation, enhanced regeneration after partial hepatectomy and fibrosis reduction in chronic liver damaging conditions, including "Western Diet" driven NAFLD. For unraveling the mechanism of Itfg1 inhibition driven accelerated liver regeneration we did in depth transcriptomic and proteomic analysis. **Results:** Knockdown of Itfg1 in immortalized mouse as well as human hepatocytes accelerates their proliferation and wound healing in vitro. In vivo knockdown of Itfg1 in hepatocytes, accelerates their ability to repopulate the liver of FAH deficient mice. Furthermore, in fully repopulated mice, where every hepatocyte expresses the shRNA targeting Itfg1, liver regeneration upon partial hepatectomy is accelerated. The enhanced regenerative capacity also attenuated TAA and "Western Diet" induced chronic damage. Itfg1 knockdown not only reduced fibrosis but also reduced steatosis in the NAFLD model. Our transcriptomic and proteomic analysis showed that Itfg1 knockdown affects fatty acid metabolism, the MAPK and AKT pathways. **Conclusion:** We identified and validated Itfg1 as a target for enhancing the endogenous regenerative capacity of the liver. Enhancing the endogenous regenerative capacity attenuates chronic liver disease. We are currently in the process to translate our results into RNAi therapeutics.



Disclosures: Torsten Wuestefeld – Cargene Therapeutics: Advisor, Yes, No;

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151 | EMPAGLIFLOZIN IS EQUALLY EFFECTIVE IN REDUCING LIVER FAT CONTENT IN T2DM PATIENTS AND IN NON-DIABETIC INDIVIDUALS, A RANDOMIZED TRIAL

Siham Abdelgani, Uth San Antonio

Background: This study was performed to examine the effect of empagliflozin on liver fat content in T2DM patients and in nondiabetic individual's, and the relationship between the decrease in liver fat and other metabolic actions of empagliflozin. **Methods:** 30 T2DM and 27 nondiabetic individual's were randomized to receive in a double blind fashion in 2:1 ratio treatment with empagliflozin or matching placebo. Patients received 75-grams OGTT, liver fat content with MRI spectroscopy before and at the end of therapy. Hepatic glucose production at the start of therapy was measured with 3H-glucose infusion. **Results:** empagliflozin caused -2.75% and -1.93% absolute reduction in liver fat content in T2DM and nondiabetic individual's, respectively, compared to +0.9% and +0.8% increase, respectively, in subjects receiving placebo, ($p < 0.05$ for both groups). The decrease in hepatic fat content was strongly influenced by baseline liver fat content and was strongly related to the decrease in body weight ($r = 0.53$, $p < 0.001$) and improvement in insulin sensitivity caused by empagliflozin ($r = -0.51$, $p < 0.001$), but was not influenced by the decrease in fasting plasma glucose, HbA1c or the increase in hepatic glucose production. **Conclusion:** empagliflozin is equally effective in reducing liver fat content in T2DM patients and in nondiabetic individual's. The decrease in liver fat content is independent of the decrease in plasma glucose concentration but is strongly related to the decrease in body weight and improvement in insulin sensitivity.

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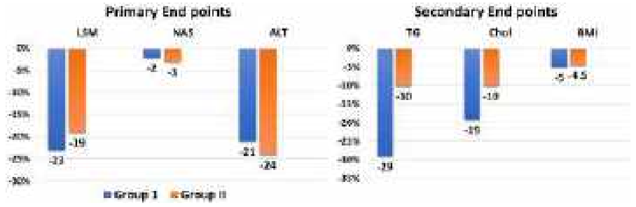
152 | SAROGLITAZAAR IS EFFECTIVE IN IMPROVING LIVER STIFFNESS MEASUREMENT AND LIVER ENZYMES IN NONALCOHOLIC STEATOHEPATITIS

Tarana Gupta[1], *Pankaj Kaushik Jr.*[2] *and Rakesh Mittal*[2], *(1)Pandit Bhagwat Dayal Sharma Institute of Medical Sciences, Rohtak, (2)Pt Bds Pgims, Rohtak*

Background: Despite advances in understanding the pathophysiology of nonalcoholic steatohepatitis (NASH), no pharmacotherapy has been proven effective in improving outcome. Peroxisome proliferator-activated receptors (PPAR) are nuclear receptors with key role in metabolic homeostasis and inflammation and PPAR knockout mice are susceptible to development of NASH. Studies have shown protective role of PPAR-± in hepatic steatosis and inflammation and PPAR-γ as insulin sensitizers. Saroglitazaar is dual PPAR ± and γ agonist approved for diabetic dyslipidemia Though the drug is approved in India for use in patients with NASH, data regarding improvement in liver fibrosis is still awaited. We compared saroglitazaar alone versus its combination with vitamin E in patients with NASH. **Methods:** This was a prospective, randomized, open label clinical trial conducted from July 2021 to December 2022 in a tertiary care center. The study was approved by institutional ethics committee and registered on CTRI vide registration no CTRI/2021/07/034946. All patients of biopsy proven NASH were randomized in 1:1 allocation ratio to receive saroglitazaar 4 mg OD (Group I) or saroglitazaar 4 mg OD with Vitamin E 400 IU OD (Group II) for a period of 6 months. The primary end points were improvement in NAS score, liver stiffness measurement (LSM) values by transient elastography and liver enzymes (SGPT). The secondary end points were improvement in BMI and serum triglycerides (TG) and cholesterol (Chol) levels. **Results:** Total 53 patients were enrolled, two patients in Group I were lost to follow up and finally, Group I ($n = 25$) and Group II ($n = 26$) were analysed. All baseline characteristics were comparable between two groups. In primary end points, LSM values improved in group I (9.1 to 7.0 kPa, $p = 0.03$), Group II (7.9 to 7.1 kPa, $p = 0.04$), SGPT values improved in Group I (101 to 81 U/L, $p = 0.02$), Group II (98 to 75 U/L, $p = 0.04$) significantly with no change in NAS score in both the groups from baseline to 24 weeks respectively. In secondary end points, significant reduction in TG and Chol in Group I (234 to 167 mg/dL, $p = 0.003$; 234 to 199 mg/dL, $p = 0.04$), Group II (223 to 188 mg/dL, $p = 0.04$; 229 to 189 mg/dL, $p = 0.007$) respectively with no change in BMI. **Conclusion:** Saroglitazaar alone was effective in improving LSM and SGPT values in NASH. However, no improvement in NAS score could be observed over a period of 24 weeks.



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153 | AN AGE-STATIN INTERPLAY IN PREVENTING THE DEVELOPMENT OF CIRRHOSIS IN A 10-YEAR COHORT OF PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)★

Georgia Sofia Karachaliou[1], Amy M Perkins[2], Chad Dorn[2], Qingyi Wei[1], Xiaoming Xu[3], Sheng Luo[3], Glenn Temple Gobbel[2], Ruth Reeves[2], Mustafa Bashir[4], Manal F. Abdelmalek[5], Anna Mae Diehl[3] and Ayako Suzuki[6,7], (1)Duke University Medical Center, (2) Vanderbilt University Medical Center, (3)Duke University, (4)Duke University, Durham, NC, (5)Mayo Clinic, Rochester, MN, (6)Durham VA Medical Center, Durham, NC, (7)Duke University, NC

Background: Statins reduce the risk of hepatic fibrosis in patients with chronic liver diseases. Since age, sex, and menopausal status modulate NAFLD pathogenesis and fibrosis risk, the effects of statins on hepatic fibrosis may vary by age and sex. We aimed to assess age-/sex-disparities in the association between statin use and the incidence of cirrhosis in patients with NAFLD. **Methods:** We developed a cohort of NAFLD patients between 2007 and 2009 (baseline period), applying the validated algorithm (PMID: 30144434) to the VA electronic health records. We created baseline variables including demographics, BMI, statin use, comorbidities, relevant co-medications, such as beta-blockers and metformin, and FIB-4 scores. The cohort was then followed for incident cirrhosis defined by ICD codes for up to ten years. We also captured cumulative standardized dose and duration of statins, BMI, and co-medication use during the follow-up and analyzed them as time-dependent covariates. Patients were censored at the diagnosis of other chronic liver diseases, alcohol use disorder, death unrelated to cirrhosis, or loss to follow-up. Cox proportional hazards regression models without and with time-dependent covariates were used to associate incident cirrhosis with statin use at baseline and during follow-up, respectively. Disparities were assessed in subgroup analyses by age (using a cut-off of 51 years, the average age at menopause in the US) and sex as well as in a model with an interaction term. **Results:** A total of 335,991 patients (median age of 62 years, male 91%, White 78%, median BMI of 31 kg/m2, DM 39%, and statin use 65% at baseline) were analyzed after excluding prevalent cirrhosis, incident cirrhosis within one-year follow-up, and no follow-up data after the index date from 346,818 NAFLD patients identified at the baseline. Cumulative incidence of cirrhosis was 2.96% (median follow-up of 117 [50, 121] months), which differed by sex and age group (d or > 50 y). After adjusting for potential confounders and baseline FIB-4 score, baseline statin use was associated with a reduced risk of developing cirrhosis (HR and 95% CI = 0.77 [0.65, 0.91]). In the models with time-dependent covariates, both cumulative standardized dose and duration during follow-up showed significant protective effects against cirrhosis development (HR and 95%CI = 0.72 [0.68, 0.76]) and 0.67 [0.63, 0.72], respectively). The effect of cumulative standardized statin dose and duration showed a significant interaction with age (interaction: $p = 0.0005$ and $p < 0.0001$, respectively), associated with stronger protection from cirrhosis development in older vs. younger subjects. **Conclusion:** Statins are more protective against cirrhosis in older subjects, and this effect is not influenced by sex.

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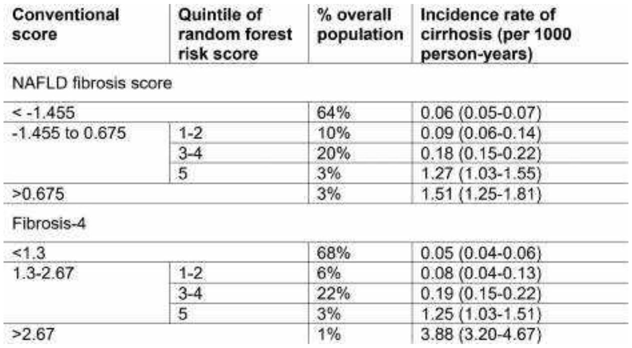
154 | MACHINE LEARNING SCORES ACCURATELY CLASSIFY INDIVIDUALS AT INDETERMINATE RISK OF INCIDENT CIRRHOSIS INTO LOW AND HIGH RISK GROUPS

Vincent Chen[1], Chinmay Raut[2], Antonino Oliveri[3], Yanhua Chen[2], Majd Aboona[4], Claire Faulkner[4], Wei Xuan Tay[5], Nicole Xinrong Han[5], Karn Wijarnpreecha[6], Yu JUN Wong[5] and Elizabeth K. Speliotes[7], (1) University of Michigan Medical Center, (2)University of Michigan, (3)University of Michigan, Ann Arbor, MI, (4) University of Arizona College of Medicine, Phoenix, AZ, (5)Changi General Hospital, (6)University of Arizona College of Medicine Phoenix, Phoenix, AZ, (7) University of Michigan Medical School, Ann Arbor, Michigan, USA

Background: Risk stratification in non-alcoholic fatty liver disease (NAFLD) using non-invasive scores including Fibrosis-4 (FIB4) and NAFLD fibrosis score (NFS) is recommended by clinical guidelines. However, FIB4 and NFS values are indeterminate in 20-50% of patients with NAFLD. We aimed to develop machine learning models to improve upon FIB4 and NFS, especially in the indeterminate-risk range. **Methods:** We included two cohorts, Michigan Medicine (MM) patients with NAFLD, and UK Biobank (UKBB) participants without excess alcohol intake or chronic liver diseases other than NAFLD. We adopted a two-stage approach to train in MM a model to identify incident cirrhosis. First, we used a least absolute shrinkage and selection operator (LASSO) model to select features. Second, we generated using those features a random forest (RF) model based on downsampling. We externally validated this model in UKBB and compared it to FIB4 and NFS based on time-dependent area under the curve (tAUC) models for risk of incident cirrhosis at 10 years. We compared incidence rates based on quintile of predicted risk by the RF model. **Results:** The MM and UKBB cohorts included 28,684 and 480,651 participants, respectively. LASSO regression identified six predictors of incident cirrhosis in MM which were included in the RF model: age, AST, ALP, platelets, diabetes, and hypertension. In the UKBB, the RF model had 10-year tAUC of 0.84 (0.82-0.86) which outperformed FIB4 [0.81 (0.79-0.83)] and NFS [0.76 (0.73-0.78)], $p < 0.05$ for both. The RF model identified considerable heterogeneity in risk of incident cirrhosis in patients with indeterminate FIB4 (1.3-2.67) or NFS (-1.455 to 0.675) with > 10-fold variation of cirrhosis incidence between the bottom quintiles (1-2) and top quintile (5) of RF model risk (Table). Patients with indeterminate FIB4/NFS and the lowest 40% of RF model risk had incidence of cirrhosis similar to those with low FIB4 (< 1.3) or NFS (< -1.455), and those in the top 20% had similar incidence to that of high NFS (> 0.675) or FIB4 (> 2.67). The RF model reclassified 30-40% of indeterminate-risk patients into high or low risk categories. These findings were consistent in subgroups including diabetes or elevated transaminases. **Conclusion:** We trained and externally validated a simple RF model that identified heterogeneity among indeterminate-risk patients. This model accurately risk stratifies 30-40% of indeterminate-risk individual's using commonly-available predictors, thus providing a scalable pathway to optimize tertiary care referrals.



Conventional score	Quintile of random forest risk score	% overall population	Incidence rate of cirrhosis (per 1000 person-years)
NAFLD fibrosis score			
< -1.455		64%	0.06 (0.05-0.07)
-1.455 to 0.675	1-2	10%	0.09 (0.06-0.14)
	3-4	20%	0.18 (0.15-0.22)
	5	3%	1.27 (1.03-1.55)
>0.675		3%	1.51 (1.25-1.81)
Fibrosis-4			
<1.3		68%	0.05 (0.04-0.06)
1.3-2.67	1-2	6%	0.08 (0.04-0.13)
	3-4	22%	0.19 (0.15-0.22)
	5	3%	1.25 (1.03-1.51)
>2.67		1%	3.88 (3.20-4.67)

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Disclosure information not available at the time of publication: Yanhua Chen, Majd Aboona, Claire Faulkner, Wei Xuan Tay, Nicole Xinrong Han

155 | NEGATIVE IMPACT OF PNPLA3 rs738409 C > G IS SIGNIFICANTLY MODIFIED BY DIETARY FACTORS, CAFFEINE AND NON-HEAVY ALCOHOL CONSUMPTION IN THE US POPULATION

Eduardo Vilar-Gomez II, Samer Gawrieh, Raj Vuppalanchi, Niharika R. Samala and Naga P. Chalasani, Indiana University School of Medicine

Background: *PNPLA3* rs738409 C > G is strongly associated with NAFLD and its severity. *PNPLA3* expression is highly regulated by changes in energy balance; however, little is known about the interplay between *PNPLA3*, dietary factors, alcohol intake, and risk of liver-related death (LRD). We examined the effect of interactions between *PNPLA3* rs738409 and dietary factors (macronutrients/coffee-tea intake) and alcohol consumption on the risk of LRD in a population-based US cohort. **Methods:** 14,797 adults enrolled in NHANES III (1991–1994) were investigated. Participants with lack of *PNPLA3* rs738409, dietary nutrients, and heavy alcohol intake (> 2 or > 3 drinks per day in women and men) were excluded. The remaining 4361 participants (study cohort) were linked to the National Death Index mortality data through December 2019. LRD was the study outcome. Associations between *PNPLA3*, dietary nutrients (% daily calories from fat, protein, carb, monounsaturated fatty acids [MUFAs], polyunsaturated fatty acids [PUFAs] and saturated fats, fiber, and cholesterol), non-heavy alcohol intake, and LRD were examined using weighted multivariable competing risk regression models, adjusted for age, sex, race/ethnicity, calorie intake, BMI, and physical activity. Multiplicative interaction terms between *PNPLA3* and variables of interest were included in all models. **Results:** The *PNPLA3* CC, CG, and GG genotypes frequencies were 55%, 36%, and 9%. There were 28 LRD (0.6%) over a mean 23.1 years follow-up. *PNPLA3* G allele was associated with LRD (sHR: 2.8, 95% CI: 1.4-5.6). Non-heavy alcohol intake (sHR: 2.2, 95% CI: 1.07-4.5), % MUFAs (sHR: 0.94, 95% CI: 0.88-0.99), cholesterol intake (mg) (sHR: 1.001, 95% CI: 1.0004-1.002), and coffee-tea intake e 3 cups/day (sHR: 0.38, 95% CI: 0.04-0.99) were also associated with risk of LRD. Compared to wild-type *PNPLA3* and non-drinkers, G allele carriage significantly increased the risk of LRD among drinkers (sHR: 3.5, 95% CI: 1.9-6.4) vs non-drinkers (sHR: 1.9, 95% CI: 0.7-5.1). Compared to wild-type *PNPLA3*, a higher risk of LRD was observed among G-allele carriers and higher consumption (top quartile) of saturated fat (sHR: 3.5, 95% CI: 1.2-9.7), and cholesterol (sHR: 3.0, 95% CI: 1.7-6.2). However, compared to wild-type *PNPLA3*, effects of the G-allele on the risk of LRD were significantly attenuated in those with higher consumption (top quartile) of coffee/tea (sHR: 0.06, 95% CI: 0.007-0.55) and MUFAs (sHR: 0.5, 95% CI: 0.1-0.9). The interactions between other macronutrients and *PNPLA3* variation did not significantly impact the risk of LRD (Table 1). **Conclusion:** Non-heavy alcohol consumption and high intake of saturated fat and cholesterol adversely whereas higher caffeine/tea drinking favorably modify the risk of liver-related death associated with *PNPLA3* rs738409. If supported by other studies, these observations will assist in the personalized management of NAFLD.

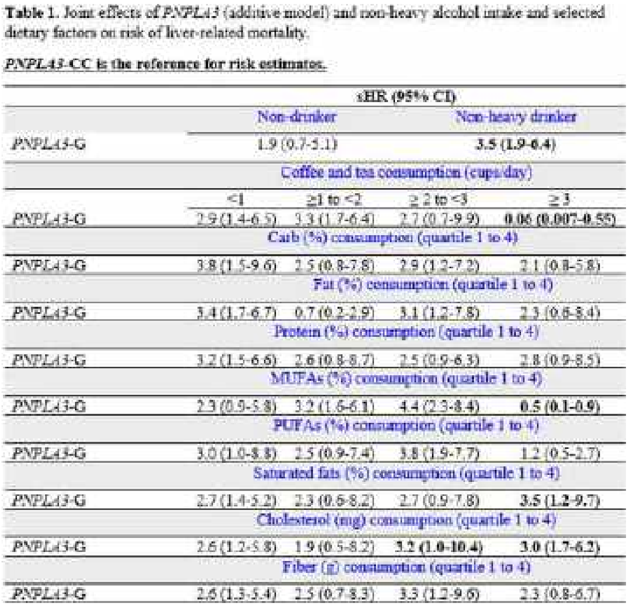


Table 1. Joint effects of *PNPLA3* (additive model) and non-heavy alcohol intake and selected dietary factors on risk of liver-related mortality.

PNPLA3-CC is the reference for risk estimates.

	sHR (95% CI)			
	Non-drinker		Non-heavy drinker	
PNPLA3-G	1.9 (0.7-5.1)		**3.5 (1.9-6.4)**	
	Coffee and tea consumption (cups/day)			
	<1	≥1 to <2	≥ 2 to <3	≥ 3
PNPLA3-G	2.9 (1.4-6.5)	3.3 (1.7-6.4)	2.7 (0.7-9.9)	**0.06 (0.007-0.55)**
	Carb (%) consumption (quartile 1 to 4)			
PNPLA3-G	3.8 (1.5-9.6)	2.5 (0.8-7.8)	2.9 (1.2-7.2)	2.1 (0.8-5.8)
	Fat (%) consumption (quartile 1 to 4)			
PNPLA3-G	3.4 (1.7-6.7)	0.7 (0.2-2.9)	3.1 (1.2-7.8)	2.3 (0.6-8.4)
	Protein (%) consumption (quartile 1 to 4)			
PNPLA3-G	3.2 (1.5-6.6)	2.6 (0.8-8.7)	2.5 (0.9-6.3)	2.8 (0.9-8.5)
	MUFAs (%) consumption (quartile 1 to 4)			
PNPLA3-G	2.3 (0.9-5.8)	3.2 (1.6-6.1)	4.4 (2.3-8.4)	**0.5 (0.1-0.9)**
	PUFAs (%) consumption (quartile 1 to 4)			
PNPLA3-G	3.0 (1.0-8.8)	2.5 (0.9-7.4)	3.8 (1.9-7.7)	1.2 (0.5-2.7)
	Saturated fats (%) consumption (quartile 1 to 4)			
PNPLA3-G	2.7 (1.4-5.2)	2.3 (0.6-8.2)	2.7 (0.9-7.8)	**3.5 (1.2-9.7)**
	Cholesterol (mg) consumption (quartile 1 to 4)			
PNPLA3-G	2.6 (1.2-5.8)	1.9 (0.5-8.2)	**3.2 (1.0-10.4)**	**3.0 (1.7-6.2)**
	Fiber (g) consumption (quartile 1 to 4)			
PNPLA3-G	2.6 (1.3-5.4)	2.5 (0.7-8.3)	3.3 (1.2-9.6)	2.3 (0.8-6.7)

Disclosures: Samer Gawrieh – Sonic Incytes: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Zydus: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Viking: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; TransMedics: Consultant, No, No; Pfizer: Consultant, No, No;

The following people have nothing to disclose: Eduardo Vilar-Gomez, Raj Vuppalanchi, Niharika R. Samala, Naga P. Chalasani

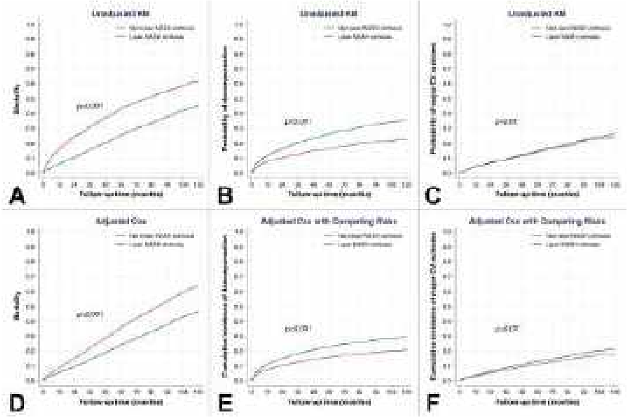
156 | MORTALITY, HEPATIC DECOMPENSATION, AND CARDIOVASCULAR OUTCOMES IN LEAN VS. NON-LEAN MASH CIRRHOSIS: A VETERANS AFFAIRS COHORT STUDY★

Basile Njei[1], *Catherine Mezzacappa*[1], *Binu V John*[2], *Marina Serper*[3], *David E. Kaplan*[4], *Tamar H. Taddei*[1] *and Nadim Mahmud*[5], *(1)Yale University, New Haven, CT, (2)University of Miami and Miami VA Health System, Miami, FL, (3)University of Pennsylvania, Philadelphia, PA, United States, (4)Division of Gastroenterology and Hepatology, Department of Medicine, Perelman School of Medicine, University of*

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

Pennsylvania, Philadelphia, PA, USA, (5)Hospital of the University of Pennsylvania

Background: Studies on incident liver and cardiovascular outcomes in lean (body mass index: BMI < 25 kg/m^2, or < 23 kg/m^2 for Asians) vs. non-lean individual's with metabolic dysfunction-associated steatohepatitis (MASH) have reported mixed results. We aimed to compare incident clinical outcomes and mortality between lean and non-lean individual's with compensated MASH cirrhosis in a large national cohort. **Methods:** This was a retrospective cohort study of patients with newly diagnosed compensated MASH cirrhosis from 1/2008-5/2021 in the Veterans Health Administration. Average BMI in the 12 months prior to cirrhosis diagnosis was used to classify lean vs. non-lean MASH, and alternate etiologies of liver disease were excluded using validated algorithms. Our primary outcome was incident hepatic decompensation. Secondary outcomes were incident major adverse cardiovascular events (MACE- a composite of myocardial infarction, cardiac arrest, stroke, heart failure, atrial fibrillation) and all-cause mortality. Multivariable Cox proportional hazard models were constructed to assess the effects of lean status on clinical outcomes and survival. Fine and Gray competing risk regression was used where applicable. **Results:** We included 15,974 MASH patients in our analytic sample: 1,731 lean and 14,243 non-lean patients. Included patients were mostly male (95%), median age was 68 years, and 67% were non-Hispanic white. At baseline, prevalence of diabetes was lower in lean vs. non-lean individual's (44.8% vs. 72.9%, $p < 0.001$). Lean individual's also had fewer cardiometabolic risk factors at baseline. In multivariable models (Figure 1), with adjustments for age, sex, race, smoking status, diabetes, MELD-Na, and alcohol use per AUDIT-C, lean status was associated with a 92% increased risk of all-cause mortality (aHR = 1.92; 95% CI: 1.77–2.08). Paradoxically, lean status was associated with a 39% decreased risk of incident hepatic decompensation (aSHR = 0.67; 95% CI: 0.58–0.77). There was no significant association between lean status and major adverse cardiovascular events (aSHR = 0.84, [95% CI: 0.70–1.01], $p = 0.07$). **Conclusion:** In patients with compensated MASH cirrhosis, lean status was associated with increased all-cause mortality and decreased risk of hepatic decompensation. Despite low prevalence of diabetes and better cardiometabolic profile, lean individual's were at equally high risk of MACE. Future studies should evaluate other drivers (e.g., extrahepatic cancer, renal disease, and genetics) of mortality in lean MASH patients.



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The following people have nothing to disclose: Basile Njei
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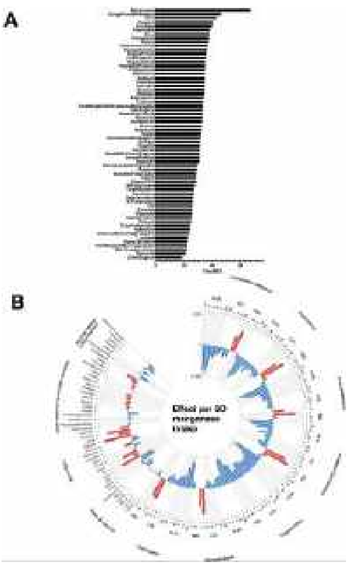
157 | MACHINE LEARNING PREDICTS DIETARY PATTERNS ASSOCIATED WITH FATTY LIVER DISEASE PROTECTION★

Simon Schophaus[1], Kate Townsend[2], Jan Niklas Clusman[1], Alexander Koch[1], Christian Trautwein[3], Kai M. Schneider[4] and Carolin Victoria Schneider[5], (1) University Hospital Rwth Aachen, Aachen, Germany, (2)University of Pennsylvania, (3)University Hospital, Rwth Aachen, (4)Medical Clinic III, Gastroenterology, Metabolic Diseases and Intensive Care, University Hospital Rwth Aachen, Aachen, Germany, (5)University Hospital Rwth Aachen

Background: Non-alcoholic fatty liver disease (NAFLD) affects a substantial proportion of the general population, but little is known about the impact of specific nutrients on its prevention. Utilizing unbiased machine learning, we aimed to investigate the association between dietary nutrients and the development of NAFLD in the large UK Biobank dataset. **Methods:** We analyzed data from the UK Biobank, focusing on individual's with dietary assessments (up to five dietary questionnaires per person) and excluding those with pre-existing liver disease. Comprehensive benchmarking revealed superiority of a random forest classifier to examine the association between dietary questionnaire nutrients and steatosis development over 11 years of follow-up. A cohort study of more than 200,000 participants was then conducted to assess the association between manganese intake and liver outcomes (ICD10 codes). All analyses were adjusted for age, sex, BMI, Townsend index of socioeconomic status, kcal, alcohol intake, protein intake, fat intake, carbohydrate intake, and multiple testing. **Results:** A random forest classifier was used to analyze the feature importance of 63 nutrients and imaging-proven steatosis in a cohort of over 35,000 UK Biobank participants. Our results showed that participants with higher dietary manganese intake were less likely to have imaging-proven steatosis, suggesting a potential protective effect of manganese against NAFLD (Figure 1 A). We then validated the importance of manganese in a cohort study of over 200,000 UK Biobank participants to examine the relationship between manganese intake and liver outcomes and found that higher manganese intake was associated with a lower risk of ICD-10 coded fatty liver ($OR = 0.851$ (0.804-0.900), $p < 0.001$), independent of other potential confounders. In addition, there was a significant effect of manganese on metabolomics available in > 49,000 individual's (Figure 1B) and showed an association with reduced VLDL secretion. **Conclusion:** Our study provides evidence that higher manganese intake may be associated with lower odds of steatosis in a large population-based sample. These findings highlight a potential role for manganese in the prevention of NAFLD, but further research is needed to confirm these findings and to investigate the underlying mechanisms. Finally, our study elucidates a comprehensive workflow that leverages the potential of machine learning techniques and vast datasets to facilitate precision nutrition strategies for the prevention of liver disease. A)Feature Importance for Predicting imaging-diagnosed steatosis using a Random Forest Model: For each input feature, we calculated %IncMSE by permuting the feature's values and measuring increase in the Mean Squared Error. B)Associations of metabolic biomarkers with manganese intake among > 49,000 participants: Hazard ratios (with 95% confidence intervals) presented per 1-SD higher metabolic biomarker.

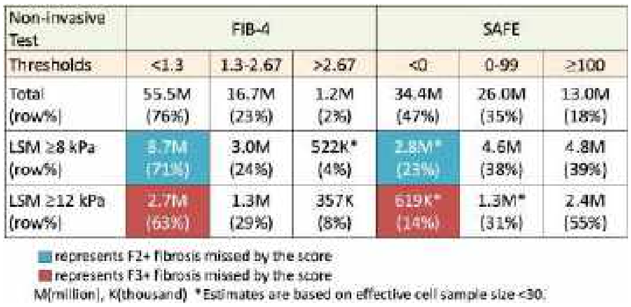


Disclosures: The following people have nothing to disclose: Simon Schophaus, Kate Townsend, Christian Trautwein, Kai M. Schneider, Carolin Victoria Schneider
Disclosure information not available at the time of publication: Jan Niklas Clusman, Alexander Koch

158 | WE ARE GOING DOWN THE WRONG PATH! THE CURRENT AASLD GUIDANCE MISCLASSIFIES MAJORITY OF PATIENTS WITH MASLD AND SIGNIFICANT FIBROSIS

W. Ray Kim, Nakia L Chung, Ajitha Mannalithara, Vivek Charu, Natalie J. Torok, Paul Yien Kwo, Allison J. Kwong and Sun H Kim, Stanford University School of Medicine

Background: Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) has extremely high prevalence in the US and globally with increasing incidence of morbidity and mortality in the population. Effective strategies to identify patients at risk of future complications, namely those with stage 2 (F2) or more advanced fibrosis represent the critically important first step in mitigating the public health impact of MASLD. Essentially all of the society guidelines, including the latest guidance from AASLD, recommend using FIB-4 < 1.3 to define low risk subjects not requiring further evaluation. We evaluate the diagnostic performance of FIB-4 in detecting F2 and F3 in the US general population, in comparison to the SAFE (Steatosis-Associated Fibrosis Estimator, Hepatology 2023;77:256) score, recently developed to detect F2 in primary care. **Methods:** We queried the most recent (2017-2020) National Health and Nutrition Examination Survey (NHANES) data, which included transient elastography. We selected adult (≥ 18 y) examinees with a controlled attenuation parameter (CAP) score ≥ 274 dB/m and without viral hepatitis or significant alcohol use. Individual's with incomplete elastography results or other missing data were excluded. Liver stiffness (LSM) of 8 kPa was taken as the threshold for F2 and 12 kPa for F3. The FIB-4 and SAFE scores were calculated using the published formulae. **Results:** The NHANES data projected to 73 million (M) US civilian adults with MASLD, of whom 12.2M (16.6%) had LSM ≥ 8kPa and 4.3M (5.9%) had LSM ≥ 12kPa. As seen in the Table, FIB-4 classified 55.5M, 16.7M and 1.2M US adults as low- (< 1.3), intermediate-, and high-risk (> 2.67), respectively. Of those, 15.7%, 17.8% and 44.5% had LSM ≥ 8kPa and 4.9%, 7.5%, and 30.4% had LSM ≥ 12kPa, respectively. More strikingly, of subjects with LSM ≥ 8kPa, 8.7M (71%) subjects would have FIB-4 < 1.3 and thus be excluded from further assessment. Similarly, of subjects with LSM ≥ 12 kPa, 2.7M (63%) would have FIB-4 < 1.3. The SAFE score classified 34.4M, 26.0M and 13.0M subjects as low-(< 0), intermediate-, and high-risk (≥ 100), respectively. Of those, 8.2%, 17.7% and 36.7% had LSM ≥ 8kPa and 1.8%, 5.2%, and 18.2% LSM ≥ 12kPa, respectively. SAFE performed better than FIB-4 in excluding fibrosis in the low-risk category. Of subjects with LSM ≥ 8kPa, 23% would have SAFE < 0 and of those with LSM ≥ 12 kPa, 14% would have SAFE < 0. As in other validation studies, SAFE had higher Area Under the Receiver Operating Characteristic curve in detecting F2 than FIB-4 (0.70 versus 0.58). **Conclusion:** When applied to population-based data representative of the US, the current guidance recommendation based on the FIB-4 score would miss the majority of patients with F2 and even F3. On the other hand, the SAFE score, designed to detect F2 in primary care, more accurately risk-stratify subjects with MASLD in the population.



Non-invasive Test	FIB-4			SAFE		
Thresholds	<1.3	1.3-2.67	>2.67	<0	0-99	≥100
Total (row%)	55.5M (76%)	16.7M (23%)	1.2M (2%)	34.4M (47%)	26.0M (35%)	13.0M (18%)
LSM ≥8 kPa (row%)	8.7M (71%)	3.0M (24%)	522K* (4%)	2.8M* (23%)	4.6M (38%)	4.8M (39%)
LSM ≥12 kPa (row%)	2.7M (63%)	1.3M (29%)	357K (8%)	619K* (14%)	1.3M* (31%)	2.4M (55%)

🟦 represents F2+ fibrosis missed by the score
🟥 represents F3+ fibrosis missed by the score
M(million), K(thousand) *Estimates are based on effective cell sample size <30.

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Disclosure information not available at the time of publication: Ajitha Mannalithara, Vivek Charu, Paul Yien Kwo, Sun H Kim

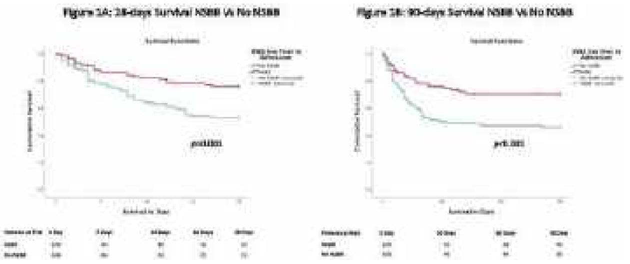
159 | NON SELECTIVE BETA BLOCKER REDUCES MORTALITY OF CIRRHOSIS PATIENTS ADMITTED TO INTENSIVE CARE UNIT WITH ACUTE DECOMPENSATION

Rahul Kumar[1,2], Su Lin[2], Gautam Mehta[2], Banwari Agarwal[3], Rajeshwar P. Mookerjee[4] and Rajiv Jalan[5,6], (1)Changi General Hospital, (2)UCL, London, (3)Royal Free Hospital, (4)Aarhus University, (5)UCL, (6) University College London Medical School

Background: Non-selective-beta-blockers (NSBB) are main stay of therapy in portal hypertension management. Apart from direct portal pressure reduction, NSBB's modulate inflammatory cascade, which could be beneficial in patients with acute decompensation (AD). We therefore aimed to evaluate effect of NSBB on 28-day mortality and markers of systemic inflammation in a propensity score matched (PSM) cohort of AD patients

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

requiring intensive care unit(ICU) admission. **Methods:** Patients were recruited from registry of AD patients requiring ICU admission. Out of the total 445 patients, 109 patients were on NSBB before admission (NSBB-group) who were PSM for pre-admission Childs-Turcotte-Pugh(CTP) score. 106 patients not on NSBB, served as the control-group. The on-admission to ICU parameters, markers of systemic inflammation; white cell count (WCC), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), C-reactive protein (CRP) and 28-days mortality were compared by standard statistical tests. **Results:** After PSM, no difference was observed in aetiology of cirrhosis, or precipitating event for AD. Pre-admission creatinine, bilirubin, INR and haemoglobin were similar between the groups. Pre-admission WCC and NLR was lower in NSBB-group, whereas CTP(median;7) and MELD(median:12) were similar. On admission to ICU, NSBB-group had lower heart rate($p < 0.001$), platelets($p = 0.010$), WCC ($p = 0.018$), NLR($p = 0.008$) and CRP($p = 0.013$). Significantly more community acquired bacterial infections ($p = 0.004$), renal($p = 0.003$) and liver($p = 0.034$) failure and higher grades of acute-on-chronic-liver-failure (ACLF)($p = 0.005$) were seen in non-NSBB-group. Significantly lower 28-day($p = 0.001$) and 90-day($p < 0.001$) mortality was seen in NSBB-group (Figure 1). Univariate and multivariable analysis for 28-days mortality showed that while ACLF at presentation and community acquired bacterial infection were independent negative predictors, prior-NSBB use was positive predictors of survival. **Conclusion:** Prior-NSBB use blunts inflammatory response favourably and is associated with improved 28 and 90-day mortality in critically-ill patients with acute decompensation (Figure 2).



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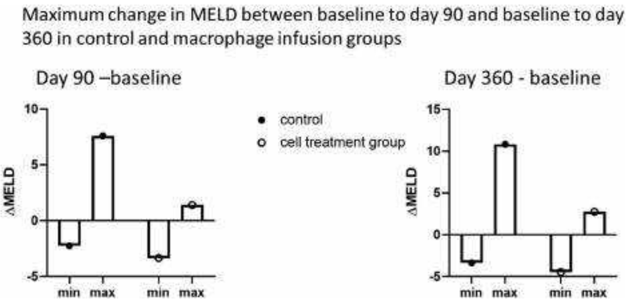
Disclosure information not available at the time of publication: Su Lin, Gautam Mehta, Banwari Agarwal, Rajeshwar P. Mookerjee, Rajiv Jalan

160 | AN OPEN-LABEL PARALLEL-GROUP, PHASE II RANDOMISED CONTROLLED TRIAL OF AUTOLOGOUS MONOCYTE DERIVED MACROPHAGE INFUSION IN COMPENSATED CIRRHOSIS

Paul N Brennan[1], Debbie Troland[1], Mark MacMillan[1], Thomas Manship[1], Francesca Moroni[1], Alison Glover[2], Catriona Graham[1], Scott Semple[1], David M Morris[1], Alasdair R Fraser[2], Chloe Pass[2], Lisa Ritchie[2], Donna Mitchell[2], Neil McGowan[2], Marc Turner[2], Neil Lachlan[3], John Dillon[4], Jonathan Andrew Fallowfield[1], John D Campbell[5] and Stuart J Forbes[1], (1)University of Edinburgh, (2)Scottish National Blood Transfusion Service, (3)Glasgow Royal Infirmary, (4)University of Dundee, (5)Glasgow University

Background: Cirrhosis is characterised by severe liver fibrosis, organ dysfunction and liver-related complications. Presently, there are no approved anti-fibrotic or pro-regenerative therapies for cirrhosis. Preclinical studies have shown bone marrow-derived macrophage injections can resolve hepatic fibrosis, stimulate regeneration and reduce inflammation. We previously demonstrated the safety of peripheral infusion of *ex vivo*-matured autologous monocyte-derived macrophages in patients with compensated cirrhosis in a Phase 1 trial. **Methods:** In a multicentre, open-label, parallel-group, Phase 2, randomised controlled trial (ISRCTN10368050), we evaluated the efficacy of autologous monocyte-derived macrophage therapy, compared with standard medical care, in a cohort of adult patients with compensated cirrhosis and MELD score e 10 and d 17. Participants were randomised 1:1, based on a minimisation algorithm using the key variable aetiology of disease (alcohol-related liver disease, non-alcoholic fatty liver disease, other). Treatment was of either three cycles of apheresis and macrophage infusion ($n = 3$) or a single apharesis and macrophage infusion ($n = 23$) of up to 10^9 macrophages; $n = 24$ participants received standard of care. Initially, the trial was designed to administer three infusions in the treatment arm, but due to the challenge of undergoing three apheresis sessions, and completing the trial within the proposed time frame, a single infusion protocol was adopted. The primary outcome was the difference in baseline to day 90 change in MELD score (ΔMELD) between treatment and control groups (ΔΔMELD). Secondary outcomes included: adverse clinical outcomes; non-invasive fibrosis markers (Liver Stiffness Measurement (LSM), serum enhanced liver fibrosis test (ELF) and Pro-C3/C3M, corrected T1 (cT1)

MRI); and health-related quality of life (HRQoL) at 90, 180, 360 days. **Results:** The ΔΔMELD between day 0 and day 90 in the treated group compared with the standard of care group was -0.87 (95% CI 1.79, 0.0; $p = 0.06$). The treatment group had less variable MELD scores than the control group (see Figure). Within the 360 days follow-up there were: 5/24 participants in the control group developed a total of 10 liver-related severe adverse events including 2 deaths, whilst no liver-related severe adverse events or deaths occurred in the treated group. There were no statistically significant differences in non-invasive fibrosis markers or HRQoL on per protocol analysis; exploratory analyses are awaited. **Conclusion:** This study reinforces the safety of macrophage cell therapy in patients with compensated cirrhosis, suggests their therapeutic potential and supports further development of macrophage therapy for liver disease.



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Disclosure information not available at the time of publication: Paul N Brennan, Debbie Troland, Mark MacMillan, Thomas Manship, Francesca Moroni, Alison Glover, Catriona Graham, Scott Semple, David M Morris, Alasdair R Fraser, Chloe Pass, Lisa Ritchie, Donna Mitchell, Neil McGowan, Marc Turner, Neil Lachlan, John Dillon, Jonathan Andrew Fallowfield, John D Campbell

161 | MAPPING IMMUNOLOGICAL LANDSCAPE IN DECOMPENSATED CIRRHOSIS PROGRESSION THROUGH MULTINOMIAL AND ORDINAL REGRESSION ANALYSIS

Zhujun Cao[1], Minghao Cai[1], Yujing Yao[2], Yuhan Liu[1], Chenxi Zhang[1], Yaoxing Chen[1], Yan Huang[1], Yide Lu[3], Ruokun Li[4], Zhuping Qian[5], Yi Zhou[6], Li Ziqiang[7], Baoyan An[1], Haiguang Xin[1], Hui Wang[1], Xiaogang Xiang[1], Richard Moreau[8,9] and Qing Xie[7], (1) Department of Infectious Disease, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, (2) Department of Biostatistics, Mailman School of Public Health, Columbia University, (3)Department of Laboratory Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, (4)Department of Radiology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, (5)Department of Nursing, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, (6)Department of Emergency, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, (7)Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, (8) European Foundation for the Study of Chronic Liver Failure (EF CLIF), Barcelona, Spain, (9)Institut National De La Santé Et De La Recherche Médicale (INSERM)

Background: Systemic inflammation is known as a major role in pathogenesis of acute-on-chronic liver failure (ACLF) from cross-sectional studies, but its detailed impacts on the dynamic trajectory of this disease from the absence of organ dysfunction (OD) to onset of OD, organ failure (OF) and eventual ACLF remains poorly understood due to challenges in collecting data and samples from individual's. Multinomial and ordinal regression analyses are useful tools to circumvent the limitation intrinsic to cross-sectional studies in cirrhosis. They identify significant predictors of different outcome categories and provide insights into the transition between stages towards ACLF. **Methods:** We investigated inflammatory signals, including blood cell counts and 21 serum biomarkers in 238 inpts with cirrhosis assigned to one of the following four stages: no OD ($n = 110$), OD ($n = 40$), OF without ACLF ($n = 54$), and ACLF ($n = 34$). The association of signals with each stage was assessed with multivariable models using multi-category outcomes without (Softmax regression) and with order (adjacent-category logit model). Prognostic ability of the signals was assessed with competing risk analysis followed by the evaluation of integrated discrimination improvement (IDI) and net reclassification improvement (NRI) of these signals to the exiting prognostic models. Another 156 cirrhosis inpts were used for validation. **Results:** Descriptive analysis: The progression of cirrhosis towards ACLF is characterized by an increasingly maladapted immune response as indicated by: 1) blunted type 1 immunity (type 1 effector IFN-γ did not change across stages); 2) abortion of type 2 immunity (production blocked between first-line cytokine, IL-25 and IL-33 second-line cytokines IL-4, IL-13); 3) imbalance of type 3 immunity (IL-22 dominant phenotype) ; 4) enhanced immunosuppression (continuous increases of anti–inflammatory markers (IL-10, sCD163), decreases in chemokines [*e.g.*, IL-8, IP-10], and a reduction in lymphocyte count) Multivariable analyses: Higher levels of IL-6, IL-10, sCD163, MCP-1, IL-25, IL-33, IL-22, or higher white-cell or neutrophil counts were associated with increased risk of getting more severe from OD towards ACLF at any disease stage (Figure 1). Prognostic analysis: The 28–day all–cause mortality can be independently predicted by the baseline levels of IL–6, sCD163, and MIP–3±, which together with blood immune cell, significantly enhanced the prognostic accuracy of CLIF-C OF (C-index [95%CI], 0.88 [0.82-0.94] vs. 0.84 [0.77-0.92], both $p = < 0.01$ by IDI and NRI). The results were validated in an independent cohort with 156 patients. **Conclusion:** Future therapies targeting the activation of type 1 immunity, restoration of type 2 immunity and balance of type 3 immunity would be important to prevent ACLF. Markers identified in this study are potential targets for developing new or improving prognostic scores currently available.

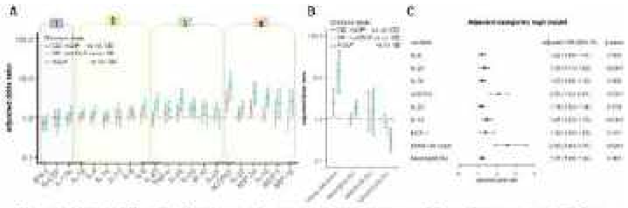

Figure 1. Adjusted effect of inflammatory markers and circulating immune cells on disease stages by Softmax regression analysis and adjacent logit model

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162 | EARLY LACTATE-GUIDED TREATMENT STRATEGIES IN CRITICALLY ILL PATIENTS WITH CIRRHOSIS AND SEPSIS

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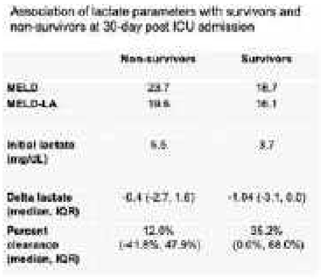
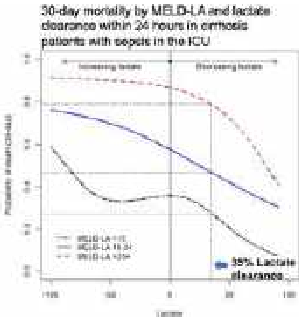
Background: Inpatient mortality among cirrhosis patients requiring Intensive Care Unit (ICU) admission for sepsis is high especially in those with Acute on Chronic Liver Failure. Endpoints of early goal directed therapy within 24 hours of admission are poorly defined in cirrhosis patients. Specifically, lactate (LA) clearance is impaired in cirrhosis, but early LA-guided resuscitation strategies are part of sepsis protocols in non-liver population. Recently, Model for End-stage Liver Disease-lactate (MELD-LA) was developed and independently validated as a simple, objective marker for short term prognosis in critically ill patients with cirrhosis as compared to MELD, MELD-Sodium and ICU specific scores in multiple global populations (n = 8,640). Among cirrhosis patients with sepsis, we sought to identify MELD-LA cutoffs for 30-day mortality as well as assess early LA clearance as potential surrogate of effective goal directed therapy. **Methods:** We reviewed all patients with cirrhosis admitted to the ICU (n = 9,557, 2014-July 2022) in a large, integrated healthcare system. We examined a subset of patients with sepsis and evaluated initial MELD-LA and LA clearance within the first 24 hours. **Results:** Overall, there were 3,879 cirrhosis patients admitted with sepsis in the ICU (43.2% female, 20.5% Hispanic, 13.9% dialysis, MELD score 20.8 (8.6) and MELD-LA 17.6 (5.7). Mean initial LA was 4.5 mg/dL. At 30-day mortality was 41.1%. On adjusted analysis, MELD-LA was an independent predictor of 30-day mortality (HR 1.06 , 1.05-1.07). In patients with serial LA (n = 868), after adjusting for demographics and MELD, both initial LA (HR 1.17, 1.14-1.20) and delta LA within 24 hours (HR 1.17, 1.15-1.19) were associated with 30-day mortality. Similar findings were noted for inpatient and 1 year mortality. Survivors versus non-survivors: For survivors, the mean initial LA was lower (3.7 vs 5.5 mg/dL) with higher change in LA -1.04 mg/dL(35.2% lactate clearance) vs -0.4 mg/dL (12.0% lactate clearance) respectively (Table). The impact of LA clearance varied by presenting MELD-LA. Achieving a LA clearance of 35% over 24 hours was associated with a decline in 30-day mortality of 25% (MELD-LA < 15), 18% (MELD-LA 15-24) and 9% (MELD-LA 25+) (Figure). **Conclusion:** Mean LA at presentation for patients with cirrhosis is high at admission for those with sepsis. A goal reduction of initial LA by one-third over 24 hours may suggest response to early goal directed therapy. A combination of MELD-LA at presentation along with LA clearance within 24 hours may allow for earlier risk stratification in critically ill ICU patients with cirrhosis.



Association of lactate parameters with survivors and non-survivors at 30-day post ICU admission

	Non-survivors	Survivors
MELD	23.7	18.7
MELD-LA	19.6	16.1
Initial lactate (mg/dL)	5.5	3.7
Delta lactate (median, IQR)	-0.4 (-2.7, 1.6)	-1.04 (-3.1, 0.0)
Percent clearance (median, IQR)	12.0% (-41.8%, 47.9%)	35.2% (0.0%, 68.0%)



30-day mortality by MELD-LA and lactate clearance within 24 hours in cirrhosis patients with sepsis in the ICU

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163 | UNMASKING THE HIDDEN PATTERNS: MACHINE LEARNING IDENTIFIES AND PREDICTS CLUSTERS WITH DISTINCT PROFILES AND OUTCOMES IN ACUTE-ON-CHRONIC LIVER FAILURE (CLUSTER-ACLF)

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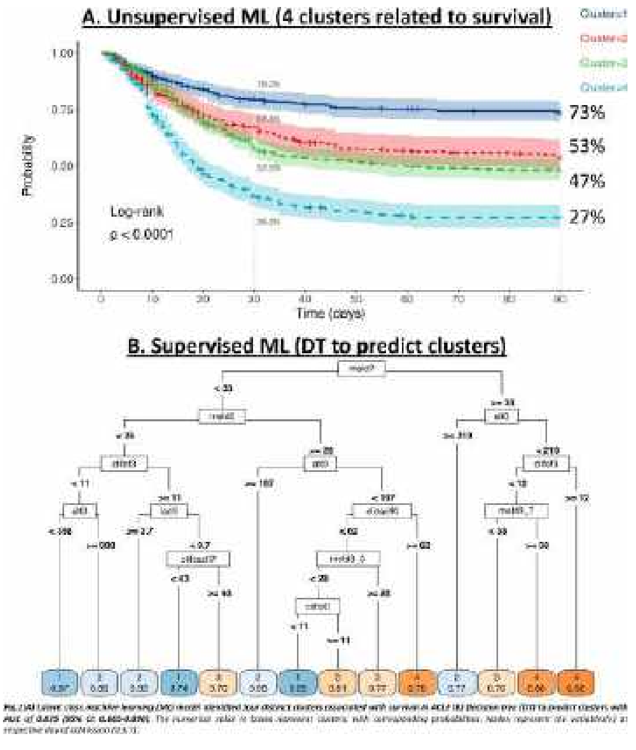
Background: Heterogeneity among patients with acute-on-chronic liver failure (ACLF) confer variable outcomes (mortality-range: 0-100%). While prognostic scores capture the known associations, machine learning (ML) can identify the intricate hidden patterns between patient characteristics without any explicit hypothesis or labelling that remain unexplored in ACLF. We employed ML to explore, describe, and predict unknown clusters in ACLF patients. **Methods:** We applied unsupervised ML on the data of 1568 ACLF patients defined by APASL or EASL criteria, recruited ambispectively over 2015-2023 with a 90-day follow-up at a tertiary care centre. After initial processing and evaluation of cluster tendency, the data, including clinical details, investigations, and organ failures at day-0, 3, and 7 of admission, were subjected to distance, density, and model-based clustering. We interpreted a final model with least BIC and identified clusters through inferential statistics. Then, we explored the cluster associations with disease evolution and mortality. Finally, we employed supervised ML in 70% of data to train the models and 30% of remaining data to predict and interpret the clusters. **Results:** We enrolled ACLF patients aged 44.3 (11.3) years, 87% males, 62.9% with alcoholic hepatitis, 29.6% with APASL, 15.5% with EASL, 54.9% with both APASL and EASL criteria, and a MELD of 29(7) with survival of 50.5%. Nonsurvivors were likely to have both EASL+APASL or EASL-ACLF, > 1 acute precipitant, tense ascites, grade III-IV HE, infection, organ failures, and poor severity scores ($p < 0.001$, each). Of nine algorithms, the latent class model identified four distinct clusters. Cluster 1 vs. 2 (HR: 1.94), 1 vs.3 (HR: 2.23), and 1 vs.4 (HR: 4.12) were associated with mortality (Fig.1A), that remained significant after adjustment for CLIF-C ACLF or MELD or AARC score ($p < 0.001$, each). Patient's stratification into clusters could increase the discriminative ability of CLIF-C ACLF for mortality prediction by 11%. Distinct clinical profiles, organ failures, and severity scores were attributed to the clusters. APASL-ACLFs were frequently noted (70%) in cluster1. Females, acute or chronic viral hepatitis was common and alcoholic hepatitis, infections, and tense ascites were less prevalent in cluster2. Clusters 1 to 4 had an increasing gradient of severity, organ failures, mortality, EASL+APASL ACLF, infections, > 1 acute precipitant, alcoholic hepatitis, tense ascites, and grade III-IV HE ($p < 0.001$). While extreme gradient boost was best (AUC: 0.989), an interpretable decision tree could also predict clusters with very good AUC of 0.875 (Fig.1B). **Conclusion:** ML for the first time could identify and precisely predict hidden clusters with distinct phenotypes and outcomes in ACLF. Stratification of patients into clusters can guide their prognosis, resource allocation, intensive care management, and liver transplant discussions in ACLF.



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

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

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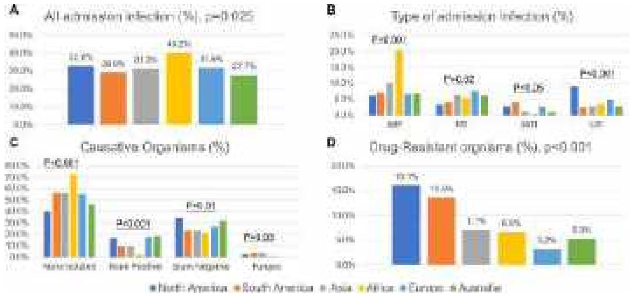
Background: Regional differences in environment, health-care system, microbiology lab capabilities, countermeasures of drug resistance may greatly impact the occurrence and evolution of infection in cirrhosis. We aimed to assess the prevalence, characteristics, clinical impact, and variations in infection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



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

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

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

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

(ALD). Females are at higher risk of developing ALD compared to males secondary to biologic and social-cultural factors. However, whether this sex difference persists after an episode of acute alcoholic hepatitis (AH) is unknown. This study aimed to evaluate the association between female sex and incident cirrhosis after first presentation of AH in the general population. **Methods:** Retrospective population-based cohort study of routinely collected healthcare data from Ontario, Canada. AYAs (aged 13-39) with a first presentation of AH as the most responsible diagnosis at emergency room (ER) or hospital admission were identified from 2002 to 2021 and followed to 2022. Incident cirrhosis was defined based on validated coding. The association between female sex and incident cirrhosis from 6 months post-discharge onward was evaluated using competing risks regression where liver transplant (LT) and death were competing events to cirrhosis with adjustment for age, income quintile, rurality, co-morbid illness, immigration status, and disease severity (ER vs. inpatient). **Results:** Overall n = 3,340 AYAs with first presentation of AH were identified; median age at presentation was 33 years (IQR 28-36), n = 1,190 (36%) were female, n = 4,717 (70%) had healthcare encounters related to alcohol within the 2-years prior to AH presentation, n = 2,801 (70%) required hospital admission, and n = 624 (19%) had cirrhosis and/or decompensation at index. Of those requiring hospital admission, the median length of stay was 5 days (IQR 3-8), n = 465 (17%) required ICU level care, n = 76 (2%) required hemodialysis and n = 91 (3%) died before discharge. After a median follow-up of 4 years (IQR 2-9 y), n = 603 (22%) died and n = 7 (< 1%) received LT. In total n = 2,690 (81%) were alive and without cirrhosis at 6 months post discharge of which n = 789 (29%) were diagnosed with cirrhosis during follow-up (n = 325 [35%] in females; n = 464 [26%] in males, $p < 0.001$), and of those, n = 320 (41%) were decompensated. After adjusted competing risks regression, female sex was associated with a 47% higher subhazard of cirrhosis compared to male sex (sHR 1.47, 95% CI 1.23-1.76, $p < 0.001$) in addition to older age (sHR 1.05, 95% CI 1.03-1.06) and higher co-morbidity (sHR 1.36, 95% CI 1.01-1.82; Table). The cumulative incidence of death at 1-, 5-, and 10-years was 9%, 22%, and 31% respectively without difference between sexes ($p = 0.06$). **Conclusion:** Almost 1/3rd of young adults with first presentation of AH develop cirrhosis after a median of 4 years and this risk is 50% higher for females vs. males. Whether this is secondary to differences in biologic or sociocultural factors such as ongoing alcohol use or engagement in medical care or alcohol use disorder treatment requires further investigation.

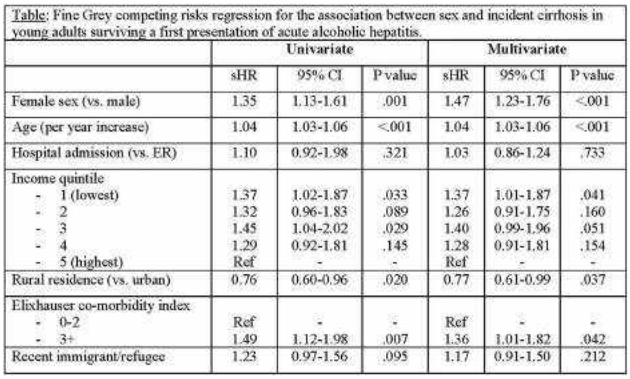

Table: Fine Grey competing risks regression for the association between sex and incident cirrhosis in young adults surviving a first presentation of acute alcoholic hepatitis.

	Univariate			Multivariate		
	sHR	95% CI	P value	sHR	95% CI	P value
Female sex (vs. male)	1.35	1.13-1.61	.001	1.47	1.23-1.76	<.001
Age (per year increase)	1.04	1.03-1.06	<.001	1.04	1.03-1.06	<.001
Hospital admission (vs. ER)	1.10	0.92-1.98	.321	1.03	0.86-1.24	.733
Income quintile						
- 1 (lowest)	1.37	1.02-1.87	.033	1.37	1.01-1.87	.041
- 2	1.32	0.96-1.83	.089	1.26	0.91-1.75	.160
- 3	1.45	1.04-2.02	.029	1.40	0.99-1.96	.051
- 4	1.29	0.92-1.81	.145	1.28	0.91-1.81	.154
- 5 (highest)	Ref	-	-	Ref	-	-
Rural residence (vs. urban)	0.76	0.60-0.96	.020	0.77	0.61-0.99	.037
Elixhauser co-morbidity index						
- 0-2	Ref	-	-	Ref	-	-
- 3+	1.49	1.12-1.98	.007	1.36	1.01-1.82	.042
Recent immigrant/refugee	1.23	0.97-1.56	.095	1.17	0.91-1.50	.212

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166 | SPIRONOLACTONE THERAPY ASSOCIATES WITH REDUCED INCIDENT ALCOHOL-ASSOCIATED LIVER DISEASE IN HIGH RISK PATIENTS: A RETROSPECTIVE COHORT STUDY

Jay Luther[1], Augustin Vannier[2], Wei Zhang[1], Rachael Mahle[1], Russell P. Goodman[3] and Esperance Schaefer[3], (1)MGH, (2)University of Chicago, (3) Massachusetts General Hospital

Background: Effective treatment for alcohol use disorder (AUD) is the cornerstone of preventing the development of alcohol-associated liver disease (ALD). Recent preclinical and epidemiological data suggest spironolactone, a mineralocorticoid receptor antagonist, reduces alcohol consumption (PMID: 36123420) and may be a promising option to treat AUD. However, its impact on the development of ALD in high risk patients is unknown. **Methods:** This retrospective cohort study used the Mass General Brigham Biobank, an ongoing research initiative that had recruited 127 480 patients at the time of this study. International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revision diagnosis codes were used to identify patients with AUD and no ALD at study entry, as well as the primary outcome of incident ALD during study follow-up. Patients with ascites were excluded from study enrollment. Treatment with spironolactone was defined by documentation of >3 prescriptions. Patients were considered to be treated if they initiated spironolactone before the relevant outcome. Alcohol use was assessed through a one-time questionnaire that included a linear scale of standard drink consumption, with higher scores correlating with more alcohol use. Cox proportional hazards models adjusting for potential confounders were used to calculate hazard ratios (HR) and 95% confidence intervals (CIs). **Results:** The cohort comprised 9635 patients with AUD, of whom 566 (5.9%) were treated with spironolactone before a diagnosis of ALD. In total, 1135 patients (11.8%) developed ALD over a median follow-up time of 9.7 years. Patients treated with spironolactone were more likely to be older, obese, and receive concurrent medical addiction therapy and less likely to receive psychotherapy and have a concurrent substance use disorder compared to patients never receiving therapy. Treatment groups were similar in viral hepatitis status, homelessness, ethnicity, and sex. In a multivariable analysis accounting for age, sex, ethnicity, BMI, viral hepatitis status, receipt of alcohol therapy, concurrent substance disorder, psychiatric disease, congestive heart failure, and hypertension, spironolactone therapy was associated with a decreased incidence of ALD (HR: 0.68; 95% CI, 0.38-0.93; $p=0.02$). We did not observe a dose-dependent association between spironolactone and likelihood of ALD (HR: 0.99; 95% CI: 0.98-1.00; $p=0.27$). Notably, AUD patients treated with spironolactone reported less alcohol use compared to those not receiving treatment (linear drinking score of 3.2 in treated group versus 3.9 in the untreated group, $p=0.02$). **Conclusion:** Spironolactone therapy is associated with reduced alcohol use and incident ALD in patients with AUD and may offer a novel therapeutic strategy in limiting the development of ALD in high-risk patients.

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167 | PHOSPHATIDYLETHANOL MONITORING OF POST-TRANSPLANT ALCOHOL CONSUMPTION AMONG ALCOHOL AND NON-ALCOHOL-RELATED LIVER TRANSPLANT RECIPIENTS

Mayan Teles[1], Fnu Baimaji[1], Sarah Andrews[1], Mandana Khalili[2], Hannah C. Sung[1], Andrew M. Cameron[1], Oluwaseun Falade-Nwulia[1], Geetanjali Chander[3], Mary E. McCaul[1] and Po-Hung (Victor) Chen[1], (1)Johns Hopkins University, (2)University of California, San Francisco, (3)University of Washington

Background: Accurate alcohol assessments after liver transplants (LT) are crucial for understanding alcohol use and guiding treatment, particularly among LT recipients with prior alcohol-related liver disease (ALD). Biomarkers offer objective measures of alcohol exposure, but LT centers have not universally implemented routine biomarker use. Phosphatidylethanol (PEth) is a blood biomarker capable of detecting alcohol use during the prior 3-4 weeks. We assessed universal PEth testing for quantifying post-LT alcohol use in ALD and non-ALD LT recipients. **Methods:** We identified consecutive LT recipients with routine clinical PEth testing from a single LT center and compared three groups: standard LT (SLT; e 6 months alcohol-free at LT), early LT (ELT; <6 months alcohol-free at LT), and non-ALD. The primary outcome was post-LT alcohol use, defined by positive PEth tests (i.e., >20 ng/mL). We used the Kruskal-Wallis test for between-group comparisons of continuous variables. Kaplan-Meier estimates analyzed times to the earliest positive PEth test, stratified by LT recipient group and compared by the log-rank test. We also created a multivariable Cox model to estimate hazard ratios for post-LT alcohol use, adjusting for age (using a five-knot restricted cubic spline), gender, and race/ethnicity. Our alpha was 0.05. **Results:** We included 159 LT recipients: 56 (35%) SLT, 42 (26%) ELT, and 61 (39%) non-ALD. Among the subjects, 64 (40%) were women, 123 (77%) identified as white, and the median age was 55 (IQR 45-62) years. The median follow-up time was 172 (IQR 69-288) days, and each LT recipient had a median of 8 (IQR 4-13) PEth tests. Overall, 26 (16%) LT recipients had at least one positive PEth test: 14 (25%) SLT, 9 (21%) ELT, and 3 (5%) non-ALD. Among those with positive PEth tests, the median time to the first positive test was 81 (IQR 57-120) days after hospital discharge from LT. Kaplan-Meier curves depicted significantly different times to the first positive PEth test between the groups ($p=0.05$) (Figure). Relative to SLT recipients, ELT recipients had similar risks of post-LT alcohol use (aHR 0.81; 95% CI 0.32-2.1), but non-ALD recipients had significantly lower risks (aHR 0.11; 95% CI 0.03-0.45). **Conclusion:** Our analysis of PEth results depicted different timing and risks of post-LT alcohol use between the three LT recipient groups. Prior studies suggested that self-reporting may underestimate actual alcohol use. Therefore, routine PEth testing, especially during the first 180 days post-LT, may help delineate alcohol use patterns to guide targeted addiction care.

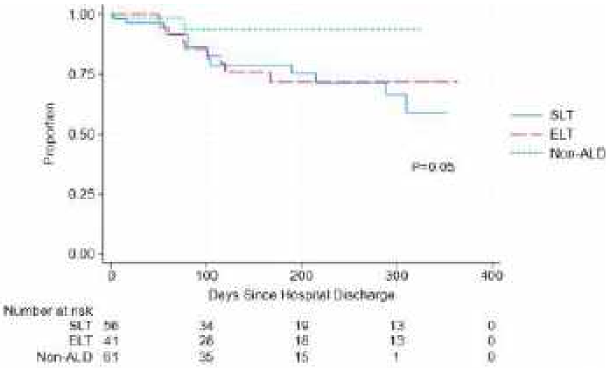

Figure. Kaplan-Meier curves for times to first positive phosphatidylethanol tests, stratified by transplant recipient groups. SLT, standard liver transplant; ELT, early liver transplant; ALD, alcohol-associated liver disease

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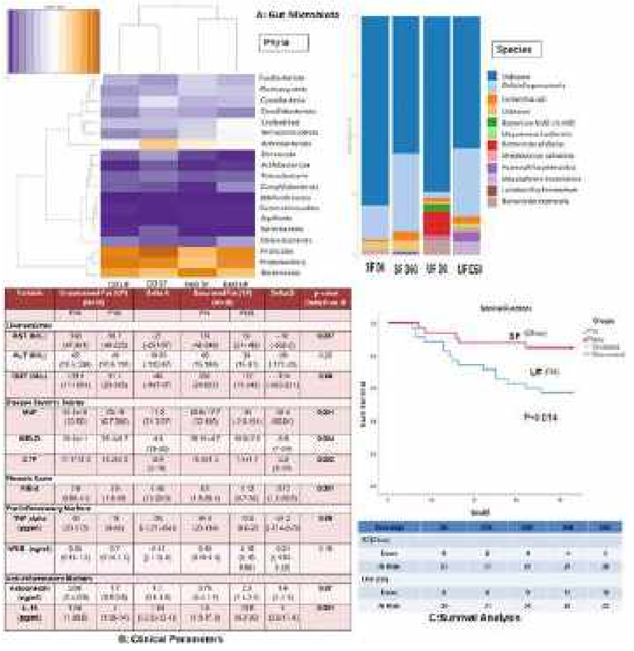
168 | SATURATED FAT FAVORABLY ALTERS THE GUT MICROBIOTA AND IMPROVES SURVIVAL IN PATIENTS WITH SEVERE ALCOHOLIC HEPATITIS: A RANDOMIZED CONTROLLED TRIAL★

Harshita Tripathi[1], Jaya Benjamin[2], Shvetank Sharma[1], Rakhi Maiwall[2], Vinod Arora[1], Chhagan Bihari[3], Guresh Kumar[1], Yogendra Kumar Joshi[2] and Shiv Kumar Sarin[3], (1)Institute of Liver and Biliary Sciences, New Delhi, India, (2)Institute of Liver and Biliary Sciences, New Delhi, (3)Institute of Liver and Biliary Sciences

Background: Severe alcoholic hepatitis (SAH) is associated with malnutrition, dysbiosis and inflammatory cytokines augmenting liver injury resulting in high mortality. Experimental studies have reported that in comparison to unsaturated fat (UF), saturated fat (SF) improves dysbiosis, inflammation, liver enzymes and protects against alcoholic liver injury, but effect on clinical outcome and gut microbiota (GM) in SAH patients is lacking. Aim: Primary aim was to compare the effects of diet rich in SF versus UF on 60-day mortality. Secondary aims included effects on clinical outcomes, inflammatory markers and GM profile. **Methods:** Of 169 SAH patients screened, 67 with mDF between 32-100, without sepsis, acute kidney injury (AKI), or malignancy were randomized into SF (Ghee i.e., clarified butter; n = 34) or UF (Soyabean Oil; n = 33) arm. Patients in both arms received 35 kcal and 1.2-1.5g protein/ kg /day (55-60% carbohydrate, 20% protein, 30-35% fat) for 60 days. GM was assessed using 16S V3-V4 region analysis by Novaseq. Changes in the clinical [MELD, CTP, mDF, FIB-4], biochemical, pro-inflammatory [TNF-±, NF-κB] and anti-inflammatory [IL-10, adiponectin] parameters, at 60-days were assessed. **Results:** Baseline parameters [age 40 ± 7.37 yrs; ascites 47 (84%); BMI 21.3 ± 3.8 kg/m^2; mDF 62.4 ± 21.4; MELD 28 ± 9.3; CTP 10.6 ± 1.4], GM phyla and species were comparable between groups. SF and UF were well tolerated. 60 day mortality was significantly lower in SF (12.2%) vs. UF (33%) arm; $p = 0.014$ (Fig.1 C) as per ITT analysis. Five patients from each arm were lost to follow-up. A significant improvement in AST, ALT, IL-10 levels and a trend towards reduction in TNF-± levels was seen in SF compared to UF (Fig.1-B). In the GM, commensal taxa like *Bacteriodes plebius*, *B. coprocoia*, Denoccota, Fusobacteria and Bacterium NLAE-z1-H40 increased significantly only in SF group ($p < 0.05$). But, pathogenic taxa, Protobacteria, Deferribacterota, Aquificota, Bdellovibrionota, Camplylobacteria, Acidobacteria, Verrucomicrobiota, Desulfobacteriota, *Klebisella pneumonia*, *Escherichia coli*, *Haeomophilus pittmaniae*, increased in the UF group. ($p < 0.05$) (Fig. 1-A). **Conclusion:** Two months of saturated fat as a therapeutic intervention, improved survival in SAH patients compared with unsaturated fat. This could be related to promotion of the growth of commensal bacteria which attenuated inflammation, disease severity and improved liver disease indices.



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

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

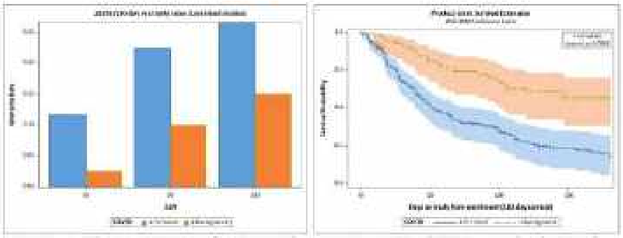

Figure 1A. Mortality comparison pre-Covid vs. during Covid Figure 1B. Survival probabilities pre-Covid vs. during Covid

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

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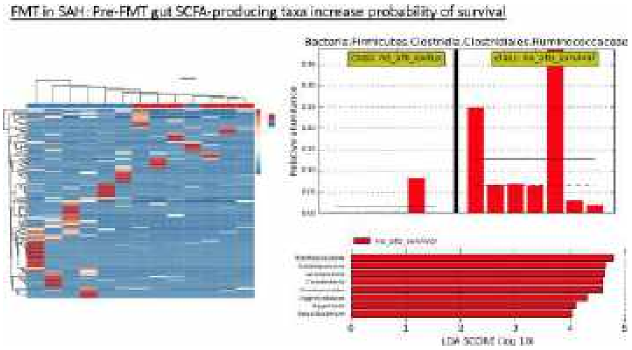
Background: New therapeutic alternatives to corticosteroids in severe alcohol-associated hepatitis (SAH) is unmet need. Fecal microbiota transplantation (FMT) has been proposed as it targets well-established pathophysiological pathway but, data is scarce and many unanswered questions remain. One of the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



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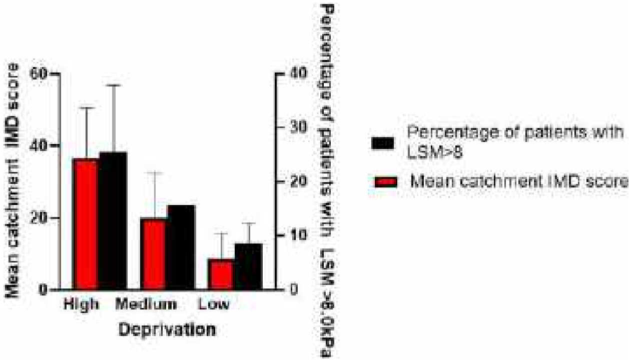
Disclosure information not available at the time of publication: Katarina Soltys, Natalia Bystrianska, Daniela Žilinčanová, Peter Bánovčin, Jan Burea, Tomas Koller

171 | THE RISK OF LIVER FIBROSIS IS GREATEST IN AREAS OF HIGHER SOCIOECONOMIC DEPRIVATION: A RISK-FACTOR BASED POPULATION SCREENING STUDY

Huw Purssell[1,2], Lucy Bennett[3], Oliver Street[2], Jennifer Scott[2], Karen Piper Hanley[2], Indra Neil Guha[3], Neil A Hanley[1,2], Varinder Singh Athwal[1,2] and ID LIVER consortium, (1)Manchester University NHS Foundation Trust, (2)University of Manchester, (3)Nihr Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, UK

Background: Early detection of liver disease has been identified as a public health priority in the UK. Symptoms are rare before advanced stages and case finding using risk factors improves identification. In financially constrained health systems, case finding in areas with greater disease burden is prudent. Socioeconomic deprivation is associated with advanced liver disease. We assessed the incidence of liver disease by population deprivation using a community case finding pathway. **Methods:** 6 primary care practices (PCP) were selected from different socioeconomic areas of Manchester, UK. A mean Index of Multiple Deprivation (IMD) score was calculated for each PCP based on its catchment area. PCPs were grouped into low (n = 3), medium (n = 1) and high deprivation (n = 2). Patients were identified using SNOMED codes for risk factors, including Type 2 diabetes, Body Mass Index > 30kg/m^2, harmful alcohol consumption (> 280/ > 400 grams ethanol in females/males per week), abnormal ALT or hepatic steatosis. Patients with e 2 risk factors were invited to a one stop community assessment. A sub-group of patients with 1 risk factor were invited depending on capacity. Patients underwent a clinical history, full liver blood based aetiological screen and transient elastography (TE). Fibrosis was assessed with FIB-4 score and TE. Fibrosis risk was determined by a liver stiffness measurement (LSM) > 8.0kPa and FIB-4 > 1.30. **Results:** A total population of 63,143 patients were investigated, of which 7813 (12.4%) had e 1 risk factor. 5839 (74.7%) and 1974 (25.3%) patients had 1 and e 2 risk factors respectively. 1907 (1557x e 2 risk factors, 350x 1 risk factor) patients were invited for assessment of which 430 (22.5%) patients attended. 300 (69.8%) patients were diagnosed with NAFLD. 38 (8.8%) patients were identified with alcohol related liver disease and 53 (12.3%) patients had mixed alcohol and metabolic disease. 59 (13.7%) patients had a LSM > 8.0 kPa. More patients from areas of high deprivation (26 (21.9%) patients) had risk of liver fibrosis compared to areas of medium (14/89 (15.7%) patients) and low deprivation (21/222 (9.5%) patients) (X^2 (2, N = 430) = 9.99, *p* = 0.0068)(Figure 1). Adjusting for age and gender, patients from areas of high deprivation were significantly more likely to have fibrosis risk than those from areas of low deprivation (adjusted OR 1.02, *p* = 0.012, 95% CI 1.004-1.035). **Conclusion:** Proactive community-based case finding for liver disease is best targeted in areas of high deprivation to improve diagnostic yields.



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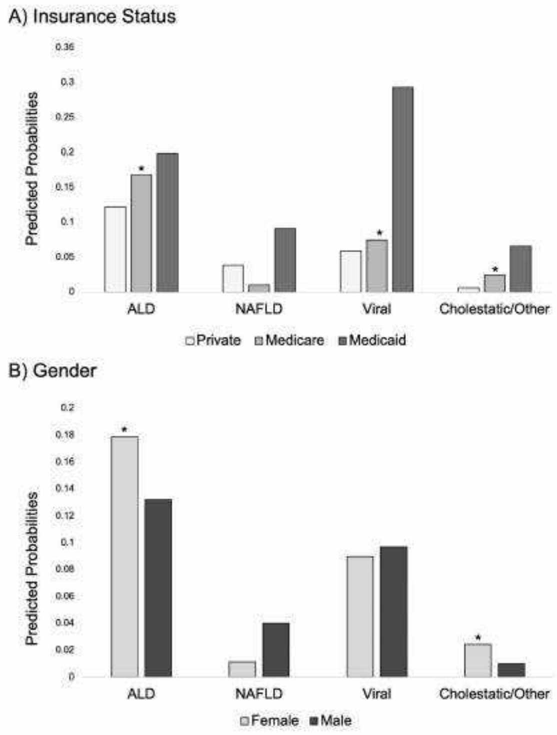
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

172 | PSYCHOSOCIAL AND DEMOGRAPHIC DISPARITIES IN ACCESS TO LIVER TRANSPLANTATION ACROSS ETIOLOGY OF LIVER DISEASE: AN ANALYSIS OF 2,391 TRANSPLANT EVALUATIONS

Sasha Deutsch-Link[1], *Andrew M Moon*[2], *Robert S Sandler*[1] *and Marina Serper*[3], *(1)University of North Carolina, (2)University of North Carolina, Durham, NC, (3)University of Pennsylvania, Philadelphia, PA, United States*

Background: The rising prevalence of alcohol-associated liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) has led to increases in the need for liver transplantation (LT). The purpose of our study was to investigate disparities in access to LT, and whether those disparities were consistent across etiology of liver disease. **Methods:** We performed a retrospective study of 2,391 LT evaluations at a single tertiary transplant center. Multivariable logistic regression analysis adjusting for race and ethnicity, gender, age, evaluation MELD-Na, insurance, Community Health Score, and the Stanford Integrated Psychosocial Assessment for Transplant (SIPAT) score was used to assess disparities in overall transplant waitlisting and in being declined for waitlisting due to psychosocial reasons. We also performed interaction analyses to investigate whether these disparities were differential across etiology of liver disease. **Results:** The cohort included 2,391 patients evaluated for transplant. In multivariable models the following factors were associated with increased risk of declining for LT waitlist: Medicaid insurance (OR 2.44, 95% CI 1.76-3.37), Medicare insurance (OR 1.71, 95% CI 1.39-2.11), a high-risk SIPAT score (OR 1.77, 95% CI 1.42-2.21), Black race (OR 1.41, 95% CI 1.06-1.87) and older age (OR 1.03, 95% CI 1.02-1.04). The following variables were associated with declining for waitlisting due to psychosocial reasons: ALD (OR 2.43, 95% CI 1.20-4.93), Black race (1.76, 95% CI 1.10-2.82), Medicaid insurance (OR 2.09, 95% CI 1.31-3.31), and a high risk SIPAT score (OR 6.21, 95% CI 4.08-9.45). The risk of being declined for waitlisting due to psychosocial reasons was differentially higher in patients with Medicare insurance with ALD compared to private insurance and in women with ALD (Figure 1). **Conclusion:** Several sociodemographic factors contribute to disparities in transplant access. Among patients with ALD, female patients and patients on public insurance experience even more pronounced barriers to transplant waitlisting. This may reflect a combination of stigma, bias in transplant provider perception, and increased psychosocial barriers in this population. Future directions should include interventions to address bias in the transplant evaluation process and on improving psychosocial resources in higher-risk populations.

Figure 1. Predicted Probability of Not Being Waitlisted for Psychosocial Reasons Across Etiology of Liver Disease



*Significant at $p < 0.10$; cutoff chosen due to interaction analysis, which often uses significance at p< 0.10-0.20. ALD; alcohol-associated liver disease. NAFLD; non-alcoholic fatty liver disease. A) Reference group: private insurance. B) Reference group: male. All interaction analysis adjusted for age, MELD-Na, and evaluation year.

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173 | IMPACT OF SOCIAL DETERMINANTS OF HEALTH ON TIME TO TREATMENT INITIATION AND PROGRESSION OF HEPATOCELLULAR CANCER

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Background: While studies have associated social determinants of health (SDOH) with hepatocellular carcinoma (HCC) treatment delay of > 3 months, there is limited data on SDOH impacting expedited treatment and subsequent outcomes. This study investigates whether components of SDOH are associated with progression-free survival for HCC within Milan criteria and their effect on time to initiate HCC treatment. **Methods:** We conducted a retrospective cohort study of adults diagnosed with HCC within Milan criteria from 2010 to 2021 at an urban liver transplant center. Patients who were not treated or received initial curative surgery (transplant or resection) were excluded. Patients with expedited therapy (< 45 d from diagnosis) were compared to those with non-expedited therapy (e 45 d). Demographic data was gathered via chart review. Patients were geospatially mapped by address and linked to a Federal Information Processing Standards (FIPS) code and SDOH data from the 2020 U.S. Census. Our primary outcome was progression free survival. Secondary outcomes included time from diagnosis to treatment. T-tests, chi-square tests, logistic and cox univariate regression analyses were performed. **Results:** Of 1401 patients with HCC, 235 (17%) were included. Our sample had an average age of 63 years and consisted of 64% males, 52% Hispanics, and 85% T1 tumors by TNM staging (Table 1). There was a notable trend towards increased progression free survival for those treated in < 45 days ($p = 0.094$). A smaller proportion of non-White patients received expedited treatment compared to White patients (37% vs 58%, $p = 0.01$). SDOH associated with delayed therapy included higher social vulnerability index ($p = 0.013$), minority status ($p = 0.03$), income below 150% poverty line ($p = 0.007$), vulnerable housing/transportation ($p = 0.032$), vulnerable socioeconomic status ($p = 0.027$), educational level below high school ($p = 0.003$), and limited English ($p = 0.033$). Though larger tumors received more expedited therapy ($p = 0.019$), tumor size e 2 cm was associated with rapid disease progression ($p = 0.015$). **Conclusion:** SDOH clearly impact time to HCC treatment initiation and cancer progression. Despite the expedited group's larger tumor size and the faster progression of larger tumors, there was a trend towards improved progression-free survival for patients receiving expedited treatment before 45 days. These findings underscore the importance of early treatment and implementing interventions to mitigate SDOH disparities in care of patients burdened by HCC.

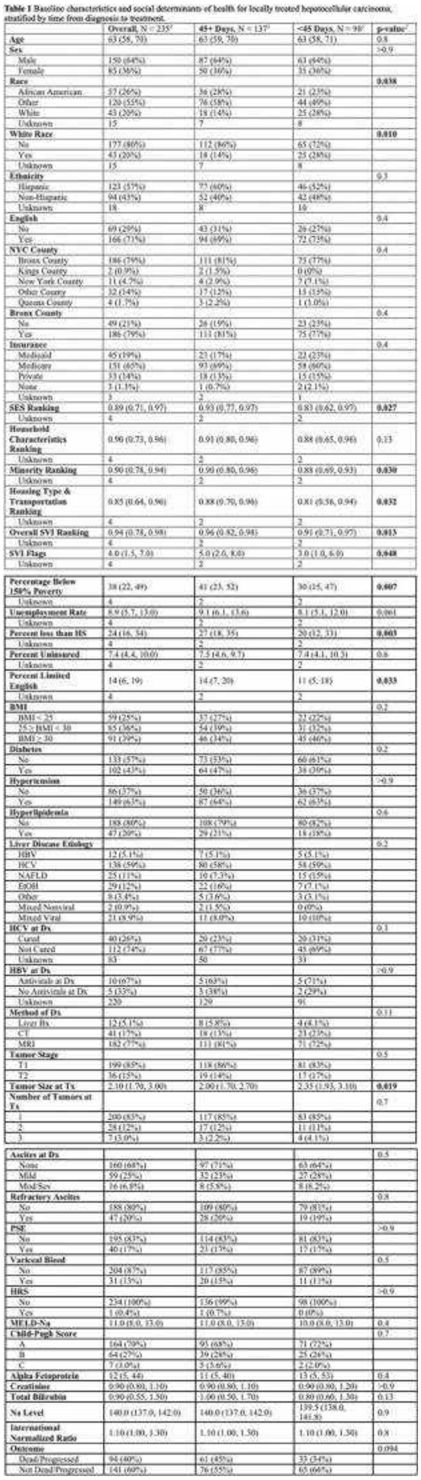

Table 1 Baseline characteristics and social determinants of health for locally treated hepatocellular carcinoma, stratified by time from diagnosis to treatment.

	Overall, N = 235^1	45+ Days, N = 137^1	<45 Days, N = 98^1	p-value^2
Age	63 (58, 70)	63 (59, 70)	63 (58, 71)	0.8
Sex				>0.9
Male	150 (64%)	87 (64%)	63 (64%)	
Female	85 (36%)	50 (36%)	35 (36%)	
Race				**0.038**
African American	57 (26%)	36 (28%)	21 (23%)	
Other	120 (55%)	76 (58%)	44 (49%)	
White	43 (20%)	18 (14%)	25 (28%)	
Unknown	15	7	8	
White Race				**0.010**
No	177 (80%)	112 (86%)	65 (72%)	
Yes	43 (20%)	18 (14%)	25 (28%)	
Unknown	15	7	8	
Ethnicity				0.3
Hispanic	123 (57%)	77 (60%)	46 (52%)	
Non-Hispanic	94 (43%)	52 (40%)	42 (48%)	
Unknown	18	8	10	
English				0.4
No	69 (29%)	43 (31%)	26 (27%)	
Yes	166 (71%)	94 (69%)	72 (73%)	
NYC County				0.4
Bronx County	186 (79%)	111 (81%)	75 (77%)	
Kings County	2 (0.9%)	2 (1.5%)	0 (0%)	
New York County	11 (4.7%)	4 (2.9%)	7 (7.1%)	
Other County	32 (14%)	17 (12%)	15 (15%)	
Queens County	4 (1.7%)	3 (2.2%)	1 (1.0%)	
Bronx County				0.4
No	49 (21%)	26 (19%)	23 (23%)	
Yes	186 (79%)	111 (81%)	75 (77%)	
Insurance				0.4
Medicaid	45 (19%)	23 (17%)	22 (23%)	
Medicare	151 (65%)	93 (69%)	58 (60%)	
Private	33 (14%)	18 (13%)	15 (15%)	
None	3 (1.3%)	1 (0.7%)	2 (2.1%)	
Unknown	3	2	1	
SES Ranking	0.89 (0.71, 0.97)	0.93 (0.77, 0.97)	0.83 (0.62, 0.97)	**0.027**
Unknown	4	2	2	
Household Characteristics Ranking	0.90 (0.73, 0.96)	0.91 (0.80, 0.96)	0.88 (0.65, 0.96)	0.13
Unknown	4	2	2	
Minority Ranking	0.90 (0.78, 0.94)	0.90 (0.80, 0.96)	0.88 (0.69, 0.93)	**0.030**
Unknown	4	2	2	
Housing Type & Transportation Ranking	0.85 (0.64, 0.96)	0.88 (0.70, 0.96)	0.81 (0.56, 0.94)	**0.032**
Unknown	4	2	2	
Overall SVI Ranking	0.94 (0.78, 0.98)	0.96 (0.82, 0.98)	0.91 (0.71, 0.97)	**0.013**
Unknown	4	2	2	
SVI Flags	4.0 (1.5, 7.0)	5.0 (2.0, 8.0)	3.0 (1.0, 6.0)	**0.048**
Unknown	4	2	2	
Percentage Below 150% Poverty	38 (22, 49)	41 (23, 52)	30 (15, 47)	**0.007**
Unknown	4	2	2	
Unemployment Rate	8.9 (5.7, 13.0)	9.1 (6.1, 13.6)	8.1 (5.1, 12.0)	0.061
Unknown	4	2	2	
Percent less than HS	24 (16, 34)	27 (18, 35)	20 (12, 33)	**0.003**
Unknown	4	2	2	
Percent Uninsured	7.4 (4.4, 10.0)	7.5 (4.6, 9.7)	7.4 (4.1, 10.3)	0.6
Unknown	4	2	2	
Percent Limited English	14 (6, 19)	14 (7, 20)	11 (5, 18)	**0.033**
Unknown	4	2	2	
BMI				0.2
BMI < 25	59 (25%)	37 (27%)	22 (22%)	
25 ≥ BMI < 30	85 (36%)	54 (39%)	31 (32%)	
BMI ≥ 30	91 (39%)	46 (34%)	45 (46%)	
Diabetes				0.2
No	133 (57%)	73 (53%)	60 (61%)	
Yes	102 (43%)	64 (47%)	38 (39%)	
Hypertension				>0.9
No	86 (37%)	50 (36%)	36 (37%)	
Yes	149 (63%)	87 (64%)	62 (63%)	
Hyperlipidemia				0.6
No	188 (80%)	108 (79%)	80 (82%)	
Yes	47 (20%)	29 (21%)	18 (18%)	
Liver Disease Etiology				0.2
HBV	12 (5.1%)	7 (5.1%)	5 (5.1%)	
HCV	138 (59%)	80 (58%)	58 (59%)	
NAFLD	25 (11%)	10 (7.3%)	15 (15%)	
EtOH	29 (12%)	22 (16%)	7 (7.1%)	
Other	8 (3.4%)	5 (3.6%)	3 (3.1%)	
Mixed Nonviral	2 (0.9%)	2 (1.5%)	0 (0%)	
Mixed Viral	21 (8.9%)	11 (8.0%)	10 (10%)	
HCV at Dx				0.3
Cured	40 (26%)	20 (23%)	20 (31%)	
Not Cured	112 (74%)	67 (77%)	45 (69%)	
Unknown	83	50	33	
HBV at Dx				>0.9
Antivirals at Dx	10 (67%)	5 (63%)	5 (71%)	
No Antivirals at Dx	5 (33%)	3 (38%)	2 (29%)	
Unknown	220	129	91	
Method of Dx				0.11
Liver Bx	12 (5.1%)	8 (5.8%)	4 (4.1%)	
CT	41 (17%)	18 (13%)	23 (23%)	
MRI	182 (77%)	111 (81%)	71 (72%)	
Tumor Stage				0.5
T1	199 (85%)	118 (86%)	81 (83%)	
T2	36 (15%)	19 (14%)	17 (17%)	
Tumor Size at Tx	2.10 (1.70, 3.00)	2.00 (1.70, 2.70)	2.35 (1.93, 3.10)	**0.019**
Number of Tumors at Tx				0.7
1	200 (85%)	117 (85%)	83 (85%)	
2	28 (12%)	17 (12%)	11 (11%)	
3	7 (3.0%)	3 (2.2%)	4 (4.1%)	
Ascites at Dx				0.5
None	160 (68%)	97 (71%)	63 (64%)	
Mild	59 (25%)	32 (23%)	27 (28%)	
Mod/Sev	16 (6.8%)	8 (5.8%)	8 (8.2%)	
Refractory Ascites				0.8
No	188 (80%)	109 (80%)	79 (81%)	
Yes	47 (20%)	28 (20%)	19 (19%)	
PSE				>0.9
No	195 (83%)	114 (83%)	81 (83%)	
Yes	40 (17%)	23 (17%)	17 (17%)	
Variceal Bleed				0.5
No	204 (87%)	117 (85%)	87 (89%)	
Yes	31 (13%)	20 (15%)	11 (11%)	
HRS				>0.9
No	234 (100%)	136 (99%)	98 (100%)	
Yes	1 (0.4%)	1 (0.7%)	0 (0%)	
MELD-Na	11.0 (8.0, 13.0)	11.0 (8.0, 13.0)	10.0 (8.0, 13.0)	0.4
Child-Pugh Score				0.7
A	164 (70%)	93 (68%)	71 (72%)	
B	64 (27%)	39 (28%)	25 (26%)	
C	7 (3.0%)	5 (3.6%)	2 (2.0%)	
Alpha Fetoprotein	12 (5, 44)	11 (5, 40)	13 (5, 53)	0.4
Creatinine	0.90 (0.80, 1.10)	0.90 (0.80, 1.10)	0.90 (0.80, 1.20)	>0.9
Total Bilirubin	0.90 (0.55, 1.50)	1.00 (0.50, 1.70)	0.80 (0.60, 1.30)	0.13
Na Level	140.0 (137.0, 142.0)	140.0 (137.0, 142.0)	139.5 (138.0, 141.8)	0.9
International Normalized Ratio	1.10 (1.00, 1.30)	1.10 (1.00, 1.30)	1.10 (1.00, 1.30)	0.8
Outcome				0.094
Dead/Progressed	94 (40%)	61 (45%)	33 (34%)	
Not Dead/Progressed	141 (60%)	76 (55%)	65 (66%)	

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174 | THE SOCIAL DETERMINANTS OF ACCESS TO CURATIVE THERAPIES FOR HEPATOCELLULAR CARCINOMA: A PROSPECTIVE COHORT STUDY

Lauren D. Nephew[1], Susan Rawl[1], Allie Carter[1], Eric S. Orman[1], Archita Parikh Desai[1], John Holden[2], Marwan S. Ghabril[1], Kavish R. Patidar[3], Nicole Garcia[1], Meera Farzana Iyengar[1], Gabriella Aitcheson[1], Eleazar Montalvan[1] and Naga P. Chalasani[4], (1)Indiana University, (2)Indiana University School of Medicine, (3) Section of Gastroenterology, Department of Medicine, Baylor College of Medicine and Michael E. Debakey Veterans Affairs Medical Center, (4)Indiana University Medical Center, Indianapolis, IN

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death, with high morbidity and mortality among vulnerable populations. We hypothesized the social determinants of health (SDOH), downstream social risks, and health behaviors impact access to curative therapies. **Methods:** Adult patients were prospectively enrolled from three hospitals in the Indianapolis area from 6/2019-11/2021. Sixteen individual and area-level SDOH within three access to care domains were collected using structured interviews and validated questionnaires (Panel A). Multinominal multivariable logistic regression was used to explore the associations between these SDOH and the outcomes of being alive without curative therapy, and having been transplanted/resected, or deceased at one year. Multivariable Cox survival analysis was used to explore time to death. **Results:** Of 139 patients with well characterized HCC 14.4% were Black and 7.9% were Hispanic. Most were Childs Pugh Category A (61.9%) and hepatitis-C virus was the most common underlying liver disease (46.5%). Annual household incomes of < $15,000 were reported by 21.6% of participants, and 7.9% reported trouble with transportation to medical appointments. 47.1% of patients lacked knowledge of their underlying liver disease. Brief Health literacy (BRIEF) scores were significantly lower, indicating worse health literacy, among those who died during the study period compared to those who were transplanted ((8.3 ± 3.8 vs. 10.5 ± 3.4) or still alive (10.7 ± 3.7) ($p = 0.013$) (Panel B). On average the cohort was followed 483 days; 31.6% (n = 44) underwent transplant/resection and 19.4% (n-27) were deceased at follow-up. Multivariable multinomial logistic regression analysis showed that higher health literacy was associated with a greater odds of being transplanted/resected compared to deceased (OR 1.206 95% CI 1.047-1.389, $p = 0.009$) and higher odds of being alive without transplant compared to deceased (OR 1.213 95% CI 1.065-1.381, $p = 0.004$). Recent alcohol use was associated with lower odds of being transplanted/resected compared to being alive (OR 0.243 95% CI 0.076-0.779, $p = 0.017$). On multivariable survival analysis health literacy scores were associated with survival (HR 0.87, 95% CI 0.80-0.96). **Conclusion:** Low health literacy and recent alcohol are strong determinants of receiving curative therapies for HCC and survival. These social risks are modifiable from within the health care system.

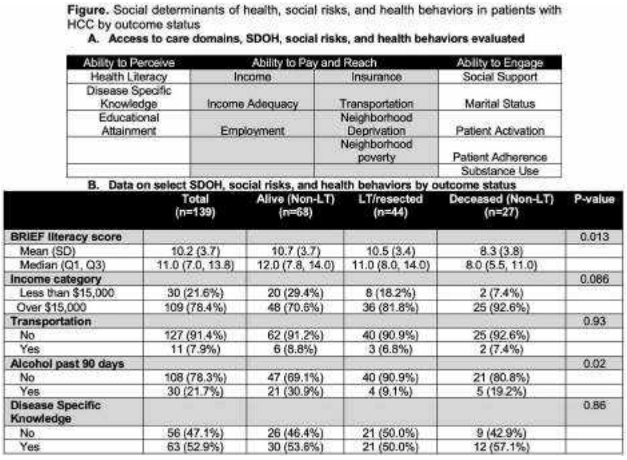

Figure. Social determinants of health, social risks, and health behaviors in patients with HCC by outcome status

A. Access to care domains, SDOH, social risks, and health behaviors evaluated

Ability to Perceive	Ability to Pay and Reach		Ability to Engage
Health Literacy	Income	Insurance	Social Support
Disease Specific Knowledge	Income Adequacy	Transportation	Marital Status
Educational Attainment	Employment	Neighborhood Deprivation	Patient Activation
		Neighborhood poverty	Patient Adherence
			Substance Use

B. Data on select SDOH, social risks, and health behaviors by outcome status

	Total (n=139)	Alive (Non-LT) (n=68)	LT/resected (n=44)	Deceased (Non-LT) (n=27)	P-value
BRIEF literacy score					0.013
Mean (SD)	10.2 (3.7)	10.7 (3.7)	10.5 (3.4)	8.3 (3.8)	
Median (Q1, Q3)	11.0 (7.0, 13.8)	12.0 (7.8, 14.0)	11.0 (8.0, 14.0)	8.0 (5.5, 11.0)	
Income category					0.086
Less than $15,000	30 (21.6%)	20 (29.4%)	8 (18.2%)	2 (7.4%)	
Over $15,000	109 (78.4%)	48 (70.6%)	36 (81.8%)	25 (92.6%)	
Transportation					0.93
No	127 (91.4%)	62 (91.2%)	40 (90.9%)	25 (92.6%)	
Yes	11 (7.9%)	6 (8.8%)	3 (6.8%)	2 (7.4%)	
Alcohol past 90 days					0.02
No	108 (78.3%)	47 (69.1%)	40 (90.9%)	21 (80.8%)	
Yes	30 (21.7%)	21 (30.9%)	4 (9.1%)	5 (19.2%)	
Disease Specific Knowledge					0.86
No	56 (47.1%)	26 (46.4%)	21 (50.0%)	9 (42.9%)	
Yes	63 (52.9%)	30 (53.6%)	21 (50.0%)	12 (57.1%)	

Disclosures: Lauren D. Nephew – Delfi diagnostic: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;

Eric S. Orman – Biovie: Advisor, No, No; Salix: Independent contractor (including contracted research), No, No;

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175 | PSYCHOSOCIAL NOT CLINICAL FACTORS PREDICT LIVER TRANSPLANT LISTING AMONG SAFETY-NET REFERRALS

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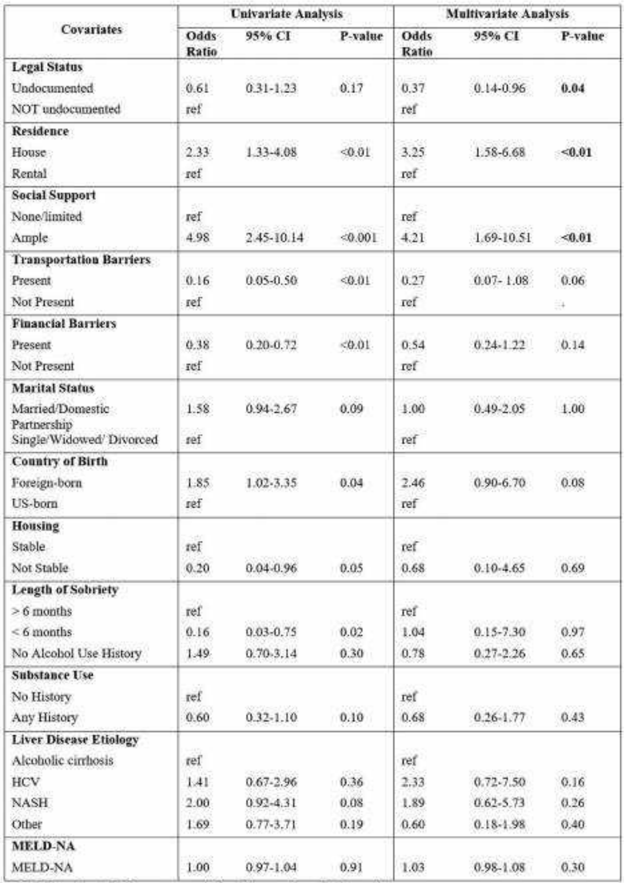
Background: Due to socioeconomic and healthcare access challenges, safety-net patients with liver disease face substantial disadvantages. Little is known about which factors – including psychosocial factors – impact listing for liver transplantation (LT) among the safety-net population. **Methods:** This was a multi-site retrospective study of adult patients who received outpatient hepatology care and were referred for LT between 2016 and 2022 from LA General Medical Center, which is one of the largest municipal safety-net hospitals and serves as the referring center to two transplant centers (Keck USC or UCLA). Demographics, clinical data, and LT evaluation outcomes were collected from the medical record. Among those who completed LT evaluation, detailed psychosocial data from the initial LT social work assessment were collected. Univariate and multivariate analyses were performed to determine clinical and psychosocial predictors of LT listing. **Results:** Out of 318 referred safety-net patients, 238 were evaluated for LT, with 233 having received a listing decision (135 listed, 98 declined). 80.0% had Medi-Cal insurance, 34.3% were primarily English-speaking, 53.1% were unemployed, and 44.3% had less than a high school education. Patients were similar in age, race/ethnicity, sex, disease etiology, and clinical decompensation by listing status. Per univariate analysis, listed patients were more likely to be legal residents than undocumented, live in a house, have ample social support, be married, be foreign-born, and have NASH. They were less likely to have transportation and financial barriers, unstable housing, and limited sobriety. After adjusting for age, evaluation site, and race/ethnicity, multivariable analysis identified legal status (OR 0.37, 95% CI 0.14-0.96), social support (OR 4.21, 95% CI 1.69-10.51), and living in a house (OR 3.25, 95% CI 1.58-6.68) as independent predictors of listing (Table). There was a non-significant trend towards higher odds of listing if foreign-born and no transportation barriers. Among 98 declined patients, the most common reasons for denial were lack of social support (23), being too early for LT (22), limited sobriety (19), HCC tumor burden (15), adherence concerns (14), and comorbidity (11). **Conclusion:** Among safety-net patients, psychosocial rather than clinical factors were predictive of LT listing. Targeted efforts to modify these factors may mitigate disparities in the LT listing process for underserved populations.



Covariates	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Legal Status						
Undocumented	0.61	0.31-1.23	0.17	0.37	0.14-0.96	**0.04**
NOT undocumented	ref			ref		
Residence						
House	2.33	1.33-4.08	<0.01	3.25	1.58-6.68	**<0.01**
Rental	ref			ref		
Social Support						
None/limited	ref			ref		
Ample	4.98	2.45-10.14	<0.001	4.21	1.69-10.51	**<0.01**
Transportation Barriers						
Present	0.16	0.05-0.50	<0.01	0.27	0.07- 1.08	0.06
Not Present	ref			ref		
Financial Barriers						
Present	0.38	0.20-0.72	<0.01	0.54	0.24-1.22	0.14
Not Present	ref			ref		
Marital Status						
Married/Domestic Partnership	1.58	0.94-2.67	0.09	1.00	0.49-2.05	1.00
Single/Widowed/ Divorced	ref			ref		
Country of Birth						
Foreign-born	1.85	1.02-3.35	0.04	2.46	0.90-6.70	0.08
US-born	ref			ref		
Housing						
Stable	ref			ref		
Not Stable	0.20	0.04-0.96	0.05	0.68	0.10-4.65	0.69
Length of Sobriety						
> 6 months	ref			ref		
< 6 months	0.16	0.03-0.75	0.02	1.04	0.15-7.30	0.97
No Alcohol Use History	1.49	0.70-3.14	0.30	0.78	0.27-2.26	0.65
Substance Use						
No History	ref			ref		
Any History	0.60	0.32-1.10	0.10	0.68	0.26-1.77	0.43
Liver Disease Etiology						
Alcoholic cirrhosis	ref			ref		
HCV	1.41	0.67-2.96	0.36	2.33	0.72-7.50	0.16
NASH	2.00	0.92-4.31	0.08	1.89	0.62-5.73	0.26
Other	1.69	0.77-3.71	0.19	0.60	0.18-1.98	0.40
MELD-NA						
MELD-NA	1.00	0.97-1.04	0.91	1.03	0.98-1.08	0.30

*Models adjusted for age, race/ethnicity, and evaluation site

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176 | FOOD INSECURITY AND HOUSEHOLD INCOME SUBSTANTIALLY INCREASE THE RISK OF NAFLD AMONG ADOLESCENT CHILDREN IN THE UNITED STATES

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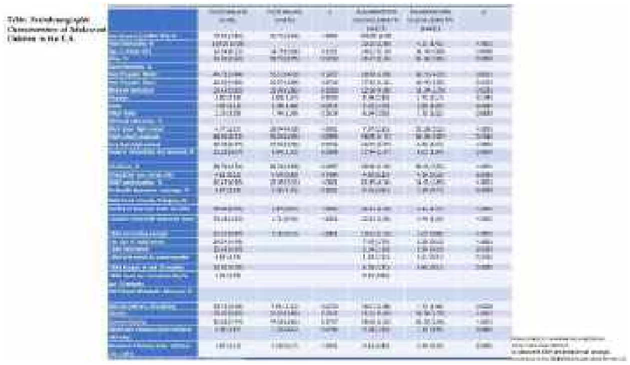
Church, VA, (3)The Global Nash Council, Washington, DC, (4)School of Public Health, University of Haifa, Haifa, Israel; Department of Gastroenterology, Tel-Aviv Medical Center, Tel-Aviv, Israel, (5)Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Barcelona, Spain, (6)Center for Outcomes Research in Liver Diseases, Washington, DC, (7)Inova Medicine, Inova Health System, Falls Church, VA

Background: Food insecurity can increase the risk for NAFLD. We assessed the association between food insecurity and NAFLD among adolescents in the United States. **Methods:** Data for adolescents (aged 12-18) from the National Health and Nutrition Examination Survey (2017-2018) were analyzed. Food insecurity was assessed using the U.S. Department of Agriculture (USDA) Child Food Security Survey Module, including 8 food security questions. Adolescents with 2 or more affirmative responses are classified as having food Insecurity according to USDA guidelines. Participation in Supplemental Nutrition Assistance Program (SNAP) was defined as anyone in household participating in the past 12 months. Low household (HH) income level was defined as household income < 138% federal poverty level [FPL]). NAFLD was defined by transient elastography (TE) with a controlled attenuation parameter (CAP) of e 285 dB/m without other causes of liver disease. Significant fibrosis (SF) and advanced fibrosis (AF) was defined by TE liver stiffness > 8.0 kPa and 13.1 kPa, respectively. **Results:** Among 771 adolescents included in NHANES 2017-2018 [mean age 14.7 years; 52.5% male; 50.9% white, 12.7% Black, and 16.7% Mexican American, 7.7% Hispanic and 4.5% Asian], 9.8% reported food insecurity and 10.8% had NAFLD; 22.5% obesity; 45.4% central obesity; 1.0% diabetes; 20.9% Pre-diabetes; 4.5% hypertension, 41.6% hyperlipidemia, 17.3% high C-reactive; 2.5% SF; and 0.5% AF. Of the adolescents who were considered food insecure, 98.9% relied on low-cost food, 93.2% couldn't get balanced meal and 51.5% did not eat enough food. Compared to the food-secure adolescents, food-insecure adolescents had higher rates of NAFLD (18.7% vs. 9.9%) and higher rates of advanced hepatic fibrosis (2.8% vs. 0.3%). Furthermore, they were more likely to be non-US citizens (88.8% vs. 95.6%), live with lower HH income (70.4% vs. 25.7%) and lower head of HH education (29.2% vs. 17.0%) and higher rates of SNAP participation (62.4% vs. 25.1%). There were no differences in metabolic diseases (T2D etc.) according to food insecurity. A model adjusted for demographic, metabolic diseases and SNAP participation showed that food insecurity (Odds ratio [OR] = 2.62, 95% confidence interval [1.07-6.41]), obesity (OR = 15.56 [7.71-31.50]), and hypertension (OR = 4.93 [2.67-9.14]) were independently associated with NAFLD. An additional multivariable model showed that living in a food-insecure adolescents living in lower HH income was associated with an even higher risk of NAFLD (OR = 4.79 [1.44-15.86]) versus adolescents living in higher HH income. **Conclusion:** Food insufficiency and low household income drive NAFLD risk for adolescents.



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177 | CHARACTERISTICS AND OUTCOMES OF TRANSGENDER PATIENTS WITH CIRRHOSIS: A NATIONAL COHORT STUDY★

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Background: The American Association for the Study of Liver Diseases has stated that fostering a "supportive environment for transsexual individual's seeking hepatology care" is an important goal. However, the landscape of transgender patients with cirrhosis is largely unknown. We aimed to assess the clinical characteristics of transgender patients with cirrhosis and quantify their outcomes. **Methods**: We retrospectively analyzed a large national insurance registry (Optum) between 2008-2021, including

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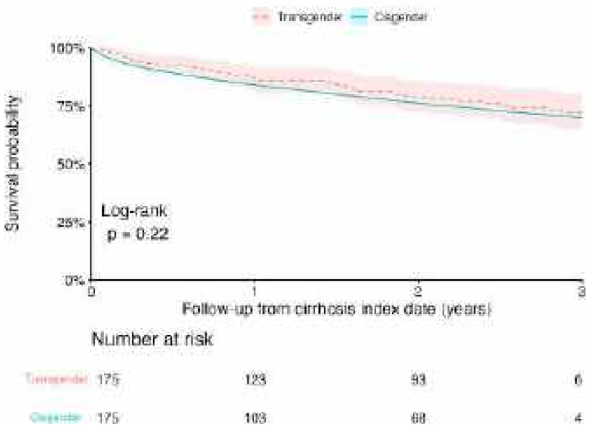
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

adults with cirrhosis identified by validated ICD-9/10 codes. Liver transplant recipients were censored at transplant. Transgender patients were identified using a billing code definition validated in a large national insurance registry (89% true-positive rate and 0.05% false-negative rate). Inverse-probability treatment weighting (IPTW) was used to balance trans- and cis-gender populations on individual level characteristics, such as age, reported gender, Charlson comorbidity index, cirrhosis etiology and decompensation status. The outcome was all-cause mortality. Patients were censored at 3-years of follow-up. **Results**: Among 55,741,658 adults in Optum, 28,672 (0.05%) were transgender. Among 282,106 adults with cirrhosis, 175 (0.06%) were transgender, with median follow-up of 2.4 years (IQR 0.9-4.2). Among patients with cirrhosis, trans- (vs. cis-) gender patients were younger (median age [IQR]: 62 [50-69] vs. 65 [57-72], $p < 0.001$), more likely to have alcohol (105 [60%] vs. 143,175 [51%], $p = 0.02$) or viral (65 [37%] vs. 79,406 [28%], $p = 0.01$) as cirrhosis etiologies, diagnoses of anxiety (111 [63%] vs.106,031 [38%], $p < 0.001$), depression (113 [65%] vs. 107,755 [38%], $p < 0.001$), and HIV (14 [8%] vs. 3,971 [1%], $p = 0.001$). Trans- (vs. cis-) gender patients had a similar likelihood of liver decompensation during follow-up (86 [51%] vs. 139,265 [49%], $p = 0.70$), and undergoing liver transplantation (4 [2%] vs. 4,763 [2%], $p = 0.54$). In IPTW-weighted survival analysis, probability of 3-year survival (72% vs. 70%, $p = 0.54$) (Figure 1), and 3-year liver decompensation (33% vs. 40%, $p = 0.94$) were similar. Trans- (vs. cis-) gender patients with cirrhosis spent more time receiving healthcare outside the home (median utilization per 100 days [IQR]: 3.1 days [0.9-9.9] vs. 1.5 days [0.3-5.1], $p < 0.001$). **Conclusion**: In this national study of insured persons with cirrhosis, the proportion of transgender patients was similar to the overall Optum population. We found that trans- (vs. cis-) gender patients have different clinical characteristics and greater healthcare utilization, but have similar liver decompensation, transplant, and mortality rates. These findings may help inform gender-inclusive hepatology care.

Figure 1. IPTW-Weighted Survival Probability in Trans- vs. Cis-gender Patients with Cirrhosis



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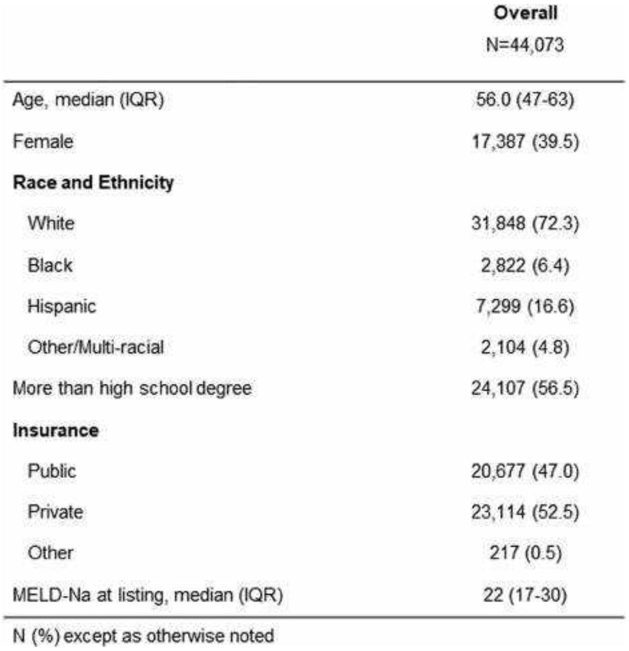
178 | RACIAL AND ETHNIC DISPARITIES IN WAITLIST MAINTENANCE: UPDATING LABS AND REMAINING ACTIVE

Alexandra Strauss[1], Vedant S. Jain[2], Jennifer Motter[3], Tanjala S. Purnell[1], Dorry L. Segev[4] and Allan B. Massie[4], (1)Johns Hopkins University, (2)Carle Illinois College of Medicine, (3)New York University, (4)NYU Langone Health

Background: Despite liver transplant (LT) waitlist prioritization being based on model for end stage liver disease (MELD) score, situations arise when patients are not optimally represented: 1) "inactive" and 2) lower MELD due to missing MELD "recertification". LT candidates are required to update, or "recertify", their labs within a certain amount of time based on their MELD (e.g., MELD e 25 requires recertification by 7 days or MELD decreases to last lower value and then to 6 if missed again). Also, patients become inactive for many reasons, some related to waitlist maintenance, and inactive status is associated with higher waitlist mortality. Social determinants of health may disproportionally impact patients leading to racial disparities in recertifying MELD and remaining active. We aimed to examine the association between race/ethnicity and these sub-optimal states. **Methods:** We studied national registry data (SRTR) on adult, first-time LT waitlist registrants 1/2017-9/2022. Patients who ever received MELD exception points or were classified as Status 1 were excluded. For Model 1, the outcome event was defined as ever missing lab recertification or being inactive due to "candidate cannot be contacted", "candidate work-up not complete", "insurance issues", or "medical non-compliance". Model 2 was only ever missing recertification, and Model 3 was any of the above inactive reasons. We performed multivariable modified Poisson regression with robust variance estimator to examine race/ethnicity disparities in the outcome. Models were adjusted for gender and age. **Results:** Of the 44,073 candidates, 6.4% were Black and 16.6% were Hispanic. There were 12,940 (29.4%) candidates that did not recertify MELD labs on schedule and 3,173 candidates (7.2%) that were inactive for any of the specified reasons as listed above. In adjusted analysis Model 1, Black candidates were at 11% higher risk (aRR 1.11, 95%CI 1.05-1.17, $p < 0.001$), and Hispanic candidates were at 24% higher risk (aRR 1.24, 95%CI 1.20-1.28), $p < 0.001$). For Model 2, effect sizes were similar. For Model 3, Black candidates were at 21% higher risk (aRR 1.21, $p = 0.004$) and Hispanic candidates were 12% higher risk (aRR 1.12, $p = 0.01$). **Conclusion:** Black and Hispanic LT candidates are at higher risk of not recertifying their MELD labs or becoming inactive, which may lead to worse waitlist outcomes. Further research and interventions to support waitlist maintenance at the patient and transplant center level are needed for personalized approaches.



	Overall N=44,073
Age, median (IQR)	56.0 (47-63)
Female	17,387 (39.5)
Race and Ethnicity	
White	31,848 (72.3)
Black	2,822 (6.4)
Hispanic	7,299 (16.6)
Other/Multi-racial	2,104 (4.8)
More than high school degree	24,107 (56.5)
Insurance	
Public	20,677 (47.0)
Private	23,114 (52.5)
Other	217 (0.5)
MELD-Na at listing, median (IQR)	22 (17-30)

N (%) except as otherwise noted

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f 179 | HIGH BLOOD LEVELS OF LEAD ARE ASSOCIATED WITH LIVER FIBROSIS AND SHORTENED TELOMERES IN AFRICAN AMERICANS IN A U.S. NATIONAL COHORT

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Background: Environmental pollutants cause liver damage and telomere shortening. Effects may vary by race/ethnicity. This study examined interactions among liver-related outcomes, telomere length, and environmental pollutants by race/ethnicity. **Methods:** The study included 36,092 adults (age e 20 y old) in the National Health and Nutrition Examination Survey (NHANES, 1999-2018) with data on blood levels of cadmium (Cd), lead (Pb) and mercury (Hg); 1,242 had data on 34 polychlorinated biphenyls (PCBs); and 7,360 had data on telomere length. Advanced liver fibrosis (LF) was defined as ALT elevation (e 40 IU/L, men; e 31 IU/L, women) and FIB-4 e 2.67 and/or Forns e 6.9 and/or APRI e 1.5. Shortened telomeres were in the 1st quartile (Q1) of length. Associations between advanced LF and pollutants were analyzed by multivariable logistic regression (MVL); mixtures were analyzed by weighted quantile sums (WQS) models. **Results:** High (Q4) blood levels of Pb were significantly associated with advanced LF in non-Hispanic (NH)-Blacks, but not in any other racial/ethnic group in MVL models adjusted for survey cycle, age, sex, BMI, smoking status, alcohol use, diabetes, and poverty: Odds ratio = 2.35, (95%CI, 1.43-3.85) (Fig 1A). Cd was associated with advanced LF in all racial/ethnic groups (Fig 1A). In WQS mixture analysis of three metals, Pb was the most significant contributor to the association between toxic exposure and advanced LF in NH-Blacks, while Cd was the most significant contributor in other groups. High (Q4) blood levels of Pb were associated with shortened telomeres in NH-Blacks and Mexican Americans (Fig 1B); Q4 blood levels of Cd were associated with shortened telomeres in NH-Whites (Fig 1B). Shorter telomeres were associated with higher risk of advanced LF (Fig 1C). In WQS mixture analysis of metals and PCBs, Cd and PCB199 were the most significant contributors to the significant association between toxic exposures and advanced LF (Fig 1D), while PCB126, Cd, and Pb were the most significant contributors to the significant association between toxic exposures and ALT elevation (Fig 1E). **Conclusion:** Innovations in statistics allow mixtures to be analyzed. WQS mixture analysis of common pollutants revealed that Pb is associated with advanced LF in NH-Blacks. This hepatotoxic effect may be mediated by telomere shortening, which was associated with Pb exposure in NH-Blacks and Mexican Americans. Pollution may be contributing to liver-related healthcare disparities.

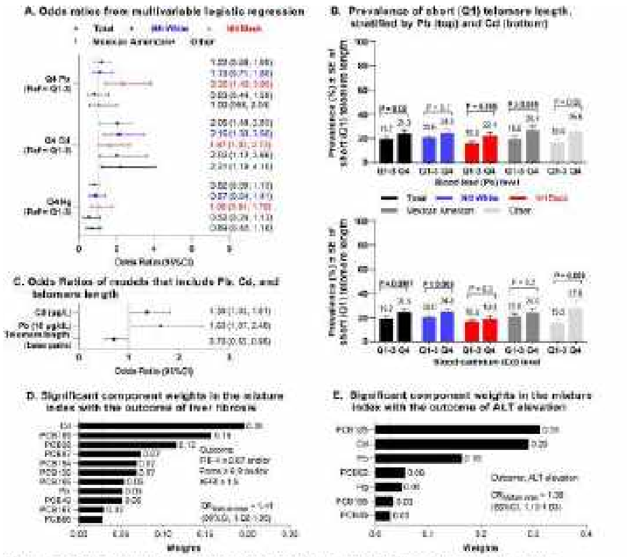

Fig. 1. Association between heavy metals/polychlorinated biphenyls (PCB) exposure and liver fibrosis. **(A) Odds ratios from multivariable logistic regression.** In multivariable logistic regression models with outcome of advanced fibrosis, adjusting for survey cycle, age, gender, BMI, smoking status, alcohol use, diabetes and poverty, the odds ratios (OR) of 4th quartile (Q) blood lead (Pb), Q4 blood cadmium (Cd), and Q4 blood mercury (Hg) were plotted stratified by racial groups including total, non-Hispanic White (NH White, blue), non-Hispanic Black (NH Black, red), Mexican American, and other race. **(B) Prevalence of short (Q1) telomere length, stratified by Pb (top) and Cd (bottom).** Age-standardized weighted prevalence of short telomere length was calculated in each racial group [NH White (blue), NH Black (red), Mexican American (dark grey), Other race (light grey)] in high (Q4) vs. low (Q1-3) blood level of Pb (top) and Cd (bottom); differences between groups were tested by univariate t statistic. Statistical significance was a two-sided P value <0.05. **(C) Odds Ratios of models that include Pb, Cd, and telomere length.** In multivariable logistic regression models with outcome of advanced fibrosis with 7,380 participants and 89 advanced fibrosis cases, adjusting for age, gender, BMI, smoking status, alcohol use, poverty, and diabetes, the ORs of blood Cd (μg/L), Pb (10 μg/dL) and telomere length (base pairs) were plotted. **(D) Significant component weights in the mixture index with the outcome of liver fibrosis.** Blood metals (Pb, Cd, Hg) and 34 PCBs were analyzed in mixture analysis weighted quantile sums (WQS) model with outcome of liver fibrosis (FIB-4 ≥2.67 and/or Forns ≥6.9 and/or APRI ≥1.5). The significant influential components were reported in bar plot (by default, the significant metals/PCBs in mixture equal to the inverse of the number of elements in the mixture, which was 1/37 = 0.027, purple dash line). **(E) Significant component weights in the mixture index with the outcome of ALT elevation.** Blood metals (Pb, Cd, Hg) and 34 PCBs were analyzed in mixture analysis WQS model with outcome of ALT elevation (>40 IU/L for men, >31 IU/L for women). The significant influential components were reported in bar plot (by default, the significant metals/PCBs in mixture equal to the inverse of the number of elements in the mixture, which was 1/37 = 0.027, purple dash line).

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180 | STAKEHOLDER ENGAGEMENT TO IDENTIFY KEY DETERMINANTS OF VIRAL HEPATITIS AND LIVER CANCER SCREENING AND CARE IN ASIAN AMERICAN COMMUNITIES

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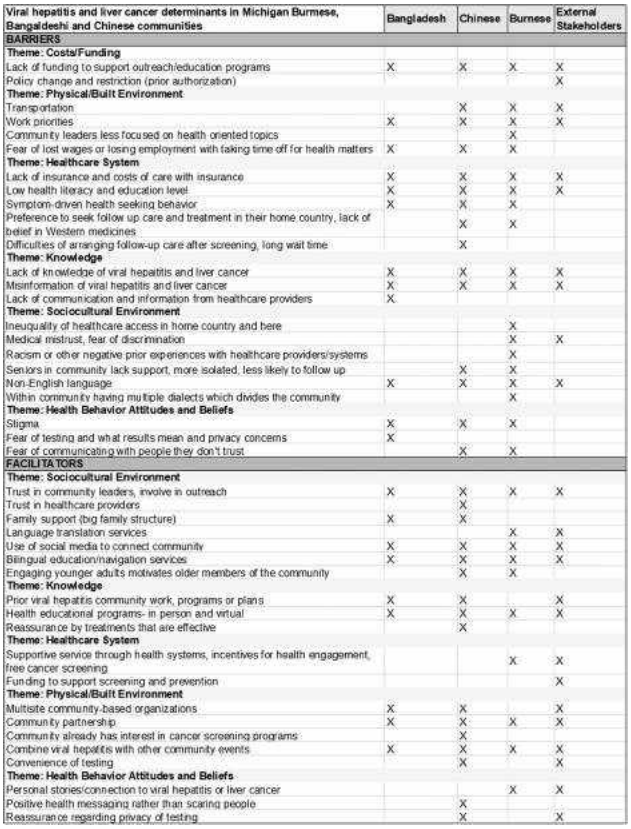
Background: Viral hepatitis screening and link to care is a key cancer control strategy to prevent development of liver cancer, especially in underserved populations. We lack data on determinants for viral hepatitis and liver cancer screening and care particularly in geographically spread Asian American (AA) populations. **Methods:** We engaged: 1) external stakeholders across Michigan and 2) leaders from 3 Michigan AA communities (Bangladesh, Burmese, Chinese) to identify determinants of viral hepatitis and cancer screening. External stakeholders organizations from state government, community partners, and the Rogel Michigan Medicine Cancer center participated in a focus group to identify broad viral hepatitis and cancer screening and care determinants for Michigan AA communities. We conducted 1:1 semi-structured interviews with 2-5 leaders from each AA community. The interviews assessed 1) general cancer screening, 2) viral hepatitis and liver cancer knowledge and beliefs, 3) health concerns/access. The focus group and interviews were conducted in English, audiotaped and transcribed. A rapid data analysis approach was used to identify key determinants and then grouped by themes informed by the National Institute of Minority Health and Health Disparities Framework. **Results:** Eight representatives from external stakeholders participated in the focus group and 11 community leaders from the 3 AA groups participated in interviews. A summary of determinants (barriers [B] and facilitators [F]) is included in the Table grouped by themes. According to AA community leaders, top health concerns included diabetes, hypertension, mental health and chronic diseases. Shared barriers included non-English language, lack of education, misinformation, transportation, lack of insurance, costs of care with insurance, stigma, fear of lost wages and lack of funding for outreach activities. Shared facilitators included trust in community leaders, bilingual services, health education programs and community partnership. Unique determinants within communities included: 1. Burmese: experiencing racism when seeking healthcare (B), multiple dialects within community (B), multiple religious affiliations that further silo communities based on dialects (B), 2. Bangladesh: prior hepatitis outreach activities (F), multisite community organizations (F) and 3. Chinese: positive health messaging (F), reassuring community about treatment options (F), trust in healthcare providers (F). External stakeholders did not identify many determinants raised by AA community leaders representing a learning opportunity. **Conclusion:** While many determinants of viral hepatitis and liver cancer outreach efforts are shared across in Michigan AA communities, some barriers and facilitators vary by communities. To adapt or develop viral hepatitis and cancer outreach, tailored interventions to address community specific determinants are needed.



Viral hepatitis and liver cancer determinants in Michigan Burmese, Bangaldeshi and Chinese communities	Bangladesh	Chinese	Burmese	External Stakeholders
BARRIERS				
Theme: Costs/Funding				
Lack of funding to support outreach/education programs	X	X	X	X
Policy change and restriction (prior authorization)				X
Theme: Physical/Built Environment				
Transportation		X	X	X
Work priorities	X	X	X	X
Community leaders less focused on health oriented topics			X	
Fear of lost wages or losing employment with faking time off for health matters	X	X	X	
Theme: Healthcare System				
Lack of insurance and costs of care with insurance	X	X	X	X
Low health literacy and education level	X	X	X	X
Symptom-driven health seeking behavior	X	X	X	
Preference to seek follow up care and treatment in their home country, lack of belief in Western medicines		X	X	
Difficulties of arranging follow-up care after screening, long wait time		X		
Theme: Knowledge				
Lack of knowledge of viral hepaitits and liver cancer	X	X	X	X
Misinformation of viral hepatitis and liver cancer	X	X	X	X
Lack of communication and information from healthcare providers	X			
Theme: Sociocultural Environment				
Ineuquality of healthcare access in home country and here			X	
Medical mistrust, fear of discrimination			X	X
Racism or other negative prior experiences with healthcare providers/systems			X	
Seniors in community lack support, more isolated, less likely to follow up		X	X	
Non-English language	X	X	X	X
Within community having multiple dialects which divides the community			X	
Theme: Health Behavior Attitudes and Beliefs				
Stigma	X	X	X	
Fear of testing and what results mean and privacy concerns	X			
Fear of communicating with people they don't trust		X	X	
FACILITATORS				
Theme: Sociocultural Environment				
Trust in community leaders, involve in outreach	X	X	X	X
Trust in healthcare providers		X		
Family support (big family structure)	X	X		
Language translation services			X	X
Use of social media to connect community	X	X	X	X
Bilingual education/navigation services	X	X	X	X
Engaging younger adults motivates older members of the community		X	X	
Theme: Knowledge				
Prior viral hepatitis community work, programs or plans	X	X		X
Health educational programs- in person and virtual	X	X	X	X
Reassurance by treatments that are effective		X		
Theme: Healthcare System				
Supportive service through health systems, incentives for health engagement, free cancer screening			X	X
Funding to support screening and prevention				X
Theme: Physical/Built Environment				
Multisite community-based organizations	X	X		X
Community partnership	X	X	X	X
Community already has interest in cancer screening programs		X		
Combine viral hepatitis with other community events	X	X	X	X
Convenience of testing		X		X
Theme: Health Behavior Attitudes and Beliefs				
Personal stories/connection to viral hepatitis or liver cancer			X	X
Positive health messaging rather than scaring people		X		
Reassurance regarding privacy of testing		X		X

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181 | SOCIAL DETERMINANTS OF HEALTH ARE ASSOCIATED WITH ADHERENCE TO MONITORING AMONG IMMIGRANTS WITH CHRONIC HEPATITIS B: A MULTICENTER STUDY

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Background: Immigrants are the largest subgroup living with chronic hepatitis B (HBV) infection in the United States (US). Close monitoring is recommended for all patients with chronic HBV regardless of disease activity. It is not well understood how immigration factors and social determinants of health (SDOH) impact downstream adherence to HBV monitoring among immigrants. **Methods:** We conducted a multicenter multilingual survey study among foreign-born adults with chronic HBV at three sites in California and Washington D.C. between 7/2021-2/2023. Participants were surveyed regarding 1) immigration factors such as birth country, time in the US, and citizenship status 2) acculturation including the Vancouver Index of Acculturation and language preferences 3) SDOH such as education, income, employment, and insurance and 4) clinical factors such as specialty care, treatment status, and evidence of end-stage liver disease. Primary outcome was optimal adherence to monitoring, defined as % of time with at least annual testing of HBV DNA, ALT, and ultrasound (if indicated for cancer surveillance per AASLD guidelines) while under care. Outcomes data were retrospectively collected through electronic medical records. Stepwise backwards logistic regression was used to examine factors associated with outcome. **Results:** 217 participants (median 57 y, 55% male) completed the survey from 27 birth countries, with highest representation from China (30%), Vietnam (16%), and South Korea (10%). 6% were from Latin America. A minority (29%) were recently immigrated within the past 20 years and 63% were US citizens. Nearly all participants (92%) reported seeing a specialist for HBV, with 74% currently on treatment. 119 participants (55%) had optimal adherence to monitoring over median 4 years (2-7) under care. Immigration factors, degree of acculturation and language were not associated with adherence. Factors associated with more optimal adherence on multivariate testing included younger age (OR 0.96, 95% CI 0.93-0.99), on treatment (vs not: OR 2.7, 1.2-5.9), currently employed (vs not; OR 2.2, 1.0-5.0), and higher education (college vs high school; OR 3.6, 1.4-9.0; graduate degree vs high school: OR 3.2, 1.1-9.6). **Conclusion:** SDOH rather than immigration-related factors influenced likelihood of adherence to guideline-recommended monitoring of chronic HBV infection among immigrants. Efforts to improve monitoring should target socially disadvantaged foreign-born.

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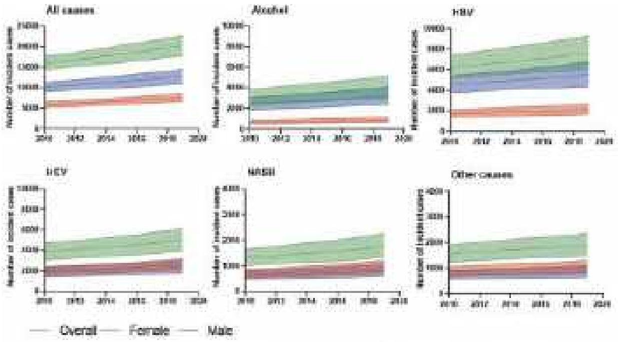
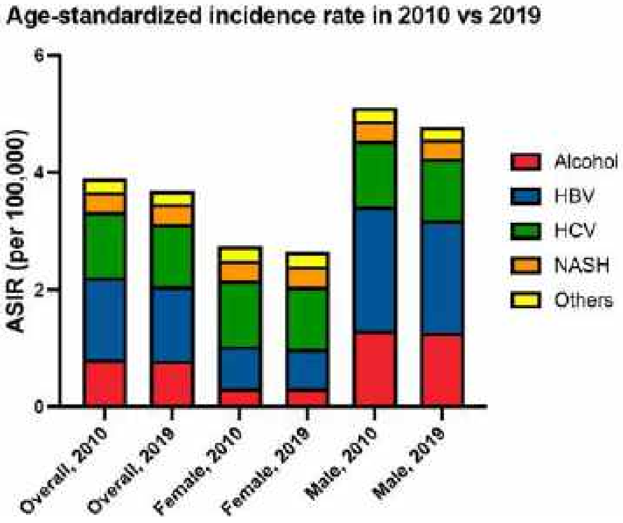
182 | UNVEILING THE TOTAL BURDEN OF LIVER CANCER IN LOW SOCIO-DEMOGRAPHIC INDEX COUNTRIES FROM 2010-2019: EPIDEMIOLOGICAL TRENDS, ETIOLOGY, AND GENDER SPECIFIC PATTERNS

Gautam Maddineni[1], Silpa Choday[2], Kelsey Theriault[1], Abraham Bell[3], Dustin Paul Begosh[1], Magdy El-Din[1] and Karn Wijarnpreecha[4], (1)Florida State University, (2)Creighton University, (3)Florida State University, Cape Coral, FL, (4)University of Arizona College of Medicine Phoenix, Phoenix, AZ

Background: Liver cancer poses a significant health challenge worldwide, but its burden in low Socio-Demographic Index (SDI) countries remains understudied. These countries face unique obstacles, including limited healthcare resources, inadequate screening programs, and a higher prevalence of risk factors like hepatitis B and C. Liver cancer has become a pressing public health issue, impacting individual's, communities, and healthcare systems in low SDI countries. This abstract explores the total burden of liver cancer in these regions, focusing on epidemiological trends, etiology, and the disease's impact on morbidity, mortality, and socioeconomic factors. Understanding these challenges can guide interventions, prevention efforts, and resource allocation to alleviate the burden of liver cancer and improve health outcomes in vulnerable populations. **Methods:** This study utilized data from the Global Burden of Disease Study 2019 (GBD 2019), which assesses disease burden and risk factors across 204 countries and territories. We extracted data on liver cancer incidence, deaths, and disability-adjusted life years (DALYs) from low SDI countries between 2010 and 2019. Various statistical techniques were employed to address data heterogeneity, and a Bayesian geospatial regression analysis was used to estimate liver cancer-related mortality. The study included comprehensive stratification by country, sex, and year, and proportional models were applied to determine the contribution of different etiologies to liver cancer cases. **Results:** The burden of liver cancer in low SDI countries increased in incidence and DALYs from 2010 to 2019, with a higher prevalence observed among males. Alcohol-related liver cancer cases continued to rise, predominantly affecting males. The incidence rate remained stable in females, but DALYs increased. Hepatitis B-related liver cancer showed a declining trend, with decreasing rates in both incidence and deaths. Hepatitis C-related liver cancer also decreased, but males had a higher frequency of deaths despite females being the most affected. Non-alcoholic steatohepatitis (NASH)-related liver cancer cases increased significantly, particularly among females. Other causes of liver cancer demonstrated an upward trend in frequency (Image). **Conclusion:** This study provides insights into the burden of liver cancer in low SDI countries, highlighting different etiologies. The overall burden of liver cancer is decreasing, particularly for hepatitis B and C cases. However, viral hepatitis cases still lack adequate treatment, emphasizing the importance of early detection and treatment to prevent liver cirrhosis and cancer. Metabolic-related liver cancer, including NASH, is a growing concern globally and in low SDI countries. Prevention and control strategies specific to these regions are crucial to reducing the burden of liver cancer. Ref: https://vizhub.healthdata.org/gbd-results/.





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183 | PATIENTS WITH ACUTE ON CHRONIC LIVER FAILURE ARE AT HIGHER RISK OF PROCEDURAL-RELATED BLEEDING

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Background: Patients with decompensated cirrhosis are frequently hospitalized and often undergo multiple invasive procedures. We aimed to define the incidence of procedural-related bleeding in patients with acute on chronic liver failure (ACLF) and to compare it with that of patients without ACLF. **Methods:** Prospective, multicenter, international cohort study of hospitalized patients with cirrhosis undergoing non-surgical procedures. Patients were followed until 28 days from admission, death, liver transplantation, and/or undergoing surgery. Procedural bleeding was defined according to ISTH definitions and defined as major, clinically relevant non-major (CRNMB), and other. The risk of the procedure was judged to be low or high risk based on recent AASLD guidelines. ACLF at admission was defined according to European Foundation for the Study of Chronic Liver Failure. **Results:** A total of 1,051 patients undergoing 2,688 non-surgical procedures were enrolled from 20 centers in North and South America. 224 (21.3%) of the patients enrolled had ACLF on admission versus 827 patients without ACLF on admission. At admission patients with ACLF more commonly had ascites, AKI and infection. Length of stay was longer in patients with ACLF (mean 17.4 d ACLF vs. 11.9 d non-ACLF) and they underwent more procedures while hospitalized (mean 3.3 ACLF vs. 2.3 non-ACLF). Proportion of high risk procedures in patients with ACLF was lower compared to patients without ACLF (4.9% ACLF vs. 10.5% non-ACLF, $p < 0.001$). Prior to procedures coagulation parameters were significantly different in patients with ACLF ((platelets (k/uL) 100 ACLF vs. 116 non-ACLF $p < 0.001$; INR 2.1 ACLF vs. 1.7 non-ACLF, $p < 0.001$; fibrinogen (mg/dL) 181 ACLF vs 201 non-ACLF, $p = 0.005$). Patients with ACLF were more likely to receive pre-procedure prophylaxis with platelet and plasma transfusion. A total of 76 procedural related bleeding events were identified in this cohort (25 major, 30 clinically relevant non-major, and 21 other bleeds). Bleeding was more prevalent in patients with ACLF compared to patients without ACLF (14.2% ACLF vs. 5.3%, $p < 0.001$) with a relative risk of bleeding for patients of 2.69 [95% CI 1.74, 4.13] (See Table). Non-procedural related bleeding while hospitalized occurred more frequently in patients with ACLF (21% ACLF vs. 15% non-ACLF, $p = 0.035$). Patients with ACLF had higher mortality and more commonly underwent liver transplantation during 28-day follow up. **Conclusion:** Prior studies have demonstrated patients with ACLF have unique hemostatic profiles compared to patients with decompensated cirrhosis. Patients with ACLF are more likely to develop procedural related bleeding despite undergoing lower risk procedures more commonly compared to patients with decompensated cirrhosis without ACLF. Factors which may explain this observation include increased number of procedures, comorbidities, and severity of liver disease.

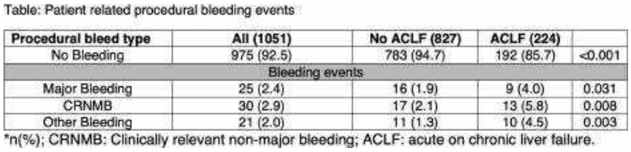

Table: Patient related procedural bleeding events

Procedural bleed type	All (1051)	No ACLF (827)	ACLF (224)	
No Bleeding	975 (92.5)	783 (94.7)	192 (85.7)	<0.001
Bleeding events				
Major Bleeding	25 (2.4)	16 (1.9)	9 (4.0)	0.031
CRNMB	30 (2.9)	17 (2.1)	13 (5.8)	0.008
Other Bleeding	21 (2.0)	11 (1.3)	10 (4.5)	0.003

*n(%); CRNMB: Clinically relevant non-major bleeding; ACLF: acute on chronic liver failure.

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184 | REDUCE DOSE SAFETY OF DIRECT ORAL ANTICOAGULANTS IN CIRRHOTIC PATIENTS AND PORTAL VEIN THROMBOSIS WITH COEXISTENT SIGNIFICANT THROMBOCYTOPENIA: A MULTI-COUNTRY STUDY

Julton Tomanguillo Chumbe[1], Mark Ayoub[2], Lauren Searls[2], Frank Annie[2], Harleen Chela[2], Nadeem Anwar[1] and Ebubekir Daglilar[1], (1)West Virginia University - Charleston Area Medical Center, Charleston, WV, (2)Charleston Area Medical Center/WVU Charleston Division

Background: Treating portal vein thrombosis in patients with cirrhosis becomes increasingly challenging when there is also significant thrombocytopenia ($<50*10^3$/uL). As suggested by various international medical societies, a 50% reduction in the standard anticoagulation dosage has been recommended for individual's with significant thrombocytopenia. In this study, our goal was to evaluate the safety of using reduced doses of direct oral anticoagulants (DOAC) among cirrhotic patients who have PVT and coexisting significant thrombocytopenia. **Methods:** Adult patients 18 years and old with the diagnosis of cirrhosis and significant thrombocytopenia, as defined by platelet count between 30 and $49*10^3$/uL, were identified using TriNetX between 2007 and 2020. TriNetx includes a total of 106 different health care organizations from 14 different countries. Patients with cirrhosis with significant thrombocytopenia were divided into two cohorts; the first cohort comprised patient receiving 50% reduced-dose DOAC (Apixaban or Rivaroxaban), and a second cohort did not receive any anticoagulation therapy. We compared the rate of mortality and significant bleeding such as intracranial bleeding and gastrointestinal bleeding between propensity matched (PSM) pairs of patients. **Results:** A total of 2,245 patients with cirrhosis and significant thrombocytopenia were included in this analysis. Of these 16% ($n = 350$) were on DOAC, and 84% ($n = 1,890$) were not on anticoagulation. The raw data showed a higher rate of key comorbidities in the DOAC group, such as chronic heart failure (21.7% vs 7.1%, $p < 0.001$), diabetes mellitus (51.0% vs 29.9%, $p < 0.001$), and CKD (35.8% vs 13.9%, $p < 0.001$). Subsequently, two well-matched cohorts were created using a 1:1 propensity-scored matching model (329/329). No significant difference was noted between the two groups in the rate major bleedings at 6 or 12 months. At 6-months intracranial hemorrhage (3.04% vs 3.04%, $p = 1.00$), gastrointestinal bleeding (16.41% vs 12.15%, $p = 0.475$), and over-all mortality (20.97% vs 21.58%, $p = 0.84$). At 12-months intracranial hemorrhage (3.04% vs 3.04%, $p = 1.00$), gastrointestinal bleeding (19.14% vs 14.28%, $p = 0.09$), and over-all mortality (24.62% vs 24.62%, $p = 1.00$). **Conclusion:** In a large multi-country study, the use of reduced dosed DOAC in patient with cirrhosis and significant thrombocytopenia was not significantly associated with major bleedings such as intracranial hemorrhage or gastrointestinal bleeding up to 12-months when compared with patient not on anticoagulation.

Disclosures: The following people have nothing to disclose: Julton Tomanguillo Chumbe, Mark Ayoub, Lauren Searls, Frank Annie, Harleen Chela, Nadeem Anwar, Ebubekir Daglilar

185 | LIVER LYMPHANGIOGENESIS MITIGATES THE PROGRESSION OF FIBROSIS★

Jain Jeong[1], Yilin Yang[2], Teruo Utsumi[3], Matthew McConnell[2], Rolando Garcia-Milian[1], Xuchen Zhang[2], Shi-Ying Cai[2], James L. Boyer[1] and Yasuko Iwakiri[1], (1) Yale School of Medicine, New Haven, CT, (2)Yale University, New Haven, CT, (3)VA Connecticut Health Care

Background: Chronic inflammation due to various etiologies leads to liver fibrosis and subsequently cirrhosis. The liver lymphatic system helps to reduce inflammation. We hypothesized that the liver lymphatic system ameliorates liver fibrosis/cirrhosis. **Methods:** Mice with different stages of liver fibrosis were generated using bile duct ligation (BDL) surgery. Liver lymphatic endothelial cells (LECs) from different stages of liver fibrosis were isolated for RNA sequencing. Liver samples from control and primary sclerotic cholangitis (PSC) patients were analyzed. **Results:** Hepatic lymphatic vessel (LV) numbers were significantly increased until 2 weeks after BDL (fibrosis stage), but decreased by 4 weeks (cirrhosis stage). To determine whether this drop in LV numbers further promotes liver fibrosis, we blocked new LV formation in BDL mice using MAZ51, an inhibitor of VEGFR3 and found aggravated liver fibrosis by increased Sirius Red (1.4-fold, $p < 0.05$), hydroxyproline (1.9-fold, $p < 0.05$), increased MPO-positive neutrophil number (2.8-fold, $p < 0.05$), and decreased lymphatic drainage (2.5-fold, $p < 0.05$). These results suggest that decreased lymphatic drainage promotes liver fibrosis progression. In contrast, administration of VEGF-C, the most potent factor promoting new LV formation, via AAV8-VEGF-C significantly increased LV numbers and inhibited liver fibrosis as indicated by decreased Sirius Red (1.4-fold, $p < 0.05$), hydroxyproline (1.4-fold, $p < 0.05$), and CD68-positive macrophage number (1.7-fold, $p < 0.05$). Transcriptomic analysis of LECs revealed increased TGFβ signaling, which is known to inhibit lymphangiogenesis in cirrhotic mouse livers. Blocking TGFβ signaling via LY364947 significantly increased LV numbers (2.0-fold, $p < 0.001$) and area (1.8-fold, $p < 0.01$) in cirrhotic mouse livers. In livers from PSC patients, we found increased LV number in compensated (3.5-fold, $p < 0.001$, $n = 7$) and decompensated (2.5-fold, $p < 0.05$, $n = 6$) cirrhosis. Importantly, hepatic LV number decreased in decompensated cirrhotic liver (1.4-fold, $p < 0.05$) compared to compensated cirrhotic patients. Histological analysis showed co-localized pSMAD2 expression increased in liver LECs in decompensated liver cirrhosis, indicating TGFβ-driven lymphatic dysfunction may contribute to the decompensation of liver cirrhosis. **Conclusion:** The liver lymphatic system inhibits liver fibrosis and progression to liver cirrhosis. VEGF-C-driven lymphangiogenesis and lymphatic drainage could be a novel therapy for liver fibrosis/cirrhosis.

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Disclosure information not available at the time of publication: Teruo Utsumi, Rolando Garcia-Milian, Xuchen Zhang, Shi-Ying Cai

186 | A COMPARATIVE ANALYSIS OF OUTCOMES BETWEEN DIRECT ORAL ANTICOAGULANTS AND LOW-MOLECULAR-WEIGHT HEPARIN OR VITAMIN K ANTAGONISTS IN BUDD-CHIARI SYNDROME: A GLOBAL MULTICENTER PROPENSITY-MATCHED STUDY

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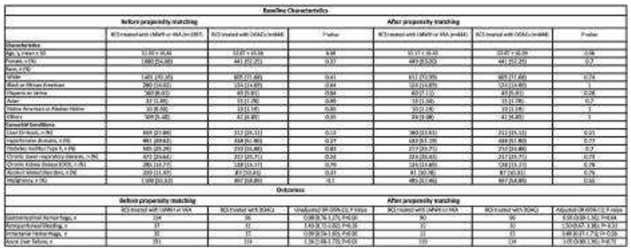
Background: In patients with Budd Chiari syndrome (BCS), the current treatment guidelines recommend a step-up approach starting with lifelong anticoagulation with low-molecular-weight heparin (LMWH) or vitamin K antagonists (VKA). Although direct oral anticoagulants (DOAC) may simplify patient management, there is limited data on the safety and efficacy of DOAC in patients with BCS. This study used a large research network to compare the outcomes of patients with BCS treated with DOACs, LMWH, and VKAs. **Methods:** In this retrospective cohort study and time-to-event analysis, we utilized the TriNetX electronic health records network, which encompasses over 100 million patients, from January 1st, 2015, to December 31st, 2020. The primary cohort included patients aged 18 years or older diagnosed with BCS. We performed (1:1) propensity score matching age, gender, race, and comorbidities, including Liver Cirrhosis, Diabetes Mellitus, Hypertension, Chronic kidney disease, and malignancy. Two matched control cohorts were created: one consisting of patients with BCS treated with LMWH or VKAs, and the other comprising patients treated with DOACs (including dabigatran, rivaroxaban, apixaban, and edoxaban). Using a Cox model, we estimated the incidence of gastrointestinal bleeding, retroperitoneal hemorrhage, Intracranial hemorrhage, and acute liver failure between propensity score-matched pairs of patients. **Results:** We identified 2,841 patients with BCS who met the inclusion criteria. Among them, 1,997 patients were treated with LMWH or VKAs, while 844 patients were treated with DOACs. Both groups had a majority of female and Caucasian patients, and there were no statistically significant differences in comorbid conditions before and after propensity matching (Table 1). Although there was a higher incidence of acute liver failure in the LMWH/VKA group before propensity matching, this difference did not remain statistically significant after matching. Additionally, there were no significant differences in the incidence of gastrointestinal bleeding, retroperitoneal hemorrhage, and intracranial hemorrhage between the two groups, both before and after propensity matching. **Conclusion:** Based on a large nationwide study, BCS patients treated with DOACs showed comparable rates of gastrointestinal bleeding, retroperitoneal hemorrhage, intracranial hemorrhage, and acute liver failure to those treated with LMWH or VKAs. LMWH or VKA treatment requires continuous monitoring, which may affect patient compliance. Our study suggests that DOACs could serve as an effective and safe long-term anticoagulation alternative for these patients. However, further confirmation through larger prospective studies is necessary.



Disclosures: The following people have nothing to disclose: Abdullah Sohail, Khadija Naseem, Muhammad Mujtaba Bhinder, Ahmad Khan

187 | BAR501, A SELECTIVE GPBAR1 AGONIST, REDUCES VASCULAR INFLAMMATION AND ATHEROSCLEROSIS IN A MOUSE MODEL OF MASLD

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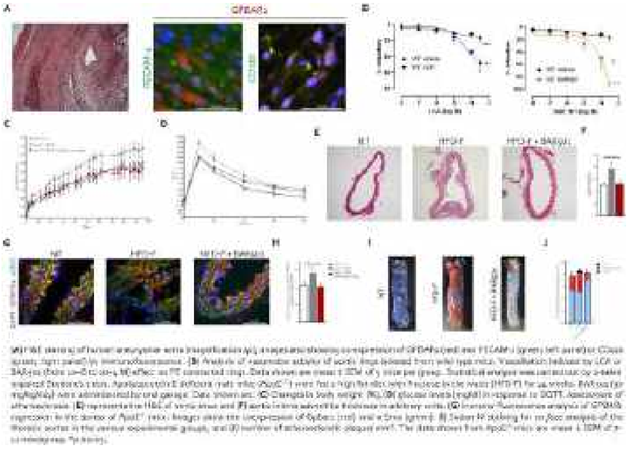
Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), represent the most common cause of chronic liver disease in Western countries. MASLD patients are at increased risk for developing clinically meaningful cardiovascular diseases (CVD), including stroke and coronary artery disease and its fatal and nonfatal ischemic complications. It is widely established that the CV component dictates the patient outcomes more frequently and to a greater extent than does the progression of the liver component and it is the most common cause of death for MASLD patients. There are no drugs specifically approved for the treatment of CVD and liver components of MASLD. In this scenario, there is therefore a constant search for new therapeutic targets and new therapies for the treatment of CVD in patients with MASLD. GPBAR1is a receptor, belonging to the family of bile acid receptors (BARs), activated by secondary bile acids and their derivatives. Activation of GPBAR1 increases energy expenditure in the adipose tissue and promotes the release of Glucagon-like peptide (GLP)-1 and FGF15. Furthermore, GPBAR1 is expressed by cells of innate immunity and endothelial cells and their systemic activation counter-regulates leukocytes/endothelial cells adhesion and contribute to the vasodilatory properties of bile acids. The purpose of this study was to evaluate the effect of GPBAR1 activation in a mouse model of atherosclerosis. **Methods:** Apolipoprotein E deficient mice (ApoE$^{-/-}$), a standard model of atherosclerosis, were fed with HFD-F alone or with BAR501 for 14 weeks and then sacrificed. The aortic rings, aorta and liver were isolated and analyzed. **Results:** The GPBAR1 expression in the atherosclerotic plaques in rodent and patient's aorta, highlighted by IF staining, confirmed the involvement of the receptor in the atherosclerotic process. BAR501 in ApoE$^{-/-}$ mice exposed to HFD-F decreased body weight gain and increased insulin sensitivity. Furthermore, the administration of BAR501 induced an increase in the plasma concentration of GLP-1 and FGF15. Activation of GPBAR1 also resulted in the reduction of thickness and atheroma area in the aorta with a decrease in infiltrating GPBAR1^{+} immune cells. The transcriptome analysis of the aorta showed a anti-inflammatory activity of BAR501 that down-regulated the expression of many genes belonging to inflammatory pathways. Macrophages represent the main actors of the atherosclerosis process; the analysis of macrophage subpopulations extracted from the spleen of mice from the different experimental groups showed a systemic anti-inflammatory activity exerted by BAR501, with an increase of IL10^{+}/IL6^{+} macrophages ratio. **Conclusion:** GPBAR1 activation reduces systemic inflammation induced by a high-fat diet thereby reducing atherosclerotic lesions in the aorta, suggesting that BAR501 therapy may represent a potent new treatment for MASLD-related CVD.



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188 | SAFETY OF DOACS IN PATIENTS WITH CHILD-PUGH CLASS C CIRRHOSIS AND ATRIAL FIBRILLATION

Mark Ayoub[1], Julton Tomanguillo Chumbe[1], Morgan Koontz[2], Ebubekir Daglilar[1], Nadeem Anwar[1] and Vishnu Naravadi[1], (1)West Virginia University - Charleston Area Medical Center, Charleston, WV, (2) Health Services & Outcomes Research, Charleston Area Medical Center

Background: Anticoagulation (AC) is the mainstay of thromboprophylaxis for stroke prevention in atrial fibrillation (AF) and is recommended. Cirrhosis is a risk factor for AF development; hence, AF is common in patients with cirrhosis. The hemostatic pathways in cirrhosis are imbalanced which makes their response to anticoagulation unpredictable. While Direct-Oral Anticoagulants (DOACs) are shown to be safe and effective in patients with AF without cirrhosis, they are hardly studied in patients with cirrhosis. Therefore, this study aims at comparing safety and evaluating different outcomes in patients with Child C cirrhosis receiving anticoagulation for AF. **Methods:** We queried the Global Collaborative Network TriNetX- a de-identified database of healthcare organizations from four different countries. Patients with Child-Pugh class C cirrhosis and atrial fibrillation were divided into three cohorts; the first cohort included patients on DOACs (apixaban or rivaroxaban), second cohort included patients not on any anticoagulation, third cohort included patients on warfarin. Two well-matched cohorts were created using 1:1 propensity-scored matching model between cohorts. Three study arms were created after propensity matching. We compared the rates of intracranial hemorrhage, embolic stroke, gastrointestinal (GI) bleed, mortality, and transplant status. **Results:** A total of 16,029 patients met the inclusion criteria. Of those, 20.2% (n = 3,235) were on DOACs, 47.1% (n = 7,552) were not on any anticoagulation, and 32.7% (n = 5,242) were on warfarin. In the first study arm comparing patients on AC vs no AC, a statistically significant benefit was identified in terms of 3-year mortality risk (47% vs 71%, $p < 0.0001$) and the transplant status (17% vs 5%, $p < 0.0001$) among patients on AC.

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

However, no significant difference was identified regarding intracranial hemorrhage (3.1% vs 2.7%, $p = 0.19$) and GI bleeding risk 18.8% vs 19.5 %, $p = 0.3$). In the second arm we compared patients on DOACs vs no AC, there was again identified a mortality benefit (40% vs 72%, $p < 0.0001$) and a higher transplant rate (9% vs 3.2%, $p < 0.0001$) with DOACs. The rates of intracranial hemorrhage (6% vs 4%, $p = 0.03$) were higher in patients on DOACs compared to no AC. In the third arm we compared patients on DOAC's vs Warfarin, a statistically significant lower risk of intracranial hemorrhage (6.6% vs 8.7%, $p = 0.004$) and GI bleed (2% vs 2.4%, $p < 0.0001$) was identified in patients on DOACs with no difference in the mortality rate (42% vs 43.7%, $p = 0.2$) or the transplant status (8.3% vs 7.1%, $p = 0.9$) (Please see table). **Conclusion:** Anticoagulation is safe in patients with Child-Pugh class C cirrhosis with atrial fibrillation and may provide a mortality benefit. DOACs are a safer alternative to warfarin with a lower risk of intracranial hemorrhage and GI bleed. The higher rates of embolic stroke in patients on AC is likely a selection bias as patients with stroke are more likely to be placed on AC.

	AC	No AC	P value	DOAC	No AC	P value	DOAC	Warfarin	P value
Intracranial Hemorrhage	3%	2.7%	0.19	6.2%	4.9%	0.03	6.6%	8.7%	0.004
Embolic Stroke	0.9%	0.5%	0.03	1.1%	0.5%	0.009	1.2%	1.4%	0.63
GI bleed	18.8%	19.5%	0.3	19.4%	21.5%	0.065	2%	2.4%	0.0001
Mortality in 3 years	47.4%	71.2%	0.00001	40.1%	72.4%	0.00001	42%	43.7%	0.2
Median Survival Days	715 days	66 days		898 days	65 days				
Transplant	17%	5.2%	0.0001	9.3%	3.2%	0.0001	8.3%	7.1%	0.092
Median Platelet Count	140K	70K		150K	70K		150K	150K	

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189 | HBV VIRUS-HOST CHIMERA DNA SERVES AS A PERSONALIZED CIRCULATING BIOMARKER FOR RESIDUAL TUMORS AFTER SURGICAL RESECTION OF HEPATOCELLULAR CARCINOMA

Gar-Yang Chau[1], Wei-Chen Lee[2], Ming-Chih Ho[3], Teng-Wei Chen[4], Rey-Heng Hu[3], Tsung-Han Wu[2], Hao-Jan Lei[1], Shu-Cheng Chou[1], Hsiu-Lung Fan[4], Ting-Jung Wu[2], Cheng-Maw Ho[3], Hong-Shiue Chou[2], Sheng-Tai Tzeng[5], Ya-Chun Wang[5], Shiou-Hwei Yeh[6] and Pei-Jer Chen[3], (1)Taipei Veterans General Hospital Department Surgery, (2)Linkou Chang Gung Memorial Hospital, (3)National Taiwan University Hospital, (4)Tri-Service General Hospital, (5)TCM Biotech International Corp., (6)College of Medicine, National Taiwan University

Background: Early recurrence of hepatocellular carcinoma (HCC) after surgical resection compromises patient survival. Timely detection of minimal residual tumor is helpful in recurrence monitoring and evaluating treatment strategies. This study examined the feasibility of virus-host chimera DNA (vh-DNA) generated from integration sites of hepatitis B virus (HBV) in the HCC chromosome as a personalized circulating biomarker for residual tumors after surgery. **Methods:** The tumor-specific vh-DNA integration sites were determined in 148 HBV-related HCC patients by capture-based next-generation sequencing (NGS). For each individual HCC, vh-DNA was quantified using a customized droplet digital PCR (ddPCR) assay in plasma samples collected pre-operation and within 14 months after surgery, and the results were compared with the clinical outcomes. **Results:** HBV integrations were identified in 132 out of 148 patients with HBV-related HCC (89.2%). The preoperative blood vh-DNA concentration was correlated with tumor size ($r = 0.73$, detection limit at 1.5 cm). Among the 113 patients who completed the postoperative follow-up, the positive predictive value (PPV) of vh-DNA for tumor recurrence was 71% (17/24), and the negative predictive value (NPV) was 92% (82/89). The smallest recurrent HCC with detectable circulating vh-DNA was 0.8 cm, and the average leading time of vh-DNA detection was 158 days earlier than computed tomography scanning. A total of 78% (18/23) of recurrences originated from the same HCC clones sharing the same vh-DNA, suggesting that most of the early recurrence came from residual tumor cells. Moreover, logistic regression analysis showed that vh-DNA was an independent risk factor for predicting early recurrence ($p < 0.0001$). When vh-DNA combined with the serum markers AFP and PIVKA-II, the sensitivity and specificity of recurrent HCC were 95.8% (23/24) and 95.5% (85/89), respectively. **Conclusion:** This study demonstrates that vh-DNA can serve as a personalized circulating tumor marker for HBV-related HCC patients. Utilizing vh-DNA to monitor the presence of residual tumors after surgery could be a promising solution for prognosis assessment, recurrence monitoring, and guiding adjuvant therapies in the future.

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190 | MULTI-ANCESTRY WHOLE GENOME SEQUENCING (WGS) AND META-ANALYSIS TO IDENTIFY LOCI ASSOCIATED WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)★

Chinmay Raut[1], Yanhua Chen[1], Antonino Oliveri[1], Mary F Feitosa[2], Jeffrey R O'Connell[3], Kathleen A Ryan[3], Jerome I Rotter[4], Stephen S Rich[5], Kendra A Young[6], Aaron Hakim[7], Patricia A Peyser[1], Lawrence F Bielak[1], Michelle T Long[8,9], Ching-Ti Liu[10], Elizabeth K. Speliotes[11], Nicholette D Palmer[12] and NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium and the GOLD Consortium, (1)University of Michigan, (2)Washington University School of Medicine in St. Louis, (3)University of Maryland-Baltimore, (4)The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, (5)University of Virginia, (6) University of Colorado Anschutz, (7)Brigham and Women's Hospital, Harvard Medical School, (8)Boston University School of Medicine, (9)Novo Nordisk a/S, (10)Boston University School of Public Health, (11) University of Michigan Medical School, (12)Wake Forest School of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common cause of chronic liver disease in the US. Notably, disease prevalence differs greatly by race/ethnicity, with the highest prevalence in those of Hispanic and Asian ancestry, and the lowest prevalence in those of African ancestry. To date, studies have identified common variants associated with MASLD in predominantly European or American populations. We have conducted the largest-to-date multi-ancestry whole genome sequencing (WGS) association study to identify rare variants that promote MASLD in the NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. **Methods:** Study- and ethnic/race-stratified association analyses were conducted in six cohorts with imaging-measured hepatic steatosis using SAIGEgds adjusted for age, sex, alcoholic drinks per week, and principal component estimates of admixture. Stratified results were meta-analyzed for Hispanic Ancestry, non-Hispanic European Ancestry, non-Hispanic African Ancestry, and non-Hispanic Chinese Ancestry individual's and for an overall analysis using a fixed-effects meta-analysis in METAL. Cochran's Q test and the I2 metric were used to identify and quantify heterogeneity. **Results:** The meta-analysis included 16,664 individual's with imaging-measured hepatic steatosis. Of these, 9,443 were of European Ancestry, 5,918 were of African Ancestry, 937 were of Hispanic Ancestry and 366 were of Chinese Ancestry. The ethnic/race-stratified meta-analysis identified six variants significantly associated ($p < =$5E-08) with MASLD, i.e. European Ancestry (n = 2), African Ancestry (n = 4), including variants in/near PNPLA3, TM6SF2, PPP1R3B, LINC01684, and SLC2A1. An additional 15 variants trended toward association ($p < =$5E-07) i.e. European Ancestry (n = 1), African Ancestry (n = 11), Hispanic Ancestry (n = 2), and Chinese Ancestry (n = 1) with MASLD. **Conclusion:** In a large, multiethnic analysis of imaging-measured hepatic steatosis, we replicated loci previously associated with MASLD and identified possible new race-specific loci. Several variants were trending toward association and will benefit from ongoing analyses to include 6,492 additional samples.

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Elizabeth K. Speliotes:

Disclosure information not available at the time of publication: Yanhua Chen, Mary F Feitosa, Jeffrey R O'Connell, Kathleen A Ryan, Jerome I Rotter, Stephen S Rich, Kendra A Young, Aaron Hakim, Patricia A Peyser, Lawrence F Bielak, Michelle T Long, Ching-Ti Liu, Nicholette D Palmer

191 | NOVEL SERUM METABOLOMIC SIGNATURE OF PNPLA3 HOMOZYGOSITY IN HUMAN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Carolin Victoria Schneider[1], Yazhou Chen[1], Kai M. Schneider[2] and Rohit Loomba[3], (1)Rwth Aachen, (2) Medical Clinic III, Gastroenterology, Metabolic Diseases and Intensive Care, University Hospital Rwth Aachen, Aachen, Germany, (3)University of California, San Diego, San Diego, CA

Background: The patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene is strongly implicated in the development of metabolic dysfunction-associated steatohepatitis (MASH). Gene silencing approaches are being considered for treatment of MASH but there are limited blood-based biomarkers of PNPLA3 homozygosity. There's an unmet need to develop a serum-based biomarker panel that is specific for PNPLA3 homozygosity and could then be used to assess the pharmacodynamics response to PNPLA3 targeted therapies. **Methods:** We examined an extensive lipidomic and metabolomic dataset derived from the UK Biobank (Access number 71300). First, we selected the 4018 homozygous carriers of PNPLA3 rs738409_G. We then performed a 1:1 propensity score matching of non-carriers based on age, sex and BMI. Liver fat content was evaluated by proton density fat fraction on MRI in a subset of UKB participants (n = 323 homozygous and 347 non-carriers). The resulting dataset was split into an

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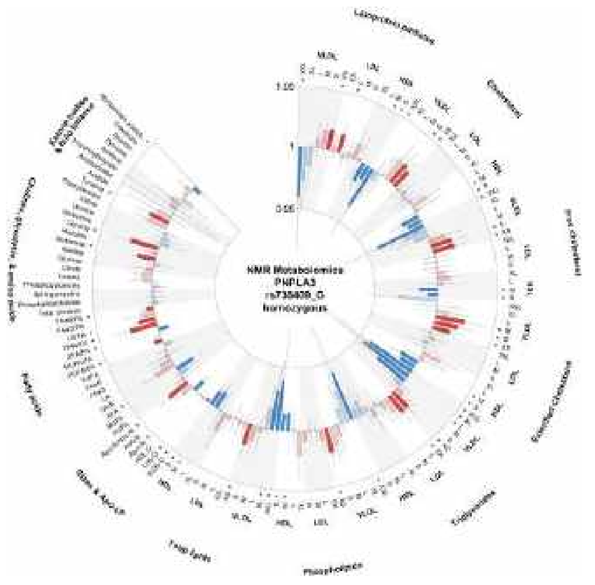
85% training set and a 15% test set. After benchmarking, a random forest machine learning algorithm was chosen as the predictive model, **Results:** The mean liver fat content of PNPLA3 homozygotes versus non-carriers was 8.1% versus 4.3%. The PNPLA3 rs738409_G homozygotes exhibited a distinct metabolic profile compared to non-carriers (Figure 1). In the training cohort, a panel consisting of 9 metabolites and 1 routine hepatic screening parameter including saturated fatty acids to total fatty acids percentage, phospholipids to total lipids in IDL percentage, glutamine, glycine, phospholipids to total lipids in chylomicrons and extremely large VLDL percentage, average diameter for LDL particles, tyrosine, phospholipids to total lipids in very small VLDL percentage, cholesteryl esters to total lipids in small LDL percentage and alanine aminotransferase (ALT) was able to differentiate between PNPLA3 homozygotes versus non-carriers with an AUROC of .90 (95%CI: 0.89-0.90, *p*-value < 0.001), while ALT alone only received an AUROC of **.71** (95%CI: 0.71-0.71, *p*-value < 0.001). The results remained consistent in the validation cohort with a statistically significant AUROC of **.63** (95%CI: 0.63-0.63, *p*-value < 0.001). Among these top 9 differentially expressed metabolites, we examined which increased with liver fat content among participants with PNPLA3 homozygosity and observed that phospholipids to total lipids in IDL percentage, glutamine, average diameter for LDL particles and glycine decreased as the liver fat content increased, while all others increased. **Conclusion:** Here, we demonstrate a novel metabolomics signature of PNPLA3 homozygosity, and a set of metabolites that change with changes in liver fat content among those with PNPLA3 homozygosity. These data have major clinical implications in clinical drug development and companion diagnostics for PNPLA3 targeted therapies. Figure 1: Metabolic profile of PNPLA3 rs738409_G homozygotes compared to non-carriers.



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192 | DYNAMIC EVOLUTION OF CIRCULATING TUMOR DNA IN PATIENTS WITH HEPATOCELLULAR CARCINOMA ACROSS TUMOR STAGES AND TREATMENTS

Claudia Campani[1,2], Sandrine Imbeaud[1], Marianne Ziol[1,3], Pierre Nahon[4,5], Sabrina Sidali[1,6], Alix Demory[1,7], Olivier Seror[8], Valerie Taly[9], Pierre Laurent-Puig[10], Nathalie Ganne-Carrié[1,7], Jessica Zucman-Rossi[4] and Jean-Charles Nault[1,7], (1)Cordeliers Research Center, Inserm 1138, "Functional Genomics of Solid Tumors" Lab, Paris, France, (2)Internal Medicine and Hepatology Unit, Department of Experimental and Clinical Medicine, University of Florence, (3)Anatomopathology Department, Avicenne Hospital, AP-HP, France, (4)Cordeliers Research Center, Functional Genomics of Solid Tumors Team, (5) Avicenne Hospital, Hepatology, (6)Beaujon Hospital, Hepatology, (7)Hepatology Department, Avicenne Hospital, AP-HP, France, (8)Avicenne Hospital, Interventional Radiology, (9)Centre De Recherche Des Cordeliers, Paris, France, (10)Department of Genomic Medicine of Tumours and Cancers, European Hospital George-Pompidou

Background: Circulating tumor DNA (ctDNA) is a promising non-invasive biomarker in cancer management. We aimed to assess the dynamic evolution of ctDNA in patients with hepatocellular carcinoma (HCC). **Methods:** A total of 832 plasmas collected in 173 patients with HCC and 56 patients with chronic liver diseases without HCC were studied. We evaluated the quantity of cell free DNA (cfDNA) and search for mutations in *TERT* promoter (*TERT*p.), *CTNNB1*, *TP53*, *PIK3CA* and *NFE2L2* by ultra-deep next generation sequencing and for *TERT*p. by digital droplet PCR. 250 tumor samples from the same patients were sequenced for 39 driver genes. **Results:** Among the 173 HCC patients, 82% were male (median age 63), 73% had cirrhosis. The etiologies of the underlying liver diseases were hepatitis B (28%), hepatitis C (42%), NAFLD (26%) and chronic alcohol intake (40%). Tumors were classified BCLC 0 (23%), BCLC A (44%), BCLC B (21%) and BCLC C (12%). Tumor sequencing identified mutations in *TERT*p. (71%), *TP53* (28%), *CTNNB1* (27%), *ATM* (15%), *ARID1A*(13%), *ARID2* (8%), *NFE2L2* (2%) and *PIK3CA* (2%). Among

the 776 plasmas of patients with HCC, 502 were collected in patients with an active HCC (aHCC), 158 24 hours after a locoregional treatment and 116 in patients with a past history of HCC but without active HCC at sampling (iHCC). Median cfDNA quantity was higher in aHCC than iHCC (0.27 vs 0.16 ng/μL, $p < 0.001$). Within the 502 plasmas of patients with an aHCC we identified the following mutations in 46% of them (24% patients had normal serum AFP): *TP53* (29%), *TERT*p. (27%), *CTNNB1* (13%), *PIK3CA* (0.4%) and *NFE2L2*(0.2%). CfDNA mutation rate increased across tumor stages (16% BCLC 0, 25% BCLC A, 42% BCLC B and 58% BCLC C; $p < 0.001$). The presence of mutations, particularly in the *TERT*p. and *TP53*, was associated with overall survival and recurrence/progression-free survival, both when considering all plasma samples and in the analysis of various treatment subgroups. Among 116 iHCC plasmas, 26 (22%) had mutations; in 21 cases mutations were concordant with those observed in a previous plasma sample or in a tumor from the same patient. Regarding plasmas obtained before and 24 hours after locoregional treatments an increase in cfDNA level (0.19 before vs 0.63 after, $p < 0.001$) and in mutation rate (31% vs 44%, $p < 0.001$) was observed at H24. Finally, a total of 179 plasmas in 50 patients with unresectable HCC treated by atezolizumab/bevacizumab were analyzed. Baseline cfDNA mutations were observed in 49% of cases; serum AFP was normal in 24% of these patients. Mutations in cfDNA observed at baseline disappeared in all patients with a radiological response at 12 weeks. In contrast, persistence of mutations under treatment was significantly associated with radiological progression ($p = 0.005$). **Conclusion**: Circulating tumor DNA offers dynamic information about tumor biology representing a non-invasive tool potentially useful to guide HCC clinical management.

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193 | SINGLE-NUCLEI TARGETED DNA SEQUENCING REVEALS PATTERNS OF SELECTIVE CLONAL EVOLUTION DURING HEPATOCELLULAR CARCINOMA (HCC) PROGRESSION★

Josephine Zhang[1], *Akanksha Suresh*[1], *Lea Lemaitre*[1], *Rachel Agoglia*[2], *Brittney Otero*[2], *Reshma Reguram*[1], *Vivek Charu*[3], *Brendan Visser*[1], *Andrew Bonham*[1] *and Renumathy Dhanasekaran*[1], *(1)Stanford University, (2) Mission Bio, (3)Stanford University School of Medicine*

Background: Single-cell technologies address the critical issue of tumor heterogeneity in hepatocellular carcinoma (HCC), but face challenges such as complex cell isolation, need for fresh samples, and limited genomic coverage from low DNA content. To overcome these obstacles, we developed a robust workflow for single-nucleus DNA sequencing from frozen HCC tissue, utilizing a custom amplicon panel to elucidate genetic events in HCC clonal evolution. **Methods:** Under IRB approval, we collected eight paired frozen HCC tissue samples from the tumor core and edge of four treatment-naive patients. Enzymatic nuclei extraction generated single-nuclei droplet suspensions, followed by Tapestri platform barcoding, amplicon library creation, and Illumina sequencing (Fig 1A). We curated a consensus panel of HCC-specific genes from five public databases and designed 146 amplicons to target 204 mutations in 44 frequently mutated genes. Our analysis was augmented with bulk DNA sequencing data from six external studies comprising 1122 samples. **Results:** We isolated and genotyped 13,718 nuclei through single-nuclei targeted DNA sequencing, identifying 23 total single-nucleotide variants (SNVs), insertions, and deletions. *TP53, PIK3CA,* and *TRMT9B* were the most frequently mutated and 12 mutations (52%) occurred on chromosome 8. Using the variants identified in each patient, we compared the subclone architecture between the tumor core and edge. The dominant clone in the edge showed a 10.8-fold enrichment (SEM = 3.5) versus the core (Fig 1B). We also examined copy number variations (CNVs) relative to the least mutated clone in each sample and found 10 total CNVs in chromosomes 1, 4, 8, 13, 16, and 17. In five samples, there was a loss in chromosome 17 that corresponded to decreased ploidy of *TP53*. Chromosome 8 was frequently affected by copy number alterations, where *ZFHX4*, *XKR9*, and *ZFAT* were amplified while *ERI1*, *PDGFRL*, and *XPO7* were deleted. These genes are clustered on either chromosome arm, suggesting that partial chromosome deletion contributes to tumor progression (Fig 1C). Our workflow achieved comprehensive coverage of HCC-specific genetic events, as the alterations we identified were present in 50% of patients in the external HCC cohort (n = 1122) (Fig 1D). Moreover, patients with alterations in genes found in the tumor edge had significantly poorer survival rates (median 70.1 vs 83.6 mo, $p = 0.04$). **Conclusion:** In summary, we optimized a novel workflow that enabled in-depth study of intratumoral clonal evolution in HCC through targeted sequencing of 13,718 single nuclei isolated from frozen tissue. We revealed a higher frequency of genetic alterations in the tumor core than edge, indicating the selection of invasive subclones during tumor

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

progression. Our workflow overcomes the obstacles of traditional single-cell studies while achieving high-resolution insights that reflect true genetic alterations driving clonal evolution in HCC.

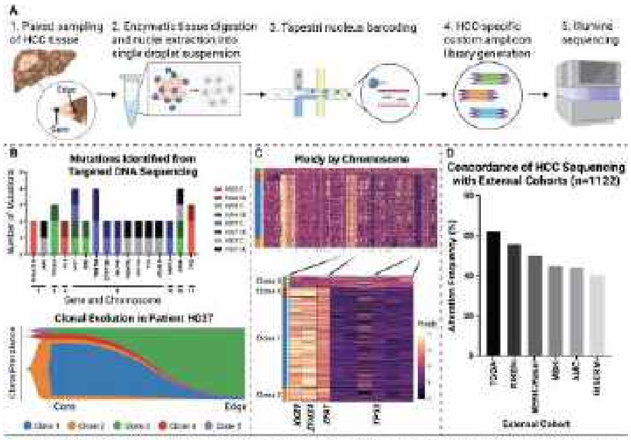

Figure 1. A) Study design: Paired sampling of tumor core and edge from HCC tissue followed by enzymatic tissue digestion and nuclei extraction, Tapestri barcoding, HCC-specific custom amplicon library generation, and Illumina sequencing. B) Mutations (SNVs and indels) were identified in 16 genes and were most prevalent in chromosome 8. Across patients, we observed selection of an invasive clone in the edge, as seen in the representative patient H037. C) CNVs were observed across the genome, primarily as copy number losses. In 5 of 8 samples, there was a copy number loss of *TP53*. Copy number alterations were also prevalent in genes on chromosome 8, including *XKR9*, *ZFHX4*, and *ZFAT*. D) We validated the concordance of our sequencing results with six public bulk sequencing databases and found that 50% of patients in the external cohorts had at least one genetic alteration identified in edge samples.

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194 | TARGETED THERAPY ADAPTED TO TUMOR BIOLOGY IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA OR HEPATOCHOLANGIOCARCINOMA REFRACTORY TO ATEZOLIZUMAB/BEVACIZUMAB

Wendy Limousin[1], Pierre Laurent-Puig[2,3,4], Marianne Ziol[1,5,6], Nathalie Ganne-Carrié[1,7], Pierre Nahon[1,7], Amal Ait-Omar[8], Olivier Seror[1,9], Sabrina Sidali[10], Claudia Campani[1,11], Pierre Blanc[12], Alban Lermine[12], Laetitia Marisa[12], Jessica Zucman-Rossi[1] and Jean-Charles Nault[1,7], (1)Cordeliers Research Center, Functional Genomics of Solid Tumors Team, (2) Cordeliers Research Center, Inserm, Cnrs Snc 5096, (3)Medical Biology Laboratory Seqoia, (4)Department of Genomic Medicine of Tumours and Cancers, European Hospital George-Pompidou, (5)Avicenne Hospital, Pathology, (6)Avicenne Hospital, Centre De Ressources Biologiques, (7)Avicenne Hospital, Hepatology, (8)Avicenne Hospital, Gastroenterology, (9) Avicenne Hospital, Interventional Radiology, (10) Beaujon Hospital, Hepatology, (11)University of Florence, Italy, (12)Medical Biology Labratory Seqoia

Background: The "French Medicine Genomic program 2025" is an academic research program that allows to perform whole-genome/exome/RNA sequencing in advanced cancer refractory to systemic treatments to give access to off-labeled therapies adapted to genomic alterations in clinical practice. We reported results in intermediate and advanced hepatocellular carcinoma (HCC) and hepato-cholangiocarcinoma (H-CCK). **Methods:** In one center, all patients with HCC or H-CCK who progressed under or did not respond to Atezolizumab/Bevacizumab with available tumor frozen samples benefited from whole-genome/exome and RNA sequencing. Targeted therapies were matched to the genomic alterations following recommendation of a molecular tumor board. Subsequent radiological response and overall survival were assessed. **Results:** Between September 2020 and January 2023, among 135 patients with primary liver cancer treated by Atezolizumab/Bevacizumab, twenty patients benefited from genomic analysis after progression (16 HCC; 4 H-CCK). 19 patients had analyzable data, 70% were male, median age was 57 years, 65% had metastatic disease and 45% had vascular invasion. The main driver genes altered in these 19 HCC/HCC-K were *TP53* (47%), *RB1* (37%), *TERT* promoter (32%), *PTEN* (21%), *CCND1/FGF19* amplification (21%), *CTNNB1* (16%), *ARID1A* (16%), *PIK3CA* (16%), *ALB* (16%), *CDKN2A* (11%) and *TSC1* (11%). Mutational signatures of exposure to aflatoxin B1 were identified in 5 patients and of aristolochic acid in1 patient. A high homologous recombination score (defined by a score > 42) in 1 patient. One constitutional variant in *TMEM127* predisposing to pheochromocytoma triggered family screening Among these 19 patients, 14 patients (76%) harbored at least one actionable genomic alteration among whom 9/14 received an adapted targeted therapy (45%). One patient with H-CCK showing *CDK4* amplification was treated by Palbociclib, he experienced a partial radiological response during 16 months. Another patient with H-CCK and high *HER2* overexpression and a high homologous recombination score was treated by Trastuzumab/Olaparib with had a stable disease at the first imaging evaluation. One patient with an HCC and biallelic inactivation of *TSC2* silencing its gene expression, harbored a complete radiological response under Everolimus. The remaining six treated patients (6 HCC) harbored a progressive disease including three patients treated by Trametinib, two by Everolimus and one by Olaparib. **Conclusion:** Molecular based guided therapy is feasible in patients with HCC and H-CCK and progressing under atezolizumab/bevacizumab. Forty-

five percent received a therapy adapted to a genomic alteration with a clinical benefit in one third of them.
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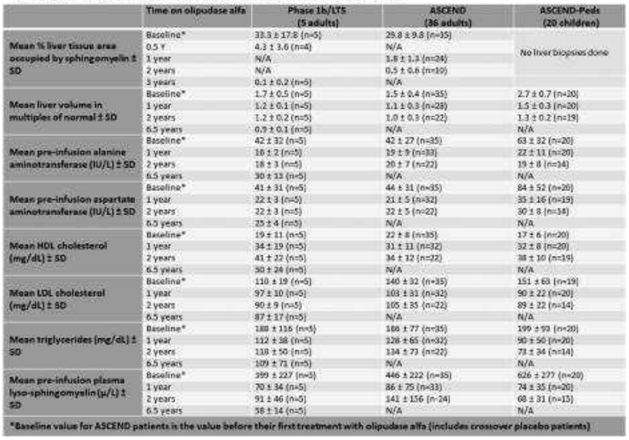
195 | LONG-TERM IMPROVEMENTS IN LIVER AND LIPID OUTCOMES IN ADULTS AND CHILDREN WITH ACID SPHINGOMYELINASE DEFICIENCY TREATED WITH OLIPUDASE ALFA ENZYME REPLACEMENT THERAPY

Beth Linda Thurberg[1], Jaya Ganesh[2], Roberto Guigliani[3], Nathalie Guffon[4], Robin Lachmann[5], Eugen Mengel[6], Maurizio Scarpa[7], Melissa P Wasserstein[8], Mario Aguiar[9], Nicole Armstrong[9] and Monica Kumar[9], (1)Beth Thurberg Orphan Science Consulting, LLC, (2) Mount Sinai School of Medicine, (3)Ufrgs, HCPA, Inagemp, DASA and Casa Dos Raros, (4)Centre De Référence Des Maladies Héréditaires Du Métabolisme, Hôpital Femme Mère Enfant- Hospices Civils De Lyon, (5)Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery, (6)Sphincs Gmbh, Institute of Clinical Science for Lysosomal Storage, (7) Regional Coordinator Centre for Rare Diseases, University Hospital of Udine, (8)Children's Hospital at Montefiore, Albert Einstein College of Medicine, (9) Sanofi

Background: Acid sphingomyelinase deficiency (ASMD) is a progressive, multisystemic, and debilitating lysosomal storage disease. Sphingomyelin accumulation in liver, lungs, and other tissues leads to hepatosplenomegaly, pulmonary disease, liver dysfunction, and dyslipidemia in most patients. Liver disease is a primary cause of death. Olipudase alfa, IV recombinant human ASM (Sanofi), is approved in > 35 countries for non-CNS manifestations of ASMD in adults and children. **Methods:** We report liver and lipid values at baseline and after 2Y of olipudase alfa treatment in ongoing clinical trials and extensions (NCT02004691, NCT02292654 NCT02004704, NCT01722526): ASCEND (35 adults); ASCEND-Peds (20 children); Phase 1b (5 adults, for whom 6.5Y data are also available). We also report Spearman correlations between baseline liver volume and percent liver tissue area occupied by sphingomyelin in all adult patients (Phase 1b and ASCEND). **Results:** Table 1 shows values at baseline and after 1, 2, and 6.5 years of treatment. Liver biopsy data showed ~30% tissue area occupied by sphingomyelin at baseline, with ~90% clearance after 0.5-1Y of olipudase alfa. Percent liver tissue area occupied by sphingomyelin correlated with liver volume in multiples of normal ($r = 0.48$, $p = 0.0017$). Mean baseline plasma lyso-sphingomyelin was > 40x normal in all three cohorts, with 6mo decreases of e 65% sustained over time. At baseline, most patients had hepatomegaly, low HDL cholesterol, high LDL cholesterol, and high triglycerides; approximately half had elevated liver transaminases. After 2Y of treatment, liver volumes in most patients were d 1.25 multiples of normal (mean reductions: 30% in ASCEND, 49% in ASCEND-Peds, 30% reduction in Phase 1b with 44% reduction after 6.5Y) and mean HDL cholesterol had increased 65% in ASCEND, 137% in ASCEND-Peds, and 115% in Phase 1b (171% increase at 6.5Y). Mean LDL cholesterol, triglycerides, and liver transaminases decreased in all cohorts within 1Y to normal/near-normal values and were maintained over time. Spleen volume, respiratory function, disease biomarkers, and in children, height Z-scores, also improved with olipudase alfa treatment. Olipudase alfa was generally safe and well tolerated; most adverse events (AEs) were mild or moderate with no trial withdrawals due to drug-related AEs. **Conclusion:** Olipudase alfa treatment resulted in sustained improvements or normalization in liver and lipid parameters in adults and children with ASMD.

Table 1. Liver and lipid values in clinical trials of olipudase alfa



	Time on olipudase alfa	Phase 1b/LTS (5 adults)	ASCEND (36 adults)	ASCEND-Peds (20 children)
Mean % liver tissue area occupied by sphingomyelin ± SD	Baseline*	33.3 ± 17.8 (n=5)	29.8 ± 9.8 (n=35)	No liver biopsies done
	0.5 Y	4.3 ± 3.6 (n=4)	N/A	
	1 year	N/A	1.8 ± 1.3 (n=24)	
	2 years	N/A	0.5 ± 0.6 (n=10)	
	3 years	0.1 ± 0.2 (n=5)	N/A	
Mean liver volume in multiples of normal ± SD	Baseline*	1.7 ± 0.5 (n=5)	1.5 ± 0.4 (n=35)	2.7 ± 0.7 (n=20)
	1 year	1.2 ± 0.1 (n=5)	1.1 ± 0.3 (n=28)	1.5 ± 0.3 (n=20)
	2 years	1.2 ± 0.2 (n=5)	1.0 ± 0.3 (n=22)	1.3 ± 0.2 (n=19)
	6.5 years	0.9 ± 0.1 (n=5)	N/A	N/A
Mean pre-infusion alanine aminotransferase (IU/L) ± SD	Baseline*	42 ± 32 (n=5)	42 ± 27 (n=35)	63 ± 32 (n=20)
	1 year	16 ± 2 (n=5)	19 ± 9 (n=33)	22 ± 11 (n=20)
	2 years	18 ± 3 (n=5)	20 ± 7 (n=22)	19 ± 8 (n=14)
	6.5 years	30 ± 13 (n=5)	N/A	N/A
Mean pre-infusion aspartate aminotransferase (IU/L) ± SD	Baseline*	41 ± 31 (n=5)	44 ± 31 (n=35)	84 ± 52 (n=20)
	1 year	22 ± 3 (n=5)	21 ± 5 (n=32)	35 ± 16 (n=19)
	2 years	22 ± 3 (n=5)	22 ± 5 (n=27)	30 ± 8 (n=14)
	6.5 years	25 ± 4 (n=5)	N/A	N/A
Mean HDL cholesterol (mg/dL) ± SD	Baseline*	19 ± 11 (n=5)	22 ± 8 (n=35)	17 ± 6 (n=20)
	1 year	34 ± 19 (n=5)	31 ± 11 (n=32)	32 ± 8 (n=20)
	2 years	41 ± 22 (n=5)	34 ± 12 (n=22)	38 ± 10 (n=19)
	6.5 years	50 ± 24 (n=5)	N/A	N/A
Mean LDL cholesterol (mg/dL) ± SD	Baseline*	110 ± 19 (n=5)	140 ± 32 (n=35)	151 ± 63 (n=19)
	1 year	97 ± 10 (n=5)	103 ± 31 (n=32)	90 ± 22 (n=20)
	2 years	90 ± 9 (n=5)	105 ± 35 (n=22)	89 ± 22 (n=14)
	6.5 years	87 ± 17 (n=5)	N/A	N/A
Mean triglycerides (mg/dL) ± SD	Baseline*	188 ± 116 (n=5)	186 ± 77 (n=35)	199 ± 93 (n=20)
	1 year	112 ± 38 (n=5)	128 ± 65 (n=32)	90 ± 50 (n=20)
	2 years	118 ± 50 (n=5)	134 ± 73 (n=22)	73 ± 34 (n=14)
	6.5 years	109 ± 71 (n=5)	N/A	N/A
Mean pre-infusion plasma lyso-sphingomyelin (µ/L) ± SD	Baseline*	399 ± 227 (n=5)	446 ± 222 (n=35)	626 ± 277 (n=20)
	1 year	70 ± 34 (n=5)	86 ± 75 (n=33)	74 ± 35 (n=20)
	2 years	91 ± 46 (n=5)	141 ± 156 (n-24)	68 ± 31 (n=15)
	6.5 years	58 ± 14 (n=5)	N/A	N/A

*Baseline value for ASCEND patients is the value before their first treatment with olipudase alfa (includes crossover placebo patients)

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196 | SERUM Z POLYMER LEVELS AND FACTORS AFFECTING INCREASED LIVER FIBROSIS ARE ASSOCIATED WITH FUTURE SEVERE LIVER DISEASE OUTCOMES IN A PROSPECTIVE COHORT OF ADULTS WITH ALPHA-1-ANTITRYPSIN DEFICIENCY★

Anandini Suri[1], Zidong Zhang[1], Brent Neuschwander-Tetri[1], Rohit Loomba[2], David A. Brenner[3], Andrew Wilson[4], Danielle Carpenter[1], Rosemary Negy[1] and Jeff Teckman[1], (1)Saint Louis University, (2)University of California, San Diego, San Diego, CA, (3)Sanford Burnham Prebys Medical Discovery Institute, (4)Boston University

Background: Outcomes of adults with ZZ alpha-1-antitrypsin deficiency (AATD) liver disease is variable and unpredictable. There is a lack of prospective data,

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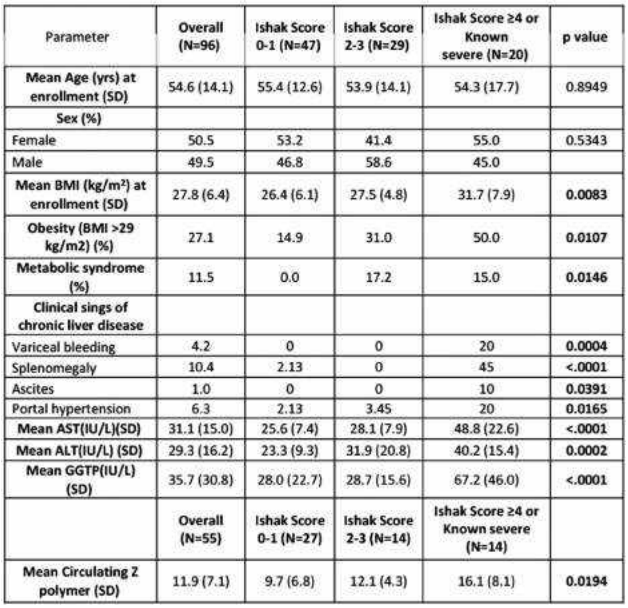
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

including on the utility of liver biopsy. Hypothesis: Prospective clinical and biopsy data will identify factors associated with severe liver disease outcomes in AATD. Objective: Use data from a prospective, multi-center adult cohort of AATD ZZ subjects with protocol enrollment liver biopsies to identify the prognostic value of clinical markers and biopsy for the development of severe liver disease outcomes. **Methods:** Homozygous ZZ AATD adults enrolled prospectively at 3 US sites with standardized clinical evaluations, followed annually with standardized data collection and outcomes recorded. Liver biopsy obtained at enrollment, unless previous biopsy confirmed cirrhosis (grouped as Ishak > 4). Fibrosis scored using Ishak score (stage 0 – stage 6). Minimal fibrosis defined as Ishak 0-1, increased fibrosis as Ishak e 2. Severe liver disease outcomes defined as death related to liver disease, liver transplantation or listing. **Results:** 96 subjects enrolled; 51% had increased fibrosis at enrollment (49% Ishak 0-1, 36% Ishak 2-3, and 15% cirrhotic at enrollment). 62% had normal FEV1 (> 80% predicted), 37% on AAT protein replacement. Serum Z polymer levels were associated with increased fibrosis. Mean serum Z polymer levels increased with the degree of fibrosis (9.7 ±6.8 Ishak 0-1, vs 12.1 ± 4.3 Ishak 2-3, vs 16.1 ± 8.1 for Ishak e 4 ; $p = 0.0194$). Mean BMI and prevalence of obesity increased with degree of fibrosis (Table 1).Clinical signs of advanced liver disease, and relevant elevations in ALT, AST, and GGT were evident with cirrhosis only. 8 severe liver disease related outcomes were reported in median 3.8 years of follow up; 3 liver disease related deaths, 3 liver transplants and 2 on transplant waiting list. All those with significant events had increased fibrosis on enrollment biopsy (100% with severe outcome, vs 46.9% without severe outcome, $p < 0.001$). Increased BMI and obesity were associated with increased fibrosis and liver related events. Serum Z polymer levels were higher in those with future adverse events (18.2 ± 9.2 vs 11 ± 6.3; $p = 0.011$). Low APRI score (< 0.5) and FIB –4 score (< 1.3) had a NPV of 98% in predicting future severe liver disease related events. Elastography scores, FEV1, smoking and alcohol consumption patterns were not associated with significant fibrosis or adverse liver outcomes. **Conclusion:** Significant fibrosis is prevalent in adults with ZZ AATD. Clinical signs of liver disease and elevations of liver enzymes are often delayed until cirrhosis develops. Serum Z polymer levels could be a biomarker to detect fibrosis early and predict outcomes. High BMI and obesity are associated with increased fibrosis and adverse liver disease outcomes. Increased fibrosis at enrollment biopsy is a strong predictor of future severe liver disease outcomes in this cohort.

Table 1 : Factors affecting fibrosis on liver biopsy in adults with ZZ alpha 1 antitrypsin liver disease



Parameter	Overall (N=96)	Ishak Score 0-1 (N=47)	Ishak Score 2-3 (N=29)	Ishak Score ≥4 or Known severe (N=20)	p value
Mean Age (yrs) at enrollment (SD)	54.6 (14.1)	55.4 (12.6)	53.9 (14.1)	54.3 (17.7)	0.8949
Sex (%)					
Female	50.5	53.2	41.4	55.0	0.5343
Male	49.5	46.8	58.6	45.0	
Mean BMI (kg/m²) at enrollment (SD)	27.8 (6.4)	26.4 (6.1)	27.5 (4.8)	31.7 (7.9)	**0.0083**
Obesity (BMI >29 kg/m2) (%)	27.1	14.9	31.0	50.0	**0.0107**
Metabolic syndrome (%)	11.5	0.0	17.2	15.0	**0.0146**
Clinical sings of chronic liver disease					
Variceal bleeding	4.2	0	0	20	**0.0004**
Splenomegaly	10.4	2.13	0	45	**<.0001**
Ascites	1.0	0	0	10	**0.0391**
Portal hypertension	6.3	2.13	3.45	20	**0.0165**
Mean AST(IU/L)(SD)	31.1 (15.0)	25.6 (7.4)	28.1 (7.9)	48.8 (22.6)	**<.0001**
Mean ALT(IU/L) (SD)	29.3 (16.2)	23.3 (9.3)	31.9 (20.8)	40.2 (15.4)	**0.0002**
Mean GGTP(IU/L) (SD)	35.7 (30.8)	28.0 (22.7)	28.7 (15.6)	67.2 (46.0)	**<.0001**
	Overall (N=55)	**Ishak Score 0-1 (N=27)**	**Ishak Score 2-3 (N=14)**	**Ishak Score ≥4 or Known severe (N=14)**	
Mean Circulating Z polymer (SD)	11.9 (7.1)	9.7 (6.8)	12.1 (4.3)	16.1 (8.1)	**0.0194**

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197 | ARBM-101 AS A SAFE AND POTENT THERAPEUTIC OPTION FOR WILSON DISEASE

Eun-Jung Kim[1], Dasol Kim[1], Banu Akdogan[2], Noreene M Shibata[3], Judith Sailer[4], Adriana Fontes[2], Dongsik Park[1], Hongjae Lee[1], Chunwon Jung[1], Byongkeol Min[1], Eok Park[1], TaeWon Kim[1], Seoyoung Choi[1], Alan DiSpirito[5], Bernhard Michalke[2], Weonbin Im[1], So-Young Eun[1], Hans Zischka[2] and Valentina Medici[3], (1) Arbormed Co., Ltd., (2)Helmholtz Center Munich, German Research Center for Environmental Health, (3) University of California Davis, Sacramento, CA, (4) Technical University of Munich, School of Medicine, (5) Iowa State University

Background: Wilson disease (WD) is a rare genetic disorder that can progress to either acute or chronic liver diseases due to excess copper accumulation in the liver derived from disruptive mutations affecting the

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

ATP7B gene with consequent copper metabolism and trafficking disturbances. In current clinical practice, reduction of excess liver copper and amelioration of the subsequent liver pathology by the approved copper chelators is often inadequate. Our recent reports showed the potential of ARBM-101 as a drug candidate that promptly removes excess copper by increasing its fecal excretion through the bile in a WD rat model of severe (acute) liver damage. Here, we extend our studies on the effects of ARBM-101 to a mouse model of chronic liver damage due to spontaneous hepatic copper accumulation. Moreover, we present our evaluation of the ARBM-101 *in vitro* safety profile and further understanding of its mode of action have strengthened its therapeutic potential. **Methods:** To test whether ARBM-101 can protect mice from developing advanced liver damage, a genetic mouse model of WD, the $Atp7b^{-/-}$mouse, was treated i.p. every other day for two weeks followed by maintenance injections every two weeks over 3 months. To test whether ARBM-101 protects animals from acute liver failure and death, LPP rats were treated with ARBM-101 at different disease stages, using several parameters including body weight loss and elevation of liver enzymes to determine disease severity. *In vitro* inhibitor assays were performed to understand entry/exit mechanisms of ARBM-101 in HepG2 cells in the presence or absence of copper. Ceruloplasmin activity assays were also performed using human serum samples. **Results:** Similar to WD rats, the $Atp7b^{-/-}$ mice treated with ARBM-101 showed a pattern of predominant fecal copper excretion with improved parameters of liver damage. Further, we report the rescue of male WD rats, from severe disease stages by ARBM-101, showing normalization of liver enzymes and stabilization of body weight. Ceruloplasmin activity in human sera was not significantly affected by addition of excess ARBM-101 *in vitro*. Potential mechanisms of ARBM-101-mediated copper excretion have been unraveled with involved transporters, including MRP2, as organic anion transporters. **Conclusion:** Our data highlight the excellent therapeutic potential and safety profile of ARBM-101 for acute and chronic liver diseases in WD.

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198 | EVALUATION OF NON-CERULOPLASMIN COPPER BY PROTEIN SPECIATION (NCC-SP) AND 24-HOUR URINARY COPPER EXCRETION (UCE) FOR MONITORING CHELATOR TREATMENT IN PATIENTS WITH WILSON DISEASE.

Peter Ott[1], Thomas Damgaard Sandahl[1], Omar F Kamlin[2], Michael L. Schilsky[3] and On Behalf of The CHELATE Trial Investigators, (1)Aarhus University, (2) Orphalan, (3)Yale University

Background: NCC and UCE are recommended for treatment monitoring in Wilson Disease (WD)(1). NCC is assumed to reflect the bioavailable copper (Cu) in plasma and is in equilibrium with the pool of stored Cu. UCE reflects body stores of Cu and is also influenced by the cupriuretic effect of therapy. Current methods to estimate NCC are flawed. The novel assay, NCC-Sp, is an accurate and reproducible method for NCC determination, and therefore was used as the primary endpoint in the CHELATE trial (NCT03539952, sponsor, Orphalan, France) (2). Our aim was to compare NCC-Sp and UCE in the study population. **Methods:** We performed a secondary analysis on measurements from all specimens from 53 adults with stable WD on d-penicillamine (DPA). Samples were collected for NCC every 4 weeks after screening until the primary endpoint (24w post-randomization) and end of the extension period (48w). UCE was collected at -12w, -8w, -4w, randomization (0w), 4w, 24w and 48w. After a 12-week run-in period, patients were randomized to continue DPA (N = 27) or switched to trientine tetrahydrochloride (TETA4; N = 26) mg-for-mg and followed for 24 weeks. Cu was measured by ICP mass spectrometry. NCC-Sp is the total serum Cu minus ceruloplasmin-Cu as separated by anion exchange chromatography (2). **Results:** Data from 496 NCC-Sp and 296 UCE measurements were analyzed. A large fraction of NCC-Sp (27%) and UCE (58%) values (Figure) were outside recommended target ranges for stable patients (1). Following randomization NCC-Sp declined from 84.4 ± 22.3 to 53.4 ± 18.3 μg/L in the DPA arm and from 67.0 ± 33.1 to 57-6 ± 29.8 μg/L in the TETA4 arm, likely due to further de-coppering, but without correlation between UCE and change in NCC-Sp. UCE and NCC-Sp were weakly correlated, but the correlation was statistically significant (DPA arm: $r^2 = 0.04$, $p = 0.001$; TETA4: $r^2 = 0.12$, $p = 0.0001$). UCE did not correlate with dose (mg/kg) overall; however, UCE/mg dose was higher with DPA (mean ± SD 0.66 ± 0.35 μg/24H/mg dose) compared with TETA4 (0.33 ± 0.18; $p < 0.001$). Following randomization there was no correlation with either NCC-Sp or change in NCC-Sp to dose prescribed. NCC-Sp and not UCE correlated positively to

AST (Figure). The relationship to ALT was similar but weaker (UCE: DPA $r^2 = 0.008$, NS; TETA4 $r^2 = 0.17$, $p = 0.04$. NCC-Sp: DPA: $r^2 = 0.017$, $p = 0.04$; TETA4 $r^2 = 0.023$, $p = 0.02$). **Conclusion:** Though different cupriuretic effects of TETA4 and DPA were observed in the study, a similar overall effect on NCC-Sp indicated copper balance was maintained. NCC-Sp but not UCE correlated with ALT and AST, suggesting its greater utility for monitoring chelator therapy. The large fraction of treated patients outside recommended target ranges for UCE and NCC suggests re-evaluation of target ranges is necessary including correlation with clinical and biochemical outcomes. 1. Schilsky ML et al. Hepatology 2022. 2. Schilsky ML et al. Lancet Gastroenterol Hepatol 2022.

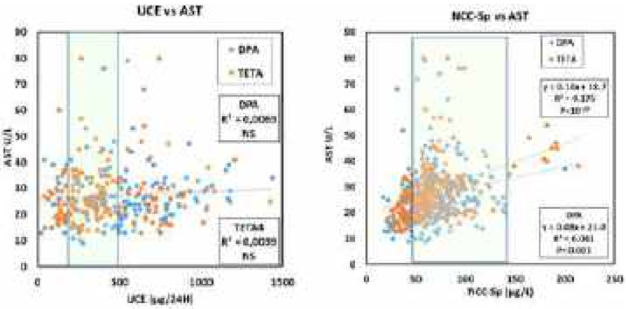

Figure. Panel A: UCE versus ASL. Panel B. NCC-Sp versus AST. In both panels, the currenly recommended (1) ranges for UCE and NCC are marked in shaded green.

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199 | DECREASED PREGNANE X RECEPTOR (PXR) EXPRESSION PROMOTES LIVER NODULE DEVELOPMENT IN Atp7b-/- MICE

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Background: Wilson's disease (WD) is an autosomal recessive disorder caused by inactivating mutations in the copper (Cu^{++}) transporting P-type ATPase. Loss of Atp7b function prevents translocation of Cu^{++} into the trans-Golgi network and excretion into bile. Cu^{++} exposure results in oxidative stress, inflammation, and mitochondrial dysfunction and fibrosis, cirrhosis, and liver failure. WD patients and *Atp7b*$^{-/-}$ mice have a progressive course of hepatocellular pathology, which includes regenerative hepatic nodule growth. An abundance of pregnane X receptor (PXR) response elements were recently identified in down-regulated gene sets identified by microarray analysis in pre-symptomatic *Atp7b*$^{-/-}$ mice, suggesting a link between xenobiotic and metabolic pathways in WD. Further, PXR mRNA expression was decreased in *Atp7b*$^{-/-}$ mice. We tested the hypothesis that decreased PXR activity exacerbates the progressive hepatic pathology in *Atp7b*$^{-/-}$ mice. **Methods:** H&E, Ki-67, and CK-19 staining was performed on liver sections of *Atp7b*$^{-/-}$, DKO$^{Atp7b/PXR}$, and

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

wild-type mice. RNA-Sequencing analysis was performed with 3-, 6-, and 12-month-old liver tissues from $Atp7b^{-/-}$, $DKO^{Atp7b/PXR}$, and wild-type mice. **Results:** Hepatocellular pathology and liver nodule development was more advanced in $DKO^{7b:PXR}$ mice vs. $Atp7b^{-/-}$ mice. At 12 months of age $DKO^{Atp7b:PXR}$ and $Atp7b^{-/-}$ livers displayed prominent histologic abnormalities including mild microsteatosis, hepatocellular ballooning, apoptosis, and mild lobular inflammation. H&E staining revealed clear demarcation between nodules and normal tissue. Nodules of $Atp7b^{-/-}$ mice displayed more Ki-67 staining than the adjacent normal tissue (Ki-67 index 5.5% normal tissue vs. 28% nodule). Ki-67 staining in nodules of $DKO^{Atp7b:PXR}$ livers was less than $Atp7b^{-/-}$ mice, which is suggestive of dynamic molecular shifts to limit further cell proliferation. Normal tissue areas in the $Atp7b^{-/-}$ and $DKO^{Atp7b:PXR}$ livers displayed increased and diffuse glutamine synthetase (GS) staining, which is characteristic of hepatocellular stress; however, normalized GS staining around the central vein was displayed in adjacent nodular sections. $Atp7b^{-/-}$ and $DKO^{Atp7b:PXR}$ livers displayed increased CK-19 staining and ductular reaction with bile duct proliferation and inflammation. Chemical Carcinogenesis, Metabolic, PPAR Signaling, and Cell Signaling pathways were enriched in 3-, 6-, and 12-month-old $Atp7b^{-/-}$ mice. We found unique and abundant enrichment of pathways related to protein metabolism and cytoskeleton regulation in $DKO^{Atp7b:PXR}$ relative with $Atp7b^{-/-}$ mice. Pathway analysis of nodules revealed an abundance of immune function and cell adhesion pathways in nodules of $DKO^{Atp7b:PXR}$ relative to nodules of $Atp7b^{-/-}$ mice. **Conclusion:** Impaired PXR activity increases copper-induced hepatocellular pathology. These findings reveal a new target in the development of hepatic pathology in WD.

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200 | METABOLIC SYNDROME ASSOCIATED FATTY LIVER DISEASE IS A SIGNIFICANT RISK FACTOR FOR THE DEVELOPMENT OF HEPATIC EVENTS IN ALPHA-1-ANTITRYPSIN PI*ZZ INDIVIDUALS

Aron Zachary Evans[1], *Sameer Prakash*[1] *and Arvind R. Murali*[1,2], *(1)University of Iowa Hospitals and Clinics, (2) Orlando Health*

Background: Patients with Alpha-1-antitrypsin Pi*ZZ homozygotes are at risk for developing liver cirrhosis and hepatocellular carcinoma. However, there is a high degree of variability in the clinical manifestations of patients with A1AT Pi*ZZ suggesting that genetic and environmental disease modifiers play an important role in the disease process. The prevalence of nonalcoholic fatty liver disease (NAFLD) has been rising worldwide. We aimed to determine the impact of NAFLD in the development of hepatic events in patients with A1AT Pi*ZZ homozygotes. **Methods:** All patients with A1AT Pi*ZZ homozygous state seen at a large tertiary care academic institution were identified using the data pooling technique by the information and technology department at University of Iowa Hospitals and Clinics. Patients with NAFLD were identified using ICD codes. Clinical and demographic data as well as hepatic events (ascites, hepatic encephalopathy, esophageal varices, or hepatocellular carcinoma), if any, were also extracted. Logistic regression analysis was performed to determine the impact of NAFLD in the development of hepatic events in patients with A1AT ZZ. Odds ratio (OR) with 95% confidence intervals were calculated. **Results:** We identified 53 patients with A1AT ZZ phenotype, 29 (55%) were males. Twenty (38%) of the 53 A1AT ZZ patients had a diagnosis of NAFLD. Of the 53 patients, 14 (26%) developed hepatic events. Eleven (55%) of the 20 patients with A1ATD and NAFLD developed hepatic events, while only 3 (9%) of the 33 patients with A1ATD and without NAFLD developed hepatic events ($p < 0.001$). On logistic regression analysis, NAFLD was significantly associated with the development of hepatic events in patients with A1AT Pi*ZZ, unadjusted OR 12.2 (CI: 2.78-53.6), $p < 0.001$). When adjusted for age, sex, and BMI, NAFLD remained a significant risk factor for the development of hepatic events in patients with Pi*ZZ with an adjusted OR 15.2, (CI: 2.5-94.4), $p = 0.003$. **Conclusion:** A1AT ZZ homozygous individual's who also develop NAFLD have a higher risk for the development of hepatic events as compared to those who do not have NAFLD. A1AT ZZ patients should thus be screened for the presence of fatty liver disease and aggressive control of metabolic risk factors should be initiated. A1AT ZZ patients should be strongly advised to avoid weight gain and follow a healthy lifestyle as early in life as possible. Larger studies are needed to confirm our findings.

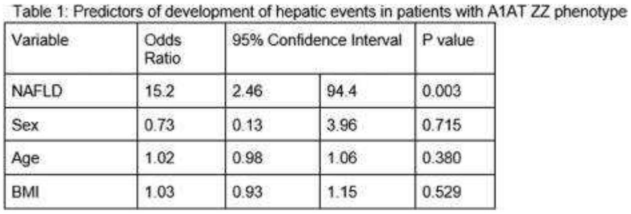

Table 1: Predictors of development of hepatic events in patients with A1AT ZZ phenotype

Variable	Odds Ratio	95% Confidence Interval		P value
NAFLD	15.2	2.46	94.4	0.003
Sex	0.73	0.13	3.96	0.715
Age	1.02	0.98	1.06	0.380
BMI	1.03	0.93	1.15	0.529

Disclosures: The following people have nothing to disclose: Aron Zachary Evans, Sameer Prakash, Arvind R. Murali

201 | THREE-DIMENSIONAL MR ELASTOGRAPHY IDENTIFIES PORTAL HYPERTENSION IN CIRRHOSIS: A PROSPECTIVE MULTICENTER STUDY

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Background: To develop a non-invasive multivariate models based on Three-dimensional MR elastography (3D-MRE) to determine portal hypertension (PH), particularly to diagnose clinically significant portal hypertension (CSPH, HVPG > 10mmHg) and severe portal hypertension (SPH, HVPG > 12mmHg), using HVPG as the gold standard. **Methods:** This prospective, multicenter study enrolled patients with cirrhosis scheduled for HVPG, and who intended to undergo MR imaging (including 3D-MRE and diffusion-, T1-, and T2-weighted imaging) before the HVPG procedure. A total of 57 patients were recruited from five institutions. Multiple viscoelastic parameters of the liver and spleen, as well as shear stiffness (SS) ratios and subtraction values, were evaluated independently by two radiologists. Univariable and multivariable linear regression analyses were conducted to assess the associations between mechanical parameters and HVPG. Univariable and multivariable logistic regression analyses were used to predict CSPH and SPH, respectively. **Results:** HVPG showed the strongest positive correlation with splenic SS at 60Hz (r = 0.785; *p* < 0.001), followed by hepatic SS at 30Hz (r = 0.631; *p* < 0.001), splenic SS at 30Hz (r = 0.612; *p* < 0.001), hepatic SS at 60Hz (r = 0.547; *p* < 0.001). Multivariable linear regression analysis showed splenic SS at 60Hz (β = 1.017; 95% CI: 0.71, 1.325; *p* < 0.001), liver SS ratio (β = -2.359; 95% CI: -4.477, -0.241; *p* = 0.03), and liver stiffness difference (β = 1.169; 95% CI:0.251,2.087; *p* = 0.001) was the independent factors determining HVPG. Approximately 56.5% of the total variability in HVPG was explained by these 3 variables (adjusted R 2 = 0.565). Logistic regression analysis showed splenic SS at 60Hz (OR = 2.217 [95% CI:1.292, 3.803]; *p* = 0.004) and liver SS at 30Hz (OR = 6.211 [95% CI: 1.218, 31.669]; *p* = 0.028) were independently associated with CSPH, establishing a model with excellent performance in diagnosing CSPH(area under the receiver operating characteristic curve [AUC], 0.975 [95% CI: 0.79, 0.99]). As for SPH, it showed splenic SS at 60Hz (OR = 1.65 [95% CI:1.25,2.16]; *p* = 0.001) were independently associated with HVPG, also with better performance (AUC, 0.969 [95% CI: 0.81, 0.98]). **Conclusion:** 3D-MRE with dual frequencies is a very promising method in both predicting HVPG and diagnosing the presence CSPH and SPH. Splenic stiffness at 60Hz, combining liver stiffness ratio (60Hz/30Hz) and differences (60Hz-30Hz), was the independent parameters associating HVPG.

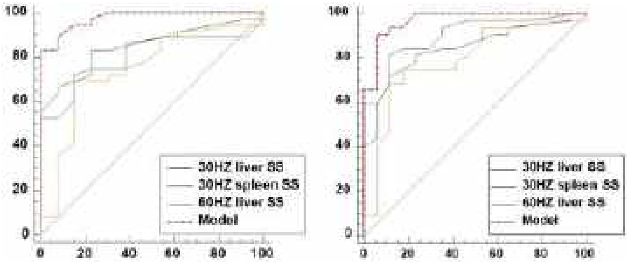

Figure 1 (A-B) ROC analysis for diagnosing clinically significant portal hypertension (A) and severe portal hypertension (B)

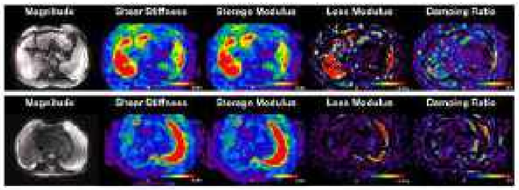

Figure 2 (A-B) Representative Magnetic Resonance Elastography (MRE) images at 60Hz for two patients. The top row shows MRE images for a patient with hepatic shear stiffness of 6.5 kPa and splenic shear stiffness of 6.1 kPa, with a HVPG measurement of 11 mmHg. The bottom row shows MRE images for a patient with hepatic shear stiffness of 3.5 kPa (mildly elevated) and splenic shear stiffness of 12.6 kPa, with a HVPG measurement of 18 mmHg. The HVPG result is more strongly correlated with the splenic shear stiffness than that of the liver stiffness.

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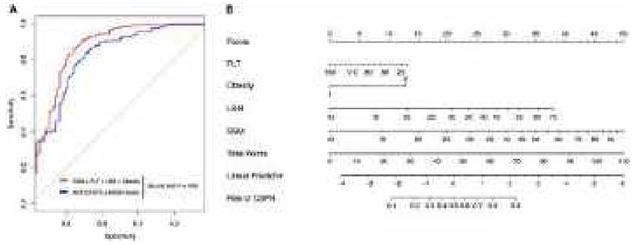
202 | SPLEEN STIFFNESS MEASUREMENT BY A DEDICATED 100Hz VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY PROBE IMPROVES THE NON-INVASIVE DIAGNOSIS OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION IN A PROSPECTIVE MULTICENTER STUDY

Mathias Jachs[1], Petra Fischer[2], Aitor Odriozola[3], Lucile Moga[4,5], Wilhelmus J. Kwanten[6], Dario Saltini[7], Fanny Turon[8], Angelo Armandi[9,10], Yuly Paulin Mendoza[11], Elba Llop[12], Maria Grasso[13], Emma Vanderschueren[14], Julia Thalhammer[15], Carlos Pardo[8], Lotte Schoenmakers[6], Georg Semmler[1], Lukas Hartl[15], Wim Laleman[14], Vincenza Calvaruso[16], Jose Luis Calleja[12], Annalisa Berzigotti[17], Jörn M. Schattenberg[18], Juan Carlos Garcia-Pagan[8], Filippo Schepis[7], Antonio Colecchia[7], Sven Francque[19], Pierre-Emmanuel Rautou[4,5], Ángela Puente[3], Jose Ignacio Fortea[3], *Bogdan Procopet[2], Thomas Reiberger[15] and Mattias Mandorfer[20], (1)Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria, (2)Luliu Hatieganu University of Medicine and Pharmacy, 400012 Cluj-Napoca, Romania, (3)Marqués De Valdecilla University Hospital, (4)Université Paris-Cité, (5)Hôpital Beaujon, (6)University of Antwerp, (7) University of Modena & Reggio Emilia and Azienda Ospedaliero-Universitaria Di Modena, (8)University of Barcelona, (9)Department of Medical Sciences, University of Torino, (10)University Medical Center Mainz, (11)Bern University Hospital, University of Bern, (12)Universidad Autonoma De Madrid, (13)University of Palermo, (14)University Hospitals Leuven, (15)Medical University of Vienna, (16)Gastroenterology & Hepatology Unit, Department of Health Promotion, Mother & Child Care, Internal Medicine & Medical Specialties (PROMISE), University of Palermo, Palermo, Italy, (17)Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, (18)University of Mainz, (19)Translational Sciences in Inflammation and Immunology, Laboratory of Experimental Medicine and Paediatrics, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium, (20)Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna*

Background: Non-invasive diagnostic tools for clinically significant portal hypertension (CSPH) have been developed in the ANTICIPATE study/subsequent work (liver stiffness measurement (LSM) and platelet count (PLT) ± BMI) and endorsed by the Baveno VII consensus. A dedicated 100Hz probe for spleen stiffness measurement (SSM) substantially increased its clinical applicability, but limited data exists on the diagnostic performance of SSM (100Hz) for CSPH as well as its ability to improve the ANTICIPATE ± NASH models. **Methods:** Twelve specialized, high-volume European centers contributed data from prospectively characterized compensated advanced chronic liver disease (cACLD, defined by LSM e 10kPa or F3/4 fibrosis) patients who underwent paired assessment of the hepatic venous pressure gradient (HVPG), LSM, and SSM from 2021-2023. The goal was to refine the non-invasive diagnosis of CSPH by adding SSM to LSM/PLT ± BMI, and to compare the algorithm's diagnostic performance to the ANTICIPATE ± NASH models. In line with previous work, the analysis was restricted to patients with Child-Turcotte-Pugh A stage disease. All area under the receiver operating characteristics curve (AUC) analyses were derived from bootstrapping ($n = 2000$). **Results:** Overall, 244 cACLD patients were included. Most had NAFLD (40.2%) or ALD (36.1%), followed by viral (14.8%) and other (8.9%) etiologies. The median BMI was 28.9 (IQR: 24.8; 33.6) kg/m^2, and 43.0% were obese (BMI e 30). The median HVPG was 11 (8; 15) mmHg (CSPH prevalence: 64.8%), and the median LSM, SSM and PLT were 22.5 (14.8; 33.2)kPa, 45.6 (33.0; 66.5)kPa, and 129 (92; 183)G/L, respectively. SSM and LSM yielded a comparable AUC for CSPH (SSM: 0.778, LSM: 0.755, DeLong-test: $p = 0.546$). In logistic regression analysis, SSM, LSM, PLT and obesity (BMI e 30) were independently associated with CSPH. The combined model had an AUC for CSPH diagnosis of 0.864. Notably, its diagnostic performance was superior to the ANTICIPATE ± NASH model (AUC: 0.814, DeLong test: $p = 0.008$). A nomogram was developed to facilitate point-of-care risk stratification (Figure). Results were confirmed by cross-validation after randomly splitting the data into a 1:1 train/test cohort matched by CSPH prevalence (data not shown) **Conclusion:** SSM by the novel, dedicated 100Hz module improves the non-invasive diagnosis of CSPH vs. established tools, which tend to be slightly less accurate in the context of contemporary (predominantly NAFLD/ALD) cohorts.



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Disclosure information not available at the time of publication: Lotte Schoenmakers, Juan Carlos Garcia-Pagan, Filippo Schepis, Antonio Colecchia, Jose Ignacio Fortea

203 | PLACEMENT OF A TRANS-JUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS) MODIFIES THE EXPRESSION OF PROINFLAMMATORY CYTOKINES IN CIRCULATING MONOCYTES EXPOSED TO LIPOPOLYSACCARIDE

Mirella Pastore, Francesco Vizzutti, Nadia Navari, Davide Roccarina, Martina Rosi, Valentina Adotti and Fabio Marra, University of Florence

Background: Recent data have indicated that decompensated cirrhosis is characterized by an imbalance in the innate immune system, leading to low-grade systemic inflammation. In particular, inflammatory cytokines secreted by monocytes and macrophages have been implicated in the pathogenesis of portal hypertension and its complications. Additionally, MerTK-expressing monocytes participate in the determination of severity of acute liver failure. Trans-jugular intrahepatic portosystemic shunt (TIPS) is currently used for the treatment of complications of portal hypertension, but whether portosystemic derivation results in changes in the biology of inflammatory cell is currently unknown. **Methods:** Fifteen patients with severe portal hypertension referred for TIPS placement were enrolled. During the TIPS procedure, blood from the portal and jugular vein was drawn, and at 4 weeks after TIPS placement a sample from a peripheral vein was repeated. Monocytes were isolated from peripheral blood mononuclear cells by adherence after Ficoll-Hypaque purification, and stimulated with LPS (1 μg/ml) for 2, 8 and 24 hours. Gene expression was evaluated by real-time PCR. **Results:** Upon exposure to LPS, a significant increase in gene expression of IL-1beta, IL-6, TLR4 and MERTK was observed in monocytes isolated from either the portal or the jugular vein. Basal and LPS-stimulated mRNA levels of these molecules were markedly lower in the post-TIPS compared to pre-TIPS, in particular after exposure to LPS. Expression of the anti-inflammatory cytokine, IL-10, was significantly increased after LPS stimulation for 2 and 8 hours. After TIPS, mRNA levels of IL-10 were reduced in unstimulated conditions but increased after LPS stimulation for 2 hours. **Conclusion:** Reduction of portal pressure through TIPS placement is associated with reduced expression of pro-inflammatory mediators and modulation of anti-inflammatory IL-10. Increased portal pressure in cirrhotic patients may be a direct modulator of the complex changes in the inflammatory balance observed in these patients.

Disclosures: Francesco Vizzutti – Gore: Speaking and Teaching, No, No;

Fabio Marra – Gore: Speaking and Teaching, No, No;

The following people have nothing to disclose: Mirella Pastore, Nadia Navari, Davide Roccarina, Martina Rosi, Valentina Adotti

204 | INCREASING LIVER STIFFNESS VALUES ABOVE 20 KILOPASCALS ARE ASSOCIATED WITH HIGHER RISKS OF DECOMPENSATED CIRRHOSIS AND MORTALITY BUT NOT HCC

Philip Vutien[1,2], Nicole J. Kim[2,3], Joleen A Borgerding[2], Kay Johnson[4], Kristin Berry[2], Lauren A. Beste[1,5] and George Ioannou[2,6], (1)University of Washington, (2) *Veterans Affairs Puget Sound Healthcare System, (3) University of Washington, Seattle, WA, (4)Veterans Affairs Puget Sound Health Care System, (5)VA Puget Sound Healthcare System, (6)University of Washington Medical Center*

Background: FibroScan®-derived liver stiffness (LS) values above a threshold of 20 kilopascals (kPa) has been used to guide endoscopic screening for gastroesophageal varices. However, there is limited data on the clinical significance of LS values above this threshold. We aimed to assess whether LS values e 20 kPa are associated with death, decompensation, and hepatocellular carcinoma (HCC). **Methods:** We identified 20,776 patients who underwent Fibroscan LS measurement since 1/2014 at the Veterans Affairs Healthcare System and after excluding those with HCC, decompensation (ascites, hepatic encephalopathy, or gastro-esophageal variceal bleeding), or liver transplantation prior to LS measurement. Baseline characteristics were ascertained within 1 year prior to LS date. Patients were followed from LS date until 1/2022 for death, hepatic decompensation, variceal bleeding alone, and HCC. We used multivariable Cox proportional hazards regression to determine the association between LS measurements and these outcomes. **Results:** Among the 20,776 patients, 95.5% were male and mean age was 63.8 ± 9.6 years. LS values were $<$ 20 kPa in 17,175 (82.7%), 20 to $<$ 40 kPa in 2,724 (13.1%), 40 to $<$ 60 kPa in 470 (2.3%) and 60 to 75 kPa in 407 (2%). The etiology of liver disease was due to chronic hepatitis C infection in 50.2%, non-alcoholic fatty liver disease in 22.2%, and alcohol-related liver disease in 10.6%. Over a mean follow-up of 2.6 ± 1.8 years after LS date, 2,635 patients died, 1,106 had hepatic decompensation (of whom 211 had variceal bleeding), and 815 were diagnosed with HCC. Compared to those with LS values 20 to $<$ 40 kPa, risk of mortality, decompensation, and variceal bleeding was lower for those with LS $<$ 20 kPa and higher across increasing LS groups (Table). With regards to HCC incidence, compared to those with LS 20 to $<$ 40 kPa (2.6 per 100 Person-Years [P-Ys]), the incidence was higher for those with 40 $<$ 60 kPa (3.9 per 100 P-Ys) but not 60 to 75 kPa (2.3 per 100 P-Ys). On multivariable analysis, compared to the referent LS group 20 to $<$ 40 kPa, those in the 40 to $<$ 60 kPa and 60 to 75 kPa groups had significantly higher risks of death (aHRs 1.46 [95% CI 1.10-1.94] and 2.04 [95% CI 1.50-2.77]), decompensation (aHRs 2.04 [95% CI 1.46-2.87] and 3.80 [95% CI 2.82-5.11]), variceal bleeding (aHRs 3.43 [95% CI 1.96-5.97] and 2.94 [95% CI 1.66-5.21]), but not HCC (aHRs 1.23 [95% CI 0.82-1.84] and 0.87 [95% CI 0.51-1.47]). Compared to those with LS 20 to $<$ 40 kPa, those with LS $<$ 20 kPa had significantly lower risks of mortality (aHR 0.62 [95% CI 0.54-0.71]), decompensation (aHR 0.40 [95% CI 0.33-0.49]) and HCC (aHR 0.44 [95% CI 0.35-0.55]). **Conclusion:** Compared to a referent group of 20-40 kPa, higher LS values are associated with increased risk of death, decompensation, and variceal bleeding. Higher LS values beyond this referent group are not associated with an increased risk of HCC. Lower LS ($<$ 20 kPa) is associated with lower risk of all outcomes.

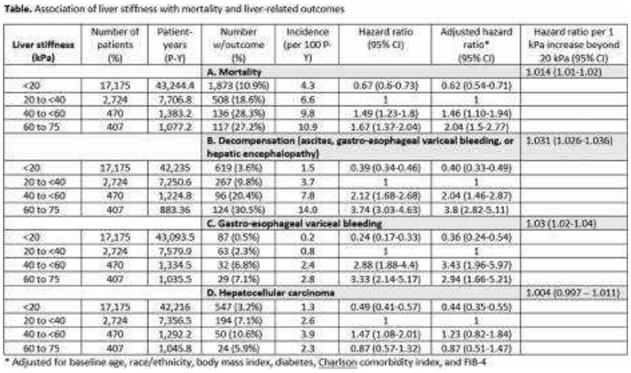

Table. Association of liver stiffness with mortality and liver-related outcomes

Liver stiffness (kPa)	Number of patients (%)	Patient-years (P-Y)	Number w/outcome (%)	Incidence (per 100 P-Y)	Hazard ratio (95% CI)	Adjusted hazard ratio* (95% CI)	Hazard ratio per 1 kPa increase beyond 20 kPa (95% CI)
			A. Mortality				1.014 (1.01-1.02)
<20	17,175	43,244.4	1,873 (10.9%)	4.3	0.67 (0.6-0.73)	0.62 (0.54-0.71)	
20 to <40	2,724	7,706.8	508 (18.6%)	6.6	1	1	
40 to <60	470	1,383.2	136 (28.3%)	9.8	1.49 (1.23-1.8)	1.46 (1.10-1.94)	
60 to 75	407	1,077.2	117 (27.2%)	10.9	1.67 (1.37-2.04)	2.04 (1.5-2.77)	
			B. Decompensation (ascites, gastro-esophageal variceal bleeding, or hepatic encephalopathy)				1.031 (1.026-1.036)
<20	17,175	42,235	619 (3.6%)	1.5	0.39 (0.34-0.46)	0.40 (0.33-0.49)	
20 to <40	2,724	7,250.6	267 (9.8%)	3.7	1	1	
40 to <60	470	1,224.8	96 (20.4%)	7.8	2.12 (1.68-2.68)	2.04 (1.46-2.87)	
60 to 75	407	883.36	124 (30.5%)	14.0	3.74 (3.03-4.63)	3.8 (2.82-5.11)	
			C. Gastro-esophageal variceal bleeding				1.03 (1.02-1.04)
<20	17,175	43,093.5	87 (0.5%)	0.2	0.24 (0.17-0.33)	0.36 (0.24-0.54)	
20 to <40	2,724	7,579.9	63 (2.3%)	0.8	1	1	
40 to <60	470	1,334.5	32 (6.8%)	2.4	2.88 (1.88-4.4)	3.43 (1.96-5.97)	
60 to 75	407	1,035.5	29 (7.1%)	2.8	3.33 (2.14-5.17)	2.94 (1.66-5.21)	
			D. Hepatocellular carcinoma				1.004 (0.997 – 1.011)
<20	17,175	42,216	547 (3.2%)	1.3	0.49 (0.41-0.57)	0.44 (0.35-0.55)	
20 to <40	2,724	7,356.5	194 (7.1%)	2.6	1	1	
40 to <60	470	1,292.2	50 (10.6%)	3.9	1.47 (1.08-2.01)	1.23 (0.82-1.84)	
60 to 75	407	1,045.8	24 (5.9%)	2.3	0.87 (0.57-1.32)	0.87 (0.51-1.47)	

* Adjusted for baseline age, race/ethnicity, body mass index, diabetes, Charlson comorbidity index, and FIB-4

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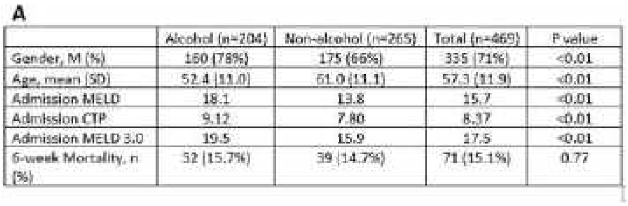
205 | ALCOHOL-RELATED CIRRHOSIS EXPERIENCES LOWER 6-WEEK MORTALITY AFTER ACUTE VARICEAL BLEEDING COMPARED TO OTHER ETIOLOGIES USING A LARGE PROPENSITY SCORE MATCHED INTERNATIONAL COHORT

Adam Buckholz[1], Yu JUN Wong[2], Rochelle Wong[3], Michael P. Curry[4], Gyorgy Baffy[5], Erik Chak[6], Tarun Rustagi[7], Le Shaun Ang[8], Wen Hui Leia Teo[8], Arpan Mohanty[9] and Brett Fortune[10], (1)New York Presbyterian Hospital Program, (2)Department of Gastroenterology & Hepatology, Changi General Hospital, Singapore, (3)Weill Cornell Medicine, NY, (4) Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (5)VA Boston Healthcare System, (6)Univ of California Davis School of Medicine, (7)California Pacific Medical Center, (8)Changi General Hospital, (9)Boston University School of Medicine, (10) Montefiore Medical Center

Background: Acute variceal bleeding (AVB) is a cause of serious morbidity and mortality in cirrhosis. While more severe disease (e.g. higher Child-Turcotte-Pugh [CTP] score) has been shown to correlate with worse outcomes after AVB, it is unclear if this correlation remains universal across all cirrhosis etiologies. Using a large multinational cohort of AVB patients, this study aims to compare the 6-week mortality after AVB between alcohol-related (AR) and non-alcohol-related (NAR) cirrhosis patients, adjusting for CTP score. **Methods:** Patients with cirrhosis hospitalized for AVB from 2012-2020 were retrospectively identified from 7 hospitals in the US and Singapore. Those receiving pre-emptive TIPS or liver transplant were excluded. AR cirrhosis was defined based on significant alcohol history during medical chart review. All patients were managed with endoscopy, antibiotics, and vasoactive therapy. The primary outcome was 6-week mortality (Baveno 6). A quasi-experimental method, using propensity score matching with the nearest 3 neighbors and maximum caliper distance of 0.1, was performed in a logit model, adjusting for age, gender, and CTP score. This was iteratively performed to evaluate the average treatment effect on the treated (ATET: the estimated causal effect of a variable [AR cirrhosis] on the observed difference in outcomes) in all patients, those with advanced disease (CTP > 7), and those with CTP C 10-13 or CTP B with active hemorrhage on endoscopy, where a negative ATET value represents 6-week mortality benefit. **Results:** A total of 469 patients (204 [44%] with AR disease) were included. The baseline characteristics were similar across sites with the exception that the Singapore cohort was older, had less alcohol use, and had more HBV-related cirrhosis. The AR cirrhosis cohort had more men, lower age, and higher admission MELD/CTP/MELD 3.0 scores. Overall 6-week mortality was 15% with no differences between AR and NAR cirrhosis ($p = 0.77$, [Fig A]). Adjusting for CTP score, AR cirrhosis was associated with lower 6-week mortality risk (OR 0.49, 95% CI 0.27-0.90, $p = 0.02$) [Fig B]. After propensity matching with age, gender and CTP score, there was a significant mortality reduction from AR cirrhosis etiology among those with CTP B and active bleeding or CTP C (n = 199, ATET -0.23, 95% CI -0.35, -0.10, $p < 0.01$) as well as those with CTP > 7 (n = 272, ATET -0.16, 95% CI -0.31, -0.01, $p = 0.04$). The overall beneficial effect from having AR cirrhosis compared to other etiologies neared significance (n = 469, ATET -0.09, 95% CI -0.20, +0.02, $p = 0.10$). **Conclusion:** In a large multinational cohort of patients with AVB who did not undergo TIPS, we found that patients with AR cirrhosis have lower 6-week mortality than those with other etiologies, particularly at higher CTP scores. This highlights the importance of underlying disease etiology on AVB outcomes and warrants further investigation to elucidate the impact of therapeutics on these subgroups.



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	Alcohol (n=204)	Non-alcohol (n=265)	Total (n=469)	P value
Gender, M (%)	160 (78%)	175 (66%)	335 (71%)	<0.01
Age, mean (SD)	52.4 (11.0)	61.0 (11.1)	57.3 (11.9)	<0.01
Admission MELD	18.1	13.8	15.7	<0.01
Admission CTP	9.12	7.80	8.37	<0.01
Admission MELD 3.0	19.5	15.9	17.5	<0.01
6-week Mortality, n (%)	32 (15.7%)	39 (14.7%)	71 (15.1%)	0.77

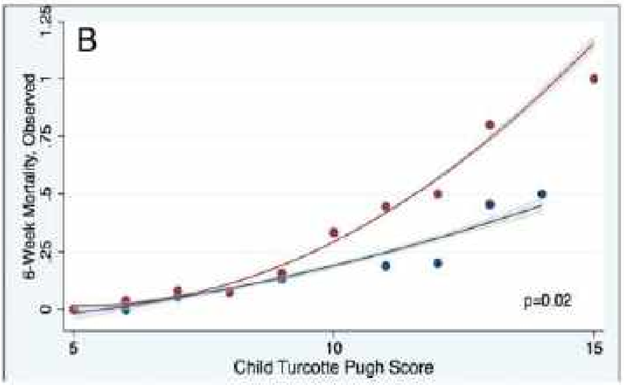

Figure: [A] Baseline characteristics of those with and without alcohol-related cirrhosis. [B] Scatter plot demonstrating observed 6-week mortality at each CTP Score. At higher CTP score, those with alcohol-related cirrhosis (BLUE) have significantly lower rate of 6-week mortality when compared to non-alcohol etiologies (RED, p-value = 0.02).

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The following people have nothing to disclose: Adam Buckholz
Disclosure information not available at the time of publication: Rochelle Wong, Gyorgy Baffy, Erik Chak, Tarun Rustagi, Le Shaun Ang, Wen Hui Leia Teo, Arpan Mohanty

206 | CARVEDILOL PLUS NUCS TO PREVENT THE PROGRESSION OF ESOPHAGEAL VARICES IN VIROLOGICAL SUPPRESSED HBV-CIRRHOSIS PATIENTS: A RANDOMISED, OPEN-LABEL TRIAL

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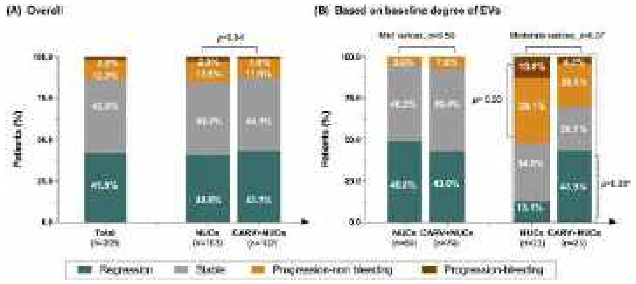
Background: Portal hypertension progression can be relieved after controlling the etiology of liver cirrhosis. Whether beta-blockers could additionally enhance the effects during treatment, particularly for mild esophageal varices (EVs), was unclear. This study aims to assess the efficacy of add-on carvedilol to delay EVs progression during anti-HBV treatment in HBV-related cirrhosis. **Methods:** This randomised controlled trial enrolled patients with HBV-related cirrhosis and mild/moderate EVs. The participants were randomly assigned to receive NUCs or carvedilol 12.5 mg plus NUCs (1:1 allocation ratio). The primary endpoint was the progression rate of EVs at 2 years of follow-up (NCT 03736265). **Results:** Totals of 238 patients (mild EVs, 77.3%) were randomised into 119 NUCs and 119 carvedilol plus NUCs (CARV combination group). Among them, 205 patients (86.1%) completed paired endoscopies. EVs progression rate was 15.5% (16/103) in NUCs group and 12.7% (13/102) in CARV combination group (RR = 0.80, 95%CI 0.36-1.77, $p = 0.59$). Subgroup analysis on moderate EVs showed CARV combination group had a more favorable effect in promoting EVs regression (43.5% vs. 13.1%, $p = 0.03$) than NUCs alone, but not in mild cases ($p = 0.50$). The incidence of liver-related events (decompensation, hepatocellular carcinoma, or death/liver transplantation) within 2 years was similar between the two groups (11.2% vs. 10.4%, $p = 0.88$). **Conclusion:** In virological suppressed HBV-cirrhosis patients, the added carvedilol strategy was non-inferior to NUCs monotherapy to prevent progression in esophageal varices. However, the carvedilol-added approach might improve the outcome for patients with moderate varices.



Disclosures: The following people have nothing to disclose: Bingqiong Wang, Jialing Zhou, Xiaoning Wu, Yameng Sun, Lei Li, Ping Li, Minghui Li, Wei Jiang, Mingyi Xu, Bo Feng, Xiaoyuan Xu, Jilin Cheng, Wen Xie, Tao Han, Xiaozhong Wang, Hai Li, Hongxin Piao, Xinyu Zhao, Shuyan Chen, Tongtong Meng, Qiushuang

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

Guan, Fandong Meng, Yuanyuan Kong, Xiaojuan Ou, Jidong Jia, Hong You

207 | A RANDOMIZED CONTROLLED TRIAL COMPARING SUSTAINED LOW EFFICIENCY DIALYSIS WITH CONTINUOUS RENAL REPLACEMENT THERAPY FOR SEPSIS-ASSOCIATED ACUTE KIDNEY INJURY IN CRITICALLY ILL PATIENTS WITH CIRRHOSIS (NCT04494542)

Rakhi Maiwall[1], Neha Chauhan[2], Ashinikumar Kumar Hidam[2], Sherin Thomas[2], Chandani Bhagat[2], Prashant Aggarwal[2], Shivali Panwar[2], Harsh Vardhan Tevethia[1] and Shiv Kumar Sarin[3], (1)Institute of Liver and Biliary Sciences, New Delhi, (2)Institute of Liver and Biliary Sciences, (3)Ilbs

Background: Continuous renal replacement therapy (CRRT) is the preferred mode of dialysis in critically ill hemodynamically unstable patients and in addition removes the inflammatory cytokines that accumulate in sepsis. Sustained low-efficiency dialysis (SLED) is a hybrid modality of intermittent dialysis with the advantage of metabolic control, hemodynamic stability, at a reduced cost. We aimed to compare CRRT versus SLED in patients with cirrhosis and sepsis-associated AKI(SA-AKI) in preventing the incidence of intradialytic hypotension (IDH). **Methods:** Prospective single-center open-label randomized controlled trial wherein critically ill patients with cirrhosis (CICs) with SA-AKI and norepinephrine dose < 0.10 ug/kg/min) were randomized to CRRT versus SLED. Pre and post (8 hours) rotational thromboelastometry (ROTEM, n = 62) and inflammatory cytokines was performed in 20 patients (10-CRRT, 10-SLED). **Results:** A total of 62 patients were randomized to SLED (n = 31) vs. CRRT (n = 31). The baseline characteristics were comparable. The mean age was 45.7 ± 10.8 years, 95% males, 81% alcohol-related, with arterial lactate 2.3 ± 1.9 umol/L ,serum creatinine 3.1 ± 2.1 mg/dl, MELD 53.4 ± 9.7 and SOFA score 12.6 ± 2.9. The indication for dialysis was metabolic acidosis in 90%. The norepinephrine (NE) dose was comparable at baseline [(0.06 ± 103) vs (0.7 ± 10.3) ug/kg/min; *p* = 0.13). On intention-to-treat analysis, the development of IDH was lower in CRRT [11(35.5%) vs. 22 (71%);*p* = 0.01). There was no difference in 28-day mortality [(12(38.7%) vs.14(45.2%); *p* = 0.19], the recovery of AKI at day 14 [11 (35.5%) vs. 7 (22.6%); *p* = 0.40] but reduction in SOFA score by 2 points was higher in CRRT[13 (41.9%)vs.4(12.9%); *p* = 0.02] with a significant lower NE dose at day 2 [(0.9 ± 0.16) vs. (0.17 ± 0.11) ug/kg/min ;*p* = 0.03) vs. SLED respectively. A significant reduction in arterial lactate from baseline [(2.1 ± 1.9 to 1.9 ± 1.1; *p* = 0.047) was noted in CRRT vs. SLED (2.0 ± 1.9 to 2.2 ± 1.8; *p* = 0.33)]. The days of mechanical ventilation and ICU stay were not different. There were 7(22.5%) patients with protocol violation in SLED group who required CRRT due to IDH. The median duration of CRRT was 48 (IQR 15-116 hours) while the mean number of SLED sessions were 3 ± 2.1. A significant derangement in coagulation by ROTEM was noted more with SLED. Inflammatory cytokines (serum ferritin, c-reactive protein) showed significant reduction with CRRT vs. SLED while levels of interleukin-6 increased after CRRT. (Figure) **Conclusion:** CRRT compared to SLED is a better modality which lowers the incidence of IDH achieves better lactate clearance and reduction in SOFA scores in cirrhosis patients with SA-AKI but does not confer any survival benefit. CRRT is possibly more effective in clearing inflammatory cytokines and causes lesser impairment in coagulation compared to SLED. Large controlled trials are required for exploring the observed benefits of CRRT in CICs.

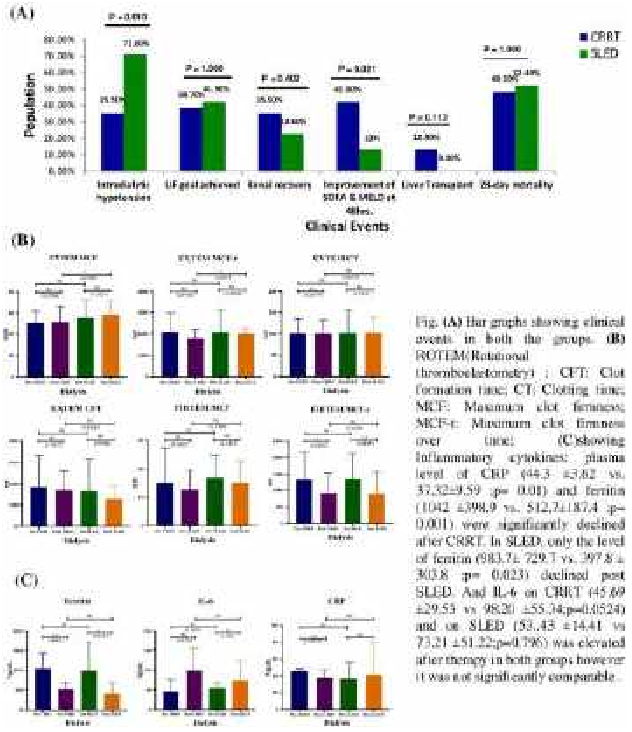

Fig. (A) Bar graphs showing clinical events in both the groups. (B) ROTEM(Rotational thromboelastometry) ; CFT: Clot formation time; CT: Clotting time; MCF: Maximum clot firmness; MCF-t: Maximum clot firmness over time; (C)showing Inflammatory cytokines: plasma level of CRP (44.3 ±3.82 vs. 37.32±9.59 ;p= 0.01) and ferritin (1042 ±398.9 vs. 512.7±187.4 ;p= 0.001) were significantly declined after CRRT. In SLED, only the level of ferritin (983.7± 729.7 vs. 397.8 ± 303.8 ;p= 0.023) declined post SLED. And IL-6 on CRRT (45.69 ±29.53 vs 98.20 ±55.34;p=0.0524) and on SLED (53.43 ±14.41 vs 73.21 ±51.22;p=0.796) was elevated after therapy in both groups however it was not significantly comparable.

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Disclosure information not available at the time of publication: Neha Chauhan, Ashinikumar Kumar Hidam, Sherin Thomas, Chandani Bhagat, Prashant Aggarwal, Shivali Panwar

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208 | ALBUMIN IS INTERNALIZED BY PRIMARY MONOCYTES USING CLATHRIN-INDEPENDENT ENDOCYTOSIS WHICH IS REQUIRED FOR ITS ANTI-INFLAMMATORY EFFECT

Mireia Casulleras[1,2], Irini Evnouchidou[3], Eva Boisel[3], Marta Duran-Güell[1], Berta Romero-Grimaldo[4], Bryan J. Contreras[4], Cristina López-Vicario[1], Richard Moreau[5], Vicente Arroyo[6], Loredana Saveanu[3] and Joan Claria[1,2], (1)Hospital Clínic-Idibaps, Barcelona, Spain, (2)European Foundation for the Study of Chronic Liver Failure, Barcelona, Spain, (3)University of Paris, Center of Research on Inflammation, Inserm U1149, Cnrs ERL8252, Hôpital Beaujon, Assistance Publique-Hôpitaux De Paris, (4)Hospital Clínic-Idibaps, (5) European Foundation for the Study of Chronic Liver Failure, Paris, France, (6)European Foundation for the Study of Chronic Liver Failure and Grifols Chair, Barcelona, Spain

Background: Albumin has been shown to modulate systemic inflammation in patients with decompensated liver cirrhosis receiving infusions of this protein as therapy. Although the anti-inflammatory effect of albumin has been described to be secondary to its internalization into mononuclear leukocytes, the cell type and the mechanism by which albumin is internalized by these immune cells are at present unknown. **Methods:** The internalization of tetramethylrhodamine isothiocyanate (TRITC)-labelled albumin by B and T lymphocytes and different subsets of monocytes and dendritic cells was scrutinized by flow cytometry using the expression of distinct surface markers. The albumin-binding receptor(s) was identified by albumin immunoprecipitation and untargeted proteomics. Albumin uptake and intracellular trafficking in primary monocytes was examined by confocal microscopy and the endocytic routes involved in the internalization of TRITC-albumin were screened in THP-1 cells transduced with shRNA lentivirus blocking different key cellular endocytic pathways. **Results:** Albumin was predominantly endocytosed and intracellularly accumulated by classical monocytes, which are highly phagocytic. In these cells and during the first 30 min after incubation, albumin was mainly located in early EEA1-positive endosomes whereas at later time points the albumin signal was also located in LAMP1-positive lysosomes. The shRNA lentivirus screening showed that albumin internalization was dependent on dynamin 2, ARF6 and ARF1, which are clathrin-independent routes. Untargeted proteomics of immunoprecipitated albumin identified two transmembrane proteins, the neonatal Fc receptor (FcRn) and CD44, as potential albumin receptor candidates. Of note, unlike THP-1 cells, classical monocytes freshly isolated from blood donors tested positive for intracellular albumin signal, indicating that the internalization of albumin by immune cells is a common occurrence in humans. **Conclusion:** These findings offer new perspectives for the understanding of the mechanisms involved in the interaction of the albumin molecule with the immune system in those conditions where this protein is therapeutically used, as is the case of decompensated cirrhosis liver patients.

Disclosures: Richard Moreau – RESOLUTION Tx: Consultant, No, No;

The following people have nothing to disclose: Mireia Casulleras, Irini Evnouchidou, Eva Boisel, Marta Duran-Güell, Berta Romero-Grimaldo, Bryan J. Contreras, Cristina López-Vicario, Vicente Arroyo, Loredana Saveanu, Joan Claria

209 | ROLE OF LONG TERM ALBUMIN THERAPY IN TREATMENT OF DECOMPENSATED CIRRHOSIS

Deepanshu Khanna and Premashis Kar, Max Superspeciality Hospital, Vaishali

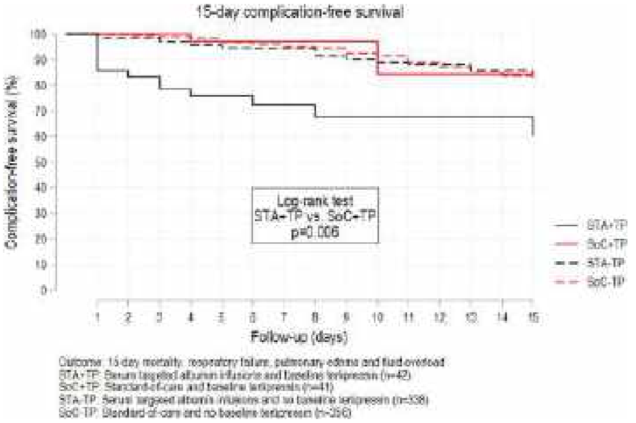
Background: Cirrhosis now has the 10th highest mortality rate worldwide. Most cirrhosis deaths are caused by the emergence of clinical decompensation, and 4%–12% of those who have the disease, experience at least one episode of decompensation per year. These patients are highly susceptible to infections due to increased systemic inflammation leading to kidney failure and death. Aim was to study the efficacy of albumin in reducing episodes of decompensation, preventing bacterial infection, kidney dysfunction and mortality. **Methods:** Study involved patients with Child B or C cirrhosis with albumin level below 30 g per litre, who were administered 20% human albumin weekly with standard medical treatment for 3 months or or till serum albumin levels are 4.0 g/dL (whichever is earlier) and compared with age and sex matched controls who received only standard medical treatment. The primary end-point was 6 month mortality, and the secondary end-points were reduction in infections, kidney dysfunction, ascites recurrence, hepatic encephalopathy, gastrointestinal bleed and complications of cirrhosis. **Results:** From September 2021 to January 2023, 88 cases and 86 controls were taken and followed up for 6 months. Overall 6-month survival was not statistically significant between groups (95.1% vs 91.9%; $p=0{\cdot}330$). Incidence of Recurrence of ascites (34.09% v/s 59.3%, $p<0.001$), Kidney dysfunction (6.8% v/s 24.4%, $p<0.001$), hepatic encephalopathy (15.9% vs 37.2%, $p=0.015$), Spontaneous bacterial peritonitis (7.9% vs 18.6%, $p=0.002$), Non SBP infections (7.9% vs 18.6%, $p=0.038$) were significantly less in cases as compared with controls, however Gastrointestinal bleed (14.8% vs 17.4%, $p=0.632$) was not statistically significant. **Conclusion:** Long-term Human albumin acts as a disease modifying treatment in patients with decompensated cirrhosis.

Disclosures: The following people have nothing to disclose: Deepanshu Khanna, Premashis Kar

210 | HIGH DOSES OF ALBUMIN INCREASES MORTALITY AND COMPLICATIONS IN TERLIPRESSIN TREATED PATIENTS WITH CIRRHOSIS: INSIGHTS FROM THE ATTIRE TRIAL★

Nikolaj Torp[1,2], Louise China[3], Mads Israelsen[4], Aleksander Krag[2,5] and Alastair O'Brien[3], (1)Odense University Hospital, (2)University of Southern Denmark, Odense, Denmark, (3)University College London, (4) Liver Research Centre, Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark, (5)Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark

Background: The CONFIRM trial revealed potential harm with terlipressin in a subset of patients, who developed respiratory failure. It remains unclear to what degree concomitant albumin contributes to the undesirable outcomes of terlipressin treatment. Using ATTIRE trial data, we compared safety of serum targeted albumin infusions to standard-of-care in patients with cirrhosis receiving terlipressin. **Methods:** ATTIRE was a randomized controlled trial of albumin infusions in 777 patients hospitalized with cirrhosis and hypoalbuminemia (<3.0 g/dL). Patients were randomized to serum targeted albumin (STA) infusions, aiming for a serum albumin level >3.0 g/dL, or standard-of-care (SoC), where albumin infusions was allowed as per clinical guidelines. At trial enrollment, 42 patients received terlipressin in the STA group (STA+TP) and 41 in SoC group (SoC+TP). Patients not receiving terlipressin at enrollment, served as controls (STA-TP, $n=338$ and SoC-TP, $n=356$). We studied mortality at day 15 and complications from trial SAE reporting. The primary outcome was a composite of 15-day complication-free survival (15-day mortality, respiratory failure, pulmonary edema and fluid overload). **Results:** Terlipressin indications were variceal bleed (74%), hepatorenal syndrome (23%) and hypotension (3%). Patients in the STA+TP group received higher albumin doses compared to the SoC+TP group (mean±SD: 209 ±125 grams vs. 96±162 grams, $p<0.001$). Baseline disease severity was similar between the two groups (median MELD: STA+TP = 19 [15-23] vs. SoC+TP = 18 [14-24], $p=0.520$). The STA+TP group had a significantly lower 15-day complication-free survival than the SoC+TP group (Figure, $p=0.006$). Compared to patients without terlipressin use at enrollment, the prognosis was also worse for STA+TP vs. STA-TP ($p<0.001$), but similar between SoC+TP and SoC-TP ($p=0.809$). Mortality rate during the 15-day follow-up was 21% in STA+TP and 7% in SoC+TP. The risk of respiratory failure was 7% (STA+TP) and 2% (SoC+TP), despite similar renal function at baseline (median creatinine: STA+TP = 1.0 mg/dL [0.7-1.6] vs. SoC+TP = 0.9 mg/dL [0.7-1.5], $p=0.752$). Adjusting for disease severity, the increased risk of 15-day mortality and complications persisted in the STA+TP group (sHR = 5.63, 95% CI: 1.60; 19.86, $p=0.007$), independently of baseline MELD (HR = 1.05, 95% CI: 1.02; 1.08, $p=0.002$). A subgroup analysis of variceal bleed patients treated with terlipressin, showed a markedly higher risk of 15-day mortality and complications in the STA+TP group (19%) compared to the SoC+TP group (0%, $p=0.011$). **Conclusion:** High albumin doses, due to serum targeted albumin infusions, is associated with an increased risk of mortality and complications in patients with cirrhosis receiving terlipressin, independently of disease severity. These findings suggest a cautious use of concomitant albumin to terlipressin, outside current dosing recommendations and indications.



Disclosures: Aleksander Krag – Novo Nordisk: Advisor, No, No; Novo Nordisk: Speaking and Teaching, No, No; Boeringer Ingelheim: Advisor, No, No; Siemens: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Siemens: Advisor, No, Yes; Resalis Therapeutics: Advisor, No, No; Takeda: Advisor, No, No; Astra: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Echosense: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant

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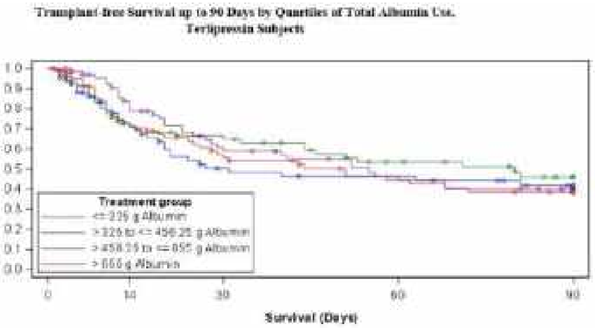
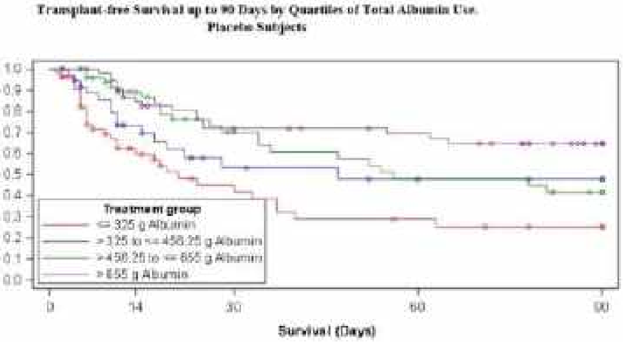
Disclosure information not available at the time of publication: Louise China, Alastair O'Brien

211 | ALBUMIN DOSING WITH TERLIPRESSIN FOR THE TREATMENT OF HRS-AKI: A DOUBLE-EDGED SWORD

Florence Wong, Toronto General Hospital, Toronto, ON, Canada, S. Chris Pappas, Orphan Therapeutics, Michael P. Curry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, Pratima Sharma, University of Michigan, Ann Arbor, MI and Khurram Jamil, Mallinckrodt Pharmaceuticals, Bridgewater, NJ

Background: Current guidelines for the diagnosis of HRS-AKI require the use of albumin as volume expander to exclude pre-renal azotemia. The treatment of HRS-AKI (hepatorenal syndrome) also recommends the use of terlipressin with albumin at a dose of 20-40g per day. However, the optimal dose of albumin to be given in the pre- and during treatment remains unclear. We evaluated total albumin use in the two largest placebo-controlled, randomized trials of terlipressin plus albumin versus placebo in patients with HRS-AKI. **Methods:** Pooled data from the two trials (CONFIRM-NCT02770716 and REVERSE-NCT01143246) were used to determine transplant-free survival (TFS) and HRS reversal by total albumin quartiles; total albumin included albumin given up to 14 days prior to randomization and concomitant albumin given during study treatment. TFS was analyzed using a Kaplan-Meier product limit method; HRS reversal was defined as serum creatinine d 1.5 mg/dL by day 14 or discharge. **Results:** The 4 quartiles of total albumin dose given were d 325g (Gp A), > 325 to d 456.25g (Gp B), > 456.25 to d 655g (Gp C), and > 655g (Gp D). HRS reversal rates for the terlipressin patients were 33.7%, 31.9%, 27.8% and 38.2% for Gp A to D respectively. Similarly, the placebo group had comparable proportions of patients who achieved HRS reversal, being 12.7%, 24.3%, 15.4% and 18.4% for Gp A to D respectively. Therefore, there was no dose-response relationship between total albumin use and HRS reversal for either treatment group. The TFS by day 90 for the terlipressin patients were 25.6%, 29.0%, 27.8% and 27.9% for Gp A to D respectively. The corresponding TFS by Day 90 for the placebo patients were 14.5%, 18.9%, 28.8% and 45.4%. Therefore, once again, there was no relationship between total albumin use and TFS by Day 90 in the terlipressin group. In contrast, TFS by Day 90 increased in the placebo group with increasing albumin dose used, being 14.5%, 18.9%, 28.8% and 45.4%. for Gp A to D respectively. Importantly, there was a significant difference in placebo versus terlipressin TFS at Day 90 in the > 655 g albumin quartile (terlipressin 27.9% vs. placebo 45.5%, $p = 0.044$). The lower TFS by Day 90 amongst terlipressin patients who received more than655g of albumin appears to be related in part to death from respiratory failure/sepsis/septic shock (terlipressin 12.6% vs placebo 3.0%). **Conclusion:** These results demonstrate that there does not appear to be an easily identifiable optimal dose of albumin during terlipressin therapy. The relationship between albumin use and the balance between efficacy and safety is complex; this "double-edged sword" underscores the need for careful patient selection and monitoring of albumin use to avoid volume overload.





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Pratima Sharma: Pratima Sharma

212 | SAFETY AND EFFICACY OF DAPAGLIFLOZIN IN RECURRENT ASCITES: A PILOT STUDY

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Background: The pathophysiology of ascites in cirrhosis entails vasodilatation with the consequential activation of sympathetic nervous system and renin-angiotensin-aldosterone system, leading to retention of sodium and water. Dapagliflozin, a sodium glucose linked transporter-2 inhibitor, induces natriuresis and is beneficial in patients with heart failure. We hypothesised that a similar natriuretic effect may improve mobilization of ascites in patients with cirrhosis. In this pilot study, we evaluated the efficacy and safety of dapagliflozin in patients with cirrhosis with recurrent ascites. **Methods:** Forty patients with recurrent ascites and cirrhosis were randomized 1:1 in a double blinded fashion to receive either dapagliflozin (10 mg/day) with standard medical therapy (Group A) or placebo with standard medical therapy (Group B). The primary outcome was control of ascites at 6-months. Secondary outcomes were urine output, 24-hour urinary sodium, estimated glomerular filtration rate, HbA1c, mean arterial pressure, Child Turcotte Pugh (CTP), model for end stage liver disease (MELD) scores and survival at 6-months, incidence of acute kidney injury (AKI), infections, hepatic encephalopathy, hyponatremia, hypokalemia, hepatocellular carcinoma, diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic coma. **Results:** The 2 groups were comparable at baseline. Complete and partial control of ascites at 6-months were seen in 3 (15%) and 11 (55%) patients in Group A which was significantly better than that in Group B (complete control: 0, partial resolution: 7 (35%), $p = 0.01$). Change in urinary sodium was significantly higher in Group A [13.3 (-10.9 to 30.1) vs -4.4 (-16.4 to 5.6), $p < 0.001$]. However, there was no difference in change in urine output, estimated glomerular filtration rate, HbA1c, mean arterial pressure, CTP or MELD scores between the groups at 6-months. Incidence of AKI (50% vs 15%, $p = 0.04$) and infections (55% vs 20%, $p = 0.04$) were significantly higher in Group A but there was no difference in hepatic encephalopathy, hyponatremia, hypokalemia, hepatocellular carcinoma, diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic coma. Survival at 6-months was similar in the 2 groups (65% vs 68.2%, $p = 0.75$). **Conclusion:** Significantly better control of ascites and higher natriuresis are observed with dapagliflozin. However, it does not improve disease severity scores or survival, and is associated with increased AKI and infections (NCT05014594).

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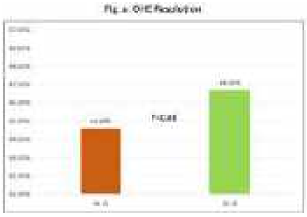
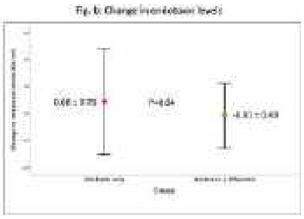
213 | ADDITION OF RIFAXIMIN TO BROAD-SPECTRUM ANTIBIOTICS HAS NO BENEFICIAL ROLE IN CRITICALLY ILL CIRRHOSIS PATIENTS WITH ACUTE OVERT HEPATIC ENCEPHALOPATHY- A DOUBLE-BLIND, RANDOMIZED CONTROLLED TRIAL

Anand V. Kulkarni, Mahathi Avadhanam, Pooja Karandikar, Anand Gupta, Asim Ahmed Zuberi, Venu

Simhadri, Sowmya T R, Manasa Alla, Shantan Venishetty, Mithun Sharma, Nageshwar D Reddy and Padaki Nagaraja Rao, Aig Hospitals, Hyderabad, India

Background: Critically ill cirrhosis (CIC) patients admitted to the intensive care unit (ICU) are usually on broad-spectrum intravenous antibiotics due to suspected infection or as a protocol. Few reports have suggested rifaximin to be beneficial in acute overt hepatic encephalopathy (OHE). However, the role of rifaximin in patients on broad-spectrum antibiotics admitted to ICU is still unclear. Therefore, we aimed to assess the efficacy of addition of rifaximin to broad-spectrum antibiotics for CIC patients admitted to ICU for OHE. **Methods:** In this double-blind trial, patients with OHE admitted to ICU were randomized to receive antibiotics alone (Gr. A) or antibiotics with rifaximin (Gr. B). All patients received lactulose. The primary objective was to compare the resolution of HE (defined as 2-grade reduction and/or complete resolution of HE by West-Haven criteria) among the two groups. The secondary objective was to compare the time taken for the resolution of HE, in-hospital mortality, nosocomial infection, endotoxin levels, and predictors of HE resolution. **Results:** 184 patients (age-47.8 ± 11.7 y; females-11.4%; alcohol-66.3%; MELD-29.4 ± 9.4; 92 patients in each group) were included. Baseline characteristics, including age, sex distribution, and severity scores, were similar among both groups. The most common precipitant of OHE was constipation with dyselectrolytemia in both groups (41%). The median number of stools passed per day in both groups was similar (4 [0-6] vs. 4 [2-6] in Gr.B; $p = 0.86$). Forty-one percent in Gr. A and 50% in Gr. B received L-ornithine L-aspartate infusion concomitantly ($p = 0.3$). The most common antibiotic used was carbapenems, followed by cephalosporin with beta-lactamase inhibitor in both groups. The proportion of patients achieving HE resolution was similar in both groups (44.6% [95%CI, 32-70.5] in Gr. A vs. 46.7% [95%CI, 33.8-63] in Gr. B; $p = 0.88$) (Fig. a). Time to achieve the primary objective was 3.65 ± 1.82 days and 4.11 ± 2.01 days in Gr. A and B, respectively ($p = 0.27$). In-hospital mortality was similar among both groups (62% vs. 50% in Gr. B; $p = 0.13$). Seven percent and 13% in Gr. A and B developed nosocomial infections ($p = 0.21$). 12% and 14.1% in Gr. A and B ($p = 0.82$) needed the addition of another antibiotic or upgradation to carbapenems. Baseline endotoxin levels (1.22 ± 0.72 vs. 1.3 ± 0.86 EU/ml; $p = 0.8$) and the delta change in levels of endotoxin at the resolution of HE were similar among both groups (Fig. b). On multivariate Cox regression analysis, a higher SOFA score predicted a lesser chance of OHE resolution (hazard ratio [HR], 0.85 [0.79-0.92];$p < 0.001$), while higher albumin levels increased the chance of OHE resolution (HR, 1.6 [1.06-2.4]; $p = 0.02$). **Conclusion:** The addition of rifaximin to broad-spectrum antibiotics has no beneficial role in critically ill cirrhosis patients with acute OHE admitted to ICU.





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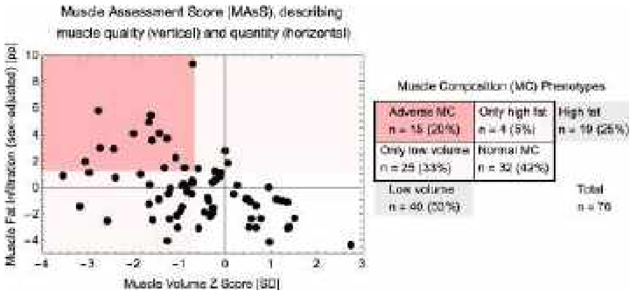
214 | MUSCLE FAT INFILTRATION IS ELEVATED IN PREFRAIL AND MODERATELY PHYSICALLY IMPAIRED PATIENTS – INTERIM RESULTS FROM THE PROSPECTIVE MULTI-CENTER CIRRHOSIS COHORT STUDY ACCESS-ESLD

Mikael Fredrik Forsgren[1,2], Wile Balkhed[1], Patrik Nasr[1], Daniel Sjögren[3], Jennifer Linge[1,2], Anna Cederborg[1], Markus Holmberg[1], Nils Dahlström[1], Henrik Stjernman[3], Martin Rejler[3], Stergios Kechagias[4], Olof Dahlqvist Leinhard[1,2] and Mattias Ekstedt[4], (1)Linköping University, (2)Amra Medical AB, (3)County Hospital Jönköping, (4)Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

Background: Physical frailty and sarcopenia are related but not fully overlapping, and links to outcomes and health care utilization in liver cirrhosis. Physical frailty may be assessed with Liver Frailty Index (LFI) or Short Performance Physical Battery (SPPB), and sarcopenia is typically assessed by measuring muscle size using imaging. A magnetic resonance imaging (MRI) based assessment (Muscle Assessment Score [MAsS]) combining sex-adjusted thigh muscle fat infiltration (MFI) and muscle volume z-score (MVZ), has been developed to describe muscle health. Large population studies have shown that MAsS better predicts physical function and hospitalization than its individual components. MAsS can be used to detect muscle composition (MC) phenotypes, of which adverse MC (high MFI & low MVZ) independently predicts all-cause mortality. The aim was to assess the association of MAsS and L3 skeletal muscle index (L3-SMI) with physical frailty tests (SPPB & LFI) and assess

MC phenotypes in ACCESS-ESLD – a prospective longitudinal multi-center cohort study of patients with liver cirrhosis. **Methods:** MAsS and L3-SMI were measured using AMRA® Researcher based on an 8 min MRI acquired on the same day as SPPB and LFI. SPPB was grouped as very low-to-low (<7), moderate (7-9), and high (10-12) physical performance. LFI was grouped as frail (>4.5), prefrail (3.8-4.4), less robust (3.2-3.7), and robust (<3.2). MC phenotypes were defined according to literature. T-tests were used for statistical testing. **Results:** The first 76 patients (46 males; BMI 29.5 ± 6.3 kg/m^2; Age 66 ± 10 yrs; mainly alcohol related cirrhosis and NAFLD, but also hepatitis B and C, and autoimmune diseases) were included. Patients with moderate (compared to high) physical performance had increased MFI from baseline (+1.77 pp, $p = 0.020$). There was no difference in MVZ nor L3-SMI. Only 3 patients had very low-to-low physical performance. MFI was higher in frail (+3.70 pp, $p = 0.035$) and prefrail (+1.16 pp, $p = 0.040$) compared to robust, and in frail (+2.98 pp, $p = 0.035$) compared to less robust. MVZ was lower in prefrail (-0.72 SD, $p = 0.049$) and less robust (-0.86 SD, $p = 0.029$) compared to robust. There was no difference for L3-SMI. Patients with adverse MC (n = 15) had higher LFI (3.98 v 3.49, $p = 0.040$), lower SPPB (8.93 v 10.26, $p = 0.020$), and lower L3-SMI (42.5 v 49.3, $p = 0.035$) compared to all other MC phenotypes (see MC prevalences in Fig) without differences in BMI or age. **Conclusion:** Results suggest that 20% of patients with cirrhosis have adverse MC, a large group (53%) low muscle volume, and few (5%) only high fat (see Fig). MFI was significantly higher with reduced physical function and by increasing frailty index. Adverse MC, as detected by MAsS, showed significantly higher frailty and lower physical performance, unrelated to age and BMI. These results indicates that MFI could be used as a frailty marker and that MAsS describes both frailty and sarcopenia in patients with liver cirrhosis.



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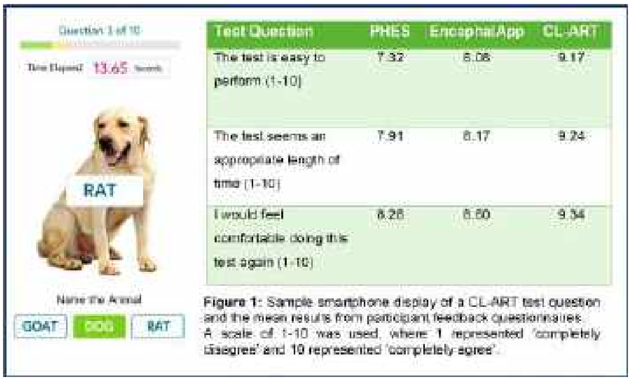
215 | CL-ART: A NOVEL SMARTPHONE APPLICATION THAT CAN HELP PREDICT FUTURE HOSPITALISATION SECONDARY TO CIRRHOSIS ACUTE DECOMPENSATION

Kohilan Gananandan[1], Ann-Sophie Frees Wietz[2], Ahmed El Shabrawi[1], Ann Catrine Daugaard Mikkelsen[2], Maria Pilar Ballester[1], Konstantin Kazankov[2], Anu Balaji[3], Ravan Boddu[3], Ravi Kumar[3], Karen Louise Thomsen[1,2] and Rajeshwar P. Mookerjee[1,2], (1)University College London, (2)Aarhus University, (3)Cyberliver Limited

Background: Hepatic encephalopathy (HE) is the most frequent cirrhosis complication leading to hospital admissions and is associated with significant mortality. The aim of this study was to determine the ability of the CyberLiver-Animal Recognition Test (CL-ART) to predict future hospitalisation due to decompensation, especially through HE, comparing its performance to established HE tests. **Methods:** A prospective study of cirrhosis patients applying three different cognitive tests at two tertiary hepatology centres was performed. The CL-ART involved a timed (usually <30 seconds) recognition of animals using a smartphone app (Figure 1). EncephalApp Stroop Test and Psychometric Hepatic Encephalopathy Score (PHES) were chosen as test comparisons. Follow-up clinical data was collected for a 6-month period. **Results:** 43 healthy controls and 103 cirrhosis patients were included (median CL-ART time 15.7s vs 24.0s). The baseline characteristics of the cirrhosis patients were 65% male, median age 58, Child-Pugh Score 8 [IQR 7-10], MELDNa 15 [IQR 11-19], CLIF-C AD 48 [IQR 44-52]. CL-ART demonstrated a good correlation with EncephalApp ($r = 0.81$, $p < 0.001$) and PHES ($r = -0.63$, $p < 0.001$). When analysing patients admitted due to HE during their follow-up, baseline CL-ART was significantly higher compared to participants who were not hospitalised (31.5 vs 22.6s, $p < 0.001$) with an AUROC of 0.85 (95% CI 0.77-0.93) for predicting future HE admissions. This was comparable to EncephalApp (AUROC 0.83, 95% CI 0.74-0.92) and ammonia (AUROC 0.81, 95% CI 0.71-0.91). In multiple logistic regression analysis, CL-ART remained an independent predictor of future HE admissions (OR 1.15, $p = 0.049$). Using the Youden index, the optimal CL-ART cut-off to predict HE-related admissions is 26s (sensitivity 91.7%, specificity 71.4%). When analysing all subsequent admissions due to any decompensation event, baseline CL-ART scores were significantly higher in those subsequently hospitalised (27.0 vs 21.3s, $p < 0.001$) with an AUROC of 0.76 (95% CI 0.66-0.85). Finally, the CL-ART also demonstrated superior participant useability (Figure 1). **Conclusion:** This study demonstrates that CL-ART can help predict hospitalisation due to all decompensation, with highest sensitivity and specificity for HE-related admissions. Its rapid testing, smartphone application and high useability mean it can be used remotely, and therefore, play a crucial role in predicting decompensation, enabling early community intervention.



Test Question	PHES	EncephalApp	CL-ART
The test is easy to perform (1-10)	7.32	6.08	9.17
The test seems an appropriate length of time (1-10)	7.91	6.17	9.24
I would feel comfortable doing this test again (1-10)	8.28	6.60	9.34

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

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

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

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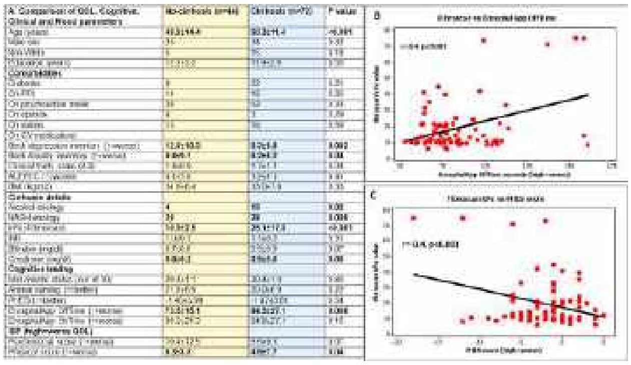
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

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



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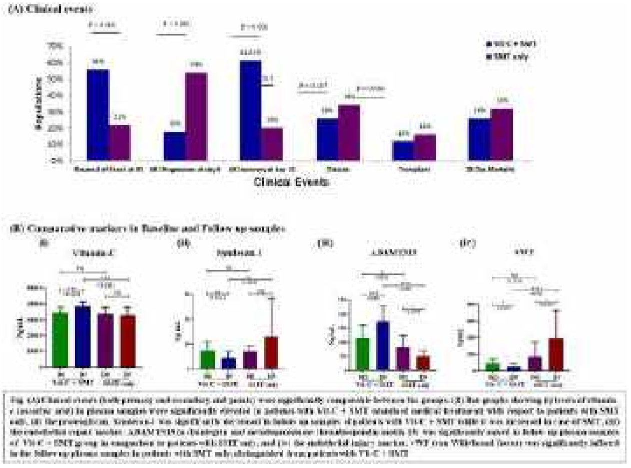
217 | EFFICACY OF VITAMIN C ON AKI OUTCOMES IN CRITICALLY ILL PATIENTS WITH CIRRHOSIS AND MULTIDRUG-RESISTANT BACTERIAL INFECTIONS- A RANDOMIZED CONTROLLED TRIAL [NCT04494451

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

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



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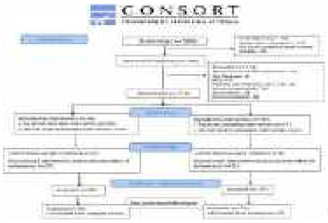
Disclosure information not available at the time of publication: Ashinikumar Kumar Hidam, Neha Chauhan, Samba Siva Rao Pasupuleti, Vikas Khillan, Anupam Kumar, Sherin Thomas

218 | COMPARISON OF BOLUS VERSUS CONTINUOUS INFUSION OF TERLIPRESSIN IN CIRRHOTIC PATIENTS WITH SEPTIC SHOCK: A RANDOMIZED CONTROLLED TRIAL (NCT 04819568)★

Priti Jain, Rakhi Maiwall, Shiv Kumar Sarin and Manoj Kumar Sharma, Institute of Liver and Biliary Sciences

Background: In-hospital mortality of cirrhosis patients with septic shock is higher than in other patients and exceeds 70%. These patients have high output cardiac failure secondary to severe systemic vasodilatation which is refractory to catecholamines. Terlipressin, as a second vasopressor, can provide the severe systemic vasodilation and improve macro and microcirculation. Terlipressin has been used either as continuous infusion or boluses in hepatorenal syndrome. However, at present none of studies reveal which would be a better mode of administration considering the reversal of hemodynamic and safety of patients. We aimed to study the efficacy of continuous infusion of terlipressin (T-CON) versus intermittent boluses (T-BOL) in reversal of septic shock in cirrhosis patients. **Methods:** In this study, 115 patients requiring noradrenaline more than 0.5 ug/kg/min to maintain mean arterial pressure (MAP) of more than 65 mm Hg were randomized into T-CON (n = 55) at 2mg/24`hour continuous infusion and T-BOL (n = 57) at intermittent boluses of same dosage. The dose was increased to maximum 4 mg. Primary end-point was reversal of shock over 72 hours. Secondary end-points included rebound hypotension, treatment-related adverse effects, effect on hemodynamic and mortality at 28 days. **Results:** Baseline parameters [aged (years) 47.41 ± 9.91 vs. 47.41 ± 9.95; $p = 0.44$, males (%) 93.1 vs. 96.4; $p = 0.68$, alcohol (%) 70.4 vs. 73.9; $p = 0.73$] were comparable in two groups; including serum lactate (μmol/L) [2.32 ± 0.95 vs. 2.55 ± 1.12; $p = 0.24$], SOFA scores [12.43 ± 3.62 vs. 12.48 ± 3.50; $p = 0.94$], MELD Na [33.13 ± 5.27 vs. 31.25 ± 8.01; $p = 0.16$] and MAP [73.88 ± 6.21 vs. 73.35 ± 6.18; $p = 0.65$]. Pneumonia is most common source of sepsis [89.7% vs. 77.2%; $p = 0.08$] in both the groups. On intent to treat analysis, reversal of shock at 72 hours [65.5% vs. 42.1%; $p = 0.02$] was significantly better in T-CON. Better improvement in hemodynamics, systemic vascular resistance [47.8% vs. 23.8%; $p = 0.04$], cardiac index [47.6% vs. 23.5%; $p = 0.06$] and lactate improvement [48.1% vs. 44.7%; $p = 0.84$] was achieved in T-CON. Significantly fewer incidences of rebound hypotension [43.1% vs. 78.9%; $p = 0.03$] and adverse effects of terlipressin [51.7% vs. 75.4%; $p = 0.01$] were noted in T-CON group. Common terminology criteria for adverse events (CTCAE) grading showed more incidence of Grade 3 [20% vs. 25.6%] and Grade 4 [46.6% vs. 44.2%]. Adverse events causing protocol violation (CTCAE 2-5) [37.9% vs. 57.9%; $p = 0.04$] were significantly higher in the T-BOL. Even on per-protocol analysis, reversal of shock was better in T-CON [69.4% vs. 41.7%; $p = 0.03$]. The duration of ICU stay, mechanical ventilation and 28 days mortality were not different between groups. **Conclusion:** Continuous infusion of terlipressin is superior to intermittent boluses as a second vasopressor in cirrhosis patients with septic shock by better improvement of hemodynamic and sustained reversal of shock.



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219 | RISK AND PREDICTORS OF HEPATIC DECOMPENSATION IN GREY ZONE PATIENTS BY THE BAVENO VII CRITERIA: A COMPETING RISK ANALYSIS

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

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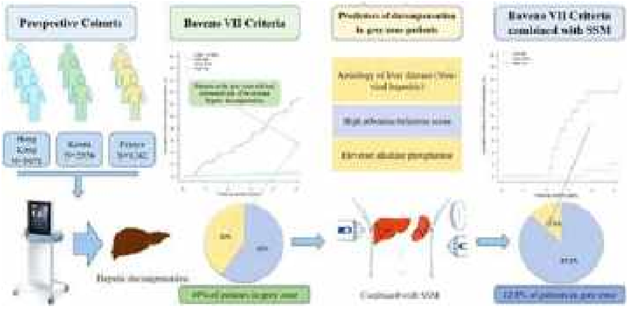
Background: Baveno VII was proposed for non-invasive identification of clinically significant portal hypertension. However, a substantial proportion of patients is classified in the grey zone (i.e., liver stiffness 15-24.9 kPa and/or platelet count < 150 ×10^9/L). We aimed to evaluate the risk and predictors of hepatic decompensation in grey zone patients and determine the prognostic role of spleen stiffness measurement (SSM). **Methods:** Prospective cohorts (from Hong Kong, Korea and France) of patients who had undergone transient elastography examination for chronic liver disease were included. The risk of hepatic decompensation was estimated using competing risk regression with hepatocellular carcinoma and non-liver related death as competing events. **Results:** We identified 2763 compensated advanced chronic liver disease (cACLD) patients. There were 1243 (44.9%) and 536 (19.4%) patients in the Baveno VII grey zone and high-risk groups, respectively. The cumulative incidence of decompensation at 5 years was significantly different among the low-risk (0.6% [95% CI, 0.2-1.3%]), grey zone 4.2% (95% CI, 3.1-5.4%) and the high-risk groups (11.4% [95% CI, 8.7-14.6%]). By competing risk analysis, aetiology of liver disease (non-viral hepatitis), albumin-bilirubin score and alkaline phosphatase level were independently associated with decompensation in grey zone patients (Figure). The combination of Baveno-VII and spleen stiffness significantly reduced patients classified into the grey zone (12.8% in cACLD patients), while maintaining high discrimination of decompensation in the low- and high-risk groups. **Conclusion:** Patients in the grey zone of the Baveno VII criteria remain at high risk of hepatic decompensation. Clinical risk factors and spleen stiffness can further stratify the risk in such patients.


Prospective Cohorts
Baveno VII Criteria
Predictors of decompensation in grey zone patients
Baveno VII Criteria combined with SSM
Hepatic decompensation
Combined with SSM

Disclosures: Grace Lai-Hung C Wong – Gilead Sciences, Inc.: Advisor, No, No; Janssen: Advisor, No, No; Abbott Diagnostics: Speaking and Teaching, No, No; AbbVie: Speaking and Teaching, No, No; Ascletis: Speaking and Teaching, No, No; Bristol Myers Squibb: Speaking and Teaching, No, No; Echosens: Speaking and Teaching, No, No; Gilead Sciences, Inc.: Speaking and Teaching, No, No; Janssen: Speaking and Teaching, No, No; Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Victor De Ledinghen – E-Scopics: Consultant, Yes, No; Terry Cheuk-Fung Yip – Gilead Sciences: Consultant, No, No; Gilead Sciences: Speaking and Teaching, No, No;

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220 | MIRNAS EMBEDDED IN HEPATOCYTE DERIVED EXTRACELLULAR VESICLES PROMOTE ENDOTHELIAL CAPILLARIZATION IN CHRONIC LIVER DISEASE

Laia Abad-Jordà[1], María Andrés-Rozas[2], Ana Martínez-Alcocer[3], Nicolò Manicardi[1], Juan Jose Lozano[4], Gabriela Chullo[5], Filippo Landi[5], Yilliam Fundora[6], Sergi Guixé-Muntet[1], Anabel Fernandez-Iglesias[7] and Jordi Gracia-Sancho[1,8], (1)Idibaps - Hospital Clínic Barcelona - Ciberehd, Barcelona, Spain, (2)Barcelona Liver Bioservices (BLB), (3)Idibaps - Hospital Clínic, Barcelona, Spain, (4)Ciberehd, Madrid, Spain, Madrid, Spain, (5)Hospital Clínic Barcelona, Spain, (6)Liver Transplant Unit, Institut Clínic De Malalties Digestives I Metabòliques (ICMDM), Hospital Clínic, University of Barcelona, Barcelona, Spain, (7)Idibaps/Hospital Clínic Barcelona/Ciberehd, Barcelona, Spain, (8)Inselspital - University of Bern, Bern, Switzerland

Background: Liver cells paracrinally affect neighboring cells through the release of extracellular vesicles (EVs), which may contain microRNAs (miRNAs). Our aim was to investigate the role of miRNAs enclosed in hepatocyte-derived EVs as modulators of endothelial dedifferentiation in chronic liver disease (CLD). **Methods:** EVs were purified from the supernatant of healthy (CT) or cirrhotic (CH) primary hepatocytes (hepEVs) from human and rat livers. *In vivo*: Healthy rats were intravenously treated with fluorescence-labelled hepEVs-CT, hepEVs-CH or vehicle (n = 10) to evaluate their biodistribution, sinusoidal endothelial uptake, and

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

LSEC phenotype through transcriptomic analysis and vWF and eNOS protein expression (n = 6). *In vitro*: Human hepEVs miRNAs profile was analyzed and those significantly deregulated in CH were validated in rat hepEVs by qPCR (n = 3 & 9, respectively). Exogenous over-expression of deregulated miRNAs was performed in CT-LSECs, followed by RNAseq and data analysis using Ingenuity Pathway Analysis (IPA) (n = 5). Endothelial deregulations due to miRNAs overexpression was compared to primary cirrhotic rat LSECs (n = 6) and human cirrhotic liver tissue (ethanol etiology, n = 12). **Results:** Upon in vivo administration, hepEVs-CH mostly accumulated in the liver, inducing endothelial dysfunction as suggested by the deregulation of 144 genes involved in pro-fibrogenic and inflammatory pathways, together with vWF upregulation and eNOS reduction. Characterization of human hepEVs-CH showed 37 miRNAs significantly deregulated in comparison to hepEVs-CT, being miR-A and miR-B validated in rat hepEVs-CH. Interestingly, miR-B target genes were significantly downregulated in CH-LSECs. Transcriptome analysis of LSECs transfected with miR-A or miR-B revealed 868 and 771 genes significantly deregulated vs miR-control. Moreover, the transcriptome of miR-B transfected cells showed 51% homology with CH-LSECs supporting the key role of miR-B in LSEC dedifferentiation. Indeed, IPA confirmed miR-B detrimental effects promoting deregulation in molecular processes involved in fibrogenesis, inflammation and cell death. Differential expression of specific genes of such pathways was confirmed in CH-LSECs and in endothelial population of human liver tissues, suggesting new potential targets for LSEC amelioration in CLD. **Conclusion:** miRNAs embedded in hepatocytes' EVs actively contribute to endothelial dedifferentiation in CLD. We propose this paracrine route as a novel therapeutic approach for endothelial dysfunction and portal hypertension in cirrhosis.

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221 | CARVEDILOL TO PREVENT DECOMPENSATION OF CIRRHOSIS IN PATIENTS WITH CLINICALLY SIGNIFICANT PORTAL HYPERTENSION STRATIFIED BY NOVEL NON-INVASIVE MODEL: AN INTERNATIONAL MULTICENTER STUDY

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Modena, (28)Zhongda Hospital, Medical School, Southeast University, Nanjing, Jiangsu, China, Lanzhou, China

Background: The non-invasive models stratifying clinically significant portal hypertension (CSPH) are limited. We aim to develop a novel non-invasive model for predicting CSPH in patients with compensated advanced chronic liver disease, and investigate whether carvedilol could prevent hepatic decompensation in high-risk CSPH patients stratified by the novel model. **Methods:** In this study, the derivation cohort (n = 819) from a meta-analysis of 6 studies was used to identify risk factors and develop a novel noninvasive model for predicting CSPH. The novel model was validated in hepatic venous pressure gradient (HVPG) cohort (n = 151) and was further assessed for the ability of predicting hepatic decompensation in follow-up cohort (n = 1,102). The carvedilol-treating cohort (n = 51) was included to prove that carvedilol could prevent hepatic decompensation in high-risk CSPH patients stratified by the novel model. **Results:** In derivation cohort, liver stiffness measurement and platelets were identified as independent risk factors of CSPH and fitted to develop the novel CSPH risk model. A novel CSPH model was established as follows: 0.093510*LSM (kPa) - 0.01005*PLT (×10^9/L)-0.11. The novel model performed significantly better (all $p < 0.05$) than other methods in HVPG cohort (Figure 1A). The risk of CSPH was stratified by the cut-off values at -0.68 and 0. The cumulative incidences (1.7% vs 2.5% vs 15.8%) of decompensation were significantly different in the low-, middle- and high-risk ($p < 0.001$, Figure 1B) groups in follow-up cohort. The high-risk CSPH patients stratified by the novel model from carvedilol-treating cohort had significantly lower rates of decompensation than those of non-selective beta-blockers untreated high-risk CSPH patients from follow-up cohort ($p < 0.05$, Figure 1 C&D). **Conclusion:** Treatment with carvedilol among high-risk CSPH patients stratified by the novel model significantly reduces the risk of hepatic decompensation.

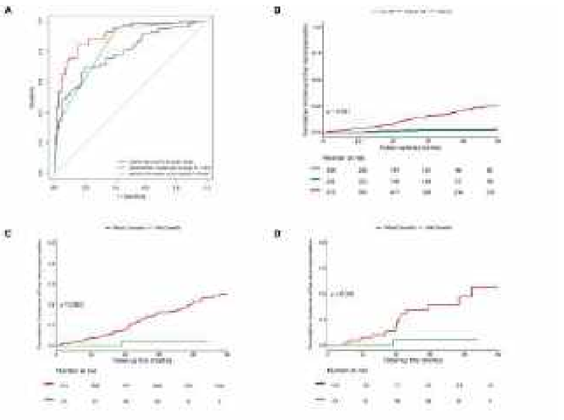

Figure 1. Performance of the CSPH risk model for predicting portal hypertension. A. Performance of different models for diagnosis of clinically significant portal hypertension. B. The cumulative incidence of liver decompensation in follow-up cohort. C. Decompensation according to treatment group before PSM. D. Decompensation according to treatment group after PSM.

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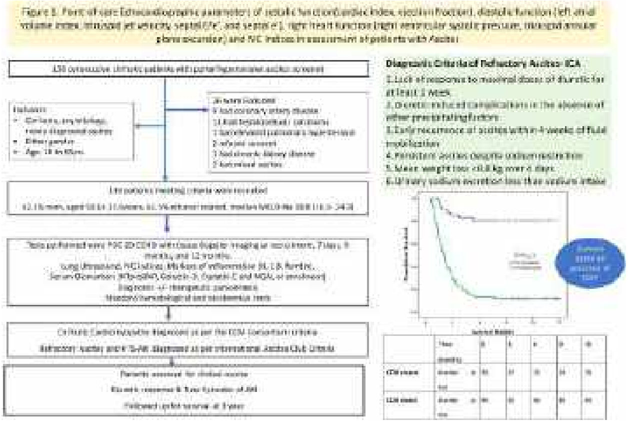
Hiroko Iijima – Canon Medical Systems: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
The following people have nothing to disclose: Chuan Liu, Hong You, QingLei Zeng, Eugene Wong, Ivica Grgurevic, Bingtian Dong, Gou Wei, Shenghong Ju, Qian Yu, Masashi Hirooka, Hirayuiki Enomoto, Amr Shaaban Hanafy, Zhujun Cao, Xiemin Dong, Young Kul Jung, Taehyung Kim, Yohei Koizumi, Yoichi Hiasa, Takashi Nishimura, Chuanjun Xu, Xinru Guo, Xiaoling Lan, Changxiang Lai, Shirong Liu, Fang Wang, Ying Guo, Jiaojian Lv, Jie Li, Liting Zhang, Yuqing Wang, Er Hei Dai, Qing Xie, Chuxiao Shao, Zhensheng Liu, Federico Ravaioli, Antonio Colecchia, Gao-Jun Teng, Xiaolong Qi

222 | POINT-OF-CARE ECHOCARDIOGRAPHY TO ASSESS IMPACT OF CIRRHOTIC CARDIOMYOPATHY AND CARDIORENAL BIOMARKERS IN PATIENTS WITH CIRRHOSIS AND REFRACTORY ASCITES

Kamal Kajal[1], Madhumita Premkumar[2], Manhal Izzy[3], Vishesh Kumar[1], Bhupendra Kumar Sihag[4], Ajay K. Duseja[5], Smita Divyaveer[4], Ankur Gupta[4], Sahaj Rathi[1], Arka De[1], Sunil Taneja[5], Ajay Bahl[4], Virendra Singh[6], Nipun Verma[5], Harish Bhujade[1], Sreedhara B Chaluvashetty[1] and Deepy Z[4], (1)Post Graduate Institute of Medical Education and Research, (2) Postgraduate Institute of Medical Education & Research, Chandigarh, India, (3)Vanderbilt University Medical Center, (4)Postgraduate Institute of Medical Education and Research, (5)Post Graduate Institute of Medical Education and Research, Chandigarh, India, (6)Punjab Institute of Liver and Biliary Sciences, Mohali, India, Chandigarh, CH, India

Background: Point-of-care echocardiography (POC-Echo) can be used to evaluate Cirrhotic Cardiomyopathy (CCM) and inferior vena cava (IVC) dynamics. The impact of cardiac function and IVC dynamics on cirrhosis progression towards refractory ascites and HRS-AKI is yet to be defined. This study aims to evaluate the utility of CCM markers and IVC changes, assessed by POC-Echo, in predicting adverse outcomes in patients with cirrhosis and ascites. **Methods:** Serial POC-Echo was done at presentation, at 1 week following 1st paracentesis, and subsequently at 3 & 6 months from 1st assessment in decompensated patients with ascites. Clinical data, diuretic response, cardiac & renal biomarkers were prospectively collected at presentation, and at 6 & 12 months. CCM was defined as per CCM consortium 2020 criteria. Refractory ascites and HRS-AKI were diagnosed as per International Ascites Club 2015 criteria. Patients with coronary artery disease, valvular heart disease, those on dialysis, uncontrolled thyroid disease, portopulmonary hypertension, dilated cardiomyopathy, and hepatocellular carcinoma were excluded. (Figure 1) **Results:** We enrolled 130 cirrhotic patients with ascites at presentation [(62% men, aged 50 ± 12years, 61.5% alcohol-related, median MELD-Na 18.8 (16.3- 24.3)]. There were 34(28.3%) patients with CCM at presentation. Twenty-four patients subsequently developed refractory ascites (18.4%), and 22 (16.9%) patients developed at least 1 episode of HRS-AKI on 1-yr follow up. Overall mortality was 22(17%) at 1 year. When adjusted for age, gender, presence of diabetes, and etiology of liver disease, MELD-Na (aHR 1.3,95%CI: 1.2-2.4, $p < 0.001$), NT-proBNP (aHR 1.1, 95% CI: 1.01-1.31, $p = 0.032$), low Cardiac index at presentation (aHR 0.9, 95%CI:0.7-0.9, $p = 0.022$) and Cystatin C (aHR 1.2, 95%CI: 1.1-3.2, $p < 0.001$) predicted 1-year mortality. IVC dynamics showed poor association with diuretic response or HRS-AKI. CCM markers, namely, septal E/e' representing filling pressures (aHR 1.3, 95%CI: 1.3-4.3, $p = 0.033$) and e' representing myocardial relaxation (aHR 0.98, 95% CI 0.7-0.9, $p = 0.045$) were predictive of development of HRS-AKI on follow up. A reduction in cardiac index by 24% at 7 days predicted poor diuretic response, and preceded fall in mean arterial pressure. On adjustment for MELDNa, presence of CCM at baseline was associated with subsequent HRS-AKI [OR 3.2, 95%CI: 1.9-6.8, $p < 0.001$) and mortality [OR 4.1, 95% CI: 1.4-9.6, $p = 0.012$), but did not predict risk of refractory ascites. **Conclusion:** Cirrhotic cardiomyopathy is independently associated with HRS-AKI and 1-year mortality in patients with cirrhosis and ascites. Impaired cardiac index, which can represent undiagnosed CCM, may limit the potential for resolution of ascites. POC-Echo can predict prognosis and may inform therapeutic strategies in cirrhosis with ascites.



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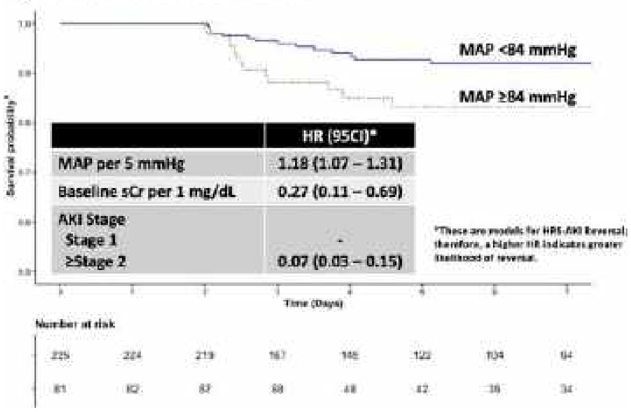
223 | MEAN ARTERIAL PRESSURE: A TARGET FOR ACUTE KIDNEY INJURY RESPONSE REGARDLESS OF ACUTE KIDNEY INJURY TYPE

Giuseppe Cullaro[1]*, Arjun Sharma*[2]*, Jessica Beth Rubin*[1]*, Jin Ge*[1]*, Andrew Allegretti*[3]*, Kavish R. Patidar*[4] *and Jennifer C. Lai*[2]*, (1)University of California, San Francisco, (2)University of California-San Francisco, (3) Massachusetts General Hospital, (4)Section of Gastroenterology, Department of Medicine, Baylor College of Medicine and Michael E. Debakey Veterans Affairs Medical Center*

Background: Acute kidney injury (AKI) is a deadly complication of cirrhosis, and treatments are limited. Vasoconstrictors have been used to treat hepatorenal syndrome AKI (HRS-AKI), but the impact of augmenting mean arterial pressure (MAP) on all AKI types has not been studied, limiting the application of clinically-proven treatments for HRS-AKI to non-HRS-AKI. Herein, we precisely characterize the impact of MAP on AKI reversal, independent of subtype. **Methods:** Among decompensated cirrhosis patients in our ongoing, prospective cohort, we identified incident AKI episodes AKI was defined as a e 50% increase in creatinine (sCr) from an outpatient baseline, a minimum of 7 days prior, that required hospitalization and lasted > 48 hours. AKI was staged according to guidelines using the peak hospitalization sCr.

AKI type was defined per guidelines and independently validated by 3 investigators. AKI reversal was defined as a return in sCr to within 0.3mg/dL of baseline. To determine the impact of MAP on AKI reversal, we completed time-dependent Cox-regression models with time beginning at the time of peak sCr and ending at death, discharge, or AKI reversal. We determined the optimal MAP cut-off for AKI reversal by comparing log-rank statistics. To investigate if the initial MAP or MAP trajectories were associated with AKI reversal, we calculated time-dependent MAP intercepts and slopes over time. **Results:** Among 1,626 participants (43% Female, 21% NAFL, 88% White) with a median MELDNa of 16 (14-20) followed for a median 1.5 years (0.6 – 3.5), we identified 306 episodes of AKI that lasted at least 48 hours and required hospitalization. Of these 306 episodes of AKI, 140 (46%) were HRS-AKI. As compared to those with non-HRS-AKI, those with HRS-AKI had significantly lower MAPs (73 v. 78), more severe AKI episodes (≥ Stage 2 AKI: 85% v. 72%), and less AKI reversal (16% v. 30%)($p \leq 0.004$ for all). In time-dependent Cox models accounting for baseline sCr and AKI stage, each 5 mmHg increase in MAP was associated with 1.18x (1.07–1.31) the hazard of AKI reversal. AKI type (e.g., HRS-AKI) was not associated with AKI reversal in uni- or multivariable analyses ($p > 0.05$ for both). There was no interaction between AKI type and MAP ($p > 0.05$). In univariable, time-dependent Cox models, the optimal MAP cutoff most associated with AKI reversal was ≥ 84mmHg ($p = 0.005$) (Figure 1). In time-dependent Cox models accounting for baseline sCr and AKI stage, both MAP slope (aHR 2.2 (1.3 – 3.6) per 1 mmHg increase per minute) and MAP intercept (1.01 per 1 mmHg increase (1.01 – 1.02)) were significantly associated with AKI reversal. **Conclusion:** Our analysis highlights that MAP, specifically ≥ 84 mmHg, is associated with AKI reversal, independent of AKI type. This was true for both initial MAP (intercept) and the change in MAP over time (slope). Our data support the investigation of strategies to maintain a MAP ≥ 84 mmHg among all cirrhosis patients with AKI, regardless of AKI type.

Figure 1. Survival Plot for Full AKI Reversal



	HR (95CI)*
MAP per 5 mmHg	1.18 (1.07 – 1.31)
Baseline sCr per 1 mg/dL	0.27 (0.11 – 0.69)
AKI Stage Stage 1 ≥Stage 2	- 0.07 (0.03 – 0.15)

*These are models for HRS-AKI Reversal; therefore, a higher HR indicates greater likelihood of reversal.

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The following people have nothing to disclose: Jessica Beth Rubin, Kavish R. Patidar
Disclosure information not available at the time of publication: Arjun Sharma, Andrew Allegretti, Jennifer C. Lai

224 | IMPROVED MEAN ARTERIAL PRESSURE FROM BASELINE TO THE END OF TREATMENT WITH TERLIPRESSIN IS ASSOCIATED WITH HEPATORENAL SYNDROME REVERSAL: A POOLED ANALYSIS OF 3 PHASE III STUDIES

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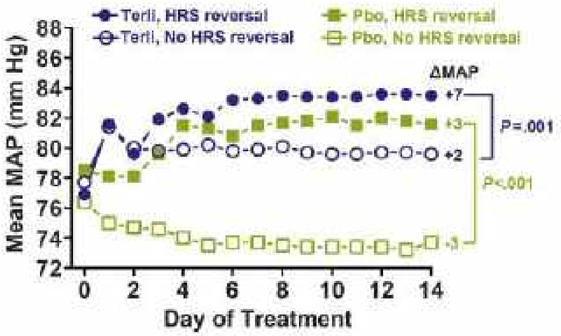
Background: Hepatorenal syndrome type 1 (HRS-1) is a rapidly progressive form of renal failure associated with high mortality in patients (pts) with decompensated cirrhosis and ascites. The FDA-approved vasopressin analogue, terlipressin (terli), improves renal function in pts with HRS-1 by reducing portal hypertension and increasing effective arterial volume and mean arterial pressure (MAP)—a marker of the hemodynamic response to treatment. Using the largest-to-date, prospective database of terli for the treatment of HRS, this subgroup analysis compared the change in MAP (ΔMAP) from baseline (BL) to the end of treatment (EOT) based on HRS reversal status and treatment group. **Methods:** Pooled data from the safety population (ie, treated pts) from 3 Phase III studies (OT-0401, REVERSE, and CONFIRM) were used to compare HRS reversal (defined as a serum creatinine ≤ 1.5 mg/dL while on treatment, by EOT or discharge), and ΔMAP from BL to EOT (Day 0 to Day 14) by HRS reversal status and treatment group. MAP was averaged daily, before and 2 hours post-injection (4 per day) of terli or placebo (pbo); if data were missing, the last observation was used. Associated p values were determined via a chi-square test (HRS reversal), ANOVA and Kruskal-Wallis test (ΔMAP by HRS reversal status), or a Wald test (odds ratio determined via logistic regression analysis). **Results:** In the pooled population (N = 598), 349 pts received terli and 249 pts received pbo. HRS reversal was achieved by more pts treated with terli than pbo (34% [117/349] vs 17% [42/249], $p < 0.001$). Mean MAP (± SD, mm Hg) at BL was similar between pts who achieved HRS reversal and those who did not, regardless of treatment (terli, 77 ± 11 vs 78 ± 13; pbo, 79 ± 10 vs 76 ± 11; Figure); whereas, pts who achieved HRS reversal had a significant ΔMAP (mean ± SD, mm Hg) from BL to EOT versus those with no HRS reversal (terli, +7 ± 11 vs +2 ± 13, $p = 0.001$; pbo, +3 ± 9 vs -3 ± 11, $p < 0.001$; Figure). A ΔMAP of e 5 mm Hg was significantly associated with HRS reversal (odds ratio [95% confidence interval]: terli, 2.427 [1.531–3.846] $p < 0.001$; pbo, 2.545 [1.282–5.051] $p = 0.008$), regardless of treatment. **Conclusion:** In this analysis, significantly more terli-treated pts than pbo-treated pts achieved HRS reversal. A greater increase in MAP from BL to EOT was noted among those pts who achieved HRS reversal, with an increase in MAP of e 5 mm Hg significantly associated with the odds of achieving HRS reversal, regardless of treatment.

Figure. Daily MAP in Patients Treated with Terlipressin or Placebo by HRS Reversal Status, Pooled Safety Population



HRS, hepatorenal syndrome; MAP, mean arterial pressure; ΔMAP, change in mean arterial pressure from baseline (ie, Day 0) to Day 14; Pbo, placebo; Terli, terlipressin.

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and manages the funds), No, No; Mallinckrodt Pharmaceuticals: Consultant, Yes, No; CymaBay: Advisor, No, No; Glaxo-Smith-Kline: Advisor, No, No; Ipsen: Advisor, No, No; Mirum: Advisor, No, No; Glaxo-Smith-Kline: Speaking and Teaching, No, No; Intra-Sana: Speaking and Teaching, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
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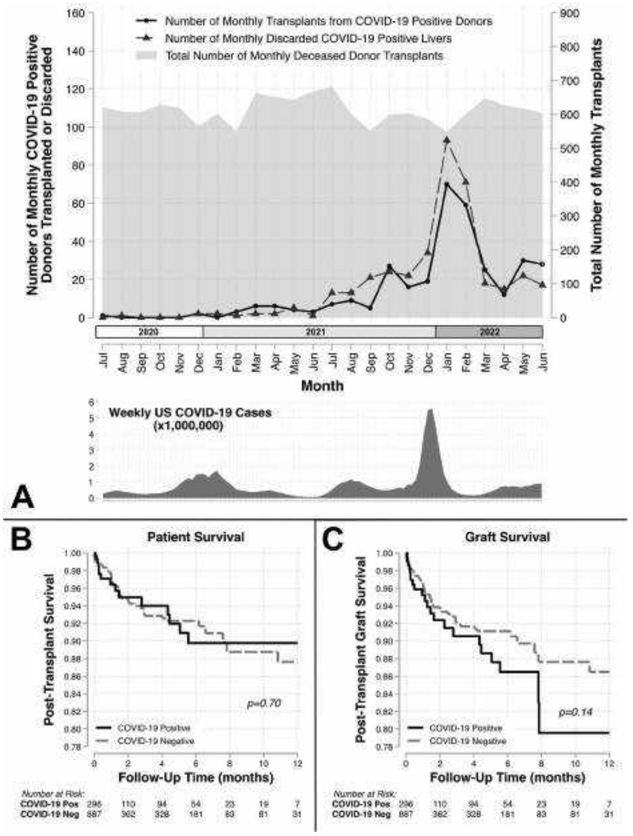
225 | TRENDS IN UTILIZATION AND POST-TRANSPLANT OUTCOMES IN COVID-19 POSITIVE DECEASED DONOR LIVER TRANSPLANTATION★

Roy X Wang, Samir Abu-Gazala and Nadim Mahmud, Hospital of the University of Pennsylvania

Background: Initial recommendations from scientific societies cautioned against procurement of livers from COVID-19(+) donors. Growing evidence supports the short-term safety of liver transplantation from COVID-19(+) donors. We described usage of liver transplants from COVID-19(+) donors during the COVID-19 pandemic and characterized associated transplant outcomes using data from the United Network for Organ Sharing registry. **Methods:** Liver transplant recipients from 7/2020-7/2022 were included in our retrospective cohort study. COVID-19(+) donors were identified by nucleic acid test or antigen positive testing. Trends in procurement of COVID-19(+) livers were compared against incident COVID-19 cases in the United States. Propensity score matching was used to account for differences between patient groups and to generate a 3:1 controls:cases matched cohort. Kaplan-Meier analysis was performed to plot survival distributions between donor COVID-19 status and transplant outcomes in the matched cohort. Fine and Gray competing risks regression (competing event = retransplantation) and standard Cox regression were performed to evaluate the association between donor status and patient and allograft survival, respectively. **Results:** The analytic cohort included liver transplants from 13,096 COVID-19(-) and 299 COVID-19(+) donors. Increased utilization of COVID-19(+) organs was observed after peaks in COVID-19 cases in the US (Figure A). COVID-19(+) donors were younger (median age 38 vs 41, $p < 0.001$), more likely to be donors after brain death (94.0% vs 88.8%, $p = 0.005$), and more likely to be in certain UNOS regions ($p < 0.001$). No significant differences in demographic data were observed between recipients of COVID-19(-) vs COVID-19(+) livers. After one year of post-transplant follow-up, no differences in patient survival (log-rank $p = 0.70$; subhazard ratio [sHR]: 1.11, 95% confidence interval [CI]: 0.61-2.00, $p = 0.74$; Figure B) or allograft survival (log-rank $p = 0.14$; hazard ratio [HR]: 1.44, 95% CI: 0.88-2.36, $p = 0.14$; Figure C) were noted between transplant from COVID-19(+) and COVID-19(-) donors. **Conclusion:** Patient and allograft survival were similar at one year post-transplant in a large cohort comparing COVID-19(-) and COVID-19(+) donors. Utilization of livers from COVID-19(+) donors paralleled disease incidence in the US and varied across UNOS region. Liver transplant from COVID-19(+) donors has acceptable short-term outcomes and may represent an opportunity to expand organ access.



Disclosures: Nadim Mahmud – Grifols: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
The following people have nothing to disclose: Roy X Wang, Samir Abu-Gazala

226 | PREDICTORS OF HOSPITAL-RELATED OUTCOMES OF COVID-19 INFECTION IN LIVER TRANSPLANT RECIPIENTS IN UNITED STATES: A NATIONWIDE INPATIENT STUDY

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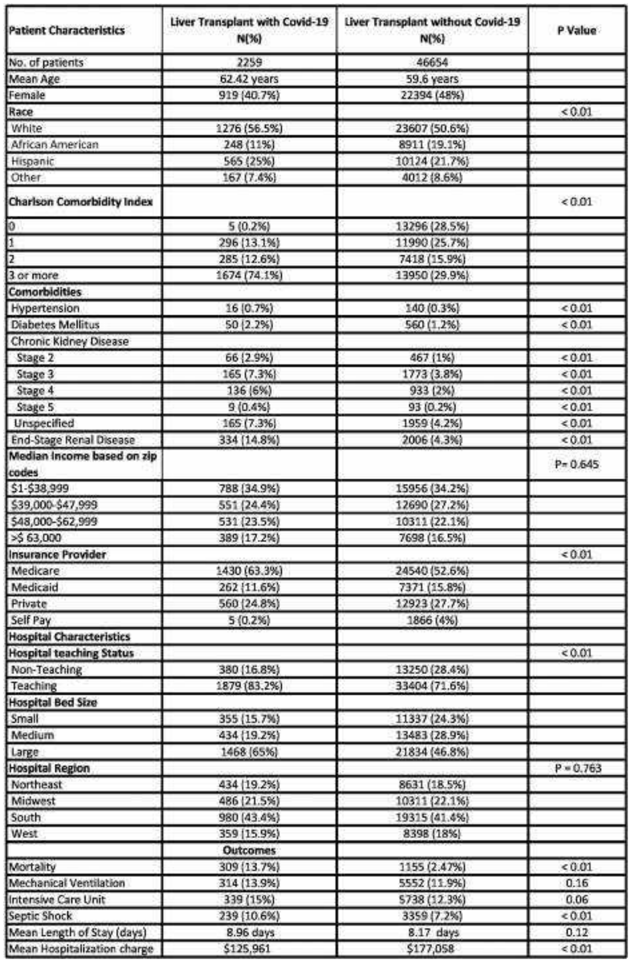
Background: Liver Transplant (LT) recipients are vulnerable to severe infections because of their immunocompromised status. Previous studies had conflicting results regarding the impact of COVID-19 infection on LT recipients. However, most of these studies were single-centered, had a small sample size, or lacked national-level data. In this study, we utilized a large inpatient database to investigate hospital-related outcomes in LT recipients with concurrent COVID-19 infection. **Methods:** We queried the 2020 National Inpatient Sample database to identify LT recipients with COVID-19 hospitalizations who underwent LT in the index hospitalization or had a history of LT. We excluded patients aged < 18 years and trauma-related hospitalizations. Our primary outcomes included comparing all-cause inpatient mortality, mechanical ventilation (MV), and intensive care unit (ICU) utilization between COVID and non-COVID groups. Secondary outcomes included resource utilization, including length of stay (LOS) and total hospitalization charges in both groups. We conducted univariate and multivariate regression analyses to identify the independent predictors of mortality. **Results:** A total of 2,259 adult LT recipients hospitalizations with concurrent COVID-19 infection were identified. The mean age of these patients was 62.42 vs. 59.60 years for the LT without COVID-19 group; the majority were male (59.3% vs. 52%) and Caucasian (56.5% vs. 50.6%) in both groups. Patients with LT and COVID-19 infection had higher mortality (13.70% vs. 2.47%, $p = 0.01$) and developed more septic shock (10.6% vs. 7.2%; $p = 0.01$) but had no increase in ICU utilization (11.3% vs.12.3%; $p = 0.06$) or MV requirement (13.9% vs. 11.9%; $p = 0.16$) as compared to the non-COVID group. Regarding resource utilization, mean LOS (8.96 d vs. 8.17 d; $p = 0.12$) was similar, but mean hospitalization charges were higher in the non-COVID group ($125,961 vs. $177,058; $p = 0.00$). On univariate and multivariate logistic regression analyses, COVID-19 infection, septic shock, MV, and ICU were independent predictors for mortality. **Conclusion:** We found that COVID-19 infection is an independent predictor of mortality in LT recipients, with a 5-fold increase in mortality compared to LT patients without COVID-19. This data (2020) predates the availability of COVID vaccines, and many LT recipients have since been vaccinated. It will be interesting to see if these trends are present for subsequent years of the pandemic. Moreover, when these patients acquire infection, they should be treated promptly with the latest therapies to improve their clinical outcomes.



Patient Characteristics	Liver Transplant with Covid-19 N(%)	Liver Transplant without Covid-19 N(%)	P Value
No. of patients	2259	46654	
Mean Age	62.42 years	59.6 years	
Female	919 (40.7%)	22394 (48%)	
Race			< 0.01
White	1276 (56.5%)	23607 (50.6%)	
African American	248 (11%)	8911 (19.1%)	
Hispanic	565 (25%)	10124 (21.7%)	
Other	167 (7.4%)	4012 (8.6%)	
Charlson Comorbidity Index			< 0.01
0	5 (0.2%)	13296 (28.5%)	
1	296 (13.1%)	11990 (25.7%)	
2	285 (12.6%)	7418 (15.9%)	
3 or more	1674 (74.1%)	13950 (29.9%)	
Comorbidities			
Hypertension	16 (0.7%)	140 (0.3%)	< 0.01
Diabetes Mellitus	50 (2.2%)	560 (1.2%)	< 0.01
Chronic Kidney Disease			
Stage 2	66 (2.9%)	467 (1%)	< 0.01
Stage 3	165 (7.3%)	1773 (3.8%)	< 0.01
Stage 4	136 (6%)	933 (2%)	< 0.01
Stage 5	9 (0.4%)	93 (0.2%)	< 0.01
Unspecified	165 (7.3%)	1959 (4.2%)	< 0.01
End-Stage Renal Disease	334 (14.8%)	2006 (4.3%)	< 0.01
Median Income based on zip codes			P= 0.645
$1-$38,999	788 (34.9%)	15956 (34.2%)	
$39,000-$47,999	551 (24.4%)	12690 (27.2%)	
$48,000-$62,999	531 (23.5%)	10311 (22.1%)	
>$ 63,000	389 (17.2%)	7698 (16.5%)	
Insurance Provider			< 0.01
Medicare	1430 (63.3%)	24540 (52.6%)	
Medicaid	262 (11.6%)	7371 (15.8%)	
Private	560 (24.8%)	12923 (27.7%)	
Self Pay	5 (0.2%)	1866 (4%)	
Hospital Characteristics			
Hospital teaching Status			< 0.01
Non-Teaching	380 (16.8%)	13250 (28.4%)	
Teaching	1879 (83.2%)	33404 (71.6%)	
Hospital Bed Size			
Small	355 (15.7%)	11337 (24.3%)	
Medium	434 (19.2%)	13483 (28.9%)	
Large	1468 (65%)	21834 (46.8%)	
Hospital Region			P = 0.763
Northeast	434 (19.2%)	8631 (18.5%)	
Midwest	486 (21.5%)	10311 (22.1%)	
South	980 (43.4%)	19315 (41.4%)	
West	359 (15.9%)	8398 (18%)	
	Outcomes		
Mortality	309 (13.7%)	1155 (2.47%)	< 0.01
Mechanical Ventilation	314 (13.9%)	5552 (11.9%)	0.16
Intensive Care Unit	339 (15%)	5738 (12.3%)	0.06
Septic Shock	239 (10.6%)	3359 (7.2%)	< 0.01
Mean Length of Stay (days)	8.96 days	8.17 days	0.12
Mean Hospitalization charge	$125,961	$177,058	< 0.01

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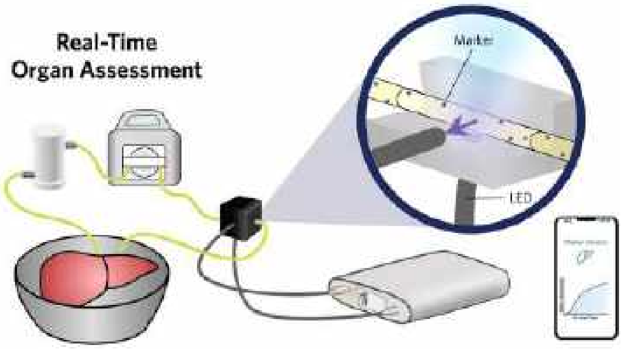
227 | REAL-TIME MEASUREMENTS OF BIOMARKERS FOR GRAFT ASSESSMENT AND PATIENT MONITORING

Florian Huwyler[1], Janina Eden[2], Jonas Binz[1], Leslie Cunningham[1], Richard Sousa Da Silva[2], Max Hefti[1], Pierre A. Clavien[3], Philipp Dutkowski[2] and Mark William Tibbitt[1], (1)ETH Zurich, (2)University Hospital Zurich, (3)University of Zürich

Background: Due to a global shortage of liver grafts, transplant surgeons increasingly resort to transplanting DCD (donated after circulatory death) organs. However, these organs are more susceptible to complications as a result of increased ischemic reperfusion injury. The worst of which is primary non-function, requiring an urgent re-transplantation. To date, there is no reliable metric to estimate the amount of reperfusion injury prior to transplantation. Clinical studies have demonstrated a correlation between flavin mononucleotide (FMN) in the perfusate of hypothermically perfused (HOPE) liver grafts and the risk of post-operative complications, related to mitochondrial damage. These findings indicate that FMN can be used as a biomarker for liver graft quality and motivate the need for robust real-time measurement of FMN. **Methods:** We developed a portable spectrofluorometric device, that can be used directly in the operating room during HOPE, which measures FMN concentration in the perfusate in real-time. Continuous FMN measurements were collected for 26 extended criteria DCD liver grafts prior to being transplanted or discarded. **Results:** Our real-time measurements show that FMN concentration in the perfusate not only indicates severe risk of complications, but also correlates with patient recovery after transplantation. Specifically, post-transplant transaminase expression and coagulation factor synthesis correlated with released FMN. This demonstrates how our technology can be used to assess DCD grafts prior to transplantation, mitigating the risk of non-anastomotic complications and primary non-function. The same approach can be used to also measure other biomarkers non-invasively in perfusate, or even dialysate of dialysis patients. **Conclusion:** Here, we show how liver specific biomarkers that previously were only used in research, could be successfully translated to clinical practice. Further, unprecedented continuous real-time data provides better data sets for research and improved patient diagnosis.



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Disclosure information not available at the time of publication: Janina Eden, Jonas Binz, Richard Sousa Da Silva, Max Hefti, Pierre A. Clavien, Philipp Dutkowski, Mark William Tibbitt

228 | EARLY GRAFT FAILURE AFTER LIVING DONOR LIVER TRANSPLANT

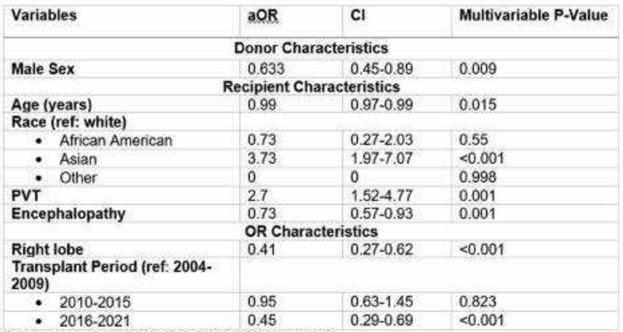
Ahmad Anouti[1], Moustafa Al Hariri[2], Lisa B. VanWagner[3], William M. Lee[3], Arjmand R. Mufti[3], Mark Pedersen[4], Jigesh Shah[1], Steven Hanish[1], Parsia A. Vagefi[5], Thomas G. Cotter[4] and Madhukar Patel[3], (1) University of Texas Southwestern, (2)Qatar University, (3)University of Texas Southwestern Medical Center, (4) University of Texas Southwestern Medical Center, Dallas, TX, (5)UT Southwestern Medical Center

Background: Living donor liver transplantation (LDLT) has been increasing in the United States (US). While data exists on longer-term patient and graft outcomes, a contemporary analysis of short-term outcomes is needed to better understand risk factors and opportunities for improvement. **Methods:** Adult (≥ 18 y) LDLT recipients from January 2004 to December 2021 were analyzed from the United States Scientific Registry of Transplant Recipients (SRTR). Graft status at 30 days was assessed with graft failure defined as retransplantation or death. Bivariate analysis of continuous and categorical variables was performed, and a multivariable logistic regression was used to identify risk factors of early graft failure. **Results:** During the study period, 4,544 LDLTs were performed with a graft failure rate of 3.4% (155/4544) at 30 days. Grafts from male donors (aOR: 0.63, CI: 0.45-0.89, $p = 0.009$), right lobe grafts (aOR: 0.41, CI: 0.27-0.62, $p < 0.001$), older recipient age (aOR: 0.99, CI: 0.97-0.99, $p = 0.015$), and higher recipient albumin (aOR: 0.73, CI: 0.57-0.93, $p = 0.011$) were associated with superior early graft outcomes, whereas, Asian recipient race (vs. White;

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

aOR: 3.37, CI: 1.98-7.07, $p < 0.001$) and a history of recipient PVT (aOR: 2.7, CI: 1.52-4.77, $p = 0.001$) were associated with inferior outcomes. LDLTs performed during the most recent 2016-2021 period (compared to 2004-2009 and 2010-2015) resulted in significantly superior outcomes (aOR: 0.45, $p < 0.001$, CI: 0.23-0.69) (Table 1). **Conclusion:** Our study demonstrates that while short-term adult LDLT graft failure is uncommon, there are opportunities for optimizing outcomes by prioritizing right lobe donation, improving candidate nutritional status, and careful pretransplant risk assessment of candidates with known PVT. Notably, a period effect exists whereby increased LDLT experience in the most recent era correlated with improved outcomes.

Table 1: Multivariable analysis of early graft failure in LDLT recipients.



Variables	aOR	CI	Multivariable P-Value
Donor Characteristics			
Male Sex	0.633	0.45-0.89	0.009
Recipient Characteristics			
Age (years)	0.99	0.97-0.99	0.015
Race (ref: white)			
• African American	0.73	0.27-2.03	0.55
• Asian	3.73	1.97-7.07	<0.001
• Other	0	0	0.998
PVT	2.7	1.52-4.77	0.001
Encephalopathy	0.73	0.57-0.93	0.001
OR Characteristics			
Right lobe	0.41	0.27-0.62	<0.001
Transplant Period (ref: 2004-2009)			
• 2010-2015	0.95	0.63-1.45	0.823
• 2016-2021	0.45	0.29-0.69	<0.001

aOR: Adjusted Odds Ratio; PVT: Portal Vein Thrombosis

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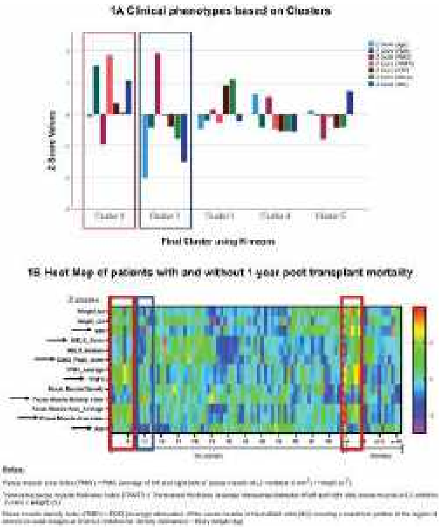
229 | PHENOTYPIC CLUSTERING IDENTIFIES HIGH-RISK PROFILES FOR SARCOPENIA & 1-YEAR POST-TRANSPLANT MORTALITY IN PATIENTS WITH END-STAGE LIVER DISEASE

Hiteshi Dhami- Shah[1], Gautham Pranesh[2], Disha Mogre[3], Ameet Mandot[1], Rashmi Badhe[1], Parul Garde[1], Madhuri Nigudkar[3], Anuradha Ramesh[3], Jagmeet Madan[3] and Samir Ramnik Shah[1], (1)Global Hospitals, Mumbai, (2)Mitopower LLC, (3)SVT College of Home Science

Background: Sarcopenia in end-stage liver disease (ESLD) has been identified as a risk factor for increased mortality. Radiological parameters; psoas muscle area index (PMAI) & transverse psoas muscle thickness index (TPMTI) assess muscle quantity. While psoas muscle density index (PMDI) assesses muscle quality. Both identify muscle wasting, atrophy & myosteatosis. Aim: The study evaluated ESLD phenotypes & their association with 1-year post-transplant mortality. The relationship between high PMAI/TPMTI & low PMDI, suggesting a possibility of larger but weaker muscles due to myosteatosis was investigated. **Methods:** A total of 101 ESLD subjects were included. A retrospective analysis was conducted on 86 subjects with complete data. Clinical characteristics (age, PMAI, TPMTI, PMDI, CTP score, MELD score, BMI) were normalized using z-scores. Hierarchical & k-means clustering identified distinct phenotypes. Mortality rates across clusters were analyzed to identify high-risk groups. **Results:** Five distinct phenotypes were identified. Cluster 1 represented individual's with an average age & high PMAI, TPMTI, BMI & low PMDI. CTP & MELD scores were close to average. Cluster 2 comprised young subjects with low PMAI, BMI, CTP, MELD & high PMDI. Cluster 3 was similar to Cluster 2, with younger subjects & baseline PMAI, PMDI, BMI & low TPMTI. CTP & MELD scores were high. Cluster 4 consisted of older individual's with high PMDI & low PMAI, TPMTI, BMI, CTP & MELD. Cluster 5 represented a baseline age group with baseline PMAI, high BMI & low PMDI, TPMTI, CTP & MELD. Cluster 1 had the highest mortality rate 41.7% & Cluster 2 had the lowest mortality rate (0%) compared to the overall mortality rate of 19.8%. Clusters 3, 4, & 5 had similar mortality rates of 17.4%, 17.9%, & 15.8%, respectively. **Conclusion:** Clustering effectively identified high-risk phenotypes for sarcopenia & 1-year mortality in ESLD patients. Cluster 1, despite average age & baseline MELD, exhibited the highest mortality rate with low PMDI & high PMAI, TPMTI, & BMI. This suggests the possibility of myosteatosis contributing to mortality. Cluster 2 represented the lowest-risk group with younger patients having low BMI, MELD & high PMDI. These findings have implications for risk stratification & potential interventions to improve outcomes in this vulnerable patient population post-transplant.



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230 | PREHABILITATION IN LIVER TRANSPLANT CANDIDATES IMPROVES FRAILTY METRICS LEADING TO IMPROVED SURVIVAL

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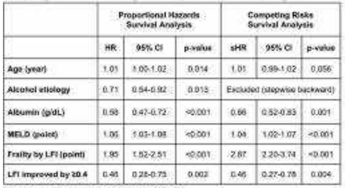
Background: An outpatient prehabilitation strategy is feasible and effective in improving frailty in liver transplant (LT) candidates. We previously showed that attendance to physical therapy (PT) sessions results in a significant reduction in mortality, but were unable identify the frailty change threshold that yields such benefit. The aim of this study was to determine the impact of variation of frailty metrics on mortality and to identify a minimum clinically important difference that could provide a survival advantage to LT candidates with frailty. **Methods:** LT candidates who attended PT consultation at our center between 2018 and 2022 were prospectively included. All patients received a personalized prehabilitation prescription and regular follow-up visits with a dedicated LT PT. Physical fitness assessment included the LFI and 6-min walk test (6MWT). Changes in LFI and 6MWT between PT visits were averaged and used as a measure of prehabilitation engagement/success. Multivariable survival models, including competing risks models against LT, were fit to investigate the impact of frailty metrics and prehabilitation engagement on mortality. **Results:** A total of 1275 patients were prospectively included (59% male, age 57 ± 11, BMI 30 ± 7, MELD 14 ± 6) and their data collected during 1973 PT visits (193 attended two visits, 162 attended three or more). Main indications for LT were alcohol (31%) and NAFLD (29%). Median LFI was 3.79 (3.21-4.41) and 23% were frail, whereas median 6MWT was 336 m (243-404) and 26% were frail; between-metrics agreement was 83%. In subjects who improved their LFI score (n = 227/351), the absolute change was -0.38 (-0.17 to -0.84), whereas for 6MWT (n = 209/332), the absolute change was 54 m (25-105). A total of 677 (55%) patients were waitlisted, LT occurred in 462 (37%) and death in 335 (26%). LFI improvement by 0.4 was associated with lower pre-transplant mortality (Table 1 and Figure 1). Sensitivity analyses restricted to patients with two or more LT PT visits did not change the findings. Surprisingly, improvement in 6MWT was not associated with a survival advantage. **Conclusion:** Prehabilitation in LT candidates was associated with significant improvement in LFI and 6MWT. A minimum improvement in LFI by 0.4 was associated with better survival, independently of frailty status, and it could be used as an objective and clinically relevant on-training endpoint for frailty intervention.

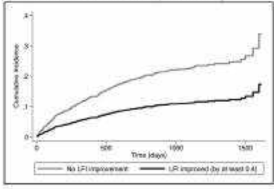
Table 1: Cox proportional hazards multivariable survival analysis; Competing risks model including liver transplantation as a competing risk.



	Proportional Hazards Survival Analysis			Competing Risks Survival Analysis		
	HR	95% CI	p-value	sHR	95% CI	p-value
Age (year)	1.01	1.00-1.02	0.014	1.01	0.99-1.02	0.056
Alcohol etiology	0.71	0.54-0.92	0.013	Excluded (stepwise backward)		
Albumin (g/dL)	0.58	0.47-0.72	<0.001	0.66	0.52-0.83	0.001
MELD (point)	1.06	1.03-1.08	<0.001	1.04	1.02-1.07	<0.001
Frailty by LFI (point)	1.95	1.52-2.51	<0.001	2.87	2.20-3.74	<0.001
LFI improved by ≥0.4	0.46	0.28-0.75	0.002	0.46	0.27-0.78	0.004

All models adjusted by sex and number of PT visits.

Figure 1: Competing-risks regression curve. LFI improvement by at least 0.4 was associated with improved mortality.



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231 | IMPACT OF COMORBIDITIES ON LIVER TRANSPLANTATION: A PROSPECTIVE AND MULTICENTRIC ANALYSIS

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Universitario Rio Hortega, (8)H. De Asturias, (9)H. Puerta De Hierro, (10)H. U Alicante, (11)H. De Cruces, (12)CH Canarias, (13)H Val D'hebron, (14)Complexo Hospitalario Universitario De Santiago, Coruña, (15)HU La Fe, (16)University of Navarra, (17)CNIO, (18) Itainnova, (19)Universidad De Zaragoza, (20)Servicio De Aparato Digestivo. Hospital General Universitario Gregorio Marañón

Background: Comorbidity plays an important role in the mortality of patients both on the waiting list and after liver transplantation (LT). To analyze the impact of comorbidities on LT, a prospective and multicentre study (HEPA_TIC) has been launched. **Methods:** Analysis of 1440 consecutive patients included in LT waiting list, in 18 Spanish hospitals, from October 2019 to October 2022. Retransplantation, multivisceral transplantation and patients younger than 16 years were excluded. Comorbidities at the time of listing, and follow-up variables were collected. The analysis of comorbidities was disaggregated by sex. To group comorbidities, three types of unsupervised algorithms were applied using matching-learning: agglomerative clustering, Kmodes, and spectral clustering. Groups were compared by the log Rank test in their evolution. **Results:** Patients were predominantly male (76.6%) with a median age of 61.7 years IQR (56-66); 60.7 years in females IQR (54-67) and 61.8 in males (57-66) ($p < 0.05$). Decompensated cirrhosis was the most frequent indication with no differences in both sexes. Hepatocellular carcinoma was significantly more frequent in males (45.9% vs. 24.6%; $p < 0.001$). The most frequent comorbidities were diabetes and arterial hypertension. Diabetes, COPD and cardiovascular disease were significantly higher in men ($p < 0.05$), while chronic kidney disease was higher in women ($p < 0.05$). Only 8.1% of the listed patients had no comorbidities. The number of comorbidities was higher in males than in females ($p < 0.001$). 34% of the listed men and 19.8% of the women had more than three comorbidities. The number of comorbidities was associated with lower survival after liver transplantation ($p = 0.04$). The three types of algorithms grouped patients into clusters that differed in the prevalence of various comorbidities. Follow-up analyses found significant differences ($p > 0.05$) in survival after transplantation among the clusters defined by the algorithms. Metabolic syndrome represented the greatest difference between the groups. Groups with a higher prevalence of this syndrome had a lower survival rate after transplantation. **Conclusion:** Comorbidities are highly prevalent in patients with liver disease on the transplant waiting list, and they differ between men and women. A higher number of comorbidities is associated with lower survival after transplantation. There are patterns of patients with different comorbidities that exhibit differences in survival after LT.

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232 | NON-ALCOHOLIC STEATOHEPATITIS (NASH) HAS BECOME THE MOST COMMON INDICATION FOR LIVER TRANSPLANTATION AMONG CANDIDATES WITH HEPATOCELLULAR CARCINOMA IN THE UNITED STATES

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Background: High prevalence of obesity in the U.S. is driving the burden of non-alcoholic steatohepatitis (NASH) and associated adverse clinical outcomes including NASH-related end-stage liver disease and hepatocellular carcinoma (HCC). Our aim was to assess the most recent trends in patients with chronic liver disease (CLD) listed for liver transplantation (LT) in the U.S. using a national registry. **Methods:** The Scientific Registry of Transplant Recipients (SRTR) was used to select adult (e 18 y at listing) LT candidates included between 2013-2022. Primary and secondary listing etiologies were used to identify patients with the most common etiologies of CLD. **Results:** There were 116,292 LT candidates with a known etiology of CLD. In candidates without HCC, the most common CLD etiology was alcoholic liver disease (ALD) which increased from 23% (2013) to 48% (2022); the most rapid increase happened

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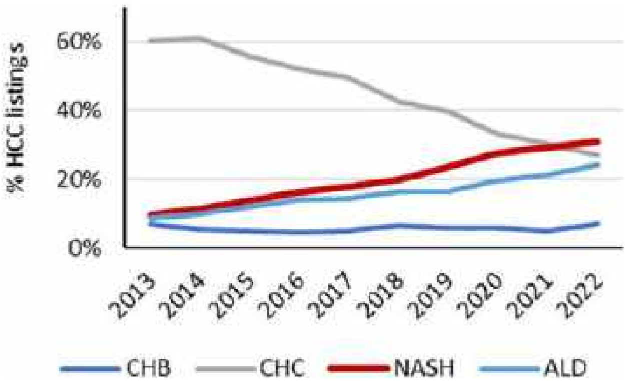
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

between 2019-2022 (from 38% to 48%). The second most common indication for non-HCC LT was NASH, the proportion of which increased from 19% (2013) to 27% (2022). In contrast, rates of chronic hepatitis C (CHC) decreased from 28% (2013) to 4% (2022) and chronic hepatitis B (CHB) declined from 1.8% (2013) to 1.1% (2022) (all trend $p < 0.01$). Cumulatively, 21% (n = 24,657) of candidates listed for LT had HCC. However, the proportion of HCC decreased from 24-25% (2013-2016) to 17% (2021-2022). Among candidates with HCC, the proportion of CHC decreased from 60% (2013) to 27% (2022) while NASH increased from 10% to 31% and ALD from 9% to 24%, respectively (all trend $p < 0.0001$) (Figure). On the other hand, the proportion of CHB remained stable between 5 to 7% (trend $p = 0.62$). Among candidates with HCC, the rapid increase in the proportion of NASH continued during the most recent study years: 20% (2018) to 28% (2020) to 31% (2022), and the increasing trend remained significant overtime after adjustment for candidates' age, sex, ethnicity, obesity, and type 2 diabetes. The average magnitude of increase in the proportion of NASH in candidates with HCC in 2018-2022 was +2.8 percentage points per year ($p < 0.0001$). **Conclusion:** The impact of different etiologies of CLD to LT burden in the U.S. has been changing over the last decade. ALD and NASH remain the two most common indications for non-HCC-LT, while NASH is currently the most common indication for HCC-LT.



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233 | PREDICTORS OF RENAL RECOVERY AND SURVIVAL OUTCOMES IN LIVER TRANSPLANT RECIPIENTS MEETING SLK ELIGIBILITY CRITERIA

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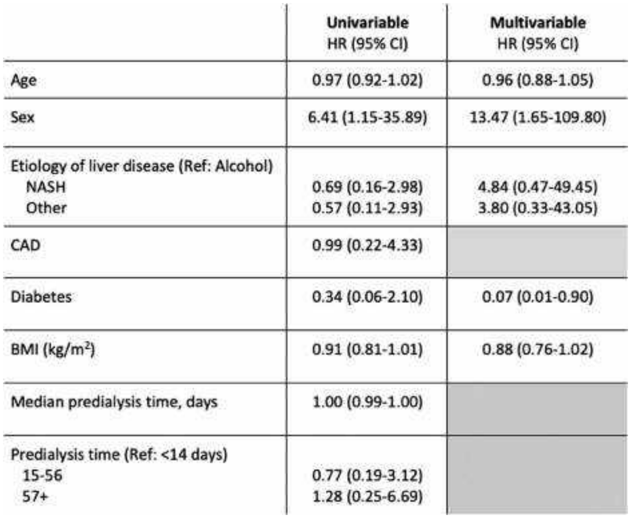
Background: The 2017 UNOS simultaneous liver-kidney transplant (SLK) policy establishes the minimum eligibility criteria for SLK listing and a mechanism to expedite kidney after liver transplantation (Safety Net). Candidate selection for SLK versus Safety Net requires further refinement. Our AIMS were two-fold: 1) to analyze the pre- and post-liver transplant progress of patients eligible for SLK, who instead underwent liver transplant (LT); 2) to compare the outcomes of these patients with a historical cohort of SLK patients. **Methods:** Single center retrospective chart review was completed for LT recipients with eGFR (estimated glomerular filtration rate) < 35 ml/min at time of LT or had a kidney transplant evaluation episode opened prior to LT from 2017-2022. These patients were compared to patients that received SLK from 2007-2016, prior to the 2017 policy change. Demographic data and clinical data, length of hospital stay, number of hospital days post-transplant, and survival data were collected. Renal recovery was defined as recovery of eGFR to > 20ml/min post LT. **Results:** 45 LT recipients who qualified for potential SLK from 2017-2022 and 55 patients who received SLK from 2007-2016 were compared. Of these 45 patients (Safety Net group), 17 patients received a kidney transplant after a liver transplant (KALT), and 28 patients received a liver transplant alone (LTA). Median follow-up time was 6.4 years in the SLK group and 2.2 years in the safety net group. No difference was found in overall three-year post-LT survival between patients who did or did not receive SLK ($p = 0.14$) (Table). Among the 28 patients that received LTA, 19 achieved renal recovery within 12 months, 7 were declined for KALT (4 for frailty and 3 for other causes) and 2 died. Five of these patients remain on dialysis. In the patients with renal recovery, average eGFR 1-year post-transplant was 35 ml/min. In a multivariable logistic regression model adjusted for age and sex, predictors of renal recovery included male sex ($p = 0.02$) and absence of diabetes ($p = 0.04$). Between the KALT and LTA groups, there were no significant differences in days in hospital after transplant, length of ICU stays, number of hospitalizations, or episodes of rejection. **Conclusion:** Safety Net protocol provides similar survival in patients that receive a liver transplant alone compared to a historical SLK cohort. In our cohort, 19 out of 28 potential SLK candidates recovered renal function post LT, with male sex and absence of diabetes predicting recovery.



	Univariable HR (95% CI)	Multivariable HR (95% CI)
Age	0.97 (0.92-1.02)	0.96 (0.88-1.05)
Sex	6.41 (1.15-35.89)	13.47 (1.65-109.80)
Etiology of liver disease (Ref: Alcohol)		
NASH	0.69 (0.16-2.98)	4.84 (0.47-49.45)
Other	0.57 (0.11-2.93)	3.80 (0.33-43.05)
CAD	0.99 (0.22-4.33)	
Diabetes	0.34 (0.06-2.10)	0.07 (0.01-0.90)
BMI (kg/m²)	0.91 (0.81-1.01)	0.88 (0.76-1.02)
Median predialysis time, days	1.00 (0.99-1.00)	
Predialysis time (Ref: <14 days)		
15-56	0.77 (0.19-3.12)	
57+	1.28 (0.25-6.69)	

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Disclosure information not available at the time of publication: Xingxing Cheng, Bonnie Chow, Meera Bhargava, Thomas Pham, Paul Yien Kwo

234 | ESTIMATING GFR IN PATIENTS WITH DECOMPENSATED CIRRHOSIS AWAITING TRANSPLANT: UPDATED GRAIL WITHOUT RACE PERFORMS BETTER THAN CKD EPI 2021

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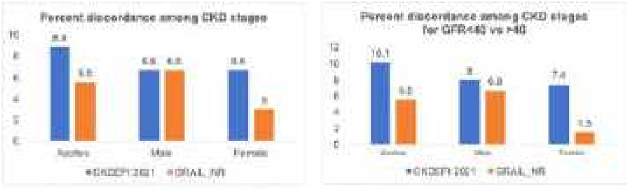
Background: Accurate estimation of glomerular filtration rate (GFR) is important for decisions regarding dual organ transplantation and patient management on the waitlist. Currently, a novel race free equation (CKD-EPI AS, Inker et al. NEJM 2021) is the reference standard for estimating GFR across the US. However, its performance in patients with cirrhosis was never validated. Further, performance of CKD EPI AS 2021 may be suboptimal in cirrhosis patients with low GFR, ascites and frail patients (AASLD 2022). We have shown that liver specific equations (GFR assessment in liver disease, GRAIL, Asrani et al. Hepatology 2019) have better performance as compared to other GFR equations. We sought to develop and validate an updated GRAIL without race (GRAIL_NR). **Methods:** We examined all cirrhosis patients with protocol measured GFR between 1985-2015 using iothalamate clearance. We estimated GFR using novel non-race equations: CKD-EPI 2021, CKD-EPI refit to liver population, as well as GRAIL_NR. Model was developed using cumulative probability models, associations between variables and mGFR were examined via linear association and restricted cubic spline and validated using split sample. The final components were age, sex, albumin, creatinine, and BUN. Addition of interactions or other variables (BSA, serum sodium) did not appreciably improve performance. We compared Concordance Correlation Coefficient, bias, precision, % agreement CKD stages and measurements within 30% of mGFR (p30). We further examined performance in relevant subsets: ascites, sex and low GFR (GFR < 40 vs > 40 ml/min/1.73m^2). **Results:** Updated GRAIL_NR was more precise and had higher concordance (0.82, 0.79-0.85) as compared to CKD-EPI 2021 (0.78, 0.74-0.81) as well as refit CKD-EPI AS_Liver (0.77, 0.73-0.81). As compared to CKD-EPI 2021, updated GRAIL_NR had lower bias (-0.8 vs. +1.56, mGFR-eGFR), higher percent agreement for CKD staging (95.4% vs. 93.3%), higher agreement for low GFR vs high GFR (cutoff 40, 95.4% vs. 93.7%) and higher measurements within 30% of mGFR (78.7% vs. 74.3%). We examined differences in relevant subsets. Percent discordance between estimated CKD stage and actual CKD stage was lower with GRAIL_NR in patients with ascites and females. (Figure) This was especially pronounced when limited to patients with GFR < 40ml/min/1.73m^2 **Conclusion:** A race-free eGFR equation developed and validated in patients with may help guide decision making in patients with decompensated cirrhosis listed for transplantation, especially in subsets where prediction of renal function is suboptimal.



Percent discordance between estimated CKD stage and actual CKD stage was lower with GRAIL_NR in patients with ascites and females. This was especially pronounced when limited to patients with GFR<40ml/min/1.73m^2

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235 | ABILITY OF SECOND HARMONIC GENERATION/TWO-PHOTON EXCITATION FLUORESCENCE IMAGING AND AI ANALYSIS TO DETECT AND QUANTIFY DRUG-INDUCED, PARAMETER-LEVEL CHANGES OF FIBROSIS: RESULTS FROM THE FALCON-1 CLINICAL TRIAL

Kutbuddin Akbary[1], Dean Tai[2], Ya-Yun Ren[1], Anne Minnich[3] and Edgar D. Charles[3], (1)Histoindex Pte Ltd, *(2)Histoindex Pte Ltd, Singapore, (3)Bristol Myers Squibb*

Background: FDA recommended histopathological end-points for NASH clinical trials may not be fully evaluated by conventional histological staging. Shorter time frames in NASH trials make it difficult to assess changes in treatment-induced fibrosis with current classification systems. Assessment of specific morphological fibrosis parameters and their quantification in specific zones of NASH-CRN classification, can be done by SHG/TPE-based AI platforms. NASH-CRN parameters may map overall fibrosis changes, but any specific drug-induced changes may not be fully quantified by these alone. This detailed analysis helps overcome limitations of conventional histological examination and describe fibrosis changes and drug-induced effects. **Methods:** Biopsy slides were obtained from FALCON-1 clinical trial (24-week randomized double-blind, placebo-controlled phase 2 study of 10, 20, and 40 mg pegbelfermin in NASH patients, NCT03486899). SHG/TPE microscopy and AI analysis were used to estimate NASH-CRN fibrosis parameters as continuous variables for 176 paired biopsy slides. Additional Zone 2 fibrosis parameters were evaluated to measure drug-induced effects. Based on pathologist classification of changes in fibrosis stage of biopsies comparing baseline and post-treatment slides, they were divided into three groups: Progressive (1-stage or more increase in fibrosis), Regressive (1-stage or more decrease in fibrosis), and No-change (no change in fibrosis stage). These changes were depicted using radar maps with normalized values. **Results:** In regressive group, there was reduction of fibrosis as per NASH-CRN parameters in both treatment and placebo cohort, measured by SHG/TPE microscopy and AI analysis. Reductions in placebo cohort were statistically insignificant; in treatment cohort (which included patients of all drug doses combined), reduction in fibrosis of periportal and perisinusoidal regions were statistically significant (Figure 1A). Fibrosis measurements in No-change group follow similar pattern of reduction as in Regressive group (Figure 1B). Specific Zone 2 fibrosis parameters (S1-S3) for treatment-cohort of all 3 groups are shown in Figure 1C. These show statistically significant reductions in fibrosis parameters post-treatment, despite being labelled as regressive, no-change and progressive by pathologist classifications. Parameters S1-S3 in placebo-cohort also show reductions, but were statistically insignificant. **Conclusion:** SHG/TPE-based AI platforms allowed for quantification and mapping of specific parameters revealing improvement in both NASH-CRN and Zone 2 fibrosis parameters not seen in manual NASH-CRN staging. They may be able provide quantitative drug-induced specific changes in fibrosis which can be more sensitive than manual staging. This may be ideal for phase 2 clinical trials which have short time frames, and help better design and strategize phase 3 trials.

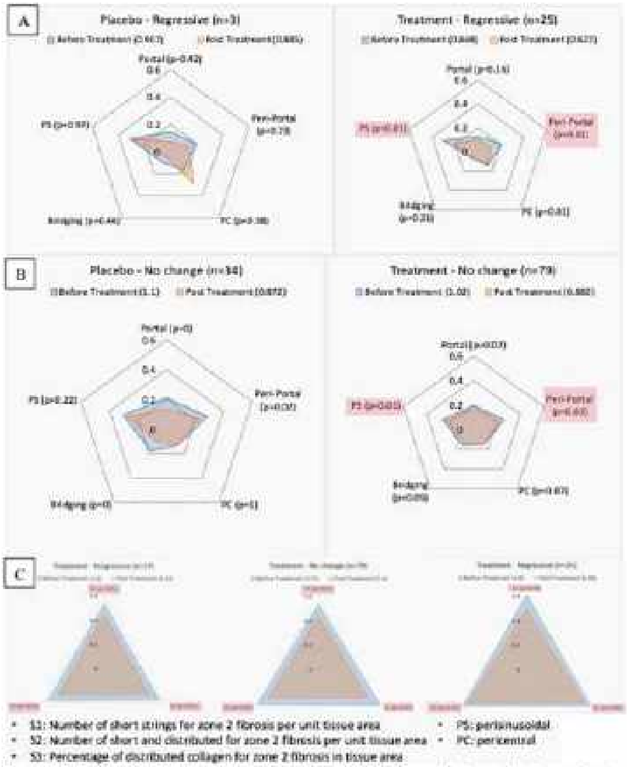

Figure 1: Highlighted p-values indicate statistically significant difference between baseline and post-treatment values. **(A)** Biopsies in Regressive group showing overall reduction in NASH-CRN fibrosis parameters in both the placebo and treatment cohort. **(B)** Biopsies in No-change group showing similar reductions in NASH-CRN fibrosis parameters. **(C)** Specific Zone 2 fibrosis parameters showing statistically significant reductions in all the three groups of biopsies. These parameters, not described in the NASH-CRN classification, may indicate drug- induced fibrosis reductions.

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Edgar D. Charles – Bristol Myers Squibb: Employee, Yes, No; Bristol Myers Squibb: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

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236 | DEVELOPMENT AND VALIDATION OF THE NAFLD FAMILIAL RISK SCORE TO DETECT ADVANCED FIBROSIS: A PROSPECTIVE, MULTICENTER STUDY

Daniel Q Huang[1], *Noora Ahlholm*[2], *Panu Luukkonen*[2], *Kimmo Porthan*[2], *Maral Amangurbanova*[3], *Ricki Bettencourt*[3], *Harris Siddiqi*[3], *Vanessa Cervantes*[4], *Christie Hernandez*[3], *Scarlett Lopez*[4], *Egbert Madamba*[3], *Lisa M. Richards*[3], *Katriina Nemes*[2],

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

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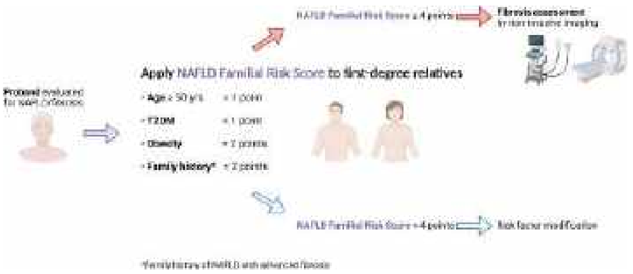
Background: Nonalcoholic fatty liver disease (NAFLD)-related fibrosis is heritable, but it is unclear how family history may be used to identify first-degree relatives with advanced fibrosis. We aimed to develop and validate a simple risk score to identify first-degree relatives of probands who have undergone assessment of liver fibrosis who are at higher risk of NAFLD with advanced fibrosis. **Methods:** This prospective, cross-sectional, familial study consisted of a derivation cohort from San Diego,USA, and a validation cohort from Helsinki, Finland. This study included consecutive adult probands ($n = 242$) with NAFLD and advanced fibrosis, NAFLD without advanced fibrosis, and non-NAFLD, with at least one of their first-degree relatives. All included probands and first-degree relatives underwent evaluation of liver fibrosis, the majority by magnetic resonance elastography.Models were derived utilizing the UCSD (derivation) cohort to detect the presence of NAFLD with advanced fibrosis. Univariable and multivariable logistic regression analyses were performed in the UCSD (derivation) cohort for factors associated with NAFLD and advanced fibrosis. To develop a simple risk score based on a points system, regression coefficients from the logistic regression model were transformed into scores by rounding to an integer. The score was then externally validated in the Helsinki (validation) cohort. **Results:** A total of 396 first-degree relatives (64% male) were included. The median (IQR) age and BMI were 47 (32-62) years and 27.6 (24.1-32.5) kg/m^2, respectively. Age (1-point), type 2 diabetes (1-point), obesity (2-points) and proband with NAFLD and advanced fibrosis (2-points) were predictors of advanced fibrosis among first-degree relatives in the derivation cohort ($n = 220$) and formed the NAFLD Familial Risk score. The area under the receiver operator characteristic curve (AUC) of the NAFLD Familial Risk score for detecting advanced fibrosis was 0.94 in the validation cohort ($n = 176$). The NAFLD Familial Risk score outperformed the Fibrosis-4 index in the validation cohort (AUC 0.94 versus 0.70, $p = 0.02$). **Conclusion:** The NAFLD Familial Risk Score accurately identifies NAFLD with advanced fibrosis in first-degree relatives of probands who have undergone an assessment of liver fibrosis. It is simple, does not require a calculator or extensive laboratory investigations, and may be a helpful alternative to FIB-4 for screening first-degree relatives. These data may have implications for surveillance in NAFLD.


Proband evaluated for NAFLD/fibrosis
Apply NAFLD Familial Risk Score to first-degree relatives
• Age ≥ 50 yrs = 1 point
• T2DM = 1 point
• Obesity = 2 points
• Family history* = 2 points
NAFLD Familial Risk Score ≥ 4 points
Fibrosis assessment by non-invasive imaging
NAFLD Familial Risk Score < 4 points
Risk factor modification
*Family history of NAFLD with advanced fibrosis

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Rohit Loomba – Aardvark Therapeutics: Consultant, No, No; Altimmune: Consultant, No, No; Anylam/Regeneron: Consultant, No, No; Amgen: Consultant, No, No; Arrowhead Pharmaceuticals: Consultant, No, No; AstraZeneca: Consultant, No, No; Bristol-Myer Squibb: Consultant, No, No; CohBar: Consultant, No, No; Eli Lilly: Consultant, No, No; Galmed Pharmaceuticals: Consultant, No, No; Gilead: Consultant, No, No; Glympse Bio: Consultant, No, No; Hightide: Consultant, No, No; Inipharma: Consultant, No, No; Intercept: Consultant, No, No; Inventiva: Consultant, No, No; Ionis: Consultant, No, No; Janssen Inc.: Consultant, No, No; Madrigal Pharmaceuticals: Consultant, No, No; Metacrine, Inc.: Consultant, No, No; NGM Biopharmaceuticals: Consultant, No, No; Novartis: Consultant, No, No; NovoNordisk: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Sagimet Biosciences: Consultant, No, No; Theratechnologies: Consultant, No, No; 89 bio: Consultant, No, No; Terns Pharmaceuticals: Consultant, No, No; Viking Therapeutics: Consultant, No, No; 89 bio: Stock – privately held company (individual stocks and stock options), No, No; Sagimet Biosciences: Stock – privately held company (individual stocks and stock options), No, No; Arrowhead Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AstraZeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boehringer-Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol-Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Eli Lilly: Grant/Research Support (research funding from ineligible companies should be

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237 | THE IMPACT OF GENETIC RISK ON THE PREVALENCE OF ADVANCED FIBROSIS AND CIRRHOSIS IN PROSPECTIVELY ASSESSED PATIENTS WITH TYPE 2 DIABETES

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Background: Genetic factors contribute to the risk and severity of NAFLD and fibrosis, however, the utility of genetic testing to stratify the risk for advanced fibrosis and cirrhosis among patients with type 2 diabetes mellitus (T2DM) remains poorly characterized. **Methods:** This prospective study enrolled adults age e 50 years with T2DM recruited from primary care or endocrinology clinics. Participants underwent a standardized clinical research visit with fasting labs and detailed assessment for other causes of liver disease. Polygenic risk score (PRS) was the sum of established risk alleles in *PNPLA3*, *TM6SF2* and *SERPINA1* minus the protective variant in *HSD17B13* and dichotomized into low and high risk according to the median. Magnetic resonance elastography (MRE), vibration controlled transient elastography (VCTE) and controlled attenuation parameter (CAP) were performed. Advanced fibrosis was defined as MRE e 3.63 kPa, or VCTE e 8.8 kPa if MRE was not available. Cirrhosis was defined as MRE e 4.67 kPa or VCTE e 15 kPa if MRE was not available. **Results:** Of 382 included patients the mean age and BMI were 64.8 (± 8.4) years and 31.7 (± 6.2) kg/m^2, respectively. The cohort was 61.5% female, and 40.9% Hispanic. The prevalence advanced fibrosis and cirrhosis was 12.3% and 5.24%, respectively and higher PRS was associated with higher risk of cirrhosis (2.7% vs. 7.5%, $p = 0.037$) (Fig. 1a). Evaluating *PNPLA3* alone revealed that patients with CG or GG vs. CC were associated with higher risk of both advanced fibrosis (15.2% vs. 8.2%, $p = 0.042$) and cirrhosis (7.1% vs. 2.5%, $p = 0.046$) (Fig. 1b). The prevalence of advanced fibrosis and cirrhosis by PRS was further stratified by the Fibrosis-4 (FIB-4) index categories; < 1.3, 1.3-2.67 and > 2.67. High PRS was associated with an increased risk of advanced fibrosis among those with low FIB-4 index (FIB-4 < 1.3) (9.6% vs 2.3%, $p = 0.036$) but was not significantly different in other FIB-4 categories. **Conclusion:** Utilizing a well-phenotyped, prospective cohort of adults with T2DM we found that genetic risk amplifies the prevalence of advanced fibrosis and cirrhosis, and evaluating *PNPLA3* alone stratifies patients well. Adding an assessment of genetic risk to recent recommendations to screen at risk populations, including T2DM, may add precision to identifying patients at the greatest risk of liver related morbidity and mortality and identify patients with low FIB-4 who are still at risk for liver related morbidity and mortality.

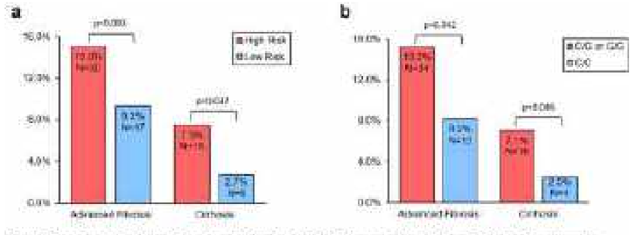

Figure 1. Prevalence of advanced fibrosis and cirrhosis in adults 50 years or older with type 2 diabetes. Prevalence was stratified by (a) overall polygenic risk score and (b) *PNPLA3* allele genetic risk alone (C/G or G/G confer risk).

Disclosures: Rohit Loomba – Aardvark Therapeutics: Consultant, No, No; Altimmune: Consultant, No, No; Anylam/Regeneron: Consultant, No, No; Amgen: Consultant, No, No; Arrowhead Pharmaceuticals: Consultant, No, No; AstraZeneca: Consultant, No, No; Bristol-Myer Squibb: Consultant, No, No; CohBar: Consultant, No, No; Eli Lilly: Consultant, No, No; Galmed Pharmaceuticals: Consultant, No, No; Gilead: Consultant, No, No; Glympse Bio: Consultant, No, No; Hightide: Consultant, No, No; Inipharma: Consultant, No, No; Intercept: Consultant, No, No; Inventiva: Consultant, No, No; Ionis: Consultant, No, No; Janssen Inc.: Consultant, No, No; Madrigal Pharmaceuticals: Consultant, No, No; Metacrine, Inc.: Consultant, No, No; NGM Biopharmaceuticals: Consultant, No, No; Novartis: Consultant, No, No; NovoNordisk: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Sagimet Biosciences: Consultant, No, No; Theratechnologies: Consultant, No, No; 89 bio: Consultant, No, No; Terns Pharmaceuticals: Consultant, No, No; Viking Therapeutics: Consultant, No, No; 89 bio: Stock – privately held company (individual stocks and stock options), No, No; Sagimet Biosciences: Stock – privately held company (individual stocks and stock options), No, No; Arrowhead Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AstraZeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boehringer-Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol-Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Eli Lilly: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Galectin Therapeutics: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Galmed Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Hanmi: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Inventiva: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Ionis: Grant/Research

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

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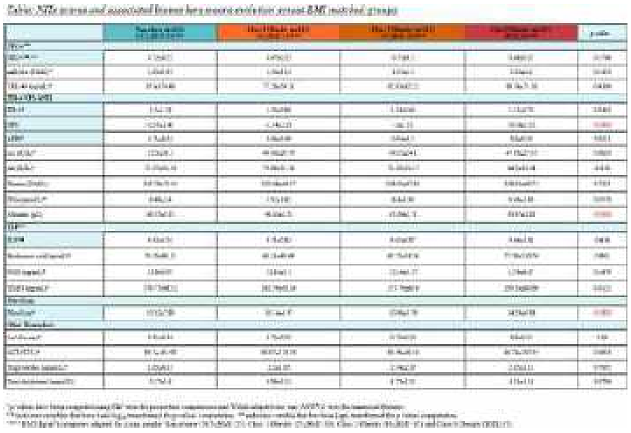
Background: While obesity is a risk factor for NAFLD, patients across the BMI spectrum are affected by the disease, creating a need for reliable non-invasive tests (NITs) with performances that are not affected by BMI. While most of standard NITs are designed to detect advanced fibrosis, NIS2+™, an optimization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

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



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Stephen A Harrison – Terns: Consultant, No, No; Viking: Consultant, No, No; Pinnacle Clinical Research: Executive role , No, No; Northsea: Consultant, No, No; Novartis: Consultant, No, No; Novo Nordisk: Consultant, No, No; Perspectum: Consultant, No, No; Poxel: Consultant, No, No; Sagimet: Consultant, No, No; Sonic Incytes: Consultant, No, No; Hepta Bio: Consultant, No, No; Hightide: Consultant, No, No; HistoIndex: Consultant, No, No; Intercept: Consultant, No, No; Madrigal: Consultant, No, No; Medpace: Consultant, No, No; NGM Bio: Consultant, No, No; Altimmune: Consultant, No, No; AstraZeneca: Consultant, No, No; Axcella: Consultant, No, No; Chronic Liver Disease Foundation: Consultant, No, No; Echosens: Consultant, No, No; Genfit: Consultant, No, No; Gilead: Consultant, No, No; GSK: Consultant, No, No; Hepion: Consultant, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Metacrine: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; NGM Bio: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; NorthSea: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Poxel: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Sagimet: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Viking: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Akero: Consultant, No, No; Hightide: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Corcept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Cymabay: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Enyo: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Galectin: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Galmed: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genentech: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genfit: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution

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Bérénice Alard – GENFIT S.A.: Employee, Yes, No;

Jérémy Magnanensi – GENFIT S.A.: Employee, Yes, No;

Quentin M. Anstee – AstraZeneca, Boehringer Ingelheim, Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Alimentiv, Akero, AstraZeneca, Axcella, 89Bio, Boehringer Ingelheim, Bristol Myers Squibb, Galmed, Genfit, Genentech, Gilead, GlaxoSmithKline, Hanmi, HistoIndex, Intercept, Inventiva, Ionis, IQVIA, Janssen, Madrigal, Medpace, Merck, NGMBio, Novartis, Novo: Consultant, No, No; Fishawack, Integritas Communications, Kenes, Novo Nordisk, Madrigal, Medscape, Springer Healthcare: Speaking and Teaching, No, No; Elsevier Ltd: Royalties or patent beneficiary, No, Yes;

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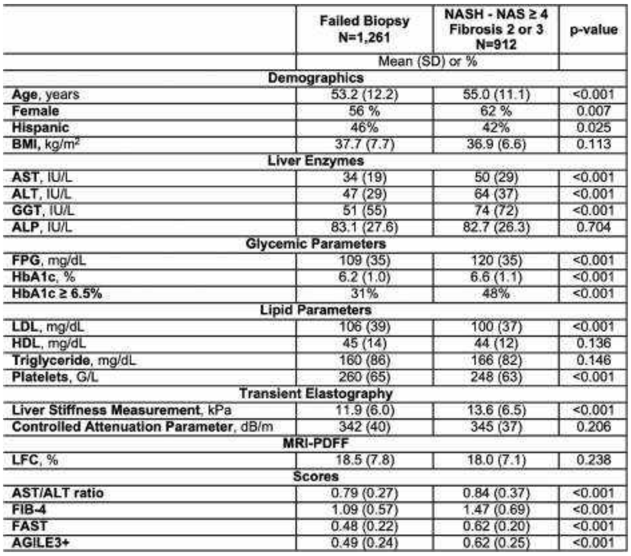
239 | CLINICAL, BIOLOGICAL AND IMAGING PREDICTORS OF AT-RISK METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH): COMBINED DATA FROM MULTIPLE THERAPEUTIC TRIALS INCLUDING MORE THAN 6,000 PATIENTS (IN COLLABORATION WITH NAIL-NIT CONSORTIUM)

Stephen A Harrison[1], Julie Dubourg[2], Naim Alkhouri[3], Mazen Noureddin[4], Jörn M. Schattenberg[5] and Sophie Jeannin[2], (1)Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom, (2) Summit Clinical Research, San Antonio, TX, (3)Arizona Liver Health, Phoenix, AZ, (4)Houston Research Institute, Houston, TX, (5)I. Department of Medicine, University Medical Centre Mainz, Johannes Gutenberg University, Mainz, Germany, Mainz, Germany

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

2.67, ≥ 2.67), the at-risk MASH population represented 31%, 56%, and 75% of the patients, respectively. The proportion of at-risk MASH patients was 35% in patients with HbA1c < 6.5% compared to 53% in patients with HbA1c ≥ 6.5%. In the population with FAST ≥ 0.50, 76% of patients with HbA1c ≥ 6.5% were "at-risk MASH" compared to 64% with HbA1c < 6.5%. Similarly, in the subgroup with FAST ≥ 0.67, patients with HbA1c ≥ 6.5% had a higher probability of at-risk MASH (78%) compared to those with HbA1c < 6.5% (70%). **Conclusion:** Simple non-invasive biomarkers can help stratify at-risk MASH patients. We recommend using the FAST-score as a simple tool to target at-risk MASH patients with a cutoff point of 0.5 for patients with HbA1c ≥ 6.5% and 0.67 for patients with HbA1c < 6.5%.



	Failed Biopsy N=1,261	NASH - NAS ≥ 4 Fibrosis 2 or 3 N=912	p-value
	Mean (SD) or %		
Demographics			
Age, years	53.2 (12.2)	55.0 (11.1)	<0.001
Female	56 %	62 %	0.007
Hispanic	46%	42%	0.025
BMI, kg/m^2	37.7 (7.7)	36.9 (6.6)	0.113
Liver Enzymes			
AST, IU/L	34 (19)	50 (29)	<0.001
ALT, IU/L	47 (29)	64 (37)	<0.001
GGT, IU/L	51 (55)	74 (72)	<0.001
ALP, IU/L	83.1 (27.6)	82.7 (26.3)	0.704
Glycemic Parameters			
FPG, mg/dL	109 (35)	120 (35)	<0.001
HbA1c, %	6.2 (1.0)	6.6 (1.1)	<0.001
HbA1c ≥ 6.5%	31%	48%	<0.001
Lipid Parameters			
LDL, mg/dL	106 (39)	100 (37)	<0.001
HDL, mg/dL	45 (14)	44 (12)	0.136
Triglyceride, mg/dL	160 (86)	166 (82)	0.146
Platelets, G/L	260 (65)	248 (63)	<0.001
Transient Elastography			
Liver Stiffness Measurement, kPa	11.9 (6.0)	13.6 (6.5)	<0.001
Controlled Attenuation Parameter, dB/m	342 (40)	345 (37)	0.206
MRI-PDFF			
LFC, %	18.5 (7.8)	18.0 (7.1)	0.238
Scores			
AST/ALT ratio	0.79 (0.27)	0.84 (0.37)	<0.001
FIB-4	1.09 (0.57)	1.47 (0.69)	<0.001
FAST	0.48 (0.22)	0.62 (0.20)	<0.001
AGILE3+	0.49 (0.24)	0.62 (0.25)	<0.001

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240 | DEVELOPMENT OF A NON-INVASIVE CLASSIFIER (FAST-3) TO PREDICT ADVANCED FIBROSIS IN MASH IN LIEU OF LIVER BIOPSIES IN U.S. ADULTS WITH MASLD

Pankil Shah[1], Phillip Leff[2], Rida Nadeem[3], Ria Kundu[3] and Naim Alkhouri[3], (1)Uthealth San Antonio, (2)TBA, (3)Arizona Liver Health, Phoenix, AZ

Background: Metabolic dysfunction-associated steatohepatitis (MASH) diagnosis and scoring depend on invasive liver biopsies by measuring metabolic dysfunction-associated steatotic liver disease (MASLD) activity score (NAS) and fibrosis score. However, a quantitative estimation of the combined effect of clinically available laboratory measures and transient elastography parameters (controlled attenuation parameter [CAP] and liver stiffness score [LSM]) as a screening / diagnostic test for advanced MASH has been suggested. In this study, we aimed to develop such a non-invasive classifier for MASH (NAS > 4 and fibrosis stage > 3 [F3]) in lieu of histological assessment by liver biopsies in adult patients with MASLD. **Methods:** We used a retrospective cohort study of 258 adult patients with MASLD who had undergone biopsy and transient elastography (FibroScan®) assessment. A predictive logistic regression-based algorithm utilizing clinical and controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) measured by FibroScan® devices was developed and internally validated to predict MASH(NAS4/F3) (confirmed with liver biopsy). Fractional polynomial forms of the predictors were evaluated, and the final model was built with L1 penalization (LASSO) using 10-fold cross-validation to obtain the optimum penalty factor. The developed model was examined for calibration (calibration plot), discrimination (AUROC), and performance (Brier score, Sensitivity, Specificity, positive predictive value [PPV], negative predictive value [NPV]). Optimal Cutpoints for 'rule-in' and 'rule-out' criteria were developed. Optimism and unbiased estimates from internal validation were obtained using 2000 bootstrapped samples. All tests were two-sided with a significant *p*-value set at 0.05. **Results:** Our predictive algorithm (FAST-3) utilized five clinical variables (sex, body mass index (BMI), aspartate aminotransferase (AST), bilirubin, and platelet count), controlled attenuation parameter (CAP), and liver stiffness measurement (LSM). The classifier demonstrated good calibration (calibration plot), discrimination (AUROC: 0.77 (0.71 – 0.83), and performance (Brier score 0.13 (0.11 – 0.16)). Optimal cutpoints for 'rule-in' and 'rule-out' criteria were evaluated and showed excellent PPV and NPV (PPV: 45% and NPV: 95%). **Conclusion:** The potential utility for a non-invasive classifier (FAST-3) as a replacement for invasive liver biopsies to identify patients with advanced fibrosis in MASH (NAS4/F3) is enormous. We demonstrate excellent performance and internal validity for this index. The results from this study should be validated in a multi-center prospective cohort study, especially with high representation from Hispanic and other at-risk minority groups.

Table 3: Comparing the point estimates of sensitivity, specificity, PPV, and NPV for FAST with the unbiased estimates for the current algorithm in relation to their Rule-in and Rule-out cutoffs to predict NASH(NAS4/F3).

	Rule in		*Rule out*	
	FAST	FAST3	FAST	FAST3
Specificity	0.71	0.89 (0.85, 0.94)		
PPV	0.33	0.46 (0.31, 0.62)		
Sensitivity			0.59	0. 0.88 (0.79, 0.97)
NPV			0.88	0.95 (0.92, 0.99)

Figure 3: Calibration plot showing agreement between prediction and observed risk of NASH(NAS4/F3)

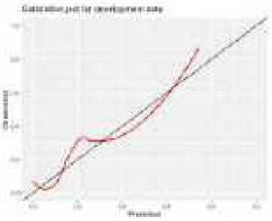
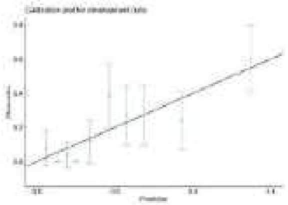


Figure 4: Calibration plot for development data showing the agreement by decile of predicted risk for NASH(NAS4/F3)



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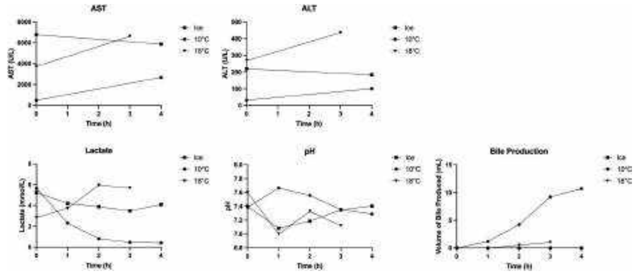
1000-A | EXTENDED STATIC STORAGE AT 10°C DEMONSTRATES SUPERIOR LIVER FUNCTION COMPARED TO STANDARD STORAGE ON ICE OR AT 18°C

Kaitlyn M. Tracy[1], Timothy R. Harris[1], Michael Cortelli[1], Sean A. Francois[1], William D. Tucker[1], Yutaka Shishido[1], Carl A. Johnson Jr.[1], Alexandra DeBose-Scarlett[1], Kimya Raietparvar[2], Tioluwanimi Adesanya[2], Nancy Cardwell[1], Caitlin T. Demarest[1], Rei Ukita[1], Chetan Pasrija[1], Muhammad Ameen Rauf[1] and Matthew Bacchetta[1,2], (1)Vanderbilt University Medical Center, (2)Vanderbilt University

Background: While the use of donation after cardiac death (DCD) allografts is one mechanism to expand the liver donor pool, these organs are at substantially higher risk of ischemic cholangiopathy. Recent innovations in normothermic and hypothermic machine perfusion are promising to decrease the risk of long-term biliary complications, however, these techniques may be cost prohibitive for widespread adoption at present. Due to these limitations, there is a need to re-evaluate and optimize conventional static cold storage. **Methods:** A porcine DCD model was developed using hypoxia-induced cardiac arrest to mimic human DCD. Livers were procured in standard fashion. During back bench preparation, cannulae were placed in the inferior vena cava, hepatic artery, portal vein, and common bile duct. The organ was placed in static storage for 18 hours either on ice (standard practice), at 10°C, or at 18°C with $n = 1$ per experimental group. After static storage, hepatic function was evaluated on a normothermic machine perfusion (NMP) platform with autologous porcine blood over 4 hours. Livers were assessed using markers of hepatocellular injury, metabolic performance, and biliary viability. **Results:** Mean warm ischemia and cold ischemia times were 23±2.6 minutes and 18±0.16 hours, respectively. At completion of NMP, AST and ALT were lowest in the 10°C group (2673 U/L and 100 U/L, respectively) compared to ice (5870 U/L, 184 U/L) or 18°C (6615 U/L, 436 U/L). Lactate normalized during NMP of the 10°C liver (0.41 mmol/L) but remained elevated for livers stored on ice (4.08 mmol/L) and at 18°C (5.68 mmol/L). At conclusion of NMP, pH was 7.40 and 7.28 for ice and 10°C groups, respectively, with greater bicarbonate required for the liver stored on ice (78mEq and 15mEq, respectively). The liver stored at 18°C demonstrated persistent acidosis (pH 7.1) despite 53mEq bicarbonate administered. The liver stored at 10°C produced 10.7mL of bile with a favorable bile glucose to perfusate glucose ratio (0.07) whereas livers stored on ice and 18°C made no bile and 1.0mL of bile, respectively, with an unfavorable ratio of 0.79 at 18°C. **Conclusion:** After extended static storage, the liver stored at 10°C demonstrated decreased hepatocellular injury, superior metabolic function, and preserved biliary viability compared to livers stored either on ice or at 18°C. These findings suggest that static storage at 10°C, compared to conventional storage on ice, may improve DCD allograft function and extend permissible preservation time.



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1001-A | G-CSF-MOBILIZED AUTOLOGOUS PERIPHERAL BLOOD CD34-POSITIVE CELL INFUSION THERAPY FOR HCV-RELATED DECOMPENSATED CIRRHOSIS

Toru Nakamura[1,2], Atsutaka Masuda[1,2], Makoto Kako[3], Hirayuiki Enomoto[4], Masaki Kaibori[5], Yasuyuki Fujita[6], Kyoko Tanizawa[6], Tetsuya Ioji[6], Hideki Iwamoto[1,2], Hironori Koga[1,2], Hiroyuki Suzuki[1,2], Tomoyuki Takashima[4], Haruki Uojima[3,7], Hidekazu Yamamoto[5], Kazunori Yoh[4,8], Atsuhiko Kawamoto[6], Shuhei Nishiguchi[4,9], Takuji Torimura[1,10] and Takumi Kawaguchi[1], (1)Kurume University School of Medicine, (2)Research Center for Innovative Cancer Therapy, Kurume University, (3)Shonan Kamakura General Hospital, (4)Hyogo Medical University, (5)Kansai Medical University, (6)Foundation for Biomedical Research and Innovation at Kobe, (7)Research Institute, National Center for Global Health and Medicine, (8)Yoh Digestive Clinic, (9)Kano General Hospital, (10)Omuta City Hospital

Background: Preclinical studies have shown that peripheral blood (PB)-CD34$^+$ cell transplantation reduced established liver fibrosis and promote hepatic regeneration. Based on many basic animal studies, we have done a prospective clinical trial for patients with decompensated cirrhosis and demonstrated that autologous G-CSF-mobilized PB-CD34$^+$ cell therapy is feasible, safe, and effective in slowing the decline of hepatic residual function. The aim of the study is to investigate the efficacy and safety of G-CSF-mobilized autologous PB-CD34$^+$ cells cell infusion therapy compared with standard medical therapy for HCV-related decompensated cirrhosis. **Methods:** We did a multicenter, open-label, randomized control trial. Patients were randomly assigned (2:1) to the CD34$^+$ cell transplant (cell transplant) or standard medical therapy (standard treatment) group and followed up for 52 weeks. The primary endpoints were the non-progression rate in Child-Pugh (CP) score at 24 weeks post-enrollment and the safety of the protocol treatment. Patients in the cell transplant group were admitted to the hospital and received G-CSF injections for 5 days to mobilize CD34$^+$ cells from bone marrow. On Day 4-5, leukapheresis was done and CD34$^+$ cells were isolated using CliniMACS magnetic cell sorter. On Day 5, the isolated CD34$^+$ cells were then infused through the hepatic artery. Patients assigned to the standard treatment group continued treatment that had been initiated prior to enrollment. **Results:** Fourteen patients were enrolled (cell transplant group: 10, standard treatment group: 4). The primary endpoint was 90% in the cell transplant group and 100% in the standard treatment group, with no significant differences between groups. When the evaluation method was changed from the non-progression rate in CP score to the improvement rate in CP score by one or more points, the cell transplant group was superior, with 50% of patients in the cell transplant group compared to 25% in the standard treatment group. In addition, 40% of patients in the cell transplant group improved from decompensated to compensated cirrhosis. In the secondary endpoints, serum albumin levels tended to increase in the cell transplant group. Significant intergroup differences were also observed in the MELD score (change at 8, 12, and 36 weeks post-enrollment), total bilirubin level (change at 12 weeks post-enrollment), and QOL endpoints (change in physical function and body pain at 52 weeks post-enrollment). For safety evaluation, 3 serious adverse events occurred in the cell transplant group and 1 in the standard treatment group. There were no deaths due to cirrhosis, no all-cause mortality, and no occurrence of hepatocellular carcinoma in all patients. **Conclusion:** Autologous PB-CD34$^+$ cell infusion therapy is a beneficial treatment for decompensated cirrhosis. This therapy may have the potential to escape decompensated cirrhosis, resulting in avoiding liver transplantation.

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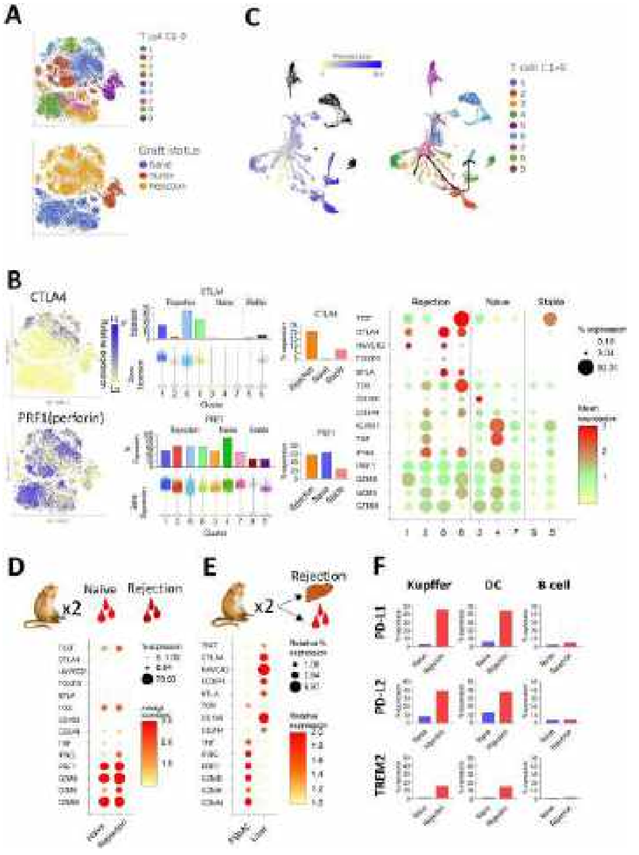
1002-A | IMMUNE MODULATION OF T CELLS IN THE LIVER ALLOGRAFT REVEALED BY SINGLE-CELL SEQUENCING IN CYNOMOLGUS MONKEY MODEL

Hiroshi Sakai[1,2], Erik Berglund[1], Sulemon Chaudhry[1], Yojiro Kato[1], Erin Duggan[1], Joshua Weiner[1], Paula Alonso-Guallart[1], Nathaly Llore[1], Karina Bruestle[1], Jeffrey Stern[1], Benjamin Piegari[1], Dilrukshi Ekanayake-Alper[1], Mercedes Martinez[3], Genevieve Pierre[1], Diane Ordanes[1], Dominik Hajosi[1], Fei Huang[1], Brittany R Bhola[1], Alina Iuga[1], Tomoaki Kato[4], Megan Sykes[1] and

Adam D. Griesemer[1,5], (1)Columbia University, Columbia Center for Translational Immunology, New York, NY, (2)Hiroshima University, (3)Newyork-Presbyterian, Department of Pediatrics, (4)New York-Presbyterian, Department of Surgery, (5)NYU Langone Health

Background: Liver is an immune regulatory organ. Operational tolerance to liver transplants (Tx) occurs in some patients with stable liver function for several years, while it is not generally seen in other Tx. To obtain a better understanding of the mechanisms involved in T cell reactivity in the liver allograft and enable the discovery of therapeutic targets for rejection (Rej) and tolerance, we profiled the transcriptomes of more than 125,000 single cells isolated from 17 livers and 4 peripheral blood samples and analyzed bulk mRNA from 48 liver biopsies in the monkey liver Tx model. **Methods:** Cynomolgus recipients received orthotopic liver allograft Tx with tacrolimus-based immunosuppression. Graft immune status, stable or Rej were defined based on liver function tests and pathology. Graft wedge biopsies were done at stable or Rej phases. Naïve control livers were obtained from naïve cynomolgus monkeys. Single cell RNA sequences were done by 10x genomics. Bulk mRNA were analyzed by nanoString. **Results:** The transcriptional profiles of individual cells in the liver enabled us to identify 9 T cell subsets based on their molecular and functional properties and delineate their developmental trajectory. 4 subsets (1,2,6 and 8) of T cells in the Rej livers, 3 subsets (3,4 and 7) in the naïve livers and 1 subset (9) in the stable liver were identified (Fig A). Specific subsets such as exhausted CD8 T cells and Tregs are preferentially enriched in the Rej liver grafts. Genes related to cytotoxicity were expressed on both Rej and naïve subsets with no noticeable differences, while exhaustion markers were preferentially expressed on Rej liver(Fig B). The expression of exhaustion markers did not correlate with cytotoxic markers, indicating they are not upregulated by cytotoxic cell activities. Trajectory analyses identified the cell development from naïve to the end of cell activation, exhaustion, and senescence/apoptosis subsets (8 and 6) in the Rej livers (Fig C). Circulating T cells showed different properties from T cells in the liver graft: cytotoxicity markers on the circulating T cells were slightly upregulated at Rej phase compared to naïve liver, while exhaustion markers showed low expression with no difference between naïve and Rej phase(Fig D). When T cells in the liver and in the circulation at the same time of Rej were compared, exhaustion markers were preferentially expressed on liver T cells, whereas cytotoxic markers were more upregulated on circulating T cells (Fig E). Kupffer cells and DC, but not B cells in the Rej liver, upregulated PD-L1, PD-L2 and TREM2, a marker of immunosuppressive myeloid cells (Fig F). Consistent findings were seen in the bulk mRNA analyses for 48 liver samples. **Conclusion:** Liver allograft microenvironment may modulate T cell activation by immune checkpoint where antigen presenting cells such as Kupffer cells and DC may contribute, suggesting the spontaneous resolution of Rej inducing operational tolerance.



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1003-A | PERIHEPATIC IMPLANTS OF 3D ENGINEERED ENDOTHELIAL CELLS MATRICES PROTECT FIBROTIC LIVER FROM INJURY AND INFLAMMATION

Mireia Medrano-Bosch[1], Alazne Moreno-Lanceta[1,2], Blanca Simón-Codina[1], David Saavedra-Pérez[3], Laura

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

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Background: Endothelial cells (ECs) display a myriad of protective roles that contribute to tissue homeostasis (i.e. modulation of the immune system and secretion of growth factors). Embedding healthy ECs in a 3D collagen-based scaffold shields their immunogenicity and maximizes their protective roles. Indeed, matrix-embedded endothelial cells (MEECs) protect the healthy liver against acute ischemic injury. Here, we explore the impact of MEECs on injury and inflammation in the setting of pre-existing fibrotic liver disease and cirrhosis. **Methods:** Liver slices from cirrhotic patients ($n = 6$) were co-cultured in direct contact with acellular matrices or MEECs. Viability was examined after 24 hours by measuring ATP levels in human hepatic homogenates. The expression of genes associated with hepatic injury, inflammation, and regeneration was quantified by Real-time PCR in human samples. Experimental fibrosis was induced in BALB/c mice ($n = 12$) by i.p. injection of CCl_4 for 8 weeks, after which acellular matrices or MEECs were placed in the perihepatic space between the median and right lobes, or subcutaneously. Liver integrity, inflammation, fibrosis, and regeneration were evaluated one week later. *In vitro*, MEECs and 2D-ECs gene expression patterns were compared to decipher potential drivers of immunomodulation, extracellular matrix remodeling, and regeneration. **Results:** Human liver slices in contact with MEECs exhibited greater viability than slices exposed to acellular matrices (ATP/Protein, 1.4 ± 0.5 pmol/µg vs 1.9 ± 0.5, $p < 0.05$). This viability improvement was accompanied by an identical magnitude of induction of hepatic expression of the metabolic enzyme CYP2B6 (3.8 ± 3.0 vs 5.1 ± 3.4 fold change (fc), $p < 0.05$) and an even greater increase in hepatocyte growth factor expression (HGF, 1.0 ± 0.2 vs 2.2 ± 0.6 fc, $p < 0.05$). These effects were associated with an increase in the expression of anti-inflammatory genes (Arg1, MRC1, MMP9) and a reduction in NOS2 expression in human liver slices treated with MEECs. Fibrotic livers of mice treated with perihepatic implants of MEECs also showed a decrease in inflammation and liver damage that was accompanied by a decrease in fibrosis, and an increase in hepatic regeneration. In contrast, subcutaneous implants of MEECs did not exert any effect on inflammation, liver damage, fibrosis, or regeneration. Mechanistically, MEECs expressed higher levels of anti-inflammatory chemokines (CXCL16 and CX3CL1), extracellular matrix modulators (matrix metalloproteinase 2 and fibronectin 1), and growth factors (HGF and fibroblast growth factor 2) than 2D-ECs. **Conclusion:** 3D-engineered ECs matrices protect human cirrhotic liver from injury and inflammation in short-term treatment, and boost regeneration, reduce inflammation, injury, and fibrosis in long-term therapy in fibrotic livers. This study highlights the potential therapeutic utility of MEECs for chronic liver disease.

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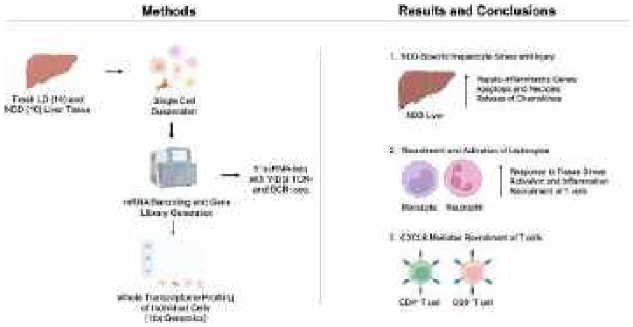
f 1004-A | SINGLE CELL ATLAS OF LIVING DONOR LIVER BIOPSIES REVEALS HEPATO-INFLAMMATORY GENE ACTIVATION AND T CELL RECRUITMENT IN THE NEUROLOGICALLY DECEASED DONOR LIVER★

Diana Nakib[1,2], Catia Perciani[1], Sai Chung[1,2], Damra Camat[1,2], Lewis Liu[1,2], Xue Zhong Ma[1], Justin Manuel[1], Blayne Sayed[1,3], Mark Cattral[1], Gonzalo Sapisochin[1], Anand Ghanekar[1,3], Markus Selzner[1], Nazia Selzner[1,2], Sonya A MacParland[1,2] and Ian McGilvray[1], (1) University Health Network, (2)University of Toronto, (3) The Hospital for Sick Children

Background: Living donor (LD) liver transplantation represents 1 in 8 liver transplantations in Canada and has led to successful outcomes for patients on waitlists for neurologically-deceased donor (NDD) livers. Although short term recipient outcomes are similar between LD and NDD liver transplantations, it is unclear if there are fundamental differences in the donor tissue types. For example, hepatocyte stress, immune infiltration, and inflammation may differ. Studies have demonstrated an upregulation of inflammatory genes during the preparation, preservation and reperfusion of LD and NDD transplanted livers, which could have important impacts on transplant success. Here we used single cell transcriptomics to build an atlas of the cellular landscapes of LD and NDD livers, and have uncovered pathways of cellular stress and inflammation unique to NDD livers. **Methods:** We employed 10x Genomics 5' single-cell RNA sequencing with T cell receptor (TCR) and B cell receptor (BCR) sequencing to examine the cellular landscapes of NDD liver caudates (n = 10) and LD liver biopsies (n = 10) collected immediately after laparotomy. In addition to LD liver biopsies, we collected matched blood (n = 10). **Results:** Our atlas demonstrates the presence of expected human hepatic cell populations in both the NDD and LD liver. We confirm the increased expression of pro-inflammatory genes in NDD-specific hepatocyte populations, examples include *TGM2*, *NAMPT* and *SERPINE1*, which are involved in myeloid polarization, recruitment and activation. We observe several NDD-specific myeloid populations. These include a recently-recruited neutrophil population enriched in inflammatory genes (*S100A8/9*), chemokine receptors (*CXCR1/2*), and *CXCL8*, a gene involved in T cell and myeloid recruitment to the liver. Through gene set enrichment analysis, we observe that the NDD-specific myeloid populations, as well as NDD-specific neutrophils, are enriched in pathways related to leukocyte activation, responses to inflammation and stress, in addition to the regulation and activation of T cells. After excluding any lymphocytes sharing gene expression profiles with circulating PBMCs, TCR sequencing reveals a significant increase in the clonotypic diversity of both naive CD4+ and effector memory CD8+ T cells in NDD livers in comparison to LD livers. However, BCR sequencing reveals similar clonotypic diversity of mature and antibody-secreting B cells in the NDD and LD liver. This suggests increased T cell-specific recruitment and infiltration of the NDD liver that is not observed in the LD liver. **Conclusion:** Our results reveal that the NDD liver experiences an upregulation of hepato-inflammatory genes across cell types that is associated with the recruitment of a neutrophil-T-cell axis not observed in the LD liver.



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1005-A | A NOVEL PROTOCOL OF LIVING DONOR LIVER TRANSPLANTATION FOR NON-RESECTABLE PERIHILAR CHOLANGIOCARCINOMA

Ken Fukumitsu, Kojiro Taura, Takashi Ito, Takayuki Anazawa, Kazuyuki Nagai, Yoichiro Uchida, Takamichi Ishii and Etsuro Hatano, Kyoto University

Background: Liver transplantation for unresectable perihilar cholangiocarcinoma has been widely performed depending on Mayo protocol. This protocol, however, is based on the condition of deceased donor liver transplantation (DDLT), and since nobody knows the timing of the donor's allocation in advance, patients should wait with an administration of anticancer drugs until transplantation. On the other hand, in Japan, liver transplantation for perihilar cholangiocarcinoma is limited to living donor liver transplantation (LDLT). Adding to this, the resume of chemotherapy has been advanced recently, and a novel resume for cholangiocarcinoma has been approved. **Methods:** The following two improvements were adjusted in LDLT for perihilar cholangiocarcinoma. 1. Change in the order of induction of radiotherapy and chemotherapy. LDLT has the advantage that the schedule of the operation date can be decided in advance. Therefore, the date of liver transplantation was set when donor eligibility and response to treatment were confirmed, and then radiotherapy was added retroactively from the date of the transplantation. 2. Change the resume of chemotherapy. The chemotherapy regimen was changed from 5-FU and Capecitabin to combination of Gemcitabine, Cisplatin and S-1(GCS), has been proven to be effective to cholangiocarcinoma. **Results:** Three patients underwent LDLT, one of whom underwent pancreatoduodenectomy (PD) with liver transplantation simultaneously. The first patient had hilar cholangiocarcinoma with primary sclerosing cholangitis (PSC) and still alive without recurrence. The second patient had hilar cholangiocarcinoma with hepatic hilum lymph node metastasis, which turned out to be negative after chemotherapy. Presently this patient has recurrence in bone and performing chemotherapy. The third patient was a hilar cholangiocarcinoma with PSC that had extended to the pancreas, so PD was performed simultaneously, who is still alive without recurrence. **Conclusion:** The protocol of LDLT for perihilar cholangiocarcinoma was improved depending on the advantages to DDLT. Our protocol for LDLT can be performed safely, and further investigation will be necessary.

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1006-A | ACCURATE PREDICTION OF LIVER WAITLIST MORTALITY AND 1-YEAR POST-TRANSPLANT SURVIVAL WITH MACHINE LEARNING

Rowland Pettit[1,2], Britton Marlatt[3], Selim Uzgoren[3], Jim Havelka[3], Anil Shetty[3], George Cholankeril[2] and Abbas Rana[2], (1)Mass General Brigham, (2)Baylor College of Medicine, (3)Informai

Background: The UNOS database provides valuable data for studying transplantation outcomes, while the application of machine learning (ML) algorithms has gained attention in this field. This study aims to utilize XGBoost, a powerful ML algorithm, to predict transplantation outcomes using the UNOS database and compare its performance to the SRTR models. By leveraging ML techniques and the comprehensive data from UNOS, we aim to enhance our predictive capabilities and decision-making in transplantation. **Methods:** We conducted a retrospective analysis of 139,323 adult liver transplant (LT) recipients from the UNOS database. Using XGBoost, we predicted waitlist mortality and one-year post-transplant survival. The XGBoost model was trained through 60 iterations using Bayesian Search Cross Validation and its performance was evaluated using AUCROC. We identified the top 10 features for waitlist mortality prediction based on XGBoost's importance scores, which were validated using 4-fold cross-validation. Additionally, we performed statistical bootstrapped comparisons with Cox proportional hazards and SRTR models to assess the accuracy and reliability of XGBoost in predicting long-term post-transplant outcomes. **Results:** Our study showed that XGBoost outperformed SRTR models in predicting 1-year survival after liver transplant (LT), with a significantly higher discriminative ability (c-statistic: XGBoost 0.73 vs. SRTR 0.62, $p < 0.001$). For 90-day waitlist mortality, our top-performing XGBoost model achieved strong predictive metrics: AUC-ROC 0.8027, AUC-PR 0.8147, and F1-Score 0.7711. The XGBoost algorithm identified the top 10 important features for waitlist mortality, including variables related to life support, previous transplant, MELD/PELD score, listing center code, diagnosis codes, UNOS/OPTN region, ABO blood group, VAD/TAH, and ascites. These features significantly improved the accuracy of identifying patients at higher risk of waitlist mortality. **Conclusion:** XGBoost demonstrated superior performance over Cox proportional hazard models in predicting 1-year survival after liver transplant. We successfully developed a clinically relevant XGBoost model for 90-day waitlist mortality, achieving high clinical utility (AUC-ROC > 0.8). These findings suggest the potential of AI-based models, such as XGBoost, to improve transplant decision-making and should be considered for integration into the workflow.

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Britton Marlatt – InformAI: Employee, Yes, Yes;
Selim Uzgoren – InformAI: Employee, Yes, No;
Jim Havelka – InformAI: Employee, Yes, No;
Anil Shetty – InformAI: Advisor, No, No;
The following people have nothing to disclose: George Cholankeril, Abbas Rana

1007-A | ACUITY CIRCLES IMPROVED DISPARITY IN ACCESS TO LIVER TRANSPLANT FOR HISPANICS AND ASIANS BUT NOT AFRICAN AMERICANS

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Background: The Organ Procurement and Transplantation Network (OPTN) adopted a new liver allocation system based on acuity circles (AC) in February 2020. Understanding the impact of the AC on existing racial and ethnic disparities in waitlisted liver transplant (LT) candidates is vital to inform further policy development. **Methods:** OPTN data were queried to identify eligible adult patients (age ≥ 18 y) on the LT waitlist before and after implementing the AC (pre-AC, 1/1/2017 – 2/3/2020, post-AC, 2/4/2020 – 12/31/2022). Cox proportional hazard model with Model of End-Stage Liver Disease score (MELD) and recipient age as a time-dependent covariate (TDC), and Fine-Gray regression model with LT and death/drop-out (D/D) as competing risks were used to assess probability of receiving LT in different racial/ethnic minorities compared to Caucasians. Fine-Gray model was performed by censoring candidates who were on the waiting list before the implementation of the AC and remained on the list thereafter. The two models were employed to address the limitations of the Fine-Gray model, which does not adequately incorporate the TDC, and the Cox model, which does not account for competing risks. Other confounders included candidates' sex, age, etiology of liver disease, presence of HCC, body mass index (BMI) and MELD score, at listing. **Results:** This analysis included a total of 39,227 patients pre-AC and 38,443 patients post-AC. Despite overall improvements post-AC, racial/ethnic disparities persist in LT and D/D rates

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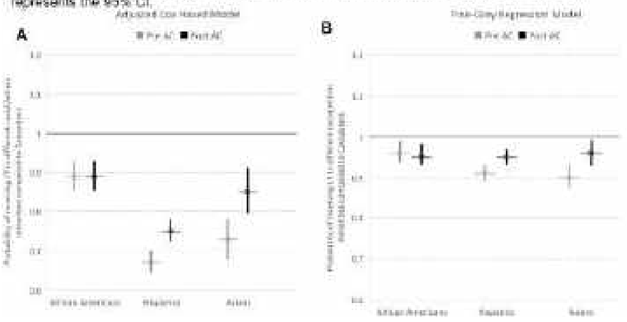
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

compared to Caucasians (LT: 64% to 67%, D/D: 17% to 16%): African Americans (LT: 63% to 66%, D/D: 20% to 17%), Hispanics (LT: 60% to 65%, D/D: 23% to 20%), Asians (LT: 59% to 64%, D/D: 20% to 16%), pre- and post-AC, respectively ($p < 0.001$). Cox model with TDC (Figure A) showed adjusted hazard ratio (aHR) of receiving LT in African Americans compared to Caucasians pre- and post-AC was 0.90 (95% confidence interval [CI] 0.85-0.94) in both groups. In comparison, among Hispanics, HR of receiving LT was 0.67 (95% CI 0.65-0.70) pre-AC which improved to 0.75 (0.73-0.78) post-AC. While aHR for Asians pre-AC was 0.73 (95% CI 0.68-0.78), it increased to 0.85 post AC (0.80-0.91). Fine-Gray competing risk regression model showed similar outcomes (Figure B): transplant probability of African Americans compared to Caucasians pre-AC was 0.96 (95% CI 0.94-0.99) and post-AC it remained unchanged (aHR of 0.95, 95% CI 0.93-0.98). In Hispanics, pre-AC aHR was 0.91 (95% CI 0.89-0.93) vs. 0.95 (0.93-0.97) post-AC. The aHR for Asians was 0.90 (95% CI 0.87-0.94) pre-AC vs. 0.96 (0.82-0.99) post-AC. **Conclusion:** Racial and ethnic disparities still exist among all LT candidates with non-Caucasian races/ethnicities after implementing the AC. In both of our censored regression models, the AC allocation system has improved access to LT in Hispanics and Asians but not for African Americans.

Figure: Transplant probability in different racial/ethnic groups compared to Caucasians: (A) Adjusted Cox hazard, (B) Fine-Gray regression model. The star represents the HR value while the bar represents the 95% CI.



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Disclosure information not available at the time of publication: David Axelrod

1008-A | ASSESSING NEIGHBORHOOD LEVEL SOCIAL VULNERABILITY AMONG EARLY LIVER TRANSPLANT RECIPIENTS AT FOUR CENTERS

James Flanary[1], *Po-Hung (Victor) Chen*[1], *Alexandra Strauss*[1], *Nicole M. Welch*[2], *Annette Bellar*[2], *Courtney B. Sherman*[3], *Bilal Hameed*[4], *Mandana Khalili*[3], *Srinivasan Dasarathy*[5], *Elizabeth King*[1] and *Andrew M. Cameron*[1], *(1)Johns Hopkins University, (2) Cleveland Clinic, (3)University of California, San Francisco, (4)University of California San Francisco, San Francisco, CA, (5)Cleveland Clinic Foundation*

Background: Some liver transplant centers have adopted the practice of early liver transplants (ELT) for candidates with alcohol-related liver disease and less than six months of abstinence at listing. As this practice has gradually become more common, we sought to evaluate whether the population undergoing ELT is representative of the population in need. Our study quantified sociodemographic characteristics for the ZIP codes in which ELT recipients resided and compared those with sociodemographic characteristics of all other ZIP codes in the referral region. **Methods:** All ZIP code tabulated areas within a 150 nautical mile (Nmi) radius of the four participating transplant centers were included. Geographically, these centers represent the mid-Atlantic (Johns Hopkins), south (Cleveland Clinic-Florida), midwest (Cleveland Clinic-Ohio), and west (University of California-San Francisco) regions of the United States. Recipients of ELT underwent transplant between 2019 and 2023. Sociodemographic variables were obtained from the 2020 American Community Survey data and the social vulnerability metric (SVM). The SVM is an ecologic measure of social determinants of health for each ZIP code. We stratified ZIP codes according to whether or not any patient who underwent ELT resided within that ZIP code. For each transplant center, chi-squared tests compared sociodemographic characteristics between ZIP codes with ELT patients to ZIP codes without ELT patients. **Results:** Each center had between 14 and 71 ZIP codes in which ELT recipients resided. The most common racial category of ZIP codes with ELT recipients was either predominantly white or racially integrated. At each center, over 60% of ZIP codes with ELT recipients were within 50Nmi of the transplant center. At one center, ZIP codes with ELT recipients had lower vulnerability ($p < 0.001$), less poverty (17% vs. 34%, $p = 0.005$), and higher MHI (20% vs. 53%, $p < 0.001$) than other ZIP codes in the referral region. However, these differences did not persist when we restricted ZIP codes to within the state of the center. The remaining three centers did not have significant differences in these characteristics (Table). **Conclusion:** The majority of ELT recipients come from ZIP codes in relative proximity to a center that is currently offering ELT. Within these ZIP codes, there is a trend toward ELT recipients residing in ZIP codes with less social vulnerability, or in other words, more favorable sociodemographic characteristics. Further analysis is necessary to define the population that could benefit from ELT and whether there are individual's within socially vulnerable neighborhoods that lack access.

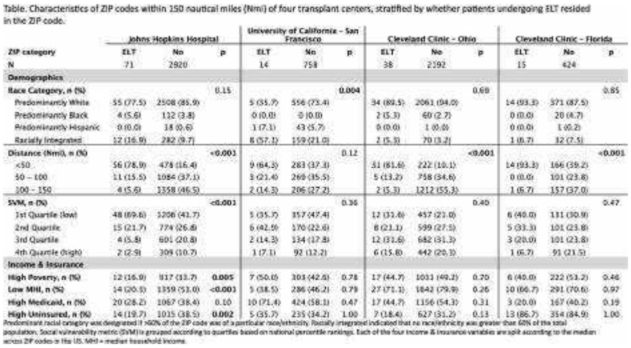

Table. Characteristics of ZIP codes within 150 nautical miles (Nmi) of four transplant centers, stratified by whether patients undergoing ELT resided in the ZIP code.

	Johns Hopkins Hospital			University of California – San Francisco			Cleveland Clinic – Ohio			Cleveland Clinic – Florida		
ZIP category	ELT	No	p	ELT	No	p	ELT	No	p	ELT	No	p
N	71	2920		14	758		38	2192		15	424	
Demographics												
Race Category, n (%)			0.15			**0.004**			0.60			0.85
Predominantly White	55 (77.5)	2508 (85.9)		5 (35.7)	556 (73.4)		34 (89.5)	2061 (94.0)		14 (93.3)	371 (87.5)	
Predominantly Black	4 (5.6)	112 (3.8)		0 (0.0)	0 (0.0)		2 (5.3)	60 (2.7)		0 (0.0)	20 (4.7)	
Predominantly Hispanic	0 (0.0)	18 (0.6)		1 (7.1)	43 (5.7)		0 (0.0)	1 (0.0)		0 (0.0)	1 (0.2)	
Racially Integrated	12 (16.9)	282 (9.7)		8 (57.1)	159 (21.0)		2 (5.3)	70 (3.2)		1 (6.7)	32 (7.5)	
Distance (Nmi), n (%)			<0.001			0.12			<0.001			<0.001
<50	56 (78.9)	478 (16.4)		9 (64.3)	283 (37.3)		31 (81.6)	222 (10.1)		14 (93.3)	166 (39.2)	
50 – 100	11 (15.5)	1084 (37.1)		3 (21.4)	269 (35.5)		5 (13.2)	758 (34.6)		0 (0.0)	101 (23.8)	
100 – 150	4 (5.6)	1358 (46.5)		2 (14.3)	206 (27.2)		2 (5.3)	1212 (55.3)		1 (6.7)	157 (37.0)	
SVM, n (%)			<0.001			0.36			0.40			0.47
1st Quartile (low)	48 (69.6)	1206 (41.7)		5 (35.7)	357 (47.4)		12 (31.6)	457 (21.0)		6 (40.0)	131 (30.9)	
2nd Quartile	15 (21.7)	774 (26.8)		6 (42.9)	170 (22.6)		8 (21.1)	599 (27.5)		5 (33.3)	101 (23.8)	
3rd Quartile	4 (5.8)	601 (20.8)		2 (14.3)	134 (17.8)		12 (31.6)	682 (31.3)		3 (20.0)	101 (23.8)	
4th Quartile (high)	2 (2.9)	309 (10.7)		1 (7.1)	92 (12.2)		6 (15.8)	442 (20.3)		1 (6.7)	91 (21.5)	
Income & Insurance												
High Poverty, n (%)	12 (16.9)	917 (31.7)	**0.005**	7 (50.0)	303 (42.6)	0.78	17 (44.7)	1031 (49.2)	0.70	6 (40.0)	222 (53.2)	0.46
Low MHI, n (%)	14 (20.3)	1359 (51.0)	<0.001	5 (38.5)	286 (46.2)	0.79	27 (71.1)	1842 (79.9)	0.26	10 (66.7)	291 (70.6)	0.97
High Medicaid, n (%)	20 (28.2)	1067 (38.4)	0.10	10 (71.4)	424 (58.1)	0.47	17 (44.7)	1156 (54.3)	0.31	3 (20.0)	167 (40.2)	0.19
High Uninsured, n (%)	14 (19.7)	1015 (38.5)	**0.002**	5 (35.7)	235 (34.2)	1.00	7 (18.4)	627 (31.2)	0.13	13 (86.7)	354 (84.9)	1.00

Predominant racial category was designated if >60% of the ZIP code was of a particular race/ethnicity. Racially integrated indicated that no race/ethnicity was greater than 60% of the total population. Social vulnerability metric (SVM) is grouped according to quartiles based on national percentile rankings. Each of the four income & insurance variables are split according to the median across ZIP codes in the US. MHI = median household income.

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Disclosure information not available at the time of publication: Elizabeth King, Andrew M. Cameron

1009-A | COMBINED HEART-LIVER TRANSPLANT VS HEART TRANSPLANT ALONE: A SINGLE CENTER EXPERIENCE

Ritika M. Mazumder, Andrew Ford, Omar T. Sims and Jamak Modaresi Esfeh, Cleveland Clinic

Background: Combined heart-liver transplantation (CHLT) is a viable option for treating concomitant heart and liver failure. Indications for CHLT, however, are not well defined. The objectives of this study were to describe pre-transplant characteristics and post-transplant survival among patients with liver fibrosis who underwent CHLT versus heart transplantation (HT) alone. The incidence of decompensated cirrhosis after HT was also investigated. **Methods:** All adult heart transplants with liver fibrosis at our center from January 2009 to August 2022 were included in the analysis. **Results:** A total of 52 patients (HT = 42; CHLT = 10) met inclusion criteria. Heart failure etiology in the HT group included 9 ischemic cardiomyopathy (21%), 23 non-ischemic cardiomyopathy (55%), and 10 congenital heart diseases (24%). The CHLT group included 1 (10%), 5 (50%), and 4 (40%), respectively. The HT group had 9 (21%) cases of primary liver disease and 33 (79%) cases of congestive hepatopathy, while the CHLT group had 5 (50%) cases of primary liver disease and 5 (50%) cases of congestive hepatopathy. The preoperative LV ejection fraction for HT and CHLT averaged 29+20% and 38+14%. The pre-transplant MELD-Xi for HT and CHLT was 11.2 +6.5 and 9.16+5.0. F1 fibrosis (52%) was more common in the HT group and F4 fibrosis (80%) was more common in the CHLT group. Portal hypertension (PHTN) was present in 40% of HT patients and 90% of CHLT patients. Over the median follow-up of 3.7 (IQR 1.2-9.1) years, none of the CHLT patients and 14

(33%) HT patients died; the crude mortality rate between HT and CHLT did not differ statistically ($p = 0.6$, Figure 1). None of the HT patients progressed to decompensation (e.g., new ascites, variceal bleed, jaundice or hepatic encephalopathy) within 6 months of transplantation. **Conclusion:** Despite preexisting liver disease and PHTN, HT and CHLT patients had similar survival outcomes. Furthermore, HT patients with compensated liver disease did not progress to decompensation after transplantation. Further research is needed to determine selection criteria for patients undergoing CHLT and ensure efficient utility of limited organs.

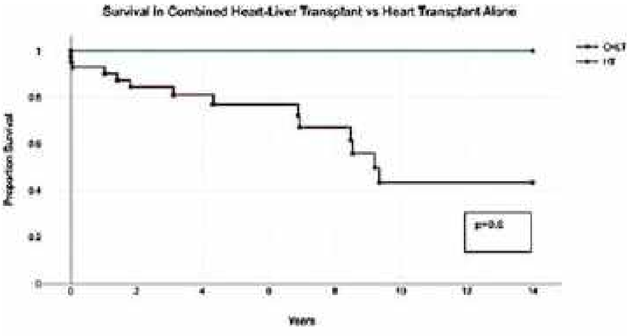

Figure 1: Kaplan-Meier Survival Analysis in HT vs CHLT

Disclosures: The following people have nothing to disclose: Ritika M. Mazumder

Disclosure information not available at the time of publication: Andrew Ford, Omar T. Sims, Jamak Modaresi Esfeh

1010-A | CORRELATION OF TUMOR RESPONSE FOLLOWING LIVER DIRECTED THERAPY FOR HEPATOCELLULAR CARCINOMA : A RADIOLOGICAL / PATHOLOGICAL CORRELATION

Mohammad Bourmaf[1], *Kabir Chhabra*[1], *Mohammed Rifat Shaik*[2], *Dabin Choi*[1], *David Lee*[1], *Hyun S. Kim*[1] *and Kirti Shetty*[3], *(1)University of Maryland Medical Center, (2)University of Maryland Medical Center Midtown Campus, (3)Department of Hepatology and Liver Transplantation, the University of Maryland, School of Medicine, Baltimore, MD, USA*

Background: Liver directed therapy (LDT) for HCC is essential to “bridge” patients to liver transplantation (LT). The Liver Reporting and Data System Treatment Response Algorithm (LR-TR) categorizes tumor response to LDT but questions persist regarding its generalizability. We therefore undertook this study in a HCC population undergoing LT after LDT to (1) correlate LR-TR findings to pathological tumor necrosis on explant (2) correlate degree of tumor necrosis to HCC recurrence post LT. **Methods:** A pathological database identifying all patients who underwent LT for HCC between January 2019 and June 2022 was utilized and clinical variables were extracted from the electronic medical record. Pre-LT imaging study for LIRADS-TR assessment was required to be within 90 days of LT and explant sectioning at 5 mm intervals described HCC characteristics. The following LIRADS-TR classifications were used – viable, equivocal, and non-viable. The corresponding percentage of explant necrosis was as follows: > 90%, 50-89%, < 50%. For continuous variables, means and standard deviations were calculated if normally distributed and medians (interquartile ranges IQR) were calculated if non normally distributed. Chi-square tests and Fisher exact tests were used to test between group differences for categorical variables. All *p*-values were reported as two-sided and a *p*-value < 0.05 was considered statistically significant. Institutional Review Board approval was obtained. **Results**: 50 patients underwent a total of 83 LDT sessions (median 2, range 1 – 5 sessions / patient) – details in table 1. Radiological - pathologic correlation of 48 paired HCCs are summarized in table 2. Of note, 90% of tumors that were non-viable by LR-TR criteria showed > 90% necrosis on explant pathology (correlation coefficient: $p = 0.05$,) However, LR– equivocal and LR-viable lesions showed inconsistent correlation. HCC recurrence was noted in 9 patients (18%) at a median of 382 days post LT (range 78 – 790 d). Of these, 2 patients had 100 % necrosis, 3 had < 50% necrosis, and 4 had 50 -89 % necrosis on explant. **Conclusion:** The LI-RADS TR algorithm for assessing HCC response to liver directed therapy performed well in our study cohort for predicting non-viable tumor on explant analysis. However, there was a lack of correlation for equivocal and viable lesions. This observation is consistent with known tumor biology, as lack of enhancement on imaging shows imperfect correlation to pathological tumor necrosis. Additionally, different forms of liver directed therapy may produce sequelae that are not well-captured by the LR-TR classification system. It is therefore crucial for the liver imaging community to continue its refinement of diagnostic techniques to capture tumor response to therapy. This will enable optimization of pre-transplant therapies to minimize HCC recurrence rates.

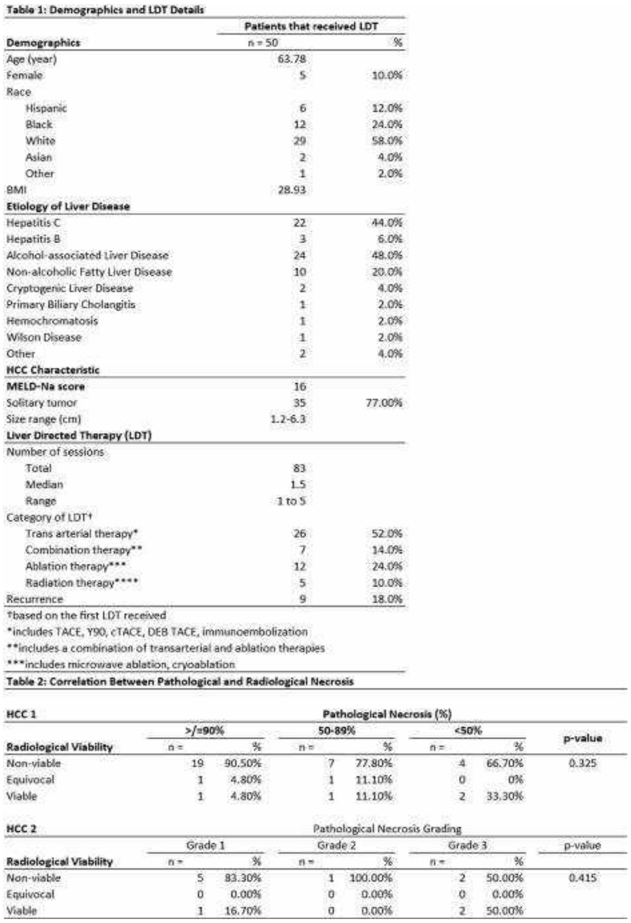

Table 1: Demographics and LDT Details

	Patients that received LDT	
Demographics	n = 50	%
Age (year)	63.78	
Female	5	10.0%
Race		
Hispanic	6	12.0%
Black	12	24.0%
White	29	58.0%
Asian	2	4.0%
Other	1	2.0%
BMI	28.93	
Etiology of Liver Disease		
Hepatitis C	22	44.0%
Hepatitis B	3	6.0%
Alcohol-associated Liver Disease	24	48.0%
Non-alcoholic Fatty Liver Disease	10	20.0%
Cryptogenic Liver Disease	2	4.0%
Primary Biliary Cholangitis	1	2.0%
Hemochromatosis	1	2.0%
Wilson Disease	1	2.0%
Other	2	4.0%
HCC Characteristic		
MELD-Na score	16	
Solitary tumor	35	77.00%
Size range (cm)	1.2-6.3	
Liver Directed Therapy (LDT)		
Number of sessions		
Total	83	
Median	1.5	
Range	1 to 5	
Category of LDT†		
Trans arterial therapy*	26	52.0%
Combination therapy**	7	14.0%
Ablation therapy***	12	24.0%
Radiation therapy****	5	10.0%
Recurrence	9	18.0%

†based on the first LDT received

*includes TACE, Y90, cTACE, DEB TACE, immunoembolization

**includes a combination of transarterial and ablation therapies

***includes microwave ablation, cryoablation

Table 2: Correlation Between Pathological and Radiological Necrosis

HCC 1	**Pathological Necrosis (%)**						
	>/=90%		**50-89%**		**<50%**		**p-value**
Radiological Viability	n =	%	n =	%	n =	%	
Non-viable	19	90.50%	7	77.80%	4	66.70%	0.325
Equivocal	1	4.80%	1	11.10%	0	0%	
Viable	1	4.80%	1	11.10%	2	33.30%	

HCC 2	Pathological Necrosis Grading						
	Grade 1		Grade 2		Grade 3		p-value
Radiological Viability	n =	%	n =	%	n =	%	
Non-viable	5	83.30%	1	100.00%	2	50.00%	0.415
Equivocal	0	0.00%	0	0.00%	0	0.00%	
Viable	1	16.70%	0	0.00%	2	50.00%	

Disclosures: The following people have nothing to disclose: Mohammad Bourmaf, Kabir Chhabra, Mohammed Rifat Shaik, Dabin Choi, David Lee, Hyun S. Kim, Kirti Shetty

f 1011-A | CYSTATIN C: A BETTER MARKER THAN SERUM CREATININE FOR e STAGE 2 ACUTE KIDNEY INJURY (AKI) AND WAITLIST MORTALITY (WLM) AMONG DECOMPENSATED CIRRHOSIS PATIENTS

Giuseppe Cullaro, University of California, San Francisco, Kavish R. Patidar, Section of Gastroenterology, Department of Medicine, Baylor College of Medicine and Michael E. Debakey Veterans Affairs Medical Center, Andrew Allegretti, Massachusetts General Hospital and Jennifer C. Lai, University of California-San Francisco

Background: Serum creatinine (sCr) is known to be an inaccurate metric, varying by sex, race, and functional status. Cystatin C (cysC) is an affordable, widely available metric that decreases these inaccuracies and is recommended by the National Kidney Foundation. Herein, we compare the association between sCR and cysC with Stage 2 AKI and WLM occurrence. **Methods**: In our ongoing, prospective cohort, we measured sCr and cysC levels at outpatient “Phase 1” visits. To quantify the variation in cysC and sCr, we calculated cysC to sCr ratios (CYS/CR), categorizing patients by the median value of < or e 1.46. We utilized linear regression to determine the factors most associated with CYS/CR. To determine if cysC was more strongly associated with key outcomes (e Stage 2 AKI – a e 200% increase in sCr from baseline; WLM – death or delisting for sickness) than sCr, we compared univariable Cox-regression models using the Likelihood Ratio Test. We repeated these comparisons in populations most impacted by inaccuracies in sCr — women, frail patients (Liver Frailty Index [LFI] e 4.2), and Childs C patients. **Results**: Among 528 participants, those with a high vs. low CYS/CR were more likely to be female (59 v. 31%), frail (38 v. 26%), have Child C cirrhosis (62 v. 50%), and experience WLM (27 v. 17%) (p d 0.01 for all, Table 1). In multivariable linear regression, the factors associated with CYS/CR were: LFI per 1 point (B 0.07, 95CI 0.03 – 0.12); female sex (B 0.20, 95CI 0.20 – 0.35); Child C cirrhosis (B 0.13, 95CI 0.06 – 0.20). In univariable Cox regression, only cysC was associated with WLM (cysC: HR1.3 $p < 0.001$; sCr: HR 1.2, $p = 0.1$). cysC (vs. sCr) was more strongly associated with WLM (Log-Likelihood Difference [LLD] 5.4, $p < 0.001$). This was observed in women (LLD 1.9), frail patients (LLD 1.5), and Child C patients (LLD 1.4) ($p < 0.001$ for each). In univariable Cox regression, only cysC was associated with Stage 2 AKI (cysC: HR1.3, $p = 0.04$; sCr: HR 1.1, $p = 0.4$). cysC (vs. sCr) was more strongly associated with Stage 2 (LLD 2.7, $p < 0.001$). This was also seen in women (LLD 0.1), frail patients (LLD 0.2), and Child C patients (LLD 0.9) ($p < 0.001$ for all). **Conclusion:** CysC is more strongly associated with AKI and WLM than sCr. CYS/CR varies substantially by sex, frailty, and Child class, suggesting an underestimation of kidney dysfunction in these groups. Our data support the routine measurement of cysC among decompensated cirrhosis patients.

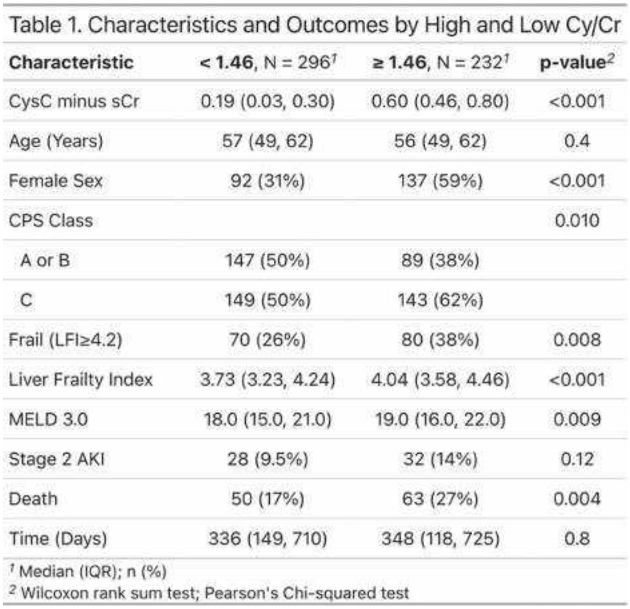

Table 1. Characteristics and Outcomes by High and Low Cy/Cr

Characteristic	< 1.46, N = 296[1]	≥ 1.46, N = 232[1]	p-value[2]
CysC minus sCr	0.19 (0.03, 0.30)	0.60 (0.46, 0.80)	<0.001
Age (Years)	57 (49, 62)	56 (49, 62)	0.4
Female Sex	92 (31%)	137 (59%)	<0.001
CPS Class			0.010
A or B	147 (50%)	89 (38%)	
C	149 (50%)	143 (62%)	
Frail (LFI≥4.2)	70 (26%)	80 (38%)	0.008
Liver Frailty Index	3.73 (3.23, 4.24)	4.04 (3.58, 4.46)	<0.001
MELD 3.0	18.0 (15.0, 21.0)	19.0 (16.0, 22.0)	0.009
Stage 2 AKI	28 (9.5%)	32 (14%)	0.12
Death	50 (17%)	63 (27%)	0.004
Time (Days)	336 (149, 710)	348 (118, 725)	0.8

[1] Median (IQR); n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test

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1012-A | DISPARITIES IN LIVER TRANSPLANT EVALUATION (LTE): PREDICTORS OF LTE CLOSURE AT A LARGE U.S. TRANSPLANT CENTER

Caroline McLeod[1], Alex R. Jones[2], Olgert Bardhi[1], Prajwal Gowda[3], Dyanna Gregory[1], Alvaro Noriega Ramirez[2], Haley Holderness[3], Jeremy Louissaint[2], Thomas G. Cotter[2], Nicole E. Rich[2], Madhukar Patel[2], Arjmand R. Mufti[2], Lisa B. VanWagner[2], Amit G. Singal[2] and Sarah Rosanna Lieber[2], (1)UT Southwestern Medical Center, (2)University of Texas Southwestern Medical Center, (3)UT Southwestern School of Medicine

Background: Liver transplantation (LT) is a lifesaving surgery for patients with end stage liver disease; however, access is fraught with inequities. Race, sex, and socioeconomic disparities have been described among listed and transplanted individual's. However, upstream factors have been understudied in the LT evaluation (LTE) process. Therefore, we aimed to provide an in-depth analysis of sociodemographic and psychosocial factors associated with LTE closure. **Methods:** A retrospective chart review of a random selection of adult LT candidates evaluated between 2015-2020 was performed and stratified by evaluation outcome: closed, waitlisted, or transplanted. Bivariate and multivariable logistic regression assessed for associations between psychosocial and medical factors and LTE closure. **Results:** A total of 161 LTE closures were compared to 127 waitlisted or transplanted individual's (Table 1). The most common reasons for LTE closure were medical (62.7%), followed by psychosocial (30.4%) and personal choice (6.8%). The most common medical reasons for LTE closure were non-liver related comorbidities (47.5%) and improvement in health no longer requiring LT (35.6%). The most common psychosocial reasons were ongoing substance use (30%) and failure to identify social support (30%). Among LTE closures, 37% had an incomplete evaluation— the most frequent components not completed were cardiac (76%), preventive health testing (66%), radiology (64%), and social work (62%) visits. Compared to those waitlisted/transplanted, LTE closures occurred in patients who were older, had lower income levels, less reliable access to transportation, pre-existing psychiatric comorbidity, higher SIPAT scores, and needed simultaneous liver-kidney transplant (SLK) (Table 1). In multivariable analysis, factors significantly associated with LTE closure included older age (aOR 3.03 [95% CI 1.31, 7.00]), need for SLK (aOR 5.62 [1.70, 18.53]), psychiatric history (aOR 2.25 [1.03, 4.92]), and substance use history (aOR 2.95 [1.26, 6.91]) adjusting for sex, education, income level, race, ethnicity, insurance type, transplant indication, and being seen in a satellite clinic. **Conclusion:** Older patients, SLK candidates, or individual's with prior psychiatric or substance use histories are more likely to have an LTE closed independent of important social determinants of health. A complex interplay of factors including socioeconomic status, race/ethnicity, and psychosocial history likely exists and needs to be investigated to overcome inequities in LT access.

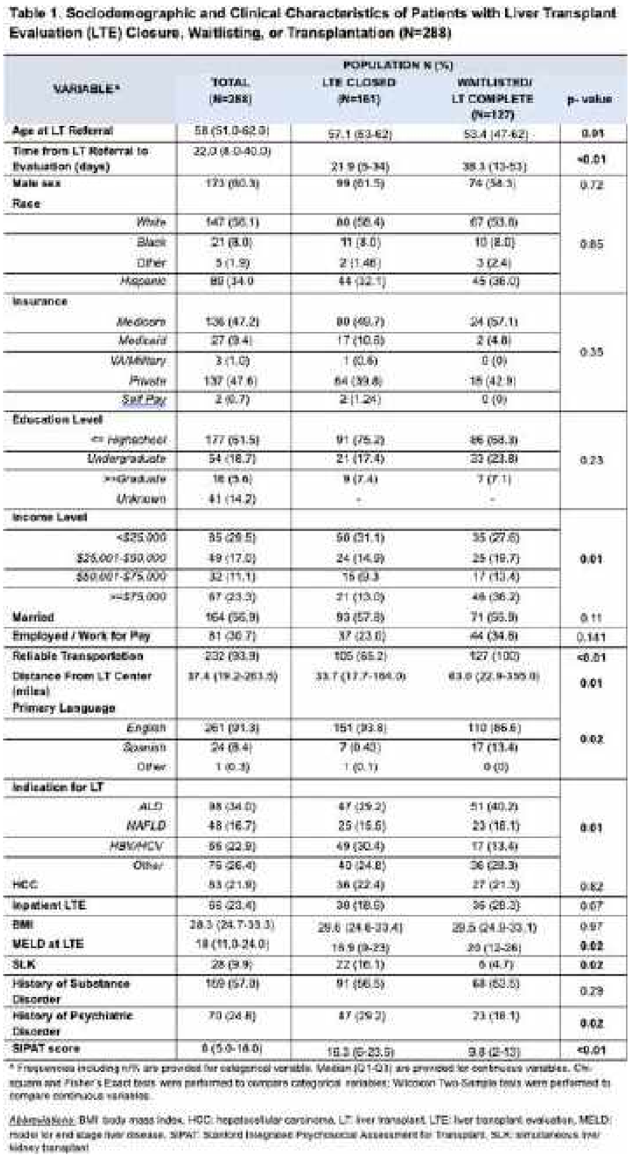

Table 1. Sociodemographic and Clinical Characteristics of Patients with Liver Transplant Evaluation (LTE) Closure, Waitlisting, or Transplantation (N=288)

VARIABLE*	POPULATION N (%)			
	TOTAL (N=288)	LTE CLOSED (N=161)	WAITLISTED/ LT COMPLETE (N=127)	p- value
Age at LT Referral	58 (51.0-62.0)	57.1 (53-62)	53.4 (47-62)	0.01
Time from LT Referral to Evaluation (days)	22.0 (8.0-40.0)	21.9 (9-34)	38.3 (13-53)	<0.01
Male sex	173 (60.3)	99 (61.5)	74 (58.3)	0.72
Race				0.85
White	147 (56.1)	80 (58.4)	67 (53.6)	
Black	21 (8.0)	11 (8.0)	10 (8.0)	
Other	5 (1.9)	2 (1.46)	3 (2.4)	
Hispanic	89 (34.0	44 (32.1)	45 (36.0)	
Insurance				0.35
Medicare	136 (47.2)	80 (49.7)	24 (57.1)	
Medicaid	27 (9.4)	17 (10.5)	2 (4.8)	
VA/Military	3 (1.0)	1 (0.6)	0 (0)	
Private	137 (47.6)	64 (39.8)	18 (42.9)	
Self Pay	2 (0.7)	2 (1.24)	0 (0)	
Education Level				0.23
<= Highschool	177 (61.5)	91 (75.2)	86 (68.3)	
Undergraduate	54 (18.7)	21 (17.4)	33 (23.8)	
>=Graduate	16 (5.6)	9 (7.4)	7 (7.1)	
Unknown	41 (14.2)	-	-	
Income Level				0.01
<$25,000	85 (29.5)	50 (31.1)	35 (27.6)	
$25,001-$50,000	49 (17.0)	24 (14.9)	25 (19.7)	
$50,001-$75,000	32 (11.1)	15 (9.3	17 (13.4)	
>=$75,000	67 (23.3)	21 (13.0)	46 (36.2)	
Married	164 (56.9)	93 (57.8)	71 (55.9)	0.11
Employed / Work for Pay	81 (30.7)	37 (23.0)	44 (34.6)	0.141
Reliable Transportation	232 (93.9)	105 (65.2)	127 (100)	<0.01
Distance From LT Center (miles)	37.4 (19.2-263.5)	33.7 (17.7-164.0)	63.0 (22.9-335.0)	0.01
Primary Language				0.02
English	261 (91.3)	151 (93.8)	110 (86.6)	
Spanish	24 (8.4)	7 (0.43)	17 (13.4)	
Other	1 (0.3)	1 (0.1)	0 (0)	
Indication for LT				0.01
ALD	98 (34.0)	47 (29.2)	51 (40.2)	
NAFLD	48 (16.7)	25 (15.6)	23 (18.1)	
HBV/HCV	66 (22.9)	49 (30.4)	17 (13.4)	
Other	76 (26.4)	40 (24.8)	36 (28.3)	
HCC	63 (21.9)	36 (22.4)	27 (21.3)	0.82
Inpatient LTE	66 (23.4)	30 (18.6)	36 (28.3)	0.07
BMI	28.3 (24.7-33.3)	28.6 (24.6-33.4)	29.5 (24.9-33.1)	0.97
MELD at LTE	18 (11.0-24.0)	15.9 (9-23)	20 (12-26)	0.02
SLK	28 (9.9)	22 (16.1)	6 (4.7)	0.02
History of Substance Disorder	159 (57.8)	91 (56.5)	68 (53.5)	0.29
History of Psychiatric Disorder	70 (24.8)	47 (29.2)	23 (18.1)	0.02
SIPAT score	8 (5.0-18.0)	16.3 (6-23.5)	9.8 (2-13)	<0.01

* Frequencies including n/% are provided for categorical variable. Median (Q1-Q3) are provided for continuous variables. Chi-square and Fisher's Exact tests were performed to compare categorical variables; Wilcoxon Two-Sample tests were performed to compare continuous variables.

Abbreviations: BMI: body mass index, HCC: hepatocellular carcinoma, LT: liver transplant, LTE: liver transplant evaluation, MELD: model for end stage liver disease, SIPAT: Stanford Integrated Psychosocial Assessment for Transplant, SLK: simultaneous liver kidney transplant

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Disclosure information not available at the time of publication: Prajwal Gowda, Dyanna Gregory, Alvaro Noriega Ramirez, Haley Holderness, Arjmand R. Mufti

1013-A | DO WE STILL NEED MICROSCOPE SURGERY IN HEPATIC ARTERY ANASTOMOSIS TO DECREASE THE INCIDENCE OF COMPLICATIONS IN LIVING DONOR LIVER TRANSPLANTATION? SYSTEMATIC REVIEW AND META-ANALYSIS

Beshoy Effat Elkomos, General Surgery Department - Ain Shams University, Philopateer Effat Alkomos, Faculty of Medicine - Ain Shams University, Mina Effat Alkomos, Gastroentrology Department, St. Joseph's University, Paterson, NJ, USA and Amr Abdelaal, General Surgery Department- Ain Shams University Hospital

Background: Hepatic artery thrombosis (HAT) is the most serious vascular complication after LT. Moreover, in comparison to DDLT, HA anastomosis is more challenging in LDLT With a lot of controversial topics about the use of microscopic surgery in LDLT. We aimed to Compare the use of microscopic and loupe surgery in hepatic artery anastomosis in adult and pediatric LDLT to decrease the incidence of vascular complications **Methods:** PubMed, Scopes, Web of Science, and Cochrane Library were searched for eligible studies from inception to April 2023 and a systematic review and a meta-analysis were done **Results:** According to our eligibility criteria, 10 studies with a total of 1939 patients were included. In comparison to microscopic surgery, loupe anastomosis has a similar incidence of Hepatic artery thrombosis. (Thrombosis, RR = 0.96, 95% CI = 0.26-3.48, $p = 0.95$). In addition to that, no significant difference was detected between the two types in terms of stenosis, decreased blood flow and hospital stay. (Decreased blood flow, RR = 0.68, 95% CI = 0.01-86.65, $p = 0.88$), (Stenosis, RR = 1.81, 95% CI = 0.19-17.21, $p = 0.60$) and (Hospital stay, MD = 1.16, 95% CI = -3.79-6.11, $p = 0.65$). However, the operative time was longer in the case of microscopic surgery (Anastomotic time, MD = 24.09, 95% CI = 7.79-40.39 $p = 0.004$) **Conclusion:** With an equal incidence of complications and shorter operative time, Loupe anastomosis offers a great alternative to microscopic surgery in HA anastomosis

Disclosures: The following people have nothing to disclose: Beshoy Effat Elkomos, Philopateer Effat Alkomos, Mina Effat Alkomos, Amr Abdelaal

1014-A | DUAL SMALL MOLECULE INHIBITORS PROMOTE LIVER REGENERATION THROUGH YAP ACTIVATION IN HEALTHY AND DISEASED MURINE PARTIAL HEPATECTOMY MODELS

Ryan Watkins[1], EeeLN Buckarma[1], Chantal McCabe[1], Patrick Starlinger[1], Gregory J. Gores[1], Weijun Shen[2] and Rory Smoot[3], (1)Mayo Clinic, (2)Calibr at Scripps, (3)Mayo Clinic Rochester, Rochester, MN

Background: Pharmacologically enhancing liver regeneration after hepatectomy may avert complications such as post hepatectomy liver failure, a morbid condition. Yes-associated protein (YAP), a transcriptional co-activator, is instrumental in liver regeneration. We have shown that small molecule inhibitors NSC87877 (NSC) and mCLC846 (mCLC) enhance liver regeneration individually. Both activate YAP through the non-canonical and canonical pathways respectively. We have also previously shown that their underlying regenerative augmentation differs molecularly. Herein, we investigated the effects combined therapy with NSC and mCLC in murine partial hepatectomy models across multiple disease states including diet induced non-alcoholic steatohepatitis (NASH). **Methods:** Mice were treated with mCLC (100 mg/kg/d) and NSC (15 mg/kg/d) or vehicle immediately before and after standard two-thirds partial hepatectomy (PH). Twelve-week-old male C57BL/6J mice were utilized. RNA-sequencing was performed from liver lysate using Illumina Hi-Seq4000 followed standard bioinformatic analysis. Additional murine models underwent PH included: mice aged to 34 weeks under normal conditions (chow control) or with a high fat, high cholesterol, and high glucose and fructose diet to induce non-alcoholic steatohepatitis (NASH), homozygous null Mdr2 (Mdr2-/-), representing a model of primary sclerosing cholangitis, and extended hepatectomy in wild type mice (90% liver excision) with a right posterior lobe remnant, mirroring small for size syndrome. Liver regeneration was assessed by liver to body weight ratio 72 hours following surgery. Proliferation was assessed by immunoblot for proliferating cellular nuclear antigen (PCNA). **Results:** Wild type mice treated with NSC/mCLC had significantly increased liver to body weight ratio 72h post PH as compared to vehicle (5.6 % vs 2.6 %, $p < 0.001$) with elevated PCNA in treated mice. Transcriptomic analysis of regenerating remnants 40h following PH treated with NSC/mCLC identified upregulated genes consistent with the termination phase of liver regeneration, indicating an accelerated timeline. Mice undergoing extended hepatectomy had increased liver to body weight ratio when compared to vehicle treated mice (1.85 % vs 2.57 %, $p < 0.01$). Mdr2-/- mice regeneration was enhanced with NSC/mCLC with increased liver to body weight ratio (3.39 % vs 4.01 %, $p < 0.05$) which was not observed with single agent treatment. Chow control had increased liver to body weight ratio post PH (2.49 % vs 3.11 %, $p < 0.001$) with a 10-fold increase in PCNA. NASH mice survival was severely reduced when compared to chow controls 72h post PH (22.2 % vs 100 %, $p < 0.01$). Treated NASH mice had improved survival (58.3 % vs 22.2 %, $p < 0.05$). **Conclusion:** Dual YAP activation enhanced liver regeneration in healthy and deranged regenerative models: small for size syndrome, primary sclerosing cholangitis, and NASH with enhanced survival in NASH.

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Disclosure information not available at the time of publication: EeeLN Buckarma, Chantal McCabe, Patrick Starlinger, Weijun Shen, Rory Smoot

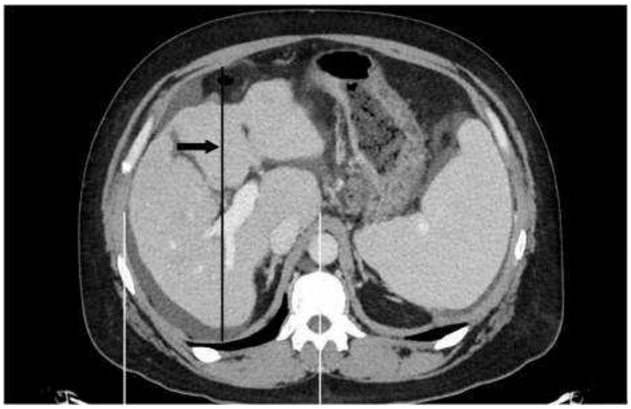
1015-A | EVALUATING THE CORRELATION BETWEEN AP DIAMETER, BODY SURFACE AREA AND HEIGHT FOR LIVER TRANSPLANT DONORS AND RECIPIENTS FOR THE ERA OF CONTINUOUS DISTRIBUTION

Catherine Kling[1], Christopher Little[1], Scott W. Biggins[2] and James D. Perkins[1], (1)University of Washington, (2) University of Washington, Seattle, WA

Background: Shorter height and lower body surface area (BSA) correlate with reduced deceased donor liver transplant (DDLT) access, resulting in longer waitlist times, higher incidence of waitlist mortality, and a lower overall transplant rate compared to larger candidates. To mitigate this disparity in the coming era of Continuous Distribution, implementable size-matching measures should be introduced to guide allocation policy and decision making. Liver anteroposterior (AP) diameter on cross-sectional imaging is considered an important measure of liver usability for DDLT, though it is not regularly obtained nor recorded in the United Network for Organ Sharing (UNOS) data sets. As such, we sought to correlate height and BSA, two universally available characteristics, to AP diameter in donors and recipients. Multivariable competing risk analysis was then used to correlate these variables with waitlist outcomes. **Methods:** AP diameter was measured via cross-sectional imaging in 143 DDLT donor-recipient pairs from a single center between 2021-2022 (Figure 1. AP diameter [black line] measured at the mid-hepatic point halfway between the mid-vertebral body [medial white line] and inner abdominal wall [lateral white line] at the level of the right hepatic vein). Linear, Pearson's and PhiK correlation coefficients were used to correlate

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

BSA and height to AP diameter. Competing risk analyses of waitlist outcomes were performed using UNOS data collected from 6/18/2013-3/20/2020. **Results:** Amongst DDLT donors, BSA correlated better with AP diameter than height (PhiK $R^2 = 0.63$ vs 0.20). For recipients, neither BSA nor height were good predictors of AP diameter (PhiK $R^2 = 0.34$ and 0.43). However, in a subset of recipients without ascites (35.7% of recipients), BSA did correlate well to AP diameter (PhiK $R^2 = 0.63$) but not to height. In the multivariable competing risk models, both taller height and greater BSA were associated with increased access to DDLT, decreased delisting for death or critical illness, and decreased dependence on living donor liver transplant; however, the BSA model slightly outperformed that of height (model concordance 0.748 vs 0.747). **Conclusion:** Taken together, these findings indicate that BSA correlates well with AP diameter in donors and recipients without ascites and serves as an effective predictor of waitlist outcomes. We posit that BSA can therefore be used as a surrogate for AP diameter to optimize donor liver allocation to small recipients.



Disclosures: Scott W. Biggins: Scott Biggins, Christopher Little, James D. Perkins

1016-A | EVALUATION OF LIVER REGENERATION CAPACITY WITH THE USE OF GENABILIC ACID, SILYMARIN-CURCUMIN, GANODERMA LUCIDUM, AMINO ACID-MULTIVITAMIN MIXTURE, AND 2-METHYL-2-PHENOXY-PROPIONIC ACID BEFORE PARTIAL HEPATECTOMY: BIOCHEMICAL AND IMMUNOHISTOCHEMICAL EFFECTS IN RATS

Sencan Acar[1]*, Hüseyin Çakıroğlu*[2]*, Erdem Çokluk*[2]*, Özcan Budak*[2] *and Ahmet Tarık Eminler*[2]*, (1)Amasya University Sabuncuoglu Serefeddin Eah, (2)Sakarya University Faculty of Medicine*

Background: Remnant liver tissue is essential for the surgery of primary liver tumor, metastasectomy, or donor hepatectomy. There are various supplements that are stated to increase liver regeneration. We aimed to show whether there is an effective supportive treatment that can increase the safety of donors with insufficient remnants, as well as expand the donor pool, in countries where living donor liver transplantation is performed intensively, as in our country. Therefore, in our study to investigate the effects of different substance extracts on the regeneration capacity of residual liver tissue after hepatectomy. **Methods:** Rats of equal age and approximately equal weight were grouped into 6 groups: Group 1 = Sham group; Group 2 = Genabilic acid, 3/7 days, 6 weeks oral gavage, 10 mg/kg; Group 3 = Silymarin+curcumin, 6 weeks oral gavage, 200mg/kg+40mg/dose/day; Group 4 = Ganoderma lucidum, 900mg/kg oral gavage for 6 weeks; Group 5 = Mixture containing group B vitamins, amino acids, l-carnitine and sugars, 4 ml/kg for 1 week, IP; Group 6 = Phenoxy-2-methyl-2-propionic acid, 10 mg/kg for 1 week, IP. Subjects' mTOR, insulin, nesfatin, and leptin levels were checked. Proliferating cell nuclear antigen (PCNA) was performed for regeneration control and immunohistochemically, Ki-67, mTOR, VEGF, FGF, HGF, and Calpain-10 stainings were conducted from the liver. **Results:** In the comparison of the Sham group and the other groups; there was a significant difference in terms of insulin with group 4 ($p = 0.041$) and nesfatin with group 3 ($p < 0.001$) The other markers were similar. Proliferating cell nuclear antigen, Ki-67, mTOR, and Calpain-10 were significantly different in all groups ($p < 0.001$). It was also significantly different in terms of VEGF, FGF, and HGF with the other groups except group 4. **Conclusion:** It was determined that the silymarin-curcumin mixture was more successful in suppressing hunger hormones with an increase in nesfatin level, while Ganoderma lucidum caused a decrease in insulin levels. Considering the fact that regeneration of the liver with fibrosis is an undesirable situation, although it is thought that Ganoderma lucidum does not affect FGF levels, it creates a healthier regeneration tissue, but this has not been proven by immunostaining. In conclusion, no single agent is ideal in the prophylaxis of possible hepatic failure after hepatectomy. It is thought that combinations may be required in the use of such agents. It is clear that further research is needed.

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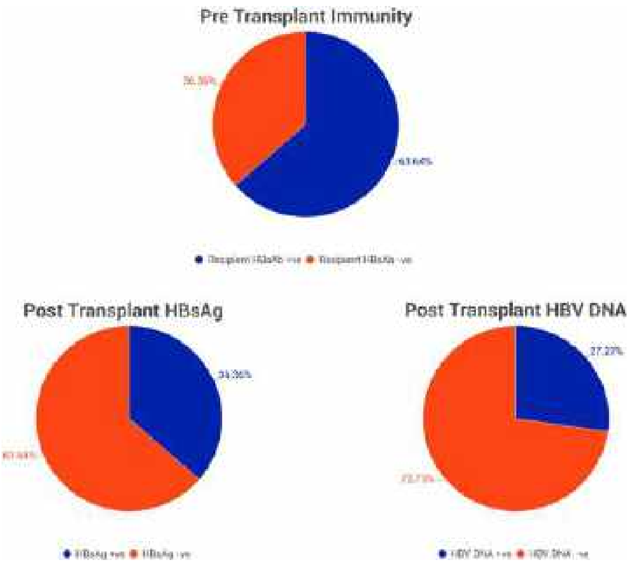
1017-A | EXPERIENCE IN USE OF DONORS WITH ACTIVE HEPATITIS B FOR LIVER TRANSPLANT

Media N Ismael[1], Juan Gonzalez[1], Steve Shen[1], Andreas Zori[2], Consuelo Soldevila-Pico[1] and Roniel Cabrera[1], (1)University of Florida, (2)University of Florida, Gainesville, FL

Background: Organ shortage remains a major challenge in liver transplantation (LTx). Efforts have been made to increase the donor pool with high-risk organs but experience with active hepatitis B (HBV) liver donations lags behind. Careful selection of recipients and effective antiviral prophylaxis can reduce the risk of HBV transmission in the context of LTx. In this report, we summarize our center's experience in utilizing donor livers with active HBV **Methods:** Patients who underwent LTx at the University of Florida between 2020 and 2022 were retrospectively reviewed. Transplants from donors with HBV nucleic acid test (NAT) positive or hepatitis B surface antigen (HBsAg) positive livers were included in the study. Donor and recipient viral serologies pre- and post-transplant, treatment algorithms, and post-transplant management and survival were reviewed. **Results:** Eleven patients received LTx from donors with active HBV infection. Eight were men (72.7%) with a median age of 53 and MELD of 19 at transplant. The wait time ranged from a month to eight months. Only one recipient had chronic HBV infection prior to LTx, and none had active or previous hepatitis C (HCV). Seven patients had immunity to HBV at transplant (63.6%). Two donors were HCV antibody positive and two HCV NAT positive. The two patients who received livers from HCV NAT positive received Epclusa post-transplant. All patients received Hepatitis B immunoglobulin (HBIG) after transplant and placed on antiviral therapy for HBV. Everyone received immunosuppression per protocol with a short steroid taper, tacrolimus, and mycophenolate. Four showed positive HBsAg post-transplant with two of them developing low level viremia in the immediate post-transplant period that resolved within days. Only one patient had graft rejection that responded to pulse steroids. There were two deaths in this cohort, one due to cardiopulmonary arrest and the other due to liver failure with unclear etiology. Although this patient developed detectable sAg, HBV DNA was never detectable. The remaining patients did not have significant complications post-transplant with 6 surviving more than a year and the rest being transplanted within the past year. **Conclusion:** Utilizing donors with active HBV for LTx is feasible with good outcomes. There were no definite HBV related complications and viral suppression was achieved in all patients. Pre-transplant vaccination of recipients along with vigilant post-transplant follow up and a standardized protocol of testing ensure ability to control HBV and prevent viremia.



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Disclosure information not available at the time of publication: Juan Gonzalez, Steve Shen, Consuelo Soldevila-Pico, Roniel Cabrera

1018-A | EXPERIENCES OF ALCOHOL-RELATED LIVER DISEASE LIVER TRANSPLANT RECIPIENTS WITH AND WITHOUT 6 MONTHS OF PRE-TRANSPLANT ABSTINENCE

Janetta Brundage[1], Mayan Teles[1], Aura Abdeon[1], Andrea F. DiMartini[2], Geetanjali Chander[3], Olivia Kates[4], Hannah C. Sung[4], Andrew M. Cameron[1] and Po-Hung (Victor) Chen[4], (1)Johns Hopkins University, (2)University of Pittsburgh, (3)University of Washington, (4)Johns Hopkins University School of Medicine

Background: Historically, transplant centers have required liver transplant (LT) candidates with alcohol-related liver disease (ALD) to demonstrate 6 months of alcohol abstinence prior to receiving their LT, known as the "6-month rule." Differences in experiences between those transplanted before (early LT) and after (standard LT) 6 months of alcohol abstinence are understudied. Our qualitative study aimed to assess similarities and differences in ALD LT recipients' alcohol-related experiences and identify potential unique experiences of early LT recipients. Understanding these similarities and differences could help determine applicability of the 6-month rule. **Methods:** We conducted in-depth, semi-structured interviews (n = 39) with LT recipients from a single center from 2 patient groups: (a) early LT (ELT), who had < 6 months of alcohol abstinence prior to LT (n = 20) and (b) standard LT (SLT), who had e 6 months of alcohol abstinence prior to LT (n = 19). We inductively analyzed interviews and generated themes within and across groups. **Results:** Across ELT and SLT groups, participants described similar alcohol-related experiences before their transplant. Some participants did not know that their level of alcohol use was causing damage to the point of needing a liver transplant. Others perceived that their alcohol use was "heavy" but did not, at the time, feel concerned because they were able to maintain relationships and work. Still others described their alcohol use as negatively impacting their relationships. ELT participants questioned if they were "deserving" of a LT more explicitly than SLT participants. An ELT participant expressed that they had felt "guilty" when they were accepted for a liver transplant after being denied at another center for not having at least 6 months of alcohol abstinence. The participant elaborated, "I can't take somebody else's liver because I don't deserve it." **Conclusion:** Themes indicate a lack of substantial differences between ELT and SLT experiences with alcohol. However, questioning their worthiness for transplant seems to be more pronounced with the ELTs. Our qualitative work has generated a hypothesis that differential perceptions in self-worth between ELT and SLT groups may not be attributable to alcohol-related history, but rather their experiences around the stigmatizing "6-month rule." Patient perceptions of bypassing the "6-month rule" may reinforce alcohol-related self-stigma.

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1019-A | FACTORS ASSOCIATED WITH RECEIVING A LIVER TRANSPLANT FROM DECEASED DONORS LOCATED FAR FROM THE TRANSPLANT HOSPITAL

Neha Godbole, University of Miami and David Goldberg, University of Miami School of Medicine

Background: Increased distance between donor hospitals and transplant centers is associated with added logistics and cold ischemia times due to travel. Importing organs is associated with higher costs associated with travel by air of the organ (+/- the procuring team) and at times additional import fees. There are known disparities in access to a transplant based on insurance type, although these largely are related to access to the waitlist. However, because transplant centers often receive higher reimbursement from private insurers and Medicare, compared to Medicaid, there is the potential for disparities in receipt of far donors as a function of a patient's insurance. We sought to explore the association between insurance type and receipt of a far donor among liver transplant recipients. **Methods:** We conducted a retrospective cohort study using OPTN/UNOS study of adult deceased donor liver transplant recipients from 1/1/2015-3/31/2023. The outcome was defined as being transplanted with a liver from a donor located "far" from the transplant hospital (primary: 500 miles; secondary: 250 miles). Mixed effects logistic regression models were fit to evaluate the association between insurance type and receipt of a liver from a far donor, with state modeled as a random effect to account for baseline variability in reimbursement rates for patients with Medicaid based on state of residence. **Results:** Several clinical variables were associated with receipt of a liver transplant from a donor located far from the transplant hospital (Table 1). Increased MELD score was associated with a decreased odds of receiving a donor from a far hospital, while being mechanically ventilated or in the intensive care unit were associated with an increased odds. However, even after accounting for key clinical and demographic covariates, there was no significant difference in the odds of receiving a transplant from a donor located far from the transplant hospital for patients with Medicaid insurance compared to those with private or Medicare insurance (Table 1). Patients with "other" insurance were less likely to receive a transplant from a "far" donor using the secondary outcome definition of far as >250 nautical miles from the transplant center to donor hospital. **Conclusion:** Although there are different clinical factors associated with receiving a liver transplant from a donor located far from the transplant hospital, patients with Medicaid insurance are no less likely to receive a transplant from a far donor. This despite the fact that Medicaid reimbursement rates for transplant are often less than private insurers and Medicare, and far donors are associated with increased costs. Even though there are disparities in access to the waitlist based on insurance type, a surrogate for socioeconomic status to some degree, it is reassuring that once waitlisted, transplant decisions and donor selection do not appear to be influence by potential differences in reimbursement.

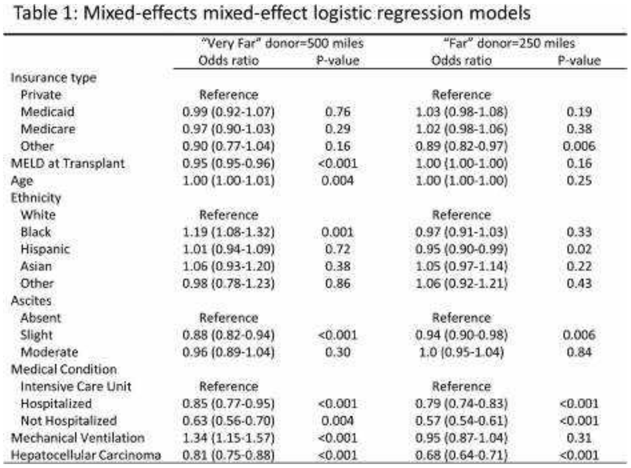


Table 1: Mixed-effects mixed-effect logistic regression models

	"Very Far" donor=500 miles		"Far" donor=250 miles	
	Odds ratio	P-value	Odds ratio	P-value
Insurance type				
Private	Reference		Reference	
Medicaid	0.99 (0.92-1.07)	0.76	1.03 (0.98-1.08)	0.19
Medicare	0.97 (0.90-1.03)	0.29	1.02 (0.98-1.06)	0.38
Other	0.90 (0.77-1.04)	0.16	0.89 (0.82-0.97)	0.006
MELD at Transplant	0.95 (0.95-0.96)	<0.001	1.00 (1.00-1.00)	0.16
Age	1.00 (1.00-1.01)	0.004	1.00 (1.00-1.00)	0.25
Ethnicity				
White	Reference		Reference	
Black	1.19 (1.08-1.32)	0.001	0.97 (0.91-1.03)	0.33
Hispanic	1.01 (0.94-1.09)	0.72	0.95 (0.90-0.99)	0.02
Asian	1.06 (0.93-1.20)	0.38	1.05 (0.97-1.14)	0.22
Other	0.98 (0.78-1.23)	0.86	1.06 (0.92-1.21)	0.43
Ascites				
Absent	Reference		Reference	
Slight	0.88 (0.82-0.94)	<0.001	0.94 (0.90-0.98)	0.006
Moderate	0.96 (0.89-1.04)	0.30	1.0 (0.95-1.04)	0.84
Medical Condition				
Intensive Care Unit	Reference		Reference	
Hospitalized	0.85 (0.77-0.95)	<0.001	0.79 (0.74-0.83)	<0.001
Not Hospitalized	0.63 (0.56-0.70)	0.004	0.57 (0.54-0.61)	<0.001
Mechanical Ventilation	1.34 (1.15-1.57)	<0.001	0.95 (0.87-1.04)	0.31
Hepatocellular Carcinoma	0.81 (0.75-0.88)	<0.001	0.68 (0.64-0.71)	<0.001

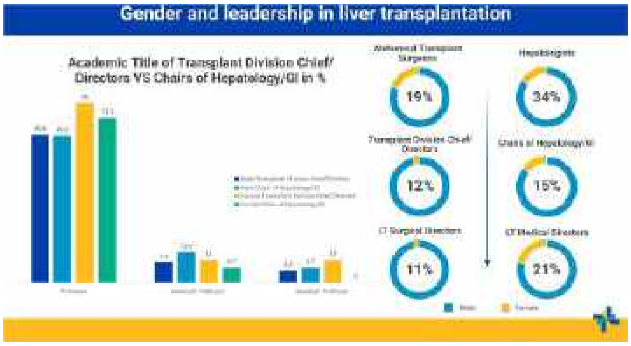
Disclosures: David Goldberg – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;

The following people have nothing to disclose: Neha Godbole

1020-A | GENDER AND LEADERSHIP IN LIVER TRANSPLANTATION

Nazokat Otajonova[1], *Luis Garrido-Treviño*[2], *Giovanna Saracino*[2], *Sumeet Asrani*[2] *and Anji Wall*[3], *(1)Baylor, (2) Baylor University Medical Center, Dallas, TX, (3)Baylor University*

Background: Women are underrepresented in leadership positions throughout the world. We hypothesized that there are significant differences in leadership opportunities for women across transplantation in the US. **Methods:** We performed a cross-sectional study of 13 leadership position types of 114 transplant centers in the US. Data was collected from the OPTN and individual departments. We examined gender, terminal degrees, years in practice, academic degrees, and additional leadership roles. **Results:** *Overall:* In US programs, only 18.7% of abdominal transplant surgeons (132/705) and 33.5% of transplant hepatologists (226/674) were female. Among transplant surgeons, the female sex was associated with higher degrees ($p = 0.02$): more females had a master's (11.5% vs. 5.3%) or Ph.D. (13.7% vs. 12.3%) as compared to males. *Leadership:* Only 10-20% of leadership positions were held by females: LT Surgical Director (10.5%), LT Medical Director (21.1%), Transplant division chief (11.9%), and Hepatology/Gastroenterology chief (15.4%). Centers having female Division Chiefs/Directors were more likely to have female LT Surgical Directors ($p = 0.02$). A larger percentage of females needed to be full professors: For females, 80% and 73.3% of women needed to be a professor to advance to these chief roles; for males, it was 65.8% and 65.2% respectively. There was a significant difference by sex and academic rank ($p = <0.01$) for liver transplant medical directorship. Women were more likely to be assistant professors (8, 33.3%), whereas men were more likely to be professors (33, 37.1%) or associate professors (20, 27.5%). **Conclusion:** Less than 20% of transplant leadership positions are secured by females. Despite comprising a substantial proportion of the medical workforce, and holding additional professional titles, women still encounter substantial obstacles in securing leadership positions within transplant centers and academia.

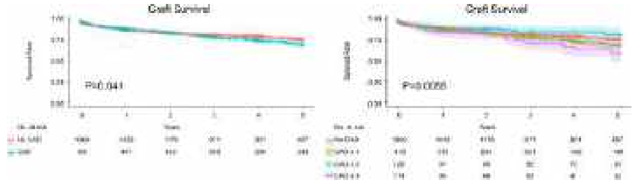


Disclosures: The following people have nothing to disclose: Nazokat Otajonova, Luis Garrido-Treviño, Giovanna Saracino, Sumeet Asrani, Anji Wall

1021-A | IMPACT OF DONOR CORONARY ARTERY DISEASE ON PATIENT AND GRAFT SURVIVAL AMONG LIVER TRANSPLANT RECIPIENTS IN THE UNITED STATES★

Kenji Okumura, Ryosuke Misawa, Abhay Dhand, Suguru Ohira, Hiroshi Sogawa, Roxana I. Bodin, Gregory R. Veillette, David C. Wolf and Seigo Nishida, Westchester Medical Center

Background: While routine donor coronary angiograms are not performed routinely, but the impact of incidental coronary artery disease (CAD) detected during the donor evaluation process on liver graft outcomes is unknown. The aim of this study was to assess the impact of donor CAD on patient and graft survival in Liver transplant (LT) recipients. **Methods:** Data from adult LT recipients who received livers from donors with coronary artery angiograms in the United Network for Organ Sharing (UNOS) between 2002 and 2022 was analyzed. CAD was defined as $>50\%$ obstruction of one or more coronary arteries on angiogram. **Results:** During the study period, 2663 LT recipients (CAD $N = 665$ vs non-CAD $N = 1998$) were identified. In 665 donors, 120(18%) had 3-vessel, 126 (19%) had 2-vessel and 419 (63%) has 1-vessel CAD. Donors with CAD were older (median age: 50 vs 45 y, $p < 0.001$), had lower BMI (26.9 vs 27.4 hours, $p = 0.018$), higher rate of hypertension (54% vs 37%, $p < 0.001$) and diabetes (21% vs 9.9%, $p < 0.001$), with lower HCV-NAT positive rates (1.8% vs 4.3%, $p = 0.035$). The quality of livers as assessed by serum bilirubin and macro/micro steatosis were equal in both groups. LT recipients in CAD group had lower MELD score (24 vs 26, $p = 0.002$). Five-year overall survival (CAD 72.9% vs non-CAD 77.7%, $p = 0.079$) and five-year graft survival (CAD 69.5% vs non-CAD 75.6%, $p = 0.041$) were worse in CAD group (Figure). No difference was seen in risk of vascular thrombosis post-LT in both groups. In multivariable cox-regression analysis, significant risk factors for five year-graft failure were donor 3-vessel CAD (hazard ratio, 1.64; 95% CI: 1.11-2.43; $p = 0.014$) and donor hypertension (hazard ratio, 1.30; 95% CI: 1.09-1.56; $p = 0.003$). **Conclusion:** Risk of five-year graft failure among LT recipients was increased when using livers from donors with known 3-vessel CAD and hypertension.



Disclosures: The following people have nothing to disclose: Kenji Okumura
Disclosure information not available at the time of publication: Ryosuke Misawa, Abhay Dhand, Suguru Ohira, Hiroshi Sogawa, Roxana I. Bodin, Gregory R. Veillette, David C. Wolf, Seigo Nishida

1022-A | IMPACT OF ETIOLOGY ON THE PREDICTION OF WAITLIST MORTALITY IN LIVER TRANSPLANT CANDIDATES

Nakia L Chung[1], Ajitha Mannalithara[1], W. Ray Kim[2] and Allison J. Kwong[1], (1)Stanford University School of Medicine, (2)Stanford University School of Medicine, Woodside, CA

Background: The US organ allocation system does not take into account liver disease etiology in the assessment of medical urgency gauged by the Model for End-Stage Liver Disease (MELD). The epidemiology and demographics of patients undergoing liver transplant (LT) have changed rapidly, including rising prevalence of alcohol-associated liver disease (ALD). MELD equations have not previously considered the possible contribution of the underlying etiology of liver disease to the prediction of waitlist mortality. Patients with different diagnoses may have different mortality risk. We tested whether the association between waitlist mortality and MELD differ by etiology. **Methods:** We evaluated all new adult waitlist registrations from Jan, 2016 to Dec, 2022 in the OPTN registry. Patients with exception points at listing or previous history of liver transplant were excluded. MELD-Na and MELD 3.0 was calculated for each new listing, and etiology was categorized into (ALD), non-alcoholic steatohepatitis (NASH), viral, cholestatic, and other based on listing diagnosis. ALD was subset into alcohol-associated hepatitis (AH) and

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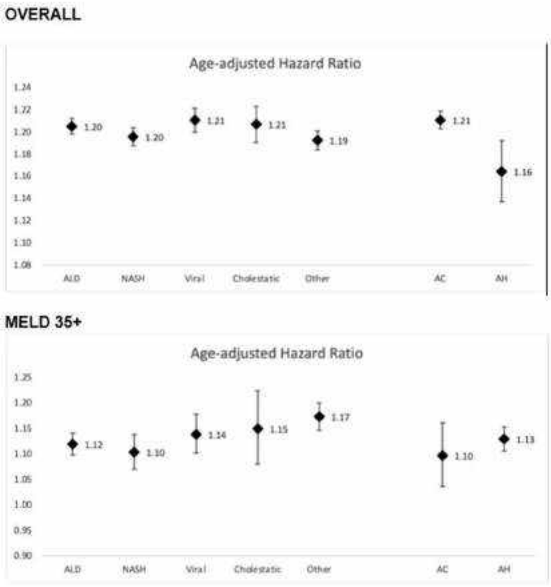
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

alcohol-associated cirrhosis (AC). Cox regression analysis was used to evaluate the hazard of 90-day waitlist mortality from registration, with censoring at liver transplant and adjustment for age. The effect of a 1-unit change in MELD was reported by etiology and MELD category (< 15, 15-24, 25-34, and 35+). **Results:** There were 69,390 eligible adults with end-stage liver disease listed for primary liver transplant, 25,107 (36%) with a primary diagnosis of ALD, 14,335 (21%) with NASH, 9,828 (14%) with viral hepatitis, 4,289 (6%) with cholestatic liver disease, and 15,768 (23%) with other diagnosis. Patients with ALD had higher median MELD-Na than other diagnoses (24 v 17, $p < 0.01$), and those with AH had higher MELD-Na than those with AC (36 v 23, $p < 0.01$). The age-adjusted hazard ratio for 90-day mortality was similar across etiologies, with a hazard ratio of 1.20, indicating a 20% increase in mortality risk for each 1-unit change in MELD-Na (Figure). The overall hazard ratio for AH was lower than all other diagnoses including AC, at 1.16 (95% CI 1.13-1.19), but similar to other etiologies at comparable MELD (35+). The results did not change materially when the data was analyzed using MELD 3.0. **Conclusion:** Given the increasing prevalence of ALD, AH, and NASH among liver transplant candidates, it is crucial to determine if the current tools used to predict waitlist mortality retain precision. In the current study, we demonstrated no significant etiologic differences using MELD-Na or MELD 3.0. Our study suggests that there currently is no need to adjust the MELD score for the underlying etiology of liver disease.

Figure. Age-adjusted hazard ratios for each 1-unit change in MELD-Na, (A) overall and (B) MELD 35+.



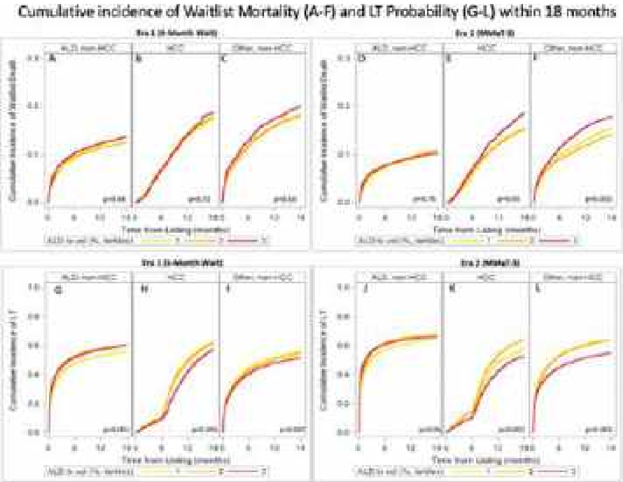
Disclosures: The following people have nothing to disclose: Nakia L Chung, W. Ray Kim, Allison J. Kwong

Disclosure information not available at the time of publication: Ajitha Mannalithara

1023-A | IMPACT OF HIGH-VOLUME TRANSPLANTATION OF ALCOHOL-ASSOCIATED LIVER DISEASE ON WAITLIST OUTCOMES TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA AND OTHER INDICATIONS

Divya Ayyala[1], Jennifer L. Dodge[1], Kali Zhou[2], Norah Terrault[1] and Liyun Yuan[1], (1)University of Southern California, (2)University of Southern California, Los Angeles, CA

Background: Liver transplantation (LT) for alcohol-associated liver disease (ALD) is rising with potential effects for patients listed for LT with hepatocellular carcinoma (HCC) or Other indications (non-ALD, non-HCC). **Methods:** Using U.S. adults (N = 56,696) listed for primary LT from 10/8/2015 to 12/31/2021 with LT indications of HCC (N = 13,274), ALD (N = 20,570), and Other (N = 22,752), we examined the impact of center-level LT volume for ALD (ATxV, low to high tertiles T1◄T3) on waitlist outcomes within HCC policy Era 1 (6-month wait) and Era 2 (MMAT-3). The outcomes were (1) waitlist mortality (death, dropout on the waitlist for clinical deterioration) and (2) LT within 18 months. Multivariable competing risk regression estimated the adjusted sub-hazard ratios (sHR) for risk of waitlist outcomes with interaction effects to test whether ATxV had a differential impact by indication. **Results:** Of 56,596 candidates listed (31,293 in Era 1 and 25,303 in Era 2), the cumulative incidence of waitlist mortality did not differ by AtxV for HCC ($p = 0.48$) or Other ($p = 0.16$) (Figure B,C) in Era 1 and differed significantly by ATxV in Era 2 for HCC ($p = 0.03$) and Other indications ($p < 0.001$) with the highest mortality in ATxV T3 (Figure E,F). However, in Era 2, the adjusted waitlist mortality sHR for candidates listed at high (T3) vs low (T1) AtxV centers did not differ significantly among those with ALD [0.99 (0.66-1.26)], HCC [1.15 (0.96-1.38), interaction $p = 0.22$], and Other [1.13 (0.87-1.46), interaction $p = 0.16$] suggesting no differential effect of AtxV on waitlist mortality by indication. The cumulative incidence of LT differed by AtxV tertile for HCC (Era 1: $p < 0.001$, Era 2: $p < 0.001$) and Other indications (Era 1: $p = 0.007$, Era 2 $p < 0.001$) in Era 1 (Figure H,I) and Era 2 (Figure K,L) with the lowest incidence in T3. The adjusted LT sHR in Era 2 for candidates listed at high (T3) vs low (T1) AtxV centers did not differ significantly among those with ALD [1.04 (0.89-1.34) but was lower among HCC [0.89 (0.72-1.11, interaction $p = 0.08$] and Other indications [0.82 (0.67-1.01), interaction $p = 0.02$)] suggesting a potential differential effect of ATxV on LT by indication. **Conclusion:** High volume of LT for ALD has not negatively impacted waitlist mortality for HCC and other indications. However, we identified a potential adverse effect on LT probabilities for HCC and Other indications in MMAT-3 Era emphasizing the need for continued monitoring.

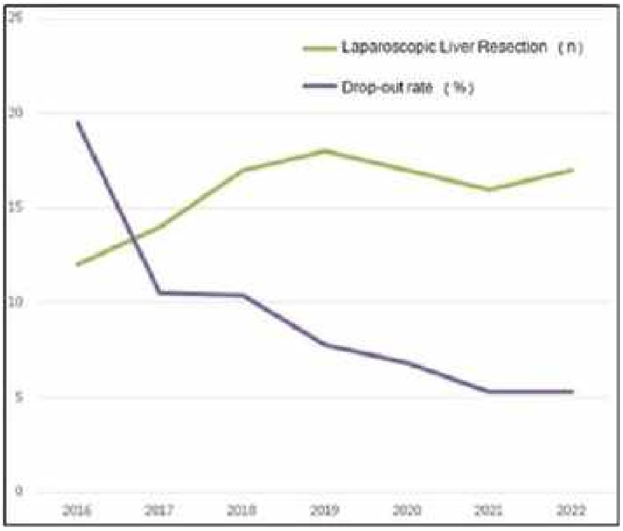


Disclosures: Kali Zhou – Gilead Inc: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
Norah Terrault – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;
The following people have nothing to disclose: Divya Ayyala
Disclosure information not available at the time of publication: Jennifer L. Dodge, Liyun Yuan

1024-A | IMPACT OF LAPAROSCOPIC LIVER RESECTION FOR ACCESS TO THE WAITING LIST OF A SINGLE REGIONAL CENTER FOR LIVER TRANSPLANTATION IN SOUTHERN ITALY: ANALYSIS OF ENTRY AND DROP-OUT FLOWS OF PATIENTS WITH END-STAGE-LIVER-DISEASE.

Duilio Pagano[1], Fabrizio Di Francesco[1], Giuseppe Cabibbo[2], Sergio Li Petri[1], Ciro Celsa[2], Pasquale Bonsignore[1], Sergio Calamia[1], Alessandro Tropea[1], Caterina Accardo[1], Ivan Vella[1], Roberta Vella[1], Alessandro Grova[2], Marco Barbara[1] and Salvatore Gruttadauria[1,3], (1)University of Pittsburgh Medical Center in Italy, (2)Section of Gastroenterology & Hepatology, Department of Health Promotion Sciences Maternal and Infant Care, Internal Medicine and Medical Specialties, Promise, University of Palermo, (3) University of Catania, Catania, Italy

Background: Hepatocellular carcinoma (HCC) is the most common primary liver cancer, and both liver resection (LR) and liver transplantation (LT) are considered potentially curative options. We aimed to explore the impacting role of minimally invasive approach on entry and drop-out flows waiting list of a single regional center for LT in southern Italy with a very low deceased donation rate. **Methods:** We retrospectively analyzed our experience performed during a 7-year period between January 2016 and February 2023 in patients treated for end-stage-liver-disease (ESLD) and/or with surgically unresectable early and intermediate stage HCC. Linear correlation was used to evaluate dependence between the number of laparoscopic LR (LLR) treatments for HCC on the following flows of enrollments on the waiting list during the study period:-Enrollments present at the beginning of the year.-Enrollments that took place during the year, the Intention-To-Treat (ITT, present at the beginning of the year+admissions during the year).-Registrations present at the end of the year, and waiting for transplants for transplanted patients. **Results:** There were 282 HCC patients treated with a first-line approach of LLR ($n = 116$) or open LRs ($n = 166$), with an incremental number of LLR per months. Considering the number of LLR and the rate of drop-out of ITT population and the number of enrolled patients per year, we observed a strong inverse linear correlation (rho = -0.82, $p = 0.023$). (Figure 1) **Conclusion:** Minimally invasive surgical therapies for HCC has a specific impact on drop-out percentage of overall ITT population, and waiting time for transplants for transplanted HCC patients.



Disclosures: Giuseppe Cabibbo – Bayer: Consultant, No, No; EISAI: Consultant, No, No; IPSEN: Consultant, No, No; MSD: Consultant, No, No; ASTRAZENECA: Consultant, No, No; ROCHE: Consultant, No, No;
The following people have nothing to disclose: Duilio Pagano, Fabrizio Di Francesco, Sergio Li Petri, Ciro Celsa, Pasquale Bonsignore, Sergio Calamia,

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

Alessandro Tropea, Caterina Accardo, Ivan Vella, Roberta Vella, Alessandro Grova, Marco Barbara, Salvatore Gruttadauria

1025-A | IMPROVED ACCESS TO DECEASED DONOR LIVER TRANSPLANTATION FOR VETERANS AT VA TRANSPLANT CENTERS IN ASSOCIATION WITH THE MISSION ACT

Shivram Ayyappan Chandramouli[1], Samuel J. Kesseli[2], Andrew Barbas[2], Carl L. Berg[2] and Cynthia Moylan[2], (1) Duke University Health System, (2)Duke University

Background: The MISSION Act, effective June 6th, 2019, was designed to increase veteran access to providers outside the Veterans Affairs (VA) Health System. This was predicted to increase veteran access to geographically close non-VA transplant centers and decrease the VA transplant volume. There is limited data comparing pre- and post-MISISON Act trends in liver transplant (LT). Our aim was to explore pre- and post-MISSION Act LT rates, waitlist deaths, and 1-year graft survival at VA and non-VA centers. **Methods:** We conducted a retrospective cohort study using the Scientific Registry of Transplant Recipients (SRTR) data on LT across two, 2-year time periods before and after MISSION Act. Probabilities of expected LT outcomes are publicly available statistics calculated by the SRTR using Cox proportional hazard models based on national data. Three large volume VA LT centers (Portland, OR; Pittsburgh, PA; and Houston, TX) were considered, with all other LT centers designated as non-VA. We compared VA and non-VA for observed-to-expected (O:E) LT rates, waitlist deaths, and 1-year graft survival. Statistical analysis was conducted using RStudio. **Results:** Pre-MISSION Act, 14,513 deceased donor LTs (DDLTs) were performed between December 31, 2016, and December 30, 2018, with 163 (1.12%) performed at a VA center (Table 1). We found a significant difference between O:E LT rates at VA compared to non-VA centers (73.6% vs. 138%, $p = 0.02$). Post-MISSION Act, 14,327 DDLTs were performed between January 1, 2020, and December 31, 2021, with 89 (0.621%) performed at a VA center. O:E LT rates were no longer significantly different between VA and non-VA centers (57.0% vs. 117%, $p > 0.05$). We did not identify significant differences between VA and non-VA O:E waitlist death rates pre- (93.8% vs. 95.0%, $p > 0.05$) or post-MISSION Act (101% vs. 89.7%, $p > 0.05$) or in O:E 1-year graft survival pre- (93.9% vs. 160%, $p > 0.05$) or post-MISSION Act (90.2% vs. 86.5%, $p > 0.05$). **Conclusion:** The MISSION Act was intended to increase veteran access to non-VAHS. Our analysis of SRTR data reveals that DDLT observed-to-expected rates at VA centers improved post-MISSION Act without significant changes in waitlist deaths or 1 year graft survival. These findings suggest VA LT centers responded to the MISSION Act by increasing their ability to serve veterans with LT needs. Further analysis is needed to understand the impact of COVID19 on these results and longer-term outcomes.

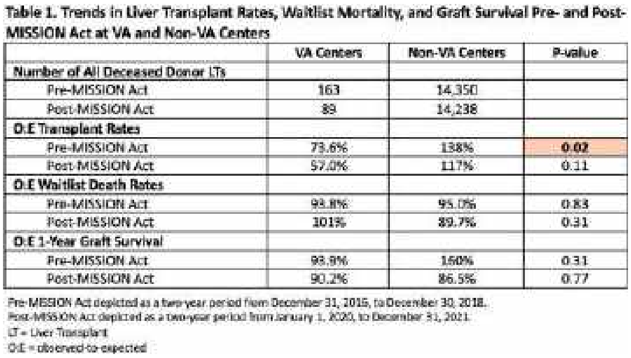


Table 1. Trends in Liver Transplant Rates, Waitlist Mortality, and Graft Survival Pre- and Post-MISSION Act at VA and Non-VA Centers

	VA Centers	Non-VA Centers	P-value
Number of All Deceased Donor LTs			
Pre-MISSION Act	163	14,350	
Post-MISSION Act	89	14,238	
O:E Transplant Rates			
Pre-MISSION Act	73.6%	138%	0.02
Post-MISSION Act	57.0%	117%	0.11
O:E Waitlist Death Rates			
Pre-MISSION Act	93.8%	95.0%	0.83
Post-MISSION Act	101%	89.7%	0.31
O:E 1-Year Graft Survival			
Pre-MISSION Act	93.9%	160%	0.31
Post-MISSION Act	90.2%	86.5%	0.77

Pre-MISSION Act depicted as a two-year period from December 31, 2015, to December 30, 2018.
Post-MISSION Act depicted as a two-year period from January 1, 2020, to December 31, 2021.
LT = Liver Transplant
O:E = observed-to-expected

Disclosures: Cynthia Moylan – Boehringer Ingelheim: Advisor, No, Yes; GSK: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;

The following people have nothing to disclose: Shivram Ayyappan Chandramouli

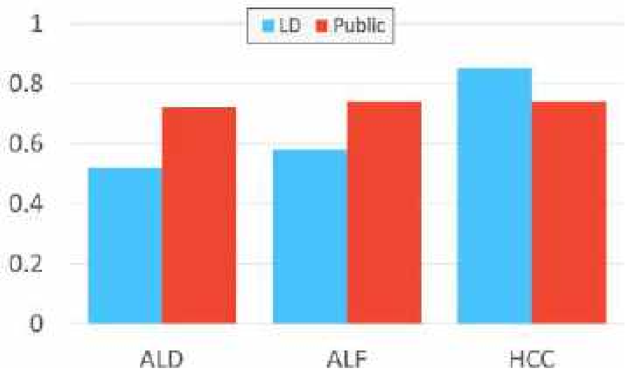
Disclosure information not available at the time of publication: Samuel J. Kesseli, Andrew Barbas, Carl L. Berg

1026-A | IMPROVING INFORMED CONSENT FOR LIVING LIVER DONORS: WHAT INFORMATION DO DONORS WANT ABOUT THEIR RECIPIENT?

Adrienne Chen[1], Allison Carroll[1], Elisa J. Gordon[2] and Josh Levitsky[1], (1)Northwestern University Feinberg School of Medicine, (2)Vanderbilt University Medical Center

Background: Living donor liver transplant (LDLT) has steadily increased over the past decade and now comprises 5-6% of all liver transplants. While information about the general donation process is disclosed during the informed consent process in LDLT evaluation, it is not known if more detailed information about recipients' short- and long-term outcomes, particularly in high-risk scenarios, would enhance living liver donors' (LDs) informed decision-making and willingness to donate. Our study aimed to assess information that prior LDs found pertinent to their donation process, and compare information needs between LDs and the general public. **Methods:** We conducted two independent online surveys of: 1) prior LDs from Northwestern Memorial Hospital, and 2) a random sample of the public via Amazon Mechanical Turk. The survey assessed three common high-risk recipient scenarios: 1) alcoholic liver disease with high relapse risk (ALD), 2) acute time frame due to acute liver failure (ALF), and 3) hepatocellular carcinoma with high recurrence risk (HCC). Likert-scale responses were dichotomized for analysis. Data were analyzed using R and Orange with chi-squared analysis or Kruskal-Wallis H test. **Results:** There were 385 total participants (LD: 96, public: 289). Most LD and public participants were White, had a college education, health literate, and in excellent or very good overall health. The LD and public groups differed significantly in average age (LD 49, public 35), female gender (LD 64%, public 35%), Hispanic/Latinx identity (LD 5%, public 50%), and income > \$75,000 (LD 73%, public 29%). Most participants were willing to donate, with the highest rate in HCC, then ALF, then ALD ($p = 0.045$) (Figure 1). The public was more likely to donate in ALD ($p < 0.001$) and ALF ($p = 0.006$), but LDs were more likely to donate in HCC ($p = 0.026$). Most LDs (81%) and public (80%) would find a consultation service (e.g., talking with a prior donor) helpful in the setting of ALF. Most participants desired more information in all scenarios, including the recipient's diagnosis, cause of liver failure, and prognosis of their condition with DDLT versus LDLT versus no transplant. **Conclusion:** Our findings suggest that LDs and the public desire information about their recipient's diagnosis, clinical condition, and projected outcomes to guide decision-making about donation. Implementation of a consultation service and rapid education in acute timelines might assist in LD decision-making with ALF. Transplant programs should assess potential LDLT recipients' willingness to share information about their diagnosis, condition, and outcomes with potential LDs to foster LD informed consent.

Figure 1. Willingness to Donate



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The following people have nothing to disclose: Adrienne Chen, Allison Carroll

Disclosure information not available at the time of publication: Elisa J. Gordon

1027-A | INDICATION MODEL FOR LAPAROSCOPIC REPEAT LIVER RESECTION IN THE ERA OF ARTIFICIAL INTELLIGENCE: MACHINE LEARNING PREDICTION OF SURGICAL INDICATION

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Background: Laparoscopic repeat liver resection (LRLR) is still a challenging technique and requires a careful selection of indications, as the adhesion range is wide and the anatomy is different from previous surgeries. However, the current difficulty scoring system is not suitable for selecting indications. The purpose of this study is to develop the indication model for LRLR using machine learning and to identify factors associated with open conversion (OC). **Methods:** Patients who underwent repeat hepatectomy at Samsung Medical Center from January 2017 to December 2021 were investigated. Machine learning methods (random forest, support vector machine [SVM], extreme gradient boosting [XGB]) and logistic regression were used to develop indication model. The performance between the models was evaluated and risk factors associated with OC were also analyzed. **Results:** The cohorts of 110 patients with LRLR and 111 patients with open repeated liver resection (ORLR) were reviewed and analyzed. The previous open approach rate was higher in the ORLR group (75.7% vs 38.2%, $p < 0.001$). In the risk factor analysis of OC, twice previous abdominal operation (OR 6.56, $p = 0.009$) was the only factor associated with OC in multivariate analysis. The performance of the indication model showed similar predictive power in both random forest ($p = 0.720$) and logistic regression ($p = 0.733$). The difference in performance between the two models was not statistically significant ($p = 0.710$). Previous laparoscopic approach, present subsegmentectomy, and left side location of the present tumor were selected as important variables in both models. **Conclusion:** The performance of the indication model for LRLR showed good predictive power in both machine learning and logistic regression. The important variables for LRLR were previous laparoscopic approach, present subsegmentectomy, and left side location of the present tumor.

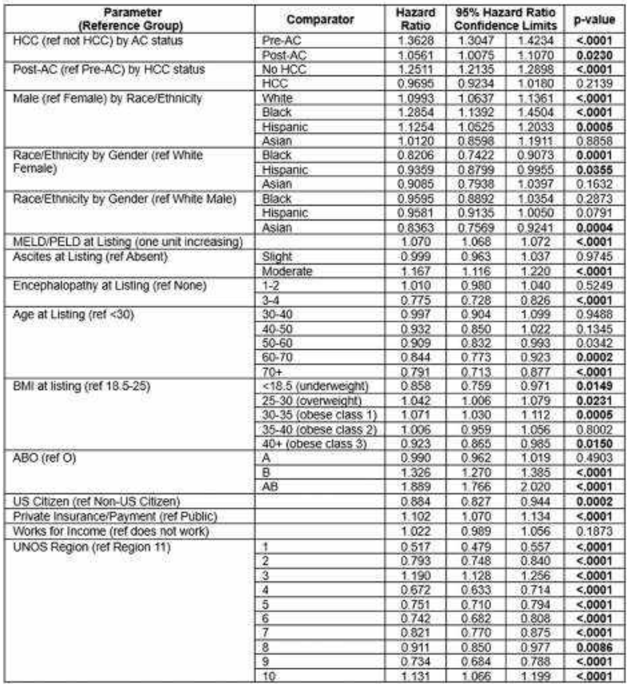
Disclosures: The following people have nothing to disclose: Eunjin Lee, Sung Jun Jo, Jong Man Kim, Jae-Won Joh, Jinsoo Rhu, Gyu-Seong Choi

f 1028-A | INTERACTIONS BETWEEN RACE/ETHNICITY AND GENDER IN LIVER TRANSPLANTS: DO ACUITY CIRCLES MATTER?

Ahila Manivannan[1], AnnMarie Liapakis[2], Anna Mae Diehl[3], Elizabeth Verna[4], Vineeta Kumar[5], Reena J. Salgia[1], Trueman Wu[1], Mei Lu[6], Neehar Dilip Parikh[7] and Michelle Jesse[1], (1)Henry Ford Health, (2)Yale University, New Haven, CT, (3)University of Chicago, (4) Columbia University Irving Medical Center, New York, NY, (5)The University of Alabama at Birmingham, (6) 156 Pocatello Rd, (7)University of Michigan

Background: Despite continued efforts, there are well-documented disparities in liver transplantation (LT) from listing through post-transplant. National policies on allocation of deceased donor liver transplants (DDLT) aim to provide consistent and equitable access. However, the impacts of Acuity Circles (AC) and interactions between race and gender on delisting due to deterioration/death or receipt of DDLT have been minimally explored. **Methods:** Using data from the United Network for Organ Sharing (UNOS), we studied listed adults for DDLT from April 3, 2017, to October 4, 2022, a 60-month period (30 mo pre- and post-AC). Fine-Gray subdistribution hazard model was used to study AC impact on LT while delisting due to deterioration/death was used as a competing risk. The model focused on AC indicator by race by gender interactions, as well as AC by hepatocellular carcinoma (HCC) diagnosis interactions. **Results:** 59,592 patients (30,202 pre-AC, 29,390 post-AC) were studied. No 3-way (AC X race X gender) interaction was detected, indicating effect of race and gender on LT was consistent pre- and post-AC periods. However, there were significant gender by race or AC by HCC interactions (Table 1): patients with HCC had greater chance for LT than non-HCC, though post-AC this effect was reduced. AC increased LT 25% in patients without HCC. Across gender, White, Black, and Hispanic men were more likely to receive transplant compared to their female counterparts. Within gender, Black and Hispanic women were less likely to receive transplant than White women, with no significant differences between White and Asian women. For men, there were no statistical difference in likelihood for transplant between White versus Black or Hispanic men, but Asian men had a lower likelihood for LT than White men. Additional significant predictors outlined in Table 1. **Conclusion:** Accounting for listing characteristics, AC did not significantly impact interactions between gender and race on receipt of LT. However, AC may have improved access to LT amongst those without HCC but may have diminished access amongst those with HCC post-AC. Regardless of AC, there were important gender-race interactions requiring closer examination, particularly where Black and Hispanic women appear disproportionately negatively impacted. The same patterns were not noted across male racial categories, suggesting future research and interventions should target those at greatest risk.

Table 1. Fine-Gray Sub-distribution Hazard Model on Transplantation



Parameter (Reference Group)	Comparator	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
HCC (ref not HCC) by AC status	Pre-AC	1.3628	1.3047	1.4234	**<.0001**
	Post-AC	1.0561	1.0075	1.1070	**0.0230**
Post-AC (ref Pre-AC) by HCC status	No HCC	1.2511	1.2135	1.2898	**<.0001**
	HCC	0.9695	0.9234	1.0180	0.2139
Male (ref Female) by Race/Ethnicity	White	1.0993	1.0637	1.1361	**<.0001**
	Black	1.2854	1.1392	1.4504	**<.0001**
	Hispanic	1.1254	1.0525	1.2033	**0.0005**
	Asian	1.0120	0.8598	1.1911	0.8858
Race/Ethnicity by Gender (ref White Female)	Black	0.8206	0.7422	0.9073	**0.0001**
	Hispanic	0.9359	0.8799	0.9955	**0.0355**
	Asian	0.9085	0.7938	1.0397	0.1632
Race/Ethnicity by Gender (ref White Male)	Black	0.9595	0.8892	1.0354	0.2873
	Hispanic	0.9581	0.9135	1.0050	0.0791
	Asian	0.8363	0.7569	0.9241	**0.0004**
MELD/PELD at Listing (one unit increasing)		1.070	1.068	1.072	**<.0001**
Ascites at Listing (ref Absent)	Slight	0.999	0.963	1.037	0.9745
	Moderate	1.167	1.116	1.220	**<.0001**
Encephalopathy at Listing (ref None)	1-2	1.010	0.980	1.040	0.5249
	3-4	0.775	0.728	0.826	**<.0001**
Age at Listing (ref <30)	30-40	0.997	0.904	1.099	0.9488
	40-50	0.932	0.850	1.022	0.1345
	50-60	0.909	0.832	0.993	0.0342
	60-70	0.844	0.773	0.923	**0.0002**
	70+	0.791	0.713	0.877	**<.0001**
BMI at listing (ref 18.5-25)	<18.5 (underweight)	0.858	0.759	0.971	**0.0149**
	25-30 (overweight)	1.042	1.006	1.079	**0.0231**
	30-35 (obese class 1)	1.071	1.030	1.112	**0.0005**
	35-40 (obese class 2)	1.006	0.959	1.056	0.8002
	40+ (obese class 3)	0.923	0.865	0.985	**0.0150**
ABO (ref O)	A	0.990	0.962	1.019	0.4903
	B	1.326	1.270	1.385	**<.0001**
	AB	1.889	1.766	2.020	**<.0001**
US Citizen (ref Non-US Citizen)		0.884	0.827	0.944	**0.0002**
Private Insurance/Payment (ref Public)		1.102	1.070	1.134	**<.0001**
Works for Income (ref does not work)		1.022	0.989	1.056	0.1873
UNOS Region (ref Region 11)	1	0.517	0.479	0.557	**<.0001**
	2	0.793	0.748	0.840	**<.0001**
	3	1.190	1.128	1.256	**<.0001**
	4	0.672	0.633	0.714	**<.0001**
	5	0.751	0.710	0.794	**<.0001**
	6	0.742	0.682	0.808	**<.0001**
	7	0.821	0.770	0.875	**<.0001**
	8	0.911	0.850	0.977	**0.0086**
	9	0.734	0.684	0.788	**<.0001**
	10	1.131	1.066	1.199	**<.0001**

Disclosures: Anna Mae Diehl – Exelixis: Advisor, No, No; AstraZeneca: Advisor, No, No; Genentech: Advisor, No, No; Replimune: Advisor, No, No; Eisai Inc: Advisor, No, No;

Neehar Dilip Parikh – Freenome: Consultant, No, Yes; Gilead: Advisor, No, Yes; Exelixis: Consultant, No, No; Astra Zeneca: Consultant, No, No; Fujifilm Medical: Consultant, Yes, Yes;

The following people have nothing to disclose: Ahila Manivannan, Vineeta Kumar, Reena J. Salgia, Mei Lu, Michelle Jesse

Disclosure information not available at the time of publication: AnnMarie Liapakis, Elizabeth Verna, Trueman Wu

1029-A | INTERNATIONAL TRAVEL FOR ORGAN TRANSPLANTATION – PROVIDER AND PATIENT PERSPECTIVES

Ann B. Nguyen[1], Hannah Roth[1], Bow Chung[1], Daniel Rodgers[1], Kevin J. Clerkin[2], Gabriel Sayer[2], Gene

Kim[1], Valluvan Jeevanandam[1], Mark Siegler[1], Nir Uriel[2] and Andrew I. Aronsohn[1], (1)University of Chicago Medical Center, (2)Columbia University Irving Medical Center, New York, NY

Background: Organ allocation in the United States (U.S.) to non-citizen, non-U.S. residents who travel for transplant (NC/NRTx) is controversial. Current policies may not be informed by the opinions of stakeholders, as there is limited data assessing knowledge or opinions of providers, patients or the general public on this issue. **Methods:** We conducted a cross-sectional, hospital-based pilot survey among providers and patients from December 2019 to June 2020 at a single large urban transplant institute. Surveys included 10 questions assessing knowledge and opinion on eligibility, prioritization, and limitations for deceased donor transplantation of different groups and 12 questions on demographic data. **Results:** 209 providers responded (61% female, median age 40) and 119 patients responded (62% female, median age 54). Awareness of eligibility for transplantation for U.S. citizens, non-U.S. citizens who reside in the U.S (NC/R) both legally and non-legally, as well as NC/NRTx was high in both groups, though both providers and patients were less aware of the eligibility of non-legal NC/R to both donate and receive organs. Overall, 79.3% of patients believed that NC/NRTx should be eligible for transplant in the U.S. compared to only 60.7% of providers ($p = 0.001$). Specifically, more providers (11.7%) than patients (4.2%) responded “Definitely not” ($p = 0.002$) and more providers (28.9%) than patients (13.6%) responded “Probably not” ($p = 0.002$). In sum, nearly 40% of providers indicated that NC/NRTx probably should not or definitely should not be allowed, as opposed to less than 18% of patients. Sub-analysis revealed that younger (< 40) and male providers were more likely to be in support of transplanting NC/NRTx. **Conclusion:** The results of our preliminary study reveal that opinions regarding transplanting NC/NRTx exist on a spectrum and differ when comparing patients with providers. As variation in the practice of transplanting NC/NRTx exists both regionally and across transplant centers, it is critical that both national and regional stakeholder voices are considered to guide future policies regarding NC/NRTx in the U.S.

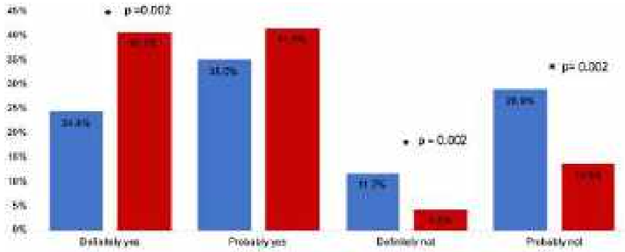


Figure 1: Opinions on Travel for Transplantation; "Do you think citizens of other countries should be allowed to travel to the U.S. in order to get organ transplants in the U.S.?"

Disclosures: The following people have nothing to disclose: Hannah Roth, Andrew I. Aronsohn

Disclosure information not available at the time of publication: Ann B. Nguyen, Bow Chung, Daniel Rodgers, Kevin J. Clerkin, Gabriel Sayer, Gene Kim, Valluvan Jeevanandam, Mark Siegler, Nir Uriel

1030-A | INTRA-OPERATIVE OUTCOMES IN DONATION AFTER CIRCULATORY DEATH LIVER TRANSPLANTATION USING NORMOTHERMIC MACHINE PERFUSION, OR NORMOTHERMIC REGIONAL PERFUSION VERSUS SUPER RAPID RECOVERY WITH STATIC COLD STORAGE

Rachel Quandahl, Shaheed Merani, Cale Kassel, Sheila Ellis, Alan N. Langnas, Benjamin Huerter and Luciano Vargas, University of Nebraska Medical Center

Background: Donation after circulatory death (DCD) is an increasingly prevalent practice in liver transplantation to address the persistent organ shortage. However, DCD liver transplantations procured with a super rapid recovery technique with static cold storage (SRR+CS) is associated with an increase in adverse outcomes including higher rates of early allograft dysfunction (EAD) and biliary complications when compared to transplants using donation after brain death. Regional perfusion (NRP) and normothermic machine perfusion (NMP) aim to reduce these complications. Outcomes related to long term graft function, patient survival, and allograft dysfunction when NRP and NMP are used in clinical transplant have been published recently. However, intra-operative hemodynamic outcomes and post-reperfusion syndrome between NMP and NRP are not well described nor compared directly. **Methods:** We performed a single-center retrospective clinical study of 50 DCD liver transplants in adult recipients using three techniques for DCD organ recovery and preservation (SRR+CS, NRP+CS, and SRR+NMP). Donor, recipient, and transplant characteristics were recorded and evaluated. Primary outcome measure was rate of post-reperfusion syndrome (as defined by Hilmi et. al.). Categorical variables were compared between groups using chi-square, and continuous variables compared using a non-parametric ANOVA. Additionally, donor and recipient variables were used to construct a binary logistic regression model for PRS. **Results:** Intra-operative outcomes demonstrated lower epinephrine dose needed on reperfusion in the SRR+NMP group (0 mcg) compared to SRR + CS (40 mcg) and NRP+CS (20 mcg), $p = 0.010$. There was a lower rate of post-reperfusion syndrome in both the NMP and NRP groups compared to the SRR + CS (33.3% in SRR+NMP,

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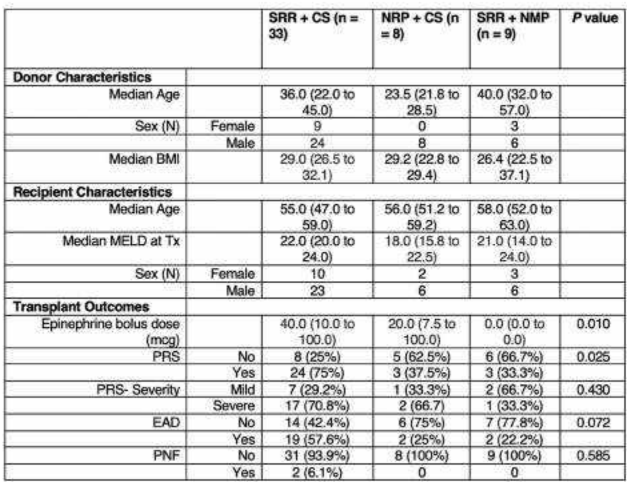
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

37.5% in NRP+CS and 75% in SRR+CS, $p = 0.025$). 70.8% of the SRR+CS group and 66.7% of the NRP+CS group were noted to have severe PRS, versus 33.3% of the SR+NMP group ($p = 0.430$). Post-transplant liver enzymes were significantly higher in the SRR+CS arm compared to NMP and NRP. Incidence of EAD and primary non-function (PNF) was not significantly different between groups. There was no difference in graft nor patient survival between groups. **Conclusion:** Machine perfusion in LT continues to demonstrate good outcomes in DCD liver grafts. Despite a growing number of publications supporting their use to lower EAD, improve biliary outcomes, and overall graft and patient survival, little has been shown on intra-operative outcomes. This study demonstrates for the first time NMP and to a certain extent, NRP, mitigates early reperfusion injury as measured by post-reperfusion syndrome when compared to SRR+CS. The lower incidence of PRS suggests a smoother hemodynamic profile and potentially improved outcomes for patients. In addition to increasing the available grafts for transplantation, NMP may also allow for higher risk patients to undergo LT.

Table 1. Donor & Recipient Characteristics, and Transplant Outcomes



		SRR + CS (n = 33)	NRP + CS (n = 8)	SRR + NMP (n = 9)	*P* value
Donor Characteristics					
Median Age		36.0 (22.0 to 45.0)	23.5 (21.8 to 28.5)	40.0 (32.0 to 57.0)	
Sex (N)	Female	9	0	3	
	Male	24	8	6	
Median BMI		29.0 (26.5 to 32.1)	29.2 (22.8 to 29.4)	26.4 (22.5 to 37.1)	
Recipient Characteristics					
Median Age		55.0 (47.0 to 59.0)	56.0 (51.2 to 59.2)	58.0 (52.0 to 63.0)	
Median MELD at Tx		22.0 (20.0 to 24.0)	18.0 (15.8 to 22.5)	21.0 (14.0 to 24.0)	
Sex (N)	Female	10	2	3	
	Male	23	6	6	
Transplant Outcomes					
Epinephrine bolus dose (mcg)		40.0 (10.0 to 100.0)	20.0 (7.5 to 100.0)	0.0 (0.0 to 0.0)	0.010
PRS	No	8 (25%)	5 (62.5%)	6 (66.7%)	0.025
	Yes	24 (75%)	3 (37.5%)	3 (33.3%)	
PRS- Severity	Mild	7 (29.2%)	1 (33.3%)	2 (66.7%)	0.430
	Severe	17 (70.8%)	2 (66.7)	1 (33.3%)	
EAD	No	14 (42.4%)	6 (75%)	7 (77.8%)	0.072
	Yes	19 (57.6%)	2 (25%)	2 (22.2%)	
PNF	No	31 (93.9%)	8 (100%)	9 (100%)	0.585
	Yes	2 (6.1%)	0	0	

Disclosures: The following people have nothing to disclose: Rachel Quandahl, Shaheed Merani
Disclosure information not available at the time of publication: Cale Kassel, Sheila Ellis, Alan N. Langnas, Benjamin Huerter, Luciano Vargas

1031-A | ISCHEMIC PRECONDITIONING AS A PROTECTIVE STRATEGY IN LIVER RESECTION: A COMPREHENSIVE SYSTEMATIC REVIEW AND META-ANALYSIS

Muhammed Elhadi Elfaituri, Ala Khaled, Hazem Faraj and Ahmed Msherghi, University of Tripoli

Background: Liver resection is an indispensable surgical treatment for various liver diseases. However, it frequently leads to ischemia-reperfusion injury (IRI), a principal cause of postoperative liver dysfunction and failure. Ischemic preconditioning (IPC), marked by short episodes of ischemia and reperfusion prior to an extended ischemic period, has demonstrated potential in mitigating IRI and improving postoperative outcomes subsequent to liver resection. This study aimed to determine the impacts of ischemic preconditioning on clinical outcomes in patients undergoing liver resection. **Methods:** We searched databases, including PubMed, Embase, and the Cochrane Library, for studies that compared IPC with standard care in liver resection up until April 2023. Primary outcomes encompassed operative time, blood loss, length of stay in ICU, and length of hospital stay, reported as Mean Difference (MD). Secondary outcomes included the number of patients requiring blood transfusion, postoperative ascites, postoperative mortality, postoperative liver failure, biliary complications, surgical site infection, and postoperative pulmonary complications, reported as Relative Risk (RR). Statistical analyses were performed using R (version 4.0.3) with the aid of metafor and meta packages. **Results:** Our meta-analysis incorporated 11 studies, accounting for 736 patients (365 in the IPC group and 371 in the control group). IPC was linked to a non-significant reduction in operative time (MD = -6.54 minutes, 95% CI = -18.43 to 5.37, $p = 0.28$, I2 = 64%), blood loss (MD = -51.2 ml, 95% CI = -107.63 to 5.23, $p = 0.08$, I2 = 71%), length of stay in ICU (MD = -0.24 d, 95% CI = -2.04 to 1.55, $p = 0.79$, I2 = 97%), and length of hospital stay (MD = -1.25 d, 95% CI = -3.03 to 0.58, $p = 0.17$, I2 = 90%). Additionally, IPC significantly decreased the risk of requiring a blood transfusion (RR = 0.70, 95% CI = 0.50 to 0.98, $p = 0.04$, I2 = 0%), yet did not significantly change the risk of developing postoperative ascites (RR = 0.59, 95% CI = 0.22 to 1.57, $p = 0.29$, I2 = 0%), postoperative mortality (RR = 1.14, 95% CI = 0.27 to 4.72, $p = 0.86$, I2 = 0%), postoperative liver failure (RR = 0.65, 95% CI = 0.34 to 1.26, $p = 0.2$, I2 = 0%), biliary complications (RR = 0.91, 95% CI = 0.49 to 1.67, $p = 0.76$, I2 = 0%), surgical site infection (RR = 0.62, 95% CI = 0.22 to 1.78, $p = 0.38$, I2 = 0%), and postoperative pulmonary complications (RR = 0.69, 95% CI = 0.29 to 1.63, $p = 0.4$, I2 = 0%). **Conclusion:** This study implies that ischemic preconditioning may reduce the need for blood transfusions in liver resection. Despite this, the significant heterogeneity in some outcomes and non-significant reductions in certain complications require cautious interpretation. Future research should prioritize large-scale, randomized trials to validate these results and further explore IPC's potential benefits and mechanisms.

Disclosures: The following people have nothing to disclose: Muhammed Elhadi Elfaituri, Ala Khaled, Hazem Faraj, Ahmed Msherghi

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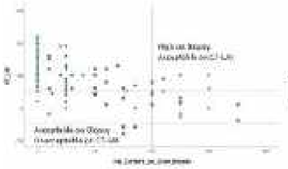
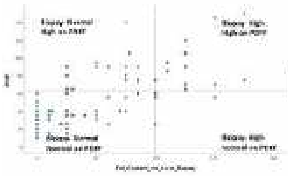
1032-A | MRI LIVER OBVIATES NEED FOR LIVER BIOPSY FOR DONORS IN A LIVING DONOR LIVER TRANSPLANT SETTING

Alisha Chaubal[1]*, Rashmi Badhe*[1]*, Ameet Mandot*[1]*, Gaurav Chaubal*[1]*, Gautham Pranesh*[2]*, Samir Ramnik Shah*[1] *and Global hospital, (1)Global Hospitals, Mumbai, (2)Mitopower LLC*

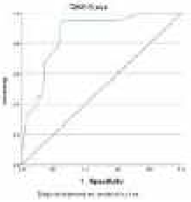
Background: Liver biopsy is the gold standard for determining acceptability of donors when CTLAI is between -5 to +5. However it is invasive and involves sampling of only a small portion of the liver. CT does not reliably detect fibrosis, iron overload and could lead to erroneous selection of donors. We propose that MRI- PDFF with elastography could overcome these deficiencies. We also wanted to determine a cut off value for fat on MRI which would correspond to 10% fat on biopsy. **Methods:** 102 prospective liver donors underwent CTLAI, MRI liver (PDFF, elastography, R2 sequencing) and liver biopsy. The strength of association between CTLAI, MRI-PDFF, fat content on biopsy was determined by non-parametric correlation. Cut offs, sensitivity and specificity for MRI-PDFF to determine steatosis and liver fat content of 10% or greater on biopsies was determined by Receiver Operator Characteristic (RoC) curves. The impacts of cut offs across tests were also determined. **Results:** Both CTLAI and MRI correlated with liver biopsy for fat but MRI had a stronger correlation. (Correlation coefficient 0.695 - MRI, -0.621 -CTLAI). Every unit increase in biopsy fat content is associated with 0.5 units increase in fat fraction on MRI. MRI with accepted cut-off of 6.25% was more sensitive than CTLAI cut off of +5 to determine liver fat > 10%(AUROC 0.859 - MRI, 0.814 - CTLAI) **Conclusion:** MRI liver is a reliable and non invasive method for donor liver assessment which supersedes CTLAI and can obviate the need for a liver biopsy. A cut off value of 6.25 % correlates with 10% macrosteatosis on a liver biopsy.



CTLAI AND FAT CONTENT ON LIVER BIOPSY



MRI - PDFF AND FAT CONTENT ON LIVER BIOPSY



AUROC FOR MRI-PDFF AT CUT OFF 6.25

Disclosures: The following people have nothing to disclose: Alisha Chaubal, Rashmi Badhe, Ameet Mandot, Gaurav Chaubal, Gautham Pranesh, Samir Ramnik Shah

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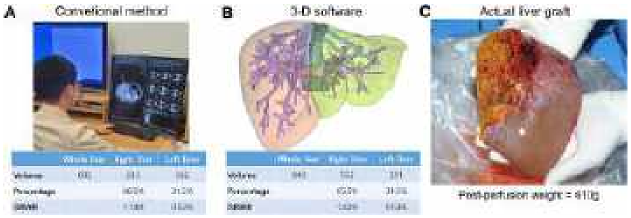
1033-A | MULTIVARIABLE LINEAR MODEL FOR PREDICTING GRAFT WEIGHT BASED ON 3-DIMENSIONAL VOLUMETRY IN REGARDS OF BODY WEIGHT CHANGE OF LIVING LIVER DONOR

Youngju Ryu[1]*, So Young Lim*[1]*, Gyu-Seong Choi*[2]*, Jong Man Kim*[2]*, Jae-Won Joh*[2] *and Jinsoo Rhu*[2]*, (1) Samsung Medical Center, (2)Samsung Medical Center, Sungkyunkwan University School of Medicine*

Background: The purpose of this study is to build a prediction model for estimating the graft weight in regards of different graft volumetry methods combined with other variables. **Methods:** Donors who underwent living donor right hepatectomy during March 2021 to March 2023 were included. Estimated graft volume measured by conventional method and 3-D software were collected as well as the actual graft weight.

Univariable linear regressions were performed for estimating the predictability. Multivariable linear regression was performed to build a prediction model with higher accuracy. Donor groups were further divided into three groups according to the 3-D volumetry of < 700 cm^3, 700 to 899cm^3, and e 900cm^3 to compare the performance of different models. **Results:** A total of 119 donors were included to the study. Conventional volumetry for predicting graft weight showed R^2 of 0.656 ($p < 0.001$) while 3-D software showed R^2 of 0.776 ($p < 0.001$). The R^2 of the multivariable model was 0.842 ($p < 0.001$) including for 3-D volume (ß = 0.623, $p < 0.001$), body mass index (ß = 7.648, $p < 0.001$) and amount of weight loss (ß = -7.252, $p < 0.001$). The median errors between different models to actual graft weight did not differ in donor groups < 700cm^3 and 700 to 899cm^3, while the median error of univariable linear model using 3-D software (122.5, IQR 61.5-179.8) was significantly higher compared to that of multivariable adjusted linear model (41.5, IQR 24.8-69.8, $p = 0.003$) in donors with estimated graft weight e 900cm^3. **Conclusion:** Univariable linear model with 3-D volumetry can be used with acceptable outcome for predicting right liver graft weight in donors with estimated graft volume less than 900cm^3. For donors with estimated graft volume e 900cm^3, multivariable adjusted linear model showed higher accuracy.

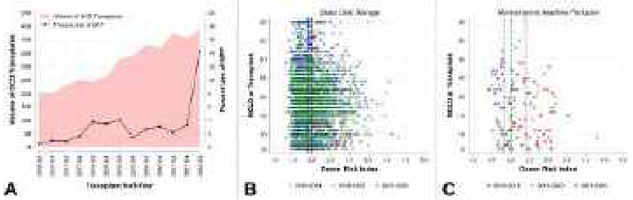


Disclosures: The following people have nothing to disclose: Youngju Ryu, So Young Lim, Gyu-Seong Choi, Jong Man Kim, Jae-Won Joh, Jinsoo Rhu

f 1034-A | NATIONAL TRENDS IN UTILIZATION OF NORMOTHERMIC MACHINE PERFUSION IN DCD LIVER TRANSPLANTATION

Helen Tang, Samir Abu-Gazala, Nadim Mahmud and Peter Abt, Hospital of the University of Pennsylvania

Background: Organ scarcity remains a key issue in liver transplantation. Among efforts to expand the donor pool, advances in ex-situ normothermic machine perfusion (NMP) have improved outcomes compared traditional static cold storage (SCS) in donation after circulatory death (DCD) organs. We aimed to characterize trends in utilization of NMP vs. SCS in DCD liver transplantation in the U.S., and to determine if use of NMP has expanded to higher-risk donor-recipient pairs over time. **Methods:** This retrospective cohort study used data from the United Network for Organ Sharing database to identify recipient-donor adult liver transplant pairs from DCD donors from 1/2016-6/2022. Use of NMP vs. SCS was ascertained following prior methods. Key donor and recipient variables were also collected. Trends in utilization of NMP for DCD transplantation were plotted. Changes in donor risk index (DRI) and components between NMP vs. SCS were assessed across transplant year eras (2016-2018, 2019-2020, 2021-2022). To visualize changes in donor-recipient "risk" over time we plotted DRI against transplant MELD in each transplant era. Statistical comparisons were made using Kruskal-Wallis or Chi-square tests, where indicated. **Results:** 3,937 SCS and 127 NMP DCD donor transplants were included in the analytic cohort. Percent utilization of NMP ranged from ~0.4% to 3.5% from 2016 to 2021, and rose significantly to 11.2% in the first half of 2022 (break of secular trend $p < 0.001$; Figure 1A). Across transplant eras, median DRI increased significantly for both SCS and NMP ($p < 0.001$; Figure 1B/C); the magnitude of increase from 2016-2018 to 2021-2022 was larger for NMP (e.g., 1.8 to 2.4 for NMP vs. 1.9 to 2.0 for SCS). With NMP DCDs, there were significant increases in donor age (median 46 vs. 27, $p = 0.004$), national share proportion (31.4% vs. 0.0%, $p < 0.001$), and "cold ischemic time" (median 9.9 hours vs. 7.2 hours, $p < 0.001$) over time. Finally, there was a shift towards including higher DRI donors and higher transplant MELD recipients with NMP in later transplant eras (Figure 1B/C). **Conclusion:** In recent years, NMP utilization has increased and expanded to donors with higher DRI and recipients with higher MELD at transplant. This suggests increasing familiarity and risk tolerance with NMP technology. As NMP remains a relatively new technique, ongoing study of patient outcomes, organ allocation practices, and utilization patterns is critical.



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The following people have nothing to disclose: Helen Tang, Samir Abu-Gazala, Peter Abt

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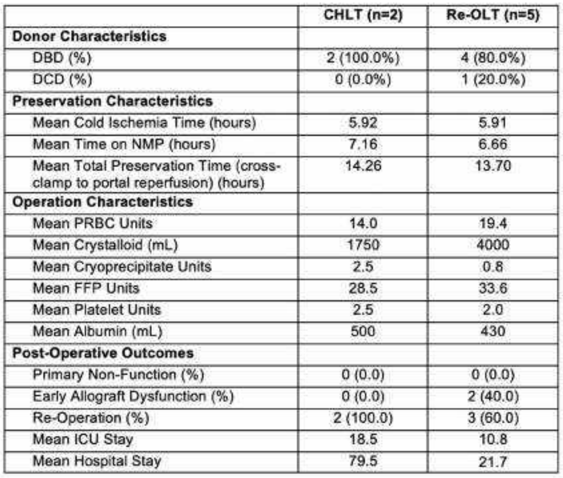
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

1035-A | NOVEL INDICATIONS FOR NORMOTHERMIC MACHINE PERFUSION: A CASE SERIES

Rachel Todd[1], Andrew Rosowicz[1], Adam Kressel[2], Guy Meyerovich[2], Matthew Holzner[2], Parissa Tabrizian[2], Chiara Rocha[2], Antonios Arvelakis[2], Joseph DiNorcia[2], Marcelo Facciuto[2], Thomas Schiano[2], M. Zeeshan Akhtar[2] and Sander S. Florman[2], (1)Icahn School of Medicine at Mount Sinai, (2)Recanati/Miller Transplantation Institute at Mount Sinai

Background: Normothermic machine perfusion (NMP) is a tool for optimizing and assessing livers for orthotopic liver transplantation (OLT), with an additional benefit of facilitating management in cases with complex recipients. Here we describe two novel indications: combined heart-liver transplantation (CHLT) and re-transplant recipients. Our aim was to use NMP to expand our ability to serve complex surgical patients whilst protecting livers by minimizing cold ischemic time. Given the rise of CHLT for congenital heart disease sequelae and increased rates of re-transplantation, safe methods for extending storage times are needed. **Methods:** This single center retrospective review from August 2022 to May 2023 of all NMP cases included indications for NMP, viability data during NMP, and donor and recipient demographic information. Post-transplantation outcomes of primary non-function, early allograft dysfunction, reoperation rate, and biliary complications were analyzed. **Results:** Two CHLT, including one post-Fontan patient, and five re-transplant candidates were allocated livers placed on the OrganOx *metra*® system for NMP out of concern for recipient case complexity. The re-transplant cohort included one pediatric recipient and one simultaneous liver kidney (SLK recipient). One of the CHLT grafts also showed moderate microvesicular steatosis on biopsy, warranting viability assessment. NMP and surgical outcomes of remaining three cases in the cohort are described in Table 1. Of note, cold ischemia time (CIT) in CHLT may have been decreased by four to six hours compared to prior studies (5). Rates of primary non-function or early allograft dysfunction were 0%. Mean peak AST was 1003. Both CHLTs required re-operation by the cardiac team for hematoma evacuation. The pediatric patient underwent reoperation for planned delayed completion of the biliary anastomosis, hematoma evacuation, and subsequent duodenal and colonic repair. Two other re-transplant patients required reoperation for hematoma evacuation. No patients have experienced biliary complications to date. **Conclusion:** To our knowledge, these are the first reported cases of NMP utilized for CHLT and re-transplant recipients. This case series of normothermic machine perfusion (NMP) demonstrates its utility as a method of increasing total storage time while minimizing graft exposure to cold ischemia.



	CHLT (n=2)	Re-OLT (n=5)
Donor Characteristics		
DBD (%)	2 (100.0%)	4 (80.0%)
DCD (%)	0 (0.0%)	1 (20.0%)
Preservation Characteristics		
Mean Cold Ischemia Time (hours)	5.92	5.91
Mean Time on NMP (hours)	7.16	6.66
Mean Total Preservation Time (cross-clamp to portal reperfusion) (hours)	14.26	13.70
Operation Characteristics		
Mean PRBC Units	14.0	19.4
Mean Crystalloid (mL)	1750	4000
Mean Cryoprecipitate Units	2.5	0.8
Mean FFP Units	28.5	33.6
Mean Platelet Units	2.5	2.0
Mean Albumin (mL)	500	430
Post-Operative Outcomes		
Primary Non-Function (%)	0 (0.0)	0 (0.0)
Early Allograft Dysfunction (%)	0 (0.0)	2 (40.0)
Re-Operation (%)	2 (100.0)	3 (60.0)
Mean ICU Stay	18.5	10.8
Mean Hospital Stay	79.5	21.7

Table 1: Preservation Characteristics and Outcomes Data for CHLT and re-transplant patients receiving livers that underwent NMP on the OrganOx *metra*® system

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1036-A | OUTCOMES OF MACHINE PERFUSION IN LIVER TRANSPLANTATION: AN ANALYSIS OF THE UNOS DATABASE

Soo Young Hwang, Harvard T.H.Chan School of Public Health, Heidi Yeh, Massachusetts General Hospital and Wei Zhang, Massachusetts General Hospital, Brookline, MA

Background: Machine perfusion has been implemented as an alternative to the conventional static cold storage preservation method to reduce ischemia-reperfusion injury through more advanced organ preservation. The use of machine perfusion was first tracked by SRTR in 2016 and various approaches including hypothermic machine perfusion (HMP) and normothermic machine perfusion (NMP) have been reported ever since. Our aim is to explore the outcomes of liver machine perfusion in liver transplantation based on the United Network for Organ Sharing (UNOS) database. **Methods:** We retrospectively analyzed all adult patients aged 18 and above who received liver transplantation from adult deceased donors aged 18 and above according to the UNOS database from 2016 to 2022. All data regarding liver transplantation and follow-up visits were retrieved at the end of 2022. Preservation time was defined as the time from cross-clamp to reperfusion, including machine perfusion time, when relevant. We compared outcomes on survival, acute rejection, and graft failure between the group that received machine perfusion versus the group that did not receive machine perfusion. The incidence rate of acute rejection was compared between the two groups. We performed a log-rank test to compare the survival function and graft survival between the two groups. **Results:** 841 patients who received liver transplantation with machine perfusion and 50,393 patients who received liver transplantation without machine perfusion were analyzed. The mean age of the donors and recipients was higher in the machine perfused group (donor 42.42 y versus 46.49 y; recipient 55.25 y versus 57.18 y) as well as the portion of patients over age 65. The machine perfused group had a statistically significantly longer preservation time of 9.32 hours compared to the non-perfused group of 5.98 hours. 76 cases (14.10%) of the machine perfused group and 4,797 cases (10.41%) of the non-perfused group were from donors after circulatory death (DCD). There was no statistically significant difference in the incidence rate (*p*-value 0.62) and the log-rank test of overall survival (*p*-value 0.3) and graft failure (*p*-value 0.4). **Conclusion:** Machine perfusion was implemented to increase the utilization of liver organs under sub-optimal quality and circumstances. Our results suggest that machine perfusion is associated with older donors, longer preservation times, and a higher portion of DCD grafts, but nevertheless has similar graft and patient survival as the non-machine perfusion group. Further epidemiological studies on the long-term outcome of machine perfusion in liver transplantation are needed to explore the effect of machine perfusion on the population level.

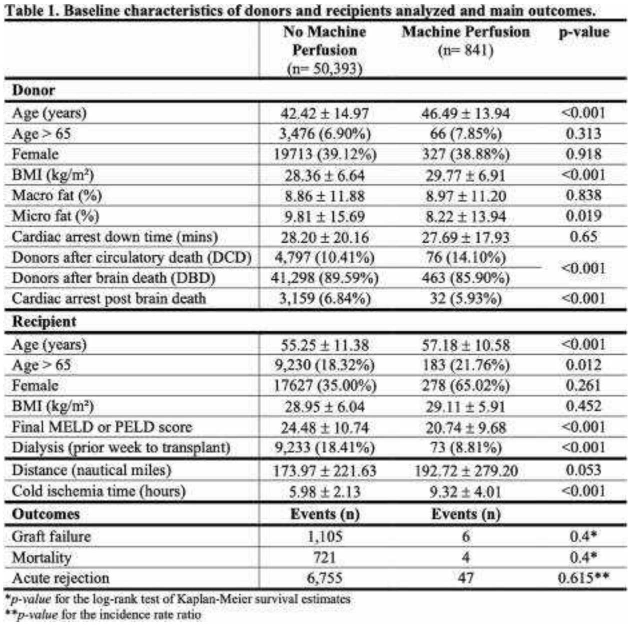

Table 1. Baseline characteristics of donors and recipients analyzed and main outcomes.

	No Machine Perfusion (n= 50,393)	Machine Perfusion (n= 841)	p-value
Donor			
Age (years)	42.42 ± 14.97	46.49 ± 13.94	<0.001
Age > 65	3,476 (6.90%)	66 (7.85%)	0.313
Female	19713 (39.12%)	327 (38.88%)	0.918
BMI (kg/m²)	28.36 ± 6.64	29.77 ± 6.91	<0.001
Macro fat (%)	8.86 ± 11.88	8.97 ± 11.20	0.838
Micro fat (%)	9.81 ± 15.69	8.22 ± 13.94	0.019
Cardiac arrest down time (mins)	28.20 ± 20.16	27.69 ± 17.93	0.65
Donors after circulatory death (DCD)	4,797 (10.41%)	76 (14.10%)	<0.001
Donors after brain death (DBD)	41,298 (89.59%)	463 (85.90%)	
Cardiac arrest post brain death	3,159 (6.84%)	32 (5.93%)	<0.001
Recipient			
Age (years)	55.25 ± 11.38	57.18 ± 10.58	<0.001
Age > 65	9,230 (18.32%)	183 (21.76%)	0.012
Female	17627 (35.00%)	278 (65.02%)	0.261
BMI (kg/m²)	28.95 ± 6.04	29.11 ± 5.91	0.452
Final MELD or PELD score	24.48 ± 10.74	20.74 ± 9.68	<0.001
Dialysis (prior week to transplant)	9,233 (18.41%)	73 (8.81%)	<0.001
Distance (nautical miles)	173.97 ± 221.63	192.72 ± 279.20	0.053
Cold ischemia time (hours)	5.98 ± 2.13	9.32 ± 4.01	<0.001
Outcomes	**Events (n)**	**Events (n)**	
Graft failure	1,105	6	0.4*
Mortality	721	4	0.4*
Acute rejection	6,755	47	0.615**

**p-value* for the log-rank test of Kaplan-Meier survival estimates
***p-value* for the incidence rate ratio

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1037-A | PERFORMANCE OF RISK MODELS FOR POST-LIVER TRANSPLANT PATIENT AND GRAFT SURVIVAL OVER TIME

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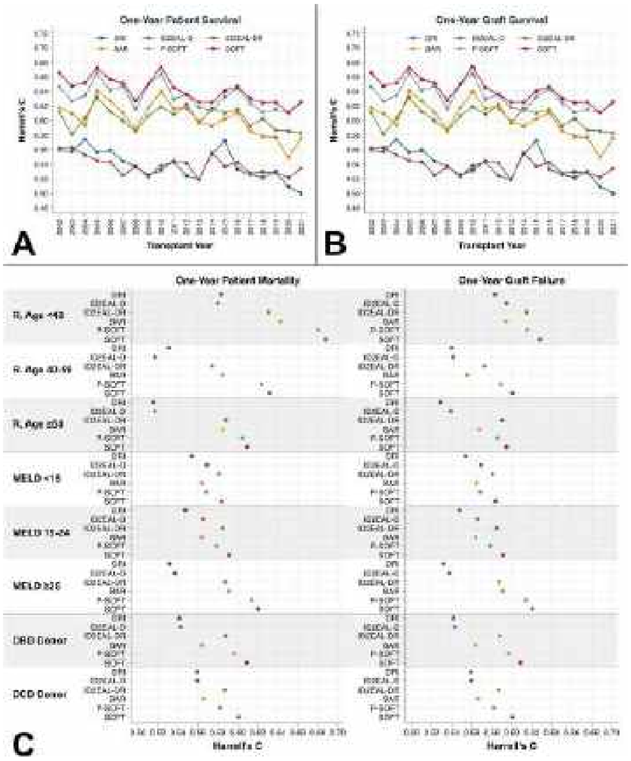
Background: Organ scarcity in liver transplantation (LT) necessitates optimal selection of recipients and donors to minimize waitlist mortality and maximize post-transplant benefit. Several scores have been developed to predict post-transplant patient and graft survival by isolating elements of donor risk, recipient risk, or both. While the donor risk index (DRI) score has been the most widely used model since its development in 2006, several other prediction models have been created since, including the BAR score, P-SOFT and SOFT scores, and the ID2EAL-D/-DR scores. No studies to date examine the performance of these models over time, which is critical in an ever-evolving transplant landscape. We evaluated the discrimination and calibration of liver transplantation risk scores over time. **Methods:** This was a retrospective cohort study of liver transplantation events in the UNOS database from 2002-2021. We used Cox regression to evaluate model discrimination (Harrell's C) and calibration (testing of calibration curves) for post-transplant patient survival and graft survival. These were evaluated at 1, 3, and 5-year post-transplant timepoints, and sub-analyses were performed in the modern transplant era (post-2014). Stratified analyses were also performed for key donor-recipient characteristics. **Results:** In the analytic cohort, a total 112,356 liver transplants were included. The SOFT score demonstrated the highest discrimination of all scores for patient and graft survival at all timepoints (Figure panels A/B). However, the ID2EAL-DR score reflected the best balance of calibration and discrimination for both outcomes at longer timepoints (3 and 5 y post-transplant; data not shown). In stratified analyses, SOFT and ID2EAL-DR scores performed especially well in younger patients and those with higher MELD scores (Figure panel C). All prediction scores had generally declining discrimination over time (increasing transplant year), and scores relying on donor factors alone for prediction (i.e., DRI and ID2EAL-D scores) had consistently poor predictive performance ($C < 0.60$). **Conclusion:** Although the SOFT and IDEAL-DR scores had the best overall performance, all prediction models demonstrated declining performance over time. This underscores the importance of periodically updating older prediction models and/or developing new models to reflect the evolving transplant field. Scores relying on donor factors alone do not meaningful inform post-transplant risk.



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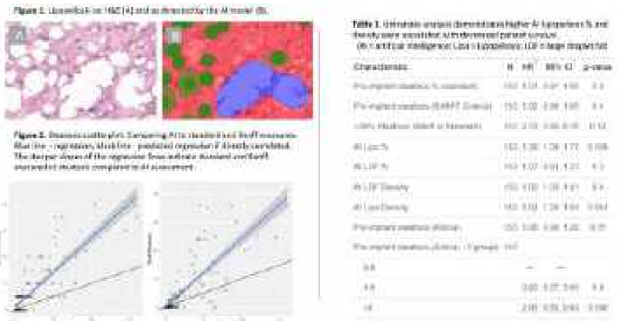
The following people have nothing to disclose: Lauren Shaffer, Samir Abu-Gazala, Peter Abt

1038-A | POST LIVER TRANSPLANT OUTCOMES ARE PREDICTED BY ARTIFICIAL INTELLIGENCE MODEL DETECTION OF LIPOPELIOSIS ON PREIMPLANT FROZEN SECTION

Suaka Kagbo-Kue[1], Maxwell Smith[1], Alyssa McGary[2], Laura Budvytyte[1], Mariah Schroeder[1], David Chascsa[2] and Rolland C Dickson[2], (1)Mayo Clinic, (2)Mayo Clinic Arizona, Phoenix, AZ

Background: Steatosis in donor liver allografts is associated with post-transplant outcomes. However, accurate estimation is limited by marked observer variability which complicates assessment of steatosis cutoff values for transplantation. We previously developed and validated an artificial intelligence (AI) model (Aiforia) for detection and quantitation of lipopeliosis (LP), large droplet fat, and overall steatosis. LP is the coalescence of fat droplets from ruptured hepatocytes (Fig 1). Our hypothesis was that steatosis parameters would correlate with patient outcomes. **Methods:** We retrospectively applied the model to consecutive liver transplant patients with > 5 years of follow-up and available preimplant frozen section slides. The model results were compared to traditional and Banff estimates for steatosis and to clinical outcomes. Continuous variables were summarized using median and interquartile range, categorical variables were summarized using the frequency and percentage. Overall patient and graft survival were estimated using Kaplan-Meier method. Univariate analyses were assessed with Cox-regression. **Results:** 161 patients met inclusion criteria and were tested with Aiforia. 8 slides failed Aiforia due to poor preparation quality. 153 patients had steatosis measures by traditional, Banff, and Aiforia. There was strong correlation between all 3 methods of assessing hepatic steatosis, however, both the traditional and Banff methods significantly overestimated the percentage of steatosis in comparison to the AI model (Fig 2). The percentage and density of LP were associated with patient survival (HR = 1.39, 95% CI 1.09, 1.77, $p = 0.009$; and HR = 1.02, 95% CI 1.00, 1.04, $p = 0.044$, respectively) (Table 1). Preimplant steatosis by all three methods did not have significant impact on survival. **Conclusion:** Our study supports previous reports of overestimation of hepatic steatosis with traditional methods and shows similar overestimation using Banff criteria. Importantly, we found measures of LP in hepatic allografts detected by our AI model were strong and better predictors of post liver transplantation outcomes than overall percentage of fat. The use of an AI model to detect LP may help guide risk assessment of steatotic hepatic allografts, potentially increasing the successful utilization of these organs. A larger series is needed to confirm these findings.



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1039-A | PSYCHOSOCIAL AND MEDICAL FACTORS ASSOCIATED WITH RECEIPT OF LIVER TRANSPLANT IN LISTED PATIENT WITH HEPATOCELLULAR CARCINOMA

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Background: Patients with hepatocellular carcinoma (HCC) are less likely to receive liver transplantation (LT) than patients without HCC. The aim of this study was to explore sociodemographic, psychosocial, and medical factors associated with progression to LT, versus delisting, in patients with HCC listed for LT. **Methods:** Prospectively maintained database from a single center tracking all patients diagnosed with HCC from 2005-2022. Amongst those listed for LT, the main outcome was receipt of transplant (versus delisting for any reason). Predictors included sociodemographic, psychosocial, and medical characteristics. Given the exploratory nature, predictors were included in the final multivariable logistic model if univariable logistic regression results approached significant ($p < 0.1$). **Results:** Among 341 patients listed with HCC; mean age 59.6 years (SD 6.8); 265 male (77.7%); racial composition was 246 White (72.1%), 50 Black (14.7%), and 45 "other" (13.2%). 261 (76.5%) underwent LT, 80 (23.5%) were delisted (any reason, majority due to disease progression/medical deterioration). Variables included in the model were age at transplant listing, marital status, whether the patient underwent treatment for HCC, and histories of tobacco use, alcohol abuse, hepatic encephalopathy, diabetes, hypertension, and dyslipidemia. Final model presented in Table 1. Significant predictors of receipt of LT in the final model included younger age at transplant listing, no history of tobacco use, and no history of alcohol abuse. **Conclusion:** HCC patients are often delisted due to HCC disease progression and/or death while on the LT waitlist. Our data suggests that patients who are listed at a younger age, do not have a history of tobacco use, or of alcohol abuse are more likely to successfully receive LT. Also, contrary to hypotheses, race/ethnicity was not significant suggesting improved equity across these groups.

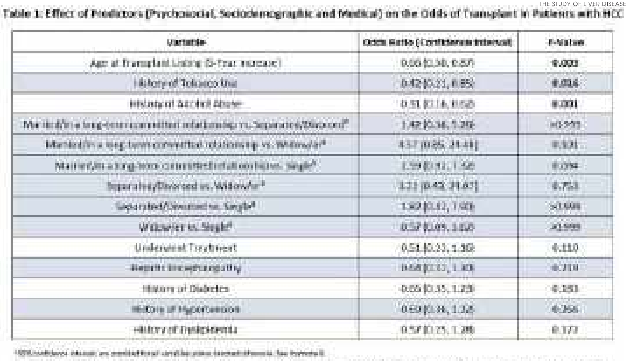

Table 1: Effect of Predictors (Psychosocial, Sociodemographic and Medical) on the Odds of Transplant in Patients with HCC

Variable	Odds Ratio (Confidence Interval)	P-Value
Age at Transplant Listing (5-Year Increase)	0.66 (0.50, 0.87)	0.003
History of Tobacco Use	0.42 (0.21, 0.85)	0.016
History of Alcohol Abuse	0.31 (0.16, 0.62)	0.001
Married/In a long-term committed relationship vs. Separated/Divorced^a	1.42 (0.38, 5.26)	>0.999
Married/In a long-term committed relationship vs. Widow/er^a	4.57 (0.85, 24.48)	0.101
Married/In a long-term committed relationship vs. Single^a	1.59 (0.92, 1.56)	0.094
Separated/Divorced vs. Widow/er^a	3.22 (0.42, 24.67)	0.753
Separated/Divorced vs. Single^a	1.82 (0.42, 7.60)	>0.999
Widow/er vs. Single^a	0.57 (0.09, 3.60)	>0.999
Underwent Treatment	0.51 (0.23, 1.16)	0.110
Hepatic Encephalopathy	0.68 (0.33, 1.40)	0.299
History of Diabetes	0.65 (0.35, 1.23)	0.183
History of Hypertension	0.63 (0.36, 1.12)	0.256
History of Dyslipidemia	0.57 (0.25, 1.28)	0.173

Disclosures: The following people have nothing to disclose: Rami M. Youssef, Mark Obri, Erika Todter, Reena J. Salgia, Michelle Jesse

1040-A | QUANTIFYING REDUCTION OF WAITLIST TIME FOR LIVER TRANSPLANT RECIPIENTS ACCEPTING HEPATITIS C-POSITIVE ORGANS

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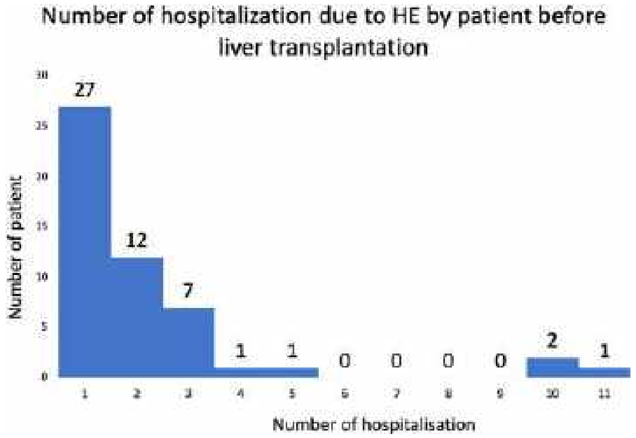
Background: There has been increased utilization of livers from hepatitis C virus (HCV)-positive donors given favorable post-transplantation outcomes for liver transplant recipients over the recent years in the era of direct-acting antiviral (DAA) therapies. While the increased use of HCV-positive organs increases the potential donor pool and presumably decreases waitlist times for liver transplant recipients, there are limited published data quantifying the reduction of time on the waitlist for patients accepting HCV-positive liver offers. There is also an assumption that acceptance of HCV-positive liver offers may enable liver transplantation at lower Model for End-Stage Liver Disease (MELD) scores, but this perceived benefit has yet to be fully elucidated. **Methods:** We conducted a single center retrospective case-control study comparing liver transplant waitlist times and MELD scores at time of transplantation between recipients receiving HCV antibody (Ab)-positive and HCV Ab-negative livers. There were 34 patients who received HCV Ab-positive livers from donors with nucleic acid amplification testing (NAAT) data available within the 5-year study period of October 2017 through October 2022. Recipients of HCV Ab-positive livers from both NAAT-positive and NAAT-negative donors were matched with 34 controls of a similar age and MELD score at time of listing (within 1 point) who were listed without acceptance of HCV-positive organs. Time on waitlist (days) and MELD scores at time of liver transplantation were calculated for each group. Time on waitlist for recipients of HCV Ab-positive livers was defined by the date from which the recipient was listed with acceptance of HCV-positive organs to the date of liver transplantation. **Results:** The average reduction of liver transplant waitlist time was 354 days (*p*-value 0.014) in patients who received HCV Ab-positive livers as compared to patients who were not listed for HCV-positive organs and received HCV Ab-negative livers, with an average and median MELD score of 20 in both groups at time of listing. There was no significant difference in MELD score at the time of transplantation between the groups with an average MELD score of 20 in patients receiving HCV Ab-positive livers and average MELD score of 19 in patients receiving HCV Ab-negative livers (*p*-value 0.65). **Conclusion:** This study supports and quantifies the assumption that acceptance of HCV-positive organs can reduce time on the liver transplantation waitlist, however, our results do not demonstrate lower MELD scores at time of transplantation for these recipients.

Disclosures: The following people have nothing to disclose: Nicholas Hebda, Altaib Al Yassin, Anita Krishnarao

1041-A | RECURRENT HEPATIC ENCEPHALOPATHY AS A MELD EXCEPTION FOR LIVER TRANSPLANTATION

Isaac Ruiz[1], Mélanie Tremblay[2], Genevieve Huard[3], Yu Shi Wang[1], Julien Bissonnette[3], Catherine Vincent[3], Chantal Bémeur[1,4] and Christopher F. Rose[2,4], (1) Centre De Recherche Du Centre Hospitalier De l'Université De Montréal, (2)Hepato-Neuro Laboratory, Centre De Recherche Du Centre Hospitalier De l'Université De Montréal, (3)Centre Hospitalier De l'Université De Montréal, (4)Université De Montréal

Background: Model for End-Stage Liver Disease (MELD) is used worldwide to prioritize patients for organ allocation for liver transplantation (LT). This robust prognostic score does not include hepatic encephalopathy (HE). Therefore, some patients with recurrent HE may thus not be well served with this system. To mitigate this gap, "recurrent hepatic encephalopathy" has been proposed as a MELD exception point. Unfortunately, there is no formal policy regarding the number and duration of hospitalizations for recurrent HE. Data are lacking to reach consensus among centers. The objective of this study was to evaluate the number and length of stay of hospitalizations due to HE in patients with cirrhosis on the LT waiting list. **Methods:** This retrospective study includes all consecutive patients who underwent LT at the Centre hospitalier de l'Université de Montréal (CHUM) between January 2019 and December 2021. Only patients with confirmed cirrhosis by clinical, radiological or pathological findings were included. Patients with multiorgan transplantations, acute liver failure, and other indications of LT without cirrhosis were excluded. Data regarding hospitalizations one year before LT were collected. Clinical, biological, and radiological characteristics were collected for each hospitalization, including HE parameters and precipitating factors. **Results:** During the study period, 181 patients were transplanted in our center. One hundred and fifty-five patients with cirrhosis were included and were divided into two groups: "HE-group", patients that developed at least one episode of HE before LT, n = 103 (66.5%); "Non-HE-group", patients without history of HE, n = 52 (33.5%). In the HE-group, the number of patients who experienced at least one hospitalization for HE was 51/103 (49.5%). The median number of hospitalizations for HE per patient was 1.0 (range 1-11; mean 2.2). The median length of stay for each hospitalization was 10.5 days (range 1-127; mean 26.1). Seven of 103 patients (6.8%) were hospitalized due to HE until LT. Figure 1 shows the number of hospitalizations due to HE per patient before LT. **Conclusion:** This study demonstrates the high prevalence of HE in the waiting list for patients with cirrhosis and provides the first data on the number and duration of hospitalizations in this vulnerable population. According to our data, 4 hospitalizations and 10 days length of stay advocates to be a good cut-off to define "recurrent HE", thus supporting expert recommendations for MELD exception points for this complication. In addition, over a period of 3 years, 4 patients will have benefited from the MELD exception. This makes this criterion.



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1042-A | RE-EVALUATING THE 6 MONTH RULE PRIOR TO LIVER TRANSPLANT: A CLINICAL PRACTICE GUIDELINE

Joanna Colleen Dionne[1], *Simon Oczkowski*[1], *Susan Abbey*[2], *Vanessa Gruben*[3], *Jennifer Chandler*[3], *Marie-Chantal Fortin*[4], *Vladimir Marquez*[5], *Sylvia Carbert*[6], *Marilyn Swinton*[1], *Ted Christou*[7], *Fatima Dharsee*[8], *Clay Gillrie*[8], *Christina Pearson*[8], *Prosanto Chaudhury*[9] *and Nazia Selzner*[2], *(1)Mcmaster University, (2)University of Toronto, (3)University of Ottawa, (4)Universite De Montreal, (5)University of British Columbia, (6)Alberta Health Services, (7)Queen's University, (8)Canadian Blood Services, (9)Mcgill University*

Background: The 6 months abstinence rule prior to liver transplant for alcohol related liver disease (ALD) prior to liver transplant (LT) has been called into question from evidence, ethical and legal lenses. The purpose of this clinical practice guideline (CPG) is to guide the assessment and management of ALD and LT. **Methods:** A committee including medical and surgical experts in liver transplant, addiction, ethics, law, methodology and patient partners developed a CPG according to GRADE Methodology. **Results:** Five conditional recommendations (very low certainty of evidence) and 2 best practice statements for patients undergoing LT were made. The recommendations included: 1) To not use the six-month rule as a sole criterion for liver transplant in ALD, 2) The definition of relapse should distinguish between: 1. non harmful relapse (e.g. occasional drinking or slip), 2. harmful drinking (e.g. physical, psychosocial implications, binge drinking/escalation drinking) and relapse monitored by biochemical markers when available, 3. During liver transplant workup, assessment of risk factor associated with post- transplant relapse (presence of uncontrolled psychiatric disease, history of smoking and multiple failed attempts of alcohol treatment) and protective factors (social support and employment) should be part of the assessment to allow for early intervention to mitigate risk factors, 4) The use of validated screening scoring systems and biomarkers for screening post-transplant relapse, 5) Integrated multidisciplinary teams with psychiatrists, addiction services to prevent relapse pre and post-transplant. The best practice statements included: 1) Listed and transplanted ALD patients should be intermittently screened for relapse pre and post-transplantation and 2) We suggest a holistic assessment for patients being evaluated for liver transplant, that not only take into account risk factors or other screening modalities, but a multi prong, multidisciplinary approach. **Conclusion:** This CPG provides evidence-based recommendations for listing and transplanting patients with ALD.

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Disclosure information not available at the time of publication: Simon Oczkowski, Susan Abbey, Vanessa Gruben, Jennifer Chandler, Marie-Chantal Fortin, Vladimir Marquez, Sylvia Carbert, Marilyn Swinton, Ted Christou, Fatima Dharsee, Clay Gillrie, Christina Pearson, Prosanto Chaudhury

1043-A | SAFETY, EFFICACY AND OUTCOMES OF INTRAOPERATIVE CONTINUOUS RENAL REPLACEMENT THERAPY FOR CRITICALLY ILL CHILDREN WITH LIVER FAILURE

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Background: Intraoperative Continuous Renal Replacement Therapy (iCRRT) has been reported to prevent life-threatening complications, facilitate fluid management and maintain metabolic homeostasis during orthotopic liver transplantation (LT) in adults with severe pre-LT renal dysfunction. However, there is a paucity of data describing safety, feasibility and efficacy of iCRRT in pediatric LT. We report our experience and clinical outcomes of critically ill children with pre-LT renal dysfunction who received iCRRT. **Methods:** We conducted a retrospective cohort study of children requiring CRRT pre-LT (>24 hours) at a quaternary, free-standing children's hospital from 2014-2022. We compared key demographic characteristics, intraoperative events and post-LT outcomes of those who needed CRRT during LT (iCRRT group) with those who did not (non-iCRRT group). Statistical analysis included Fisher's Exact and Mann-Whitney tests to measure strength of univariate associations. **Results:** Out of 306 patients who received LT during the study period, 30 (10%) were supported on CRRT, of which 11 (36%) received iCRRT. In the iCRRT group (median age 11 months [IQR 7-64], 55% females), majority (82%) had acute on chronic liver failure (ACLF) and 64% had prior abdominal surgery (excluding a Kasai portoenterostomy). The iCRRT group had longer median anesthesia and surgical time; higher proportion of patients experiencing massive blood loss (more than total blood volume (TBV) of 80ml/kg); increased PRBC requirements and total fluid resuscitation more than 3 times TBV when compared to the non-iCRRT group (Table 1). There was no difference in intraoperative serum potassium (K+), bicarbonate (HCO$_3^-$) or lactate levels between two groups. Though the iCRRT cohort had longer intensive care unit (ICU) and hospital length of stay (LOS), there was no 30-, 60- or 90-day mortality in this group and 1-year post-LT mortality rates were comparable (Table 1). One patient had a circuit malfunction in the operating room requiring cessation of CRRT. **Conclusion:** iCRRT is feasible, safe and efficacious in critically ill children with pre-LT renal dysfunction. With minimal adverse events, it can maintain acid-base, fluid and electrolyte balance while allowing for appropriately aggressive resuscitation with fluid and blood products. Candidates for iCRRT need to be carefully chosen so that this highly resource intensive therapy can be optimally deployed to benefit this fragile population.

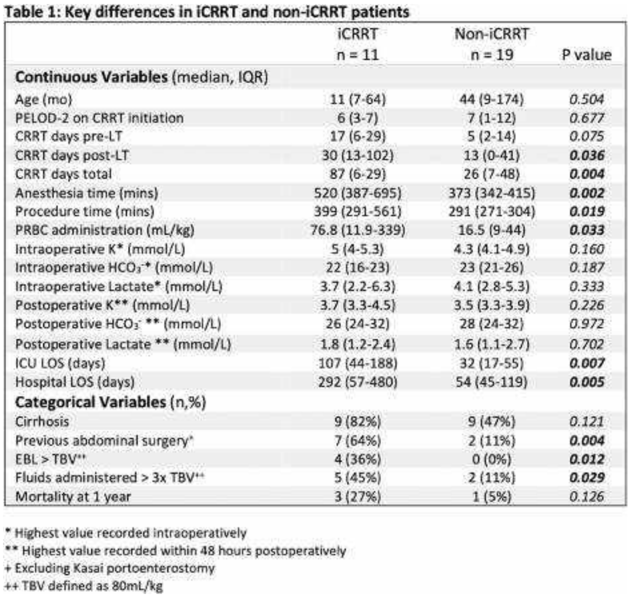

Table 1: Key differences in iCRRT and non-iCRRT patients

	iCRRT n = 11	Non-iCRRT n = 19	P value
Continuous Variables (median, IQR)			
Age (mo)	11 (7-64)	44 (9-174)	*0.504*
PELOD-2 on CRRT initiation	6 (3-7)	7 (1-12)	*0.677*
CRRT days pre-LT	17 (6-29)	5 (2-14)	*0.075*
CRRT days post-LT	30 (13-102)	13 (0-41)	***0.036***
CRRT days total	87 (6-29)	26 (7-48)	***0.004***
Anesthesia time (mins)	520 (387-695)	373 (342-415)	***0.002***
Procedure time (mins)	399 (291-561)	291 (271-304)	***0.019***
PRBC administration (mL/kg)	76.8 (11.9-339)	16.5 (9-44)	***0.033***
Intraoperative K* (mmol/L)	5 (4-5.3)	4.3 (4.1-4.9)	*0.160*
Intraoperative HCO$_3^-$* (mmol/L)	22 (16-23)	23 (21-26)	*0.187*
Intraoperative Lactate* (mmol/L)	3.7 (2.2-6.3)	4.1 (2.8-5.3)	*0.333*
Postoperative K** (mmol/L)	3.7 (3.3-4.5)	3.5 (3.3-3.9)	*0.226*
Postoperative HCO$_3^-$ ** (mmol/L)	26 (24-32)	28 (24-32)	*0.972*
Postoperative Lactate ** (mmol/L)	1.8 (1.2-2.4)	1.6 (1.1-2.7)	*0.702*
ICU LOS (days)	107 (44-188)	32 (17-55)	***0.007***
Hospital LOS (days)	292 (57-480)	54 (45-119)	***0.005***
Categorical Variables (n,%)			
Cirrhosis	9 (82%)	9 (47%)	*0.121*
Previous abdominal surgery+	7 (64%)	2 (11%)	***0.004***
EBL > TBV++	4 (36%)	0 (0%)	***0.012***
Fluids administered > 3x TBV++	5 (45%)	2 (11%)	***0.029***
Mortality at 1 year	3 (27%)	1 (5%)	*0.126*

* Highest value recorded intraoperatively
** Highest value recorded within 48 hours postoperatively
+ Excluding Kasai portoenterostomy
++ TBV defined as 80mL/kg

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1044-A | SEX DISPARITY IN LIVING DONOR LIVER TRANSPLANTATION: U.S. ANALYSIS

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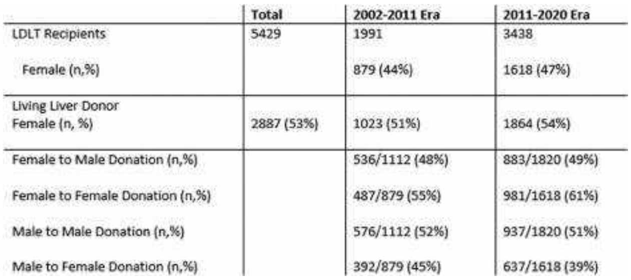
Background: Sex disparities in liver transplantation remain pervasive, including in living donor liver transplant (LDLT) where females account for the majority of living liver donors. We sought to describe sex distributions among living liver donors and LDLT recipients in the U.S. **Methods:** Using SRTR data (2002-2022), we identified all adult (> / = 18 yrs) living liver donors and all adult LDLT recipients. Data collection for living liver donors included: sex (male vs female), age at donation, marital status, education level, race/ethnicity, height, weight, hepatic lobe donated (right/left/left lateral), donor relationship to recipient, and ABO. Recipient data collection included: sex, age at transplant, MELD at listing and at transplant, race/ethnicity, liver disease etiology, height, weight, hepatic lobe received, relationship to donor, and ABO. Given the extended timeframe, we stratified the analyses by Era (Era 1:2002-2011; Era 2:2012-2022] to account for evolution in LDLT practice in the U.S. **Results:** Overall, 5429 adults [n = 1991 in Era1; n = 3438 in Era2] underwent LDLT. Adult females accounted for less than half of LDLT recipients (44% in Era1; 47% in Era2). Females represented the majority of living liver donors to adult recipients in both Eras, with increasing rates of female donors over time (51% Era1 vs 54% Era2). Female donors were more likely than male donors to donate their right lobe (93% vs 87% in Era1; 90% vs 82% in Era2, respectively), and right lobe living liver donors were more likely to be female vs male (53% vs 46% in Era1; 56% vs 43% in Era2, respectively). In Era2, females were more likely to donate to adult males, compared to males donating to adult females (49% vs 39%, respectively). (Table 1) **Conclusion:** Sex disparities are notable in LDLT in the U.S. with regards to both donors and recipients. Females account for 39% of all waitlisted liver transplant candidates [SRTR 2020 data], and account for 44-47% of LDLT recipients, but comprise over half (51-54%) of living liver donors. The interplay between anatomic differences between females and males, and societal roles and expectations that may differ in females and in males, create a complex set of interactions influencing LDLT from both the donor and recipient perspectives that warrant further evaluation.



	Total	2002-2011 Era	2011-2020 Era
LDLT Recipients	5429	1991	3438
Female (n,%)		879 (44%)	1618 (47%)
Living Liver Donor Female (n, %)	2887 (53%)	1023 (51%)	1864 (54%)
Female to Male Donation (n,%)		536/1112 (48%)	883/1820 (49%)
Female to Female Donation (n,%)		487/879 (55%)	981/1618 (61%)
Male to Male Donation (n,%)		576/1112 (52%)	937/1820 (51%)
Male to Female Donation (n,%)		392/879 (45%)	637/1618 (39%)

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Disclosure information not available at the time of publication: Kiran Bambha

1045-A | TEMPORAL TRENDS AND UTILIZATION OF MINIMALLY INVASIVE VS. OPEN LIVER RESECTIONS

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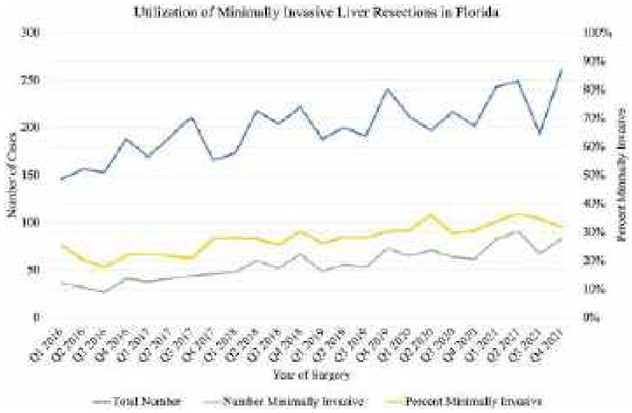
Background: Minimally invasive (MI) liver resections are increasingly common, especially after the 2008 Louisville Statement endorsement. National administrative data previously demonstrated increased frequency of MI resections following the Louisville Statement (2009-2012), but MI was still much less frequent than open. Contemporary trends and utilization have not been studied with large-scale administrative data. **Methods:** Using the Healthcare Cost and Utilization Project (HCUP) Florida State Inpatient Database (SID), we identified adult patients who underwent elective liver resections in Florida from 2016-2021 using International Classification of Disease (ICD-10) procedure codes. We identified the number of MI resections and the proportion of total resections that were MI. We used multivariable logistic regression to assess the associations between patient-level variables and receipt of a MI (laparoscopic or robotic assisted) versus open resection. **Results:** 6,828 liver resections were identified, and 4,790 met inclusion criteria. 133 pediatric, 1,753 non-elective, and 152 cases with missing demographic data were excluded. Mean age was 61.3 years and 53.2% were female. The most common indications were secondary (42.0%) and primary malignancy (24.9%). Partial hepatectomy alone (81%) was more common than lobectomy +/- partial hepatectomy (19%). Of the 4,790 included, 1,349 (28.2%) were MI procedures. The percent of total resections that were MI increased from 21.3% in 2016 to 34.1% in 2021. In multivariable analysis, patients of Black race (vs. White, Odds Ratio (OR) 0.79 [0.63-0.99]), residing in a population of 250,000 to < 1 million (vs. > = 1 million, OR 0.67 [0.57-0.78]), with a secondary malignancy (vs. primary malignancy, OR 0.63, [0.53-0.76]), with a neuroendocrine tumor (vs. primary malignancy, OR 0.51 [0.27-0.94]), and with each additional Elixhauser comorbidity (OR 0.88 [0.85-0.92]) were less likely to undergo MI resection. Patients with a benign indication (vs. primary malignancy, OR 3.03 [2.41-3.82]) and partial hepatectomy (vs. lobectomy, OR 1.94 [1.58-2.37]) were more likely to undergo MI resection. **Conclusion:** From 2016-2021, the percent of total liver resections that were minimally invasive increased each year in the state of Florida. Black patients and patients in less populated areas were less likely to undergo minimally invasive liver resections. Decreased access, patient choice, and provider preference could contribute to these differences.



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1046-A | THE COURSE OF INDETERMINATE LIVER NODULES IN THE SETTING OF LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

Mohammed Rifat Shaik[1], *Dabin Choi*[2], *Mohammad Bourmaf*[2], *Kabir Chhabra*[2], *David Lee*[2], *Zurabi Lominadze*[3], *Hyun S. Kim*[2] *and Kirti Shetty*[4], *(1) University of Maryland Medical Center Midtown Campus, (2)University of Maryland Medical Center, (3) University of Maryland Medical Center Baltimore, Baltimore, MD, (4)Department of Hepatology and Liver Transplantation, the University of Maryland, School of Medicine, Baltimore, MD, USA*

Background: The characteristic imaging appearance of hepatocellular carcinoma (HCC) usually obviates the need for tissue diagnosis. However, the presence of indeterminate liver nodules (ILN) in up to 25% of those with cirrhosis can complicate the interpretation of imaging studies. The Liver Reporting and Data System (LI-RADS®) classification has standardized ILN nomenclature with LI- RADS 3 and 4 (LR3/4) categories denoting increased risk of malignant transformation. There is limited data on the significance of LR3/4 lesions occurring against a background of known cirrhosis / HCC. It has been postulated that these premalignant lesions could assert a "field effect" on and from HCC in terms of biological behavior. We investigated the behavior of ILN in a population undergoing LT for HCC at a major US transplant center. **Methods:** This was a retrospective cohort study utilizing a pathological

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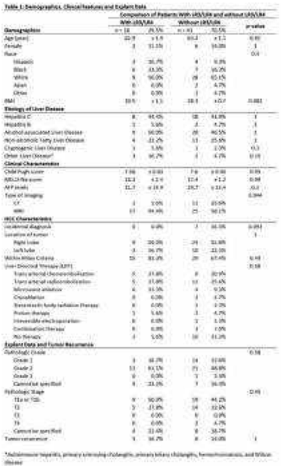
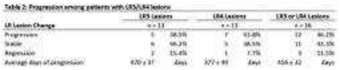
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

database identifying all patients who underwent LT for HCC. Variables of interest were extracted from the electronic medical record. All imaging studies were interpreted by experienced abdominal radiologists and discussed at a multidisciplinary conference. The index imaging study was denoted as the first study demonstrating HCC and the immediate pre-LT imaging study was within 90 days of LT. For continuous variables, means and standard deviations were calculated if normally distributed and medians (interquartile ranges IQR) were calculated if non normally distributed. Chi-square tests and Fisher exact tests were used to test between group differences for categorical variables. All *p*-values were reported as two-sided and a *p*-value < 0.05 was considered statistically significant. Institutional Review Board approval was obtained. **Results:** Between January 2019 and June 2022, a total of 72 adult LT recipients had HCC noted on explant pathology. Of these 11 were excluded due to non-availability of index imaging for discussion at our Tumor Board. The final study population included 61 patients. Of these, 44 (72%) were within Milan criteria at index imaging; those beyond were downstaged prior to LT. Fifty (81%) underwent liver directed therapy (LDT) prior to LT .Of the 11 patients who did not have LDT, 7 had HCC diagnosed on explant. A total of 13 LR3 and 13 LR4 lesions were diagnosed in 18 patients (29.5%) at index imaging.Table 1 compares those with and without these lesions. Progression to LR 5 lesions occurred in 5/13 LR3 lesions (38.5%) and 7/13 (53.8%) LR 4 lesions at median follow up to pre-LT imaging of 360 (range 90 – 1109) days .(table 2). On a patient level, 9/18 patients (50 %) had progression of LR3/4 to LR5 lesions. **Conclusion:** Fifty percent of HCC patients awaiting LT with LR3 /4 lesions noted on index MRI had progression of those lesions to HCC within a median follow up of 360 days. This progression has profound implications in terms of LT eligibility, requiring close follow up, multidisciplinary care and consideration of mass biopsy of IDL.





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1047-A | THE ROLE OF DONOR ATTITUDES, PERSONAL CHARACTERISTICS, AND RELATIONSHIPS IN THE PURSUIT OF LIVING ORGAN DONATION

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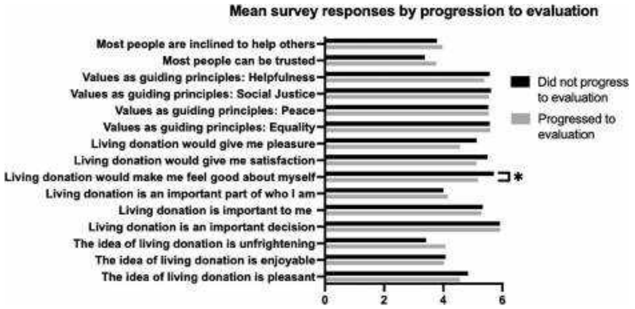
Background: There is little research to understand how personal attitudes and characteristics contribute to one's willingness to be a living liver donor, though these are known influences on blood donation and non-living organ registration status. The aim of this study is to understand how these factors influence the pursuit and completion of living donation to better understand donor recruitment and to identify potential donors most likely to progress to donation. **Methods:** A Likert scale survey was developed based on validated tools in blood donation research to identify motivations for organ donation and the qualities that make one more inclined to proceed with donation. This was distributed to all potential donors who reached out to our transplant center to inquire about living liver donation and were deemed eligible for donor evaluation. Results were compared between participants who progressed to full donor evaluation and those who did not, excluding participants who did not progress to evaluation due to recipient-related reasons. **Results:** 94 potential donors returned the survey over a 6-month period. 32 participants did not progress to evaluation due to their intended recipient no longer needing a donor and were excluded; 23 did not progress to evaluation due to personal decision; 39 did progress to evaluation, 7 of whom have donated to date. Figure 1 shows mean survey responses between two groups: those who progressed to donor evaluation and those who did not progress to donor evaluation due to personal decision. When characterizing progression to evaluation by relationship to recipient, 84% (16/19) of immediate family members, 88% (14/16) of extended family members, 50% (5/10) of altruistic donors, and 24% (4/17) of friends/community members progressed to evaluation. 36% of those who progressed to evaluation know someone who was a living organ donor, compared to 17% of those who did not progress to evaluation. **Conclusion:** There was no significant difference between these groups in personal characteristics or motivations, except for one 'warm glow' response which was greater in the group that did not progress to evaluation, which may reflect greater perceived benefit to self from donation in this group. While all participants in this study took personal initiative to reach out about living donation, their progression toward living donation after initial contact is overwhelmingly driven by close personal relationship to their recipient, independent of personal characteristics or motivations. Only a few of our potential donors presented without an intended recipient, compared to blood donation which is inherently non-directed.



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1048-A | THE ROLE OF EXCEPTION POINTS IN THE WAITLIST AND POST-TRANSPLANT OUTCOMES OF CHILDREN AND ADULTS WITH FIBROCYSTIC LIVER-KIDNEY DISEASE LISTED FOR LIVER TRANSPLANT: IMPLICATIONS FOR THE NATIONAL LIVER REVIEW BOARD ERA

Benjamin E. Rosenthal[1], Peter Abt[2], K Rajender Rajender Reddy[1] and Therese Bittermann[1], (1) University of Pennsylvania, (2)Perelman School of Medicine, University of Pennsylvania

Background: Liver transplantation (LT) in the setting of fibrocystic liver-kidney disease such congenital hepatic fibrosis (CHF) and Caroli disease (CD) is poorly understood with no prior studies in adults. Our study aims to analyze the waitlist and post-transplant outcomes of such patients listed for LT, with a particular focus on the use of exception points. **Methods:** This was a retrospective cohort study of adults and children with CHF or CD listed for LT between 1/1/2003-12/31/2022 using Organ Procurement and Transplantation Network data. Descriptive statistics were used to compare subgroups. Univariable and multivariable competing risks analysis (Fine & Gray) evaluated the factors associated with waitlist mortality, specifying transplant as a competing risk. Post-transplant patient survival was evaluated using Kaplan-Meier curves and log-rank tests. **Results:** Out of 592 patients in the study, 66.4% had CHF and 33.6% had CD. Overall, 61.8% were listed for LT alone and 38.2% for SLK. Among those listed for LT alone, 17.4% had previous kidney transplantation. Adults were frequently young (median 40 years, IQR 29, 53) and with low laboratory MELD score (median 12, IQR 6, 20). Adults had lower albumin (3.4 vs 3.6 g/dL, $p = 0.025$) at listing, more hepatic encephalopathy (35.7% vs 9.1%, $p < 0.001$), more ascites (48.7% vs 29.3%, $p < 0.001$), and were less likely to be listed for SLK compared to pediatric patients (32.8% vs 48.1%, $p < 0.001$). The majority (61.3%) of patients received exception points, most often via the non-standard exception pathway (94.0% for pediatric and 83.0% for adult). While on the waitlist, patients with exception points were more likely to undergo transplantation (87.8% vs 61.7%) and markedly less likely to be delisted for death or for being too sick (2.6% vs 11.9%, $p < 0.001$). In the final multivariable model for waitlist mortality, only receipt of exception points was significantly associated with the outcome with an adjusted SHR of 0.24 ($p = 0.002$). Despite low MELD/PELD score at listing, living donor LT was underused among LT alone recipients (n = 274; 12.6% of adult LTs, 13.0% of pediatric), even among those without exception points (n = 142; 18.8% of adult LTs, 19.5% of pediatric). Unadjusted long-term patient survival was excellent overall (71.2% at 15 y), superior in children vs adults (Figure A; $p = 0.003$), in those receiving SLK vs LT alone (Figure B; $p = 0.049$), and not different for exception point recipients in either adults (Figure C; $p = 0.282$) or children (Figure D; $p = 0.426$). **Conclusion:** Receipt of exception points supersedes all other clinical factors in predicting waitlist outcome for children and adults listed for LT with CD/CHF, with most exceptions being granted via the non-standard pathway. There is currently no National Liver Review Board guidance for CD/CHF, in whom long-term post-transplant survival is excellent, representing an unmet need.

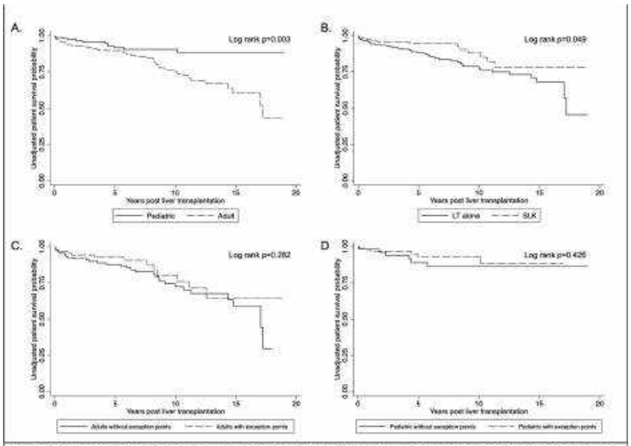

Figure A-D: Unadjusted patient survival probability for patients with Caroli disease and congenital hepatic fibrosis following liver transplant (LT) from 2003-2022 (n=425). **A.** All adult vs. pediatric LT recipients. **B.** Comparing simultaneous liver-kidney (SLK) transplant recipients vs. LT recipients alone. **C.** Adults transplanted with exception points compared to those without. **D.** Pediatric patients transplanted with exception points compared to those without.

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

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1049-A | THE SEVERITY AND DURATION OF PRE-LIVER TRANSPLANT KIDNEY DYSFUNCTION PREDICTS ELIGIBILITY FOR SAFETY NET KIDNEY AFTER LIVER TRANSPLANTATION

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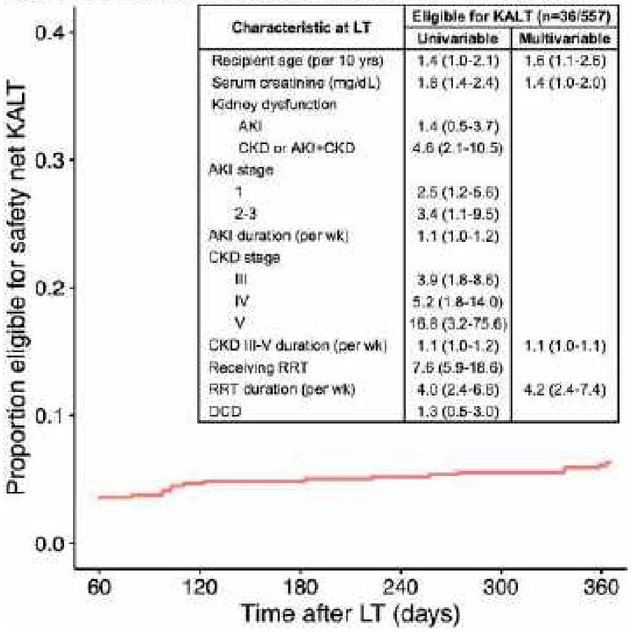
Background: Chronic kidney disease (CKD) is a major complication after liver transplantation (LT) associated with substantial morbidity and mortality. Knowing the drivers of post-LT CKD—with granular focus on the type, duration, and severity of pre-LT kidney dysfunction—can highlight intervention opportunities and inform dual-organ allocation policies. **Methods:** We retrospectively analyzed single-center data for adults who underwent liver-only deceased donor transplantation between 2016-2021. Pre-LT CKD was defined as eGFR < 60 mL/min/1.73 m^2 for e 90 days or e 72 days of renal replacement therapy (RRT). CKD stage was determined by eGFR at LT according to KDIGO guidelines. Pre-LT AKI was staged by comparing serum creatinine (sCr) at LT to baseline sCr e 7 days prior to AKI start (stage 1: sCr e 1.5x baseline, stage 2: sCr e 2x baseline, stage 3: sCr e 3x baseline or < 72 d of RRT). Patients meeting both criteria were labeled as AKI+CKD. Uni- and multi-variable logistic regression identified associations between patient characteristics and eligibility for safety net kidney after liver transplant (KALT) according to UNOS policy (eGFR d 20 mL/min/1.73 m^2 or on RRT 2-12 mo after LT). Results are expressed as median (interquartile range) or odds ratio with 95% confidence interval [OR (CI)]. **Results:** Among 557 adults [68% male; age 60 (54-65) years; MELD-Na 23 (10-35); 14% DCD], 52% had normal pre-LT kidney function, 23% had AKI, and 25% had CKD or AKI+CKD. At LT, 20% were receiving RRT for 4.0 (2.0-6.5) days. After LT, eGFR at 1-yr was 67 (54-87) mL/min/1.73 m^2. A total of 6.5% qualified for safety net KALT. Of these, 50% met criteria at 2 months, 75% by 6 months, and 83% by 9 months post-LT (Figure 1). In our final multivariable model, pre-LT factors associated with KALT eligibility were recipient age [per 10 years, OR 1.6 (1.1-2.6)], sCr [per 1 mg/dL, OR 1.4 (1.0-2.0)], CKD duration [per week, OR 1.1 (1.0-1.1)], and RRT duration [per week, OR 4.2 (2.4-7.4)]. We did not identify significant interactions between age, CKD duration, RRT duration, or DCD status. **Conclusion:** Increasing duration and severity of pre-LT kidney dysfunction correlated with eligibility for safety net KALT. Avoidance of multiple risk factors through careful recipient and donor selection along with measures (or therapies) to limit pre-LT kidney injury may reduce the risk of requiring KALT. More granular assessments (e.g., type, total duration, severity) of pre-LT kidney dysfunction must be considered in the design of future dual-organ allocation policies.

Figure 1. Cumulative incidence plot of safety net KALT eligibility.



Characteristic at LT	Eligible for KALT (n=36/557)	
	Univariable	Multivariable
Recipient age (per 10 yrs)	1.4 (1.0-2.1)	1.6 (1.1-2.6)
Serum creatinine (mg/dL)	1.8 (1.4-2.4)	1.4 (1.0-2.0)
Kidney dysfunction		
AKI	1.4 (0.5-3.7)	
CKD or AKI+CKD	4.6 (2.1-10.5)	
AKI stage		
1	2.5 (1.2-5.6)	
2-3	3.4 (1.1-9.5)	
AKI duration (per wk)	1.1 (1.0-1.2)	
CKD stage		
III	3.9 (1.8-8.6)	
IV	5.2 (1.8-14.0)	
V	16.8 (3.2-75.6)	
CKD III-V duration (per wk)	1.1 (1.0-1.2)	1.1 (1.0-1.1)
Receiving RRT	7.6 (5.9-18.6)	
RRT duration (per wk)	4.0 (2.4-6.6)	4.2 (2.4-7.4)
DCD	1.3 (0.5-3.0)	

Disclosures: Giuseppe Cullaro – Ocelot Bio: Consultant, No, No; Novo Nordisk: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, Yes; Eli Lilly: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, Yes; Retro: Consultant, No, No;

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1051-A | USING DATA-DRIVEN STRATEGIES TO IMPROVE TRANSPLANT ACCESS FOR VETERANS WITH CIRRHOSIS

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Background: Prior work has identified low rates of transplant referral for people with cirrhosis across the US. To develop a plan to evaluate and improve transplant access for Veterans in VA care, VA surgical and hepatology leadership established a VA Transplant workgroup to 1) identify factors associated with liver transplant referral in VA and 2) understand barriers to referral for transplant evaluation to target future quality improvement and outreach efforts. **Methods:** We used the VA Corporate Data Warehouse to collect data about Veterans with hepatocellular carcinoma or cirrhosis who were in VA care during 2021. Logistic regression was used to assess the factors associated with transplant evaluation referral. Subsequently, a survey of potential barriers to and facilitators of transplant evaluation and referral was sent to the clinicians who care for Veterans with cirrhosis across the VA. Results were analyzed using descriptive statistics and used to inform future improvement efforts. **Results:** Of the 99,092 Veterans with cirrhosis, 18% were ineligible for liver transplant based on age (≥ 75) or limited life expectancy. Likewise, 64,252 had low MELD, no complications of cirrhosis, and no HCC. In a single year, transplant referrals were completed for 700 Veterans, including 7.3% of the high MELD and decompensation group. Factors significantly associated with transplant referral were being younger, married, and White (versus Black), and having fewer comorbidities, higher MELD, and no history of alcohol use disorder. While a third of Veterans were rural-dwelling, 95% were within 150nm of a tertiary VA; distance was associated with referral only for Veterans with HCC. Surveys were returned by 196 clinicians from across the VA and a wide range of specialty settings. Clinicians identified the biggest barriers to transplant evaluation as provider knowledge about evaluation, length of the transplant workup, and complications with post-transplant care and the complexity of engaging with non-VA, community care transplant centers. Common misconceptions about VA liver transplantation were identified. Clinicians requested virtual tumor boards and hepatology consultation, as well as other resources to support transplant referral. VA leadership is developing a transplant implementation roadmap to actively increase referral and evaluation for transplantation for all Veterans. **Conclusion:** The Liver Transplant Workgroup identified patient- and provider-level factors associated with transplant referral for high-need Veterans in VA. Future work includes offering training and education, as well as targeted outreach to improve access and equity of transplant referral for Veterans with HCC or cirrhosis. VA's national transplant program offers an opportunity

to evaluate access and equity across the nation as well as to improve access using data-driven implementation strategies to address barriers.

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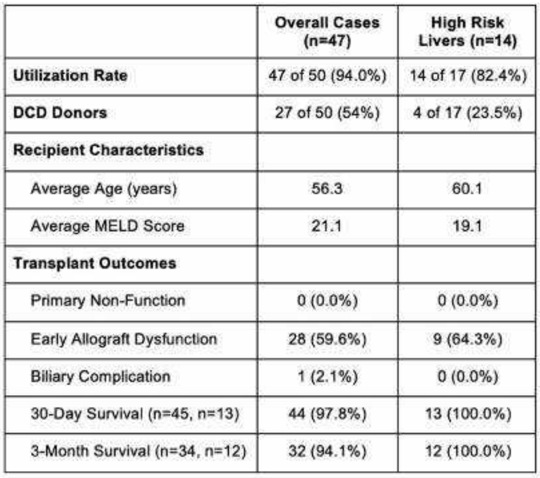
Disclosure information not available at the time of publication: Michael F. Chang, Ruben Hernaez, Joseph A. Awad, Jennifer Anwar, Pratima Sharma, Patrick Spoutz, Manimegalai Murugavel, Mark A. Wilson, Jason A Dominitz, Megan Adams

1052-A | USING NORMOTHERMIC MACHINE PERFUSION (NMP) TO ASSESS, RESUSCITATE AND RESCUE LIVERS FOR TRANSPLANTATION: FIRST 50 CASES OF A US SINGLE CENTER

Rachel Todd[1], Andrew Rosowicz[1], Matthew Holzner[2], Guy Meyerovich[2], Parissa Tabrizian[2], Chiara Rocha[2], Antonios Arvelakis[2], Joseph DiNorcia[2], Marcelo Facciuto[2], Thomas Schiano[2], M. Zeeshan Akhtar[2] and Sander S. Florman[2], (1)Icahn School of Medicine at Mount Sinai, (2)Recanati/Miller Transplantation Institute at Mount Sinai

Background: Normothermic machine perfusion (NMP) is a valuable tool used to evaluate marginal grafts for transplantation during organ preservation. Using the OrganOx *metra*® system, our goal was to expand our program's usage of marginal donor livers, benchmarking perfused livers against available viability criteria. **Methods:** This study is a single-center, retrospective review of all donor livers received at our institution for NMP evaluation from July 2022 to May 2023. A risk assessment tool was developed to evaluate the grafts chosen for NMP at our institution. Livers were deemed high risk if they met any of the following criteria: macrosteatosis > 30%, warm ischemia time > 30 minutes, prolonged donor down time, or donor hemodynamic instability requiring expedited procurement. Livers were broadly matched to recipients by placing high-risk livers in lower risk recipients. During NMP, all livers were evaluated for viability based on previously published data, including lactate clearance, glucose utilization, pH stability, and flow rates. Donor data, procedure details regarding NMP use, and recipient characteristics were collected. Post-transplant outcomes included rates of primary non-function, early allograft dysfunction (EAD), biliary complications, and 30-day/3-month recipient survival. **Results:** Over 280 days, 50 livers underwent NMP, of which 17 (34.0%) met our high-risk criteria. Mean pump perfusion time was 8.18 hours. Three of the high-risk livers did not meet viability criteria and were therefore discarded, of which two were DCD organs. Transplant outcomes are summarized in Table 1. For biliary complications, one patient experienced an anastomotic stricture. This graft did not meet our criteria for a high-risk liver. Rates of 30-day and 3-month survival were 97.8% and 94.1% respectively, and none of these patients received high-risk organs. **Conclusion:** Our center's experience demonstrates that NMP enables higher risk liver transplants to be performed safely. Our data supports the use of NMP, but caution and care are required to select the right liver for the right recipient.



	Overall Cases (n=47)	High Risk Livers (n=14)
Utilization Rate	47 of 50 (94.0%)	14 of 17 (82.4%)
DCD Donors	27 of 50 (54%)	4 of 17 (23.5%)
Recipient Characteristics		
Average Age (years)	56.3	60.1
Average MELD Score	21.1	19.1
Transplant Outcomes		
Primary Non-Function	0 (0.0%)	0 (0.0%)
Early Allograft Dysfunction	28 (59.6%)	9 (64.3%)
Biliary Complication	1 (2.1%)	0 (0.0%)
30-Day Survival (n=45, n=13)	44 (97.8%)	13 (100.0%)
3-Month Survival (n=34, n=12)	32 (94.1%)	12 (100.0%)

Table 1: Utilization rate, number of DCD donors, recipient characteristics, and transplant outcomes for entire cohort and high-risk sub-group.

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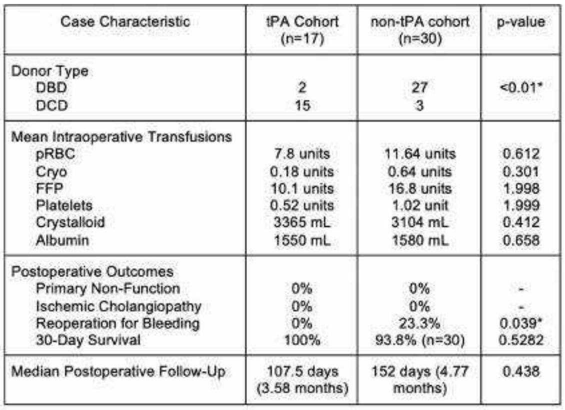
1053-A | USING NORMOTHERMIC PERFUSION AS A MECHANISM FOR TPA ADMINISTRATION OF DCD GRAFTS: A SINGLE CENTER US EXPERIENCE

Rachel Todd[1], Andrew Rosowicz[1], Guy Meyerovich[2], Matthew Holzner[2], Adam Kressel[2], Parissa Tabrizian[2], Chiara Rocha[2], Antonios Arvelakis[2], Joseph DiNorcia[2], Marcelo Facciuto[2], M. Zeeshan Akhtar[2] and Sander S. Florman[2], (1)Icahn School of Medicine at Mount Sinai, (2)Recanati/Miller Transplantation Institute at Mount Sinai

Background: Utilization of donation after circulatory death (DCD) grafts is crucial in addressing the organ shortage for liver transplantation, yet DCD grafts have exhibited inferior patient and graft survival compared to donation after brain death (DBD) grafts. Normothermic machine perfusion (NMP) has been shown to decrease rates of ischemic cholangiopathy (IC), anastomotic biliary strictures, and early allograft dysfunction (EAD) in DCD grafts. Our center currently administers 2 mg tPA intra-arterially to DCD graft recipients after reperfusion. In this study, we explored application of tPA during NMP with FFP as a plasminogen source. Our aim was to evaluate effects on blood loss and incidence of IC. **Methods:** Organs were placed on the OrganOx *metra*® system. DCD grafts were given an initial bolus of 10 mg tPA, followed by a 40 mg infusion over 90 minutes. Fresh frozen plasma (FFP) was administered simultaneously in a 100 mL bolus plus a 150 mL infusion over 90 minutes. After NMP, grafts were flushed with Custodial solution to remove all blood products and intravascular tPA, and then brought to the surgical field. Retrospective review of all NMP cases at our center was conducted, including intraoperative transfusions, post-transplant outcomes, and 30-day survival. Patients whose grafts received tPA on the OrganOx *metra*® system were compared to those not receiving tPA via Mann-Whitney U tests for continuous variables and Fisher exact tests for dichotomous variables. **Results:** In total, tPA and FFP were administered to 16 DCD grafts and two DBD grafts with concern for poor cold flush during procurement. 32 other livers placed on NMP did not receive tPA and FFP. Three grafts (1 in tPA cohort, 2 in non-tPA cohort) were discarded after failing to meet viability criteria during NMP. Mean intraoperative transfusion requirements for both groups are summarized in Table 1, with no significant increase in the tPA/FFP cohort. There was no incidence of primary non-function or ischemic cholangiopathy (median follow-up of 4.4 mo for all cases). There was a significantly higher rate of reoperation for hematoma evacuation in the non-tPA cohort. All patients in the tPA cohort achieved 30-day survival. **Conclusion:** NMP is a safe mechanism of administering tPA and FFP to pre-transplant donor livers and prevents the need to administer this agent to the recipient after reperfusion. Our initial results demonstrate a shift in clinical practice in the use of tPA administration.



Case Characteristic	tPA Cohort (n=17)	non-tPA cohort (n=30)	p-value
Donor Type			
DBD	2	27	<0.01*
DCD	15	3	
Mean Intraoperative Transfusions			
pRBC	7.8 units	11.64 units	0.612
Cryo	0.18 units	0.64 units	0.301
FFP	10.1 units	16.8 units	1.998
Platelets	0.52 units	1.02 unit	1.999
Crystalloid	3365 mL	3104 mL	0.412
Albumin	1550 mL	1580 mL	0.658
Postoperative Outcomes			
Primary Non-Function	0%	0%	-
Ischemic Cholangiopathy	0%	0%	-
Reoperation for Bleeding	0%	23.3%	0.039*
30-Day Survival	100%	93.8% (n=30)	0.5282
Median Postoperative Follow-Up	107.5 days (3.58 months)	152 days (4.77 months)	0.438

Table 1: Intraoperative transfusion requirements and postoperative outcomes for tPA and non-tPA recipients of livers that underwent NMP on the OrganOx *metra*® system.

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1054-A | UTILIZATION OF COVID-19 POSITIVE VERSUS NEGATIVE DECEASED DONORS REGISTERED FOR LIVER TRANSPLANTATION IN THE UNITED STATES

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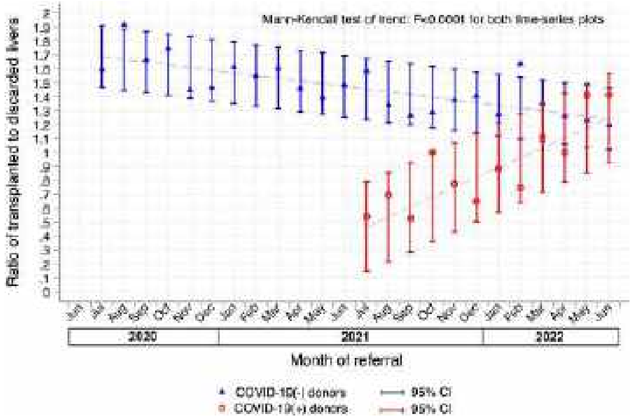
Background: COVID-19 (C19) infection in deceased donors for potential liver transplant (LT) is a commonly encountered clinical scenario. Recent literature suggests that short-term patient survival and graft survival are similar in C19(+) versus C19(-) donors. We aimed to evaluate trends in utilization of C19(+) versus (-) donors and identify variables associated with utilization versus discard. **Methods:** This was a retrospective cohort study of national registry (UNOS) deceased donors referred for possible LT between 7/2020 and 6/2022. We collected donor demographic data, categorized each individual as a donor after cardiac death (DCD) or donor after brain death (DBD), and identified corresponding UNOS regions. Donors were classified as C19(+) or (-) based on a nucleic acid or antigen test within 21 days of referral or transplant. The primary outcome was donor utilization for LT versus discard. Logistic regression was used to identify variables associated with this outcome. **Results:** We identified 23,809 deceased donors classified as follows: 9,434 (40%) C19(-) discarded, 13,654 (57%) C19(-) transplanted, 379 (2%) C19(+) discarded, and 342 (1%) C19(+) transplanted. Referred donors had median age 41 years, 63% were white, median BMI was 27, and 32% were DCD. C19(+) donors were significantly more likely to be DCD than C19(-) donors (41% vs. 32%, $p < 0.001$). During the study period, for C19(+) donors, the ratio of transplanted to discarded livers increased monotonically, while for C19(-) donors, the ratio decreased (each $P_{\text{trend}} < 0.001$; Fig. 1). In multivariable logistic regression, donor utilization was inversely associated with donor age (adjusted

OR [aOR] = 0.98, 95% CI 0.98-0.99; $p < 0.001$), DCD versus DBD classification (aOR = 0.075, 95% CI 0.070-0.080; $p < 0.001$), donor BMI (aOR = 0.96, 95% CI 0.96-0.97; $p < 0.001$), and C19(+) status (aOR = 0.78, 95% CI 0.62-0.98; $p = 0.031$). There was no interaction between C19 infection and UNOS region ($p = 0.08$). However, an interaction was identified between C19 infection and DCD vs. DBD ($p = 0.005$) such that the impact of C19(+) increased the probability of discard more for DCD than DBD, relative to C19(-). **Conclusion:** Though utilization has increased over time, a large proportion of C19(+) organs are discarded, likely in part related to higher proportion of DCD status. However, C19(+) status remained independently associated with discard after adjusting for key donor characteristics, with a particularly strong effect in DCD vs. DBD. In view of literature demonstrating acceptable post-LT outcomes for C19(+) donors, our data suggest that potentially transplantable C19(+) organs are likely being discarded.



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1055-A | 18F-FAPI PET/CT CAN ACCURATELY EVALUATE THE EARLY-STAGE OF LIVER GRAFT FIBROSIS IN ADULT LT REPICIENTS

You wei Zhao[1], Xiaohan Fang[2], Man Xie[2,3], Jinzhen Cai[4], Guangjie Yang[5] and Wei Rao Sr.[6], (1)Division of Hepatology, Liver Disease Center, the Affiliated Hospital of Qingdao University, (2)Department of Gastroenterology, the Affiliated Hospital of Qingdao University, (3)The Affiliated Hospital of Qingdao University, (4)Department of Organ Transplantation, the Affiliated Hospital of Qingdao University, (5)Department of Nuclear Medicine, the Affiliated Hospital of Qingdao University, (6)Division of Hepatology, Liver Disease Center, the Affiliated Hospital of Qingdao University, Qingdao, 37, China

Background: To explore the value of Fluorine-18 labeled fibroblast activation protein inhibitor(^{18} F-FAPI) PET/CT in the assessment of early-stage graft fibrosis (S1-S2) after liver transplantation(LT). **Methods:** A total of 17 adult LT recipients (12 males and 5 females) were enrolled in this study. All patients received liver biochemistry, routine blood, coagulation, FibroScan, ^{18}F-FAPI-PET/CT and biopsy of liver graft. Then, the predicting values of four kinds of non-invasive methods including FIB-4, APRI, liver stiffness measurement (LSM) and maximum standardized uptake value (SUVmax), were compared in the evaluation of early-stage graft fibrosis. **Results:** Among the 17 adult LT recipients, 11 (64.7%) were in stage S0 fibrosis, 5 (29.4%) were in stage S1, and 1 (5.8%) was in stage S2. There were significant differences between LSM and SUVmax in early-stage hepatic fibrosis recipients and non-hepatic fibrosis recipients ($p = 0.04$; $p = 0.02$), while there was no significant difference in FIB-4 and APRI between the two groups ($p = 0.21$; $p = 0.92$). The critical value of LSM in predicting early-stage graft fibrosis was 8.2kPa and AUROC was 0.80 ($p = 0.012$), while the SUVmax was 2.0 and AUROC was 0.92 ($p = 0.006$). **Conclusion:** ^{18}F-FAPI PET/CT can accurately evaluate the early stage of liver graft fibrosis with higher diagnostic accuracy values than FibroScan, which is expected to be a new non-invasive diagnositic tool for adult LT repicients.

Disclosures: The following people have nothing to disclose: You wei Zhao, Xiaohan Fang, Man Xie, Jinzhen Cai, Guangjie Yang, Wei Rao

1056-A | A COMPLEX CASE OF POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER WITH MULTIPLE INTRACRANIAL HEMORRHAGES IN A LIVER TRANSPLANT RECIPIENT

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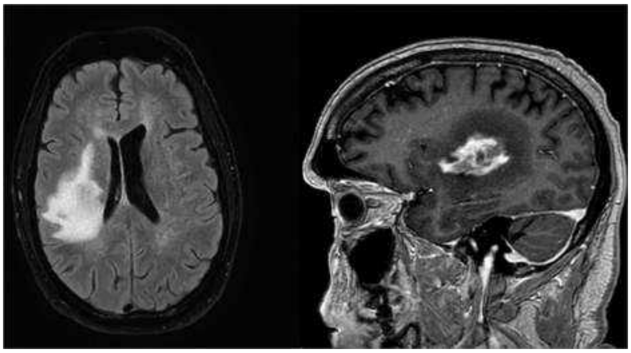
Background: Post-transplant lymphoproliferative disorder (PTLD) is a well-known complication of solid organ transplantation, often associated with Epstein-Barr virus (EBV) infection. Central nervous system

(CNS) PTLD is a rare manifestation, which can present with various neurological symptoms including intracranial hemorrhage. **Methods:** We report a 48-year-old male with a history of ulcerative colitis, primary sclerosing cholangitis, and liver transplantation who presented with multiple episodes of intracranial hemorrhage. The patient was maintained on tacrolimus and mycophenolate mofetil (MMF) for immunosuppression. Cerebrospinal fluid (CSF) analysis revealed elevated lymphocytes, low glucose, and high total protein, raising concerns for an inflammatory or malignant process. EBV DNA was not detected in the CSF, but the patient was EBV positive pre-transplant. Despite the lack of definitive tissue or cellular atypia, PTLD remained the top differential diagnosis. The patient's immunosuppression was reduced by stopping MMF, and he was started on a trial of rituximab. **Results:** Throughout his clinical course, the patient experienced multiple intracranial hemorrhages with worsening neurological symptoms, and progression of disease on MRI of the brain (*Figure 1*), ultimately leading to a brain mass biopsy. The biopsy revealed gliotic brain tissue, remote infarction, hemosiderin deposition, and lymphohistiocytic inflammation, but no definitive evidence of neoplastic or infectious processes. The patient's clinical course was complicated by post-dural puncture headaches, nausea, vomiting, and autonomic dysfunction. **Conclusion:** This case highlights the diagnostic challenges and management complexities of a presumed CNS PTLD in a liver transplant recipient with multiple intracranial hemorrhages. Despite the lack of definitive diagnostic findings, PTLD remained the most likely underlying etiology, and a multidisciplinary approach was critical in managing the patient's immunosuppression and neurological complications. This case underscores the need for further research and improved diagnostic strategies for CNS PTLD, as well as the importance of close monitoring and prompt intervention for neurological complications in transplant recipients.



Disclosures: The following people have nothing to disclose: Ahlam Alzoghoul, Umnia Shnawa, Mohammad Almeqdadi

1057-A | A DESCRIPTIVE ANALYSIS OF TWO UNITED STATES TRANSPLANT CENTERS' EXPERIENCE WITH HCV POSITIVE DONOR TO HCV NEGATIVE RECIPIENT LIVER TRANSPLANTATION

Raha Sadjadi[1], *Anudeep Neelam*[2], *Pooja Rangan*[1], *Ritwik Keshav*[1], *Giorgio A. Roccaro*[3] *and Karn Wijarnpreecha*[1], *(1)University of Arizona College of Medicine Phoenix, Phoenix, AZ, (2)Icahn School of Medicine at Mount Sinai Morningside/West, (3)Emory University School of Medicine*

Background: The liver donor pool continues to fall short of the demand for liver transplant (LT). The efficacy and safety of direct-acting antiviral agents (DAA) provides rationale for using hepatitis C virus (HCV) positive (+) donors to reduce this disparity. We describe two centers' experiences transplanting HCV + livers in to HCV negative (–) recipients with hopes of increasing utilization of HCV+ grafts for LT. **Methods:** This is a cohort study of patients who underwent LT at two transplant centers: Emory University Hospital and Banner University Medical Center Phoenix. For each center, data and outcomes were separately collected and compared between (1) LT recipients who received an HCV – graft and (2) HCV – LT recipients who received an HCV + graft. Emory data was prospectively collected from patients transplanted from 2019 – 2021. Phoenix data was retrospectively collected from patients transplanted from 2015 – 2022. We performed descriptive analyses to compare baseline demographics of the recipient and donor, immediate transplant related outcomes, and mortality in the first year following LT between HCV + and HCV – graft recipients at each center. Time to initiation of DAA in HCV+ LT recipients was also compared. **Results:** 732 LT recipients were analyzed, 112 (15.3%) from Emory and 620 (84.7%) from Phoenix. At both centers, there was no statistical difference between the group that received HCV – grafts and the group that received HCV + grafts in terms of recipient age at transplant, donor age, warm ischemic time, or graft failure/mortality in the first year following LT. In the Emory cohort, there was a statistically significant lower MELD at transplant in HCV – patients who received HCV + grafts and a shorter length of hospitalization after LT. The Emory cohort also trended towards a shorter cold ischemic time among patients who received HCV + LT. There was no difference between groups within these variables in the Phoenix cohort. Linear regression of the Emory cohort showed lower MELD at transplant drove the shorter hospital length of stay after LT. Median time to DAA at Emory was 2 days (vs 75 d at Phoenix). No Emory recipients of HCV+ grafts died. 5 HCV+ graft

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

recipients at Phoenix died from 2019 - 2020. Causes of death included (1) pneumonia, (2) graft failure/rejection, (3) metastatic angiosarcoma, (4) a combination of hemorrhagic shock, sepsis, and mesenteric ischemia with peritonitis, and (5) hemorrhagic shock. Only one of these deaths involved a donation after cardiac death graft. **Conclusion:** This multicenter experience shows that using HCV+ donors is not associated with worse immediate post-transplant outcomes or in one year post LT mortality. Our data supports widened use of HCV+ liver donors as standard practice.

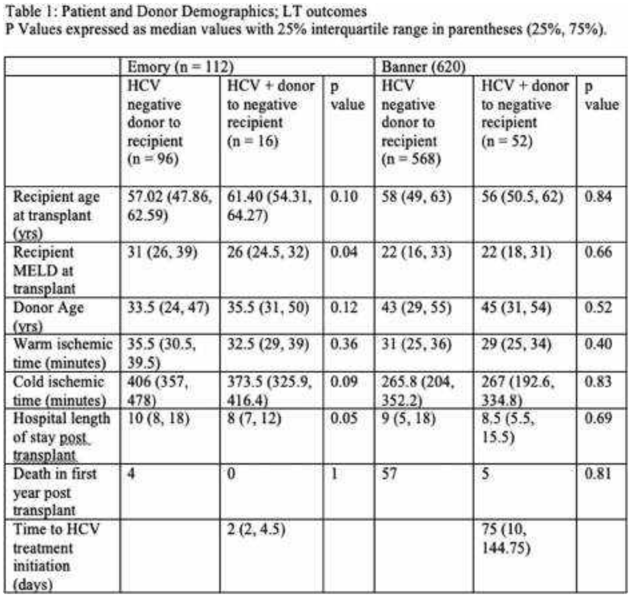


Table 1: Patient and Donor Demographics; LT outcomes
P Values expressed as median values with 25% interquartile range in parentheses (25%, 75%).

	Emory (n = 112)			Banner (620)		
	HCV negative donor to recipient (n = 96)	HCV + donor to negative recipient (n = 16)	p value	HCV negative donor to recipient (n = 568)	HCV + donor to negative recipient (n = 52)	p value
Recipient age at transplant (yrs)	57.02 (47.86, 62.59)	61.40 (54.31, 64.27)	0.10	58 (49, 63)	56 (50.5, 62)	0.84
Recipient MELD at transplant	31 (26, 39)	26 (24.5, 32)	0.04	22 (16, 33)	22 (18, 31)	0.66
Donor Age (yrs)	33.5 (24, 47)	35.5 (31, 50)	0.12	43 (29, 55)	45 (31, 54)	0.52
Warm ischemic time (minutes)	35.5 (30.5, 39.5)	32.5 (29, 39)	0.36	31 (25, 36)	29 (25, 34)	0.40
Cold ischemic time (minutes)	406 (357, 478)	373.5 (325.9, 416.4)	0.09	265.8 (204, 352.2)	267 (192.6, 334.8)	0.83
Hospital length of stay post transplant	10 (8, 18)	8 (7, 12)	0.05	9 (5, 18)	8.5 (5.5, 15.5)	0.69
Death in first year post transplant	4	0	1	57	5	0.81
Time to HCV treatment initiation (days)		2 (2, 4.5)			75 (10, 144.75)	

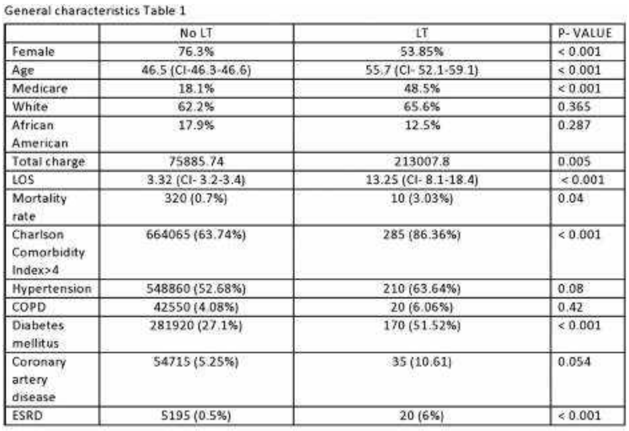
Disclosures: The following people have nothing to disclose: Raha Sadjadi, Ritwik Keshav, Giorgio A. Roccaro, Karn Wijarnpreecha

Disclosure information not available at the time of publication: Anudeep Neelam, Pooja Rangan

1058-A | BARIATRIC SURGERY OUTCOMES IN LIVER TRANSPLANT PATIENTS: INSIGHTS FROM THE NATIONAL INPATIENT SAMPLE (NIS)

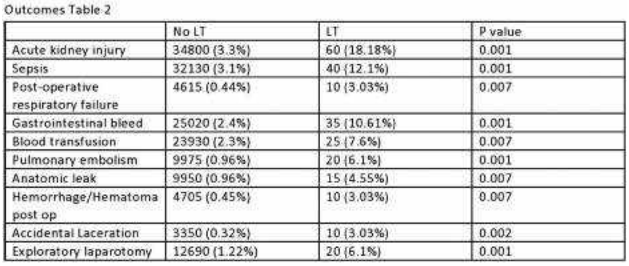
Mohamed Ahmed[1], Fouad Jaber[1], Ifrah Fatima[2], Saqr Alsakarneh[3], Islam Mohamed[3], Ahmed Elkafrawy[4] and Hassan Ghoz[1], (1)University of Missouri- Kansas City, (2)Univeristy of Missouri- Kansas City, Kansas City, MO, (3)University of Missouri-Kansas City, (4)University of Iowa Hospitals and Clinics

Background: Obesity, defined as a body mass index (BMI) > 30 kg/m2 is a worldwide epidemic. Bariatric surgery emerges as potential of cure however its safety in patients with Liver transplant (LT) remains understudied. The aim of this study is to evaluate outcomes of Bariatric surgery in LT patients. **Methods:** Patients hospitalized between 2016 and 2020 who were admitted for Bariatric surgery were identified using International Classification of Diseases Code,10th Revision Clinical Modification (ICD-10) identified from the Healthcare Cost and Utilization Project databases (HCUP) using the National inpatient sample (NIS). Patients with history of LT were compared to patients without LT. Bariatric surgeries included open and laparoscopic Roux-en-Y gastric bypass, open and laparoscopic sleeve gastrectomy, and biliopancreatic diversion-duodenal switch. **Results:** A total of 1042114 patients had Bariatric surgery, 330 (0.032%) patients had a history of LT. Mean age of the non-LT group was 46.5 (95% CI-46.3-46.6) years compared to 55.65 (95% CI- 52.1-59.1) years in the LT group. 76.3% of the non-LT group were females compared to 53.85% in the LT group. The mortality rate of the non-LT group was 0.7 % compared to 3.03% % in the other group ($p = 0.04$). Length of stay (LOS) was 3.32 (95% CI- 3.2-3.4) days in the non-LT group while it was 13.25 13.25 (95% CI-8.1-18.4) days in the LT group ($p < 0.01$). General characters are summarized in table 1. Univariate analysis showed that LT patients are more likely to have acute kidney injury (AKI), sepsis, GI bleed, need blood transfusion, pulmonary embolism, Anatomic leak and need Exploratory laparotomy (Table 2). Multivariate analysis adjusting for Age, Sex, primary payer, Race, Hospital bed size, hospital reaching status, hypertension, Diabetes and obstructive sleep apnea showed that LT does not increase mortality in patients undergoing Bariatric surgery (OR 0.0057, CI 0.0036-1.003), however it increases LOS (OR 6.49, CI 1.68-11.32). **Conclusion:** NASH is now the second leading etiology for LT in the United States and is predicted to become the first in short order. Recurrent NAFLD develops in 30%-60% of patients following LT which mean post-LT bariatric surgery incidence is likely to increase. While there is increase morbidities in this cohort of patients, it appears that mortality does not change significantly. There are some limitations in this study including inability to determine date of LT and long-term outcomes of Bariatric surgeries on weight loss.



General characteristics Table 1

	No LT	LT	P- VALUE
Female	76.3%	53.85%	< 0.001
Age	46.5 (CI-46.3-46.6)	55.7 (CI- 52.1-59.1)	< 0.001
Medicare	18.1%	48.5%	< 0.001
White	62.2%	65.6%	0.365
African American	17.9%	12.5%	0.287
Total charge	75885.74	213007.8	0.005
LOS	3.32 (CI- 3.2-3.4)	13.25 (CI- 8.1-18.4)	< 0.001
Mortality rate	320 (0.7%)	10 (3.03%)	0.04
Charlson Comorbidity Index>4	664065 (63.74%)	285 (86.36%)	< 0.001
Hypertension	548860 (52.68%)	210 (63.64%)	0.08
COPD	42550 (4.08%)	20 (6.06%)	0.42
Diabetes mellitus	281920 (27.1%)	170 (51.52%)	< 0.001
Coronary artery disease	54715 (5.25%)	35 (10.61)	0.054
ESRD	5195 (0.5%)	20 (6%)	< 0.001



Outcomes Table 2

	No LT	LT	P value
Acute kidney injury	34800 (3.3%)	60 (18.18%)	0.001
Sepsis	32130 (3.1%)	40 (12.1%)	0.001
Post-operative respiratory failure	4615 (0.44%)	10 (3.03%)	0.007
Gastrointestinal bleed	25020 (2.4%)	35 (10.61%)	0.001
Blood transfusion	23930 (2.3%)	25 (7.6%)	0.007
Pulmonary embolism	9975 (0.96%)	20 (6.1%)	0.001
Anatomic leak	9950 (0.96%)	15 (4.55%)	0.007
Hemorrhage/Hematoma post op	4705 (0.45%)	10 (3.03%)	0.007
Accidental Laceration	3350 (0.32%)	10 (3.03%)	0.002
Exploratory laparotomy	12690 (1.22%)	20 (6.1%)	0.001

Disclosures: The following people have nothing to disclose: Mohamed Ahmed, Fouad Jaber, Ifrah Fatima, Saqr Alsakarneh, Islam Mohamed, Ahmed Elkafrawy, Hassan Ghoz

1059-A | CHRONIC MYELOID LEUKEMIA IN A POST-LIVER TRANSPLANT PATIENT: A RARE COMPLICATION AND MANAGEMENT CHALLENGES

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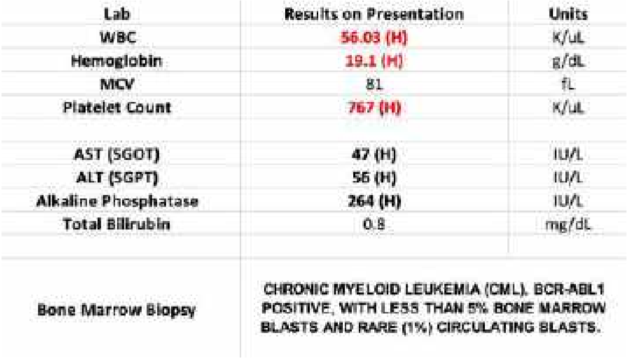
Background: Chronic myeloid leukemia (CML) is a rare complication in post-liver transplant recipients, with few cases reported in the literature. The optimal management of CML in this population remains a challenge due to potential drug interactions and adverse effects of tyrosine kinase inhibitors (TKIs) on liver function. **Methods:** We report a case of a 53-year-old male with a history of primary sclerosing cholangitis status post liver transplant in 2006, and ulcerative colitis status post total colectomy with ileostomy in place in 2008. The patient presented with worsening leukocytosis and was subsequently diagnosed with CML after confirmation of the 9;22 translocation and chronic phase disease on bone marrow biopsy (Table 1). The patient was initially started on dasatinib, but developed significant pericarditis and pericardial effusion, necessitating dose reduction and eventual discontinuation of the drug. Despite the known hepatotoxicity of TKIs, the patient's liver function remained stable on tacrolimus and prednisone immunosuppression. Further management options, including alternative TKIs such as imatinib or nilotinib, were considered in consultation with the transplant hepatology team. **Results:** This case highlights the rarity of CML as a complication in post-liver transplant patients and the challenges in managing these patients due to the potential adverse effects of TKIs on liver function and immunosuppression requirements. Previous case reports suggest that TKIs can be used in post-liver transplant patients without significant interaction with immunosuppressive agents, although hepatotoxicity remains a concern. In our patient, dasatinib was initially used, but ultimately discontinued due to significant pericarditis and pericardial effusion. The decision to switch to an alternative TKI will be based on a careful assessment of potential risks and benefits, with close monitoring of liver function and immunosuppression levels. **Conclusion:** CML in post-liver transplant patients is a rare complication with limited guidance on optimal management. This case highlights the importance of a multidisciplinary approach, including collaboration between hematology and transplant hepatology teams, to balance the potential benefits and risks of TKI therapy in this unique patient population. Further research is needed to better understand the safety and efficacy of TKI use in post-liver transplant patients with CML, as well as to establish best practices for managing these complex cases.



Lab	Results on Presentation	Units
WBC	56.03 (H)	K/uL
Hemoglobin	19.1 (H)	g/dL
MCV	81	fL
Platelet Count	767 (H)	K/uL
AST (SGOT)	47 (H)	IU/L
ALT (SGPT)	56 (H)	IU/L
Alkaline Phosphatase	264 (H)	IU/L
Total Bilirubin	0.8	mg/dL
Bone Marrow Biopsy	CHRONIC MYELOID LEUKEMIA (CML), BCR-ABL1 POSITIVE, WITH LESS THAN 5% BONE MARROW BLASTS AND RARE (1%) CIRCULATING BLASTS.	

Disclosures: The following people have nothing to disclose: Umnia Shnawa, Ahlam Alzoghoul, Mohammad Almeqdadi

f 1060-A | CLEVER-LG (CELL-FREE DNA METHYLATION WITH CLINICAL VARIABLES) FOR EARLY RECOGNITION OF LIVER GRAFT PATHOLOGY USING MACHINE LEARNING★

Soumita Ghosh[1], Cristina Baciu[1], Maryam Naghibzadeh[1], Amirhossein Azhie[2], Khairunnadiya Prayitno[1], Sara Naimimohasses[1], Sandra Elisabeth Fischer[3], Arya Rahmani[1], Elisa Pasini[1], Michael Brudno[4], Elmar Jäckel[1], Daniel De Carvalho[5] and Mamatha Bhat[3], (1)Ajmera Transplant Center, University of Toronto, Toronto, ON, Canada, (2) Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, (3)University of Toronto, (4)Department of Computer Science, University of Toronto, Toronto, on, Canada, (5)Princess Margaret Cancer Centre, University Health Network, Toronto, on, Canada

Background: Graft injury affects over 30% of Liver Transplant Recipients (LTRs) and the exact cause of injury can only be identified currently with a liver biopsy. Transplant recipients can develop graft injury due to various etiologies, such as T-cell mediated rejection (TCMR) and NASH (NASH-LT). The aim of our study was to develop a Machine Learning (ML) tool integrating clinical variables with methylation patterns on circulating DNA in plasma as a non-invasive diagnostic tool of graft pathology. **Methods:** We generated methylation profiles of circulating DNA in a pilot study of 43 LTRs (11 Non-alcoholic steatohepatitis (NASH-LT, 19 T-cell mediated rejection (TCMR), and 13 Control-LT), and developed an L2 regularized multinomial logistic regression ML approach across 101 bootstrapped models to distinguish between the graft conditions. NASH was associated with distinctive methylation patterns on genes involved in fatty acid metabolism, while activation of platelet-derived growth factors was identified in patients with TCMR. **Results:** Our ML models achieved a mean multi-classification accuracy of 0.91, with mean specificity and sensitivity of 0.94 and 0.91, respectively. Our models were found to be particularly adept at detecting TCMR and Control-LT, with mean true positive rates (TPRs) of 96% and 90%, respectively. For NASH-LT, the models achieved a performance with a mean TPR of 82%. Our one-vs-rest classification models achieved AUROCs of 0.992, 0.985 and 0.991 for TCMR, Control-LT and NASH-LT classes respectively. **Conclusion:** These results suggest that our ML tool, CleVER-LG, leveraging cell-free DNA methylation and clinical variables, is a promising non-invasive classifier of graft pathology in LTRs.

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Disclosure information not available at the time of publication: Cristina Baciu, Maryam Naghibzadeh, Amirhossein Azhie, Khairunnadiya Prayitno, Sara Naimimohasses, Arya Rahmani, Michael Brudno, Daniel De Carvalho

1061-A | CLINICAL FEATURES RELATED TO THE DEVELOPMENT OF NODULAR REGENERATIVE HYPERPLASIA POST LIVER TRANSPLANT: A CASE SERIES

Gabrielle Jutras[1], Isaac Ruiz[1], Genevieve Huard[2], Bich N. Nguyen[3], An Tang[3] and Julien Bissonnette[2], (1) Centre Hospitalier De L'université De Montréal, Montréal, QC, Canada, (2)Centre Hospitalier De l'Université De Montréal, (3)Centre Hospitalier De L'université De Montréal, Montréal, UT, Canada

Background: Nodular regenerative hyperplasia (NRH) is a rare hepatic condition that can occur before or after liver transplant (LT). It is defined by remodeling of the liver parenchyma in the form of nodules separated by trabeculae of atrophied hepatocytes. NRH has been associated with certain drugs and various hematologic and vascular conditions, but there is few data on the etiology, clinical course and prognosis in patient after liver transplantation. The aim of this study is to describe the characteristics of patients who developed a NRH after LT. **Methods:** This is a retrospective observational descriptive case series of all patients who developed a biopsy-proven NRH after LT at Centre Hospitalier de l'Université de Montréal (CHUM) between 2010 and 2020. **Results:** Of the 678 patients who underwent LT between 2010 and 2020, nine patients (1.3%) developed a NRH, of which 77.8% (7/9) were male. The mean age at LT was 57 (range 48-65). The indications for the liver transplant were decompensated cirrhosis due to alcohol (n = 1), metabolic-associated Fatty Liver Disease (MAFLD) (n = 2), primary sclerosing cholangitis (n = 3), primary biliary cirrhosis (n = 1) and acute liver failure (n = 1). The mean cold ischemia time was of 420 minutes [206-561]. The mean delay from LT to NRH diagnosis was 40 months [5-120]. At the time of diagnosis, 55.6% (5/9) were symptomatic for portal hypertension with the presence of ascites in 100% (5/5), splenomegaly in 80% (4/5) and/or esophageal varices in 40% (2/5). Only one patient had a history of azathioprine use prior to LT. Ischemic cholangiopathy was diagnosed in 66.7% (6/9) of patients with NRH, on average 21 months (range 3-46) before the diagnosis of NRH. The overall mortality rate in this cohort was 22.2% (2/9), and more precisely of 40% in symptomatic

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

patients compared with 0% in asymptomatic patients over a median follow-up of 47 months [3-124]. **Conclusion:** Our results suggest that ischemic cholangiopathy may be associated with the development of NRH after liver transplantation. To our knowledge, such an association has never been described in the literature. In addition, the mortality in symptomatic NRH patients seems to be is higher compare to asymptomatic patients. Further studies are needed to better examine these potential associations.

Disclosures: The following people have nothing to disclose: Gabrielle Jutras, Isaac Ruiz

Disclosure information not available at the time of publication: Genevieve Huard, Bich N. Nguyen, An Tang, Julien Bissonnette

f 1062-A | COGNITIVE IMPAIRMENT, FRAILTY, AND LIVER TRANSPLANT RECOVERY: EARLY RESULTS FROM LIVCOG, A PROSPECTIVE MULTICENTER COHORT

Marina Serper[1], Douglas Schaubel[2], Adwait Chafale[2], Alexander E Burdzy[2], Maria Blanco[2], Ann Tierney[2], Sumeet Asrani[3], Peter Reese[2], Julia Yoshino Benavente[4] and Michael S Wolf[4], (1)University of Pennsylvania, Philadelphia, PA, United States, (2) University of Pennsylvania, (3)Baylor University Medical Center, Dallas, TX, (4)Northwestern University

Background: Few studies in liver transplantation (LT) have comprehensively evaluated cognitive and physical health and how it affects post-transplant quality of life, function, and longitudinal health outcomes. The NIH-funded LivCog cohort study is enrolling 450 LT recipients at 4 transplant centers in Pennsylvania, Illinois, and Texas and their caregivers to comprehensively examine cognitive function, physical function and how those factors affect post-LT quality of life and health outcomes. **Methods:** All enrolled patients have detailed clinical data on demographics, comorbidity, and pre-LT liver disease severity. Serial post-LT assessments include global cognition (Montreal Cognitive Assessment [MoCA], the comprehensive NIH Toolbox (NIHTB) that tests working memory, executive function, attention, processing speed, and verbal ability, animal naming test [ANT], and patient-perceived every day cognition [ECOG]. Physical function is assessed with the liver frailty index (LFI). Health literacy is assessed with the newest vital sign (NVS). A novel LT knowledge (LTKQ) questionnaire tests relevant transplant knowledge (immunosuppression safety, lab timing, side effects, etc.). Correlations between cognitive and frailty measures were assessed with Spearman correlation coefficients. **Results:** We present baseline data on n = 89 recent LT recipients, predominantly within 1 month of LT. Median patient age is 56 (IQR: 43-62; 85% are White; 7% are Black; 1% are Asian; 9% are of Hispanic ethnicity. Prior to LT 32% had viral hepatitis, 25% had NAFLD/NASH and 39% had alcohol-associated liver disease (ALD). A total of 37% of patients were frail. Based on the MoCA (score < 26) or ANT (score < 14), 46% exhibited at least mild cognitive impairment. Using the NIHTB scores adjusted for age, sex, and education, significant impairment (defined as < 1 SD below U.S population norms) was noted for 34% for attention, 22% for processing speed, 25% for working memory, and 8% for episodic memory. A total of 28% reported significant cognitive concerns by the ECOG scale. 16% of LTRs had limited health literacy. A correlation matrix between cognitive measures and frailty is shown in Table 1. Global cognition (MoCA) exhibited significant negative correlations correlated with LFI scores, (e.g. higher frailty scores, lower cognitive function scores). However, using a more nuanced assessment of cognition (NIHTB), only the executive function and working memory domains significantly correlated with physical frailty. **Conclusion:** In early results, we document high prevalence of objective cognitive impairment, physical frailty, and self-reported cognitive concerns during early post-LT recovery. Cognitive impairment though associated with physical frailty is a distinct phenotype. The cohort will examine longitudinal cognitive, physical, and health outcome trajectories to identify distinct phenotypes of post-LT health and their predictive factors.

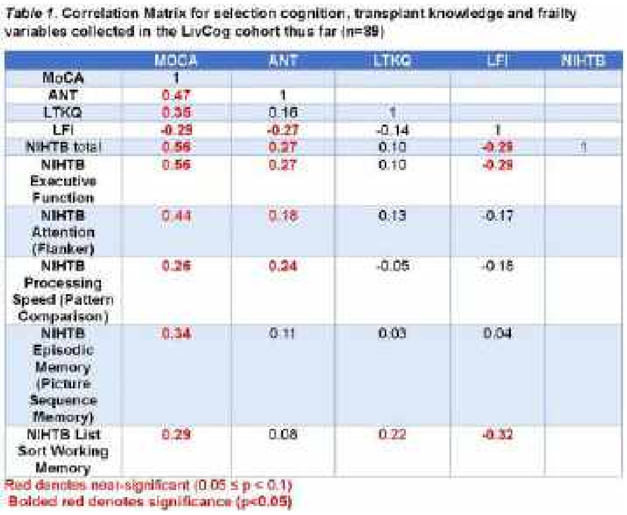

Table 1. Correlation Matrix for selection cognition, transplant knowledge and frailty variables collected in the LivCog cohort thus far (n=89)

	MOCA	ANT	LTKQ	LFI	NIHTB
MoCA	1				
ANT	0.47	1			
LTKQ	0.35	0.16	1		
LFI	-0.29	-0.27	-0.14	1	
NIHTB total	0.56	0.27	0.10	-0.29	1
NIHTB Executive Function	0.56	0.27	0.10	-0.29	
NIHTB Attention (Flanker)	0.44	0.18	0.13	-0.17	
NIHTB Processing Speed (Pattern Comparison)	0.26	0.24	-0.05	-0.18	
NIHTB Episodic Memory (Picture Sequence Memory)	0.34	0.11	0.03	0.04	
NIHTB List Sort Working Memory	0.29	0.08	0.22	-0.32	

Red denotes near-significant (0.05 ≤ p < 0.1)
Bolded red denotes significance (p<0.05)

Disclosures: Marina Serper – Grifols, SA: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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

Disclosure information not available at the time of publication: Douglas Schaubel, Adwait Chafale, Alexander E Burdzy, Maria Blanco, Ann Tierney, Peter Reese, Julia Yoshino Benavente, Michael S Wolf

1063-A | DE NOVO GASTRIC CANCER AFTER LIVER TRANSPLANT AND THE CLINICAL STRATEGY

Wei Rao Sr.[1], Qun Zhang[2], Tian Qiu-Ju[2], Zhang Bei[3], Jinzhen Cai[4] and Man Xie[5], (1)Division of Hepatology, Liver Disease Center, the Affiliated Hospital of Qingdao University, (2)The Affiliated Hospital of Qingdao University, (3)Qingdao University, (4)Department of Organ Transplantation, the Affiliated Hospital of Qingdao University, (5)Department of Gastroenterology, the Affiliated Hospital of Qingdao University

Background: De novo malignancies has gradually become the greatest threat for the long-time survival after liver transplantation. The aim of our study is to investigate the clinical manifestations of de novo gastric cancer in liver transplant (LT) recipients, identify the risk and to explore the optimized screening protocol **Methods:** Endoscopic screening was performed prospectively on LT recipients received regular follow-up in our center, endoscopic manifestation and the characteristic of de novo gastric cancer(DN-GC) was analyzed. **Results:** In total, 274 cases were enrolled, and10 cases (3.6%) of DN-GC were diagnosed. The cumulated incidence of DN-GC in 3 years ,5 years and 10 years after liver transplantation was 3.3%, 8.0% and 8.0%, respectively. 70% (7/10) of DN-GC was undifferentiated type and 80% (8/10) of them was diagnosed at early stage. The cumulated survival rate in 3 years ,5 years and 10 years among the LT recipient with DN-GC were 87.5%, 72.9% and 72.9% respectively, while those rate among the LT recipient without DN-GC were 98.8%, 97.4% and 96.3% respectively, significantly difference was observed($p = 0.004$). CAG was the only risk factor of DN-GC after liver transplantation (9/1 vs 90/174, $p = 0.003$, $X2 = 9.067$). 109 of recipient without DN-GC received twice gastroscopy and 85.3% (58/68) of the recipients with chronic superficial gastritis (CSG) in the first gastroscopy was consistently diagnosed to be CSG in the second one. 39 received third gastroscopy, and 83.3% (20/24) of the recipients with CSG in the second gastroscopy was consistently diagnosed to be CSG in the third one. **Conclusion:** The incidence of gastric cancer was significantly elevated after liver transplantation which could decrease the patient's long-term survival. CAG was the only risk factor of DN-GC and mucosal condition was relatively stable after liver transplantation, therefor, active endoscopic screening was highly recommended for the LT recipients with CAG.

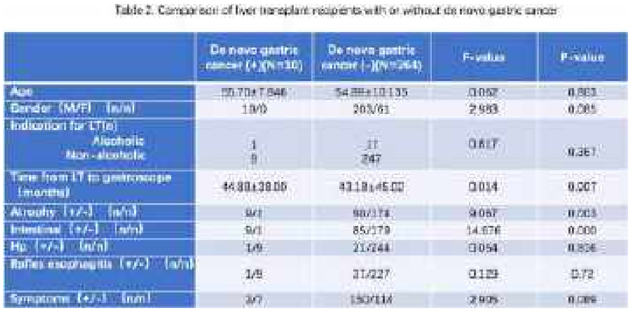


Table 2. Comparison of liver transplant recipients with or without de novo gastric cancer

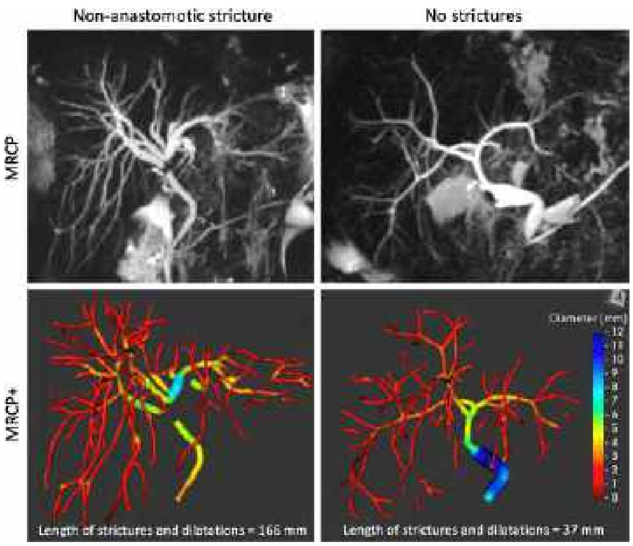
	De novo gastric cancer (+)(N=10)	De novo gastric cancer (-)(N=264)	F-value	P-value
Age	55.70±7.846	54.88±10.135	0.062	0.803
Gender (M/F) (n/n)	10/0	203/61	2.983	0.085
Indication for LT(n) Alcoholic Non-alcoholic	1 9	17 247	0.617	0.367
Time from LT to gastroscope (months)	46.80±38.06	43.18±45.02	0.014	0.907
Atrophy (+/-) (n/n)	9/1	90/174	9.067	0.003
Intestinal (+/-) (n/n)	9/1	85/179	14.676	0.000
Hp (+/-) (n/n)	1/9	21/244	0.054	0.816
Reflux esophagitis (+/-) (n/n)	1/8	37/227	0.129	0.72
Symptoms (+/-) (n/n)	3/7	150/114	2.905	0.088

Disclosures: The following people have nothing to disclose: Wei Rao, Qun Zhang, Tian Qiu-Ju, Zhang Bei, Jinzhen Cai, Man Xie

1064-A | DETECTION OF ANASTOMOTIC AND NON-ANASTOMOTIC STRICTURES USING QUANTITATIVE MRCP IN PATIENTS AFTER LIVER TRANSPLANTATION

Emmanuel Selvaraj[1], David Nasralla[2], Rajarshi Banerjee[3], John Karani[4], Arvind Pallan[5], Rutger Ploeg[1], Sara Upponi[6], Liam A. J. Young[3], Peter J. Friend[1] and Consortium for Organ Preservation in Europe (COPE), (1)University of Oxford, (2)Royal Free Hospital, (3) Perspectum Ltd., (4)King's College Hospital, (5)Queen Elizabeth Hospital, (6)Addenbrooke's Hospital

Background: Recent advances in machine perfusion technology using normothermic machine perfusion (NMP) instead of static cold storage (SCS) have reduced the insult to donor livers and improved post-transplant liver function. However in liver transplantation (LT), biliary complications remain a significant cause of morbidity and mortality. Patients with symptomatic biliary strictures often require intervention or re-transplantation. Early assessment and diagnosis of asymptomatic radiological strictures using magnetic resonance cholangiopancreatography (MRCP) may assist clinical decision making and allow evaluation whether NMP might reduce symptomatic biliary complications. Artificial intelligence-driven post-processing has enabled the quantitative assessment of MRCP and improved prognostication and monitoring of patients with biliary diseases. In this study, we studied the ability of quantitative MRCP to detect post-transplant biliary strictures. **Methods:** Patients in the COPE liver trial underwent a MRCP 6 months following LT with three radiologists performing a consensus read to detect anastomotic (AS) and non-anastomotic strictures (NAS). This study retrospectively processed the MRCP with MRCP+ (Perspectum Ltd, Oxford) to extract quantitative metrics. A principal component analysis (PCA) was performed to reduce the number of quantitative MRCP metrics considered. Differences between patients with and without strictures were assessed (Wilcoxon tests). Diagnostic accuracy was assessed with the area under the receiver operator curve (AUROC). **Results:** 86 LT recipients had a quantifiable post-LT MRCP (male sex = 71%, donation after circulatory death = 31%, NMP = 56%). Radiologists identified 7 cases of NAS and 46 cases of AS. PCA demonstrated two main components in the data, one quantifying localised strictures and dilatations and a second quantifying the average size of bile ducts of the biliary tree. The length of strictures and dilatations was the single metric most representative of both components and was higher in patients with NAS compared to those without strictures (150 mm [110-246] vs 42 mm [18-98], $p = 0.02$). The length of strictures and dilatations detected NAS with AUROC = 0.75 (0.52-0.99). Significant prediction of AS was also observed. **Conclusion:** This study shows good agreement between quantitative MRCP and consensus radiologist assessment for the detection of anastomotic and non-anastomotic strictures in LT recipients. The next step is to examine the potential of quantitative MRCP facilitating identification of clinically relevant strictures even earlier after LT.

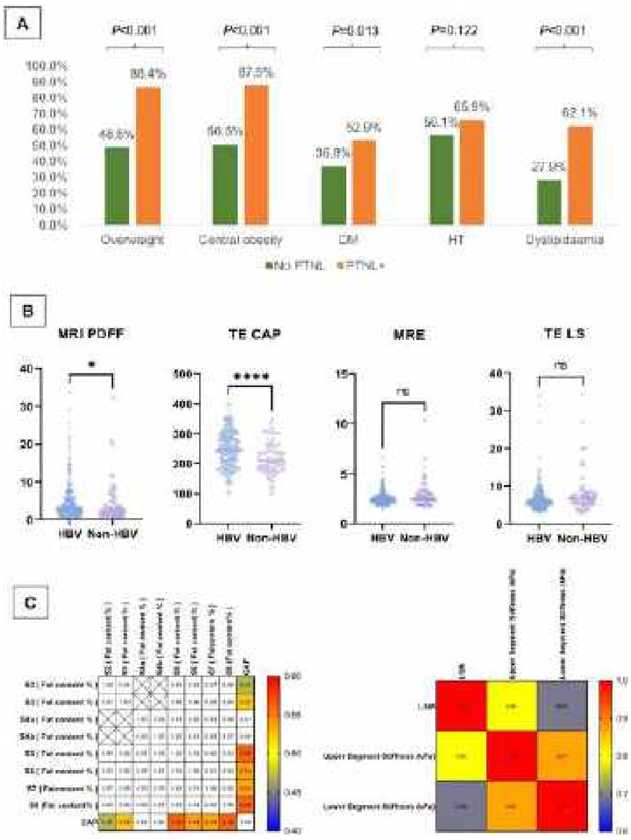

Non-anastomotic stricture
No strictures
MRCP
MRCP+
Diameter (mm)
12
11
10
9
8
7
6
5
4
3
2
1
0
Length of strictures and dilatations = 166 mm
Length of strictures and dilatations = 37 mm

Disclosures: Rajarshi Banerjee – Perspectum Ltd: Employee, Yes, No; Perspectum Ltd: Stock – privately held company (individual stocks and stock options), Yes, No;
Liam A. J. Young – Perspectum Ltd: Employee, Yes, No;
Disclosure information not available at the time of publication: Emmanuel Selvaraj, David Nasralla, John Karani, Arvind Pallan, Rutger Ploeg, Sara Upponi, Peter J. Friend

1065-A | DETECTION OF HEPATIC GRAFT STEATOSIS AND FIBROSIS AFTER LIVER TRANSPLANTATION USING MRI-PDFF & MRE TECHNIQUES

Lung Yi Mak[1], *James Fung*[1], *Gladys Lo*[2], *Christine Shing-Yen Lo*[2], *Trevor Kwan-Hung Wu*[3], *Tiffany Cho-Lam Wong*[3], *Albert Chi-Yan Chan*[3], *Wai-Kay Seto*[4] *and Man-Fung Yuen*[5], *(1)Department of Medicine, School of Clinical Medicine, the University of Hong Kong, Hong Kong SAR, (2)The Hong Kong Sanatorium and Hospital, (3)The University of Hong Kong, (4) Department of Medicine, School of Clinical Medicine, the University of Hong Kong, (5)State Key Laboratory of Liver Research, the University of Hong Kong, Hong Kong SAR*

Background: Although non-alcoholic fatty liver disease (NAFLD) is an uncommon indication for liver transplantation (LT) in Chinese, post-LT *de novo* NAFLD (PTNL) is increasingly observed, leading to graft dysfunction and fibrosis. We aimed to characterize PTNL and graft advanced fibrosis/cirrhosis (F3/F4) by magnetic resonance imaging (MRI) and transient elastography (TE) in subjects who underwent LT for non-NAFLD indications. **Methods:** Post-LT subjects were recruited for MRI and TE. MRI-proton density fat fraction (MRI-PDFF) and MR elastography (MRE) was performed using a 1.5 Tesla Optima 450W MR scanner with a 3D volumetric sequence. PTNL and F3/F4 was defined as MRI-PDFF e 5% and MRE e 3.64kPa, respectively. TE was performed by Fibroscan with controlled attenuation parameter (CAP) e 248 dB/m and liver stiffness (LS) values obtained. Graft dysfunction was defined as persistent alanine aminotransferase (ALT) e 40 U/L at e 2 consecutive measurements at follow-up (FU). **Results:** 293 subjects (70.3% male, median age at LT: 52.1) were recruited. The majority (73.4%) was transplanted for hepatitis B virus (HBV)-related complications. MRI was performed at a median time of 12.2 years post-LT. The median body mass index was 23.7 kg/m^2 (59.7% overweight), with 61.4%, 41.3%, 37.9% and 59% subjects having central obesity, diabetes, dyslipidemia and hypertension, respectively, and were present in a significantly higher proportion of patients with PTNL than without (Figure 1A). According to MRI criteria, PTNL and F3/F4 was present in 30% and 9.6%, respectively. HBV-LT was associated with higher MRI-PDFF than non-HBV-LT ($p = 0.023$) but not associated with MRE or LS values (Figure 1B). Graft dysfunction was seen in 10.7% subjects, which was associated with MRI-PDFF (OR 1.084, 95%CI 1.023-1.149, $p = 0.006$), and MRE (OR 1.437, 95%CI 1.022-2.020, $p = 0.037$). LS highly correlated with MRE (r = 0.69-0.80, $p < 0.001$; AUROC for F3/F4: 0.89), while CAP moderately correlated with MRI-PDFF ($r = 0.47$-0.56, $p < 0.001$; AUROC for PTNL: 0.83). TE measurements of CAP and LS correlated better with segments V-VIII (compared to segments II & III) and upper segment (compared to lower segment) on MRI, respectively (Figure 1C). **Conclusion:** MRI-PDFF and MRE identified a high prevalence of PTNL and F3/F4, associated with graft dysfunction and metabolic risk factors, among Chinese subjects transplanted for non-NAFLD. TE is more accurate for right hepatic lobe and upper segment measurement in the post-LT setting. Figure legend: (A) Prevalence of overweight, central obesity, diabetes mellitus, hypertension and dyslipidaemia among patients with and without PTNL. (B) MRI and TE parameters stratified by HBV-related LT or non-HBV related LT. (C) Heat map showing correlation between MRI and TE parameters.



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Man-Fung Yuen – Abbvie: Consultant, No, No; Aligos Therapeutics: Consultant, No, No; Antios Therapeutics: Consultant, No, No; Arbutus Biopharma: Consultant, No, No; Arrowhead Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Arrowhead Pharmaceuticals: Consultant, No, No; Assembly Biosciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Assembly Biosciences: Consultant, No, No; Clear B Therapeutics: Consultant, No, No; Dicerna Pharmaceuticals: Consultant, No, No; Finch Therapeutics: Consultant, No, No; Fujirebio Incorporation: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Fujirebio Incorporation: Consultant, No, No; GSK: Consultant, Yes, No; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences: Consultant, No, No; Immunocore: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Immunocore: Consultant, No, No; Janssen: Consultant, No, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Consultant, No, No; Roche: Speaking and Teaching, No, No; Sysmex Corporation: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck Sharp and Dohme: Consultant, No, No; Merck Sharp and Dohme: Speaking and Teaching, No, No; Vir Biotechnology: Consultant, Yes, No; Bristol Myers Squibb: Consultant, No, No; Springbank Pharmaceuticals: Consultant, No, No; Silverback Therapeutics: Consultant, No, No; Sysmex Corporation: Consultant, No, No; Bristol Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck Sharp and Dohme: Grant/Research

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Disclosure information not available at the time of publication: James Fung, Gladys Lo, Christine Shing-Yen Lo, Trevor Kwan-Hung Wu, Tiffany Cho-Lam Wong, Albert Chi-Yan Chan

1066-A | DOES LIVER TRANSPLANT STATUS AFFECT OUTCOMES OF PERCUTANEOUS ENDOSCOPIC GASTROSTOMY TUBE: INSIGHTS FROM THE NATIONAL INPATIENT SAMPLE (NIS)

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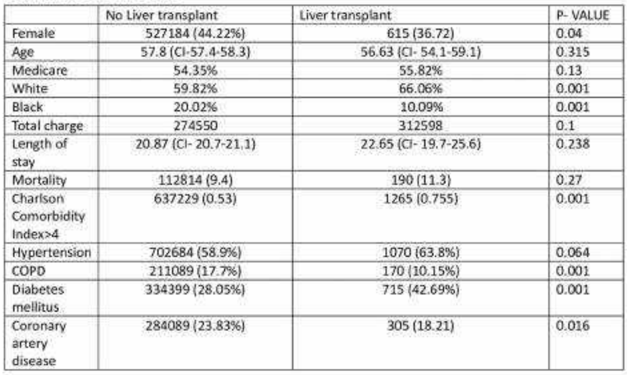
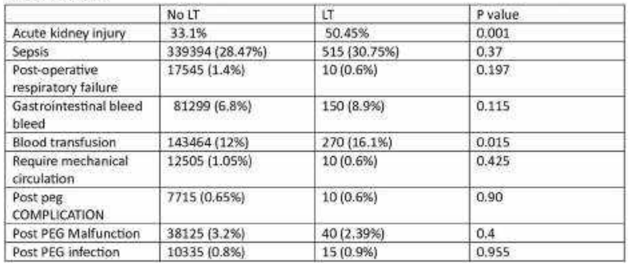
Background: Liver transplants (LT) is becoming increasingly common with 1 year survival year approaching 90%. The improved life expectancy means that eventually, those patients are more likely to need Percutaneous endoscopic gastrostomy (PEG). The data about outcomes of PEG tube insertion in LT patients are scarce. This study examines outcomes of PEG in LT patients. **Methods**: Patients hospitalized between 2016 and 2020 who were admitted for PEG tube insertion were identified using International Classification of Diseases Code,10th Revision Clinical Modification (ICD-10) identified from the Healthcare Cost and Utilization Project databases (HCUP) using the National inpatient sample (NIS). Patients with history of LT were compared to patients without LT. **Results:** A total of 1193990 patients required PEG tube insertion, 1675 patients had a history of LT. Mean age of the non-LT group was 57.8 years compared to 56.6 years in the LT group. 44.2% of the non-LT group were females compared to 36.7% in the LT group. The mortality rate of the non-LT group was 9.4% compared to 11.3% in the other group, however the difference was non-significant (0.27). Length of stay (LOS) was 20.87 (95% CI- 20.7-21.1) days in the non-LT group while it was 22.65 (95% CI- 19.7-25.6) in the LT group, again the difference was non-significant (0.23). Univariate analysis showed that LT patients are more likely to have acute kidney injury (AKI) (OR 2.05, CI 1.64-2.5) and need blood transfusion (OR 1.4, CI 1.06-1.84). Post PEG complications, malfunction and infections were similar in both groups (Table 2). Multivariate analysis adjusting for age, sex, LOS, Hypertension, COPD, Diabetes mellitus and coronary disease showed that LT does not increase mortality in patients undergoing PEG tube (OR 1.12, CI 0.78-1.61). **Conclusion:** To our knowledge this is the largest study looking at PEG tube outcomes in patients with history of LT. There appears to be no increase in mortality or LOS in this cohort. There is an increased risk of AKI and needing blood transfusion. This study is limited by inability to determine functional status of patients and other variables not coded in the NIS. Despite that, it appears that PEG tube is a safe procedure in patients with LT.

General characteristics Table 1



	No Liver transplant	Liver transplant	P- VALUE
Female	527184 (44.22%)	615 (36.72)	0.04
Age	57.8 (CI-57.4-58.3)	56.63 (CI- 54.1-59.1)	0.315
Medicare	54.35%	55.82%	0.13
White	59.82%	66.06%	0.001
Black	20.02%	10.09%	0.001
Total charge	274550	312598	0.1
Length of stay	20.87 (CI- 20.7-21.1)	22.65 (CI- 19.7-25.6)	0.238
Mortality	112814 (9.4)	190 (11.3)	0.27
Charlson Comorbidity Index>4	637229 (0.53)	1265 (0.755)	0.001
Hypertension	702684 (58.9%)	1070 (63.8%)	0.064
COPD	211089 (17.7%)	170 (10.15%)	0.001
Diabetes mellitus	334399 (28.05%)	715 (42.69%)	0.001
Coronary artery disease	284089 (23.83%)	305 (18.21)	0.016

Outcomes Table 2



	No LT	LT	P value
Acute kidney injury	33.1%	50.45%	0.001
Sepsis	339394 (28.47%)	515 (30.75%)	0.37
Post-operative respiratory failure	17545 (1.4%)	10 (0.6%)	0.197
Gastrointestinal bleed bleed	81299 (6.8%)	150 (8.9%)	0.115
Blood transfusion	143464 (12%)	270 (16.1%)	0.015
Require mechanical circulation	12505 (1.05%)	10 (0.6%)	0.425
Post peg COMPLICATION	7715 (0.65%)	10 (0.6%)	0.90
Post PEG Malfunction	38125 (3.2%)	40 (2.39%)	0.4
Post PEG infection	10335 (0.8%)	15 (0.9%)	0.955

Disclosures: The following people have nothing to disclose: Mohamed Ahmed, Ifrah Fatima, Fouad Jaber, Khaled Elfert, Saqr Alsakarneh, Islam Mohamed, Alisa Likhitsup

f 1067-A | EARLY HOSPITALIZATION FOR ACUTE KIDNEY INJURY AFTER LIVER TRANSPLANTATION IS AN INDEPENDENT RISK FACTOR FOR DE NOVO END-STAGE RENAL DISEASE★

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Background: Liver transplant (LT) recipients frequently suffer acute kidney injury (AKI). However, the clinical significance of these events with respect to long-term renal outcomes, such as *de novo* end-stage renal disease (ESRD), is not well established. **Methods:** This was a retrospective cohort study using Medicare claims data that were linked to the Organ Procurement and Transplantation Network database. All first LT alone recipients between 1/1/07-12/31/2016 were identified. Hospitalizations for AKI (+/- hemodialysis) and *de novo* ESRD (defined as new onset ESRD e 90 days post-LT) were identified using validated International Classification of Diseases 9/10 and Common Procedure Terminology codes. Multivariable Cox proportional hazards models evaluated the factors independently associated with (i) AKI hospitalization in the first year and (ii) *de novo* ESRD. Patients were censored at death, retransplantation, or end of follow-up. **Results:** The cohort included 11,326 LT recipients and was 64.0% male, 71.9% non-Hispanic White, 8.1% Black, 14.7% Hispanic with median age of 61 years (IQR 54-66). The most common listing reasons were Hepatitis C (36.3%), non-alcoholic steatohepatitis (14.5%), and alcohol-associated liver disease (21.7%). Median follow-up was 4.7 years (IQR 2.8-7.0). Overall, 5,594 AKI hospitalizations within 1-year post-LT were identified among n = 3,282 (29.0%) recipients, with 11.5% of these admissions warranting hemodialysis. Of patients not on hemodialysis pre-LT (n = 10,610), 809 (7.6%) developed *de novo* ESRD at a median 1.9 years (IQR 0.8-3.4) from LT. Black race ($p = 0.047$), eGFR < 90mL/min/1.73m^2 at LT ($p < 0.001$), diabetes ($p < 0.001$), severity of portal hypertension ($p < 0.001$), and receipt of organ procured after circulatory death ($p = 0.001$) were independently associated with an increased risk of early AKI hospitalization, while female sex ($p = 0.042$) and increasing center LT volume ($p < 0.001$) were associated with a decreased risk (Table). Patients with one readmission for AKI in the first year experienced a 63% increase in the risk *de novo* ESRD post-LT, while that of patients with e 2 was nearly 3-fold greater (Table). **Conclusion:** Nearly one-third of LT recipients were hospitalized at least once for AKI in the first year post-LT, which was in turn an independent risk factor for *de novo* ESRD. Strategies that help mitigate the risk of early AKI hospitalization, even for patients with mild renal dysfunction at LT, could therefore have the potential to reduce the long-term morbidity and mortality associated with post-LT ESRD.

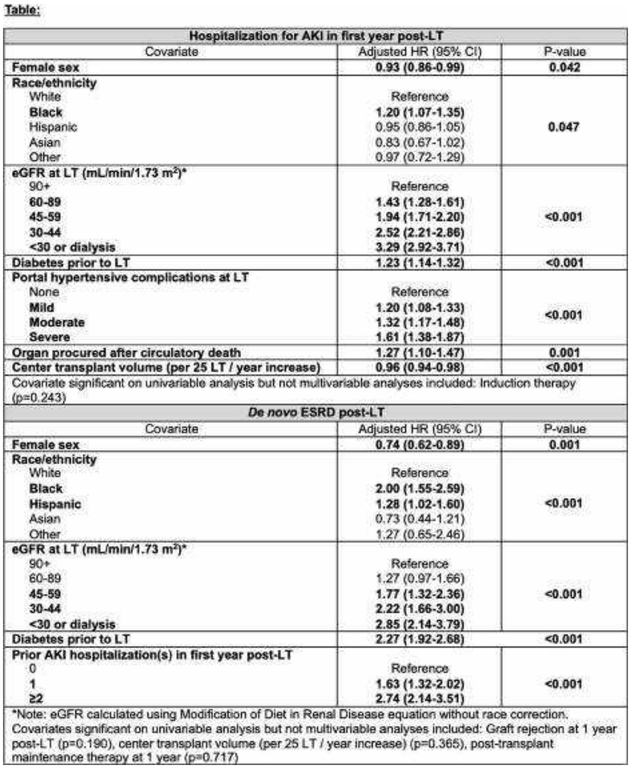

Table:

Hospitalization for AKI in first year post-LT

Covariate	Adjusted HR (95% CI)	P-value
Female sex	**0.93 (0.86-0.99)**	**0.042**
Race/ethnicity		**0.047**
White	Reference	
Black	**1.20 (1.07-1.35)**	
Hispanic	0.95 (0.86-1.05)	
Asian	0.83 (0.67-1.02)	
Other	0.97 (0.72-1.29)	
eGFR at LT (mL/min/1.73 m²)*		**<0.001**
90+	Reference	
60-89	**1.43 (1.28-1.61)**	
45-59	**1.94 (1.71-2.20)**	
30-44	**2.52 (2.21-2.86)**	
<30 or dialysis	**3.29 (2.92-3.71)**	
Diabetes prior to LT	**1.23 (1.14-1.32)**	**<0.001**
Portal hypertensive complications at LT		**<0.001**
None	Reference	
Mild	**1.20 (1.08-1.33)**	
Moderate	**1.32 (1.17-1.48)**	
Severe	**1.61 (1.38-1.87)**	
Organ procured after circulatory death	**1.27 (1.10-1.47)**	**0.001**
Center transplant volume (per 25 LT / year increase)	**0.96 (0.94-0.98)**	**<0.001**
Covariate significant on univariable analysis but not multivariable analyses included: Induction therapy (p=0.243)		

***De novo* ESRD post-LT**

Covariate	Adjusted HR (95% CI)	P-value
Female sex	**0.74 (0.62-0.89)**	**0.001**
Race/ethnicity		**<0.001**
White	Reference	
Black	**2.00 (1.55-2.59)**	
Hispanic	**1.28 (1.02-1.60)**	
Asian	0.73 (0.44-1.21)	
Other	1.27 (0.65-2.46)	
eGFR at LT (mL/min/1.73 m²)*		**<0.001**
90+	Reference	
60-89	1.27 (0.97-1.66)	
45-59	**1.77 (1.32-2.36)**	
30-44	**2.22 (1.66-3.00)**	
<30 or dialysis	**2.85 (2.14-3.79)**	
Diabetes prior to LT	**2.27 (1.92-2.68)**	**<0.001**
Prior AKI hospitalization(s) in first year post-LT		**<0.001**
0	Reference	
1	**1.63 (1.32-2.02)**	
≥2	**2.74 (2.14-3.51)**	
*Note: eGFR calculated using Modification of Diet in Renal Disease equation without race correction. Covariates significant on univariable analysis but not multivariable analyses included: Graft rejection at 1 year post-LT (p=0.190), center transplant volume (per 25 LT / year increase) (p=0.365), post-transplant maintenance therapy at 1 year (p=0.717)		

Disclosures: The following people have nothing to disclose: Ranganath G. Kathawate, Therese Bittermann

1068-A | EFFECT OF AORTIC STENOSIS ON INTRA-OPERATIVE HEMODYNAMICS AND OUTCOMES IN LIVER TRANSPLANTATION

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Background: The specific hemodynamic effects and outcomes related to aortic stenosis (AS) in patients with cirrhosis and portal hypertension who undergo liver transplant (LT) surgery are not well known. Our aim was to investigate how severity of AS may alter intra-operative hemodynamics among liver transplant candidates during liver transplant surgery. **Methods:** We performed a case-control study using a retrospective cohort of consecutive patients with AS who underwent LT at the Baylor Simmons Transplant Institute between

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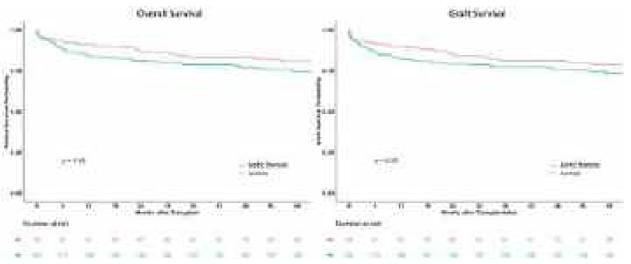
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

2010 and 2019. All patients underwent echocardiography pre-operatively. Severity of AS was defined by ASE echocardiographic criteria. Cases were matched 2:1 to controls without AS who underwent LT. Propensity score matching of cases to controls was performed by baseline covariates: age, MELD-Na, and gender. Patients who underwent definitive treatment of AS preoperatively by transcatheter replacement (TAVR) were excluded from analysis. **Results:** Overall, 106 patients with AS who underwent LT were identified; 90 (84.9%) had mild, 14 (13.2%) had moderate, and 2 (1.9%) had severe AS. Pre-operative TAVR was performed in 6 patients, including the 2 with severe AS. Compared with mild AS (n = 89), patients with moderate AS (n = 11) had lower post-bypass central venous pressure (CVP) (4 vs 7.5 mmHg, $p = 0.05$) and higher post-reperfusion arterial diastolic pressure (ADP) (65 vs 47 mmHg, $p = 0.009$) and mean arterial pressure (MAP) (79.5 vs 68.5 mmHg, $p = 0.035$). Compared with controls (n = 200), patients with AS had higher cardiac output (CO) at baseline (8.1 vs 7 L/min, $p = 0.02$) and post-bypass (8.0 vs 6.1 L/min, $p = 0.003$), lower systemic vascular resistance (SVR) at baseline (523.5 vs. 695 dyn/s/cm^{-5}, $p = 0.001$) and post-bypass (651 vs. 850 dyn/s/cm^{-5}, $p = 0.03$), and lower ADP post-reperfusion (47.5 vs. 52 mmHg, $p = 0.05$). Among our cohort of patients selected for LT, no difference in overall or graft survival was observed between AS vs controls (Figure, $p = \text{NS}$). Likewise, severity of AS defined by mild vs moderate was not associated with differences in overall or graft survival ($p = \text{NS}$). **Conclusion:** Liver transplant candidates with AS may demonstrate variations in intra-operative hemodynamics according to presence and severity of AS. Those with moderate AS appear to manifest higher diastolic pressure post liver transplant, while hemodynamic changes vs controls likely reflect compensatory changes in systemic vasodilation related to AS and underlying portal hypertension. In contrast with mild AS, selected candidates with moderate/severe AS may require additional evaluation and management to ensure these hemodynamic changes do not impact overall or graft survival.



Disclosures: James F. Trotter – hepquant: Advisor, No, No;

Stevan A. Gonzalez – Mallinckrodt Pharmaceuticals: Consultant, No, Yes; Mallinckrodt Pharmaceuticals: Speaking and Teaching, No, No; Salix Pharmaceuticals: Speaking and Teaching, No, Yes;

The following people have nothing to disclose: Seyed Khalafi, Mohanakrishnan Sathyamoorthy, Amar Gupta, Sumeet Asrani

1069-A | EFFECT OF DESENSITIZATION PROTOCOL ACCORDING TO THE DEGREE OF AMR RISK IN LIVING DONOR LIVER TRANSPLANT; RETROSPECTIVE COHORT STUDY

Jiyoon Kim[1], Sooho Kim[1], Minseo Jung[1], Ju Hyun Park[1], Nam-Joon Yi[1], Jeong-Moo Lee[1], Su Young Hong[1], Suk Kyun Hong[1], Kwang-Woong Lee[1], Kyung-Suk Suh[2] and YoungRok Choi[3], (1)Seould National University Hospital, (2)Seoul National University, (3) Seoul National University Hospital

Background: Graft failure associated with donor specific antibody (DSA) is rare but consistent in living donor liver transplant (LDLT). This study aims to analyze the outcomes of desensitization protocol according to the preoperative antibody mediate rejection (AMR) risk. **Methods:** We reviewed 998 cases of LDLT between January 1, 2012 and December 31, 2021 retrospectively. The desensitization treatment was protocolized for three different risk groups based on crossmatching(CDC), flow cytometry cross-matching (FCXM), and single antigen DSA test results: Rituximab + plasma pheresis for high risk (all positive), Rituximab only for intermediate risk (CBC-, FCXM+, DSA+), no treatment for low risk (only DSA+). The graft and patient survival of those retrospective cohort were analyzed. **Results:** From 640 ABO compatible cases there were 292(45.6%) and 348(54%) cases each before and after desensitization treatment was protocolized, with 2 (0.7%) and 4(1.1%) incidents of AMR respectively. From 69 cases with DSA test results, 20(29.0%) received Rituximab + plasma pheresis, 17(24.6%) received Rituximab only, and 32(46.4%) received no treatment. Number of cases in higher AMR risk group increased after protocol initiation($p = 10^{-8}$), while AMR risk did not show any significant difference($p = 0.69$). **Conclusion:** AMR incidence remaining relatively similar despite the significant increase in number of high-risk group recipients post protocol initiation, suggests that the desensitization treatment is effective. While we were not able to isolate the effects of treatments due to the limited number of patients with DSA test results, we were able to analyze various factors in relation to AMR. Studies including larger number of cases are needed to prove the necessity of desensitization protocol in clinical settings.

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Disclosure information not available at the time of publication: Sooho Kim, Minseo Jung, Ju Hyun Park, Nam-Joon Yi, Jeong-Moo Lee, Su Young Hong, Suk Kyun Hong, Kwang-Woong Lee, Kyung-Suk Suh

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

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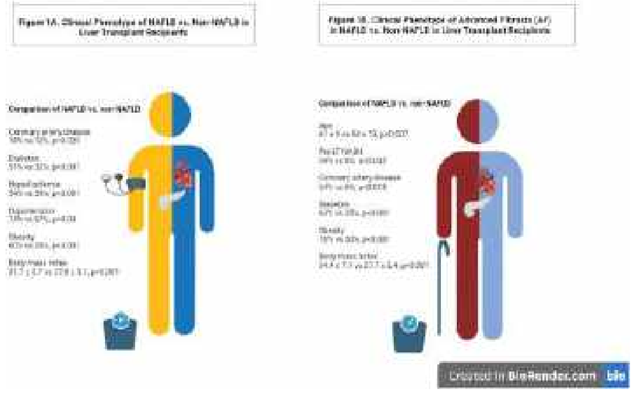
Background: Occurrence of nonalcoholic fatty liver disease (NAFLD) after liver transplantation (LT) is becoming increasingly common. While pre-LT NAFLD is associated with metabolic syndrome, the clinical phenotype of NAFLD and advanced fibrosis in LT recipients is not as well defined despite exposure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



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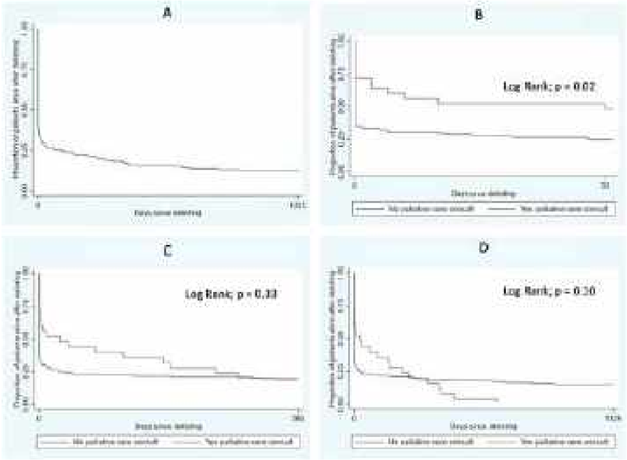
1071-A | END-OF-LIFE CARE FOR PATIENTS WITH END-STAGE LIVER DISEASE REMOVED FROM THE LIVER TRANSPLANT WAIT LIST

Danny Belza[1], Dhruval Amin[1], Anne Foley[1], Peter Lazar[2], Hye Sung Min[2], Neil Marya[2] and Navine Nasser-Ghodsi[2], (1)University of Massachusetts Memorial Health Care, (2)UMass Chan Medical School

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

Figure 1A-D. Kaplan-Meier estimates demonstrating survival of study patients. Panel A reflects overall study survival for the entire study cohort during the study period. Panels B-D demonstrate survival for patients with or without a palliative care consultation at 30 days (B), 365 days (C), and at the end of the study period (D).



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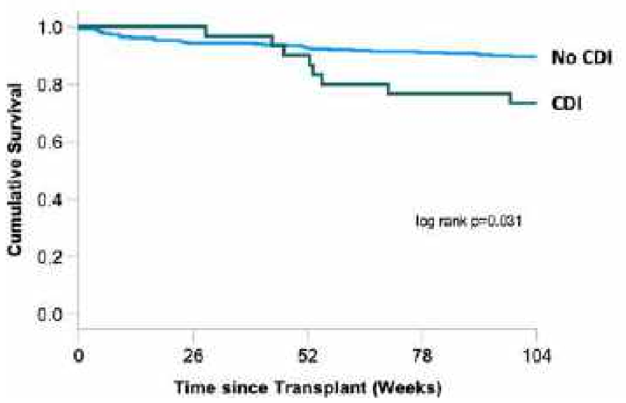
Disclosure information not available at the time of publication: Dhruval Amin, Anne Foley, Peter Lazar, Hye Sung Min, Neil Marya

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

Ahmed Mostafa Ibrahim[1], Ammad Javaid Chaudhary[1], Hope Baldwin[2], Arif Sarowar[2], Muhammad Zarrar Khan[3] and Syed-Mohammed Jafri[4], (1)Henry Ford Hospital, (2)Wayne State University School of Medicine, (3)Henry Ford Hospital, Detroit, MI, (4)Henry Ford Health System

Background: Of the multiple infections that liver transplant (LT) patients are vulnerable to, Clostridium difficile infection (CDI) is among the few that are potentially life-threatening. The incidence of CDI in this population generally ranges from 3-9%, with reports of rates as high as 30% in the literature. Risk of CDI is particularly high during the first year post-transplant when high-intensity immunosuppressive regimens are used in order to prevent transplant rejection. Despite this, information regarding factors affecting CDI occurrence in LT specifically is limited. Thus, this study aims to investigate the rate of CDI within 1 year of LT and assess for factors affecting these rates. We also intend to compare outcomes in LT occurring prior to and during the COVID-19 pandemic to evaluate for differences in the setting of heightened attention to hygiene associated with the pandemic. **Methods:** Adults (> 18 y old) who underwent LT within our health system between January 2018 and December 2021 were included in our study. Demographic (age, race, gender) and transplant-related data (transplant indication, MELD at transplant, rejection episodes) was compared between patients with and without CDI occurrence within the first year of LT. Furthermore, patients were divided into pre-COVID and COVID groups (transplants occurring in 2018 and 2020, respectively) to assess for a relationship between CDI occurrence and timing of LT with respect to the COVID pandemic. **Results:** Of the 365 LT patients included, 30 (8.2%) had a CDI event. The mean age for those with CDI was 58.73 ± 9.16 years and 17 cases (56.6%) were men. Of the 30 patients who had CDI, 13 (43.3%) had a rejection episode within 12 months of transplant. There was no statistically significant difference in terms of demographics, mean MELD score, or indication for transplant between patients with and without CDI. However, mortality rate was significantly higher in patients with CDI within 1 year of transplant compared to those without CDI (26.7% vs 12.8%, $p = 0.031$). Regarding outcomes in relation to the COVID pandemic, 9 of 81 (11.1%) patients in the pre-COVID group had CDI compared to 4 of 95 (4.2%) in the COVID group, although the difference did not reach statistical significance ($p = 0.081$). Furthermore, mortality within 1 year of transplant was higher in patients with CDI in the pre-COVID group compared to those with CDI in the COVID group (3/9 vs 0/4). **Conclusion:** Our results show a significantly higher mortality rate in patients with CDI compared to those without, underlining the devastating nature of this infection, particularly in the LT population. We also saw that a large portion of patients with CDI had at least one rejection episode within 12 months of transplant. Finally, there was a marked reduction in the occurrence of CDI within the first year following LT during the COVID era, possibly owing to the intensification of hygiene practices during this time period.

Figure 1. Kaplan-Meier curve showing the relation between C difficile infection within 1 year of liver transplant and survival over time

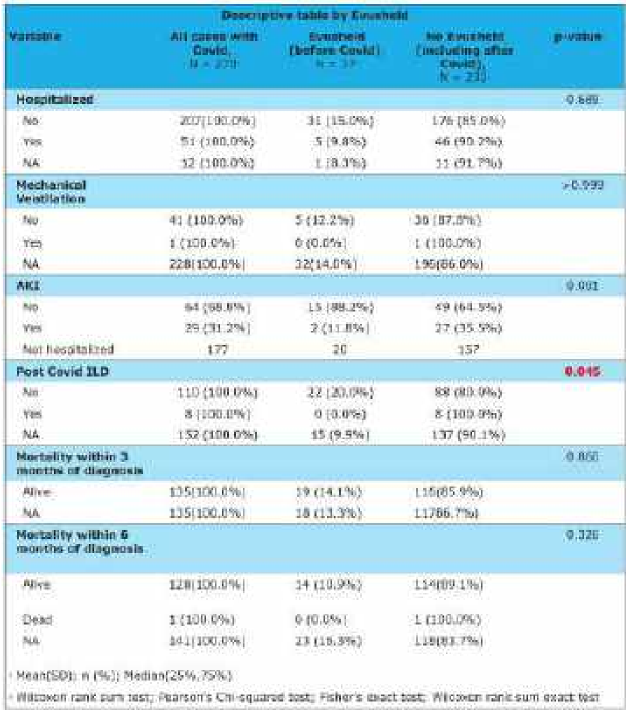


Disclosures: The following people have nothing to disclose: Ahmed Mostafa Ibrahim, Ammad Javaid Chaudhary, Syed-Mohammed Jafri
Disclosure information not available at the time of publication: Hope Baldwin, Arif Sarowar, Muhammad Zarrar Khan

1073-A | EVUSHELD IN LIVER AND KIDNEY TRANSPLANT PATIENTS – WAS IT WORTH IT?

Ammad Javaid Chaudhary[1], Hamna Fahad[1], Momin Samad[2], Sheema Rehman[2], Hope Baldwin[3], Ashley Francis[4], Fariba Rana[4], Yervant Ichkhanian[2], Diana Jomaa[5], Kartik Gupta[2] and Syed-Mohammed Jafri[6], (1) Henry Ford Hospital, Detroit, (2)Henry Ford Hospital, (3) Wayne State University School of Medicine, (4)Wayne State University, (5)Henry Ford Hospital, Detroit, Dearborn, MI, (6)Henry Ford Health System

Background: Immunosuppression in patients with solid organ transplant has raised significant concerns regarding outcomes of COVID-19 infection. Pre-exposure use of monoclonal antibodies, specific to certain viral strains as an adjunct to vaccination has been proposed to enhance the immune response following the vaccine. In this study, we aimed to assess the efficacy of the emergency use of Evusheld in this sub-population. **Methods:** This was a retrospective chart review study conducted at a tertiary care center during the time period of 2022 – 2023 during which adult patients (age > 18 y old) with liver, kidney or simultaneous Liver-Kidney transplant who received Evusheld were included. Patients' demographics, disease characteristics, and outcomes were recorded in de-identified datasheets. The primary outcome was incidence of COVID-19 positive PCR test. Secondary outcomes included: progression to Interstitial lung disease (ILD), rate of hospitalization. The Wilcoxon rank sum test, Pearson's Chi-squared test, Fisher's exact test and Wilcoxon rank sum exact test were used for univariate analyses. **Results:** Among 1149 who received solid organ transplant, 273 (23.7%) patients were diagnosed with COVID-19 from the advent of the pandemic, to February 2023. Patients infected with COVID-19 were more likely to be younger (mean age 61.6 ± 10.9 y versus 63.4 ± 11.5 y, $p = 0.007$), of white race (25.6% versus black 15.2 % and others 14.7 %, $p = 0.014$). In the total population 26% (296) received Evusheld. Among those who received Evusheld the incidence of covid was 13% (37/296) compared to 28% (236/853) in the patients who did not receive the Evusheld, $p < 0.01$. Data for post covid ILD was available in only 43.7% (118) patients. Among those with data available, prevalence of post covid ILD was 0%(0/22) and 8.1% (8/96) among those who did and did not receive evusheld respectively, p-value 0.045. Among those with data available, 16.1% (5/31) patients were hospitalized after getting Evusheld as compared to 20.7% (46/176) in patients who did not receive evusheld, $p = 0.689$. **Conclusion:** Our data shows that Evusheild may have reduced incidence of COVID-19 and provided significant protection against post infectious ILD. It also showed that incidence of COVID-19 in post-transplant patients may be much higher than previously reported. Currently, the FDA has halted all use of Evusheild due to the combined frequency of non-susceptible SARS-CoV-2 variants nationally being more than 90%. However, they do recommend keeping the unexpired batches safe for future, in case new variants show susceptibility.



Descriptive table by Evusheld

Variable	All cases with Covid, N = 270	Evusheld (before Covid) N = 37	No Evusheld (including after Covid), N = 233	p-value
Hospitalized				0.689
No	207(100.0%)	31 (15.0%)	176 (85.0%)	
Yes	51 (100.0%)	5 (9.8%)	46 (90.2%)	
NA	12 (100.0%)	1 (8.3%)	11 (91.7%)	
Mechanical Ventilation				>0.999
No	41 (100.0%)	5 (12.2%)	36 (87.8%)	
Yes	1 (100.0%)	0 (0.0%)	1 (100.0%)	
NA	228(100.0%)	32(14.0%)	196(86.0%)	
AKI				0.001
No	64 (68.8%)	15 (88.2%)	49 (64.5%)	
Yes	29 (31.2%)	2 (11.8%)	27 (35.5%)	
Not hospitalized	177	20	157	
Post Covid ILD				0.045
No	110 (100.0%)	22 (20.0%)	88 (80.0%)	
Yes	8 (100.0%)	0 (0.0%)	8 (100.0%)	
NA	152 (100.0%)	15 (9.9%)	137 (90.1%)	
Mortality within 3 months of diagnosis				0.860
Alive	135(100.0%)	19 (14.1%)	116(85.9%)	
NA	135(100.0%)	18 (13.3%)	117(86.7%)	
Mortality within 6 months of diagnosis				0.326
Alive	128(100.0%)	14 (10.9%)	114(89.1%)	
Dead	1 (100.0%)	0 (0.0%)	1 (100.0%)	
NA	141(100.0%)	23 (16.3%)	118(83.7%)	

[1] Mean(SD); n (%); Median(25%,75%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum exact test

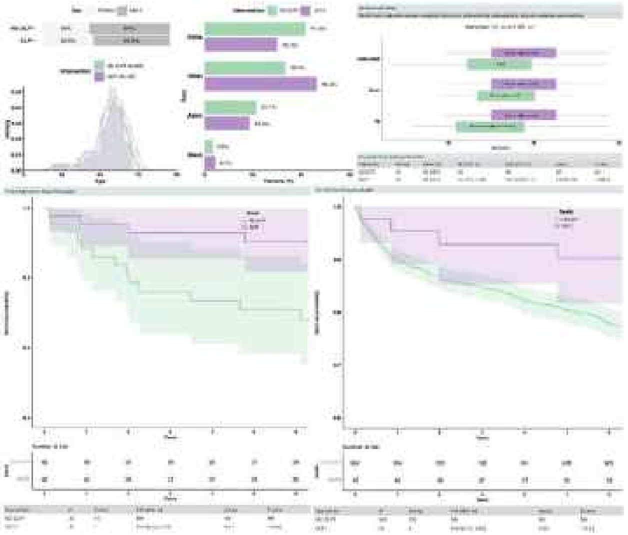
Disclosures: The following people have nothing to disclose: Ammad Javaid Chaudhary, Momin Samad, Ashley Francis, Yervant Ichkhanian, Kartik Gupta, Syed-Mohammed Jafri

Disclosure information not available at the time of publication: Hamna Fahad, Sheema Rehman, Hope Baldwin, Fariba Rana, Diana Jomaa

1074-A | EXPOSURE TO GLP1RA THERAPY IS ASSOCIATED WITH IMPROVED SURVIVAL IN POST LIVER TRANSPLANT PATIENTS WITH TYPE II DIABETES MELLITUS

Sudharshan Achalu[1], Rani Berry[2], Richie Manikat[2], Aaron Yeoh[2], Saurabh Gombar[3], Sun H Kim[1], T.Tara Ghaziani[2], Deepti Dronamraju[2], Renumathy Dhanasekaran[2], Allison J. Kwong[1], Natalie J. Torok[1], Aparna Goel[1], W. Ray Kim[4] and Paul Yien Kwo[1], (1) Stanford University School of Medicine, (2)Stanford University - School of Medicine, (3)Atropos Health, (4) Stanford University

Background: Non-alcoholic steatohepatitis (NASH) related cirrhosis is the most rapidly rising indication for liver transplantation, with high prevalence of both recurrent and de novo metabolic syndrome complications post-transplant. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have shown promise in improving cardiovascular and renal outcomes for liver transplant recipients with type 2 diabetes. Therefore, we aimed to investigate if post-transplant GLP-1RA exposure has an impact on a cohort of liver transplant recipients with type 2 diabetes. **Methods:** We conducted a retrospective review of patients who underwent orthotopic liver transplant at a single center between 2010 and 2022. Patients with a history of type 2 diabetes and at least 3 months of post-transplant GLP-1RA exposure were included in the cohort. Demographic data, along with clinical outcomes including cardiovascular events and mortality, were collected for analysis. The GLP-1RA cohort was compared to a cohort of post-transplant patients with type 2 diabetes that did not have exposure to GLP-1RA. Cohorts were compared unmatched, matched on basic demographics, and matched on high dimensionality propensity scores for survival. **Results:** We identified 43 individual's who received at least 3 months of GLP-1RA therapy post-transplant and compared with a group of 966 post-transplant individual's without GLP-1RA exposure. The mean age at the time of transplant was 55 years, with a mean follow-up duration of 4810 days. BMI [mean difference 3.4, 95% CI (-7.3,-0.59), $p = 0.01$] and weight [mean difference 11.35 lbs., 95% CI (-790,-92), $p = 0.01$] were higher in the GLP-1RA cohort after propensity matching between the two groups. When assessing mortality rates, post-transplant GLP-1RA exposure was associated with significantly improved survival in both unadjusted [HR 0.34; 95% CI (0.13-0.92), $p = 0.03$] and propensity score matching analyses [HR 0.24; 95% CI (0.08-0.74), $p = 0.01$]. **Conclusion:** Our single-center study suggests that GLP-1RA exposure for a minimum of 3 months following liver transplantation is correlated with improved survival despite having higher BMI and weight. These results, if validated in other cohorts, would warrant further exploration in prospective trials to fully evaluate the potential benefits of post-transplant GLP-1RAs in liver transplant recipients with diabetes and other metabolic complications.



Disclosures: The following people have nothing to disclose: Sudharshan Achalu, Richie Manikat, Aaron Yeoh, Allison J. Kwong, Natalie J. Torok, Aparna Goel, W. Ray Kim

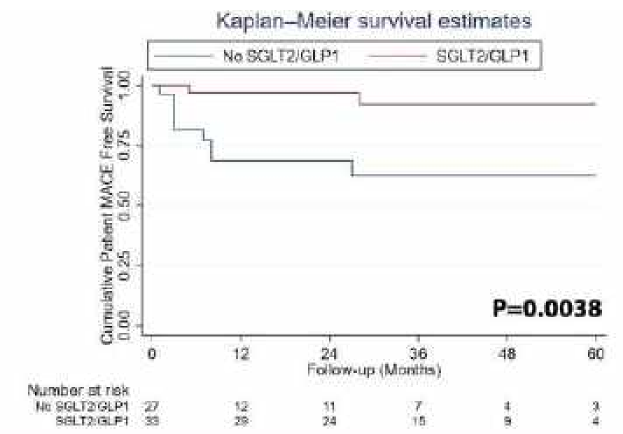
Disclosure information not available at the time of publication: Rani Berry, Saurabh Gombar, Sun H Kim, T.Tara Ghaziani, Deepti Dronamraju, Renumathy Dhanasekaran, Paul Yien Kwo

1075-A | GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS AND SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS EFFECT ON NEW ONSET POST-LIVER TRANSPLANT MAJOR ADVERSE CARDIOVASCULAR EVENTS

Kelli Kosako Yost, Qumber Ali, Megan B. Ghai, Majd Aboona, Paul Gomez, Pooja Rangan, Rohit Nathan, Mark Wong, Karn Wijarnpreecha, Moises Ilan Nevah Rubin, Michael Fallon and Ma Ai Thanda Han, University of Arizona College of Medicine Phoenix, Phoenix, AZ

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RA) and Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have gained popularity in recent years due to their cardiovascular benefits and weight loss potential in patients with type 2 diabetes mellitus. There is little data on these medications and their effect on MACE (major adverse cardiovascular events) in solid organ transplant populations. This study was done to assess the effect of a GLP-1 RA or SGLT2i on incidence of post-transplant MACE in post-liver or simultaneous post-liver kidney transplant (SLK) populations. **Methods:** A retrospective chart review was completed in a single hospital system reviewing any adult age e 18-year-old with type 2 diabetes mellitus and either solitary liver or SLK from January 2012 to March 2022. GLP-1 RA or SGLT2i usage was determined, and demographic, clinical characteristics, and outcomes were compared between the two groups. The Mann-Whitney test and Fisher's exact or Chi-square test were used for continuous and categorical variables respectively and multivariate logistic regression was used to evaluate significant differences in outcomes between the two groups. Propensity score matched MACE free survival was explored. **Results:** Among 472 included patients, 32 patients received an GLP-1 RA or SGLT2i. After controlling for age at transplant, BMI at transplant, sex, hypertension, diabetes at listing, hyperlipidemia, chronic kidney disease, and tobacco use, the use of an SGLP-1 RA or GLT2i was associated with a significantly lower number of new onset post-liver transplant MACE (OR 0.24, CI 95% 0.070-0.85, $p = 0.027$). It was still significant after controlling for aspirin and statin use (OR 0.23, CI 95% 0.66-0.81, $p = 0.022$). Propensity score matched cumulative incidence of 5-year MACE free survival is shown in the figure. **Conclusion:** The use of a GLP-1 RA or SLGT2i in post-liver or post-liver kidney transplant populations was associated with a decreased number of new-onset post-liver transplant MACE after controlling for comorbidities, aspirin use, and statin use. The cumulative incidence of 5-year post-liver transplant MACE free survival was significantly higher in the GLP-1 RA and SGLT2i group after propensity score matching. These findings warrant further prospective studies to improve outcomes in this patient population.

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



*Matched variables include sex, age at transplant, diabetes mellitus, hypertension, hyperlipidemia, tobacco use, and BMI at transplant

*MACE includes myocardial infarction, coronary revascularization (percutaneous intervention, stent placement, coronary artery bypass graphing), cerebrovascular event, or congestive heart failure.

Disclosures: Mark Wong – Gilead: Speaking and Teaching, No, Yes;
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1076-A | HEAD TRAUMA AS DONOR CAUSE OF DEATH IS ASSOCIATED WITH INCREASED GRAFT REJECTION AMONG LIVER TRANSPLANT RECIPIENTS

Ritwik Keshav, Sofia Fabrega, Pooja Rangan, Jonathan Lifshitz, Kelly Zucker, Raha Sadjadi, Rohit Nathan, Ma Ai Thanda Han, Karn Wijarnpreecha, Michael Fallon and Moises Ilan Nevah Rubin, University of Arizona College of Medicine Phoenix, Phoenix, AZ

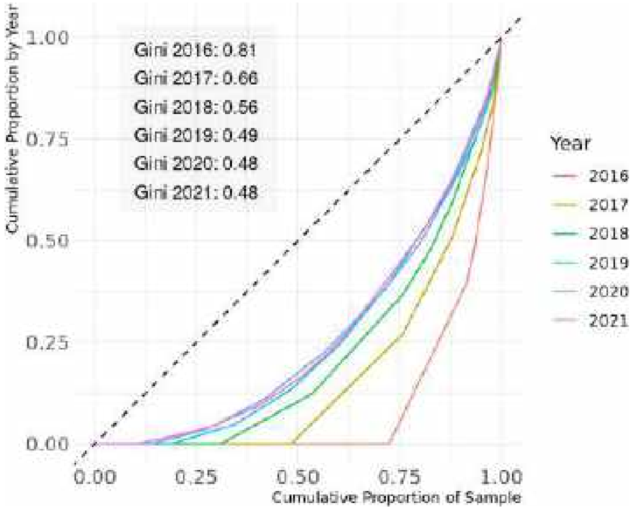
Background: As the demand for liver transplantation grows, all potential transplantable livers must be considered for a match while considering a growing list of donor criteria. Human models of brain death (BD) and traumatic brain injury show pro-inflammatory cytokine production which can elicit a maladaptive hepatic response. This pro-inflammatory response may vary in quantity and quality, depending on the cause of BD. Here we describe the effects of head trauma as a donor cause of death (DCOD) on various recipient outcomes. **Methods:** Matched liver donor-recipient data from 2013-2021 were subsetted from the United Network for Organ Sharing database and hospital system records. Inclusion criteria were single organ, deceased donor liver transplants with recipients > = 18 years. Retransplanted patients and multi-organ transplants were excluded. Other DCOD that were not head trauma (HT), anoxia (AN), or cerebrovascular/stroke (CVS) were excluded (< 5%). Descriptive statistics and backwards, stepwise-multivariable regressions were performed for multiple demographic variables and outcomes, including mortality, rejection, graft failure, hospital/ICU length of stay, and post-operative complications. **Results:** Of the 603 matched donor-recipient records included: HT (n = 183); AN (n = 259); CVS (n = 161). Donors included 225 (37.3%) females and 162 (36.7%) donations after circulatory death. Donor comorbidities included hypertension (n = 217 [36.0%]), diabetes mellitus (n = 91 [15.0%]), and tobacco use > 20 pack years (n = 108 [17.9%]). Recipients included 226 females (37.5%) and BMI was grouped into lean (BMI < 25, n = 141 [23.4%]), and non-lean (BMI > = 25, n = 462 [76.6%]). Recipient liver disease etiology included alcoholic liver disease (n = 189 [31.3%]), Hepatitis C (n = 181 [30.0%]), NASH/NAFLD (n = 102 [16.9%]), autoimmune liver disease (n = 32 [5.3%]), and all other (n = 42 [7.0%]). HT was associated with significantly higher rates of graft rejection compared to AN and CVS respectively (22.8% vs 21.5% and 11.3%, $p = 0.025$). CVS had a significantly lower aOR (0.39, CI [0.19-0.77], $p = 0.007$) compared to HT. There were no significant group differences among DCOD for all other outcomes. **Conclusion:** The proinflammatory response from BD by HT may differ from other causes of BD, with various changes in MHC expression (and other receptors) in the allograft, which stimulate rejection. Our findings suggest that optimization of immunosuppression may be warranted depending on DCOD.

Disclosures: The following people have nothing to disclose: Ritwik Keshav, Raha Sadjadi, Karn Wijarnpreecha
Disclosure information not available at the time of publication: Sofia Fabrega, Pooja Rangan, Jonathan Lifshitz, Kelly Zucker, Rohit Nathan, Ma Ai Thanda Han, Michael Fallon, Moises Ilan Nevah Rubin

1077-A | HEPATITIS C VIREMIA TRANSMISSION AFTER LIVER TRANSPLANT FROM HEPATITIS C ANTIBODY-POSITIVE AND NUCLEIC ACID TESTING NEGATIVE DONORS

Jacqueline I. Kim[1], Suhani S. Patel[1], Jeffrey Stern[1], Alejandro Torres-Hernandez[1], Patrick Grant Northup[2], Adam D. Griesemer[1], Dorry L. Segev[1], Karim Halazun[1] and Allan B. Massie[1], (1)NYU Langone Health, (2) New York University, New York, NY, United States

Background: Liver transplants from hepatitis C (HCV) positive donors to HCV negative recipients have demonstrated good patient and allograft survival, and accordingly become a standard practice at many transplant centers. However, little information is available about the risk of viremia after HCV antibody-positive (Ab+) and nucleic acid testing negative (NAT-) donor liver transplants. **Methods:** We compared adult HCV- recipients of HCV Ab+/NAT- versus Ab- donor livers between 2016-2021 in the United States. We describe donor and recipient characteristics, HCV virologic outcomes at 6 and 12-month follow-up, and changes in utilization of HCV+ grafts by donor center over time. **Results:** 858 (3.0%) of 28,546 recipients received liver transplants from HCV Ab+/NAT- donors between 2016-2021. 761 (88.7%) recipients of HCV Ab + livers presented for evaluation after 6-months, only 11 of whom (1.4%) had HCV viremia. At 12-month follow-up, 602 (79.2%) recipients of HCV Ab+ livers were evaluated, with only 2 NAT+ recipients (0.3%). Lorenz curves demonstrate greater inequity between center-level utilization of HCV Ab+ vs. Ab- grafts (Gini coefficient = 0.43 for Ab+ vs. 0.33 for Ab-), however, center-level differences in utilization of Ab+ grafts have become less pronounced over time (Gini coefficient = 0.81 in 2016 vs. 0.48 in 2021). **Conclusion:** We report a national study of adult HCV nonviremic liver transplant recipients from HCV Ab+/NAT- donors with a HCV viremia rate of < 2%, and center-level inequities in HCV + graft utilization that improved over time. Our results demonstrate that HCV+ grafts should be utilized more aggressively, particularly at low utilizing centers across the country.



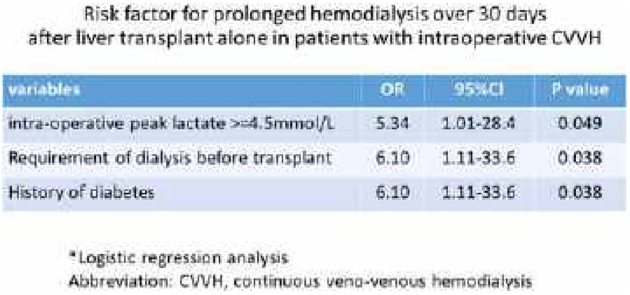
Disclosures: The following people have nothing to disclose: Jacqueline I. Kim, Jeffrey Stern, Patrick Grant Northup, Adam D. Griesemer

Disclosure information not available at the time of publication: Suhani S. Patel, Alejandro Torres-Hernandez, Dorry L. Segev, Karim Halazun, Allan B. Massie

1078-A | HIGHER INTRA-OPERATIVE PEAK LACTATE VALUE MAY BE ASSOCIATED WITH PROLONGED HEMODIALYSIS REQUIREMENT AFTER LIVER TRANSPLANT ALONE IN PATIENTS WITH PRE-TRANSPLANT KIDNEY DYSFUNCTION

Katsunori Miyake, Saleh Al-Juburi, Kathleen Young, Lucy Ching Chau, Toshihiro Kitajima, Nikuwa Wickramaratne, Ahmed Nassar, Atsushi Yoshida, Dilip Moonka, Deepak Venkat, Marwan S. Abouljoud and Shunji Nagai, Henry Ford Hospital

Background: Liver transplant alone (LTA) patients with kidney dysfunction might require intraoperative CVVH which potentially leads to prolonged post-transplant hemodialysis requirement. While pre-transplant kidney function is a well-known factor associated with the likelihood of kidney function recovery after transplant, possible association with intraoperative factors was not well studied. Intra-operative lactate could be a good surrogate marker reflecting the surgical stress such as significant blood loss, prolonged ischemia time, and marginal liver graft function. This study aimed to investigate a possible association between intra-operative peak lactate value and prolonged post-LTA hemodialysis requirement. **Methods:** Medical charts of all liver transplant patients from August 2017 to December 2022 were retrospectively reviewed. LTA patients who required intraoperative CVVH due to kidney dysfunction were eligible for this study. The association between the intra-operative peak lactate value and the requirement of hemodialysis over 30 days post-LTA was evaluated. The median intra-operative peak lactate value of the patient population (4.5mmol/L) was used as a cut-off value to dichotomize patients (low lactate group: 4.5mmol/L < , high lactate group: > = 4.5mmol/L). **Results:** Among 548 liver transplant recipients during the study period, 433 underwent LTA, of whom 46 required intraoperative CVVH. Of these 46, 7 had a history of diabetes (15.2%) and 7 required hemodialysis before transplant (15.2%). After LTA, 11 required hemodialysis over 30 days (23.9%) (prolonged post-LTA hemodialysis requirement). In univariable logistic regression analysis, the risk of prolonged post-LTA hemodialysis was significantly higher in the high lactate group, compared to the low lactate group (OR: 5.34, 95%CI: 1.01-28.4, $p = 0.049$). History of diabetes and requirement of hemodialysis before LTA was also associated with prolonged hemodialysis requirement after LTA (OR: 6.10, 95% CI: 1.11-33.6, $p = 0.038$ and OR: 6.10, 95%CI: 1.11-33.6, $p = 0.038$, respectively). In multivariable analysis, the high lactate group was considered to be an independent risk factor for prolonged post-LTA HD (OR: 13.8, 95%CI: 1.28-148.0, $p = 0.031$). **Conclusion:** Higher intra-operative peak lactate value significantly increases the risk of hemodialysis requirement over 30 days post-LTA. Intraoperative surgical stress may affect kidney function recovery and lactate values can be a good predictive marker.


Risk factor for prolonged hemodialysis over 30 days
after liver transplant alone in patients with intraoperative CVVH

variables	OR	95%CI	P value
intra-operative peak lactate >=4.5mmol/L	5.34	1.01-28.4	0.049
Requirement of dialysis before transplant	6.10	1.11-33.6	0.038
History of diabetes	6.10	1.11-33.6	0.038

*Logistic regression analysis
Abbreviation: CVVH, continuous veno-venous hemodialysis

Disclosures: The following people have nothing to disclose: Katsunori Miyake, Saleh Al-Juburi, Kathleen Young, Lucy Ching Chau, Toshihiro Kitajima, Nikuwa Wickramaratne, Ahmed Nassar, Atsushi Yoshida, Dilip Moonka, Deepak Venkat, Marwan S. Abouljoud, Shunji Nagai

1079-A | HIGHER PLATELETS LEVELS IN POSTOPERATIVE ORTHOTOPIC LIVER TRANSPLANT PATIENTS ASSOCIATED WITH HIGHER RATES OF COMPLICATIONS

Emily E Currier[1], Arif Sarowar[1] and Syed-Mohammed Jafri[2], (1)Wayne State University, (2)Henry Ford Health System

Background: Prior research into the relationship between liver transplant outcomes and platelet levels is limited, but research has shown that peri-operative thrombocytopenia is linked to decreased outcomes and thrombocytopenia on postoperative day 5 have been linked to higher 90-day mortality. However, there is little known about the effect of immediate postoperative thrombocytopenia on long-term morbidity and mortality. The aim of this research was to investigate the relationship between platelet levels immediately post-transplant and one-year postoperative morbidity, including re-hospitalization, rejection, surgical complications, and graft failure, and mortality. **Methods:** A retrospective chart review was conducted at a diverse, urban transplant center and included 828 adults who underwent orthotopic liver transplant between 2012 and 2022. Data from medical charts including platelet levels, postoperative and surgical complications, platelet infusion history, acute and chronic rejection, graft failure, and death from time of transplant one-year postoperatively was recorded and analyzed. Immediate postoperative platelets levels were defined as platelets levels available closest to transplant surgery end time. To analyze postoperative survival, participants were separated into cohorts based on immediate postop platelet levels (uL): < 60,000, 61-90,000, 91-130,000, and > 130,000. **Results:** Average preoperative platelets levels were 99,000 uL (SD = 62,000) and average postoperative levels were 77,000 uL (SD = 50,000). Average time from surgery end to measurement of immediate postoperative platelet levels was 37.5 minutes. Contrary to data published thus far, this study showed that higher immediate post-operative platelet levels were found to be associated with a higher chance of readmission ($p = 0.046$) and acute rejection ($p = 0.007$). In fact, for every one unit increase in platelets, there was a 0.2% increased risk of readmission and 0.5% increased risk of acute rejection. Overall survival rate was found to be 82.8% and there was no significant difference found between post-op platelet levels and survival rates at one-year ($p = 0.628$). Furthermore, no significant difference was found between postoperative levels and chronic rejection, surgical complications, and graft failure at one year postoperatively. **Conclusion:** Overall, this study shows that post-operative thrombocytopenia might not be as detrimental to long-term outcomes as previously thought and shows that increased platelets may pose a slight increased risk of complications.

Disclosures: The following people have nothing to disclose: Emily E Currier, Syed-Mohammed Jafri

Disclosure information not available at the time of publication: Arif Sarowar

f 1080-A | HOME-BASED LIVER FRAILTY INTERVENTION (LIFT) IS FEASIBLE AND DECREASES FRAILTY IN LIVER TRANSPLANT CANDIDATES

Avesh J. Thuluvath, Praneet Polineni, Sheila Morrissey, Kimberly Belfanti, Mohammad Nizamuddin, Osama Siddiqui, Amna Daud, Dinee Simpson, Josh Levitsky, Ann-Marie Flores, Andres Duarte-Rojo and Daniela P. Ladner, Northwestern University Feinberg School of Medicine

Background: Frailty is prevalent in liver transplant (LT) candidates and is associated with increased waitlist and post- transplant mortality and increased frequency of hospitalizations. Currently, logistically feasible and scalable interventions to decrease frailty prior to LT are lacking. In this pilot study, we tested the feasibility and effectiveness of a novel home-based

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

"LIver FrailTy" (LIFT) intervention in LT candidates. **Methods**: Adult, English-speaking patients undergoing LT evaluation at a large transplant center were prospectively enrolled in the LIFT intervention from 10/2020-12/2021. The LIFT intervention consisted of a baseline physical therapy (PT) evaluation (including measurement of the Liver Frailty Index [LFI] and 4-Meter Gait Speed [4MGS]), an individualized home exercise prescription, exercise tracking using a smart phone application, home exercise equipment, reminders to exercise and remote LFI assessments via home dynamometer. Primary outcomes were feasibility (assessed via patient feedback and retention rate, accuracy and ease of remote LFI measurement), adherence to the exercise regimen (classified as adherent, partially adherent or non-adherent if patients attempted e 75%, 50-75% or < 50% of exercises respectively), change in frailty (from baseline to last frailty assessment) and hospitalization rate. **Results**: 54 LT candidates were enrolled in the study. The mean age was 57.2 (± 9.9) years, 59% were male and the mean MELD-Na was 16.0 (± 5.8), with 70% being decompensated (Table 1). All patients remained enrolled at 1 month and 82% at 3 months. The mean follow-up time was 259 (± 200) days. 60% of eligible patients underwent e 1 remote LFI measurement and exercise prescriptions were adjusted at least once on average based on remote frailty assessment. 31% of patients were adherent to prescribed exercises, while 38% were partially adherent and 31% non-adherent. 82.5% of subjects found the smartphone application easy to use and 90% agreed that the provided equipment helped them exercise. The mean change in LFI was -0.15 (3.63 vs 3.48, $p = 0.05$) and mean change in 4MGS was 0.51 meters/sec (3.59 vs 4.10, $p = 0.05$). The mean time between baseline and final frailty assessments was 216.4 (± 157.2) days. 23 patients were transplanted and 5 patients died during the follow up period. On Poisson regression analysis, change in LFI was not predictive of hospitalization rate, LT or death. However, a higher baseline LFI was associated with an increased hospitalization rate. **Conclusion**: LIFT is a feasible and effective intervention to decrease frailty in LT candidates, but is limited by suboptimal adherence. Future LIFT modifications will target improving patient adherence in order to optimize clinical outcomes.

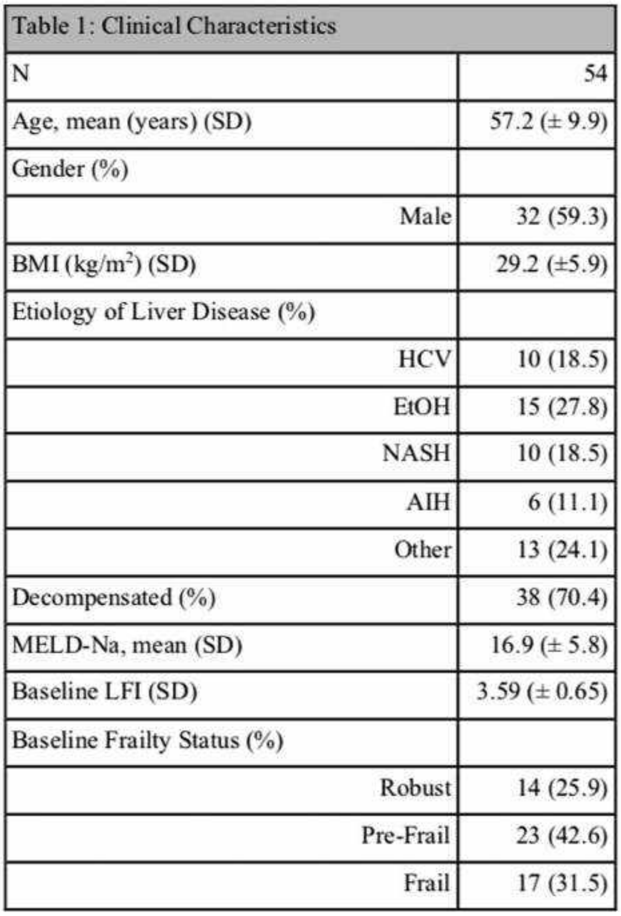


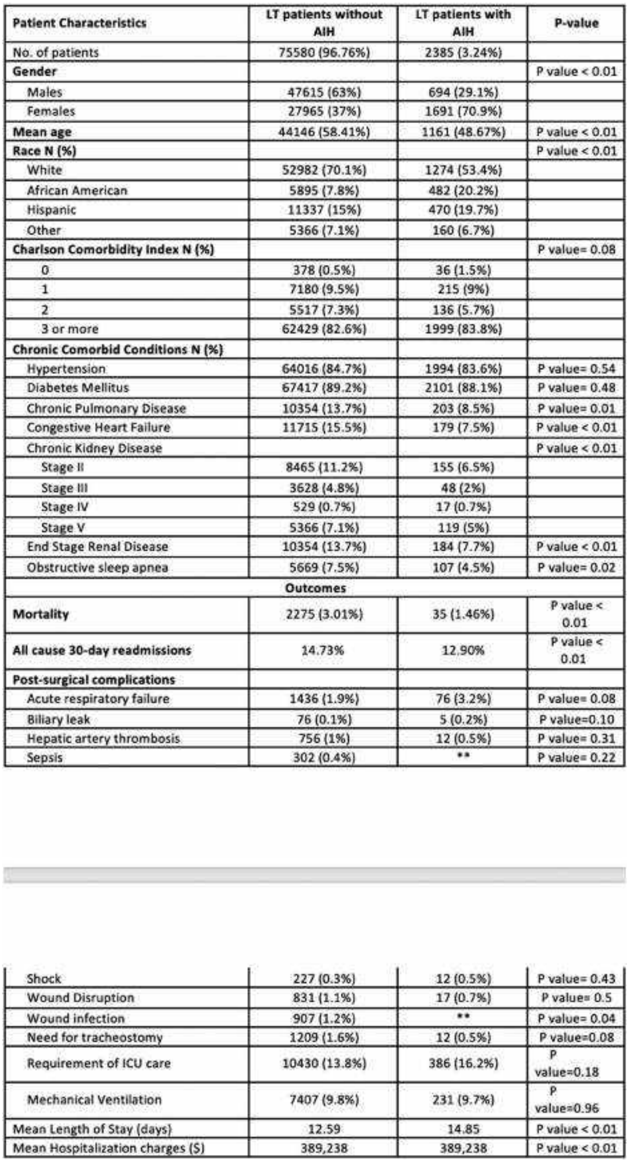
Table 1: Clinical Characteristics	
N	54
Age, mean (years) (SD)	57.2 (± 9.9)
Gender (%)	
Male	32 (59.3)
BMI (kg/m^2) (SD)	29.2 (±5.9)
Etiology of Liver Disease (%)	
HCV	10 (18.5)
EtOH	15 (27.8)
NASH	10 (18.5)
AIH	6 (11.1)
Other	13 (24.1)
Decompensated (%)	38 (70.4)
MELD-Na, mean (SD)	16.9 (± 5.8)
Baseline LFI (SD)	3.59 (± 0.65)
Baseline Frailty Status (%)	
Robust	14 (25.9)
Pre-Frail	23 (42.6)
Frail	17 (31.5)

Disclosures: Josh Levitsky – Eurofins: Advisor, Yes, No; Mallinckrodt: Speaking and Teaching, No, No;
Andres Duarte-Rojo – Axcella, Inc: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Axcella, Inc: Consultant, No, Yes; Mallinckrodt: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Echosens: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
The following people have nothing to disclose: Avesh J. Thuluvath, Praneet Polineni, Daniela P. Ladner
Disclosure information not available at the time of publication: Sheila Morrissey, Kimberly Belfanti, Mohammad Nizamuddin, Osama Siddiqui, Amna Daud, Dinee Simpson, Ann-Marie Flores

1081-A | HOSPITAL-RELATED OUTCOMES OF LIVER TRANSPLANTATION IN PATIENTS WITH AUTO-IMMUNE HEPATITIS: A NATIONWIDE ANALYSIS

Ahmad Khan[1], Khadija Naseem[2], Abdullah Sohail[3], Ammad Javaid Chaudhary[4], Emad Mansoor[5] and Seth Nathan Sclair[5], (1)Case Western Reserve University, (2)Cleveland Clinic Foundation, (3)University of Iowa, (4)Henry Ford Hospital, Detroit, (5)University Hospitals

Background: Autoimmune hepatitis (AIH) represents around 5% of liver transplants in the United States and approximately 2%-3% in Europe. Patients with AIH are typically prescribed long-term corticosteroids and immunosuppressants, which increase their vulnerability to surgical and infectious complications during the early post-transplant period of liver transplantation (LT). There is limited knowledge regarding the hospital-related outcomes for AIH patients undergoing liver transplantation. Our objective was to conduct a comprehensive nationwide analysis to examine the hospital-related outcomes in AIH patients who undergo liver transplantation. **Methods:** We conducted a search in the National Inpatient Sample (NIS) and National Readmission Database (NRD) databases to identify adult AIH patients who underwent LT between 2016 and 2020, using the diagnoses and procedural codes specified in the International Classification of Diseases 10th Revision (ICD-10). Our primary outcomes focused on various measures, including inpatient mortality, all-cause 30-day readmissions, the need for mechanical ventilation, utilization of intensive care unit (ICU) services, and the occurrence of post-operative complications such as biliary leak, sepsis, shock, wound disruption, infection, hepatic artery thrombosis, and tracheostomy requirement. Secondary outcomes encompassed resource utilization parameters, such as the mean length of hospital stay (LOS) and total charges incurred during hospitalization. **Results:** A total of 75,580 adult patients underwent LT between 2016 and 2020 and out of them 2385 had a diagnosis of AIH (3.24%). Patients in the AIH group were younger with mean age 48.67 vs. 58.4 years and mostly females 71.49% vs. 28.51%). A total of 35 (1.46%) patients didn't survive the index hospitalization. All-cause 30-day readmission after the LT was recorded as 12.90% with most common reasons for readmissions included fever (R50.9), diarrhea (R19.7), acute kidney injury (N17.9), pleural effusions (J90)and unspecified liver transplant dysfunction, failure and rejection(T86.49). As regards to, post-operative complications, the incidence of post-surgical complications in AIH patients were not higher as compared to other LT patients. However, patients in the AIH group had a higher LOS (14.85 vs. 12.59, *p*-value: < 0.001) and hospitalization charges ($389,238 vs. $306,536, *p*-value: < 0.001). **Conclusion:** We found that AIH patients had significantly lower inpatient mortality in the index hospitalization of LT; however, they had increased LOS and mean hospitalization charges. Moreover, despite their immunocompromised status, these patients aren't at increased risk of post-surgical complications.



Patient Characteristics	LT patients without AIH	LT patients with AIH	P-value
No. of patients	75580 (96.76%)	2385 (3.24%)	
Gender			P value < 0.01
Males	47615 (63%)	694 (29.1%)	
Females	27965 (37%)	1691 (70.9%)	
Mean age	44146 (58.41%)	1161 (48.67%)	P value < 0.01
Race N (%)			P value < 0.01
White	52982 (70.1%)	1274 (53.4%)	
African American	5895 (7.8%)	482 (20.2%)	
Hispanic	11337 (15%)	470 (19.7%)	
Other	5366 (7.1%)	160 (6.7%)	
Charlson Comorbidity Index N (%)			P value= 0.08
0	378 (0.5%)	36 (1.5%)	
1	7180 (9.5%)	215 (9%)	
2	5517 (7.3%)	136 (5.7%)	
3 or more	62429 (82.6%)	1999 (83.8%)	
Chronic Comorbid Conditions N (%)			
Hypertension	64016 (84.7%)	1994 (83.6%)	P value= 0.54
Diabetes Mellitus	67417 (89.2%)	2101 (88.1%)	P value= 0.48
Chronic Pulmonary Disease	10354 (13.7%)	203 (8.5%)	P value= 0.01
Congestive Heart Failure	11715 (15.5%)	179 (7.5%)	P value < 0.01
Chronic Kidney Disease			P value < 0.01
Stage II	8465 (11.2%)	155 (6.5%)	
Stage III	3628 (4.8%)	48 (2%)	
Stage IV	529 (0.7%)	17 (0.7%)	
Stage V	5366 (7.1%)	119 (5%)	
End Stage Renal Disease	10354 (13.7%)	184 (7.7%)	P value < 0.01
Obstructive sleep apnea	5669 (7.5%)	107 (4.5%)	P value= 0.02
Outcomes			
Mortality	2275 (3.01%)	35 (1.46%)	P value < 0.01
All cause 30-day readmissions	14.73%	12.90%	P value < 0.01
Post-surgical complications			
Acute respiratory failure	1436 (1.9%)	76 (3.2%)	P value= 0.08
Biliary leak	76 (0.1%)	5 (0.2%)	P value=0.10
Hepatic artery thrombosis	756 (1%)	12 (0.5%)	P value= 0.31
Sepsis	302 (0.4%)	**	P value= 0.22
Shock	227 (0.3%)	12 (0.5%)	P value= 0.43
Wound Disruption	831 (1.1%)	17 (0.7%)	P value= 0.5
Wound infection	907 (1.2%)	**	P value= 0.04
Need for tracheostomy	1209 (1.6%)	12 (0.5%)	P value=0.08
Requirement of ICU care	10430 (13.8%)	386 (16.2%)	P value=0.18
Mechanical Ventilation	7407 (9.8%)	231 (9.7%)	P value=0.96
Mean Length of Stay (days)	12.59	14.85	P value < 0.01
Mean Hospitalization charges ($)	389,238	389,238	P value < 0.01

Disclosures: The following people have nothing to disclose: Ahmad Khan, Khadija Naseem, Abdullah Sohail, Ammad Javaid Chaudhary, Emad Mansoor, Seth Nathan Sclair

1082-A | HOW STATIN USE IN LIVER TRANSPLANT RECIPIENTS IMPACTS RISK OF POST-TRANSPLANT MAJOR ADVERSE CARDIAC EVENTS AND MORTALITY

Megan B. Ghai, Kelli Kosako Yost, Pooja Rangan, Rohit Nathan, Mark Wong, Karn Wijarnpreecha, Moises Ilan Nevah Rubin, Michael Fallon and Ma Ai Thanda Han, University of Arizona College of Medicine Phoenix, Phoenix, AZ

Background: The Atherosclerotic Cardiovascular Disease (ASCVD) risk score guides the initiation of statins in adults 40 years and older. Liver transplant recipients (LTRs) are at risk of developing coronary artery disease, with a prevalence of 55.3% 5-years post-transplant. Yet, only 23-41% of LTRs that qualify for a statin are prescribed one. Here we aim to evaluate statin utilization and its impact on major adverse cardiovascular events (MACE) and mortality among LTRs. **Methods:** A retrospective analysis of adult LTRs at a single-center from January 2013 to March 2022 was performed. Patients that qualified for a statin for primary or secondary prevention of ASCVD based on the American College of Cardiology guidelines were identified. Those who had been prescribed a statin within 18 months of transplant were compared with those who had not. Descriptive statistics, including patient demographics and comorbidities were produced. New-onset MACE and mortality after 18 months of transplant were calculated. Chi-squared and Fisher's exact tests and Wilcoxon Rank Sum tests were used to assess categorical and continuous variables, respectively. Multivariate logistic regression was used to evaluate the association of statin use with mortality, adjusting for post-transplant MACE and comorbidities of ASCVD, including sex, age, body mass index, smoking, diabetes, hypertension, and hyperlipidemia. **Results:** Included were 258 LTRs ages 40-75 years, of whom 136 (52.7%) were not prescribed a statin and 122 (47.3%) were prescribed a statin (Table 1). There were no significant demographic differences between the two populations. Among the comorbidities assessed, hyperlipidemia was significantly increased among the group taking a statin (no statin = 41.9%, statin = 89.3%, $p < 0.001$). New-onset MACE events did not vary significantly between the two groups (no statin = 15.4%, statin = 18.0%, $p = 0.58$). However, mortality was lower in those prescribed a statin (no statin = 22.8%, statin = 9.8%, $p = 0.005$). The adjusted odds of death in LTRs taking a statin were significantly less than those not taking a statin (aOR = 0.21, 95% CI [0.08, 0.54], $p < 0.001$). **Conclusion:** We have shown that guideline-directed statin initiation is occurring in less than 50% of LTRs. Further, we showed that mortality is reduced among LTRs prescribed a statin, though MACE were not. This indicates that statins have a protective effect in LTRs separate from that of reducing MACE. Increased adherence to guideline-directed statin initiation among LTRs should be pursued to improve mortality.

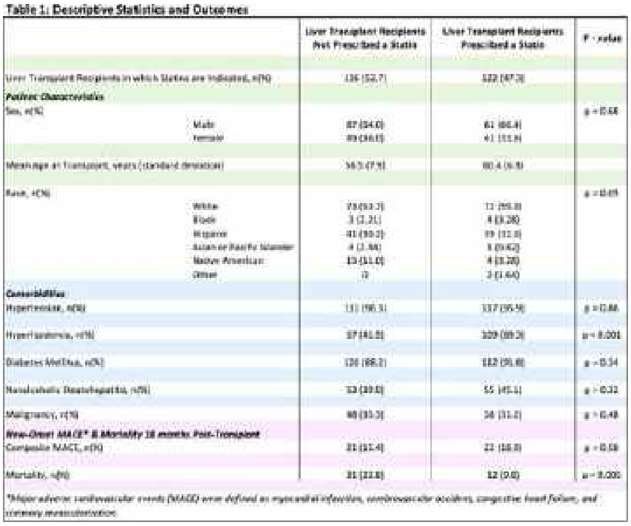


Table 1: Descriptive Statistics and Outcomes

Disclosures: Mark Wong – Gilead: Speaking and Teaching, No, Yes;

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Disclosure information not available at the time of publication: Pooja Rangan, Rohit Nathan, Moises Ilan Nevah Rubin, Michael Fallon, Ma Ai Thanda Han

1083-A | IDENTIFYING RISK FACTORS FOR POSTOPERATIVE DELIRIUM IN LIVER TRANSPLANT RECIPIENTS

Erica Roman[1], David Salerno[2], Mia Genovese[1], Arun Jesudian[3], Benjamin Samstein[4] and Danielle Brandman[5], (1)New York Presbyterian Medical Center, Weill-Cornell, (2)New York Presbyterian Weill Cornell Medical Center, (3)Weill Cornell Medicine, NY, (4) Newyork-Presbyterian/Weill Cornell Medical Center, (5) Weill Cornell Medical College, New York, NY

Background: Postoperative delirium in liver transplant recipients (LTR) is a common complication that can lead to increased length of stay (LOS) and emotional distress for both patients and caregivers. The purpose of this study was to identify the incidence and risk factors for delirium in the early post-liver transplant period. **Methods:** This was a retrospective chart review of all adult LTR who received a transplant between 1/2022 and 4/2023. In June 2022, an Enhanced Recovery After Surgery (ERAS) protocol was reviewed and implemented with all multidisciplinary team members. Elements of the protocol included reduced dose of intraoperative corticosteroids, subsequent steroid doses administered every morning instead of BID, end of case intraoperative extubation when clinically feasible, multimodal analgesia, early removal of surgical drains, implementation of dietary and physical therapy plans and education for multidisciplinary providers and patients about expected LOS. Patients were identified as having delirium via chart review and adjudication from two independent reviewers. The primary outcome was the incidence of delirium. Variables associated with delirium were assessed using logistic regression. **Results:** A total of 76 LTR were included in this analysis. The median age was 56 years (interquartile range 25-75%, 48-65), the majority of patients were male (63%), and etiology of end stage liver disease was similar between groups with the most common being NASH (24%) and alcohol-associated cirrhosis (24%). Median MELD at transplantation was 17 (11–26). The incidence of delirium was 11 (14.5%). Patients with delirium, more frequently experienced prolonged intubation greater than 48 hours (45.5% versus 3.1%; $p<0.001$) and had longer ICU length of stay (median 4 d [IQR 25-75, 3-7] versus 3 d [IQR 25-75, 2-4]; $p=0.022$). In patients receiving methylprednisolone 500 or 1000 mg, the incidence of delirium was 7 (16.3%) versus 4 (12.1%) in those receiving methylprednisolone 250 mg ($p=0.747$) In multivariable regression, independent factors associated with delirium were prolonged intubation for longer than 48 hours (adjusted odds ratio 102, 95% CI [7-1495]) and previous history of psychiatric illness (aOR 10, 95% CI [1.1-94.6]). The overall post-transplant LOS was 15 (12-29) vs 11 (9-18) days in patients with vs without delirium ($p=0.027$). Patients with and without delirium had similar rates of rejection within 90 days of liver transplant ($p=0.225$). **Conclusion:** Prolonged intubation, previous psychiatric history and longer ICU LOS were associated with delirium during the index hospitalization following liver transplantation. Early extubation post-transplant may reduce the risk of delirium, and further studies are needed to identify what other interventions help to reduce delirium in this patient population.

Disclosures: Arun Jesudian – Salix Pharmaceuticals: Speaking and Teaching, Yes, No; Salix Pharmaceuticals: Consultant, Yes, No;

The following people have nothing to disclose: Erica Roman, Mia Genovese, Benjamin Samstein, Danielle Brandman

Disclosure information not available at the time of publication: David Salerno

1084-A | IMPACT OF PHOSPHATIDYLETHANOL IN SURVEILLANCE FOR ALCOHOL USE IN POST-LIVER TRANSPLANT POPULATION.

Sergio Anthony De La Torre Jr., Brittney Ibrahim, Kabir Rahal, Katherine Meneses, Jasleen Singh, Gina Choi, Steven-Huy B. Han, Sammy Saab and Akshay Shetty, University of California, Los Angeles

Background: Alcohol-related liver disease (ALD) is the leading indication for liver transplantation in the United States, and over the last decade there has been a slow rise in the percentage of ALD patients representing the post-liver transplant (OLT) population. Therefore, there has been growing demand for improved surveillance protocols for the post-OLT patients. Phosphatidylethanol (PEth), a direct alcohol biomarker, is increasingly being utilized as a marker for alcohol use and was introduced at our institution in 2019 as part of the surveillance protocol. The aim of this study is to describe the impact of PEth in surveillance for alcohol use after liver transplant. **Methods:** Here, we conducted a single-center retrospective study to assess the impact of the introduction of PEth for surveillance of alcohol use in addition to standard of care, which included interviewing patients along with assessing random serum ethanol levels. We reviewed the impact of PEth as a marker of detecting alcohol use and its correlation with negative health outcomes by comparing two cohorts of post-OLT patients who were transplanted for ALD between 2016-2018 (before the introduction of PEth), and 2019-2022 (after the introduction of PEth). **Results:** We reviewed 235 patients who were transplanted for ALD during this time period and 43 (18.3%) patients were noted to have at least one episode of alcohol relapse after their transplant. Patients with alcohol relapse were noted to have more frequent episodes of elevated liver function tests compared to non-relapsed patients (4.37 episodes vs 2.45 episodes respectively, $p<0.001$). The number of hospitalizations was also noted to be elevated among relapsed vs non-relapsed patients, however this was not statistically significant (2.95 vs 2.60 respectively, $p=0.332$). Relapse rates between the two time periods, before and after the introduction of PEth, were similar (17% vs 19%, $p=0.613$), however detection of alcohol relapse was most commonly confirmed by PEth alone, which accounted for 75% of all relapses, closely followed by self-reporting (18.7%). No difference was noted in rates of graft rejection or mortality between the two groups, nor between patients who did or did not relapse.

Conclusion: Overall, PEth is an effective surveillance tool in the post-liver transplant population to monitor for alcohol relapse. Early detection of relapse can lead to opportunities for early intervention by providing patients resources and referring them to behavioral medicine so they may remain abstinent.

Disclosures: Gina Choi – Intercept: Speaking and Teaching, No, No; Gilead: Speaking and Teaching, No, No;

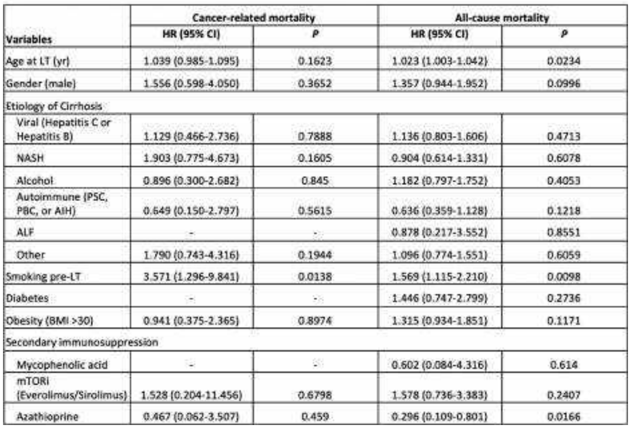
The following people have nothing to disclose: Sergio Anthony De La Torre, Brittney Ibrahim, Kabir Rahal, Katherine Meneses, Jasleen Singh, Steven-Huy B. Han, Sammy Saab, Akshay Shetty

1085-A | IMPACT OF TACROLIMUS EXPOSURE ON CANCER-RELATED MORTALITY FOLLOWING LIVER TRANSPLANT

Jiawei Cui[1], Christopher L Coe[2], Adesola Oluwagbemiga Oje[1], Ashley Spann[1], Lei Fan[1], Alexandra Shingina[1], Martha Shrubsole[1], Kymberly Watt[3], Muhamed Baljevic[1] and Manhal Izzy[1], (1) Vanderbilt University Medical Center, (2)UCLA Health, (3)Mayo Clinic, Rochester, MN

Background: Calcineurin inhibitors (CNIs), notably tacrolimus, are the mainstay of immunosuppression post-liver transplant (LT). However, CNIs are associated with carcinogenesis and prior studies suggest an association between tacrolimus exposure and De novo malignancy (DNM). DNM carries a high risk of mortality for LT recipients (LTR). This study aims to assess the impact of tacrolimus exposure on cancer-related mortality in LTRs. **Methods:** We performed a retrospective records review of adult LT only recipients who underwent LT between 1/1/2009 to 12/31/2018 at a North American Center. LT recipients whose CNI was tacrolimus were included. Patients who developed cancer within 1st year post-LT and those who exposed to cyclosporine were excluded. Demographic and clinical data were collected. Tacrolimus trough levels for each individual were measured and mean, median, and area under the curve for various periods of time (1-90 d, 91-365 d, 1-365 d, 366-730 d, and 1-730 d) were calculated. **Results:** Of 732 patients who were included, 110 developed DNM after the 1st year post-LT. Forty patients developed solid organ malignancy, 4 developed hematologic malignancy, and 71 developed skin cancer (64 non-melanoma and 7 melanoma). There were 134 deaths of which 20 were cancer-related. On univariable analysis (Table 1), only smoking was associated with cancer-related mortality. For all-cause mortality, advancing age at LT and smoking were associated with increased risk while azathioprine was protective. On multivariable analysis controlling for age at LT, gender, smoking, and pre-LT diabetes, the degree of exposure to tacrolimus during the aforementioned time intervals was not associated with cancer-related or all-cause mortality. These results did not change when tacrolimus exposure was quantified via mean, median, or area under the curve. **Conclusion:** The current study findings suggest that increased tacrolimus exposure does not impact cancer-related mortality in liver transplant recipients. The results highlight the detriment of smoking in LTRs.

Table 1



Variables	Cancer-related mortality		All-cause mortality	
	HR (95% CI)	P	HR (95% CI)	P
Age at LT (yr)	1.039 (0.985-1.095)	0.1623	1.023 (1.003-1.042)	0.0234
Gender (male)	1.556 (0.598-4.050)	0.3652	1.357 (0.944-1.952)	0.0996
Etiology of Cirrhosis				
Viral (Hepatitis C or Hepatitis B)	1.129 (0.466-2.736)	0.7888	1.136 (0.803-1.606)	0.4713
NASH	1.903 (0.775-4.673)	0.1605	0.904 (0.614-1.331)	0.6078
Alcohol	0.896 (0.300-2.682)	0.845	1.182 (0.797-1.752)	0.4053
Autoimmune (PSC, PBC, or AIH)	0.649 (0.150-2.797)	0.5615	0.636 (0.359-1.128)	0.1218
ALF	-	-	0.878 (0.217-3.552)	0.8551
Other	1.790 (0.743-4.316)	0.1944	1.096 (0.774-1.551)	0.6059
Smoking pre-LT	3.571 (1.296-9.841)	0.0138	1.569 (1.115-2.210)	0.0098
Diabetes	-	-	1.446 (0.747-2.799)	0.2736
Obesity (BMI >30)	0.941 (0.375-2.365)	0.8974	1.315 (0.934-1.851)	0.1171
Secondary immunosuppression				
Mycophenolic acid	-	-	0.602 (0.084-4.316)	0.614
mTORI (Everolimus/Sirolimus)	1.528 (0.204-11.456)	0.6798	1.578 (0.736-3.383)	0.2407
Azathioprine	0.467 (0.062-3.507)	0.459	0.296 (0.109-0.801)	0.0166

Disclosures: Kymberly Watt – Intercept - site PI: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Viking: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; Madrigal: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; JnJ: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;

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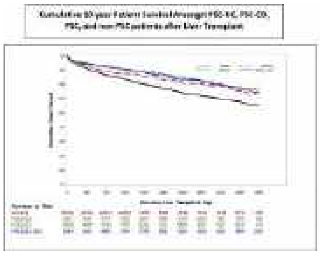
Disclosure information not available at the time of publication: Christopher L Coe, Adesola Oluwagbemiga Oje, Lei Fan, Martha Shrubsole, Muhamed Baljevic

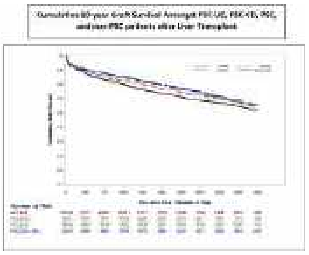
f 1086-A | IMPACT OF THE PRESENCE OF INFLAMMATORY BOWEL DISEASE ON POST-TRANSPLANT SURVIVAL IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: A PROPENSITY MATCHED CONTROLLED ANALYSIS

Maham Ghani[1], Niranjani Venkateswaran[1], Salima Makhani[2], Ethan Berman[2], Alexa Giammarino[2], Justin

Lin[1], Jeffrey Lowell[2], Keith Sultan[1], Ramona Rajapakse[3], Arun Swaminath[1] and Sanjaya Kumar Satapathy[3], (1)Northshore University Hospital/Long Island Jewish Hospital, (2)Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, (3)Northwell Health, Forest Hills, NY

Background: Liver transplant (LT) is the only curative treatment for patients with primary sclerosing cholangitis (PSC) and end-stage liver disease. The concomitant presence of inflammatory bowel disease (IBD), such as Ulcerative Colitis (UC) and Crohn's disease (CD) is common in PSC, however there is limited data on LT mortality and graft outcomes in PSC with IBD. We aimed to analyze the impact of coexistent IBD on patient and graft survival after LT. **Methods:** We conducted a retrospective analysis using the United Network for Organ Sharing-Standard Transplant Analysis and Research (UNOS-STAR) database. We evaluated 112,955 patients transplanted from April 2002 to November 2022. We excluded patients $<$ 18 years old, living donor liver transplants, split livers, non-heart beating donors, and dual transplants. Primary outcomes of interest were all-cause mortality and graft survival after LT assessed over a 10-year follow-up period. Patients with PSC were matched 1:1 with non-PSC patients based on gender, age at transplant, MELD score, and BMI. PSC patients were grouped into PSC-No IBD, PSC-CD and PSC-UC. The association between the groups and all-cause mortality and graft survival after LT was assessed using both univariate and multivariate Cox proportional regression analysis with hazards ratio and its 95% confidence interval. p values were two-sided and reported as significant at $<$ 0.05. All analyses were conducted using SAS 9.4 (SAS, Cary, NC). **Results:** After exclusion, there were 7168 patients, with 3570 in the control group and 3598 in the PSC group (550 with CD, 1804 with UC, 1244 without IBD). Kaplan-Meier survival analysis showed PSC-UC have significantly better patient survival, followed by PSC-No IBD, and then PSC-CD compared to the matched control group ($p < 0.0001$). PSC subjects have significantly better graft survival compared to the control group ($p < 0.0001$). Cox proportional hazard model analysis revealed IBD subjects have a significantly decreased risk of all-cause mortality compared to the control subjects [OR 0.650, 95% CI (0.583-0.725 $p < 0.0001$] after controlling for confounders such as diabetes, age, ventilatory support status, serum albumin, and long cold ischemia time (CIT). The cause of death did not differ significantly between the PSC and control groups. **Conclusion:** Our study finds patients with PSC-IBD have significantly improved mortality and graft survival compared to non-PSC patients, with PSC-UC having lowest mortality. This may be related to immunosuppressive medication usage, duration of disease, and pathophysiology of IBD. These findings will help inform clinical decision-making and counseling for PSC-IBD patients who are considering LT. Further investigation is needed to explore causality of this connection.





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Disclosure information not available at the time of publication: Niranjani Venkateswaran, Keith Sultan, Ramona Rajapakse, Arun Swaminath

1087-A | INCIDENCE AND RISK FACTORS OF GRAFT-VERSUS-HOST DISEASE AFTER LIVER TRANSPLANTATION: A NATIONAL STUDY 2010-2020

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Background: Graft-versus-host disease (GVHD) is a common complication of hematopoietic cell transplantation, and incidence is low in liver transplantation (LT). Estimating the incidence of GVHD after LT is challenging due to the paucity of available data collected by the United Network for Organ Sharing. Current GVHD incidence estimates are derived from single institutional studies and range from 0.1% to 2% but the national incidence of GVHD post LT is unknown. **Methods:** This retrospective cohort study used the National Readmission Database (NRD) to calculate the incidence rate of GVHD after LT within 1 year using survival analysis. Variables were extracted from the NRD including age, gender, race, median household income, and primary expected payer. The comorbidity burden was quantified using the Elixhauser index.Predictors of GVHD after LT were identified using univariate and multivariate Cox regression analysis. In-hospital all-cause mortality rates were determined using discharge status in the NRD. **Results:** From 2010 to 2020, out of 88,433 LTs, there were 383 cases of GVHD within 1 year after LT. The incidence rate of GVHD within one year after LT was 1.0% (95% confidence interval [CI], 0.8% to 1.3%). We observed no statistically significant

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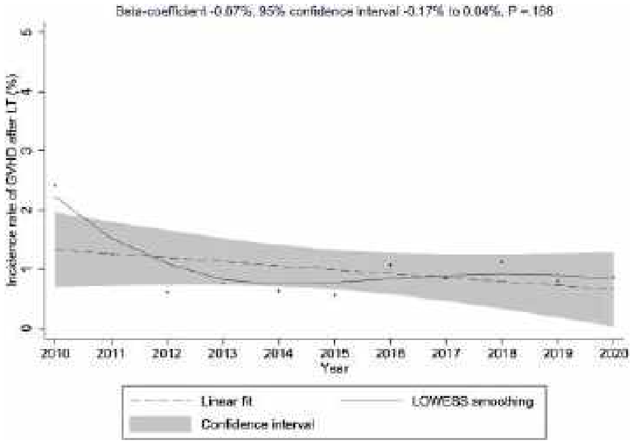
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

change in the incidence rate trend of GVHD after LT from 2010 to 2020 (beta-coefficient, -0.07%; 95% CI, -0.17% to 0.04%; $p = 0.188$). The in-hospital and calendar-year all-cause mortality rates of GVHD hospitalization were 20.8% and 41.7%, respectively. In addition, 19.1% of patients who did not pass away on the index GVHD hospitalization received a palliative care consult within that calendar year. Interestingly, alcoholic liver disease was associated with a lower risk of GVHD (adjusted hazard ratio, 0.57; 95% CI, 0.36 to 0.91; $p = 0.018$), while a higher risk was found in index hospitalizations for LT with COVID-19 infection before LT. Hematological abnormalities were commonly observed during hospitalizations related to GVHD, with essential hypertension being the most prevalent comorbidity. **Conclusion**: Our study provides the first national estimates of the incidence and mortality rates of GVHD post-LT in the United States. Patients with alcoholic liver disease undergoing LT had a lower probability of developing GVHD post-transplant. COVID-19 infection before the LT was associated with an elevated risk of GVHD. The mortality rate associated with GVHD hospitalization was high, with over 40% of patients died and about additional 20% received palliative care consult within one calendar year. Our study provides valuable insights into the incidence, risk factors, and outcomes of GVHD post-LT in the United States, and underscores the importance of addressing modifiable risk factors that may contribute to GVHD after LT.



Disclosures: The following people have nothing to disclose: Yuting Huang, Yichen Wang, Liu Yang

1088-A | INCIDENCE OF POST-TRANSPLANT DIABETES MELLITUS IN LIVER TRANSPLANT RECIPIENTS IS INFLUENCED BY OPTN REGION

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Background: Post-transplant diabetes mellitus (PTDM) is associated with significant morbidity and mortality in liver transplant recipients (LTRs). We estimated and compared the incidence of PTDM across the Organ Procurement and Transplantation Network (OPTN) in the United States. **Methods:** The OPTN database was used to identify adult, primary, deceased donor, LTRs transplanted between January 1, 2007, and December 31, 2016, with no prior history of diabetes. We compared the characteristics of LTRs with and without PTDM using chi-square and t-tests. Kaplan Meier analyses were utilized to calculate the cumulative incidence of PTDM, stratified by OPTN Region. Multivariable Cox-proportional hazards regression analyses estimated the hazards of PTDM in each OPTN Region. **Results:** LTRs who developed PTDM were predominantly White (69.7%), males (69.0%) transplanted in Regions 3 (East and West South Central / South Atlantic) (21.6%), 2 (Middle Atlantic) (14.9%), 5 (Pacific / Mountain South) (11.6%) and 4 (West South Central) (8.6%), for either hepatitis C (23.5%) or hepatocellular carcinoma (23.3%). LTRs developing PTDM differed significantly from those without PTDM with respect to numerous sociodemographic factors: gender composition, ethnicity, education, insurance status, region of transplant, BMI at transplant, indication and donor age. Overall, the cumulative incidence of PTDM at 1-year, 3-years and 5-years post-transplant was 11.9%, 15.9% and 18.7%, respectively. A statistically significant difference in time to development of PTDM was observed between the OPTN regions. Region 3 had the highest cumulative incidence of PTDM at 1-year, 3-years, and 5-years post-transplant of 17.67% (95% CI: 16.73-18.61%), 21.45% (95% CI: 20.43-22.47%) and 23.61% (95% CI: 22.49-24.73%) respectively. This was followed by Region 2, with cumulative incidence of PTDM at 1-year, 3-years, and 5-years post-transplant of 14.47% (95% CI: 13.45-15.49%), 19.91% (95% CI: 18.73-21.09%), and 23.17% (95% CI: 21.84-24.5%), respectively. Region 1 (New England) had the lowest cumulative incidence of PTDM at 1-year, 3-years, and 5-years post-transplant of 7.33% (95% CI: 6.01-8.65%), 10.00% (95% CI: 8.47-11.53%), and 11.47% (95% CI: 9.64-13.30%), respectively. There were higher adjusted hazards ratios (aHR) of PTDM (relative to Region 1), in descending order, in LTRs transplanted in Regions 3, 2, 8, 9, 4, 7 and 10 (Table 1). **Conclusion:** Significant variability exists in the incidence of PTDM across OPTN regions with highest risk in Regions 3, 2 and 8. Centers in these Regions are encouraged to re-evaluate practice policies and design interventions aimed at mitigating risk.

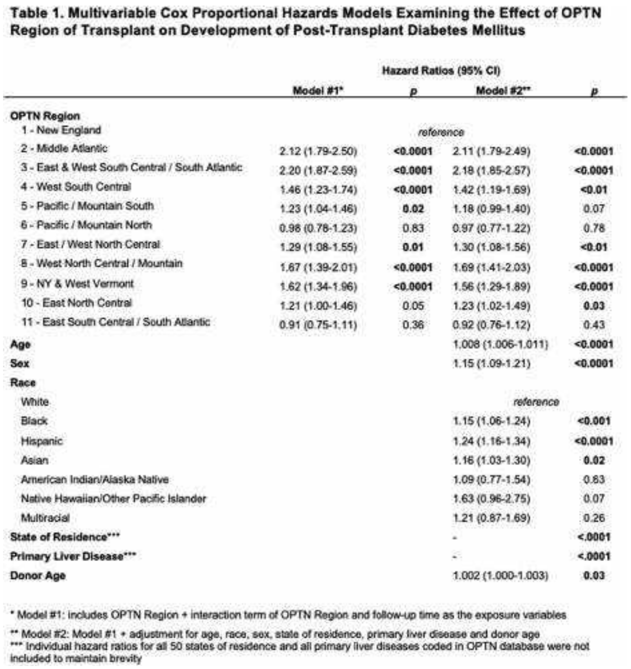

Table 1. Multivariable Cox Proportional Hazards Models Examining the Effect of OPTN Region of Transplant on Development of Post-Transplant Diabetes Mellitus

	Hazard Ratios (95% CI)			
	Model #1*	***p***	**Model #2****	***p***
OPTN Region				
1 - New England	*reference*			
2 - Middle Atlantic	2.12 (1.79-2.50)	**<0.0001**	2.11 (1.79-2.49)	**<0.0001**
3 - East & West South Central / South Atlantic	2.20 (1.87-2.59)	**<0.0001**	2.18 (1.85-2.57)	**<0.0001**
4 - West South Central	1.46 (1.23-1.74)	**<0.0001**	1.42 (1.19-1.69)	**<0.01**
5 - Pacific / Mountain South	1.23 (1.04-1.46)	**0.02**	1.18 (0.99-1.40)	0.07
6 - Pacific / Mountain North	0.98 (0.78-1.23)	0.83	0.97 (0.77-1.22)	0.78
7 - East / West North Central	1.29 (1.08-1.55)	**0.01**	1.30 (1.08-1.56)	**<0.01**
8 - West North Central / Mountain	1.67 (1.39-2.01)	**<0.0001**	1.69 (1.41-2.03)	**<0.0001**
9 - NY & West Vermont	1.62 (1.34-1.96)	**<0.0001**	1.56 (1.29-1.89)	**<0.0001**
10 - East North Central	1.21 (1.00-1.46)	0.05	1.23 (1.02-1.49)	**0.03**
11 - East South Central / South Atlantic	0.91 (0.75-1.11)	0.36	0.92 (0.76-1.12)	0.43
Age			1.008 (1.006-1.011)	**<0.0001**
Sex			1.15 (1.09-1.21)	**<0.0001**
Race				
White			*reference*	
Black			1.15 (1.06-1.24)	**<0.001**
Hispanic			1.24 (1.16-1.34)	**<0.0001**
Asian			1.16 (1.03-1.30)	**0.02**
American Indian/Alaska Native			1.09 (0.77-1.54)	0.63
Native Hawaiian/Other Pacific Islander			1.63 (0.96-2.75)	0.07
Multiracial			1.21 (0.87-1.69)	0.26
State of Residence***			-	**<.0001**
Primary Liver Disease***			-	**<.0001**
Donor Age			1.002 (1.000-1.003)	**0.03**

* Model #1: includes OPTN Region + interaction term of OPTN Region and follow-up time as the exposure variables

** Model #2: Model #1 + adjustment for age, race, sex, state of residence, primary liver disease and donor age

*** Individual hazard ratios for all 50 states of residence and all primary liver diseases coded in OPTN database were not included to maintain brevity

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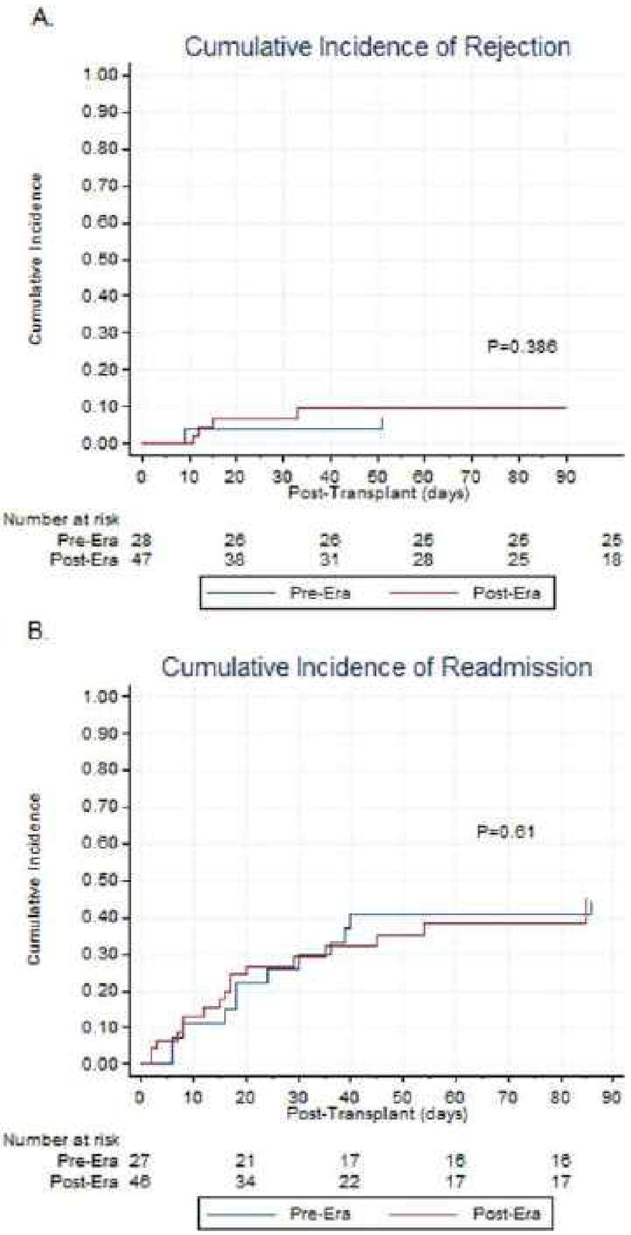
1089-A | LIVER TRANSPLANT FAST TRACK: A MULTIDISCIPLINARY APPROACH TO REDUCING LENGTH OF STAY

Mia Genovese[1], *David Salerno*[2], *Erica Roman*[1], *Arun Jesudian*[3], *Benjamin Samstein*[4] *and Danielle Brandman*[5], *(1)New York Presbyterian Medical Center, Weill-Cornell, (2)New York Presbyterian Weill Cornell Medical Center, (3)Weill Cornell Medicine, NY, (4) Newyork-Presbyterian/Weill Cornell Medical Center, (5) Weill Cornell Medical College, New York, NY*

Background: Enhanced recovery after surgery protocols have been implemented in a variety of solid organ transplant programs. The purpose of our study was to evaluate the impact of a standardized protocol in liver transplant recipients (LTR) on length of stay (LOS) during the index hospitalization post-LT. **Methods:** This was a quality improvement study of all adult LTR who received a transplant between 1/2022 and 3/2023. Patients were stratified into pre- and post-implementation groups. A Fast Track protocol was reviewed and implemented by all multidisciplinary team members in June 2022. Elements of the protocol included reduced intraoperative corticosteroids (from methylprednisolone 1000 mg to 250 mg), conversion of steroid taper to be administered once daily instead of BID, optimal end of case intraoperative extubation, multimodal analgesia, early removal of surgical drains, implementation of dietary and physical therapy plans and education for multidisciplinary providers and patients about expected LOS. The primary outcome was post-LT LOS; secondary outcomes were ICU LOS, rejection at 60 days and readmission within 30 days of discharge. **Results:** A total of 75 LTR were included with 76 distinct episodes of transplant. There were no significant differences in baseline characteristics between groups. The median age was 56 years (IQR, 48-65), the majority of patients were male (63%), and etiology of end stage liver disease was similar between groups with the most common being NASH (24%) and alcohol associated cirrhosis (24%). Median MELD at transplantation was 17 (11-26). The median length of stay was 16 days (IQR, 11-24) and 11 days (IQR, 9-17) in the pre- and post- implementation groups, respectively ($p = 0.058$). ICU LOS was 3 (IQR, 2-5) and 3 (IQR, 2-4) in the pre- and post-implementation groups, respectively ($p = 0.933$). The incidence of treated rejection at 60 days was 7.4% (95% CI, 1.9-26.5) and 9.6% (95% CI, 3.7-23.8) in the pre- and post-implementation groups, respectively ($p = 0.386$) [Figure 1A]. Readmission at 30 days was 29.6% (95% CI, 16.1-50.6) and 31.2% (95% CI, 19.3-47.8) in the pre-implementation and post-implementation groups, respectively ($p = 0.515$) [Figure 1B]. **Conclusion:** Implementation of a Fast Track protocol in a high acuity liver transplantation program was feasible and safe and may be associated with a reduction in hospital length of stay.



Disclosures: Arun Jesudian – Salix Pharmaceuticals: Speaking and Teaching, Yes, No; Salix Pharmaceuticals: Consultant, Yes, No;

The following people have nothing to disclose: Mia Genovese, Erica Roman, Benjamin Samstein, Danielle Brandman

Disclosure information not available at the time of publication: David Salerno

f 1090-A | LIVER TRANSPLANTATION FOR ALCOHOL-ASSOCIATED HEPATITIS COMPARED TO CIRRHOSIS: 273 TRANSPLANTS OVER 11 YEARS

Gene Y. Im[1], *Katrina Villanueva*[2], *Alexander Vogel*[2], *Stephanie Rutledge*[1], *Thomas Schiano*[2] *and Sander S. Florman*[2], *(1)Icahn School of Medicine at Mount Sinai, (2)Recanati/Miller Transplantation Institute at Mount Sinai*

Background: Alcohol-associated liver disease (ALD), including alcohol-associated hepatitis (AH) and alcohol-associated cirrhosis (AC), is the leading indication for LT in the U.S. Outcome studies of these LT populations with alcohol biomarker monitoring and long-term follow-up are lacking. The aim of this study is to compare the outcomes of relapse, rejection and survival in LT for AH versus AC. **Methods:** Using a prospectively-maintained database, we performed a retrospective cohort-comparison study of patients who underwent LT for ALD at our center, including AH and AC but excluding hepatocellular carcinoma, from 1/1/2012 to 1/1/2023. We gathered and analyzed data regarding patient demographics, drinking after LT from alcohol biomarker monitoring (urine ethyl glucuronide and/or phosphatidylethanol), biopsy-proven acute cellular rejection (BPAR) and patient survival. Alcohol relapse was defined as per NIAAA definitions. Statistical analyses were performed using SPSS. **Results:** Over the 11-year study period, 113 LT for AH and 160 LT for AC were performed at our center. (Figure 1) For both groups, LT volume increased during the COVID-19 pandemic (2020-23). Recipients of LT for AH vs AC were younger (median [IQR] (age 43 years [36-51] v 60 [52.5-65], $p < 0.001$) and had higher proportion of women (38% v 23%, $p = 0.008$), White race (65% v 50%, $p = 0.02$) and MELD-Na at LT (median 40 [36-40] v 33 [27-38], $p < 0.001$). Alcohol biomarker monitoring was performed after LT in 100% and 74% of LT for AH and AC recipients, respectively. While LT for AH recipients had higher rates of alcohol relapse compared to AC (32% v 18%, $p < 0.001$), rates of BPAR (11% v 14%, $p = 0.48$) and 1-year survival were similar (96% v 91%, $p = 0.15$). In contrast, recipients of LT for AH vs AC had significantly higher overall survival (94% v 82%, $p = 0.009$) at median of 2.5 years follow-up. (Figure 2) Overall, the most common causes of death were perioperative complications (43%) and cardiovascular disease (23%). **Conclusion:** Despite higher rates of relapse detected by alcohol biomarker monitoring, LT for AH recipients have higher overall survival compared to AC. This further supports the practice of LT for AH and deemphasizing the 6-month rule in favor of comprehensive psychosocial evaluations in patients with ALD.

Figure 1. Liver Transplants for Alcohol-associated Liver Disease by Year

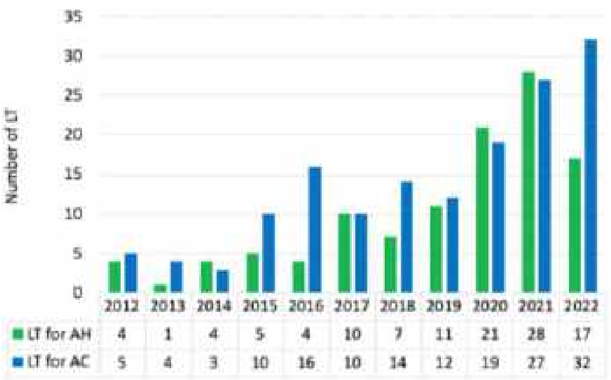
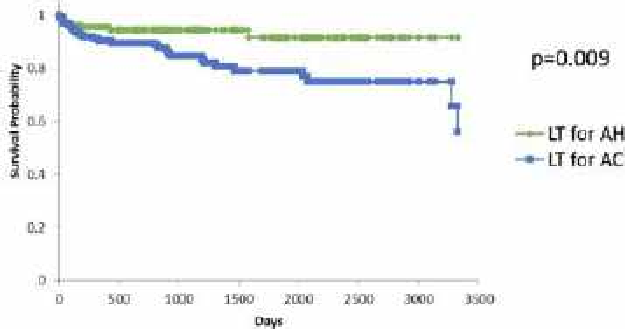


Figure 2. Kaplan-Meier survival analysis for overall survival



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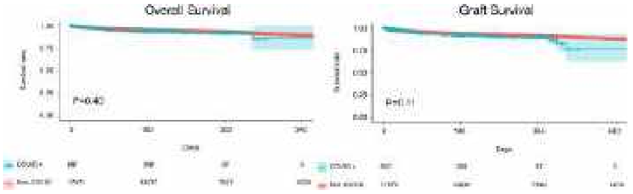
Stephanie Rutledge – Paige AI: Employee, No, No;
The following people have nothing to disclose: Alexander Vogel, Thomas Schiano
Disclosure information not available at the time of publication: Katrina Villanueva, Sander S. Florman

1091-A | LIVER TRANSPLANTATION FROM COVID POSITIVE DONORS: TRENDS IN UTILIZATION, DISCARD & LONG-TERM OUTCOMES IN THE UNITED STATE

Kenji Okumura, Ryosuke Misawa, Abhay Dhand, Hiroshi Sogawa, Gregory R. Veillette, Roxana I. Bodin, David C. Wolf and Seigo Nishida, Westchester Medical Center

Background: Transplantation of organs from COVID positive (COVID+) donors is increasing. The aim of this study was to assess the trends in utilization, discard, and longer-term outcomes in liver transplant (LT) recipients who received organs from COVID+ donors. **Methods:** Rates of utilization, discard, and outcomes of SOT from deceased donors with a recent positive COVID PCR test from respiratory tract between March 2020 and December 2022 were analyzed using the de-identified UNOS database. Post-transplant survival analysis was performed using Kaplan-Meier method and Cox-hazard proportional regression model. **Results:** Overall, during the study period, 1185 COVID+ donors led to the transplantation of 1249 kidneys, 592 livers, and 168 hearts. The center-wise acceptance rate for livers from COVID+ donors increased from 53% in 2021 to 89% in 2022. Discard rates of livers from COVID+ donors remained low (3.1%) and was not significantly different than COVID negative (COVID-) donors (4.3%). When compared to 18,009 COVID- donors, 592 COVID+ donors were younger (median 40 vs 42 y, $p = 0.019$), had similar median serum total bilirubin (0.6 mg/dl, $p = 0.15$) and similar cold ischemia time (5.81 vs 5.77 hours, $p = 0.52$). Length of hospital stay and rates of rejection prior to discharge (COVID+ 4.7% vs COVID- 4.2%, $p = 0.56$) were similar in both the groups. The median waitlist time for recipients of COVID+ organs was lower (35 vs 41 d, $p = 0.087$). The median follow-up period was 360 (172-670) days. Six-months, one-year and 18-month overall and graft survivals were comparable between recipients of COVID+ and COVID- donors (figure 1). In multivariable analysis, COVID+ was not associated with statistically significant increased risk of mortality (hazard ratio 1.22; 95% confidence interval 0.85-1.75, $p = 0.30$) or graft failure (hazard ratio 1.33; 95% confidence interval 0.98-1.79, $p = 0.066$). **Conclusion:** Utilization of livers from COVID+ donors has improved across various transplant centers in the US. Liver discard rate from COVID+ donors remain low. While longer-term outcomes of LTs from COVID+ donors are encouraging and are helping to successfully expand the donor pool, further follow up is needed to monitor for any further change in risk of graft failure.



Disclosures: The following people have nothing to disclose: Kenji Okumura
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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

1092-A | LIVER TRANSPLANTATION PROFILE AMONG TEENAGERS IN THE UNITED STATES

Maria Stepanova[1], Dipam Shah[2], Reem Al Shabeeb[2], Katherine Elizabeth Eberly[2], Veronica Nguyen[3], Janus Ong[4], Saleh A Alqahtani[5,6] and Zobair M. Younossi[3,7,8], (1)Center for Outcomes Research in Liver Diseases, Washington, DC, (2)Inova Health Systems Medicine Service Line, Falls Church, VA, (3)Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, (4)College of Medicine, University of the Philippines, Manila, Philippines, (5)Johns Hopkins University School of Medicine, (6)King Faisal Specialist Hospital and Research Center, (7)Center for Liver Disease, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, VA, (8)Inova Medicine, Inova Health System, Falls Church, VA

Background: Indications for liver transplantation (LT) may vary between different age groups. Our aim was to assess trends in indications and outcomes in teenagers listed for LT in the U.S. **Methods:** We used the Scientific Registry of Transplant Recipients (SRTR) 2008-2022 to collect data for all teenagers (13-19 y) listed for a LT in the U.S. The study outcomes were receiving a LT and time to post-transplant mortality for recipients. The cut-off date for the outcomes was March 2, 2023. **Results:** There were 2,813 teenage LT candidates listed between 2008 and 2022. Mean age was 17 years (SD 2), 45% male, 57% white, 17% black, 5% Asian, 19% Hispanic, 95% U.S. citizens, and 39% covered by Medicaid. Mean MELD score was 19.4 (SD 10.5). The most common indication for LT was acute liver disease (24%), followed by biliary atresia or hypoplasia (12%), autoimmune hepatitis (11%), and primary sclerosing cholangitis (PSC) (10%). At the same time, the prevalence of chronic viral hepatitis (B or C), NASH, and alcoholic liver disease (the most common indications for LT in adults) did not exceed 1%. Nevertheless, 2.8% of teenage candidates also had hepatocellular carcinoma (HCC). There were no significant differences in the distributions of LT indications between subgroups of younger (12-16) vs. older (17-19) teenagers, with the exception of PSC which was less common among younger patients: 8% vs. 12% ($p < 0.01$). Excluding two most recent years (2021,2022), 67% received a LT after a mean of 217 days (SD 372) after listing. This rate remained stable during the study years ($p > 0.05$). In addition, 13% of candidates were removed from the list due to improvement and 9% died or deteriorated while waiting for a LT. In multivariate analysis, independent predictors of a higher chance of receiving a LT included more recent calendar year, younger age, higher MELD score, and a listing diagnosis of acute liver disease or copper metabolism-related liver disease (all $p < 0.01$). In those who received a LT, 3-year survival was 90% with a trend in improvement from the early study years (86%) to those transplanted in 2017-2019 (91%, $p = 0.07$). Higher post-transplant mortality in adolescents was associated with older age, having Medicaid, being re-transplanted, and having HCC (adjusted hazard ratio [aHR] > 1, all $p < 0.01$), while listing diagnoses of copper and other metabolism-related liver diseases were associated with lower post-transplant mortality (aHR < 1, all $p < 0.01$). **Conclusion:** Indications for liver transplantation among teenagers in the U.S. are different from those recorded for adults or younger children. There is a trend towards improvement of post-transplant outcomes in teenagers in the U.S.

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Disclosure information not available at the time of publication: Dipam Shah, Reem Al Shabeeb, Katherine Elizabeth Eberly, Veronica Nguyen, Janus Ong

1093-A | LOW SOCIOECONOMIC STATUS IS NOT ASSOCIATED WITH LONG-TERM POST-LIVER TRANSPLANT SURVIVAL

Gabriella Aitcheson[1], Sanjna Vinze[2], Marwan S. Ghabril[1], John Holden[2], Naga P. Chalasani[3], Marco Lacerda[1], Chandrashekhar Kubal[1] and Lauren D. Nephew[1], (1)Indiana University, (2)Indiana University School of Medicine, (3)Indiana University Medical Center, Indianapolis, IN

Background: Social determinants of health (SDOH) have been associated with poor waitlist outcomes. However, it is unclear how these factors affect short and long-term post-liver transplant (LT) survival. Further understanding the full spectrum of predictors of post-LT outcomes will be an important part of continuous distribution modeling. We aim to explore the impact of individual- and area-level social determinants of health (SDOH) on this outcome. **Methods:** Adults who underwent LT at Indiana University Hospital from 12/2011 to 6/2019 were included. Demographics, clinical variables, and individual-level SDOH were collected from our transplant database and EMR. Addresses were linked to the American Community Survey to determine census-tract level SDOH and rural vs. urban residence. Low-SES was defined as being insured by Medicaid,

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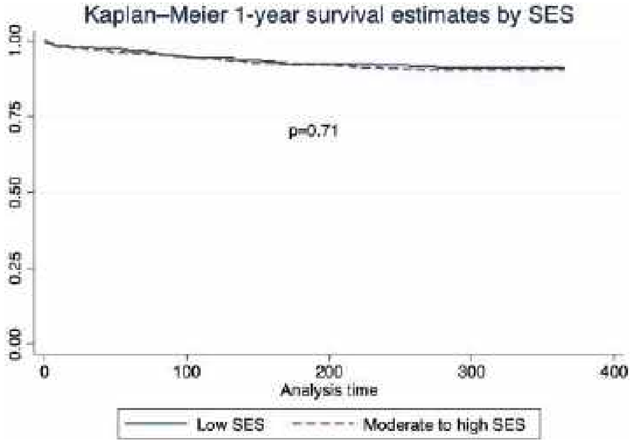
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

having disability income, or living in a neighborhood in the highest quartile for income below the federal poverty level. Multivariable Cox survival analysis was used to explore the association between these SDOH and death/graft loss at 1, 3 and 5-years. **Results:** The cohort included 687 patients with 34% women and 5% Black race. The most common etiology was viral hepatitis (47%) followed by NASH (24%). HCC occurred in 23% and the median MELD at LT was 22 (IQR 18-26). Regarding the SDOH, 39.2% of the cohort had high school level education or less, 36.5% were insured by Medicaid, 41.3% received their income from disability, 29.4% were unmarried/without partner, 20.1% of residents lived in neighborhoods in the fourth quartile for highest proportion of incomes below the federal poverty level. 65.7% of patients in this cohort were defined as low-SES. Death or graft loss occurred in 158 patients over a median follow up time of 5.7 years (IQR 4.0-7.25). Survival rates were 91.0%, 82.1%, and 62.2% at 1,3, and 5-year respectively. On multivariable 1-year survival analysis, there was a significantly higher hazard of mortality in those who received disability income (HR 4.46, 95% CI 1.83-10.89, $p < 0.001$) and those with NASH compared to hepatitis-c virus (HR 2.62, 95% CI 1.02-6.72, $p = 0.045$). Three-year survival was associated only with MELD at LT (HR 1.03, 95% CI 1.003-1.05, $p = 0.027$). There were no significant predictors of 5-year survival. Low SES did not predict 1, 3, or 5-year survival (figure). **Conclusion:** Despite a large portion of this cohort being of low SES, only disability income was associated with short-term post-LT mortality. There was no association between SDOH and longer-term survival. This suggests that thorough pre-LT evaluations may select the "fittest" candidates, even in the face of a high burden of adverse SDOH. Furthermore, as UNOS works to implement a continuous distribution model that facilitates more patient-centric and equitable organ allocation, elucidating how to equitably incorporate post-LT outcomes will be critical.



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1094-A | MULTIDISCIPLINARY CARE IMPROVES TRANSPLANT RATES IN CRITICALLY ILL PATIENTS WITH ADVANCED LIVER DISEASE

Alaina Miller[1], Aanchal Kapoor[1], Gianina Flocco[1], Stephanie Bass[1], Bridget Dolan[1], Jamak Modaresi Esfeh[2], Koji Hashimoto[1] and Christina C. Lindenmeyer[1], (1)Cleveland Clinic, (2)Cleveland Clinic, Pepper Pike, OH

Background: One of only a few liver-specific Intensive Care Units (ICU), the Medical Intensive Liver Unit (MILU) offers multidisciplinary care for critically ill patients with advanced liver disease, including patients waiting or being evaluated for liver transplant (LT). The goal of this improved care model has been to optimize and standardize evidence-based management, and to promote opportunities for LT. We aimed to determine the impact of the MILU model on end points of care and rates of LT. **Methods:** The MILU opened at a large quaternary referral LT center in August 2018. Consecutive MILU patients admitted between 08/2018 and 05/2023 were included and compared to patients admitted to the medical ICU (pre-MILU) between 09/2017 and 08/2018. Pre-MILU patients were defined as having decompensated cirrhosis or acute liver failure identified by ICD-9 codes and confirmed by chart review. Patients were followed from admission to discharge, death or LT (and if transplanted, for 12 months post-LT). MILU data was extracted from a prospectively maintained longitudinal registry; pre-MILU data was retrospectively extracted from the electronic health record. Demographics, diagnosis, clinical and transplant data was collected. The 2-sample t-test was used to compare severity of liver disease between cohorts. **Results:** Out of 1366 MILU admissions, 1011 individual patients were included in the MILU cohort; 293 patients were included in the pre-MILU cohort. The most common etiology of liver disease was alcohol-associated in both the pre-MILU and MILU cohorts

(42% versus 44%). Prior to MILU inception, only 37% of patients meeting MILU criteria were seen by Hepatology in ICU; 100% of MILU patients were co-managed by ICU and Transplant Hepatology. Compared to pre-MILU patients, MILU patients had increased severity of liver disease stratified by the MELD-Na score (24.08 vs 26.35, $p = 0.0005$). In the 12 months prior to MILU, 5 patients were bridged from ICU to LT, whereas in calendar year 2021, 30 (of 189 admitted) patients were transplanted directly from MILU, with improved 1-year post-LT survival (80% versus 93.3%). **Conclusion:** The MILU's unique clinical care pathways, the products of inter-professional collaboration and expertise, have improved care and facilitated expedited access to LT providers. Our experience demonstrates an expected temporal increase in severity of illness and enhanced collaboration, with the product being higher rates of successful LT for critically ill patients associated with improved post-LT survival. Formalized sub-specialty multi-disciplinary intensive care services may be proposed as a future standard of care for large LT centers.

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1095-A | NATURAL COURSE AND PROGNOSTIC SIGNIFICANCE OF INTRA-OPERATIVE SPONTANEOUS BACTERIAL PERITONITIS: A SINGLE-CENTER CASE-SERIES

Joseph Cappuccio[1], Karim Osman[1], Cristina Batarseh[1], Brenda Amuchi[1] and Amir Ahmed Qamar[2], (1)Lahey Hospital and Medical Center, (2)Lahey Clinic Medical Center

Background: Patients with decompensated cirrhosis carry an increased risk for life-threatening infections. Specifically, patients with clinically significant ascites may develop spontaneous bacterial peritonitis (SBP) which perturbs a high mortality rate without prompt intervention. Despite this, the post-transplant ramifications of undetected or undertreated SBP have been minimally investigated to date. As such, our evaluation tracks the natural course of specific instances of intraoperative SBP (IOSBP) identified via ascitic fluid analysis performed at the time of liver transplantation (LT). **Methods:** We retrospectively reviewed a cohort of 428 patients who underwent LT between January 2015 and December 2020. We defined IOSBP by an absolute neutrophil count (ANC) e 250/μL and/or a positive culture in ascitic fluid obtained during LT. Subjects were followed from the time of LT until last follow-up or death. **Results:** We identified fifteen total patients who met criteria for IOSBP. Of these, eleven patients (2.6%) had culture positive ascitic fluid, three (0.7%) had ANC > 250, and one (0.2%) had both culture positive ascites and ANC > 250. Of the fifteen patients identified, three patients died at the time of follow-up, and one patient died within one year of LT. Additional baseline and clinical features are available in Table 1a & b. Figure 1 describes the natural course of IOSBP for all fifteen patients. **Conclusion:** Our study adds to the limited data evaluating any prognostic link between perioperative infection and post-operative outcome in the setting of LT. Our review further suggests the possibility of an otherwise clinically silent phenomena which may persist in patients with decompensated cirrhosis even despite appropriate antimicrobial prophylaxis following index spontaneous bacterial peritonitis. Our limited sample size restricted our ability to perform a meaningful comparative statistical analysis. Still, further analyses are needed to determine pre-operative risk factors which may impact post-transplant outcomes.

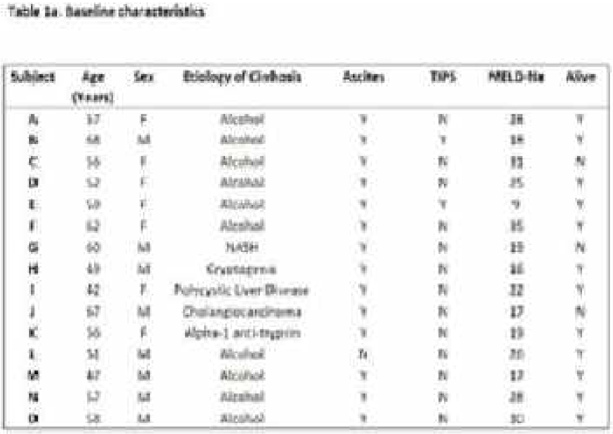


Table 1a. Baseline characteristics

Subject	Age (Years)	Sex	Etiology of Cirrhosis	Ascites	TIPS	MELD-Na	Alive
A	57	F	Alcohol	Y	N	28	Y
B	68	M	Alcohol	Y	Y	19	Y
C	56	F	Alcohol	Y	N	33	N
D	52	F	Alcohol	Y	N	25	Y
E	59	F	Alcohol	Y	Y	9	Y
F	62	F	Alcohol	Y	N	35	Y
G	60	M	NASH	Y	N	23	N
H	49	M	Cryptogenic	Y	N	16	Y
I	42	F	Polycystic Liver Disease	Y	N	22	Y
J	67	M	Cholangiocarcinoma	Y	N	17	N
K	56	F	Alpha-1 anti-trypsin	Y	N	19	Y
L	51	M	Alcohol	N	N	20	Y
M	47	M	Alcohol	Y	N	17	Y
N	57	M	Alcohol	Y	N	28	Y
O	58	M	Alcohol	Y	N	30	Y

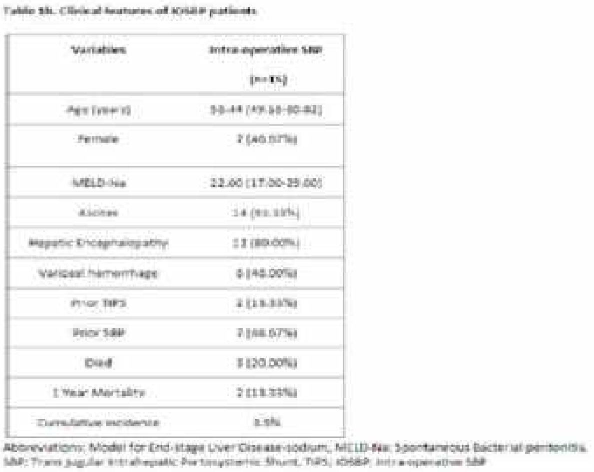
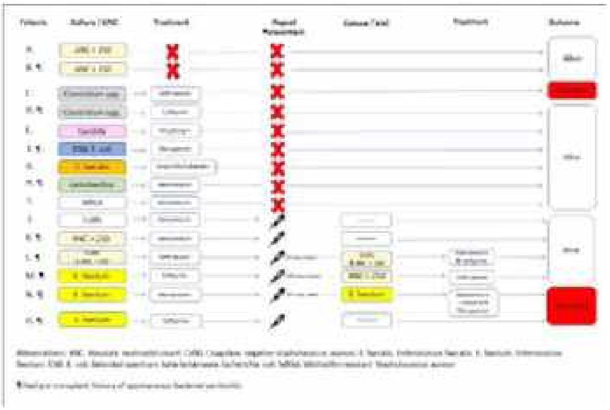


Table 1b. Clinical features of IOSBP patients

Variables	Intra-operative SBP (n=15)
Age (years)	58.44 (49.33-60.82)
Female	7 (46.67%)
MELD-Na	22.00 (17.00-25.00)
Ascites	14 (93.33%)
Hepatic Encephalopathy	12 (80.00%)
Variceal hemorrhage	6 (40.00%)
Prior TIPS	2 (13.33%)
Prior SBP	7 (46.67%)
Died	3 (20.00%)
1 Year Mortality	2 (13.33%)
Cumulative incidence	3.5%

Abbreviations: Model for End-stage Liver Disease-sodium, MELD-Na; Spontaneous bacterial peritonitis, SBP; Trans jugular intrahepatic Portosystemic Shunt, TIPS; IOSBP: Intra-operative SBP



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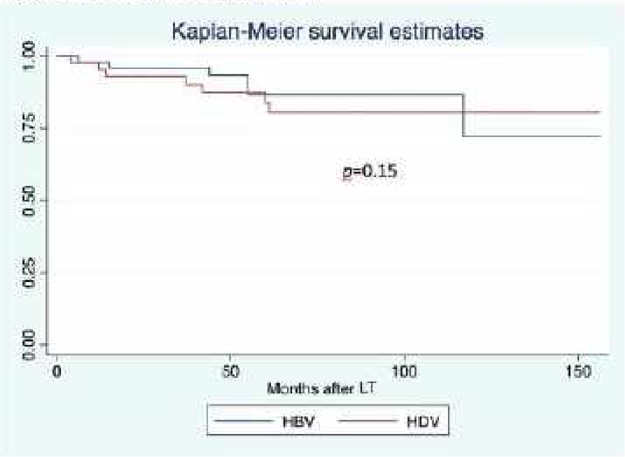
1096-A | NATURAL HISTORY OF LIVER TRANSPLANTATION FOR HBV AND HDV INFECTION OVER 30 YEARS: A SINGLE CENTER EXPERIENCE IN ITALY

Clara Dibenedetto[1], Lorenzo Canova[1], Elia Fracas[1], Elisa Farina[1], Michele Sagasta[1], Sonia Stella[1], Barbara Antonelli[2], Lucio Caccamo[2], Pietro Lampertico[1,3] and Maria Francesca Donato[1], (1)Division of Gastroenterology and Hepatology, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, (2) Division of General Surgery, Liver Transplant Center, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, (3)CRC "a. M. and a. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan

Background: Hepatitis Delta (HDV) and hepatitis B (HBV) virus infections might both induce end-stage liver disease (ESLD) and/or hepatocellular carcinoma (HCC) leading to liver transplant (LT). This study aims to compare epidemiological features and clinical outcomes of HDV and HBV recipients transplanted at Policlinico Maggiore Hospital Milan, Italy. **Methods:** We enrolled in the study 265 patients transplanted for ESLD/HCC due to HDV and HBV infections in the last 30 years. **Results:** Based on preliminary data from 104 LT recipients transplanted between 2010 to 2022, 55 showed HBV etiology (52,8%) and 49 were HDV-infected. The indication for LT for HCC was higher for HBV-LT recipients compared to HDV ones (41.5% vs 22.4%; $p = 0.494$) while ESLD was the prevalent indication in patients transplanted for HDV infection (77.6% vs 30,2%; $p < 0.001$). Acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) as indications to LT were registered in 13 (24.5%) and 2 (3.8%) HBV recipients respectively. No cases of ALF/ACLF were observed among HDV infected LT recipients. The median age at the time of transplantation was significantly lower in HDV patients compared to HBV (49 vs 60 years old respectively; $p < 0.001$). Diabetes and chronic kidney disease after LT were significantly higher in HBV recipients ($p < 0.01$ and $p < 0.006$, respectively). However, there were no significant differences in post-transplant survival (see Figure 1), recurrence of HBV infection, recurrence of HCC and episodes of graft rejection between the two groups. In 18 patients, hepatitis B immunoglobulin (HIGB) were discontinued during late post-transplant follow up and no cases of HBV recurrence were observed. Notably, 2 patients were treated with HDV therapy (bulevirtide) before transplantation. **Conclusion:** As expected HDV recipients were younger than HBV infected patients at LT, reflecting the more aggressive course of HDV infection. Nevertheless, a similar post-transplant survival was observed in both groups. Limited data are currently available regarding the impact of bulevirtide on post-transplantation outcomes. The analysis of the whole cohort of HBV and HDV transplanted patients will be presented at the meeting.

Figure 1. HBV and HDV survival post-LT



Disclosures: Pietro Lampertico – BMS: Advisor, No, No; ROCHE: Advisor, No, No; GILEAD SCIENCES: Advisor, No, No; GSK: Advisor, No, No; ABBVIE: Speaking and Teaching, No, No; MSD: Advisor, No, No; ARROWHEAD: Advisor, No, No; ALNYLAM: Advisor, No, No; JANSSEN: Advisor, No, No; SBRING BANK: Advisor, No, No; MYR: Advisor, No, No; EIGER: Advisor, No, No; ANTIOS: Advisor, No, No; ALIGOS: Advisor, No, No; VIR: Advisor, No, No;
The following people have nothing to disclose: Clara Dibenedetto, Lorenzo Canova, Elia Fracas, Elisa Farina, Michele Sagasta, Sonia Stella, Barbara Antonelli, Lucio Caccamo, Maria Francesca Donato

1097-A | NEUROLOGIC COMPLICATIONS EARLY AFTER LIVER TRANSPLANT

Michelle Knizner[1], Heather S. Snyder[1], Sarah Todd[1] and Ram M. Subramanian[2], (1)Emory University Hospital, (2)Emory University

Background: Liver transplant recipients are at risk for developing neurologic complications early after transplant. Perioperative factors may alter risk, including etiology of liver disease, Model for End-Stage Liver Disease (MELD) score, hepatic encephalopathy, and medication use. The purpose of this study was to identify perioperative risk factors for neurologic complications post-liver transplant. **Methods:** A single-center, retrospective, case-control study was conducted of adult liver transplant recipients from 2017-2022. Patients were placed into one of two cohorts: those who experienced a neurologic complication within 30 days post-transplant versus those who did not. The primary outcome was the association between perioperative factors and post-transplant neurologic complications. Secondary outcomes included incidence of neurologic complications, change in immunosuppression (IS) regimen, and hospital length of stay. **Results:** There were 614 liver transplants that occurred during the prespecified time frame, and 1 patient was excluded due to age. Of the remaining 613 patients, 162 (26%) experienced a neurologic complication and 451 did not. The following perioperative factors were significantly higher in the neurologic complication group: white race, alcoholic cirrhosis, nonalcoholic steatohepatitis, history of hepatic encephalopathy (HE), MELD score ≥ 30, chronic kidney disease, hepatorenal syndrome, need for continuous renal replacement therapy (CRRT) pre-transplant, pre-transplant hospital length of stay, and pre-transplant ICU stay. These variables were included in a binary logistic regression, and history of HE ($p < 0.001$), MELD ≥ 30 ($p = 0.04$), hepatorenal syndrome ($p = 0.04$), and CRRT ($p = 0.002$) were associated with the development of neurologic complications. The IS regimen was changed from tacrolimus to cyclosporine in 46% of patients who experienced a neurologic complication. The median post-transplant hospital length of stay was significantly longer in patients experiencing with a neurologic complication (16 d in neurologic complication arm vs. 9 d in those without neurologic complication, $p < 0.001$). **Conclusion:** Perioperative factors associated with the development of post-liver transplant neurologic complications include HE, high MELD, hepatorenal syndrome, and use of CRRT. Monitoring patients with one or more of these factors may be useful in identifying neurologic complications and optimizing management post-transplant.
Disclosures: The following people have nothing to disclose: Michelle Knizner, Heather S. Snyder, Sarah Todd, Ram M. Subramanian

1098-A | NUMBER OF LIFE-YEARS GAINED IN RELATION TO RECIPIENT AGE IN LIVER TRANSPLANT

Bishoy Lawendy[1], Shiyi Chen[2], Mouaid Alim[2,3] and Mamatha Bhat[2,3], (1)University of Western Ontario, (2) University Health Network, (3)University of Toronto

Background: Liver transplant (LT) is lifesaving for patients with end stage liver disease. However, it is unclear how many additional years of benefit are derived based on the age of the recipient, and how this compares to the life expectancy of the general population across age groups. **Methods:** We used data from the Scientific Registry of Transplant Recipients (SRTR). Adults transplanted after 1st of January 2003 surviving > 1 year or waitlisted were included. The SRTR data system includes data on all donor, waitlisted candidates, and transplant recipients in the US. Cox hazard model MVA was used to analyze the risk factors for mortality. Life expectancy was calculated as the area under survival curve. Given the limitations on SRTR dataset, our follow up was maximum 16 years. **Results:** We included 101,770 individual's (82,514 transplanted and 19,256 non-transplanted). One year post LT, life expectancy based on age of LT was: 12.46 years (20s), 12.87 years (30s), 12.72 years (40s), 11.56 years (50s), 10.91 years (60s), & 9.53 years (70s). Figure 1 displays life expectancy post LT stratified by sex and age in comparison to the US general population. Males without diabetes had significantly longer life expectancy at transplant than diabetic males: 50s (11.7 vs 10.4 y, $p = 0.0009$); 60s (11.1 vs 9.8 y, $p = 0.0002$); 70s (10.4 vs 7.2 y, $p = 0.001$). Compared to the general U.S. population, life expectancy in our study sample was significantly shorter. LT improved survival significantly relative to patients on the waitlist in all age groups with 5 years added (18-30 y old), 6.5 years added (30-50 y old), 6.4 years added (50-70 y old), & 3.9 years added (> 70 y old). In the LT cohort, the proportion of patients whose cause of death graft failure was: 22.7% (18-30 y old), 13.7% (30-50 y old), 7.1% (50-70 y old) & 2.9% (> 70 y old). Male sex, diabetes, & history of coronary artery disease were negatively correlated with survival (HR 1.19, $p < 0.001$), (HR 1.32, $p < 0.001$), (HR 1.32, $p < 0.001$). **Conclusion:** Our findings demonstrate a consistent survival benefit of LT across ages studied, and that life expectancy was not necessarily greater among younger recipients. Young recipients (18-30 y) had a higher proportion of graft failure as their cause of death. Recipients across age groups had 2.67 times greater mortality than the general population, indicating the need for significant efforts to optimize long-term survival after LT. It is important to interpret these results in the context of our follow up as our follow up was 16 years, which might underestimate life expectancy in younger patients.

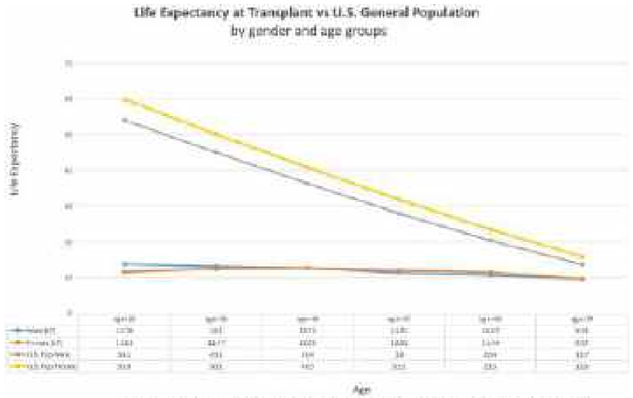


Figure 1: Life expectancy post LT stratified by sex and age in comparison to the US general population.

Disclosures: The following people have nothing to disclose: Bishoy Lawendy, Shiyi Chen, Mouaid Alim, Mamatha Bhat

1099-A | OPIOID USE AFTER LIVER TRANSPLANTATION: PREDICTORS OF HIGH RISK USE AND OPIOID-RELATED COMPLICATIONS

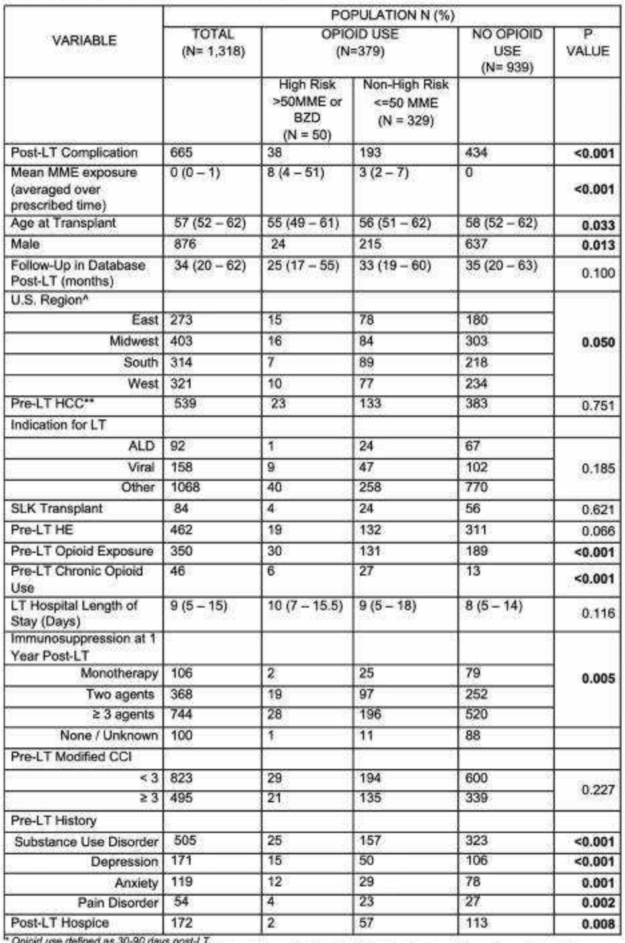
Olgert Bardhi[1], Yue Jiang[2], Alex R. Jones[1], Prajwal Gowda[3], Madhukar Patel[1], Van Ngo[1], Mary Olumesi[1], Jessica Francois Whitt[1], Raelene E. Trudeau[1], Alvaro Noriega Ramirez[1], Arjmand R. Mufti[1], Lisa B. VanWagner[1], Amit G. Singal[1] and Sarah Rosanna Lieber[1], (1)University of Texas Southwestern Medical Center, (2)Duke University Medical Center, (3)UT Southwestern School of Medicine

Background: Opioid use disorder contributes to high morbidity and mortality. Liver transplant recipients (LTRs) are a high risk population given potential preexisting substance use and psychiatric comorbidities, but limited data exist on opioid use after LT at the national level. We assessed opioid use, prescribing practices, factors associated with high-risk use, and opioid-related complications among LTRs. **Methods:** Adult LTRs were identified using CPT codes from 2006-2021 in IQVIA Pharmetrics Plus, a medical and pharmacy database nationally representative of commercially insured patients. ICD 9/10 codes were used to identify complications associated with opioid use, defined as suicide/self-harm, substance use disorder, chronic pain syndromes, altered mental status, or fractures/falls. Opioid use was evaluated 30-90 days post-LT; high risk use was defined as > 50 morphine milligram equivalents (MME) per day or concurrent benzodiazepine use. We identified factors associated with high-risk use using a multivariable logistic regression model. Landmark survival analysis using a multivariable proportional hazards regression model was used to assess associations between opioid use and complications. **Results:** We identified 1,318 LTRs, of whom 379 (28.8%) had opioid use–50 with high-risk opioid use. In multivariable analysis, female sex (aOR 2.74 [95% CI: 1.45, 5.23]), pre-LT opioid use (aOR 3.64 [1.96, 6.84]), and depression (aOR 2.15 [1.01, 4.38]), were significantly associated with high-risk opioid use. Opioid complications were observed in 231 (61%) of opioid users. In landmark analysis, non-high risk and high risk opioid use were associated with increased complications (aHR 1.43 [95% CI: 1.20, 1.70] and aHR 2.10 [1.45, 3.04], respectively). In multivariable analysis, age at LT > 50 years (aHR 1.28 [[1.06, 1.56]), pre-LT depression (aHR 1.46 [1.16, 1.84]), anxiety (aHR

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

1.45 [1.11, 1.89]), pain disorder (aHR 1.94 [1.36, 2.76]), substance use disorder (aHR 1.66 [1.40, 1.98]), modified Charlson comorbidity score > 3 (aHR 1.56 [1.29, 1.87]), alcohol-associated liver disease (aHR 1.47 [1.10, 1.98]), and pre-LT opioid use (aHR 1.22 [1.02, 1.47]) were associated with complications. **Conclusion:** More than 1 in 4 LTRs used opioids within 3 months of LT. Worse clinical outcomes were seen among opioid-users, especially those with high-risk use. Use of prescription opioids, particularly in high doses and with benzodiazepines, should be cautioned in post-LT patients especially among vulnerable populations with psychiatric comorbidities.

Table 1: Sociodemographic and Clinical Characteristics of Adult Liver Transplant Recipients Stratified by Opioid Use Post-LT* (N=1,318)



VARIABLE	POPULATION N (%) TOTAL (N= 1,318)	OPIOID USE (N=379) High Risk >50MME or BZD (N = 50)	OPIOID USE (N=379) Non-High Risk <=50 MME (N = 329)	NO OPIOID USE (N= 939)	P VALUE
Post-LT Complication	665	38	193	434	**<0.001**
Mean MME exposure (averaged over prescribed time)	0 (0 – 1)	8 (4 – 51)	3 (2 – 7)	0	**<0.001**
Age at Transplant	57 (52 – 62)	55 (49 – 61)	56 (51 – 62)	58 (52 – 62)	**0.033**
Male	876	24	215	637	**0.013**
Follow-Up in Database Post-LT (months)	34 (20 – 62)	25 (17 – 55)	33 (19 – 60)	35 (20 – 63)	0.100
U.S. Region^					**0.050**
East	273	15	78	180	
Midwest	403	16	84	303	
South	314	7	89	218	
West	321	10	77	234	
Pre-LT HCC**	539	23	133	383	0.751
Indication for LT					
ALD	92	1	24	67	0.185
Viral	158	9	47	102	
Other	1068	40	258	770	
SLK Transplant	84	4	24	56	0.621
Pre-LT HE	462	19	132	311	0.066
Pre-LT Opioid Exposure	350	30	131	189	**<0.001**
Pre-LT Chronic Opioid Use	46	6	27	13	**<0.001**
LT Hospital Length of Stay (Days)	9 (5 – 15)	10 (7 – 15.5)	9 (5 – 18)	8 (5 – 14)	0.116
Immunosuppression at 1 Year Post-LT					**0.005**
Monotherapy	106	2	25	79	
Two agents	368	19	97	252	
≥ 3 agents	744	28	196	520	
None / Unknown	100	1	11	88	
Pre-LT Modified CCI					
< 3	823	29	194	600	0.227
≥ 3	495	21	135	339	
Pre-LT History					
Substance Use Disorder	505	25	157	323	**<0.001**
Depression	171	15	50	106	**<0.001**
Anxiety	119	12	29	78	**0.001**
Pain Disorder	54	4	23	27	**0.002**
Post-LT Hospice	172	2	57	113	**0.008**

** Opioid use defined as 30-90 days post-LT.*
*** All pre-LT conditions were evaluated 6 months prior to and 30 days after LT index date in order to avoid conflicting with exposure assessment window.*
^ 7 missing
Abbreviations: ALD: alcoholic liver disease; BZD: Benzodiazepine; LT: liver transplant; MME: morphine milligram equivalents; SLK: simultaneous liver kidney; CCI: Charlson comorbidity index; HCC: hepatocellular carcinoma; HE: hepatic encephalopathy.

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1100-A | OUTCOMES ASSOCIATED WITH RECURRENT AUTOIMMUNE LIVER DISEASE FOLLOWING LIVER TRANSPLANTATION IN PATIENTS AT TERTIARY REFERRAL CENTER OF MEXICO

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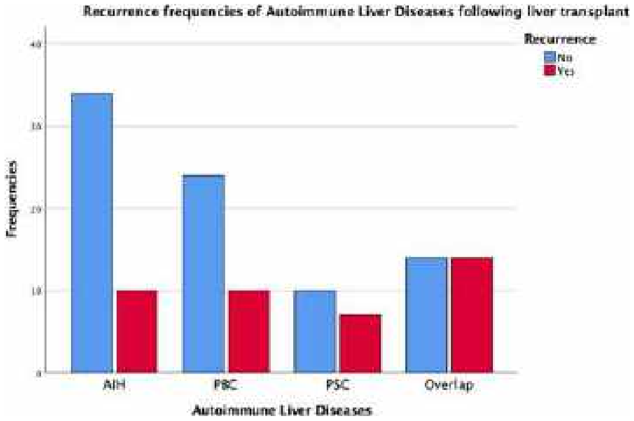
Background: Autoimmune Liver Disease (AILDs) involves Autoimmune Hepatitis (AIH), Primary Biliary Cholangitis (PBC), Primary Sclerosing Cholangitis (PSC) and Overlap Syndromes (OS). Liver transplant (LT) represents the treatment in advance stages and has a 5-year survival greater than 70%, approximately. Recurrence after LT is common (17-41%) and has been associated with decreased graft survival, the need of re-transplantation and whether it reduces long-term survival. **Aim:** To describe the prevalence of AILDs recurrence, risk factors, recurrence-free-survival (RFS) and long-term survival. **Methods:** A Cross-sectional retrospective study of patients diagnosed with AILDs (by biopsy, Cholangiopancreatography or Paris criteria according to etiology) who underwent orthotopic LT from January 2000 to December 2021, was performed. We analyzed age, sex, comorbidities, biochemical data, MELD score, Child-Pugh, presence of recurrence (based on AASLD guidelines), graft rejection and use of immunosuppressant. Frequencies, Hazard-ratios (CI95%), Student's t-test or U-Mann-Whitney, and Kaplan-Meyer survival analysis (Log-Rank) were reported. **Results:** Of 500 patients who underwent LT, 123 (24.6%) had AILDs as etiology. Female sex was the most prevalent (74.8%), mean age was 52 ± 13.3 years-old. AIH, PBC, PSC and OS corresponded to 35.8, 27.6, 13.8 and 22.7%, respectively. Most had a Child-Pugh C (61.8%). Recurrence was found in 32.5%, being more prevalent in OS (50%). The median days-to-recurrence was 881 (50-3384). RFS was lower in patients with age-at-LT < 42 years-old (Log rank $p = 0.002$), autoimmune comorbidity (Log rank $p = 0.03$), > 1.1 IgG reference levels (Log rank

$p = 0.03$) and initial immunosuppression with Basiliximab (Log rank $p < 0.001$). Elevated pre-LT IgG levels (2896.8 ± 1281 vs. 21268 ± 22 mg/dL, $p = 0.005$) and prolonged use of Mycophenolate mofetil ($p < 0.001$) were associated with overall recurrence of AILDs and AIH+OS group. Graft rejection occurred in 26% (21.1% acute), being more frequent in AIH (29.5%) and PBC (29.4%). Overall-survival at 5 and 10 years was 89 and 84%, respectively. 12.2% of patients died; initial immunosuppression with Daclizumab was associated with higher risk of mortality (HR 5.8, CI95% 0.39-0.94, $p = 0.01$) compared to Basiliximab group. **Conclusion:** The recurrence in AILDs after LT was 32.5% and agrees with previously described. RFS at 1 and 5 years are 99% and 88.8%, respectively. Factors associated with lower RFS are age < 42 years-old at LT, prolonged use of Mycophenolate Mofetil, higher levels of IgG Pre-LT and initial immunosuppression with Basiliximab. No difference in long term survival was found in the presence of recurrence. Initial induction with Daclizumab was associated with higher risk of mortality.



Disclosures: The following people have nothing to disclose: Carolina Ivette Ivette Zubia-Nevárez, Ignacio García Juárez, Leticia Martínez

1101-A | OUTCOMES FOLLOWING USE OF HEPATITIS B SURFACE ANTIGEN POSITIVE LIVER ALLOGRAFTS IN HEPATITIS B SURFACE ANTIGEN NEGATIVE RECIPIENTS

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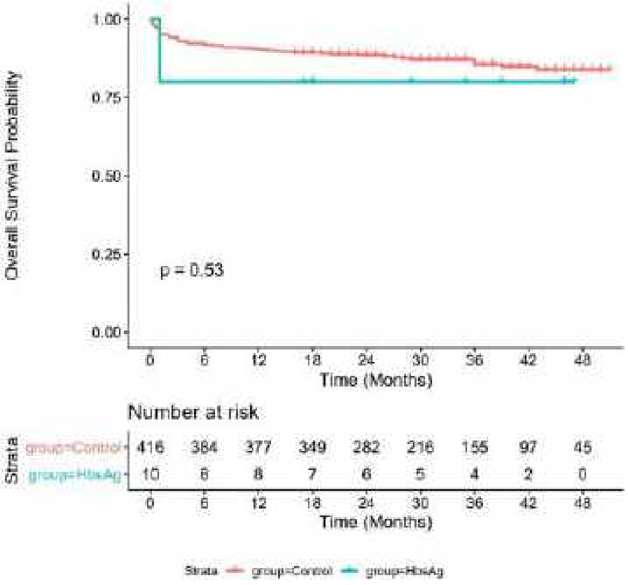
Background: Liver transplantation remains the definitive treatment for patients with cirrhosis. There is a large gap between the number of organs available and the number of organs needed. The use of hepatitis B surface antigen positive (HBsAg+) grafts remains controversial, and outcomes have yet to be defined. **Methods:** A retrospective review of using HBsAg+ organs was performed. Data were collected in accordance with hospital protocol. Post transplant monitoring of HBV DNA and HBsAg was done at 3-and 12-month intervals, followed by surveillance. Between 2019 and 2021, 10 HBsAg negative recipients at a single institution received HBsAg+ donor livers. All liver allografts were also HBV NAT+. 4 recipients were nonreactive to Anti-HBc and Anti-HBs, 5 were reactive to Anti-HBs and nonreactive to Anti-HBc and 1 was reactive to Anti-HBc and Anti-HBs. 7 were female, 3 were male, mean age at time of transplant (60.2 ± 6.0), BMI (30.8 ± 8.6), and MELD-Na (16 ± 5.7). Etiologies of cirrhosis were NASH (n = 4) alcohol (n = 3), cryptogenic (n = 1), colon metastasis (n = 1), and hepatitis C (n = 1). All patients received standard immunosuppression, and entecavir 0.5 mg daily was initiated post operatively on day 0 and continued indefinitely. **Results:** 2 patients died post-operatively at 1-month related to complications of sepsis and thrombosis, respectively. Out of the 8 patients at the 3-month mark, 4 patients had no detectable serum HBV DNA and remained undetectable. 2 recipients had detectable serum HBV DNA at 3 months, but this disappeared in subsequent evaluations. 2 patients had persistent HBV DNA levels. The first had an initial HBV DNA of 8000 IU/mL, which plateaued to 1200 IU/mL on entecavir, and switched to tenofovir alafenamide (TAF), and then tenofovir disoproxil fumarate (due to cost) and remained undetectable. The other recipient had an HBV DNA level of 4208 IU/mL, which increased to 40000 IU/mL while on entecavir, but a switch to TAF led to undetectable levels. 5 patients became HBsAg+ and 1 patient was not checked for HBsAg. 2 recipients achieved loss of HBsAg within 2 and 3 years post operatively. Kaplan Meier analysis showed no difference in survival compared to all transplants done at our center in the same period ($p = 0.53$, HR = 1.59, CI = 0.39- 6.51). **Conclusion:** There is limited guidance on the use of HBsAg+ liver allografts and experience are primarily limited to HBsAg+ recipients. In our case series, the use of these organs in HBsAg negative recipients did not affect graft function or survival.



Disclosures: The following people have nothing to disclose: Adam Seth Myer, Drake Seccurro
Disclosure information not available at the time of publication: Kenneth E. Sherman, Yeshika Sharma

1102-A | OUTCOMES IN PATIENTS WITH AND WITHOUT LIVER CIRRHOSIS FOLLOWING EMERGENCY SURGERY FOR INCARCERATED VENTRAL HERNIA

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Background: Patients with cirrhosis are complex surgical candidates, carrying high rates of morbidity and mortality. We sought to classify surgical risk in the management of incarcerated ventral hernia in patients with cirrhosis compared to patients without cirrhosis undergoing the same intervention. **Methods:** In this retrospective chart review, we identified adults who underwent emergency surgery for incarcerated ventral hernia at an academic tertiary referral and liver transplant center from October 2017- April 2023. Patients with a recorded diagnosis of cirrhosis were identified. Intraoperative and postoperative factors including length of stay (LOS), ICU LOS, and mortality at discharge and within 1 year were collected for all patients. Data were collected to determine MELD-Na and Child-Pugh-Turcotte (CPT) score for patients in the cirrhosis group. **Results:** Ninety-one patients met inclusion criteria with 64 (70%) patients in the non-cirrhosis group and 27 (29.6%) patients in the cirrhosis group (2 CPT-A, 17 CPT-B, 8 CPT-C). The cirrhosis group had significantly greater 1-year mortality (11/27; 41%) compared to the non-cirrhosis (6/64; 9%) group ($p < 0.01$). The cirrhosis group additionally had a longer mean LOS ($p = 0.01$) and required more frequent admission to the ICU ($p < 0.01$), postoperatively. Bowel resection occurred more frequently in patients with cirrhosis ($p = 0.02$). **Conclusion:** We demonstrate significantly increased morbidity and mortality in patients with cirrhosis undergoing emergency surgery for incarcerated ventral hernia. Guidelines on timing and management of surgery among patients with cirrhosis remain controversial, but consideration of elective interventions to avoid emergent surgery in patients with cirrhosis is warranted.
Disclosures: The following people have nothing to disclose: Alex Richard, Adam Skura, Nicole Cherng, Richard Perugini, James Carroll

1103-A | OUTCOMES OF ACUTE PANCREATITIS AMONG LIVER TRANSPLANTATION PATIENTS: ANALYSIS OF NATIONAL INPATIENT SAMPLES

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Background: Liver transplantation is associated with an increased burden of medical diseases including higher incidence and severity of acute pancreatitis compared to the general population. There is however scarce data related to outcomes of acute pancreatitis among patients with a transplanted liver compared to the general population. We aimed to compare these two populations and determine if hepatic transplantation status was associated with worse outcomes in acute pancreatitis. **Methods:** We identified all patients with a primary discharge diagnosis of acute pancreatitis from the 2016 to 2020 National Inpatient Sample (NIS) database and then divided them into two groups based on liver transplantation status. Patients aged less than 18 years were excluded from the analysis. Using a multivariate analysis, we assessed for differences in the primary outcome of inpatient mortality, while the secondary outcomes were hospital length of stay (LOS) and total hospital charges (THC). **Results:** Of the 1,387,709 hospitalizations with a primary diagnosis of acute pancreatitis, 1875 patients (0.01%) had prior liver transplantation. There was no statistically

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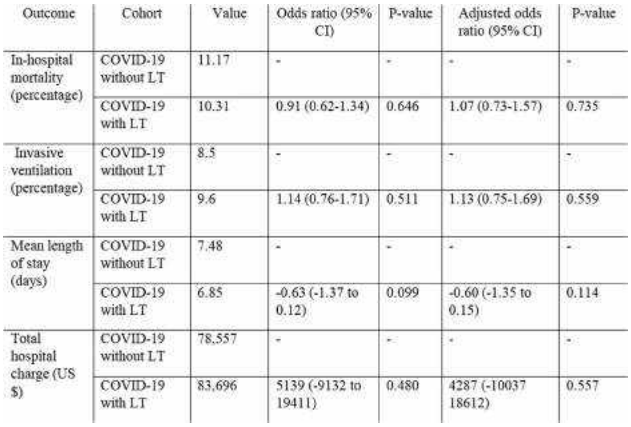
significant difference between the mortality rate in liver transplant patients (1.07%) compared to the non liver transplant patients (0.58%) with a *p* value of 0.666. Similarly, the LOS was not significantly different between the two groups with an average LOS of 4.6 days in liver transplant patients and 4.3 days in non liver transplant patients, *p* value of 0.296. The average total hospital charge for patients with acute pancreatitis was $40,854 with an average charge of $51,872 for liver transplant patients and $40,839 for non liver transplant patients. There was no statistically significant difference in total hospital charges between the two groups (*p* value of 0.899). **Conclusion:** Although liver transplantation is associated with an increase in incidence and severity of acute pancreatitis, our study did not show a statistically significant difference in mortality rates, length of hospital stay or total hospital charges between liver transplant patients and non liver transplant patients with a discharge diagnosis of acute pancreatitis. Further studies are needed to further elucidate the relationship between liver transplantation and acute pancreatitis.

Disclosures: The following people have nothing to disclose: Chidiebele Omaliko, Chukwunonso Ezeani, Ayobami Olafimihan, Oghenefejiro Ogwor, Favour Markson, Festus Ibe

1104-A | OUTCOMES OF LIVER TRANSPLANT RECIPIENTS HOSPITALIZED WITH COVID-19 INFECTION: A NATIONWIDE ANALYSIS

Abdellatif Ismail, University of Maryland Medical Center, Midtown Campus, Ahmad Khalaf, Hennepin Healthcare and Kirti Shetty, Department of Hepatology and Liver Transplantation, the University of Maryland, School of Medicine, Baltimore, MD, USA

Background: Currently, available data regarding the impact of liver transplantation (LT) on the outcomes of patients hospitalized with COVID-19 is conflicting. This study aims to compare the outcomes and resource utilization between patients with and without a history of LT hospitalized with COVID-19 infection. **Methods:** We conducted a retrospective review using the Nationwide Inpatient Sample (NIS) database, the largest all-payer inpatient database in the United States. This review included all adult patients hospitalized in 2020 with COVID-19 as the primary diagnosis in hospitals throughout the United States. Covariates retrieved included demographic variables, LT status, need for intubation, and length of stay (LOS). Univariable and multivariable logistic and linear regression analyses were conducted, adjusting for age, sex, and comorbidities. The alpha level was set at 0.05. **Results:** Out of 1,050,720 adults admitted with COVID-19 as the primary diagnosis, 1455 had a secondary diagnosis of LT. LT recipients were significantly more likely to be younger with a higher Charlson Comorbidity Index (CCI) and less likely to be Black. However, there were no statistically significant differences between the two studied groups concerning mortality and the need for invasive ventilation. There were also no differences in LOS, hospital charges, and intubation rates. Table 1 summarizes these outcomes. **Conclusion:** We compared mortality rates, need for invasive ventilation, length of stay, and total hospital charges between patients with and without LT hospitalized in the US for COVID-19 infection in 2020. We concluded that LT status did not confer higher mortality or increased resource utilization. While some previous studies have demonstrated higher susceptibility of transplant recipients to COVID-19, attributed to immunocompromised status, other registry studies have been conflicting. A recent meta-analysis showed a similar risk of adverse outcomes in LT recipients, who were also noted to have a lower mortality risk than other solid organ transplant recipients. Ours is the first study to examine outcomes in a large hospitalized cohort of LT recipients early in the COVID-19 pandemic when management guidelines were still in development. Despite these limitations, LT recipients were not demonstrated to be at risk for higher mortality. With the development of highly effective vaccines and social distancing protocols, LT recipients continue to experience equivalent risks of hospitalization and mortality compared to the general population.



Outcome	Cohort	Value	Odds ratio (95% CI)	P-value	Adjusted odds ratio (95% CI)	P-value
In-hospital mortality (percentage)	COVID-19 without LT	11.17	-	-	-	-
	COVID-19 with LT	10.31	0.91 (0.62-1.34)	0.646	1.07 (0.73-1.57)	0.735
Invasive ventilation (percentage)	COVID-19 without LT	8.5	-	-	-	-
	COVID-19 with LT	9.6	1.14 (0.76-1.71)	0.511	1.13 (0.75-1.69)	0.559
Mean length of stay (days)	COVID-19 without LT	7.48	-	-	-	-
	COVID-19 with LT	6.85	-0.63 (-1.37 to 0.12)	0.099	-0.60 (-1.35 to 0.15)	0.114
Total hospital charge (US $)	COVID-19 without LT	78,557	-	-	-	-
	COVID-19 with LT	83,696	5139 (-9132 to 19411)	0.480	4287 (-10037 18612)	0.557

Disclosures: The following people have nothing to disclose: Abdellatif Ismail, Ahmad Khalaf, Kirti Shetty

1105-A | PATIENT PERSPECTIVES ON SOLID ORGAN TRANSPLANTATION FROM DONORS WITH HEPATITIS C-VIREMIA FOR RECIPIENTS WITHOUT HEPATITIS C-VIREMIA

Karen B. Vanterpool[1], Kadiatou Diallo[1], Ellie Kim[2], Sarah E. Van Pilsum Rasmussen[2], Morgan Johnson[2], Zachary Predmore[2], Brittany Barnaba[2], Niraj Desai[2], Hannah C. Sung[2], Olivia Kates[2], Jeremy Sugarman[2] and Christine M. Durand[2], (1)New York University Grossman School of Medicine, (2)Johns Hopkins University School of Medicine

Background: Direct acting antivirals (DAAs) have enabled transplantation from donors with hepatitis C viremia to recipients without hepatitis C viremia (HCV D+/R-). These transplants have been shown to have excellent medical outcomes. Prior qualitative studies on recipient experiences with HCV D+/R- transplants have exclusively enrolled kidney and lung transplant recipients within clinical trials. Less is known about the psychosocial impact and experiences of HCV D+/R- recipients, particularly outside of clinical trials and across multiple organ types. **Methods:** We conducted in-depth, semi-structured interviews with patients at a single center who received transplants outside of clinical trials and were treated for HCV post-transplant to assess their experiences and perspectives. We used thematic analysis to analyze the interviews. **Results:** We conducted interviews between May 2020 through June 2021. We attempted to contact 32 HCV D+/R- recipients and 24 participated (kidney n = 8; lung n = 7; liver n = 5; heart n = 3; simultaneous heart and kidney n = 1). The participation rate was 73% (2 unable to contact, 5 declined, 2 ineligible). Most participants were Male (75%), White (77%), with a mean age of 64 years. Most (62%) received HCV treatment within one month following transplant (ranging from 1 d to 2 mo). Interviewees described their reasons for accepting an HCV D+ organ, challenges and concerns with HCV D+ transplants, the impact of HCV D+/R- transplants on their lives, and their overall experience with HCV D+ transplants. Interviewees' reasons for accepting an HCV D+ organ were based on perceiving it as an "expedient" pathway to transplant and a "safe" option due to the effectiveness of HCV treatment. Some interviewees were concerned about HCV treatment costs and unexpected delays in treatment. Interviewees recounted negotiations with insurance companies for coverage of HCV treatment, which delayed initiation of HCV treatment. After transplant, most did not recall experiencing stigma from others regarding the transplant, yet some reported that their families had concerns about the risk of HCV transmission. Overall, interviewees had positive transplant experiences related to survival, improved health, physical activity, and quality of life. **Conclusion:** Our findings suggest that HCV D+/R- transplant recipients of all organ types outside of clinical trials had positive experiences with little to no concerns about accepting an HCV D+ organ. However, a lack of clarity regarding HCV treatment costs and delays may raise concerns for those receiving future HCV D+/R- transplants as clinical care. Prior to transplant, patients would likely benefit from education about potential HCV treatment costs, insurance-related processes, and risks associated with delays in treatment timing.

Disclosures: The following people have nothing to disclose: Karen B. Vanterpool

Disclosure information not available at the time of publication: Kadiatou Diallo, Ellie Kim, Sarah E. Van Pilsum Rasmussen, Morgan Johnson, Zachary Predmore, Brittany Barnaba, Niraj Desai, Hannah C. Sung, Olivia Kates, Jeremy Sugarman, Christine M. Durand

f 1106-A | PATIENT REPORTED OUTCOMES AND PATIENT REPORTED OUTCOMES MEASURES POST LIVER TRANSPLANTATION: IMPROVING QUALITY OF LIFE POST TRANSPLANT

Ali Vedadi, University of Ottawa; University of Toronto

Background: Generic or condition-specific Patient-reported Outcome Measures (PROMs) are used to measure physical, mental and social aspects of health to promote patient-centered care. We aimed to identify and summarize generic and transplant specific PRO domains and PROMs that have been assessed and used in liver transplant candidates and recipients. **Methods:** We searched Medline, Embase, Cochrane Database of Systematic Reviews and Register of Trials, PsychInfo, and CINAHL from inception to now, and included studies addressed a PRO or PROM in LT candidates or recipients. Studies were screened by two or more reviewers and included if they met inclusion criteria for our study. Full-text articles were reviewed, and information pertaining to study design, location, date, PROs, PROMs administered was abstracted. **Results:** 341 studies yielded 189 unique PRO domains. Mental health domains (depression, anxiety, and guilt) were most frequently assessed, followed by domains of physical and social health. Fifty-one generic and three condition-specific unique PROMs were identified, with only 13% (n = 45) of studies including condition-specific tools. The most frequent PROMs were the SF-36, Nottingham Health Profile, Hospital Anxiety and Depression Scale, followed by the Liver Disease Quality of Life (LDQoL). The only LT-specific questionnaire identified in our search was the pLTQ, which covers

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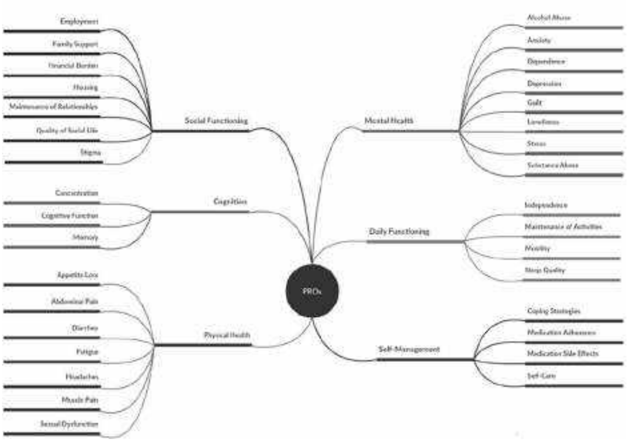
transplant-specific domains such as concerns about rejection, side effects of immunosuppressive medication, and post-surgical physical function. **Conclusion:** Very few studies used transplant-specific PROMs, which may partly be related to the scarcity of liver transplant specific instruments. Together, a core set of liver transplant specific PRO domains and recommended PROMs can facilitate standardized assessment and monitoring of key patient-valued outcomes to ensure routine clinical care is truly patient-centered.

Figure 2. Patient Reported Outcomes in liver transplant candidates and recipients

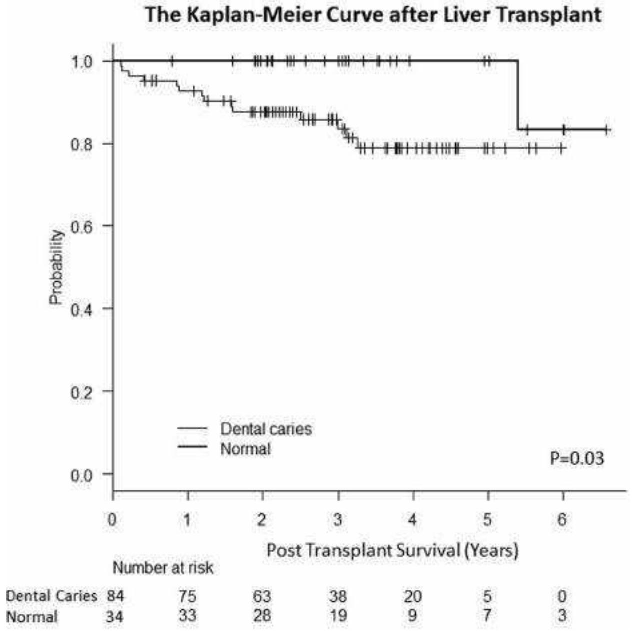

Employment
Family Support
Financial Burden
Housing
Maintenance of Relationships
Quality of Social Life
Stigma
Social Functioning
Concentration
Cognitive Function
Memory
Cognition
Appetite Loss
Abdominal Pain
Diarrhea
Fatigue
Headaches
Muscle Pain
Sexual Dysfunction
Physical Health
PROs
Mental Health
Alcohol Abuse
Anxiety
Dependence
Depression
Guilt
Loneliness
Stress
Substance Abuse
Daily Functioning
Independence
Maintenance of Activities
Mobility
Sleep Quality
Self-Management
Coping Strategies
Medication Adherence
Medication Side Effects
Self-Care

Disclosures: The following people have nothing to disclose: Ali Vedadi

1107-A | POOR DENTITION IS ASSOCIATED WITH POOR POST-TRANSPLANT SURVIVAL AMONG ALCOHOL-ASSOCIATED LIVER DISEASE PATIENTS

Tomoki Sempokuya, Patrick Twohig, Shaheed Merani and Nathalie Khoury, University of Nebraska Medical Center

Background: Alcohol-associated liver disease (ALD) has become the leading cause of liver transplantation. Previous studies have tried to identify optimal selection criteria for ALD patients, but many liver transplant centers struggle to select suitable candidates because current prediction models rely on subjective data, such as self-reported alcohol intake. Poor dental hygiene has been associated with overall adverse health outcomes, but has not been evaluated in the post-liver transplant population. Dental clearance is a routine process in most transplant centers, and dental status may provide objective data on self-care. This study evaluated an association between poor dental health and transplant outcomes. **Methods:** We retrospectively identified patients evaluated and listed for liver transplantation at the University of Nebraska Medical Center from 1/1/2015 to 1/1/2020. We then selected patients with a primary or secondary diagnosis of ALD. We obtained data on demographics, concurrent liver disease diagnosis, MELD-Na score, dental status, substance use, social work, neuropsychology, and psychiatry evaluations, committee decision, compliance status, and survival data. We separated patients into two groups: Normal dentition vs. Dental caries, including dental caries, abscess, gingivitis, and edentulous. Survival analysis was done with the Kaplan-Meier survival curve and multivariate analysis with the Cox-proportional Hazard model. **Results:** After excluding patients with unclear dental status, 177 patients were included in this study, with 125 in the dental caries group and 52 in the normal dentition group. The median MELD-Na score at the listing was 17. There were no differences in committee decisions, substance use, and underlying psychiatric comorbidities for baseline characteristics. Concurrent history of hepatitis C infections were higher in the dental caries group (25.6% vs. 9.6%). Post-transplant survival was significantly higher for the normal dentition group than the dental caries group ($p = 0.03$), but post-listing survival did not show a significant difference ($p = 0.09$). The Multivariate Cox Proportional Hazard model did not show a significant hazard ratio for dental status. **Conclusion:** This study showed a decreased post-transplant survival among ALD patients with poor dentition pre-transplant. However, this trend didn't remain significant after multivariate analysis, implying that dental status might be a proxy for other factors. Integrating objective dental status data into prediction models may improve the liver transplant selection process.

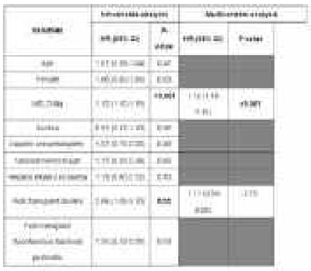


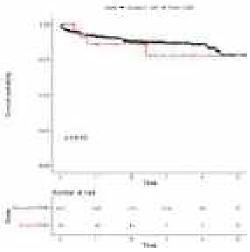
Disclosures: The following people have nothing to disclose: Tomoki Sempokuya, Patrick Twohig, Shaheed Merani, Nathalie Khoury

1108-A | POST-TRANSPLANT SPONTANEOUS BACTERIAL PERITONITIS DOES NOT WORSEN MORTALITY: A RETROSPECTIVE ANALYSIS OF POST-TRANSPLANT FACTORS AFFECTING MORTALITY

Joseph Cappuccio[1], Karim Osman[1], Brenda Amuchi[1] and Amir Ahmed Qamar[2], (1)Lahey Hospital and Medical Center, (2)Lahey Clinic Medical Center

Background: Hepatic decompensation is widely known to be associated with increased mortality in patients with cirrhosis. Spontaneous Bacterial Peritonitis (SBP) in patients with decompensated cirrhosis further compounds the risk of mortality and may hasten the need for liver transplant (LT). Many patients may continue to experience post-transplant ascites (PTA) and subsequent post-transplant SBP (PTSBP). The clinical impact of PTA and PTSBP remains unclear. Our study aims to determine the prognostic impact of PTA and PTSBP. **Methods:** The study was approved by the Institutional Review Board. Adult patients with cirrhosis, who underwent LT at our institution from 2015-2020, were retrospectively reviewed. Post-transplant ascites was defined by ascites 1 month after LT. PTSBP was diagnosed by an absolute neutrophil count e 250/µL in post-transplant ascitic fluid. Patients were followed from baseline (date of LT) until last follow-up or death. Censoring occurred at the time of last follow-up. Cumulative incidence of outcomes was determined by the Kaplan-Meier method. A Cox regression analysis was conducted to examine mortality association with various predictive factors. **Results:** 428 patients had a LT. 70 patients had PTA (16.35%) and 26 (6.07%%) had at least one episode of PTSBP. Of these, 17 patients were noted to have positive growth on culture taken from ascitic fluid. Culture species included Vancomycin Resistant Enterococcus (6), Enterococcus Faecalis (3), Extended Spectrum Beta Lactamase Klebsiella (2), Coagulase Negative Staphylococcus (2), Enterococcus Faecium (1), Methicillin Resistant Staph Aureus (1), and Streptococcus Anginosus (1). Patients developed their first episode of SBP 0.63 (0.40-3.80) months after their LT. Model for end stage liver disease (MELD-Na) score was associated with mortality in both univariable and multivariable analyses [HR 1.12 (1.10 - 1.15), $p = < 0.001$]. Further, the presence of PTA was significantly associated with mortality [HR 2.06 (1.09 - 3.70), $p = 0.03$]. PTSBP was not found to have a significant association with mortality [HR 1.35 (0.53 - 3.39), $p = 0.53$] (Table 1). The median survival of patients who developed and did not develop PTSBP was more than 5 years (Figure 1). **Conclusion:** Our study highlights that PTSBP may not be associated with worsened survival probability. Interestingly, the presence of PTA was associated with worsened mortality. We acknowledge that the limited sample size and scope of follow-up may alter our observed results. Additional studies are needed to further clarify the clinical implications associated with PTA and PTSBP as well as a potential need for standardization of screening and therapy.





Disclosures: The following people have nothing to disclose: Joseph Cappuccio, Karim Osman, Brenda Amuchi, Amir Ahmed Qamar

1109-A | PREDICTIVE ROLE OF TRICUSPID REGURGITATION SEVERITY AMONG PERI-LIVER TRANSPLANT PATIENTS: RESULTS FROM A LARGE TERTIARY CARE CENTER

Diana Jomaa[1], Yervant Ichkhanian[1], Kartik Gupta[1], Ammad Javaid Chaudhary[1] and Syed-Mohammed Jafri[2], (1)Henry Ford Hospital, (2)Henry Ford Health System

Background: Cardiovascular disease remains a major contributor to morbidity and mortality among liver transplant (LTx) patients. Tricuspid regurgitation (TR) has been known to contribute to worse outcomes pre-LTx and post-LTx due to hepatic congestion and poor cardiac reserve. In this study, we aimed to further investigate the predictive value of moderate or severe TR on the mortality of pre-and post-LTx patients. **Methods:** This was a retrospective chart review of adult patients (> 18 y of age) who were listed or received LTx during the time period of 2015-2020 at Henry Ford Hospital. Patients who were lost to follow-up post-transplant were excluded from the study. Patients' baseline disease characteristics, most recent pre-LTs transthoracic echocardiogram results were recorded in pre-designed de-identified data sheets. The primary outcome were survival at 1 year and 3 years from the initial LTx evaluation time. **Results:** A total of 1189

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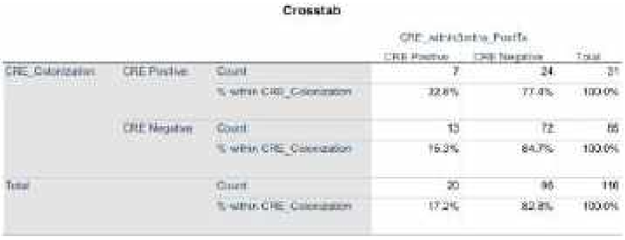
patient records were reviewed, and 609 (51%) (mean age 55.71 ± 10.89, Female 504 (42%)) satisfied the inclusion criteria and were enrolled in the study. Of the 609 patients who were listed, 404 (66%) received LTx during the duration of the study. The prevalence of moderate to severe TR was significantly higher among patients who were not listed (8.45%) as compared to patients who were listed (4.43%), ($p = 0.005$). Among the patients who received LTx (n = 404), the percentage of patients who had moderate-severe TR was 4.5% as compared to 4.4% among the patients who did not receive LTx (n = 580), ($p = 0.97$). One year survival among patients who received LTx was 94% with no significant difference in terms of the rate of moderate to severe TR among the alive vs. the deceased group (4.2% vs. 9.2%, $p = 0.284$, respectively). Similarly, three years survival among patients who received LTx, (survival rate: 84%), and there was no significant difference in-terms of rate of moderate to severe TR (4.4% vs. 5.6%, $p = 0.284$, respectively). Upon stratifying the population based on age and severity of TR, there was no association between moderate-severe TR and 3-year mortality in patients pre-LTx and post-LTx with hazard ratios of 0.744 (95% CI 0.438-1.262) and 0.877 (95% CI 0.517-1.487) respectively. **Conclusion:** Our study provides further insight into the survival rates of patients with TR pre and post-LTx. There is no association between TR and increased risk of mortality in patients pre-LTx or post-LTx. However, there may be an association between degree of TR and getting listed for Tx.

Disclosures: The following people have nothing to disclose: Diana Jomaa, Yervant Ichkhanian, Kartik Gupta, Ammad Javaid Chaudhary, Syed-Mohammed Jafri

1110-A | PREVALENCE OF PRE TRANSPLANT CARBAPENEM RESISTANT ENTEROBACTERALES (CRE) AND VANCOMYCIN RESISTANT ENTEROCOCCI (VRE) RECTAL COLONISATION AND ITS IMPACT ON POST LIVER TRANSPLANT OUTCOMES

Ameet Mandot[1], Tejas J Joshi[1], Wasim Khot[1], Uday Sanglodkar[1], Alisha Chaubal[1], Hardik R Shah[1], Gaurav Chaubal[1], Aditya Nanavati[1], Rajeev Sinha[1], Hunaid Hatimi[1], Gautham Pranesh[2] and Samir Ramnik Shah[1], (1)Global Hospitals, Mumbai, (2)Mitopower LLC

Background: The data regarding the impact of pre transplant rectal colonization with Carbapenem Resistant Enterobacterales (CRE) and Vancomycin Resistance Enterococci (VRE) organisms on post-transplant outcomes in patients undergoing Liver Transplant, especially from countries with high burden of these infections is scarce. The aim of this study was to assess the prevalence of CRE, VRE rectal colonization and its impact on post transplant outcomes in liver recipient. **Methods:** We did a retrospective cohort study of patients undergoing liver transplant from Jan 2022 to Jan 2023 at our center. We analyzed the prevalence of CRE, VRE colonization in rectal swab and data related to post transplant CRE, VRE infections & mortality from patients records till 3 months post transplant. **Results:** Amongst the 119 patients (79% males) with median age of 45 years, the prevalence of pretransplant CRE and VRE colonization was 32/118 (27.11%) and 9/117 (7.69%) respectively. At a follow up of three months, 20/117(17.09%) and 2/117 (1.71%) patients had developed post-transplant infection with CRE and VRE organisms respectively. In patients who were pretransplant colonised with CRE in rectal swab, the risk of CRE infection (22.6% vs 15.3 %, OR 1.61) [CI 0.57–4.51] and mortality (12.5% vs 4.7% OR 2.92)[CI 0.68- 12.49] within 3 months post-transplant were numerically higher but not statistically significant. There was no association of pre transplant VRE colonisation on post transplant VRE infection and mortality. Post transplant CRE and VRE infection was not associated with any increase in post-transplant mortality. **Conclusion:** There is high prevalence of CRE rectal colonization (27.11%) in patients undergoing liver transplantation in this study. In these CRE colonised recipients there is increased risk of CRE infection & mortality though not statistically significant. This raises issue of choice of pre operative prophylactic antibiotic and the need for change in those who are noted to be colonised with CRE organism.



Crosstab

			[illegible]		
			CRE Positive	CRE Negative	Total
CRE_Colonization	CRE Positive	Count	7	24	31
		% within CRE_Colonization	22.6%	77.4%	100.0%
	CRE Negative	Count	13	72	85
		% within CRE_Colonization	15.3%	84.7%	100.0%
Total		Count	20	96	116
		% within CRE_Colonization	17.2%	82.8%	100.0%

Disclosures: The following people have nothing to disclose: Ameet Mandot, Tejas J Joshi, Wasim Khot, Uday Sanglodkar, Alisha Chaubal, Hardik R Shah, Gaurav Chaubal, Aditya Nanavati, Rajeev Sinha, Hunaid Hatimi, Gautham Pranesh, Samir Ramnik Shah

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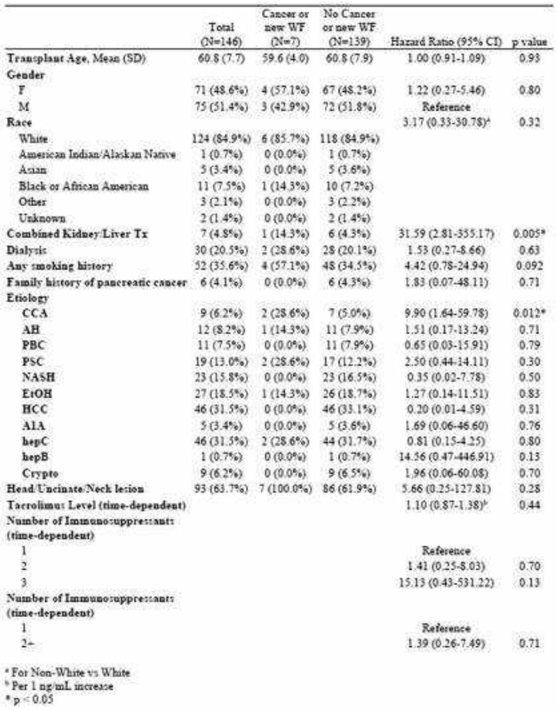
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

1111-A | PROGRESSION OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS OF THE PANCREAS AFTER LIVER TRANSPLANT

Bradley T Busebee[1], *Jerry Chin*[2], *Kristin Mara*[1], *Bradley K. Johnson*[1] *and Kymberly Watt*[3], *(1)Mayo Clinic, (2) Waikato Hospital, (3)Mayo Clinic, Rochester, MN*

Background: Liver transplantation (LT) and immunosuppression are associated with an increased risk of malignancy. Intraductal papillary mucinous neoplasms (IPMN) are relatively low-risk pre-malignant lesions, though the risk of progression is not well understood in the transplant population. **Methods:** All patients undergoing LT at a large, multi-site academic institution between 1999 and 2012 with mention of IPMN by automated chart review were reviewed. Patients with suspected IPMN within a year prior to transplant were included in the below analysis. Suspected IPMN was defined as either 1) a lesion described as a probable IPMN in a cross-sectional radiology or endoscopic ultrasound report or 2) lesions described as potential IPMNs with potential or definite pancreatic duct (PD) communication and absence of amylase and CEA levels below 250 U/L and 192 ng/mL. The primary outcome was defined as IPMN progression to cancer or development of new, worrisome features (WF) by Sendai criteria post-LT. **Results:** 146 patients with suspected IPMNs were identified. The average clinical follow-up time was 7.8 years. Pre-LT, 1 patient had worrisome features. Post-LT, 7 patients met the primary outcome (5.8%); 2 patients developed cancer associated with a suspected IPMN (1.4%), 6 developed WFs (4.2%), and 1 patient developed both cancer and a WF (0.7%). The average time to the primary outcome was 7.9 years. Cox-proportional-hazard analysis showed no significant difference in the incidence IPMN progression for age, gender, family history of pancreatic cancer, immunosuppression type ($p > 0.05$), continuous tacrolimus trough levels (HR 1.1, $p = 0.44$), or number of active immunosuppression medications (HR 1.39, $p = 0.71$), while combined kidney/liver transplantation (HR 31.6, $p = 0.005$) and pre- LT cholangiocarcinoma (HR 9.9, $p = 0.012$) were significantly associated with progression and a history of smoking (HR 4.42, $p = 0.092$) trended toward association with progression. **Conclusion:** The rate of IPMN progression in LT recipients was similar to that published previously for the general population. Novel findings include combined organ transplant and previous cholangiocarcinoma increased risk of IPMN progression, whereas immunosuppression intensity measures showed no apparent association. IPMNs are indolent lesions resulting in a small event number over long-term follow-up. Larger studies with long term follow-up are needed.



	Total (N=146)	Cancer or new WF (N=7)	No Cancer or new WF (N=139)	Hazard Ratio (95% CI)	p value
Transplant Age, Mean (SD)	60.8 (7.7)	59.6 (4.0)	60.8 (7.9)	1.00 (0.91-1.09)	0.93
Gender					
F	71 (48.6%)	4 (57.1%)	67 (48.2%)	1.22 (0.27-5.46)	0.80
M	75 (51.4%)	3 (42.9%)	72 (51.8%)	Reference	
Race				3.17 (0.33-30.78)[a]	0.32
White	124 (84.9%)	6 (85.7%)	118 (84.9%)		
American Indian/Alaskan Native	1 (0.7%)	0 (0.0%)	1 (0.7%)		
Asian	5 (3.4%)	0 (0.0%)	5 (3.6%)		
Black or African American	11 (7.5%)	1 (14.3%)	10 (7.2%)		
Other	3 (2.1%)	0 (0.0%)	3 (2.2%)		
Unknown	2 (1.4%)	0 (0.0%)	2 (1.4%)		
Combined Kidney/Liver Tx	7 (4.8%)	1 (14.3%)	6 (4.3%)	31.59 (2.81-355.17)	0.005*
Dialysis	30 (20.5%)	2 (28.6%)	28 (20.1%)	1.53 (0.27-8.66)	0.63
Any smoking history	52 (35.6%)	4 (57.1%)	48 (34.5%)	4.42 (0.78-24.94)	0.092
Family history of pancreatic cancer	6 (4.1%)	0 (0.0%)	6 (4.3%)	1.83 (0.07-48.11)	0.71
Etiology					
CCA	9 (6.2%)	2 (28.6%)	7 (5.0%)	9.90 (1.64-59.78)	0.012*
AH	12 (8.2%)	1 (14.3%)	11 (7.9%)	1.51 (0.17-13.24)	0.71
PBC	11 (7.5%)	0 (0.0%)	11 (7.9%)	0.65 (0.03-15.91)	0.79
PSC	19 (13.0%)	2 (28.6%)	17 (12.2%)	2.50 (0.44-14.11)	0.30
NASH	23 (15.8%)	0 (0.0%)	23 (16.5%)	0.35 (0.02-7.78)	0.50
EtOH	27 (18.5%)	1 (14.3%)	26 (18.7%)	1.27 (0.14-11.51)	0.83
HCC	46 (31.5%)	0 (0.0%)	46 (33.1%)	0.20 (0.01-4.59)	0.31
A1A	5 (3.4%)	0 (0.0%)	5 (3.6%)	1.69 (0.06-46.60)	0.76
hepC	46 (31.5%)	2 (28.6%)	44 (31.7%)	0.81 (0.15-4.25)	0.80
hepB	1 (0.7%)	0 (0.0%)	1 (0.7%)	14.56 (0.47-446.91)	0.13
Crypto	9 (6.2%)	0 (0.0%)	9 (6.5%)	1.96 (0.06-60.08)	0.70
Head/Uncinate/Neck lesion	93 (63.7%)	7 (100.0%)	86 (61.9%)	5.66 (0.25-127.81)	0.28
Tacrolimus Level (time-dependent)				1.10 (0.87-1.38)[b]	0.44
Number of Immunosuppressants (time-dependent)					
1				Reference	
2				1.41 (0.25-8.03)	0.70
3				15.13 (0.43-531.22)	0.13
Number of Immunosuppressants (time-dependent)					
1				Reference	
2+				1.39 (0.26-7.49)	0.71

[a] For Non-White vs White
[b] Per 1 ng/mL increase
* p < 0.05

Table 1. Summary of Cox proportional-hazards analysis of various clinical factors and IPMN progression. Time-dependent variables include tacrolimus level (representing all tacrolimus trough levels throughout follow-up) and number of immunosuppressants (representing the number of active immunosuppressant medications at any point during follow-up). Abbreviations: Tx = transplant, CCA = cholangiocarcinoma, AH = autoimmune hepatitis, PBC = primary biliary cholangitis, PSC = primary sclerosing cholangitis, NASH = non-alcoholic steatohepatitis, EtOH = alcoholic steatohepatitis, HCC = hepatocellular carcinoma, A1A = alpha-1 antitrypsin deficiency, hepC = hepatitis C, hepB = hepatitis B, Crypto = cryptogenic.

Disclosures: Kymberly Watt – Intercept - site PI: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Viking: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; Madrigal: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; JnJ: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
The following people have nothing to disclose: Bradley T Busebee
Disclosure information not available at the time of publication: Jerry Chin, Kristin Mara, Bradley K. Johnson

1112-A | RANGE OF DONOR DERIVED CELL FREE DNA IN LIVER TRANSPLANT RECIPIENTS – AN EXPLORATORY ANALYSIS

Kinnari Modi[1], *Grigoriy Shekhtman*[2], *Tara Ruder*[2], *Hellen Oduor*[1], *Mingyang Cui*[1] *and Parvez S. Mantry*[3], *(1)Methodist Dallas Medical Center, (2)Caredx, (3)The Liver Institute at Methodist Dallas*

Background: Donor-derived cell-free DNA (dd-cfDNA) is a serum biomarker widely used to detect graft injury and early rejection in solid organ transplant. Nevertheless, data on the clinical utility of dd-cfDNA in liver transplant recipients with stable allograft function is limited. Therefore, we evaluated dd-cfDNA in liver transplant recipients with normal liver function tests (LFTs). **Methods:** Data was retrospectively collected from 47 liver transplant recipients with dd-cfDNA (AlloSure, CareDx Inc.) measurements from August 2021 to April 2023 at our center. Patients with stable LFTs and no evidence of concurrent rejection were included in the analysis. For patients with multiple dd-cfDNA values, the first value with corresponding LFTs within 30 days was used. The immunosuppression (IS) regimen for these patients consisted of a combination of tacrolimus/ sirolimus/cyclosporin with mycophenolate mofetil (MMF) and/or prednisone. We assessed dd-cfDNA ranges for patients at different times in their post-transplant course. **Results:** 37 patients with dd-cfDNA assessment and LFTs WNL were included. Patients were a median of 1049 days post-transplant (PTX). Of the 37 patients, 11 (29.7%) were $<$ 1-year PTX and 26 (70.2%) were e 1-year PTX. Compared to patients $<$ 1-year PTX, patients e 1-year PTX were significantly less likely to be on triple IS and prednisone ($p < 0.01$) (Table 1). The population median dd-cfDNA in stable liver allograft recipients was 2.75%. Median dd-cfDNA were significantly higher in patients who were e 1-year PTX compared to patients $<$ 1-year PTX (2.9% vs. 1.4%, $p = 0.005$) (Fig. 1). **Conclusion:** Our data show dd-cfDNA is higher in stable liver allograft recipients e 1-year PTX compared to earlier PTX, though identifying other contributing factors in a larger population is needed. Notably, more patients $<$ 1-year PTX were on triple IS than those e 1-year PTX; therefore, determining if lower dd-cfDNA is associated with higher levels of IS may aid in the potential use of dd-cfDNA for IS titration. Prospective studies are assessing dd-cfDNA patterns in both rejection and stable liver allograft patients. Future directions include exploring the relationship of dd-cfDNA values with changes in IS regimens.

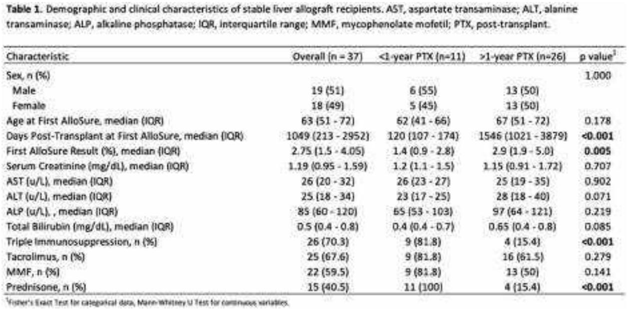


Table 1. Demographic and clinical characteristics of stable liver allograft recipients. AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; IQR, interquartile range; MMF, mycophenolate mofetil; PTX, post-transplant.

Characteristic	Overall (n = 37)	<1-year PTX (n=11)	>1-year PTX (n=26)	p value[1]
Sex, n (%)				1.000
Male	19 (51)	6 (55)	13 (50)	
Female	18 (49)	5 (45)	13 (50)	
Age at First AlloSure, median (IQR)	63 (51 - 72)	62 (41 - 66)	67 (51 - 72)	0.178
Days Post-Transplant at First AlloSure, median (IQR)	1049 (213 - 2952)	120 (107 - 174)	1546 (1021 - 3879)	**<0.001**
First AlloSure Result (%), median (IQR)	2.75 (1.5 - 4.05)	1.4 (0.9 - 2.8)	2.9 (1.9 - 5.0)	**0.005**
Serum Creatinine (mg/dL), median (IQR)	1.19 (0.95 - 1.59)	1.2 (1.1 - 1.5)	1.15 (0.91 - 1.72)	0.707
AST (u/L), median (IQR)	26 (20 - 32)	26 (23 - 27)	25 (19 - 35)	0.902
ALT (u/L), median (IQR)	25 (18 - 34)	23 (17 - 25)	28 (18 - 40)	0.071
ALP (u/L), , median (IQR)	85 (60 - 120)	65 (53 - 103)	97 (64 - 121)	0.219
Total Bilirubin (mg/dL), median (IQR)	0.5 (0.4 - 0.8)	0.4 (0.4 - 0.7)	0.65 (0.4 - 0.8)	0.085
Triple Immunosuppression, n (%)	26 (70.3)	9 (81.8)	4 (15.4)	**<0.001**
Tacrolimus, n (%)	25 (67.6)	9 (81.8)	16 (61.5)	0.279
MMF, n (%)	22 (59.5)	9 (81.8)	13 (50)	0.141
Prednisone, n (%)	15 (40.5)	11 (100)	4 (15.4)	**<0.001**

[1] Fisher's Exact Test for categorical data, Mann-Whitney U Test for continuous variables.

Disclosures: The following people have nothing to disclose: Kinnari Modi, Parvez S. Mantry

Disclosure information not available at the time of publication: Grigoriy Shekhtman, Tara Ruder, Hellen Oduor, Mingyang Cui

1113-A | RAPID DEVELOPMENT OF POST-LIVER TRANSPLANTATION NODULAR REGENERATIVE HYPERPLASIA AND PORTAL HYPERTENSION FOLLOWING PERFUSION PUMP USE: A CASE SERIES

Sachiko Oshima[1], Wei Chen[1], Aparna Rege[1], Andrew Barbas[1] and Stephanie Garbarino[2], (1)Duke University, (2)Duke University, Durham, NC

Background: Over the past two decades, solid organ transplant has increasingly relied on normothermic perfusion pumps to extend organ preservation times compared to traditional static cold storage. On September 28, 2021, the TransMedics Organ Care System (OCS) became the first perfusion pump to receive FDA approval for use in liver transplantation (LT). Since then, perfusion pump use has spread widely due to its ability to significantly extend ex-vivo organ viability time. However, limited data exists on the potential adverse consequences of widespread pump implementation. **Methods:** We present a case series of two patients who rapidly developed biopsy proven nodular regenerative hyperplasia (NRH) and portal hypertension following LT with perfusion pump utilization for deceased donor organs at a single institution in 2022-2023. **Results:** Patient one is a 56-year-old male whose donor was a 65-year-old female with chronic hepatitis C who died following a CVA. Patient two is a 50-year-old male whose donor was a 59-year-old male with no known past liver disease who died from cardiac arrest. Both donor organs were placed on the TransMedics OCS pre-transplant for 7 hours and 38 minutes and 18 hours and 29 minutes, respectively. Within weeks of transplant, both patients developed clinical signs of portal hypertension with ascites, hepatic hydrothorax and renal dysfunction requiring initiation of renal replacement therapy. Transjugular pressure readings revealed portal pressure gradients of 12 mmHg and 11 mmHg on initial biopsies which increased to peaks of 18 mmHg and 14 mmHg. Pathology was notable for NRH in both cases without evidence of rejection or fibrosis (Figure). Extensive workup did not reveal a secondary cause for portal hypertension. Both patients required prolonged hospitalizations with consideration of re-transplantation, but were eventually able to stop renal replacement therapy and diuretics with resolution of portal hypertensive symptoms. **Conclusion:** Post-LT portal hypertension resulting from NRH is a rare phenomenon, with few cases reported and none in the immediate post-transplant setting. While NRH is idiopathic in its etiology, vascular flow abnormalities have historically been linked with its development. Therefore, we hypothesize that use of normothermic perfusion pumps which were used in both cases presented here may be linked to the rapid development of post-transplant NRH. Reassuringly, both patients improved with time and did not require re-transplant.

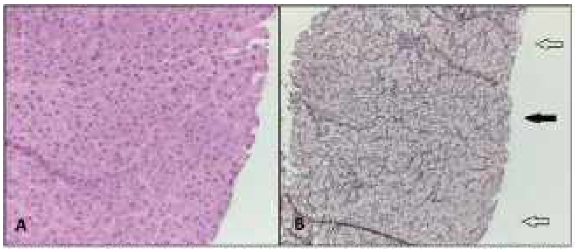


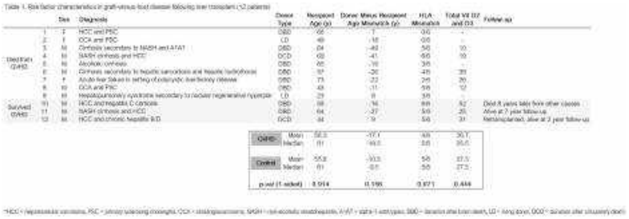
Figure: Biopsies of post-transplant liver showing features of NRH. **A.** Two populations of the hepatocytes - smaller, atrophic hepatocytes, flanked by the larger hepatocytes in the regenerative area (H&E, 100x) **B.** Reticulin stain highlights the key feature of NRH with alternately expanded (white arrows) and compressed (black arrow) hepatic plates (Reticulin, 100x).

Disclosures: The following people have nothing to disclose: Sachiko Oshima, Stephanie Garbarino
Disclosure information not available at the time of publication: Wei Chen, Aparna Rege, Andrew Barbas

1114-A | RISK FACTORS FOR GRAFT-VERSUS-HOST DISEASE IN LIVER TRANSPLANT RECIPIENTS

Frank Lee[1], *Kymberly Watt*[2], *Supavit Chesdachai*[1], *Tayyab Diwan*[1], *Timucin Taner*[1], *Charles B. Rosen*[1], *Michael D. Leise*[1] *and Julie Heimbach*[1], *(1)Mayo Clinic Rochester, Rochester, MN, (2)Mayo Clinic, Rochester, MN*

Background: Graft-versus-host disease (GVHD) following liver transplantation (LTx) is a rare and highly fatal complication with few effective treatment options. Identifying risk factors may help prevent this outcome. Cited risk factors include younger donor-older recipient age difference and greater matches between donor-recipient HLA loci. Low vitamin D has been associated with GVHD in bone marrow transplant (BMT). Our study's aim is to assess these risk factors within our single-center experience of GVHD with case-matched controls, in order to determine if avoiding donor-recipient age disparity or close HLA matches is warranted. **Methods:** A single-center retrospective study analyzed all liver transplant recipients from 2002 to 2022, identifying those diagnosed with GVHD. A 4:1 match of controls-to-cases was performed with respect to age, sex, race, and end-stage liver diagnosis. **Results:** GVHD incidence was 0.5% (12/2440 recipients). Time from transplant to presentation was 57 days on average. Time from presentation to confirmed diagnosis was 25 days on average. Clinical presentation was common in skin (12/12), bone (10/12), and gastrointestinal tract (9/12). GVHD mortality rate was 75% (9/12) with mean time from presentation to death of 119 days. 1. Donor-recipient age mismatch Donor age less than recipient age was seen in 75% of GVHD cases. Comparison of GVHD vs. control showed no statistical difference in age mismatch ($p = 0.156$). 2. HLA matching Greater HLA matching was observed in the GVHD group however was not statistically significant ($p = 0.071$). There were 2 cases in the GVHD group in which the donor graft was homozygous (single loci at A, B, DR) and had no mismatches with the recipient. 3. Vitamin D GVHD patients' vitamin D levels at time of transplant were wide-ranging (10-52 ng/mL). No statistical difference was seen between GVHD and matched controls ($p = 0.444$). **Conclusion:** Prior cited risk factors of younger donor-older recipient age difference and high HLA loci matching were not supported in this study; however, HLA loci matching may be a valid association ($p = 0.071$) but underpowered by our small sample size. Vitamin D was determined not to be a risk factor despite its association in BMT. Larger multicenter studies, which would ideally pool together these rare cases of GVHD, are required to further clarify risk factors and inform clinical judgment when selecting donor grafts to minimize GVHD risk.

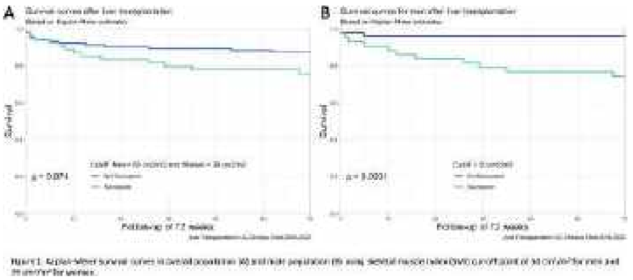


Disclosures: Kymberly Watt – Intercept - site PI: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Viking: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; Madrigal: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; JnJ: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
The following people have nothing to disclose: Frank Lee, Timucin Taner, Julie Heimbach
Disclosure information not available at the time of publication: Supavit Chesdachai, Tayyab Diwan, Charles B. Rosen, Michael D. Leise

1115-A | SARCOPENIA PREDICTS POSTRANSPLANT SURVIVAL IN HISPANIC MALE RECIPIENTS

Matías Hernández[1], Carlos Benítez[2], Cecilia Besa[1,3], Antonia Pastore[1], Catalina Grandy[1], Josefa Ghiglino[1], Constanza González[1], Leyla Hadad[1], Jacinta Hermosilla[1], Alejandro Villalon[1] and AASLD Sarcopenia-LT Authors' Group, (1)Pontificia Universidad Católica De Chile, (2)Pontificia Universidad Católica De Chile, Chile, (3)Millenium Institute for Intelligent Helthcare Engineering

Background: An association between sarcopenia and mortality post liver transplantation (LT) has been suggested; however, Skeletal Muscle Index (SMI) cut-off points have not been validated in Hispanic population. In this study, we aim to validate the currently proposed cut-off points. **Methods:** We retrospectively analyzed a cohort of liver transplant recipients at the UC-Christus Clinical Hospital between 2016 and 2020. SMI was measured in CT and MRI by two readers using NIH ImageJ software. Sarcopenia was defined as SMI < 50 cm^2/m^2 in male and < 39 cm^2/m^2 in female patients. Associations between sarcopenia and mortality were analyzed using Cox proportional hazard models. We used univariate and multivariate Cox proportional regression models to predict post-LT mortality. **Results:** 157 liver recipients were included. Mean age 58 ± 10 y/o; 59% male. Main etiologies were NASH 47%, alcohol 13%, autoimmune hepatitis 10%, PBC 7.6%, HCV 6.4%, others 16%. Serum creatinine 1.2 ± 1.0, total bilirubin 8.0 ± 11, INR 2.2 ± 2.3, Na 136.2 ± 6.2, albumin 3.2 ± 0.7, MELD-Na 26 ± 6. Child-Pugh score A/B/C: 11%/34%/55% respectively; 34.4% of patients had sarcopenia. Men had a significantly higher prevalence of sarcopenia compared to women (46.2% vs. 17.2%, $p = < 0.001$). Sarcopenic men had a longer length of stay than non-sarcopenic (24 ± 21 vs. 12 ± 5 d, $p = 0.047$). Sarcopenia was not associated with a higher mortality post-LT. However, in men, sarcopenia was associated with a higher risk of post-LT mortality (HR = 7.0, 95% CI [1.6-32], p = 0.011). In the multivariate analysis, the association between sarcopenia and post-transplant mortality in the male population remained significant (HR = 11.03, 95% IC [1.41-86.3], p = 0.022), MELD (HR = 1.1, 95% IC [1.01-1.21], $p = 0.033$), BMI (HR = 0.82, 95% IC [0.69-0.97], $p = 0.023$) and HTA (HR = 3.18, 95% IC [1-10.08], $p = 0.05$). **Conclusion:** Sarcopenia evaluated by SMI is associated to a markedly reduced survival in male liver recipients. *MH and CB share co-first authorship*



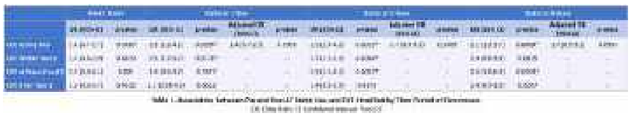
Disclosures: The following people have nothing to disclose: Matías Hernández, Carlos Benítez, Cecilia Besa, Antonia Pastore, Catalina Grandy, Josefa Ghiglino, Constanza González, Leyla Hadad, Jacinta Hermosilla, Alejandro Villalon

1116-A | STATIN USE IS NOT ASSOCIATED WITH THE INCIDENCE OF POST-LIVER TRANSPLANT ADVERSE CARDIOVASCULAR OUTCOMES

Debra W Yen, Jacob A Ciricillo, Yeshika Sharma, Askanda Osman, Michael Clanahan, Roman A Jandarov, Inuk Zandvakili and Amoah Yeboah-Korang, University of Cincinnati

Background: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality after liver transplantation (LT). Statin therapy is recommended for primary and secondary prevention of ASCVD, though statins remain underutilized in patients with liver disease. In part, adherence is hindered by safety concerns, including the rare risk of hepatotoxicity. Limited data exists on statin use and the incidence of adverse cardiovascular events (CVE) after LT. The primary aim of this study was to determine the association between statin use before or after LT and CVE post-LT. **Methods:** A retrospective review was performed of LT recipients from 2012-2016 at a single center with follow-up through Jan 2023. Hospital discharge ICD-codes and manual chart review were used to identify the primary outcome of post-LT CVE (myocardial infarction, coronary revascularization, heart failure, atrial fibrillation, ventricular tachycardia or fibrillation, cardiac arrest, or stroke). Statin use pre-LT and at 1-, 3- and 5-years post-LT were recorded. Bivariate and multivariate logistic regression were performed. **Results:** Among 364 LT recipients, 65.4% were male, 90.7% Caucasian, mean age 55.9 + 10 at LT, and NASH cirrhosis in 23.1%. 104 patients (28.8%) had a CVE post-LT. All-cause mortality post-LT was 26.9%. Incidence of post-LT CVE was 17% at year 1, 7.4% at year 2-3, and 10.4% after year 3. 49

patients (13.5%) were on statins pre-LT, 15.8% at post-LT year 1, 24.4% at post-LT year 3, and 33.7% at post-LT year 5. Pre-LT statin use was not associated with CVE at any year post-LT. In the bivariate analysis, statin use in post-LT year 1 was associated with significantly increased incidence of CVE at any year post-LT and CVE 1-year post-LT (Table 1). Statin use at 3 or 5 years post-LT was not associated with CVE after post-LT year 3. After multivariate adjustment for age at transplant and history of ischemic heart disease, CAD, diabetes, atrial fibrillation, hypertension, and heart failure, there was no association between pre or post-LT statin use and incidence of post-LT CVE or all-cause mortality. **Conclusion:** In this retrospective cohort, statin use before or after LT was not associated with incidence of post-LT CVE or all-cause mortality after multivariate adjustment of age and pre-LT CV conditions. These findings may be attributable to the majority of post-LT CVE occurring in year 1, with heart failure and atrial fibrillation being most common. However, future directions include multicenter prospective studies and further investigation of the impact of statin adherence for primary and secondary prevention on post-LT CVE.



Disclosures: The following people have nothing to disclose: Debra W Yen, Jacob A Ciricillo, Askanda Osman, Amoah Yeboah-Korang

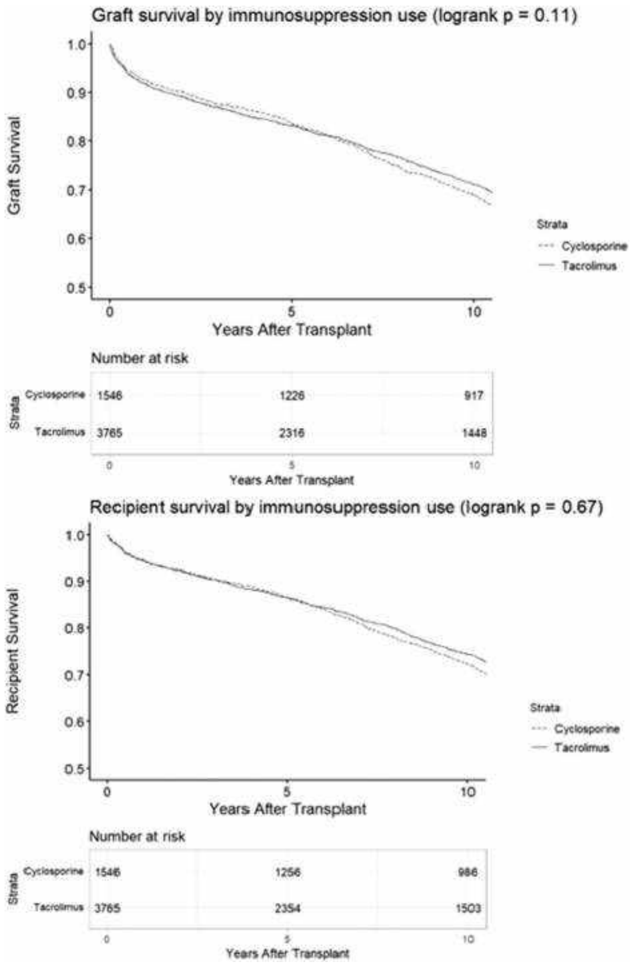
Disclosure information not available at the time of publication: Yeshika Sharma, Michael Clanahan, Roman A Jandarov, Inuk Zandvakili

1117-A | TACROLIMUS USE, COMPARED TO CYCLOSPORINE USE, IS NOT ASSOCIATED WITH WORSE GRAFT OR PATIENT SURVIVAL FOR PATIENTS TRANSPLANTED FOR PBC

Nathan Pham, Lei Yu, Nicole J. Kim, Meredith Pearson, Erin Cleveland, Iris W. Liou, Renuka Bhattacharya, Scott W. Biggins, Rotonya M. Carr and Philip Vutien, University of Washington

Background: Recurrent primary biliary cholangitis (rPBC) affects up to 46% of patients who undergo orthotopic liver transplant (OLT) for PBC. Cyclosporine use, compared to tacrolimus use, has been associated with reduced rates of rPBC. However, it is uncertain if cyclosporine use is also associated with improved graft and recipient survival in a US cohort. In this study, we aimed to assess the association between tacrolimus and cyclosporine use on graft loss and mortality among recipients transplanted for PBC. **Methods:** We analyzed all adult U.S. recipients with primary biliary cholangitis undergoing liver transplant from 1/1988 to 12/2022 in the Organ Procurement and Transplantation Network (OPTN) database. Patients were divided into tacrolimus and cyclosporine groups based on immunosuppression regimen at time of . We excluded pediatric, living donor, re-OLT, and multi-organ transplant recipients. We used Kaplan-Meier survival curves and multivariable mixed Cox proportional hazards regression (adjusting for recipient age, sex, MELD, history of hepatocellular carcinoma (HCC), donor donation after cardiac death (DCD) status, and transplant cold ischemia time) to determine the association between immunosuppressive regimen and graft loss or mortality. **Results:** Among 5311 patients, 3765 (70.9%) received tacrolimus and 1546 (29.1%) received cyclosporine. The majority (n = 1362, 88.1%) of patients who received cyclosporine underwent OLT from 1988 to 1999, while the majority of those who received tacrolimus (n = 2976, 79.0%) underwent OLT after 1999.The median follow-up time was 8.5 years (IQR 13.3 y). The overall 5-year graft survival rate was 83.2% for the tacrolimus group and 83.2% for the cyclosporine group (logrank $p = 0.11$). The overall 5-year recipient survival rate was 86.6% for the tacrolimus group and 86.5% for the cyclosporine group (logrank $p = 0.67$). There was not a significant association between tacrolimus vs. cyclosporine use and graft survival (adjusted HR 0.67, 95% CI 0.25-1.83) or patient survival (adjusted HR 0.82, 95% CI 0.26-2.64). Among those who had a listed cause of death, 19 (4.1%) in the cyclosporine group and 27 (4.5%) in the tacrolimus group died from recurrent disease ($p = 0.7$). **Conclusion:** Although prior studies have identified an association between tacrolimus and increased rates of rPBC in patients who underwent OLT for PBC, this analysis of the OPTN database demonstrated no association between use of tacrolimus or cyclosporine at discharge with regards to graft or patient survival. Future studies should continue to investigate if there a relationship between immunosuppression regimen and graft or patient survival.

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



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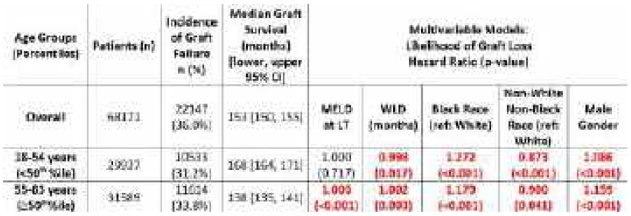
1118-A | THE ASSOCIATION OF WAITLIST DURATION WITH GRAFT FAILURE AFTER LIVER TRANSPLANT DIFFERS BASED ON AGE

Ashley Spann, Irene Feurer, Scott Rega, Seth J. Karp and Manhal Izzy, Vanderbilt University Medical Center

Background: With increasing demand for organs, patients tend to wait for long periods. Concomitantly, there has been an increase in the age of patients on the waitlist as well as transplants in older patients over the past decade. Prior data suggested adverse impact of advancing age on liver transplant outcomes. It is unknown, however, if the duration of waitlisting influences this association. We aimed to assess the joint effects of age at transplant and pre-transplant waitlist duration (WLD) on likelihood of graft failure (GF). **Methods:** This retrospective analysis analyzed adult liver only deceased-donor transplant recipients between 3/1/2002 and 1/1/2021 using Scientific Registry of Transplant Recipients Standard Analysis Files. Exclusion criteria were age < 18 years, prior transplant, being Status 1A at transplant, receiving Model for End-Stage Liver Disease (MELD) exception points for hepatocellular carcinoma, and inadequate or unavailable follow-up. The primary outcome was graft failure, defined as re-transplantation or death from any cause. Age at transplant was classified as < or e 55-years based on the 50th percentile threshold. Kaplan-Meier and Cox proportional hazards regression models analyzed the effects of age at transplant (years), age group, WLD (months), MELD at transplant, gender, race, and the age group by WLD interaction on the likelihood of GF. **Results:** A total of 61,526 patients were included (64% male, 88% white). Patient age at transplant and WLD averaged 54 ± 10 years and 7.2 ± 13.6 months. Overall analyses demonstrated that age (e 55 y), MELD at LT, WLD, race and gender were significantly associated with GF (all $p < 0.05$). A statistically significant age group by WLD interaction ($p < 0.001$) indicated that the effect of WLD on GF varied between the age groups. Subsequent age group-specific multivariable models are summarized in the Table. These multivariable models demonstrated that: 1) patients e 55 had increased likelihood of GF with longer WLD; 2) increasing MELD at LT was independently associated with GF only among patients e 55; and 3) male gender and black race were associated with increased risk of GF, whereas non-white non-Black race was associated with reduced likelihood of GF. **Conclusion:** This study highlights the differential effect of WLD on risk of graft loss in patients above and below age 55 after adjusting for effects of MELD, race and gender. For patients under age 55, longer WLD is associated with reduced likelihood of graft failure after liver transplantation. Whereas, among those 55 years or older, increased WLD and higher MELD score at LT are associated with increased likelihood of graft failure. These findings may advocate for stronger consideration of higher risk grafts in patients 55 and older to decrease WLD before further progression of severity of liver disease.



Age Groups (Percentiles)	Patients (n)	Incidence of Graft Failure n (%)	Median Graft Survival (months) [lower, upper 95% CI]	Multivariable Models: Likelihood of Graft Loss Hazard Ratio (p-value)				
Overall	68171	22147 (36.0%)	153 [150, 155]	MELD at LT	WLD (months)	Black Race (ref: White)	Non-White Non-Black Race (ref: White)	Male Gender
18-54 years (<50th %ile)	29027	10533 (31.2%)	168 [164, 171]	1.000 (0.717)	0.998 (0.017)	1.272 (<0.001)	0.873 (<0.001)	1.186 (<0.001)
55-63 years (≥50th %ile)	31589	11614 (33.8%)	138 [135, 141]	1.009 (<0.001)	1.002 (0.003)	1.179 (<0.001)	0.900 (0.041)	1.155 (<0.001)

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Disclosure information not available at the time of publication: Irene Feurer, Scott Rega, Seth J. Karp

1119-A | THE BURDEN OF PSYCHIATRIC DISEASE AND TREATMENT PATTERNS FOLLOWING LIVER TRANSPLANTATION–A LARGE NATIONAL DATABASE INVESTIGATION

Alex R. Jones[1], Yue Jiang[2], Prajwal Gowda[3], Madhukar Patel[1], Ben Lippe[1], Akhil Shenoy[4], Tami Gurley[1], Van Ngo[1], Mary Olumesi[1], Raelene E. Trudeau[1], Alvaro Noriega Ramirez[1], Layne Jordan-Genco[1], Arjmand R. Mufti[1], Amit G. Singal[1], Lisa B. VanWagner[1] and Sarah Rosanna Lieber[1], (1)University of Texas Southwestern Medical Center, (2)Duke University, (3)UT Southwestern School of Medicine, (4)Columbia University Medical Center, New York, NY

Background: Psychiatric disease is common after liver transplantation (LT) and associated with worse patient and graft outcomes. Management is essential to improving care for LT recipients yet has not been well characterized. We aimed to describe the burden of psychiatric disease and treatment patterns among a nationally representative cohort of LT recipients. **Methods:** LT recipients aged 18-64 years with e 6-month pre-LT and e 1-year post-LT outcomes from 2006-2021 were identified using IQVIA PharMetrics Plus, a nationally representative U.S. database of commercial medical and pharmacy claims. Psychiatric disease was defined using e 2 outpatient or e 1 inpatient ICD-9/10 codes. Pharmacologic therapy and psychotherapy were identified by CPT codes. We used multivariable logistic regression to identify factors associated with psychiatric disease and subsequent receipt of pharmacologic therapy. **Results:** Among 1,742 LT recipients, 496 (28%) were diagnosed with psychiatric disease (Table 1). Factors significantly associated with psychiatric disease included female sex (aOR 1.66, [95% CI 1.29, 2.13]), longer LT hospitalization length of stay (aOR 1.68 [1.31, 2.16]), modified Charlson Comorbidity Index (CCI) > 3 (aOR 1.60 [1.12, 2.26]), and pre-LT psychiatric history (aOR 6.05 [4.76, 7.74]). Among these patients, 321 (65%) received pharmacologic therapy, 161 (32%) received psychotherapy, 99 (20%) received multimodal therapy, and 113 (23%) received no therapy. Of 405 LT recipients on pharmacologic therapy pre-LT, 306 (76%) continued therapy post-LT. Predictors of receiving pharmacotherapy post-LT included HCC (aOR 2.05 [1.27, 3.35]), and pre-LT psychiatric disease (aOR 3.01 [1.97, 4.63]). SSRIs were the most prescribed medications (37%), followed by benzodiazepines (18%), and atypical antipsychotics (14%). Among all claims for psychotropic medications, 23% were prescribed by primary care providers, 10% by psychiatrists, and 7% by hepatologists. Severe psychiatric complications after LT occurred in 9 patients (2%) (1 suicidal ideation; 8 psychiatric hospitalizations). **Conclusion:** Over 1 in 4 LT recipients were diagnosed with psychiatric disease in a large national database, with two-thirds requiring pharmacologic therapy, and just under a quarter receiving no therapy. Female sex, increased comorbidity, prolonged LT length of stay and preexisting psychiatric disease were associated with psychiatric diagnosis, highlighting potential vulnerable populations in need of psychiatric monitoring and treatment post-LT.

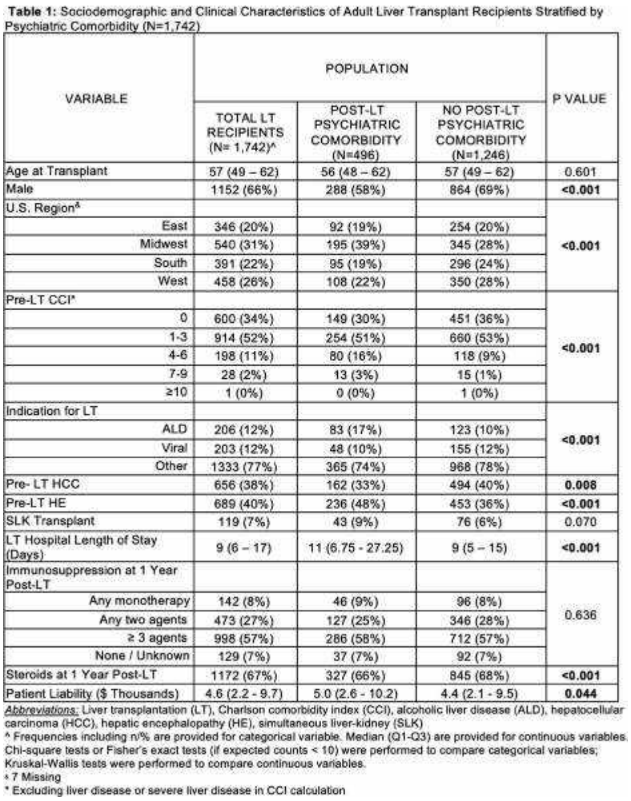

Table 1: Sociodemographic and Clinical Characteristics of Adult Liver Transplant Recipients Stratified by Psychiatric Comorbidity (N=1,742)

VARIABLE	POPULATION			P VALUE
	TOTAL LT RECIPIENTS (N= 1,742)^	POST-LT PSYCHIATRIC COMORBIDITY (N=496)	NO POST-LT PSYCHIATRIC COMORBIDITY (N=1,246)	
Age at Transplant	57 (49 – 62)	56 (48 – 62)	57 (49 – 62)	0.601
Male	1152 (66%)	288 (58%)	864 (69%)	**<0.001**
U.S. Region^&				
East	346 (20%)	92 (19%)	254 (20%)	**<0.001**
Midwest	540 (31%)	195 (39%)	345 (28%)	
South	391 (22%)	95 (19%)	296 (24%)	
West	458 (26%)	108 (22%)	350 (28%)	
Pre-LT CCI*				
0	600 (34%)	149 (30%)	451 (36%)	**<0.001**
1-3	914 (52%)	254 (51%)	660 (53%)	
4-6	198 (11%)	80 (16%)	118 (9%)	
7-9	28 (2%)	13 (3%)	15 (1%)	
≥10	1 (0%)	0 (0%)	1 (0%)	
Indication for LT				
ALD	206 (12%)	83 (17%)	123 (10%)	**<0.001**
Viral	203 (12%)	48 (10%)	155 (12%)	
Other	1333 (77%)	365 (74%)	968 (78%)	
Pre- LT HCC	656 (38%)	162 (33%)	494 (40%)	**0.008**
Pre-LT HE	689 (40%)	236 (48%)	453 (36%)	**<0.001**
SLK Transplant	119 (7%)	43 (9%)	76 (6%)	0.070
LT Hospital Length of Stay (Days)	9 (6 – 17)	11 (6.75 - 27.25)	9 (5 – 15)	**<0.001**
Immunosuppression at 1 Year Post-LT				
Any monotherapy	142 (8%)	46 (9%)	96 (8%)	0.636
Any two agents	473 (27%)	127 (25%)	346 (28%)	
≥ 3 agents	998 (57%)	286 (58%)	712 (57%)	
None / Unknown	129 (7%)	37 (7%)	92 (7%)	
Steroids at 1 Year Post-LT	1172 (67%)	327 (66%)	845 (68%)	**<0.001**
Patient Liability ($ Thousands)	4.6 (2.2 - 9.7)	5.0 (2.6 - 10.2)	4.4 (2.1 - 9.5)	**0.044**

Abbreviations: Liver transplantation (LT), Charlson comorbidity index (CCI), alcoholic liver disease (ALD), hepatocellular carcinoma (HCC), hepatic encephalopathy (HE), simultaneous liver-kidney (SLK)

^ Frequencies including n/% are provided for categorical variable. Median (Q1-Q3) are provided for continuous variables. Chi-square tests or Fisher's exact tests (if expected counts < 10) were performed to compare categorical variables; Kruskal-Wallis tests were performed to compare continuous variables.

& 7 Missing

* Excluding liver disease or severe liver disease in CCI calculation

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1120-A | THE EFFECT OF TENOFOVIR DISOPROXIL FUMARATE USE ON BONE MINERAL DENSITY IN LIVER TRANSPLANT RECIPIENTS

Ilker Turan[1], Ferit Celik[1], Alper Uysal[1], Ali Senkaya[2], Esra Nur Nur Durmazer[1], Murat Zeytunlu[3], Fulya Gunsar[1], Zeki Karasu[1] and Ulus S. Akarca[1], (1)Ege University Faculty of Medicine, Izmir, Turkey, (2) Department of Gastroenterology, (3)Ege University Faculty of Medicine, Organ Transplantation Application and Research Center, Izmir, Turkey

Background: The impact of tenofovir disoproxil fumarate (TDF) on bone mineral density (BMD) is well-known, but there is a lack of sufficient data regarding its effects in liver transplant patients. We aimed to investigate the effect of TDF use on BMD in patients who underwent liver transplantation due to hepatitis B-related liver disease. **Methods:** The results of bone densitometry [dual-energy X-ray absorptiometry (DEXA)] performed with a one-year interval were evaluated for 79 patients who underwent liver transplantation and initiated TDF between July 2009 and June 2019. Wilcoxon analysis was used to analyze research data. **Results:** Thirty patients who started TDF without baseline DEXA measurement were excluded from the identified 79 patients. Forty-nine patients who had baseline DEXA measurement before initiating the medication and had the first follow-up DEXA measurement within the first year after medication initiation were included into the study. Among the patients, 32 (65%) were male, and the mean age was 53. Patients were evaluated at the outpatient clinic every three months. Follow-up DEXA measurements were repeated in all 49 patients at the one year. The mean baseline FRAX major osteoporotic fracture risk and hip fracture risk were 3.98% and 0.48%, respectively. The mean baseline values (±SD) of bone mineral density for total hip and lumbar spine (L1-L4) were 0.93±0.15 g/cm2 and 0.95±0.34 g/cm2, respectively. After one year, BMD values for total hip and L1-L4 were 0.95±0.37 g/cm2 and 0.97±0.18 g/cm2, respectively. When comparing the two measurements, there were no significant differences in total hip ($p = 0.54$) and L1-L4 ($p = 0.07$) BMD measurements. The mean baseline T-score (±SD) for total hip and L1-L4 were -0.71±1.1 and -0.92±1.3, respectively. The T-scores for total hip and L1-L4 at the one year later were -0.86±1.1 and -1.04±1.3, respectively. The statistical analysis using Wilcoxon test for the one-year change in L1-L4 T-score revealed a significantly lower T-score measurement ($p = 0.014$). **Conclusion:** Our study demonstrated a significant decrease in lumbar BMD after one year of TDF use in liver transplant recipients.

Disclosures: The following people have nothing to disclose: Ilker Turan, Ferit Celik, Alper Uysal, Ali Senkaya, Esra Nur Nur Durmazer, Murat Zeytunlu, Fulya Gunsar, Zeki Karasu, Ulus S. Akarca

1121-A | THE NATIVE AMERICAN LIVER TRANSPLANT EXPERIENCE AT A LARGE SOUTHWESTERN LIVER TRANSPLANT CENTER

David Chascsa[1], Blanca Lizaola-Mayo[1], Caroline C Jadlowiec[1], Adam J Milam[1], Nathan L Delafied[1], Elizabeth H Stearns[1], Timethia J Bonner[2] and Rolland C Dickson[1], (1)Mayo Clinic Arizona, Phoenix, AZ, (2) Mayo Clinic

Background: Health equity in liver transplantation (LT) implies providing fair access and prioritizing patients who will most benefit from LT. American Indian (AI) patients accounted for 0.8% of LTs performed in 2020 according to OPTN, despite increased prevalence of end-stage liver disease (ESLD) in AI populations. Further highlighting the health disparity, only 30% of AIs awaiting solid organ transplantation underwent transplant compared with 49% of waiting non-Hispanic White (NHW) patients. The Mayo Clinic in Arizona (MCA) is a high-volume LT center geographically near large AI populations. We sought to characterize the LT experience of AI patients at MCA. **Methods:** This was a retrospective cohort study of all patients referred for LT at MCA from 2017 to 2022. Race and ethnicity were self-reported. Transplant specific details included total number of referred patients by race and ethnicity, number evaluated and transplanted, etiology of ESLD, graft loss and death. Stata was used to perform statistical analysis. Chi square was used to determined statistical significance with a $p\text{-value} < 0.05$. **Results:** AIs accounted for 4% ($n = 135$ of 3218) of LT referrals. Compared to Black, Hispanic and NHW cohorts, a smaller percentage of referred AI patients underwent evaluation. Evaluated AIs were statistically less likely to be listed for LT compared to NHW patients (Table 1). The percentage of referred AI patients undergoing LT

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

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

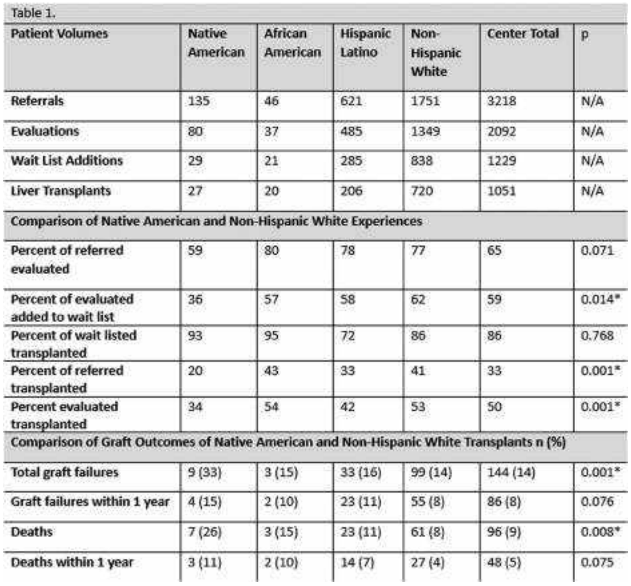

Table 1.

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

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Disclosure information not available at the time of publication: Blanca Lizaola-Mayo, Caroline C Jadlowiec, Adam J Milam, Nathan L Delafied, Elizabeth H Stearns, Timethia J Bonner, Rolland C Dickson

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

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

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

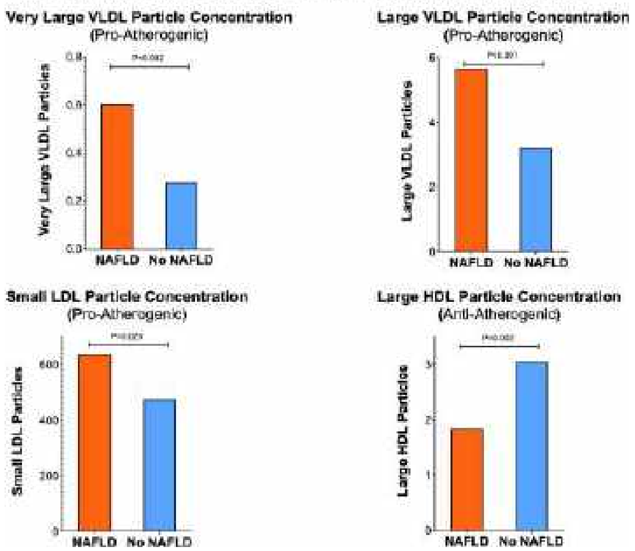

FIGURE 1: Impact of NAFLD on Lipoproteins in LT recipients

Disclosures: Margery Connelly – Labcorp: Employee, No, No;

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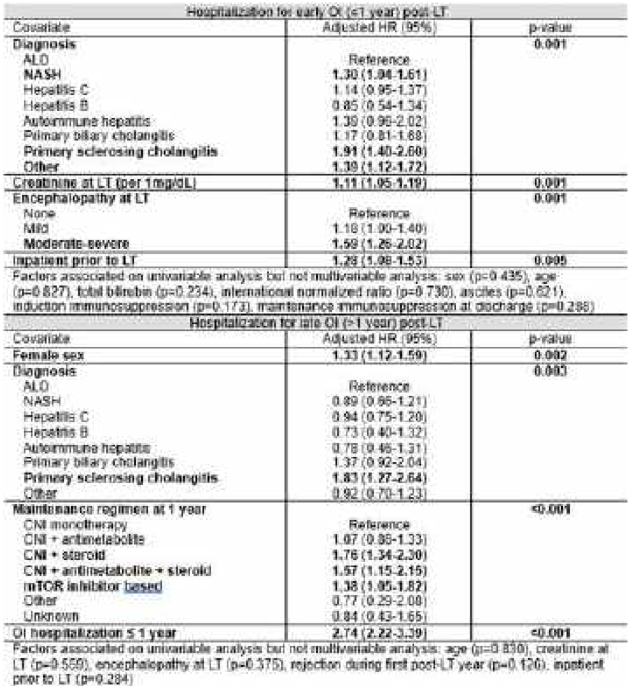
1123-A | THE ROLE OF IMMUNOSUPPRESSION REGIMEN CHOICE ON THE RISK OF EARLY AND LATE OPPORTUNISTIC INFECTIONS AFTER LIVER TRANSPLANTATION

Alyssa Mezochow[1], Ranganath G. Kathawate[2], David Goldberg[3] and Therese Bittermann[1], (1)University of Pennsylvania, (2)Wayne State University, (3)University of Miami

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



Hospitalization for early OI (≤1 year) post-LT		
Covariate	Adjusted HR (95%)	p-value
Diagnosis		**0.001**
ALD	Reference	
NASH	**1.30 (1.04-1.61)**	
Hepatitis C	1.14 (0.95-1.37)	
Hepatitis B	0.85 (0.54-1.34)	
Autoimmune hepatitis	1.39 (0.96-2.02)	
Primary biliary cholangitis	1.17 (0.81-1.68)	
Primary sclerosing cholangitis	**1.91 (1.40-2.60)**	
Other	**1.39 (1.12-1.72)**	
Creatinine at LT (per 1mg/dL)	**1.11 (1.05-1.19)**	**0.001**
Encephalopathy at LT		**0.001**
None	Reference	
Mild	1.18 (1.00-1.40)	
Moderate-severe	**1.59 (1.26-2.02)**	
Inpatient prior to LT	**1.28 (1.08-1.53)**	**0.005**
Factors associated on univariable analysis but not multivariable analysis: sex (p=0.435), age (p=0.827), total bilirubin (p=0.234), international normalized ratio (p=0.730), ascites (p=0.621), induction immunosuppression (p=0.173), maintenance immunosuppression at discharge (p=0.288)		
Hospitalization for late OI (>1 year) post-LT		
Covariate	Adjusted HR (95%)	p-value
Female sex	**1.33 (1.12-1.59)**	**0.002**
Diagnosis		**0.003**
ALD	Reference	
NASH	0.89 (0.66-1.21)	
Hepatitis C	0.94 (0.75-1.20)	
Hepatitis B	0.73 (0.40-1.32)	
Autoimmune hepatitis	0.78 (0.46-1.31)	
Primary biliary cholangitis	1.37 (0.92-2.04)	
Primary sclerosing cholangitis	**1.83 (1.27-2.64)**	
Other	0.92 (0.70-1.23)	
Maintenance regimen at 1 year		**<0.001**
CNI monotherapy	Reference	
CNI + antimetabolite	1.07 (0.86-1.33)	
CNI + steroid	**1.76 (1.34-2.30)**	
CNI + antimetabolite + steroid	**1.57 (1.15-2.15)**	
mTOR inhibitor based	**1.38 (1.05-1.82)**	
Other	0.77 (0.29-2.08)	
Unknown	0.84 (0.43-1.65)	
OI hospitalization ≤ 1 year	**2.74 (2.22-3.39)**	**<0.001**
Factors associated on univariable analysis but not multivariable analysis: age (p=0.830), creatinine at LT (p=0.559), encephalopathy at LT (p=0.375), rejection during first post-LT year (p=0.126), inpatient prior to LT (p=0.284)		

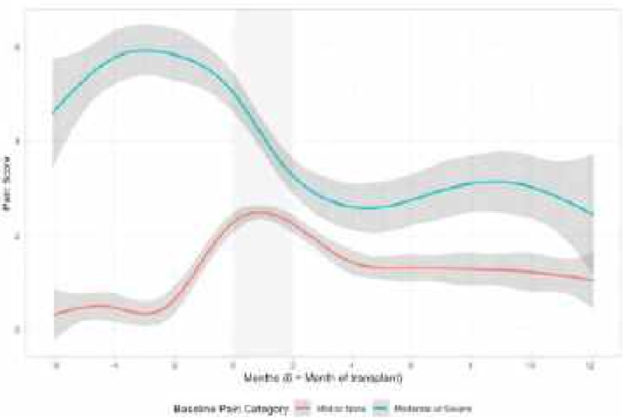
Disclosures: The following people have nothing to disclose: Alyssa Mezochow, Ranganath G. Kathawate, David Goldberg, Therese Bittermann

1124-A | TRAJECTORIES OF PAIN IN CIRRHOSIS PATIENTS FROM BEFORE TO AFTER LIVER TRANSPLANTATION

Jessica Beth Rubin[1,2], *Rebecca Loeb*[1], *Cynthia Fenton*[1] *and Jennifer C. Lai*[1], *(1)University of California-San Francisco, (2)San Francisco VA Health Care System*

Background: Pain is highly prevalent in cirrhosis patients and is often presumed to be related to complications of decompensated liver disease. Thus, we believe that pain will improve after liver transplantation (LT), though actual pain trajectories from before transplant to after transplant have not been characterized. We sought to explore the relationship between pre- and post-LT pain severity in a large retrospective cohort of cirrhosis patients. **Methods:** We included all patients with cirrhosis seen for an initial visit in UCSF hepatology clinics 2013-2022 who subsequently underwent LT. Baseline pain severity was defined as the average Numeric Rating Scale (NRS) score recorded during hepatology clinic visits over the 6 months prior to LT; post-LT pain was recorded at clinic visits from months 2-12 post-LT (excluding immediate post-operative period). Pain severity was classified using well-defined cutpoints of: none (0) mild (1-3), moderate (4-6), or severe (7-10). In addition to NRS scores, we also collected baseline sociodemographic, clinical, and laboratory variables. We created a LOESS curve to display pain severity over time by baseline pain category (no/mild vs moderate/severe), and then used generalized estimating equations to model the effect of time, baseline pain, demographic, and clinical covariates on the change in pain since baseline. **Results:** 556 patients who underwent liver transplant at UCSF met our inclusion criteria; median age was 59 (IQR 53-63); 69% were male and 43% were non-LatinX White. The most common cirrhosis etiology was alcohol (40%). A median of 1 NRS score (IQR 1-2) was recorded during the baseline period, during which 23% reported moderate/severe pain. A median of 5 pain scores (IQR 3-6) were collected during follow up from months 2-12 post-LT. Overall, pain continually decreased with each passing month over the year post-LT ($b_{time} = -0.08$). On average, patients with moderate/severe baseline pain showed a greater reduction in pain after LT compared to patients with mild/no baseline pain ($b_{bl\ pain} = -4.2$). Patients with moderate/severe pain reported an average *reduction* of 2.9 NRS points from pre- to 6-months post-LT, while those with no/mild pain reported an average *increase* of 1 NRS point during this same time period—a difference which persisted after controlling for demographic and clinical covariates (Figure). **Conclusion:** Pre-LT pain severity is the most significant predictor of change in pain after LT: patients with moderate/severe pain before LT experience meaningfully *reduced* pain within the months following transplant, whereas patients with no/mild pain experience mildly *increased* pain, trends which persist up to 1-year post-LT. These findings suggest that the most severe pain in this population may be related to cirrhosis complications and thus may also improve rapidly post-LT; these data may help providers set expectations for patients regarding pain severity in the year following LT.

Figure. Observed Pain over Time Among Cirrhosis Patients Before and After Liver Transplant



Disclosures: Jennifer C. Lai – Novo Nordisk: Advisor, No, No; Genfit: Consultant, No, No; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Vir: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gore: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Flagship Pioneering: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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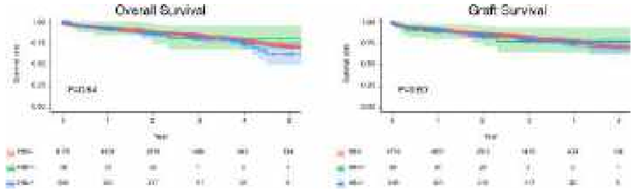
1125-A | UTILIZATION AND OUTCOMES OF HEPATITIS B VIRUS-POSITIVE GRAFTS FOR LIVER TRANSPLANTATION IN THE UNITED STATES

Kenji Okumura, Abhay Dhand, Ryosuke Misawa, Hiroshi Sogawa, Gregory R. Veillette, Roxana I. Bodin, David C. Wolf and Seigo Nishida, Westchester Medical Center

Background: As demand for transplantation increases, livers from hepatitis B virus (HBV) positive donors have been used to expand the donor pool. The aim of our study was to assess the nationwide trends and outcomes of liver transplantation (LT) while using grafts from HBV+ donors in HBV negative (HBV-) recipients. **Methods:** HBV+ grafts comprised to two groups: HBV+ donor: defined as either HBV NAT or HBV surface antigen-positive, and HBc+ donor: defined as HBV core antibody positive along with negative HBV NAT and HBV surface antigen. HBV negative donor (HBV-) was defined as HBV NAT, HBV surface antigen and HBc antibody negative. Using the United Network for Organ Sharing database between Jan-2015 to 2022, HBV+ (n = 59), HBc+ (N = 568) and HBV- (n = 9,043) adult LT recipients were identified. Multi-organ transplant and re-transplant were excluded. Propensity score matching was performed using 6 variables. Post-transplant survival analysis was performed using Kaplan-Meier method and Cox-hazard proportional regression model. **Results:** The number of LT using HBV+ grafts increased during the study period ($p < 0.032$). In HBV+ and HBc+ groups, recipients were older (median age: 59 vs 57, $p < 0.010$), had higher rates of diabetes (32% vs 27%, $p = 0.020$), lower rate of dialysis at transplant (3.4 % vs 8.3% vs 16%, $p < 0.001$), lower median MELD scores (18 vs 20 vs 25, $p < 0.001$), and lower rate of ICU admission at transplant (1.7% vs 9.9% vs 15%). There was an increase in percentage of national organ sharing ($p < 0.001$), and utilization of concurrent HCV positive organs ($p < 0.001$). Donor characteristics were similar in both the groups. Overall survival and graft survival were comparable between HBV+, HBc+ and HBV- in non-matched and matched cohorts. (figure 1). HBV+ and HBc+ grafts were not associated with any increase in mortality (HR 1.06, 95% CI 0.94-1.19, $p = 0.35$) or graft loss (HR 1.06, 95% CI 0.94-1.18, $p = 0.34$) during the median follow up period of 4 years. No seroconversion in the recipients was reported from HBV+ or HBc+ livers within three years post-transplant and no increase in rate of rejection episodes were noted within one-year post-transplant. **Conclusion:** Overall and graft survival of liver transplant recipients using HBV+ or HBc+ livers were comparable to HBV negative liver transplants. With careful recipient selection and further advances in HBV vaccination and therapeutics, LT using HBV+ donors can be used to successfully expand the donor pool.



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Disclosure information not available at the time of publication: Abhay Dhand, Ryosuke Misawa, Hiroshi Sogawa, Gregory R. Veillette, Roxana I. Bodin, David C. Wolf, Seigo Nishida

1126-A | UTILIZATION OF SGLT2 INHIBITORS AND GLP-1 AGONIST IN LIVER TRANSPLANT RECIPIENTS: ASSESSING CURRENT PRACTICE AND EXPLORING EXTRAHEPATIC MANIFESTATIONS OF POST TRANSPLANT NAFLD

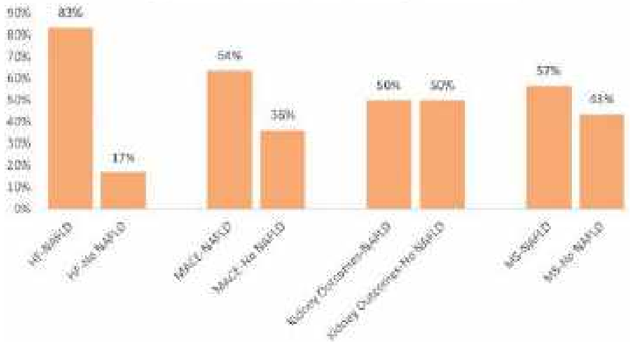
Hamza Khan, Benjamin Heriford, Lily Kuo, Jonathan Selzman and Fabian Rodas, UT Health San Antonio

Background: Nonalcoholic fatty liver disease (NAFLD) is a prevalent comorbidity among liver transplant recipients (LTR) and is associated with disease progression and complications. Despite limited data on novel diabetic agents in NAFLD and post-LTR,

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

medications such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists are increasingly being prescribed for glycemic management in this population. This study aims to evaluate the extent of utilization of SGLT2 inhibitors and GLP-1 agonists in a cohort of LTR and investigate the rates of NAFLD and extrahepatic manifestations of NAFLD. **Methods:** A retrospective chart review was conducted on patients who underwent transplantation at a large tertiary academic medical center. Inclusion criteria included liver transplantation between 2013 and 2017 and a diagnosis of type 2 diabetes mellitus (T2DM). Exclusion criteria included multiorgan transplantation or death within one year post-transplantation. Baseline data, including demographics, were obtained prior to transplantation, and subsequent follow-ups were conducted at 1, 3, and 5-year post-transplant intervals. The rates of the following complications were assessed: metabolic syndrome (MS), NAFLD (diagnosed by ultrasound or biopsy), heart failure (HF), major adverse cardiovascular events (MACE), and composite kidney outcomes. **Results:** A total of 83 patients were included in this study (75% male, 70% Hispanic, mean age 64). Among them, 73 patients (83%) underwent orthotopic liver transplantation (OLT), while 10 patients (12%) underwent living donor transplant (LDT). At 5 years of follow-up, 12 patients (15%) were prescribed a GLP-1 agonist, while 8 patients (9%) were prescribed an SGLT2 inhibitor. The rate of NAFLD was 52% (86% de novo, 14% recurrent). Extrahepatic complication rates among patients who developed NAFLD compared to those who did not develop NAFLD are detailed in Figure 1. MS was strongly correlated with the development of NAFLD ($r = 0.315$, $p = 0.004$). **Conclusion:** Patients who developed NAFLD had higher rates of HF and cardiovascular events. Patients with MS were more likely to develop NAFLD. SGLT2 inhibitors and GLP-1 agonists have shown promise in reducing these complications. Although our cohort size was insufficient to assess the long-term benefits of these agents, our findings underscore the necessity for large-scale and multicenter clinical trials to establish their safety in liver transplant recipients.

Figure 1: Rates of Complications



Disclosures: The following people have nothing to disclose: Hamza Khan, Benjamin Heriford, Lily Kuo, Jonathan Selzman, Fabian Rodas

1127-A | VACCINATION, MONOCLONAL ANTIBODY AND MYCOPHENOLATE EFFECTS ON CLINICAL OUTCOMES IN LIVER VERSUS KIDNEY TRANSPLANT RECIPIENTS WITH COVID-19 INFECTION

Ashley Francis[1], Sara Farooqui[1], Suraj Suresh[2] and Syed-Mohammed Jafri[3], (1)Wayne State University School of Medicine, (2)Henry Ford Health, (3)Henry Ford Health System

Background: We aim to evaluate how vaccination, monoclonal antibody (MAB) treatment, and mycophenolate use correlate to outcomes for liver and renal transplant (LRT) recipients infected with SARS-CoV-2. **Methods:** A retrospective study of LRT recipients diagnosed with COVID-19 between 3/2020 to 1/2022 was performed. We recorded data on patient demographics, immunosuppressants, vaccine dose numbers, MAB treatment, hospitalization, length of stay (LOS, days), mechanical ventilation (MV) use, as well as 3- and 6-month mortality. **Results:** Of 255 LRT recipients diagnosed with COVID-19, 68 (26%) liver, 177 (69%) renal, and 10 (4%) dual LRT patients were identified. When comparing liver transplant to renal transplant patients, there was no significant difference in hospitalization and mortality. Overall, no significant correlation was found between number of vaccine doses (up to 3) and hospitalization rates ($p = 0.948$), LOS ($p = 0.688$), 3-month mortality ($p = 0.549$), or 6-month mortality ($p = 0.595$). 65 (25%) patients were treated with MABs; these had fewer hospitalizations (37% vs 68% $p < 0.001$) and a trend towards reduced mortality at 3 months (11% vs 18% $p = 0.177$) and 6 months (11% vs 20% $p = 0.092$). However, when comparing 12 liver transplant to 51 renal transplant recipients treated with MABs, there was no significant difference in hospitalization or mortality at 3 or 6 months. Mycophenolate use in 199 patients was associated with increased hospitalization (62% vs 55% $p = 0.383$), MV (24% vs 10% $p = 0.135$), and mortality at 3 and 6 months respectively when compared to non-users (18% vs 9% $p = 0.099$ and 20% vs 11% $p = 0.123$). Of 78 liver transplant patients, 53 (68%) were on mycophenolate. Similarly, within this group, mycophenolate use was associated with increased hospitalization rates (58% vs 44% $p = 0.231$), and mortality at 3 and 6 months respectively when compared to non-users (19% vs 0% $p = 0.020$ and 11% vs 0% $p = 0.014$, respectively). Of 187 renal transplant patients, 152 (81%) were on mycophenolate.

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

Within this group, there was no difference in hospitalization rates among users and non-users (62% vs 62%). When comparing 47 liver to 146 renal transplant patients on mycophenolate (excluding dual LRT patients), there was no significant difference in hospitalization ($p = 0.672$) or mortality at 3 months ($p = 0.595$) or 6 months ($p = 0.530$). **Conclusion:** Our data demonstrates that MAB treatment significantly reduces hospitalizations and 3- and 6-month mortality, irrespective of the type of transplant. Mycophenolate was associated with increased hospitalizations and mortality rates, with common trends seen in liver transplant patients alone. Our data further suggests that a 3-vaccine series was inadequate to predict improvements in clinical outcomes for LRT recipients, suggesting further study of a fourth mRNA vaccine dose and the use of tixagevimab/cilgavimab.

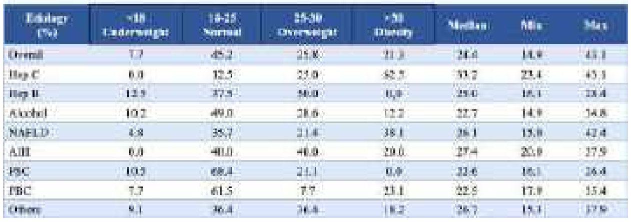
Disclosures: The following people have nothing to disclose: Ashley Francis, Sara Farooqui, Suraj Suresh, Syed-Mohammed Jafri

1128-A | WEIGHT STATUS OF PATIENTS AT THE MOMENT OF LIVER TRANSPLANTATION: NOT ONLY A PROBLEM OF NAFLD PATIENTS!

Isaac Ruiz[1], Mélanie Tremblay[2], Melissa Bouhraoua[1], Crystèle Hogue[1], Amal Trigui[1], Genevieve Huard[3], Catherine Vincent[3], Christopher F. Rose[2,4] and Chantal Bémeur[1,4], (1)Centre De Recherche Du Centre Hospitalier De l'Université De Montréal, (2)Hepato-Neuro Laboratory, Centre De Recherche Du Centre Hospitalier De l'Université De Montréal, (3)Centre Hospitalier De l'Université De Montréal, (4)Université De Montréal

Background: The global obesity epidemic continues to progress at an alarming rate. Non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of metabolic syndrome, is becoming the most common cause of end-stage liver disease (ESLD) and indication for liver transplantation (LT). Documenting the weight status of patients at the moment of the LT is imperative to better understanding of nutritional status evaluation and to improve the management pre and post-operatively of patients. The aim of this study was to evaluate the weight status as part of the nutritional status of patients at the moment of LT, overall and according to the primary liver cirrhosis etiology. **Methods:** This is a retrospective analysis including all consecutive patients who underwent LT at the Centre hospitalier de l'Université de Montréal (CHUM) between 2019 and 2021. Only patients with biological, clinical and or radiological confirmed cirrhosis were included. Presence and degree of ascites were recorded. Underweight, overweight and obesity was defined as body mass index (BMI), < 18, equal or superior to 25.0 and 30.0, respectively. Results of BMI were corrected by the presence of ascites and/or oedema. **Results:** During the study period, 181 patients were transplanted at the CHUM. 155 patients with cirrhosis were included in this study. Among them, 104/155 (67.1%) were men, mean age was 52 years old (range 18-69). At the moment of transplantation, overall median BMI was 24.4 (range 14.9 – 43.1, mean 25.5). Underweight was present in 12/155 (7.7%), overweight was present in 58/155 (25.8%), and obesity was present in 47/155 (21.3%). According to the main etiology of chronic liver disease, underweight/overweight/obesity was present in patient with NAFLD (5/21/38, %), but surprisingly also in hepatitis C (0/25/63 %), hepatitis B (12/25/0 %), primary sclerosing cholangitis (11/21/0, %), primary biliary cholangitis (8/8/23 %), and alcohol (10/29/12, %). Table 1 shows the percentage of patient per weight group, the median BMI and range of patients according to the main etiology of chronic liver disease. **Conclusion:** At the moment of LT, 55% of patient display an underweight or an overweight/obesity. This study highlights the unsatisfactory nutritional status of cirrhotic patients at the moment of the LT. Therapeutic and management strategies pre- and post-LT are mandatory using a multidisciplinary team, including nutritional intervention, while emphasizing weight stigma awareness.

Table 1. Weight status of patients according to the main etiology of chronic liver disease.



Etiology (%)	<18 Underweight	18-25 Normal	25-30 Overweight	>30 Obesity	Median	Min	Max
Overall	7.7	45.2	25.8	21.3	24.4	14.9	43.1
Hep C	0.0	12.5	25.0	62.5	33.2	23.4	43.1
Hep B	12.5	37.5	50.0	0.0	25.0	18.1	28.4
Alcohol	10.2	49.0	28.6	12.2	22.7	14.9	34.8
NAFLD	4.8	35.7	21.4	38.1	26.1	15.8	42.4
AIH	0.0	40.0	40.0	20.0	27.4	20.8	27.9
PSC	10.5	68.4	21.1	0.0	22.6	16.1	26.4
PBC	7.7	61.5	7.7	23.1	22.5	17.9	35.4
Others	9.1	36.4	36.4	18.2	26.7	15.3	37.9

Disclosures: Christopher F. Rose – Axcella: Advisor, No, Yes; Aza Technology: Advisor, No, No; Horizon Therapeutics: Speaking and Teaching, No, No; Lupin Pharma: Speaking and Teaching, No, No; Mallinckrodt: Consultant, No, Yes; Morphocell Technologies: Advisor, No, No; Neuractas: Advisor, No, Yes; River Stone: Consultant, No, Yes;

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f 1129-A | A NOVEL HCC WAITLIST DROPOUT SCORE: BIOMARKER INTEGRATED DROPOUT GRADIENT ESTIMATION (BRIDGE)★

Jonathan Li[1], Jeff Liang[2], Vatche G. Agopian[3], Kelley Nunez[4], Joshua Norman[5], Naomy Kim[2], Jung Yum[6], Shreya Gumate[7], Ari J. Cohen[8], Kambiz Kosari[2], Nicholas Nissen[2], Francis Yao[9], Paul Thevenot[10], Ju Dong Yang[2] and Neil Mehta[11], (1)UCSF, (2)Cedars-Sinai Medical Center, Los Angeles, CA, (3)David Geffen School of Medicine at UCLA, (4)Ochsner Health System, (5)Stanford Healthcare, (6)University of California, Los Angeles, (7)UCLA, (8)Ochsner Health System, New Orleans, LA, (9)University of California, San Francisco, San Francisco, CA, (10)Alton Ochsner Medical Foundation, (11)University of California, San Francisco

Background: Alpha-fetoprotein (AFP) is a well-established biomarker for HCC, but AFP-L3 and des-gamma-carboxyprothrombin (DCP) are complementary to AFP in predicting high risk explant pathology and post-transplant (LT) outcome. Additional studies have suggested that AFP-L3 and DCP are superior to AFP in predicting HCC waitlist outcome. The objective of this study is to incorporate AFP-L3 and DCP into a novel dropout risk score. **Methods:** We analyzed data from an ongoing, multicenter study of patients initially listed for transplant with HCC exception between July 2017 and August 2022 and had all three biomarkers (AFP, AFP-L3 and DCP) collected within 90 days of listing. The primary outcome was waitlist dropout due to tumor progression, clinical deterioration, or death. Using the Fine and Gray competing risk (CR) regression model (competing risk: LT), we developed a multivariate prediction model for waitlist dropout. The BRIDGE dropout risk score was then created based on the final multivariable model coefficients, which were scaled and rounded to the nearest integer to produce a simplified point scale. **Results:** Our cohort comprised 427 HCC patients from 4 high-volume LT centers with median listing AFP of 6 ng/mL (IQR 4-17), AFP-L3 8% (IQR 1-13%), DCP 1 ng/mL (IQR 0.8-3.1), Child-Pugh (CP) score 6 (IQR 5-8), and MELD-Na 10 (IQR 8-14). Overall, 53% underwent LT and 22% (n = 93) had dropout. Median follow up after listing was 12 months, and cumulative probability of dropout due to tumor progression, clinical deterioration, or death within 12 months of listing was 13.5%. On CR multivariable analysis, tumor burden beyond Milan criteria, listing AFP > 100, AFP-L3 > 35%, DCP > 7.5, and CP score were significant predictors of waitlist dropout. These five variables were used in the BRIDGE dropout risk score (Figure). Median BRIDGE score was 3 (IQR 1-10). The BRIDGE score stratified 1-year waitlist dropout probabilities ranging from 8.9% with a score < 10, 18.9% with a score of 10-18, and 43.8% with a score of > 18. The addition of AFP-L3 and DCP improved model fit compared to a model without both biomarkers by the log likelihood ratio test ($p < 0.014$). **Conclusion:** To our knowledge, this is the first multicenter study incorporating complete biomarker data (AFP, AFP-L3, DCP at listing), tumor burden and liver disease severity (MELD-Na and Child-Pugh score) into a simple, novel HCC waitlist dropout risk score (BRIDGE). The ability of the BRIDGE score to stratify patients based on risks of waitlist dropout may have important implications for the organ allocation policy that currently gives the same priority to all HCC patients listed for LT.

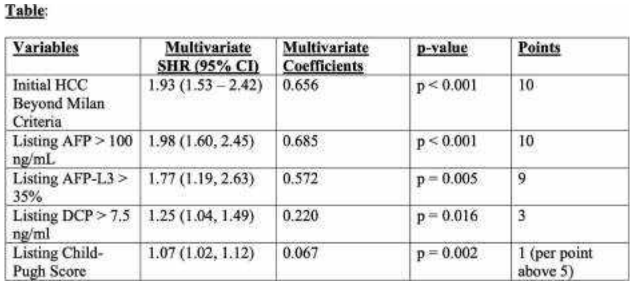

Table:

Variables	Multivariate SHR (95% CI)	Multivariate Coefficients	p-value	Points
Initial HCC Beyond Milan Criteria	1.93 (1.53 – 2.42)	0.656	p < 0.001	10
Listing AFP > 100 ng/mL	1.98 (1.60, 2.45)	0.685	p < 0.001	10
Listing AFP-L3 > 35%	1.77 (1.19, 2.63)	0.572	p = 0.005	9
Listing DCP > 7.5 ng/ml	1.25 (1.04, 1.49)	0.220	p = 0.016	3
Listing Child-Pugh Score	1.07 (1.02, 1.12)	0.067	p = 0.002	1 (per point above 5)

Disclosures: Ju Dong Yang – AstraZeneca: Consultant, No, No; Eisai: Consultant, No, No; Exact Sciences: Consultant, No, No; Exelixis: Consultant, No, No; Fujifilm Medical Sciences: Consultant, No, No; Merck: Consultant, No, No;

The following people have nothing to disclose: Jonathan Li, Jeff Liang, Jung Yum, Neil Mehta

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1130-A | ACUTE CELLULAR LIVER REJECTION FOLLOWING COVID-19 INFECTION

Stela Celaj[1], Rachel Hannum[1], Roy Frye[2] and Obaid Shakil Shaikh[3], (1)University of Pittsburgh Medical Center, (2)VA Pittsburgh Healthcare System, (3) University of Pittsburgh

Background: The management of liver transplant (LT) patients who contract COVID-19 poses

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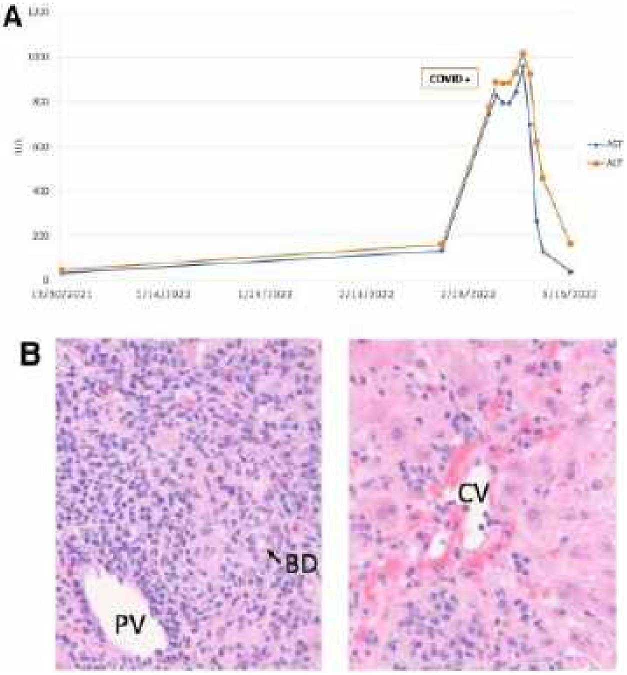
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

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



Disclosures: The following people have nothing to disclose: Stela Celaj, Rachel Hannum, Roy Frye, Obaid Shakil Shaikh

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

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

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

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

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

Figure 1.A

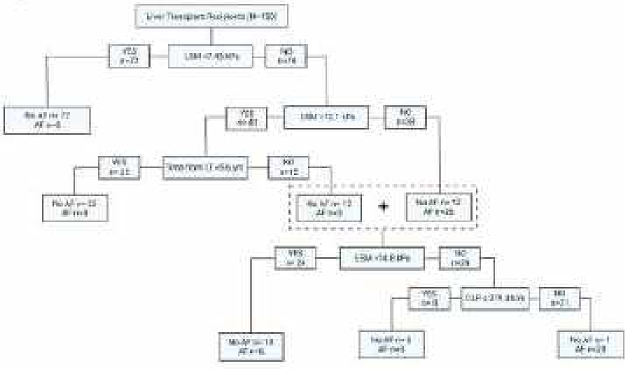
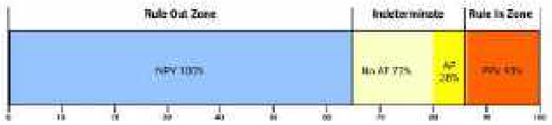


Figure 1.B



Disclosures: The following people have nothing to disclose: Dylan Vainer, Hiba Khan, Alok Baral, Shreya Garg, Audrey Ang, Vaishali Patel, Vinay Kumaran, David Anthony Bruno, Seung Lee, Amit Sharma, Mohammad S. Siddiqui

Disclosure information not available at the time of publication: Tamoore Arshad, Mark Dhinesh Muthiah, Anh Bui

1132-A | EARLY ALCOHOL RELAPSE IN LIVER TRANSPLANT RECIPIENTS ASSOCIATED WITH SIGNIFICANT HEPATIC FIBROSIS

Daniel Thomas Gildea[1], *Stephanie M Woo*[1], *Ade Waterman*[1], *Cristian D Rios Perez*[1], *Krystina A Johnson-Laghi*[1], *Amol S. Rangnekar*[1] *and Christine C Hsu*[1,2], *(1)Medstar Georgetown University Hospital, (2) National Institute of Health*

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

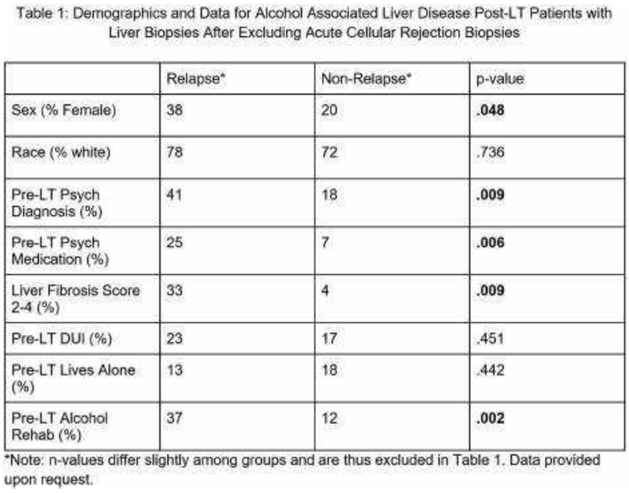


Table 1: Demographics and Data for Alcohol Associated Liver Disease Post-LT Patients with Liver Biopsies After Excluding Acute Cellular Rejection Biopsies

	Relapse*	Non-Relapse*	p-value
Sex (% Female)	38	20	**.048**
Race (% white)	78	72	.736
Pre-LT Psych Diagnosis (%)	41	18	**.009**
Pre-LT Psych Medication (%)	25	7	**.006**
Liver Fibrosis Score 2-4 (%)	33	4	**.009**
Pre-LT DUI (%)	23	17	.451
Pre-LT Lives Alone (%)	13	18	.442
Pre-LT Alcohol Rehab (%)	37	12	**.002**

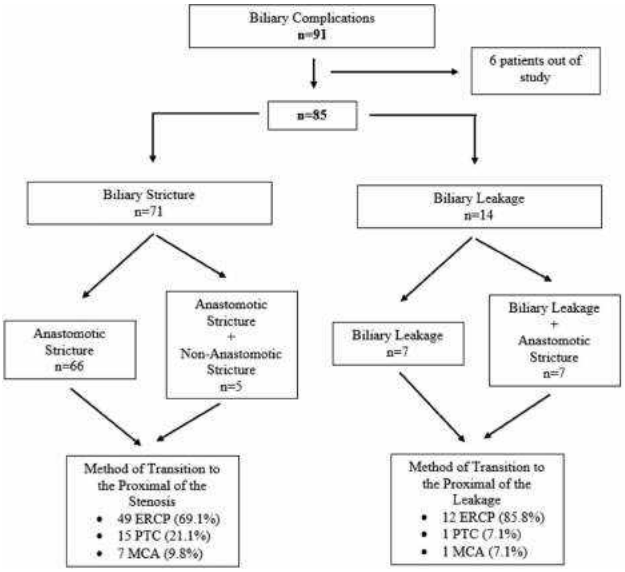
*Note: n-values differ slightly among groups and are thus excluded in Table 1. Data provided upon request.

Disclosures: The following people have nothing to disclose: Daniel Thomas Gildea, Stephanie M Woo, Ade Waterman, Cristian D Rios Perez, Krystina A Johnson-Laghi, Amol S. Rangnekar, Christine C Hsu

1133-A | ENDOSCOPIC TREATMENT OF BILIARY COMPLICATIONS AFTER LIVER TRANSPLANTATION: SINGLE TERTIARY CENTER EXPERIENCE

Bulent Odemis[1], Cagdas Erdogan[1], Muhammed Bahaddin Durak[2] and Cem Simsek[1], (1)Ankara City Hospital, Ankara, Turkey, (2)Mehmet Akif Inan Training and Research Hospital, Sanliurfa, Ankara, Turkey

Background: Biliary complications are the most common post-liver transplant (LT) complications, with an incidence of 15% - 45%. This study aimed to evaluate the efficacy and long-term outcomes of endoscopic treatment in patients experiencing biliary complications following liver transplantation. **Materials and Methods:** A retrospective study of 85 patients was conducted between March 2011 and February 2021. Inclusion criteria were elevated cholestasis enzyme levels in patients who underwent duct-to-duct anastomosis during liver transplantation and had biliary complications documented by imaging. In cases of anastomotic/non-anastomotic stenosis, the maximum number of plastic stents/metal stents were used. For stenosis that could not be passed with ERC, the percutaneous-endoscopic-rendezvous procedure was employed. Magnetic-compression-anastomosis (MCA) was utilized if the stenosis could not be passed endoscopically or percutaneously. In patients with anastomotic leakage, naso-biliary drainage tubes, plastic stents, or stents were inserted across the leak location following sphincterotomy. Clinical Success was defined as improved stricture or leakage on cholangiography and lower cholestasis enzyme levels after 12 months of endoscopic therapy. The procedure was standardized according to the single expert endoscopist's (BO) preference. **Results:** A total of 657 procedures were performed on 85 patients, with a mean follow-up of 33.8 months. Biliary stenosis was detected in 71 patients, and biliary leakage in 14 patients. ERC successfully passed the proximal end of the stenosis in 49 of 71 patients with biliary stenosis. The rendezvous method with PTC was used in 15 patients, and the MCA technique in 7 patients. Stent-free follow-up was achieved in 64.8% (46/71) of patients with biliary stenosis, with a mean treatment duration of 12.3 months and an average stent-free follow-up of 28.8 months. Endoscopic treatment is ongoing in the remaining 25 patients. In patients with anastomotic leakage, the clinical success rate of endoscopic treatment was 100%. In 10 of 14 biliary leakage patients, anastomotic leakage was repaired in a single session, with three patients requiring two sessions and one patient requiring four sessions. NBD was placed in 9 of 14 patients with biliary leak. The rate of complications was 12.3%. Twenty patients experienced stent migration. Fourteen individual's had cholangitis, 12 had pancreatitis, 5 had bleeding, and 1 had magnet migration. Four patients died throughout the follow-up period. One patient died because of the process (cholangiosepsis). The remaining 3 patients died of non-procedural causes. **Conclusion:** Combining percutaneous intervention and magnetic compression anastomosis with endoscopic treatment improves success rates in addressing liver transplantation-related biliary complications. However, a subset of patients may require longer treatment durations than anticipated.



Disclosures: The following people have nothing to disclose: Bulent Odemis, Cagdas Erdogan, Muhammed Bahaddin Durak, Cem Simsek

1134-A | FEASIBILITY OF MEDICATION ASSISTED TREATMENT FOR ALCOHOL USE DISORDER POST-LIVER: INTERIM RESULTS OF A RANDOMIZED CONTROLLED TRIAL

Divya Ayyala[1], Thomas Bottyan[2], Amandeep Sahota[3], Jennifer L. Dodge[1], Norah Terrault[1] and Hyosun Helen Han[1], (1)University of Southern California, (2)Stanford, (3)Kaiser Permanente

Background: Medication assisted treatment (MAT) for alcohol use disorder (AUD) may benefit liver transplant (LT) recipients with alcohol-associated liver disease (ALD), yet data on safety and acceptability of MAT in LT recipients are lacking. **Methods:** An interim analysis of a single-center randomized 2:1 controlled study of acamprosate 666 mg TID +standard of care (SOC) vs SOC in adults post-LT for ALD. Key inclusion criteria were adults > 18 years post-LT (spanning eras of different sobriety requirements) for ALD with creatinine clearance > 30 mL/min. The primary outcome was feasibility (acceptability and study completion rates). Secondary outcomes included safety (differences in side effects in acamprosate vs SOC) and efficacy (reduction in cravings and self-reported drinking). The Penn Alcohol Craving Scale (PACs), Timeline Followback, and side effects were ascertained weekly for 1-3 months. Relapse was defined as positive PeTh (abstracted retrospectively) or self-reported alcohol use. **Results:** Of 71 adults approached, 23 enrolled (15 acamprosate, 8 SOC), of which, 6 withdrew (2 acamprosate, 4 SOC) and 1 was lost to follow up (acamprosate). Those that declined vs enrolled were of similar age, gender, pre-LT mean SIPAT score, median duration of sobriety pre-LT, history of alcohol-associated hepatitis, rehabilitation, alcohol-related legal issues (Table). Adults that declined (vs enrolled) were temporally closer to time of LT (21.9 mo vs 38.9 mo, $p = 0.049$), more frequently had comorbid psychiatric diagnosis (36.4 vs 7.1%, $p = 0.006$), and history post-LT of slip or relapse (39.1 vs 14.6%, $p = 0.01$). Reported reasons for declining participation included absence of cravings (14.6%), abstinence > 1 year (6.3%), afraid of side-effects (35.4%), belief MAT would be unhelpful (20.8%), and lack of interest in research (6.3%) (Table). Of adults that enrolled and completed > 4 weeks of the study (8 acamprosate vs 3 SOC), mean follow-up (11.5 vs 14 weeks) and completion rates of surveys (54.8 vs 58.5%) were similar with 100% compliance to medications in the acamprosate arm. In MAT vs SOC arms, the overall severity of baseline cravings was low (median PACs: 8.4 vs 7.6%) with no difference in the mean reduction in PACs (1.33 vs -2.00, $p = 0.12$) and with no relapses in either group. Reported side effects were similar between both groups, with no treatment withdrawals due to adverse events. **Conclusion:** Low enrollment rates were likely influenced by inclusion of patients many years post-LT and patient's lack of familiarity of MAT and its benefits. Acamprosate was well-tolerated post-LT, yet concerns regarding side effects was among the most common reasons for non-participation. Earlier post-LT introduction of MAT for AUD coupled with education of patients of the value of MAT in management of AUD likely are needed to increase acceptance of MAT by LT recipients.

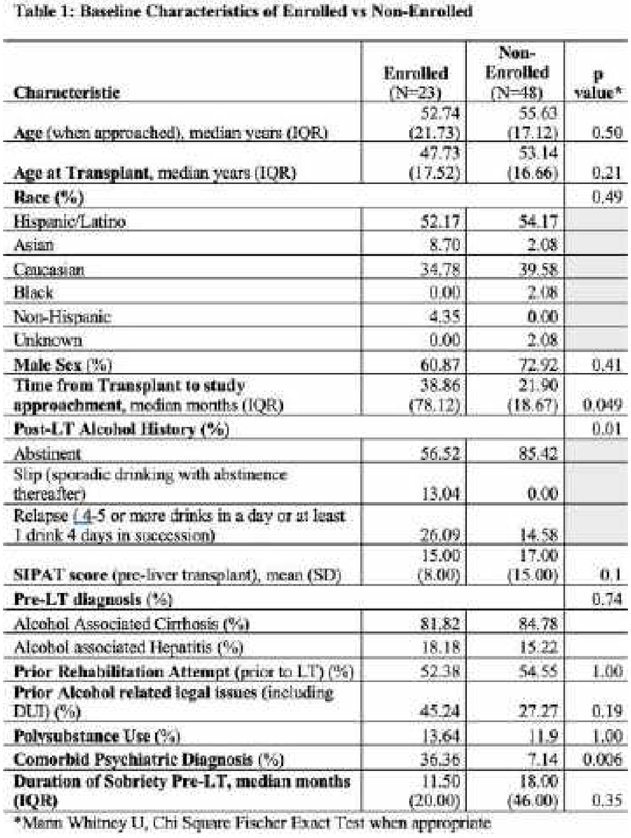


Table 1: Baseline Characteristics of Enrolled vs Non-Enrolled

Characteristic	Enrolled (N=23)	Non-Enrolled (N=48)	p value*
Age (when approached), median years (IQR)	52.74 (21.73)	55.63 (17.12)	0.50
Age at Transplant, median years (IQR)	47.73 (17.52)	53.14 (16.66)	0.21
Race (%)			0.49
Hispanic/Latino	52.17	54.17	
Asian	8.70	2.08	
Caucasian	34.78	39.58	
Black	0.00	2.08	
Non-Hispanic	4.35	0.00	
Unknown	0.00	2.08	
Male Sex (%)	60.87	72.92	0.41
Time from Transplant to study approachment, median months (IQR)	38.86 (78.12)	21.90 (18.67)	0.049
Post-LT Alcohol History (%)			0.01
Abstinent	56.52	85.42	
Slip (sporadic drinking with abstinence thereafter)	13.04	0.00	
Relapse (4-5 or more drinks in a day or at least 1 drink 4 days in succession)	26.09	14.58	
SIPAT score (pre-liver transplant), mean (SD)	15.00 (8.00)	17.00 (15.00)	0.1
Pre-LT diagnosis (%)			0.74
Alcohol Associated Cirrhosis (%)	81.82	84.78	
Alcohol associated Hepatitis (%)	18.18	15.22	
Prior Rehabilitation Attempt (prior to LT) (%)	52.38	54.55	1.00
Prior Alcohol related legal issues (including DUI) (%)	45.24	27.27	0.19
Polysubstance Use (%)	13.64	11.9	1.00
Comorbid Psychiatric Diagnosis (%)	36.36	7.14	0.006
Duration of Sobriety Pre-LT, median months (IQR)	11.50 (20.00)	18.00 (46.00)	0.35

*Mann Whitney U, Chi Square Fischer Exact Test when appropriate

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1135-A | HEPATITIS B PROPHYLAXIS AFTER LIVER TRANSPLANTATION

Maxat Doskhanov[1,2], Baimakhanov Bolatbek[3], Skakbayev Aidar[1], Shokan Kaniyev[1], Erbol Serikuly[1], Aziza Khajiyeva[1], Daniyar Mukazhanov[1], Zhambyl Ospan[1], Serik Tileuov[1], Baglan Askeyev[1] and Abzal Ismatov[1], (1)Syzganov Scientific Center of Surgery, (2) Syzganov National Scientific Center, (3)Syzganov Scientific Center of Surgery of Surgery

Background: Patients undergoing liver transplantation for hepatitis B–related liver disease are prone to recurrence. The mainstay of prophylaxis has been passive immunotherapy with hepatitis B immune globulin (HBIG). Antiviral therapy with tenofovir has proven effective in lowering hepatitis B virus (HBV) DNA and improving histology in patients with hepatitis B infection; its role in prophylaxis against hepatitis B recurrence following liver transplantation is under investigation. Viral breakthrough and resistance, however, are a significant problem with monotherapy with either HBIG or lamivudine. The efficacy of combination tenofovir /HBIG prophylaxis has not been reported. **Methods:** 96 underwent transplantation for decompensated liver disease owing to hepatitis B in Syzganov national scientific center. Mean age of patients was 42.8 ± 9 years old. 75 patients begun to receive Tenofovir (150 mg po/d) before and after transplantation. 4 patients received entacovir. Other was not received treatment. **Results:** Human immunoglobulin was not used after liver transplantation in our study, despite that no acute hepatitis was observed in any patient. On postoperative period, 3 patients had positive HbsAg At a median interval of 49.6 ± 16.1 days following tenofovir treatment, all HBV DNA–positive patients cleared HBV DNA from the serum. The median follow-up was 212,2 ± 109,7 weeks. Actuarial 5-year patient and graft survival was 75%. Only 1 patient had recurrence of hepatits B after a year of transplantation. Tenofovir suppresses HBV replication in patients awaiting liver transplantation. **Conclusion:** Tenofovir and entecavir show good results in the preoperative and postoperative period. Nucleoside analogues with good results of antiviral therapy are not an indication pre- and post operation period.

Disclosures: The following people have nothing to disclose: Maxat Doskhanov, Baimakhanov Bolatbek, Skakbayev Aidar, Shokan Kaniyev, Erbol Serikuly, Aziza Khajiyeva, Daniyar Mukazhanov, Zhambyl Ospan, Serik Tileuov, Baglan Askeyev, Abzal Ismatov

1136-A | LIVER TRANSPLANTATION MANAGES ELEXACAFTOR/TEZACAFTOR/IVACAFTOR LIVER INJURY, AND IMPROVES PULMONARY FUNCTION, WITHOUT RECURRENCE OF LIVER INJURY DESPITE RESUMPTION OF THERAPY FOLLOWING TRANSPLANTATION

Richard Gilroy[1], Sophie Hansen[1,2], Holly Rupone[2] and Laurie LeClair[2], (1)Intermountain Health, (2)University of Utah

Background: Cystic fibrosis (CF) is a potentially lethal inherited disease caused by mutations of the CF transmembrane conductance regulator (CFTR) gene. These mutations lead to impairment of CFTR mRNA and protein expression, transmembrane receptor function and stability of the transmembrane receptor. Cystic fibrosis impacts the lungs most notably; however, pancreatic and liver involvement are not uncommon. Lung disease carries the greatest morbidity and often results in recurrent infections, bronchiectasis, antibiotic resistance, and repeated hospitalizations. The CFTR modulator class of medications have the ability to enhance the transmembrane receptors function with 5 of the 6 classes of CFTR gene mutations able to be targeted by current therapies. These medications provide significant benefits, a significant reduction in pulmonary exacerbations, and when initiated early may prevent the development of CF associated complications. Unfortunately, these therapies are independently associated with elevated liver enzymes in 10% of patients and an elevated bilirubin > 2x the ULN in registry studies. **Methods:** Here we described the outcome of transplantation for a patient with cystic fibrosis, complicated by lung, pancreatic and liver disease who experienced recurrent hospitalizations prior to combination therapy with elexacaftor, tezacaftor, and ivacaftor and consequently developed cholestasis after 2 years of treatment. His drug-induced cholestasis resolved with cessation of therapy and recurrence of cholestasis occurred with resumption. During his absence of use of the medication, hospitalizations for cystic fibrosis exacerbations occurred approximately every 8 weeks, in contrast, only 1 hospitalization occured when on therapy. He was evaluated for liver transplantation with the primary indication being cystic fibrosis associated exacerbations in the absence of CFTR modulator therapy that occurred in the presence of cystic fibrosis associated cirrhosis. **Results:** His liver transplant was uncomplicated and discharge occurred on postoperative day 7. On postoperative day 30 his combination therapy of elexacaftor, tezacaftor, and ivacaftor was resumed without incident. 3 months post-transplant, his lab values are as follows: AST 29 U/L, ALT 26 U/L, alkaline phosphatase 50 U/L and bilirubin 0.8 mg/dL. There has been no hospitalization or cystic fibrosis exacerbation. **Conclusion:** This is the first reported liver transplant for cystic fibrosis in which the indication for transplantation was to provide the ability to safely reinitiate CFTR modulator therapy in a patient with compensated cystic fibrosis associated cirrhosis.

Disclosures: Richard Gilroy – Abbvie: Speaking and Teaching, No, No; Salix: Speaking and Teaching, No, No;

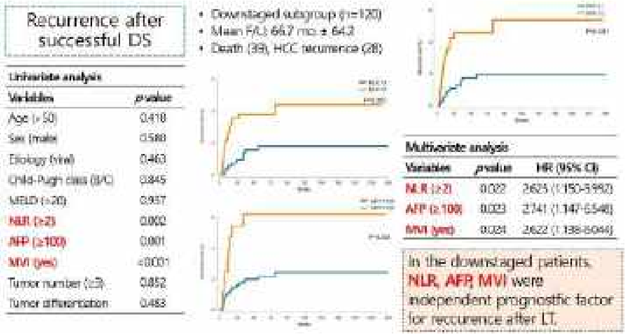
The following people have nothing to disclose: Sophie Hansen

Disclosure information not available at the time of publication: Holly Rupone, Laurie LeClair

1137-A | LONG-TERM OUTCOMES OF LIVER TRANSPLANTATION FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA BEYOND MILAN CRITERIA: A MULTICENTER COHORT STUDY

Heechul Nam[1], Pil Soo Sung[2], Hee Yeon Kim[1], Ho Joong Choi[1], Jung Hyun Kwon[1], U Im Chang[1], Chang Wook Kim[1], Si Hyun Bae[1], Young Kyoung You[1], Jong Choi[1], Seung Kew Yoon[1], Jin Mo Yang[1] and Jeong Won Jang[1], (1)The Catholic University of Korea, (2)The Catholic University Liver Research Center, Department of Biomedicine & Health Sciences, College of Medicine, the Catholic University of Korea

Background: Recent guidelines recommend that liver transplantation (LT) can be considered for patients with hepatocellular carcinoma (HCC) that exceeds Milan criteria (MC) if they have been successfully downstaged to within MC. However, multi-center studies analyzing long-term outcomes are lacking. This study aims to identify prognostic factors for overall survival (OS) and recurrence after LT in downstaged patients with HCC beyond MC. **Methods:** This is a multi-center retrospective study on consecutive patients with HCC underwent LT at 6 academic centers from September 1995 to September 2022. The associations of factors on OS and recurrence rate were analyzed using Cox proportional hazards regression and multivariable logistic regression models. **Results:** The study included 614 HCC patients who underwent LT and were categorized into three groups: within MC (n = 380), successfully down-staged (DS, n = 120), and not down-staged (NoDS, n = 114). The median age of the patients was 54 years (IQR, 50-60 y) and the majority of them were male (509 [82.9%]). The mean follow-up after LT was 77.1 months ± 67.8, corresponding to a total of 3904.6 person-years. During this follow-up period, there were 179 deaths and 104 cases of HCC recurrence. There were significant differences observed in OS based on MC and downstaging. The OS rates at 1, 3, 5, 10, and 20 years were 92.5%, 85.4%, 82.9%, 75.1%, and 63.3% for patients within MC; 89.8%, 74.8%, 68.1%, 59.5%, and 51.0% for DS; and 72.9%, 52.1%, 50.8%, 39.7%, and 36.9% for NoDS, respectively ($p < 0.001$). Recurrence rates were also significantly better for the DS group compared to the NoDS group. The recurrence rates at 1, 3, 5, 10, and 20 years were 2.5%, 6.7%, 8.8%, 9.8%, and 9.8% for patients within MC; 13.9%, 25.6%, 27.1%, 29.3%, and 29.3% for DS; and 36.3%, 43.9%, 48.5%, 48.5%, and 56.3% for NoDS, respectively ($p < 0.001$). In the DS group, independent prognostic factors associated with recurrence after LT were neutrophil-to-lymphocyte ratio (NLR) e 2 at LT (HR, 2.625; 95% CI, 1.150-5.992; $p = 0.022$), alpha-fetoprotein (AFP) e 100 (HR, 2.741; 95% CI, 1.147-6.548; $p = 0.023$), and microvascular invasion (MVI) on explant pathology (HR, 2.622; 95% CI, 1.138-6.044; $p = 0.024$). **Conclusion:** This multi-center retrospective cohort study with long-term follow-up demonstrated favorable outcomes in patients with HCC who achieved successful downstaging to meet MC before undergoing LT. Specifically, patients with NLR (< 2), AFP (< 100), and no MVI exhibited significantly lower recurrence rates and better post-LT outcomes. These findings suggest the importance of successful downstaging and highlight the potential prognostic value of NLR, AFP, and MVI in predicting outcomes after LT for HCC.



Recurrence after successful DS

- Downstaged subgroup (n=120)
- Mean F/U: 66.7 mo ± 64.2
- Death (39), HCC recurrence (28)

Univariate analysis

Variables	p-value
Age (>50)	0.418
Sex (male)	0.580
Etiology (viral)	0.463
Child-Pugh class (B/C)	0.845
MELD (>20)	0.957
NLR (>2)	0.002
AFP (≥100)	0.001
MVI (yes)	<0.001
Tumor number (≤3)	0.852
Tumor differentiation	0.483

Multivariate analysis

Variables	p-value	HR (95% CI)
NLR (≥2)	0.022	2.625 (1.150-5.992)
AFP (≥100)	0.023	2.741 (1.147-6.548)
MVI (yes)	0.024	2.622 (1.138-6.044)

In the downstaged patients, NLR, AFP, MVI were independent prognostic factor for reccurence after LT.

Disclosures: The following people have nothing to disclose: Heechul Nam, Pil Soo Sung, Hee Yeon Kim, Ho Joong Choi, Jung Hyun Kwon, U Im Chang, Chang Wook Kim, Si Hyun Bae, Young Kyoung You, Jong Choi, Seung Kew Yoon, Jin Mo Yang, Jeong Won Jang

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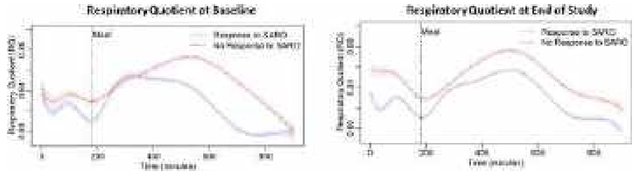
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

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

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

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



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

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

Massimo Iavarone[1], Lorenzo Canova[1,2], Eleonora Alimenti[1,3], Diego Taveggia[4], Alessio Aghemo[5,6], Gino Gobber[7], Giuseppe Cabibbo[8], Simone Veronese[9], Vincenza Calvaruso[8], Luciano Orsi[10], Paolo Caraceni[11,12] and Pietro Lampertico[1,13], (1)Division of Gastroenterology and Hepatology, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, (2) Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, (3)University of Pavia, Department of Medical Sciences, Pavia, Italy, (4) Department of Oncology and Palliative Care, Asst Lodi, Lodi, Italy, (5)Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy, (6) Division of Internal Medicine and Hepatology, Humanitas Research Hospital Irccs, Rozzano, Italy, (7) UO Palliative Care, Department of Primary Care, Apss Trento, Italy, (8)Gastroenterology & Hepatology Unit, Department of Health Promotion, Mother & Child Care, Internal Medicine & Medical Specialties (PROMISE), University of Palermo, Palermo, Italy, (9)Fondazione Faro ETS, Turin, Italy, (10)Italian Journal of Palliative Care, Italy, (11)Department of Medical and Surgical Sciences, Alma Mater Studiorum - University of Bologna, Bologna, Italy, (12)Unit of Semeiotics, Liver and Alcohol-Related Diseases, Irccs Azienda Ospedaliero-Universitaria Di Bologna, Bologna, Italy., (13)CRC "a. M. and a. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan

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

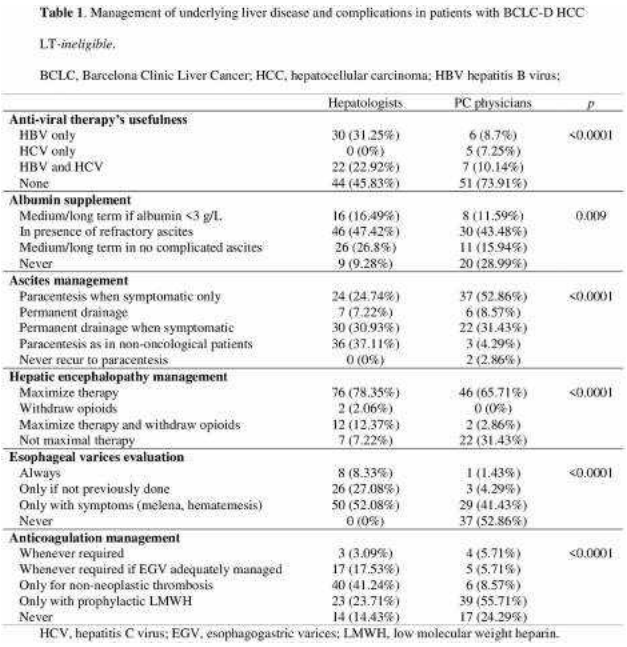

Table 1. Management of underlying liver disease and complications in patients with BCLC-D HCC LT-*ineligible*.

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; HBV hepatitis B virus;

	Hepatologists	PC physicians	*p*
Anti-viral therapy's usefulness			
HBV only	30 (31.25%)	6 (8.7%)	<0.0001
HCV only	0 (0%)	5 (7.25%)	
HBV and HCV	22 (22.92%)	7 (10.14%)	
None	44 (45.83%)	51 (73.91%)	
Albumin supplement			
Medium/long term if albumin <3 g/L	16 (16.49%)	8 (11.59%)	0.009
In presence of refractory ascites	46 (47.42%)	30 (43.48%)	
Medium/long term in no complicated ascites	26 (26.8%)	11 (15.94%)	
Never	9 (9.28%)	20 (28.99%)	
Ascites management			
Paracentesis when symptomatic only	24 (24.74%)	37 (52.86%)	<0.0001
Permanent drainage	7 (7.22%)	6 (8.57%)	
Permanent drainage when symptomatic	30 (30.93%)	22 (31.43%)	
Paracentesis as in non-oncological patients	36 (37.11%)	3 (4.29%)	
Never recur to paracentesis	0 (0%)	2 (2.86%)	
Hepatic encephalopathy management			
Maximize therapy	76 (78.35%)	46 (65.71%)	<0.0001
Withdraw opioids	2 (2.06%)	0 (0%)	
Maximize therapy and withdraw opioids	12 (12.37%)	2 (2.86%)	
Not maximal therapy	7 (7.22%)	22 (31.43%)	
Esophageal varices evaluation			
Always	8 (8.33%)	1 (1.43%)	<0.0001
Only if not previously done	26 (27.08%)	3 (4.29%)	
Only with symptoms (melena, hematemesis)	50 (52.08%)	29 (41.43%)	
Never	0 (0%)	37 (52.86%)	
Anticoagulation management			
Whenever required	3 (3.09%)	4 (5.71%)	<0.0001
Whenever required if EGV adequately managed	17 (17.53%)	5 (5.71%)	
Only for non-neoplastic thrombosis	40 (41.24%)	6 (8.57%)	
Only with prophylactic LMWH	23 (23.71%)	39 (55.71%)	
Never	14 (14.43%)	17 (24.29%)	

HCV, hepatitis C virus; EGV, esophagogastric varices; LMWH, low molecular weight heparin.

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Pietro Lampertico – BMS: Advisor, No, No; ROCHE: Advisor, No, No; GILEAD SCIENCES: Advisor, No, No; GSK: Advisor, No, No; ABBVIE: Speaking and Teaching, No, No; MSD: Advisor, No, No; ARROWHEAD: Advisor, No, No; ALNYLAM: Advisor, No, No; JANSSEN: Advisor, No, No; SBRING BANK: Advisor, No, No; MYR: Advisor, No, No; EIGER: Advisor, No, No; ANTIOS: Advisor, No, No; ALIGOS: Advisor, No, No; VIR: Advisor, No, No;

The following people have nothing to disclose: Lorenzo Canova, Eleonora Alimenti, Diego Taveggia, Gino Gobber, Simone Veronese, Vincenza Calvaruso, Luciano Orsi, Paolo Caraceni

1140-A | PROACTIVE RELAPSE PREVENTION APPROACH REDUCES RELAPSE RISK IN HIGH-RISK LIVER TRANSPLANT RECIPIENTS

Ethan Berman[1], Maham Ghani[1], Alexa Giammarino[1], Justin Lin[2], Jeffrey Lowell[1], Omoakhe Tisor[1], Michael Ramada[1], Mark Patrick Cubillan[2], Salima Makhani[1], Aaron Winnick[3], Nitzan C. Roth[3], Harmit S. Kalia[3], James S. Park[3], Alvin Htut[3], Christian Kuntzen[3], Nabil Dagher[3], Ahmed Fahmy[3], Elliot Grodstein[3], Lawrence Lau[3], Hatef Massoumi[4], Gerardo Tamayo-Enriquez[3] and Sanjaya Kumar Satapathy[3], (1)Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, (2) Northshore University Hospital/Long Island Jewish Hospital, (3)Northwell Health, Forest Hills, NY, (4)Lenox Hill Hospital

Background: Ensuring appropriate candidate selection for liver transplantation and monitoring sobriety pre-transplant are crucial for reducing the risk of alcohol relapse post-liver transplant in patients with cirrhosis. The use of Phosphatidylethanol (PEth), a biomarker for assessing chronic alcohol use, offers valuable insights into monitoring alcohol consumption over an extended period. This study aimed to evaluate the effectiveness of a proactive alcohol relapse prevention program in maintaining sobriety pre- and post-liver transplantation among high-risk individual's. **Methods:** Retrospective data were collected for patients who underwent liver transplantation for alcohol-related etiologies at a tertiary care medical center between December 2019 and May 2023. All patients participated in a structured alcohol relapse prevention program before and after transplantation. Pre- and post-transplant PEth levels were utilized to assess alcohol use and relapse. Patients were categorized as high risk if they had a positive PEth level or reported alcohol use 3 months prior to transplant. Descriptive and statistical analyses were conducted to compare relapse rates between patients with and without relapse. The Chi-square test determined the significance of relapse between high-risk and low-risk patients. **Results:** Among the 63 liver transplant recipients, 33 (52.4%) exhibited a positive PEth level or reported alcohol use within 3 months pre-transplant, and 9 (14.3%) experienced relapse after transplant. Of these, 27 (42.9%) were classified as high risk, while 36 (57.1%) were considered low risk. No statistically significant difference was observed in relapse rates between the high-risk group (n = 4, 14.8%) and the low-risk group (n = 5, 13.9%) ($p = 0.917$, OR 1.078 [95% CI 0.26-4.47]). **Conclusion:** Our study showed that transplanting high risk patients with recent alcohol use within 3 months did not have a higher relapse rate when compared to low risk patients when a proactive relapse prevention program is instituted. Further prospective studies should be completed to determine if a structured alcohol relapse prevention program significantly prevents relapse among high risk patients.

	High Risk		Low Risk		Total	
	n	%	n	%	n	%
Relapse	4	14.8%	5	13.9%	9	14.3%
No Relapse	23	85.2%	31	86.1%	54	85.7%
Total	27	42.9%	36	57.1%	63	

Disclosures: The following people have nothing to disclose: Ethan Berman, Maham Ghani, Alexa Giammarino, Justin Lin, Jeffrey Lowell, Michael Ramada, Mark Patrick Cubillan, Salima Makhani, James S. Park, Sanjaya Kumar Satapathy

Disclosure information not available at the time of publication: Omoakhe Tisor, Aaron Winnick, Nitzan C. Roth, Harmit S. Kalia, Alvin Htut, Christian Kuntzen, Nabil Dagher, Ahmed Fahmy, Elliot Grodstein, Lawrence Lau, Hatef Massoumi, Gerardo Tamayo-Enriquez

1141-A | PROGNOSTIC VALUE OF CORONARY ARTERY CALCIUM SCORING FOR LIVER TRANSPLANT RECIPIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Paul P. Hong[1], Spencer C. Lacy[1], Menhel Kinno[1] and Steven J. Scaglione[2], (1)Loyola University Medical Center, Chicago, IL, (2)Loyola University Health System

Background: Cardiovascular disease is a major cause of morbidity and mortality in liver transplant (LT) patients. Coronary angiography is the gold standard for assessing coronary artery disease, but its invasive nature has known risks and complications. Coronary artery calcium (CAC) scoring is a non-invasive assessment of coronary artery disease with an unclear role in risk stratification prior to LT. This systematic review and meta-analysis evaluated the prognostic value of CAC for preoperative risk assessment in LT recipients. **Methods:** We performed a systematic literature review to identify clinical studies that evaluated CAC in patients undergoing LT. The primary outcome of major adverse cardiovascular events (MACE) was reported as random effects risk ratio (RR) with 95% CI. **Results:** Our search yielded 2,978 potential studies. We included 6 studies reporting on 1,215 patients. There was an increased risk of MACE in patients with high CAC with an RR of 3.07 (95% CI 1.89-5.00, $p < 0.01$). The pooled composite odds ratio of CAC for predicting MACE in multivariable analysis was 3.26 (95% CI 1.75-6.06, $p < 0.01$). **Conclusion:** This systematic review and meta-analysis suggest that high CAC is associated with increased risk of MACE in LT recipients. High CAC score (> 400) may serve as a predictive model for an adverse post-LT outcome; additionally, this infers that an invasive cardiac testing may be more harmful than beneficial for this subgroup. Larger studies are needed to determine the role of CAC in cardiac risk stratification in this patient population.

Figure 1. Forest plot of major adverse cardiac events (MACE) in patients with high and low coronary artery calcium (CAC) scoring. CI, confidence interval.

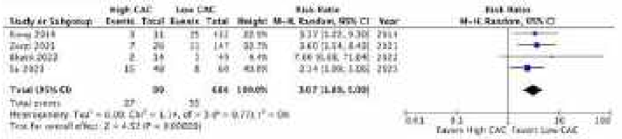
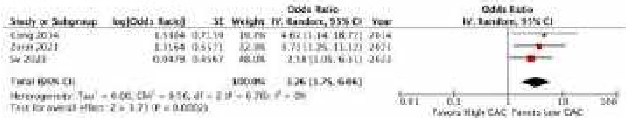


Figure 2. Forest plot of pooled odds ratios of coronary artery calcium (CAC) scoring in multivariable analysis for predicting major adverse cardiac events (MACE).



Disclosures: The following people have nothing to disclose: Paul P. Hong, Steven J. Scaglione

Disclosure information not available at the time of publication: Spencer C. Lacy, Menhel Kinno

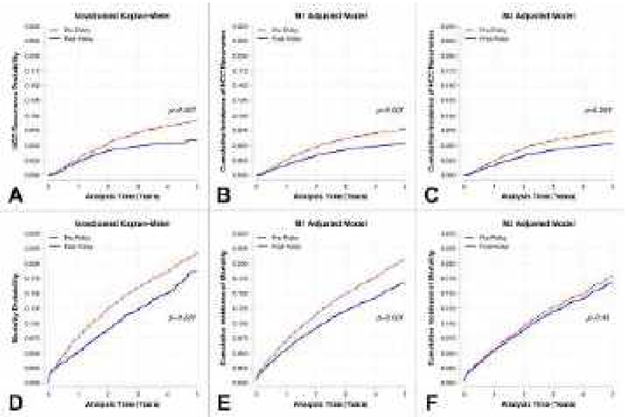
f 1142-A | SIGNIFICANT REDUCTION IN POST-TRANSPLANT HEPATOCELLULAR CARCINOMA RECURRENCE IN THE POST-SIX-MONTH WAITING POLICY ERA

Lina Yagan[1], Nadim Mahmud[1,2,3,4], Maarouf A. Hoteit[5], K Rajender Rajender Reddy[5], Peter Abt[5] and Samir Abu-Gazala[1], (1)Hospital of the University of Pennsylvania, (2)Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, (3)University of Pennsylvania Perelman School of Medicine, (4) University of Pennsylvania, (5)Perelman School of Medicine, University of Pennsylvania

Background: In 2015, the United Network for Organ Sharing (UNOS) mandated a policy change introducing a six-month waiting period before MELD exception points are granted to liver transplant (LT) candidates with hepatocellular carcinoma (HCC). This study analyzes the impact of policy and associated practice patterns on post-LT HCC recurrence. **Methods:** This was a retrospective cohort study of UNOS registry patients with HCC who underwent LT from 1/2010-5/2019. Transplant data included demographics, liver disease etiology, laboratory MELD, waitlist time, and donor after cardiac death versus donor after brain death. HCC-specific data included alpha fetoprotein, maximum viable tumor diameter + number of viable tumors on imaging, receipt of locoregional therapy (LRT), and explant pathology data used to calculate RETREAT score. The primary exposure was pre/post policy era, divided at 10/8/15. Kaplan-Meier analysis was used to evaluate unadjusted differences in HCC

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

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



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K Rajender Rajender Reddy – BMS: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Mallinckrodt Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Sequana: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Grifols: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Exact Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; HCC-TARGET: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; NASH-TARGET: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Spark Therapeutics: Consultant, No, No; Novo Nordisk: Consultant, No, No; Genfit: Consultant, No, No; BioVie: Consultant, No, No; Novartis: Advisor, No, No; Astra Zeneca: Advisor, No, No; Associate Editor Gastroenterology: Executive role , No, No; UptoDate: Royalties or patent beneficiary, No, No;
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1143-A | UTILITY OF SCORES TO PREDICT ALCOHOL USE AFTER LIVER TRANSPLANT (LT): TAKE THEM WITH A GRAIN OF SALT

Kevin Houston[1], *Nikki Duong*[2], *Richard K. Sterling*[1], *Amon Asgharpour*[1], *Sheila Bullock*[1], *Stephan Weinland*[1], *Nicole Keller*[1], *Ekaterina Smirnova*[1], *Hiba Khan*[1], *Scott C. Matherly*[1], *Joel P. Wedd*[1], *Hannah Lee*[1], *Mohammad S. Siddiqui*[1], *Vaishali Patel*[1], *Vinay Kumaran*[1], *Seung Lee*[1], *Amit Sharma*[1], *Aamir Khan*[1], *Daisuke Imai[1], Marlon Levy[1] and David Anthony Bruno[1], (1)Virginia Commonwealth University Health System, (2)Virginia Commonwealth University*

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

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

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

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

future risk of MI was noted (Figure 1B). **Conclusion:** The present study provides data demonstrating a strong association between VCTE-based parameters and clinical outcomes in LT recipients. The likely mechanism linking VCTE to non-hepatic outcomes is simultaneous activation of inflammatory and injury pathways throughout the body (i.e. heart, kidneys, liver) that compete to produce a clinical outcome.

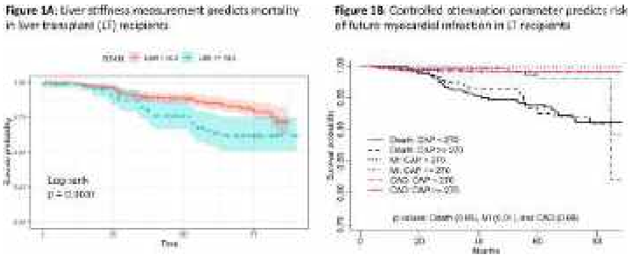
Figure 1A: Liver stiffness measurement predicts mortality in liver transplant (LT) recipients

Figure 1B: Controlled attenuation parameter predicts risk of future myocardial infarction in LT recipients

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1200-C | AN IN VITRO CULTURE MODEL FOR THE INDUCTION OF HDV REPLICATION IN A HBV EXPRESSING CELL LINE

Matthieu Blanchet[1], Lena Angelo[1], Yasmine Tetreault[1], Marwa Khabir[1], Camille Sureau[2], Andrew Vaillant[3] and Patrick Labonte[1], (1)Inrs-Centre Armand-Frappier Santé Biotechnologie, (2)Umr Inserm U 1259, (3) Replicor Inc.

Background: Individual's chronically infected with both Hepatitis B virus (HBV) and Hepatitis D virus (HDV) present an increased risk to develop cirrhosis and hepatocellular carcinoma in comparison to HBV mono-infected individual's. The number of HDV infected individual's worldwide is estimated to be between 20 and 40 million, a strong incentive to further engage in the search for new antivirals using innovative and practical *in vitro* models. Here we present the HepG2BD cell line as a novel *in vitro* culture system for inducible HDV replication in HBV replicating cells. **Methods:** Engineering: The HepG2BD cell line derives from HepG2.2.15 cells in which a HDV cDNA sequence under the control of a Tet-Off promoter is inserted into the adeno-associated virus integration site 1 (AAVS1) safe harbor site. The insertion at this precise location was conducted using the CRISPR-Cas9 technology for reliable initiation/repression of HDV RNA replication, and production of infectious HDV virions in a cell line that constitutively expresses HBV. Characterization: HDV RNA in cells and supernatants was quantified by RT-qPCR and Northern blot, HBV RNA in cells was monitored by RT-qPCR. Secreted HBV particle concentrations were evaluated by qPCR after anti-PreS1 immunoprecipitation. Secreted HBsAg was quantified by ELISA. Cellular presence and localization of HDAg in various cell culture conditions was monitored by confocal immunofluorescence. Infectivity of secreted HDV virions was measured by inoculation of NTCP-Huh7 cells followed by RT-qPCR. **Results:** The presented cell line is, to our knowledge, the first one to allow full replication of both HBV and HDV. This cell line shows proper induction of the HDV lifecycle. The interplay between HBV and HDV was detected in many instances. Differentiation into more classic hepatocyte morphology was associated with an increased concentration of both HDV and HBV in the supernatant. **Conclusion:** This new and unique model will be instrumental for the screening/characterization of new antivirals targeting both viruses (such as REP 2139). The HepG2BD cell line is also expected to help in our understanding of the dynamic interplay between the HBV and HDV lifecycles, and in identifying cellular factors involved.

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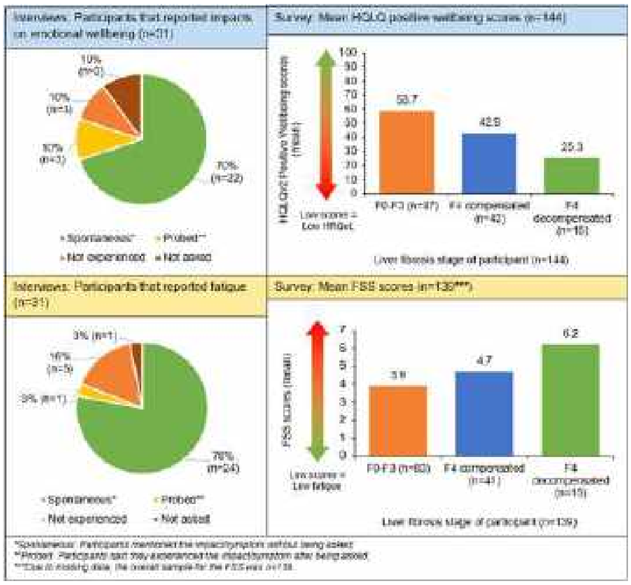
The following people have nothing to disclose: Lena Angelo, Yasmine Tetreault, Marwa Khabir, Camille Sureau, Patrick Labonte

f 1201-C | ASSESSING THE USE OF THE HEPATITIS QUALITY OF LIFE QUESTIONNAIRE (HQLQ) AND FATIGUE SEVERITY SCALE (FSS) IN HEPATITIS DELTA VIRUS PATIENTS ACROSS ITALY, GERMANY, SPAIN, AND THE US

Marvin Rock[1], Pietro Lampertico[2,3], Robert G. Gish[4], Nancy Reau[5], Heiner Wedemeyer[6], Maria Buti[7], Laura Mirams[8], Hilary Ellis[8], Teresa Taylor-Whiteley[8], Hannah Elwick[9], Nicola Williamson[9], Aishwarya Chohan[9], Margaret Guy[9], Rowena Jones[9], Caroline Burk[1], Ankita Kaushik[1] and Alon Yehoshua[1], (1)Gilead Sciences, Inc., (2)University of Milan, (3)Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, (4) Hepatitis B Foundation, La Jolla, CA, (5)Rush Medical

College, Chicago, IL, (6)Hannover Medical School, (7) Hospital Universitario Vall D'hebron and Ciberehd Del Instituto Carlos III, (8)Adelphi Real World, (9)Adelphi Values

Background: Hepatitis D virus (HDV) is the most severe form of viral hepatitis which leads to faster progression to cirrhosis and is associated with worse health-related quality of life (HRQoL). There is currently no validated HRQoL patient-reported outcome (PRO) measure in HDV. The current research aimed to qualitatively explore the HDV patient experience and relevance of the Hepatitis Quality of Life Questionnaire (HQLQv2) and the Fatigue Severity Scale (FSS) for use in HDV, and to capture quantitative, real-world insights into the experience of HDV. **Methods:** Qualitative interviews (n = 31) and a cross-sectional survey (n = 144) were conducted in parallel with adults untreated for HDV in Italy, Germany, Spain, and the US. Patients who had experienced an acute episode of liver disease, received interferon in the past six months, or were diagnosed with hepatitis C were excluded. Interview participants described their experience living with HDV and completed the HQLQv2 and FSS using a think-aloud approach to assess relevance of the instruments. Survey participants completed a set of measures quantitatively assessing HDV impacts (including the HQLQv2 and FSS). **Results:** The qualitative interview sample (63% female; mean age: 52.8) included patients with a range of liver fibrosis stages (F0-F4C). The quantitative survey sample (74% male; mean age: 52.8) included patients across all liver fibrosis stages (F0-F4D). Interviews found that fatigue was the most frequently reported symptom and HDV significantly impacted patients' emotional wellbeing. Participants understood the HQLQv2 and FSS as intended, and concepts assessed were considered relevant to HDV by most participants. Survey results highlighted that all participants experienced fatigue, but F4 participants reported more severe fatigue. Of the four HQLQv2 domains (general health distress, hepatitis-specific limitations, distress, positive wellbeing), positive wellbeing scores were significantly lower across the sample and lowest in F4D participants. **Conclusion:** HDV has a significant negative impact on patients' HRQoL with greater impacts in those with more severe HDV. Findings from both studies are complementary and confirm that the HQLQv2 and FSS are valid and appropriate for use in HDV populations across different liver fibrosis stages, assessing fatigue and HRQoL impacts. Further research to evaluate the psychometric validity of the PROs is recommended to support trial endpoints and track disease severity.



*Spontaneous: Participants mentioned the impact/symptom without being asked
**Probed: Participants said they experienced the impact/symptom after being asked
***Due to missing data, the overall sample for the FSS was n=139

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1202-C | AUTOIMMUNE HEPATITIS AFTER ANTI-SARS-COV-2 VACCINATION: SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Vaccination against severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is associated with autoimmune hepatitis. A systematic review and meta-analysis were conducted to assess the incidence of acute liver failure (ALF) following after SARS-CoV-2 vaccination. **Methods:** Patients diagnosed with autoimmune hepatitis following administration of the anti-SARS-CoV-2 vaccine from Pfizer, Moderna or AstraZeneca were eligible. ALF was diagnosed when the prothrombin time international normalized ratio exceeded 1.5 or total bilirubin level exceeded 11.7 mg/dL. **Results**: Of the 49 study participants, the majority were females ($n = 34$, 69.4%), and the median age was 62 years. Forty (81.6%) patients received mRNA vaccines, and 17 (34.7%) developed ALF. The rate of ALF was significantly lower among patients who received mRNA vaccines (28.6% vs. 77.8%, $p = 0.001$). Among the 12 patients who underwent liver biopsy, lobular hepatitis was identified in 12 (100%), eosinophilic infiltration in 6 (50%), and cholestasis and bile duct injuries in 2 (16.7%). Additionally, 4 (33.3%) patients in the non-ALF group had histologic fibrosis. Among the 35 patients who underwent autoimmune serology, anti-antinuclear antibodies were identified in 32, anti-smooth muscle antibodies in 12, and anti-mitochondrial antibodies in 4. Forty-two patients were treated with steroids with and without azathioprine; one underwent plasma exchange. Administration of Vaccines other than the mRNA vaccine (odds ratio [OR] = 15.7, 95% confidence interval [CI] = 1.32–188.0, $p = 0.029$) and an aspartate transaminase level > 1,000 IU/L (OR = 17.2, 95%

CI = 1.6–185.0, $p = 0.019$) were independent predictors of ALF. Five patients died due to autoimmune hepatitis after anti-SARS-CoV-2 vaccination. **Conclusion:** SARS-CoV-2 vaccination can cause acute live injury. Thus, patients who experience liver-related symptoms or liver enzyme abnormalities should be monitored closely.

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1203-C | AWARENESS AND ATTITUDES OF HEPATITIS D TESTING AMONG PATIENTS WITH CHRONIC HEPATITIS B INFECTION: A TERTIARY CARE CENTRE EXPERIENCE

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Background: Hepatitis D virus (HDV) infection affects 12 million people worldwide, and it always exists in the setting of hepatitis B, as it uses HbsAg for entry into the cells. The prevalence of HDV infection in HBsAg-positive patients ranges between 4.5 to 14.6%. Co-infection with HBV can result in serious and fulminant hepatitis. Superinfection with HDV accelerates cirrhosis and the risk of HCC. 10%–20% of people with HDV infection develop cirrhosis within 2 years, and 70%–80% do so within 5–10 years. Additionally, the incidence of hepatocellular carcinoma (HCC) and cirrhosis in HBV-HDV co-infection are 20% and 18%, respectively. Pegylated interferon (PEG-IFN) was the sole medication against HDV that was approved from 1980 until today. It is not a very effective treatment and carries many side effects. The prevalence of HDV infection in chronic hepatitis B patients even in the presence of hepatitis B vaccine remains underreported. Our study aims to report the prevalence of HBV/HDV co-infection with the comparison of morbidity and mortality outcomes, raise awareness of HDV testing, and analyze the attiude of hepatitis delta testing at our center. **Methods:** All patients tested for hepatitis D from September 2022-February 2023 were included. Demographic, biochemical, clinical and extensive viral serology workup was collected retrospectively. **Results:** Thirty-three patients out of the 1630 patients that were tested for hepatitis delta were found to have reactive hepatitis delta virus total antibody (0.5%). 19 patients were females and 14 were males. The mean recorded age was 47 years. 1 patient died of hepatocellular carcinoma-related complications. Eight patients with HBV/HDV coinfection had decompensated cirrhosis; 5 out of the eight had HCC. Two patients underwent liver transplantation during the above period. Decompensation was mostly characterized by varices, ascites, and hepatic encephalopathy. Median ALT was 61 U/L (range 20-2000). Median AFP was 4.8 ng/mL (range 1-11,100). **Conclusion:** Although delta serology was requested for patients with no evidence of prior hepatitis B infection such as oncology patients, we encourage more education and awareness about guidelines for hepatitis D testing. We plan to evaluate a larger number of patients with chronic HBV/HDV infection in the future, as HDV is under-evaluated in patients with advanced liver disease secondary to HBV.

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1204-C | BULEVIRTIDE: YES OR NO? TREATMENT FOR HEPATITIS D AND BEYOND

Helen Yu Xu, Jamie Olivia Yang, Phillip Chen and Steven-Huy B. Han, University of California, Los Angeles

Background: Hepatitis D virus (HDV) causes both acute and chronic liver disease that requires the co-infection of the Hepatitis B virus (HBV). Both co-infection and superinfection of HDV with HBV can lead to significant morbidity and mortality. Chronic hepatitis D infection prevalence is likely underestimated given limited screening, particularly in the United States (US). The current standard of therapy, pegylated interferon alpha, has an undesirable side effect profile and does not specifically target the HDV viral life cycle. HDV and HBV rely on the sodium taurocholate co-transporting peptide (NTCP) for hepatocyte cell receptor entry. Bulevirtide is a first-in-class entry inhibitor drug that acts on NTCP to prevent viral entry into target cells in chronic HDV infection. Bulevirtide was conditionally approved in Europe in 2020, and is currently undergoing Phase 3 clinical trials in the US. In addition to bulevirtide, a number of other novel therapies or novel applications of existing therapies for chronic Hepatitis D are in various states of investigation. **Methods:** PubMed databases were reviewed. Eighty-six articles in total were identified with keyword “bulevirtide,” of these articles, twenty were included in consideration of the review for relevance and data. Current US clinical trial data and other investigational HDV therapies were also reviewed (see Table 1). This is the most comprehensive and updated review of bulevirtide and new therapies for chronic Hepatitis D. **Results:** In European clinical trials, virologic response of HDV to various bulevirtide doses combined with tenofovir was significantly higher than with tenofovir monotherapy.

Trials that compared combination bulevirtide plus pegylated interferon alpha vs interferon monotherapy also demonstrated significant increase in virologic response, as measured by undetectable HDV RNA at the end of the trial period. Liver stiffness was significantly decreased in the immediate vs delayed bulevirtide treatment arms. Treatment with different doses of bulevirtide were comparable. Across studies, bulevirtide was well-tolerated and no significant adverse events occurred or led to treatment discontinuation. **Conclusion:** Bulevirtide represents a potential major shift in treatment for chronic HDV, for which there is significant unmet need. European data suggests a promising future for bulevirtide in the treatment of chronic hepatitis D, which is associated with severe liver disease and complications, such as high rates of hepatocellular carcinoma. Ongoing US studies will elucidate whether bulevirtide may be useful in broad and diverse populations, particularly given differences in prevalence and demographics. These data could also inform the need for updated US screening guidelines. Future studies may investigate expanding inclusion criteria to include decompensated liver disease and other co-morbid conditions.

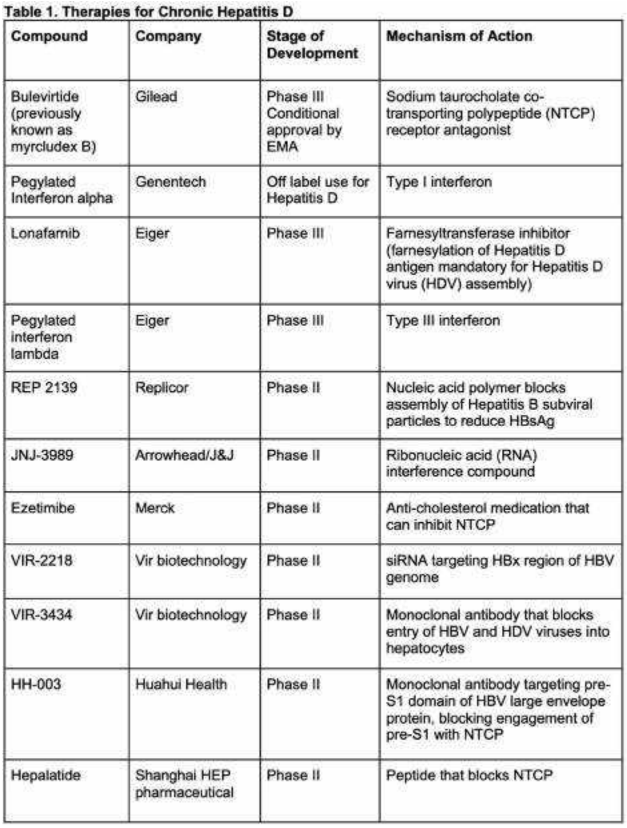

Table 1. Therapies for Chronic Hepatitis D

Compound	Company	Stage of Development	Mechanism of Action
Bulevirtide (previously known as myrcludex B)	Gilead	Phase III Conditional approval by EMA	Sodium taurocholate co-transporting polypeptide (NTCP) receptor antagonist
Pegylated Interferon alpha	Genentech	Off label use for Hepatitis D	Type I interferon
Lonafarnib	Eiger	Phase III	Farnesyltransferase inhibitor (farnesylation of Hepatitis D antigen mandatory for Hepatitis D virus (HDV) assembly)
Pegylated interferon lambda	Eiger	Phase III	Type III interferon
REP 2139	Replicor	Phase II	Nucleic acid polymer blocks assembly of Hepatitis B subviral particles to reduce HBsAg
JNJ-3989	Arrowhead/J&J	Phase II	Ribonucleic acid (RNA) interference compound
Ezetimibe	Merck	Phase II	Anti-cholesterol medication that can inhibit NTCP
VIR-2218	Vir biotechnology	Phase II	siRNA targeting HBx region of HBV genome
VIR-3434	Vir biotechnology	Phase II	Monoclonal antibody that blocks entry of HBV and HDV viruses into hepatocytes
HH-003	Huahui Health	Phase II	Monoclonal antibody targeting pre-S1 domain of HBV large envelope protein, blocking engagement of pre-S1 with NTCP
Hepalatide	Shanghai HEP pharmaceutical	Phase II	Peptide that blocks NTCP

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1205-C | BURDEN OF HEPATITIS D VIRUS INFECTION IN ITALY: INTERIM ANALYSIS FROM A PROSPECTIVE MULTICENTER NATIONWIDE STUDY

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Background: Compulsory hepatitis B virus (HBV) vaccination greatly reduced new hepatitis D virus (HDV) infections in native Italians. However, migratory flows from HDV endemic areas, fostered by labor forces globalization, are increasingly reconstituting the reservoir of HDV in Italy. We investigated the current epidemiologic and medical features of contemporary HDV cases in Italy in order to determine the burden and features of HDV infection according to Country of origin, age, and regional distribution. **Methods:** Consecutive patients with chronic HDV infection referred to 14 different third-level Italian Centers (hepatology, infectious disease, and internal medicine units) were prospectively enrolled from August 2022 to April 2023. All patients aged e 18 years, positive for hepatitis B surface antigen (HBsAg) and antibodies to HDV (anti-HD), were considered eligible. **Results:** Overall, 212 patients were recruited in the present cross-sectional study. Median age was 56 (IQR 45–62) years and most patients were males (n = 141; 66.5%). Native Italians were 127 (59.9%). Among patients born abroad, the majority (n = 72; 84.7%) were from East Europe, followed by Africa (n = 10; 11.8%), South America (n = 2; 2.4%), and West Europe (n = 1; 1.2%). Interestingly, the distribution of HDV patients born abroad appeared uneven in the Country, with a higher prevalence in North Italy as compared to the South (81 [52.9%] vs. 4 [6.8%]; $p < 0.001$). The mean number of foreign-born household members was 3.9 ± 2.4; the 7.1% was HBsAg-positive and the 4.6% was positive for anti-HD. However, the HBsAg and anti-HD serologic profile was unknown in 32.1% and 62.7% of total cases. In comparison to patients born abroad, native Italians were older (60, IQR 56–64, y vs. 43, IQR 37–50 y; $p < 0.001$), more likely to be male (72.4% vs. 57.6%; $p = 0.026$), with a more advanced liver disease (Cirrhosis: 62.8% vs. 50.0%; $p = 0.071$; hepatocellular carcinoma: 18.3% vs. 4.1%; $p = 0.004$). Conversely, patients born abroad showed higher ALT values (50, IQR 33–74 U/L vs. 36, IQR 26–59 U/L; $p = 0.005$), higher HBsAg levels (5468, IQR 672–11258 IU/mL vs. 1200, IQR 43–4440 IU/mL; $p < 0.001$), and low rate of HBV antiviral treatment (62.5% vs. 76.7%) as compared to native Italians. **Conclusion:** In Italy, patients born abroad accounted for nearly half of the overall HDV infections and will increasingly contribute to the medical burden of chronic hepatitis D in the years to come. *This research was supported by Gilead Sciences, Inc (study ID: IN-IT-980-6382).*

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1206-C | CHARACTERISTICS OF BACTERIAL LIVER ABSCESS IN THE CHANGCHUN COVID-19 EPIDEMIC AND COMPARATIVE EVALUATION OF THE PAST THREE YEARS

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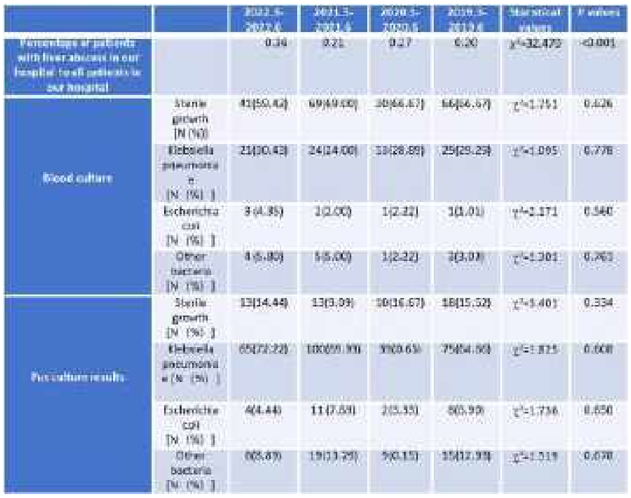
Background: During the period of the massive COVID-19 outbreak in Changchun last spring (March 1, 2022-June 30, 2022), the number of patients with bacterial liver abscess in our hospital was significantly higher than in previous years. This study provides an overview of the clinical and epidemiological characteristics of patients who developed bacterial liver abscess in the First Hospital of Jilin University during the COVID-19 outbreak last spring. **Methods:** This study screened all 37,411 patients discharged from the First Hospital of Jilin University during the COVID-19 epidemic in Changchun last spring and finally included 135 patients with bacterial liver abscess. We then collected their clinical data, outlined their clinical characteristics, and compared and analysed the incidence and causative flora of the bacterial liver abscess patients in this group with those in our hospital from March to June each year in 2019-2021. **Results:** From March to June 2022, BLA patients accounted for 0.36% of our total admissions, an increase from previous years ($p < 0.001$). The basic clinical characteristics of the 135 patients with bacterial liver abscesses are shown in Table 1. The majority of BLA patients were middle-aged and older males. The length of stay of 135 BLA patients was 11.00

(6.00,18.00) days, which was longer than in previous years ($p = 0.026$). White blood cell count, C-reactive protein, alkaline phosphatase, and urea nitrogen all increased to varying degrees compared to previous years, whereas HDL decreased to varying degrees. The blood culture were as follows($n = 69$): Aseptic growth (59.42%), Klebsiella pneumoniae (30.43%), Escherichia coli (4.35%), Mycobacterium fragilis (1.45%), Enterococcus faecalis (1.45%), Staphylococcus epidermidis (1.45%), and acid-producing Klebsiella (1.45%). The pus culture results were as follows ($n = 90$): Klebsiella pneumoniae (72.22%), aseptic growth (14.44%), Escherichia coli (4.44%), Enterococcus faecalis (2.22%), Pseudomonas aeruginosa (2.22%), Acinetobacter baumannii (1.11%), Klebsiella aerogenes (1.11%), Klebsiella acidophilus (1.11%), Enterococcus leadus (1.11%).Bacterial liver abscesses occurred in the right lobe in 58.46% of cases, and were solitary in 66.15% of cases. People with diabetic mixed bacterial liver abscesses had a significantly higher rate of *Klebsiella pneumoniae* infection (83.78%) and were more likely to have combined lung abscess bilateral pleural effusions and infectious shock than people with non-diabetic mixed bacterial liver abscesses. **Conclusion:** In conclusion, patients had longer hospital stays, higher white blood cell counts and CRP levels during the Changchun COVID-19 epidemic than during the same period in previous years. The primary causative organism was *Klebsiella pneumoniae*, and the majority of patients recovered with treatment. Mixed liver abscesses caused by *Klebsiella pneumoniae* were more common in diabetic patients.



		2022.5-2022.6	2021.5-2021.6	2020.5-2020.6	2019.5-2019.6	Statistical values	P values
Percentage of patients with liver abscess in our hospital to all patients in our hospital		0.34	0.21	0.27	0.20	χ^2=32.479	<0.001
Blood culture	Sterile growth [N (%)]	41(59.42)	69(69.00)	30(66.67)	66(66.67)	χ^2=1.751	0.626
	Klebsiella pneumoniae [N (%)]	21(30.43)	24(24.00)	13(28.89)	25(25.25)	χ^2=1.095	0.778
	Escherichia coli [N (%)]	3(4.35)	2(2.00)	1(2.22)	1(1.01)	χ^2=2.171	0.540
	Other bacteria [N (%)]	4(5.80)	5(5.00)	1(2.22)	3(3.03)	χ^2=1.301	0.763
Pus culture results	Sterile growth [N (%)]	13(14.44)	13(9.09)	10(16.67)	18(15.52)	χ^2=1.401	0.334
	Klebsiella pneumoniae [N (%)]	65(72.22)	100(69.93)	[illegible]	75(64.66)	χ^2=1.825	0.608
	Escherichia coli [N (%)]	4(4.44)	11(7.69)	2(3.33)	8(6.90)	χ^2=1.736	0.650
	Other bacteria [N (%)]	8(8.89)	19(13.29)	[illegible]	15(12.93)	χ^2=1.319	0.078

Disclosures: The following people have nothing to disclose: Yu Tian, Xiao Yu Wen, Meili Dong

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1207-C | CRISPR/Cas13a-ASSISTED ACCURATE AND PORTABLE HEPATITIS D VIRUS RNA DETECTION

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Background: Hepatitis delta virus (HDV) infection accelerates the progression of chronic hepatitis B virus infection (HBV), posing a large economic and health burden to patients. At present, there remains a lack of accurate and portable detection methods for HDV RNA. Here, we aim to establish a convenient, rapid, highly sensitive and specific method to detect HDV RNA using CRISPR-Cas13a technology. **Methods:** We downloaded the genome sequence from the HDV database, performed multisequence alignment, and designed and screened CRISPR RNA (crRNA), reverse transcription polymerase chain reaction (RT-PCR) and reverse transcription recombinase-aided amplification (RT-RAA) primers binding in the conserved sequence region. After processing the synthetic plasmids and samples using thermal shock, we established fluorescence and lateral flow strip assays based on CRISPR-Cas13a combined with RT-PCR and RT-RAA, respectively. Clinical plasma samples were further validated by a CRISPR-Cas13a-based assay. **Results:** For synthetic HDV RNA plasmids, the sensitivity of RT-PCR-CRISPR-based fluorescence assays was 1 copy/μL, higher than that of reverse transcription quantitative real-time PCR (RT-qPCR) (10 copies/μL) and reverse transcription droplet digital PCR (RT-ddPCR) (10 copies/μL); for HDV RNA-positive samples, the sensitivity of RT-RAA-CRISPR-based fluorescence and lateral flow strip assays was 10 copies/μL, as low as that of RT-qPCR and RT-ddPCR, and the assay took only approximately 85 minutes. Additionally, the positivity rates of anti-HDV IgG-positive samples detected by the RT-qPCR, RT-ddPCR, RT-PCR-CRISPR fluorescence and RT-RAA-CRISPR lateral flow strip methods were 66.7% (96/144), 76.4% (110/144), 81.9% (118/144), and 72.2% (104/144), respectively. **Conclusion:** We developed a highly sensitive and specific RT-PCR-CRISPR assay, as well as a portable and easy RT-RAA-CRISPR-based assay for the detection of HDV RNA, which could be a prospective measure for monitoring the development of HDV infection and evaluating the therapeutic effect.

Disclosures: The following people have nothing to disclose: Xiangying Zhang, Feng Ren, Yuan Tian, Zihao Fan

1208-C | DELTA DESCRIBE: A 5-YEAR SNAPSHOT OF NATIONAL DELTA HEPATITIS SCREENING IN METROPOLITAN FRANCE

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Background: HDV infection is a public health disease. In metropolitan France, very few studies focused on reference centers, assess the prevalence of HDVAb at about 4 %. We have a need of real life data on delta screening. Our objectives were to define over five years, the number of Delta tests performed, compare it to that potentially expected, and describe global characteristics of patients and prescribers. **Methods:** Retrospective study on data issued from the French Health insurance (SNDS) (2016 to 2020). A snapshot of HDV, HBV, HIV and HCV tests performed is provided; then a description of epidemiological characteristics of patients receiving HDV tests with the profile of prescribers. Extractions of SNDS data are achieved through targeting algorithms and patients'duplicates are discarded. The expected number of HDVAb tests is calculated from the estimate of the positivity of HBsAg tests prescribed in France (0,8%). **Results:** Over the five years period, 18 021 850 HCVAb, 20 127 962 HIVAb, 18 736 721 HBsAg, 88 275 HDVAb and 10 306 HDVRNA tests were performed. We observe a 30% increase of HBV tests between 2016-2019 and a decrease of 6% between 2019 and 2020 (COVID pandemic). The number of HDVAb increases by 81% between 2016 and 2019 and decreases by 5% between 2019 and 2020. The number of HDVRNA increases by 80% between 2016 and 2019 with a peak between 2019 and 2020 +26% despite the pandemic (transitional authorization of Bulevirtide in Sept 2019 and marketing in Sept 2020). Of the expected HDVAb tests, 46% only were done in 2016 and 64% in 2020. Patients were screened for HDV mainly in Paris region 31% and south of France (Occitanie, PACA, Auvergne Rhône Alpes) 24%; 40% of them corresponded to a precarious profile or migrant status. Prescribers were mainly general practitioners (GP) 64% and gynecologists 19% for HBV and GPs 78% and hepatogastroenterologists 11% for HDV. By focusing on some populations of interest: in pregnant women in 2020 only 0.16% of HBV screenings were followed by an HDV test. In patients followed for chronic HBV infection, 22.7% benefited from delta screening. **Conclusion:** In real life, HBV screening which is essential for delta screening has increased over the 5 years. The number of HDVAb tests performed was multiplied by 1.8, with a clear impact of the arrival of bulevirtide but should still be 1.5 times greater. Reflex testing for HDV should be universally accepted as it increases the number of HDV cases revealed.

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The following people have nothing to disclose: Sandrine Francois, Sophie Alain, Marilyne Debette Gratien, Paul Carrier, Celine Rigaud

1209-C | DEMOGRAPHIC AND GEOGRAPHIC PREVALENCE OF HEPATITS A IN UNITED STATES

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Background: The incidence of Hepatitis A infection has been trending down in the United States especially after the recommendation of childhood vaccination in 1996. Current infection is seen in people mostly among travelers from endemic countries or food from endemic countries. Outbreaks tend to occur in high risk population like men those who have sex with men, homeless, those with poor sanitation and those who use illicit drugs. **Methods:** This is a retrospective study of the National Inpatient Survey (NIS) database of year 2016 to 2020. Patients with the primary diagnosis of Hepatitis A and above 18 years of age were included in the study. The demographic, geographic, health insurance and prior co-morbidity information were included and further analyzed in the study. **Results:** 4000 patients were found to be admitted with the primary diagnosis of Hepatitis A infection, out of which 3990 also had coma and 10 did not have coma. 8% of the patients also had acute liver failure. 60.6% of the patients were male and 39.4% of the patients were female. The mean age of Hepatitis A patient was 43.4.81.31% were Whites, 7.58% Blacks, 4.42% Hispanics, 0.7% Asians and 1% were Native Americans.11.62% of the Hepatitis A patients had Medicare, 30.56% Medicaid, 21.59% had a private insurance and 30.56% were under self-coverage. The distribution of hospitals reporting Hepatitis A were 9.34% in the North East, 15.91% in the Mid West, 66.67% in the South and 8.08% in the West.5.43% of the Hepatitis A patient had diabetes, 21.97% had hypertension, 0.88% had heart failure, 1.52% had chronic kidney disease, 11.87% had hyperlipidemia **Conclusion:** The proportion of Hepatitis A infection seems to be high among the males than females. Whites as compared to other races and the Southern states seem to have more burden of Hepatitis A.

Disclosures: The following people have nothing to disclose: Ayusha Poudel, Sajana Poudel, Manoj Ghimire, Smriti Khanal, Anurag Adhikari

1210-C | DETECTION AND QUANTIFICATION OF HEPATITIS DELTA VIRUS RNA BY THREE DIFFERENT ASSAYS

Marta Illescas-López[1], Lucía Chaves-Blanco[1], Adolfo De Salazar[1], Melisa Hernandez[2], Raquel Carracedo[3], Laura Viñuela[1], Eduardo Lagarejos[2], Sara Pereira[3], Ana Fuentes[1], María Cea[3], Alberto De La Iglesia[4], Carolina Freyre Carrillo[5], Asunción Iborra[6], María Del Valle Odero[7], Aurora García-Barrionuevo[8], Fernando Fernández-Sánchez[9], Antonio Aguilera[10], María José Pena[2] and Federico Garcia[1], (1)Hospital Universitario Clínico San Cecilio, (2)Hospital Universitario De Gran Canaria Doctor Negrín, (3)Hospital Clínico Universitario De Santiago De Compostela, (4)Hospital Infanta Elena, (5)Hospital De Puerto Real, (6)Hospital Universitario Virgen De La Arrixaca, (7)Hospital De Jerez De La Frontera, (8)Hospital Universitario Clínico Virgen De La Victoria, (9)Hospital Costa Del Sol, (10)Complejo Hospitalario Santiago De Compostela

Background: Detection and quantification of Hepatitis delta virus (HDV) RNA in these patients is crucial for diagnosis and, recently, also for treatment management. Little is known on the impact of HDV genotype on severity of the disease and on the accuracy of viral load tests. The aim of this study was to evaluate and compare the efficacy of the three commercial assays for the detection and quantification of HDV RNA. **Methods:** Sixty-two HDV-RNA positive samples previously analysed with Hepatitis Delta RT-PCR system kit (Vircell, Granada, Spain) were tested in parallel with EurobioPlex HDV assay (Eurobio Scientific, France), and sixty-one of them with RoboGene HDV RNA Quantification kit (Roboscreen Diagnostics, Leipzig, Germany). In addition, 91 samples from HBsAg positive but anti-HDV negative were analysed. For genotyping, an amplicon-based sequencing strategy with overlapping primers was used to amplify the whole genome of HDV on a Nextseq 1000 (Illumina). **Results:** Using the EurobioPlex HDV kit, 61 samples scored positive and 1 negative; with the Robogene HDV Kit, 60 scored positive and 1 negative. Considering the qualitative result, the concordance between the Vircell Hepatitis Delta kit and the EurobioPlex HDV and the RoboGene kit was 98.4%, while the concordance between EurobioPlex HDV kit and RoboGene HDV RNA kit was 100%. All 90 samples from HBsAg positive anti HDV negative tested negative by all three HDV-RNA assays. Considering, the Robogene assay as reference, sensitivity (S), specificity (Sp), and positive (PPV) and negative (NPV) predictive values were as follows: EurobioPlex, 100% (CI 95% 94.1-100%), 100% (CI 95% 96.0-100%), 100% (CI 95% 94.1-100%), 100% (CI 95% 96.0-100%); Vircell HDV-RNA kit, 100% (CI 95% 94.1-100%), 98.9% (CI 95% 94.1-99.9%), 98.4% (CI 95% 91.3-99.9%), 100% (CI 95% 96.0-100%). In terms of quantitative results of HDV RNA (log IU/ml), correlation coefficients were: 0,703 for Hepatitis Delta RT-PCR vs EurobioPlex HDV, 0,833 for Hepatitis Delta RT-PCR vs RoboGene HDV RNA Quantification and 0,825 for EurobioPlex HDV vs RoboGene HDV RNA Quantification. The Bland-Altman statistical analysis yielded a mean bias of 2,083 Log10 UI/mL and -1,283 Log10/mL between Eurobio/Vircell and Robogene/Vircell respectively, what showed significant differences in the quantitative performance of all the three kits compared. Full HDV genome sequencing data is available in 47 samples: 41 were annotated as genotype 1 and 6 as genotype 5. **Conclusion:** The three HDV-RNA assays evaluated have shown a good concordance in terms of qualitative detection. However, we have observed important differences at the quantitative level. We highlight that these three assays are not interchangeable for monitoring HDV viral load during HDV treatment. All three systems were able to detect and quantify HDV-RNA from patients infected by genotypes 1 and 5.

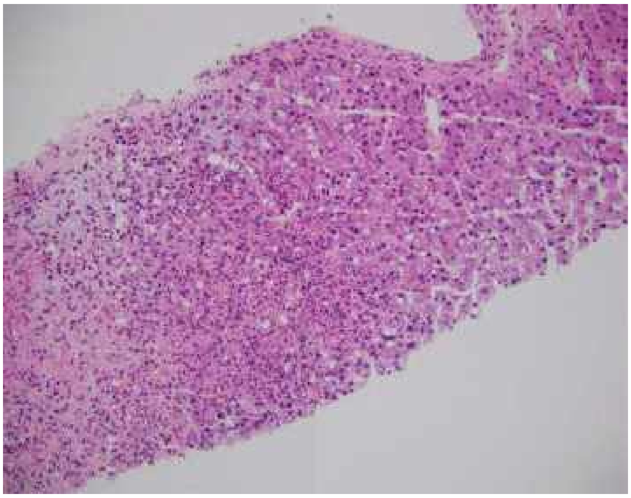
Disclosures: The following people have nothing to disclose: Marta Illescas-López, Lucía Chaves-Blanco, Adolfo De Salazar, Melisa Hernandez, Raquel Carracedo, Laura Viñuela, Eduardo Lagarejos, Sara Pereira, Ana Fuentes, María Cea, Alberto De La Iglesia, Carolina Freyre Carrillo, Asunción Iborra, María Del Valle Odero, Aurora García-Barrionuevo, Fernando Fernández-Sánchez, Antonio Aguilera, María José Pena, Federico Garcia

1211-C | DISSEMINATED HSV-2 HEPATITIS IN A LIVER TRANSPLANT PATIENT PRESENTING AS FEVER OF UNKNOWN ORIGIN

Kunal Elete, Machaiah Madhrira, Sridhar Allam, Ashraf Reyad and Randy Nguyen, Medical City Fort Worth

Background: Herpes simplex virus (HSV) is a rare cause of acute hepatitis with high mortality. Transplant recipients are at especially high-risk of opportunistic infections due to chronic immunosuppression. Here, we present a case of disseminated HSV-2 hepatitis in a liver transplant patient who presented with a fever of unknown origin (FUO). **Methods:** A 67-year-old female with a history of alcoholic cirrhosis s/p liver transplant

(2017), and end-stage renal disease due to non-recovered hepatorenal syndrome s/p renal transplant (2022) presented with recurrent fever. Patient was initially hospitalized for 1 week due to FUO. Her workup comprised of pan-cultures, a respiratory panel, and renal/liver allograft function testing were all negative. After treatment with empiric antibiotics and resolution of fevers, she was thought to have viral syndrome and discharged home. However, symptoms recurred within 48 hours of improvement. Additional workup included hepatitis panel, testing for viral and fungal infections, imaging of head/chest/abdomen, upper and lower endoscopies, lumbar puncture, and echocardiogram, which were unrevealing. With persistent fevers, increases in serum creatinine and AST from initial values were noted. She also developed two ulcerated plaque lesions on her right thumb and lower abdomen. MRI of abdomen and biopsy of skin lesions and kidney and liver transplants were pursued. **Results:** Kidney biopsy was unremarkable. Liver allograft biopsy was positive for HSV hepatitis with extensive necrosis. Skin punch biopsies showed HSV infection as well and serologic testing for HSV resulted positive for HSV-2 IgG and DNA PCR. She was started on IV Acyclovir at 10mg/kg with resolution of fevers, normalization of AST, and improvement of skin ulcers. On discharge, she was transitioned to oral Valacyclovir for an additional 3-6 months of therapy. **Conclusion:** HSV-2 typically causes genital herpes, but it can also cause systemic infections in immunocompromised hosts. Hepatitis secondary to infection with HSV-1 or HSV-2 is a rare complication that can lead to acute liver failure (ALF) if not promptly diagnosed and treated. In one study, HSV hepatitis occurred most frequently in the setting of disseminated herpes in solid organ transplant patients. Our patient was unusual with her fairly indolent course, whereas most of the literature describes patients with more fulminant courses. Early recognition, diagnosis and initiation of treatment with IV Acyclovir can help prevent ALF.



Disclosures: The following people have nothing to disclose: Kunal Elete, Machaiah Madhrira, Sridhar Allam, Ashraf Reyad, Randy Nguyen

1212-C | ENHANCING HEV DIAGNOSTIC TESTING IN RESOURCE-LIMITED SETTINGS: DEVELOPMENT AND EVALUATION OF AN IN-HOUSE ELISA METHOD FOR SEROPREVALENCE ESTIMATION IN CAMBODIA

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Background: In regions with limited access to clean water and sanitation facilities, such as Cambodia, Hepatitis E virus (HEV) is a significant public health concern. To improve diagnostic testing and public health interventions, it is essential to develop accurate and affordable methods. In this study, we aim to create an accurate in-house ELISA test for detecting HEV, compare it with a commercial kit, and estimate the prevalence of HEV in Cambodia, where the reported anti-HEV IgG positivity rate was 18.4% in 2014. **Methods:** This is a continuum of study on hepatitis B mother-to-child transmission conducted in Siem Reap, Cambodia from February 2020 to December 2021. Inhouse double antigen Sandwich ELISA method was developed to detect anti-HEV where enzyme-conjugated antigen was used instead of enzyme-conjugated secondary antibody. To validate inhouse ELISA, 262 pregnant women's serum randomly selected among overall 1565 were tested both commercial (Institute of Immunology, Japan) and inhouse ELISA. The validation of test was examined by receiver operation curve analysis using JMP 16.0 (SAS, USA). The performance of the new test was evaluated by sensitivity, specificity, positive and negative predictive values. The discriminatory power of the test was assessed by ROC curve. We also estimated Youden index and Cohen's kappa coefficient. All 1565 samples will be detected for anti-HEV using inhouse ELISA method and then estimate its prevalence. **Results:** In our preliminary study, out of 262 samples, 25 (9.5%) tested positive for the commercial anti-HEV IgG test. By ROC analysis, the

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

optimal cutoff for inhouse ELISA was 0.11 and its sensitivity and specificity were 84% and 91.2% respectively. The AUC was calculated to be 0.868, indicating good discriminatory power. The inhouse ELISA showed Youden index of 0.755 and Cohen's kappa coefficient of 0.425. The positive and negative predictive values were 0.512 and 0.982 respectively. **Conclusion:** In this study among pregnant women in Siem Reap, Cambodia, the prevalence of hepatitis E virus (HEV) infection using a commercial ELISA kit was found to be 9.5%. The newly developed in-house sandwich method demonstrated promising sensitivity and specificity in detecting HEV IgG antibodies, making it a valuable tool for screening, especially in resource-limited settings. Further we planned to test all 1565 samples by new method and will present the results at the conference.

Disclosures: The following people have nothing to disclose: Ulugbek Khudayberdievich Mirzaev, Bunthen E, Serge Ouoba, Ko Ko, Aya Sugiyama, Tomoyuki Akita, Kazuaki Takahashi, Junko Tanaka

1213-C | EPIDEMIOLOGICAL AND CLINICAL CHARACTERISTICS OF HBV AND HDV CO-INFECTED PATIENTS FOLLOWED BY THE CANADIAN HBV NETWORK

Carla S. Coffin[1], Sébastien Poulin[2], Curtis Cooper[3], Matthew Sadler[1], Karen E. Doucette[4], Gerald Y. Minuk[5], Julia Uhanova[5], Chad Saunders[1,6], Anna Manko[1], Edward V. Tam[7], Hin Hin Ko[8], Alnoor Ramji[8], Mang M. Ma[4], Carmine G. Nudo[9], Keith Tsoi[10], Tianyan Chen[11], Giada Sebastiani[12], Julie Zhu[13], David Kah Heng Wong[14], Carla Osiowy[15] and Scott K. Fung[16], (1) Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, (2)Cisss Laurentides, St-Jerome, Clinique Médicale Urbaine Du Quartier Latin, QC, Canada, (3)The Ottawa Hospital, Ottawa, ON, Canada, (4)Department of Medicine, University of Alberta, Edmonton, AB, Canada, (5)Department of Internal Medicine, University of Manitoba, MB, Canada, (6) Haskayne School of Business, University of Calgary, AB, Canada, (7)Pacific Gastroenterology Associates, Vancouver, BC, Canada, (8)Division of Gastroenterology, University of British Columbia, BC, Canada, (9)Cité-De- La- Santé De Laval, Laval, QC, Canada, (10)Mcmaster University, Hamilton, on, Canada, (11)Department of Medicine, McGill University Health Centre, Montreal, QC, Canada, (12)Department of Medicine, McGill University Health Centre, Westmount, QC, Canada, (13)Division of Gastroenterology, Health Sciences, Dalhousie University, NS, Canada, (14)Department of Medicine, University of Toronto, Toronto, ON, Canada, (15) National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB, Canada, (16)Toronto General Hospital, University of Toronto

Background: Hepatitis B virus (HBV) and Hepatitis delta virus (HDV) coinfection causes the most aggressive form of viral hepatitis in humans. There are limited epidemiological studies in North America. **Methods:** In this retrospective cohort study we analyzed demographic and clinical outcomes including non-invasive fibrosis assessment using serum fibrosis markers and transient elastography (i.e., FibroScanÒ) in HBV/HDV coinfected patients from the Canadian Hepatitis B Network. **Results:** In 158 HDV antibody positive patients, 32.9% were female (range 26.0-40.6, n = 155), mean age was 48.6 years (IQR 45.0, 49.0) and 12.7% (19/149) were born in Canada. Reported countries of origin in 126 foreign-born patients included endemic regions (i.e., Mongolia, Sudan, Liberia, Romania, Vietnam, Afghanistan, Russia, Cameroon). More patients were Black (38.3% (57/149) ($p < 0.01$) vs. 20% (30/149) Asian, 6 % (9/149) White. At initial visit, 14.4% (19/132) were HBeAg positive, median HBV DNA was 2.5 Log IU/mL (IQR 2.1, 2.8) and 74% (95/130 tested) were HDV RNA positive. Anti-HBV nucleos(t)ide analogue therapy was prescribed in 65% (104/158) of which 29.4% (31/104) were also treated with Pegylated-Interferon. Individual's were more likely to receive antiviral therapy if diagnosed with cirrhosis ($p < 0.03$). Reported health risks included any alcohol use: 34.8% (52/158), smoking (27.8%, 44/158), and hypertension 16.5% (26/158). 43.7% (69/158) were cirrhotic, 7.6% (12/158) were identified with hepatocellular carcinoma, and 4.4% (7/158) underwent liver transplantation. In those with available TE data collected to date, 64.9% (61/94) had > F2 fibrosis (TE > 7.3 kpA). In some patients with only minimal-mild fibrosis, increase in liver stiffness measurement (71.4% of those tested) and non-invasive serum markers (i.e., APRI > 1.5 in 69.2% tested) occurred between years 1- 5 of follow-up. **Conclusion:** The majority of chronic hepatitis Delta patients living in Canada are born in endemic regions and present with advanced fibrosis or end-stage liver disease (cirrhosis and HCC) at young age. Serial follow-up data in some patients show fibrosis progression based on non-invasive testing, highlighting need for close follow-up. Funding: Gilead

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Scott K. Fung – Gilead Sciences, Inc.: Speaking and Teaching, No, No; AbbVie: Speaking and Teaching, No, No; Lupin: Speaking and Teaching, No, No; Gilead Sciences, Inc.: Advisor, No, No; AbbVie: Advisor, No, No; Novo Nordisk: Advisor, No, No; Pfizer: Advisor, No, No; Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;

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Disclosure information not available at the time of publication: Sébastien Poulin, Curtis Cooper, Matthew Sadler, Karen E. Doucette, Julia Uhanova, Chad Saunders, Anna Manko, Edward V. Tam, Mang M. Ma, Carmine G. Nudo, Keith Tsoi, Julie Zhu, David Kah Heng Wong, Carla Osiowy

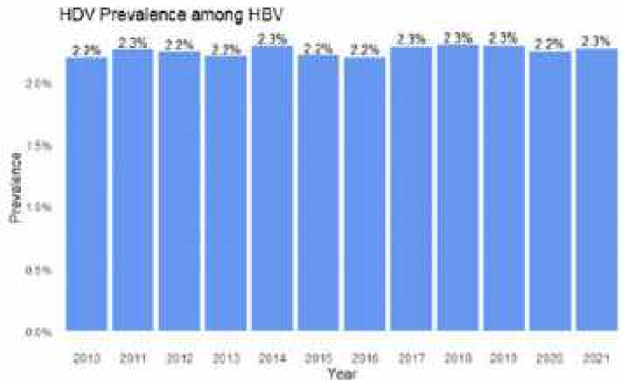
1214-C | EPIDEMIOLOGY OF HEPATITIS DELTA INFECTION: REAL-WORLD DATA FROM A LARGE HEALTHCARE PROVIDER IN ISRAEL

Rawi Hazzan[1,2], Marvin Rock[3], Ankita Kaushik[3], Odelia Liani[4], Yonatan Green[4], Eran Bar-Haim[4], Clara Weil[5], Sivan Gazit[5] and Chong Hoon Kim[3], (1)Azrieli Faculty of Medicine, Bar-Ilan University, (2)Maccabi Healthcare Services, (3)Gilead Sciences, Inc., (4)Gilead Sciences Israel Ltd, (5)Kahn Sagol Maccabi Research and Innovation Center, Maccabi Healthcare Services

Background: Hepatitis delta virus (HDV) infection occurs in patients with underlying hepatitis B virus (HBV) infection and is associated with more rapid liver disease progression. The epidemiology and characteristics of HDV patients in Israel are not well described. This study aimed to describe the prevalence and incidence of HDV among adults in Israel. **Methods:** A retrospective cohort study was performed using anonymized data from Maccabi Healthcare Services (MHS) covering 1.8 million adults in Israel. Chronic HBV with/without HDV was defined using diagnosis and laboratory data from 1/1/1998 to 12/31/2010. Prevalence cohorts included all HBV monoinfection (HBV-mono) or HDV patients aged e 18 years in 2010-2021. Incidence cohorts included patients newly diagnosed with HBV-mono or HDV in 2010-2021 at age e 18 years. Period and annual HDV prevalence rates and incidence rates were calculated among (1) all chronic HBV patients and (2) all MHS members (enrolled e 1 d in a given period). For the incidence calculation, the denominator excluded individual's with HDV diagnosis prior to the start of the period. Patient characteristics among prevalent HBV-mono and HDV patients at the end of the study period (2021) were described. **Results:** In 2010-2021, the average annual HDV prevalence and incidence rates among HBV patients (general population) were 2.3% (0.012%) and 0.11% (0.59/100,000), respectively. The prevalence and incidence of HDV among HBV patients in 2021 was 2.3% and 0.07%. The number of HDV patients increased from 159 in 2010 to 208 in 2021. In 2021, prevalent HDV patients (n = 208) had a mean [sd] age of 54.5 [13.3] years, and 54.3% were males; prevalent HBV-mono patients (n = 2,795) had a mean age of 53.3 [13.9] years, and 57.9% were males.

Conclusion: Results of this real-world analysis indicate that HDV prevalence and incidence were 2.3% and 0.1% among HBV-infected adults in Israel during 2021, respectively. The number of prevalent HDV patients increased from 159 to 208 from 2010 to 2021. Given the low rates of screening and diagnoses of HDV globally, findings from this study underscore the need for continued efforts in the early identification of HDV infection among people with HBV infection and for the development of effective strategies for the management and treatment of the prevalent as well as incident patients with HDV.

Figure 1: Annual prevalence of HDV among chronic HBV patients (2010-2021)



Disclosures: Rawi Hazzan – Gilead Sciences, Inc.: Consultant, No, No;
Marvin Rock – Gilead Sciences, Inc.: Employee, No, No;
Ankita Kaushik – Gilead Sciences, Inc.: Employee, No, No;
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Yonatan Green – Gilead Sciences Israel Ltd: Employee, No, No;
Eran Bar-Haim – Gilead Sciences Israel Ltd: Employee, No, No;
Chong Hoon Kim – Gilead Sciences, Inc.: Employee, No, No;
The following people have nothing to disclose: Clara Weil, Sivan Gazit

1215-C | EPIDEMIOLOGY OF HEPATITIS E VIRUS IN PATIENTS WITH CHRONIC LIVER DISEASE ACROSS SOUTH AMERICA

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Background: Hepatitis E virus (HEV) is a zoonotic disease frequently associated with self-limited acute hepatitis. Multiple studies have reported that individual's with immunosuppression and/or chronic liver diseases can develop chronic HEV. The epidemiology of the virus is understudied in the Hispanic population. This study aimed to describe the frequency of HEV infection in patients with chronic liver diseases across Latin America. **Methods:** We evaluated the presence of IgG anti-HEV (ELISA, Diapro) in 716 serum samples collected from patients in 6 countries of Latin America through the ESCALON network (http://www.escalon.eu): Argentina (n = 162), Brazil (n = 54), Chile (n = 123), Colombia (n = 260), Ecuador (n = 61) and Peru (n = 56). Causes of chronic liver diseases included: hepatocellular carcinoma (HCC, n = 170), cirrhosis (CR, n = 387), infection with hepatitis B virus (HBV, n = 26) or hepatitis C virus (HCV, n = 14) and non-alcoholic fatty liver disease (NAFLD, n = 119). **Results:** The mean age of the patients was 62.9 years (range 18-91), 56.4% were male and 43.6% female. The global IgG anti-HEV prevalence in the continent was 16.1% (115/716). Out of this, 38.6% were female (44/114) and 61.4% male (70/114). Specific seropositivity rates by country were: 1.9% (3/162) in Argentina, 14.8% (8/54) in Brazil, 48.8% (60/123) in Chile, 8.5% (22/260) in Colombia, 18% (11/61) in Ecuador and 19.6% (11/56) in Peru. When stratified by liver disease, the prevalence was: 20.1% (78/387) in patients with cirrhosis, 19.4% (33/170) in HCC, 1.7% (2/119) in NAFLD, 3.8% (1/26) in subjects with HBV infection and 7.1% (1/14) in those with HCV infection. **Conclusion:** This is the first study addressing HEV in patients with chronic liver disease in multiple countries in Latin America, and the first report overall of HEV among some of the countries, such as Ecuador and Peru. We found a high prevalence of IgG anti-HEV in all groups of patients compared to the general population, particularly in Chile. In depth studies to understand the the implications of this increased sero-epidemiology are needed.

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Disclosure information not available at the time of publication: Maria Belen Pisano, Anabella Fantilli, Domingo Balderramo, Jhon Edison Prieto Ortiz, Marco

Arrese, Enrique Carrera, Javier Diaz Ferrer, Angelo Mattos, Andre Boonstra, Viviana Elizabeth Re

1216-C | EVALUATING THE REGIONAL PREVALENCE AND INCIDENCE OF HEPATITIS DELTA VIRUS AMONG ADULTS WITH HEPATITIS B VIRUS INFECTION IN ITALY

Pietro Lampertico[1,2], Elisa Giacomini[3], Melania Dovizio[3], Luca Degli Esposti[3], Melania Leogrande[3], Ankita Kaushik[4], Chong Hoon Kim[4] and Marvin Rock[4], (1)Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, (2)CRC "a. M. and a. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, (3)Clicon S.r.l. Società Benefit, Health, Economics & Outcomes Research, (4)Gilead Sciences, Inc.

Background: Hepatitis delta virus (HDV) occurs as a co- or superinfection with hepatitis B virus (HBV), causing a more severe form of viral hepatitis than HBV infection alone. Yet, the epidemiology of HDV in Italy is not well characterized. This study aimed to evaluate the national and regional prevalence and incidence of HDV infection among adults in Italy. **Methods:** A retrospective observational study was conducted using administrative databases derived from a sample of local health units that covered around 12 million persons across Italy. Such databases contain all the healthcare resources and services reimbursed by the National Health System funded on the principle of universal coverage for all citizens. Adults with e 1 diagnosis (*ICD-9-CM* or exemption code) of HDV or HBV were screened from Jan 1, 2014, to Dec 31, 2020; patients with HDV or HBV monoinfection were identified from Jan 1, 2015, to Dec 31, 2019 (identification period), with their index date defined as the first diagnosis. Annual prevalence was calculated based on the lifetime prevalence approach for which adults diagnosed on or before the year of assessment were included. Incidence was measured as the proportion of newly diagnosed adults with HDV (numerator) among patients diagnosed with HDV or HBV (denominator). **Results:** Among 11,161 patients with HBV monoinfection or HDV screened during the study period, 9,045 met inclusion criteria. The average annual HDV prevalence and incidence among patients with HBV in Italy throughout the study period were 6.8% and 0.8%, respectively. The average annual prevalence of HDV among the Northern and Central regions was 4.5% and 5.5%, respectively, while the average annual prevalence was numerically higher in the Southern region at 8.9%. **Conclusion:** Overall average annual prevalence and incidence of HDV in Italy were 6.8% and 0.8% between 2015 and 2020. HDV prevalence was higher in the Southern region of Italy compared with its Northern and Central regions, perhaps due to greater influx of immigration to Southern Italy. Findings from this study underscore the need for continued efforts in the early identification of HDV infection among people with HBV infection and for the development of effective strategies in the treatment and management of HDV, considering prioritization based on the regional prevalence and incidence.

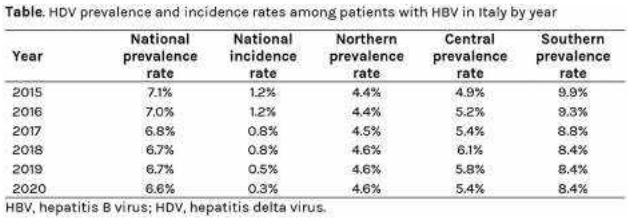

Table. HDV prevalence and incidence rates among patients with HBV in Italy by year

Year	National prevalence rate	National incidence rate	Northern prevalence rate	Central prevalence rate	Southern prevalence rate
2015	7.1%	1.2%	4.4%	4.9%	9.9%
2016	7.0%	1.2%	4.4%	5.2%	9.3%
2017	6.8%	0.8%	4.5%	5.4%	8.8%
2018	6.7%	0.8%	4.6%	6.1%	8.4%
2019	6.7%	0.5%	4.6%	5.8%	8.4%
2020	6.6%	0.3%	4.6%	5.4%	8.4%

HBV, hepatitis B virus; HDV, hepatitis delta virus.

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Ankita Kaushik – Gilead Sciences, Inc.: Employee, No, No;
Chong Hoon Kim – Gilead Sciences, Inc.: Employee, No, No;
Marvin Rock – Gilead Sciences, Inc.: Employee, No, No;
The following people have nothing to disclose: Elisa Giacomini, Melania Dovizio, Luca Degli Esposti, Melania Leogrande

1217-C | EVALUATION OF EUROBIOPLEX EBX-071, A NEW COMMERCIAL KIT FOR HDV VIRAL LOAD QUANTIFICATION

Athenaïs Gerber[1], Emeline Huault[2], Valerian Delagarde[1], Emmanuel Gordien[1], Frederic Le Gal[1], Claude Giry[2] and Segolene Brichler[1], (1)CHU Avicenne, (2)Eurobio Scientific

Background: HBV-HDV coinfection leads to the most severe form of chronic viral hepatitis, however only few virological tools are currently available. Both commercial and in-house RT-qPCR tests are used for RNA quantification worldwide but results are not yet fully

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

standardized. The first pangenomic EurobioPlex HDV kit (EBX-004, Eurobio Scientific) was commercialized in 2016. Here we evaluated the performances of its new version EBX-071. **Methods:** We used the WHO International Standard to evaluate repeatability and reproducibility, and samples from our collection, with diverse genotypes and viral loads (VL), to assess sensitivity (lower limit of detection LLOD and quantification LLOQ) and specificity. A large study with clinical samples containing all 8 circulating genotypes was also performed to compare the older (EBX-004) and new (EBX-071) tests from Eurobio. **Results:** Quantification standards are now provided in a ready-to-use format, and the whole process is validated with the simultaneous detection of an endogenous internal control. We obtained a valid result for 98.3% of all samples (1453/1478). Coefficients of variation were $<5\%$ for repeatability and $<10\%$ for reproducibility, with every tested condition ($1/100^{e}$ and $1/1000^{e}$ WHO, $n=24$ each for repeatability and $n=120$ for reproducibility). A 100% specificity was observed when testing 100 HBV/HDV negative blood donor samples, 100 HBV positive/HDV negative patient samples and 25 samples positive for another virus (HIV, HAV, HBV, HCV, HEV). No interference or inhibition was noted with high titers of triglyceride or bilirubin. Similar results were observed on paired plasma and serum samples ($n=24$, mean difference of 0.1 log IU/mL). LLOD and LLOQ were found at 20 IU/mL and 50 IU/mL respectively (serial dilutions of the WHO standard, HDV-1 genotype, confirmed with samples of all genotypes). 98.9% concordant results were obtained when comparing EBX-004 and EBX-071 tests (6 discordant results/561 tests, all concerning samples with $VL<3$ log IU/mL), however the latter gave lower results (constant difference of 0.88 log IU/mL). WHO standard quantification with the EBX-071 kit led to values very close to its theoretical value (2.75 vs 2.76 log IU/mL at $1/1000^{e}$). **Conclusion:** The performances of the EurobioPlex EBX-071 test, when operated on a CFX96 device along with a m2000sp RNA extraction, are very good and in accordance with state-of-the-art recommendations. The kit was also improved for practical use. A very important point is the recalibration of the standard curve to allow a better targeting on the WHO standard, which represents a big step towards HDV VL universal harmonization.

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Disclosure information not available at the time of publication: Emeline Huault, Valerian Delagarde, Frederic Le Gal, Claude Giry

1218-C | FINDINGS FROM A ROUTINE SCREENING PROGRAM FOR HEPATITIS DELTA VIRUS AMONG HEPATITIS B SURFACE ANTIGEN POSITIVE PATIENTS IN A CHICAGO-BASED HEALTHCARE SYSTEM

Bijou Hunt[1], Maggie Li[2], Andrea Nunez-Garcia[1] and Nancy Glick[1], (1)Sinai Chicago, (2)Northwestern University

Background: In 2022, eight US-based sites with routine hepatitis B (HBV) screening in place implemented universal hepatitis delta virus (HDV) screening among patients testing positive for hepatitis B surface antigen (HBsAg). Here we focus on outcomes from one of the eight sites, a Chicago-based healthcare system. **Methods:** A daily report was run to return a list of all patients testing positive for HBsAg (HBV+) across the system (inpatient, outpatient, and emergency department). For those HBV+, testing was manually added for HDV antibody (Ab) and ribonucleic acid (RNA) tests. Data for these patients was abstracted from the EMR and aggregated for the period 4/15/2022 – 2/28/2023. **Results:** A total of 6,631 patients were tested for HBsAg. While the majority of HBsAg testing occurred among non-Hispanic (NH) black patients (30.6%), HBV + occurred most frequently among NH Asian (54.5%), followed by NH Black (21.2%), and NH White (9.8%), and was infrequent among Hispanic/Latino patients (0.8%, $n=1$). Females were slightly more likely to be tested for HBsAg (53.5%), but made up a smaller proportion of HBV+ (42.4%). Outpatient testing locations performed the most HBsAg tests and returned the largest proportion of HBV+. Of the 6,631 patients tested for HBsAg, 2% were HBV+ ($n=132$); of these, 71% were successfully tested for HDV Ab and RNA ($n=94$). Among the 94 tested for HDV, 3 were HDV Ab positive (HDV Ab+) (3.2%) and 2 were RNA positive (RNA+) (2.1%). All HDV Ab+ cases were tested in outpatient locations associated with large immigrant patient populations. The two RNA+ cases occurred among patients from Ukraine and Eritrea; both were male and mean age was 40 years. **Conclusion:** Guidelines for HDV screening among HBV+ differ with some suggesting a risk-based approach and others a universal approach; data collected thus far do not yet provide solid support for one of these over the other. Implementing HDV screening is greatly facilitated when a routine HBV screening program is already in place. However, even for sites with an existing HBV screening program, challenges will arise in the lab process where insufficient samples result in an inability to process the follow-up HDV testing; and where lack of available reflex testing will require add-on testing that may result in missed follow-up HDV testing. Based on the data collected to date, it is too soon to draw conclusions about the epidemiology, surveillance, and policy implications for screening guidelines.

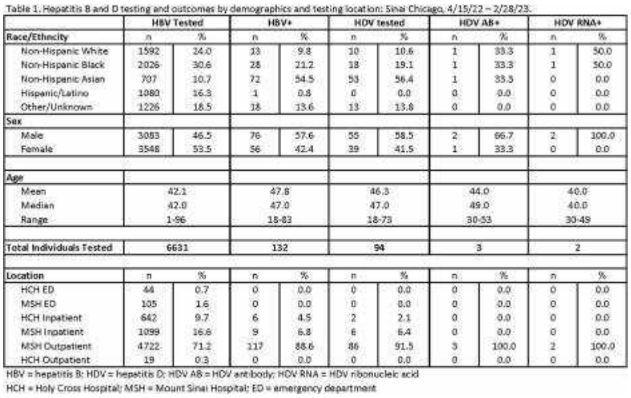

Table 1. Hepatitis B and D testing and outcomes by demographics and testing location: Sinai Chicago, 4/15/22 – 2/28/23.

	HBV Tested		HBV+		HDV tested		HDV AB+		HDV RNA+	
Race/Ethnicity	n	%	n	%	n	%	n	%	n	%
Non-Hispanic White	1592	24.0	13	9.8	10	10.6	1	33.3	1	50.0
Non-Hispanic Black	2026	30.6	28	21.2	18	19.1	1	33.3	1	50.0
Non-Hispanic Asian	707	10.7	72	54.5	53	56.4	1	33.3	0	0.0
Hispanic/Latino	1080	16.3	1	0.8	0	0.0	0	0.0	0	0.0
Other/Unknown	1226	18.5	18	13.6	13	13.8	0	0.0	0	0.0
Sex										
Male	3083	46.5	76	57.6	55	58.5	2	66.7	2	100.0
Female	3548	53.5	56	42.4	39	41.5	1	33.3	0	0.0
Age										
Mean	42.1		47.8		46.3		44.0		40.0	
Median	42.0		47.0		47.0		49.0		40.0	
Range	1-96		18-83		18-73		30-53		30-49	
Total Individuals Tested	6631		132		94		3		2	
Location	n	%	n	%	n	%	n	%	n	%
HCH ED	44	0.7	0	0.0	0	0.0	0	0.0	0	0.0
MSH ED	105	1.6	0	0.0	0	0.0	0	0.0	0	0.0
HCH Inpatient	642	9.7	6	4.5	2	2.1	0	0.0	0	0.0
MSH Inpatient	1099	16.6	9	6.8	6	6.4	0	0.0	0	0.0
MSH Outpatient	4722	71.2	117	88.6	86	91.5	3	100.0	2	100.0
HCH Outpatient	19	0.3	0	0.0	0	0.0	0	0.0	0	0.0

HBV = hepatitis B; HDV = hepatitis D; HDV AB = HDV antibody; HDV RNA = HDV ribonucleic acid
HCH = Holy Cross Hospital; MSH = Mount Sinai Hospital; ED = emergency department

Disclosures: The following people have nothing to disclose: Bijou Hunt

Disclosure information not available at the time of publication: Maggie Li, Andrea Nunez-Garcia, Nancy Glick

1219-C | HDV PERSISTS IN HUMAN HEPATOCYTES UNDERGOING CELL DIVISION IN HUMAN LIVER CHIMERIC MICE BUT IS POTENTLY INHIBITED BY PEGYLATED INTERFERON-ALPHA TREATMENT

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Background: The endogenous interferon response is not sufficient to abrogate hepatitis D virus (HDV) replication, nor to inhibit cell division-mediated spread of HDV in vivo *(Giersch, Gut 2019)*. However, studies in humanized mice stably infected with both HDV and hepatitis B virus (HBV) demonstrated the ability of pegylated interferon-alpha (pegIFN±) to suppress patient-derived HDV strains *(Giersch, JHEPRep 2023)*. Moreover, in vitro studies showed that IFNa exerts stronger anti-HDV activities in hepatoma cells undergoing cell division (*Zhang, JHepatol 2022*). The aim of this study was to investigate the impact of cell division and pegIFN± treatment on HDV replication *in vivo*. **Methods:** To promote division of virally-infected human hepatocytes in vivo, uPA/SCID/IL2R$\gamma^{-/-}$ (USG) mice (N = 15) received primary human hepatocytes (PHH) isolated from a mouse previously reconstituted with adult PHH and stably infected with HBV and HDV (HBV viremia 1.7 ´ 10^9; HDV 5.3´ 10^8). Virological markers and IFN response were analyzed by qRT-PCR, ELISA and immunofluorescence. From week 1 to 8 after PHH transplantation, half of the mice received pegIFN± s.c. (25ng/g biweekly) to assess its impact on HDV, HBV and cell proliferation, as determined by ELISA (human serum albumin), human B-globin/ng liver DNA and histology. **Results:** In an environment supporting cell proliferation, transplanted PHH underwent strong expansion ($2\log_{10}$ HSA increase already at 5 weeks) both in untreated mice and in animals receiving pegIFN±. In untreated mice, the overall intrahepatic HDV RNA level increased as PHH expanded ($\Delta 1.57\log_{10}$, w5), while HDV RNA levels per PHH remained unchanged. In contrast, overall intrahepatic HBV markers decreased during the first 5 weeks of cell division, resulting in an increased proportion of PHH appearing HDAg-positive but HBcAg-negative. Seven weeks of pegIFN± promoted stronger reduction of intrahepatic HBV DNA and RNA levels (median $2.7\log_{10}$ and $2.2\log_{10}$), compared to untreated group. Strikingly, pegIFNa treatment resulted in undetectable levels of HDV viremia ($\Delta > 3l\log_{10}$, compared to untreated), HDV RNA and HDAg-positive PHH in the liver, despite high levels of chimerism. Strong induction of human IFN-responsive genes was confirmed in all mice receiving pegIFN±. **Conclusion:** In line with previous in vitro studies, HDV can persist in hepatocytes undergoing cell division in vivo but is potently inhibited by pegIFN± in PHH during cell expansion.

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The following people have nothing to disclose: Annika Volmari, Tassilo Volz, Marc Lütgehetmann

Disclosure information not available at the time of publication: Simon P Fletcher, Meghan Holdorf, Robert C Muench

1220-C | HEALTHCARE RESOURCE UTILIZATION AND COSTS OF HDV INFECTION VS HBV MONOINFECTION ACROSS DISEASE STATES IN A HOSPITAL RECORDS DATABASE FROM SPAIN

Maria Buti[1], Marvin Rock[2], Meritxell Ascanio[3], Josep Darba[4] and Chong Hoon Kim[2], (1)Hospital Universitario Vall D'hebron and Ciberehd Del Instituto Carlos III, (2) Gilead Sciences, Inc., (3)Bcn Health Economics & Outcomes Research SL, (4)University of Barcelona

Background: Hepatitis delta virus (HDV), which requires the presence of hepatitis B virus (HBV) for transmission, results in the most severe form of viral hepatitis. This retrospective study compares healthcare resource utilization (HCRU) and costs of HDV infection vs HBV monoinfection by disease states in Spain. **Methods:** Patients aged e 18 years with e 1 *ICD-9/10-CM* diagnosis code for HDV or HBV between Jan 1, 2000 and Dec 31, 2019 (study period) were identified in the Spanish National Health System's Hospital Discharge Records Database (Conjunto Mínimo Básico de Datos). Patients with a first diagnosis between Jan 1, 2001 and Dec 31, 2018 and those with continuous enrollment for e 12 months before and after first diagnosis were selected. Baseline (BL) characteristics and clinical comorbidities were recorded from the year before first diagnosis. Patient groups were propensity score matched (1:5) according to BL characteristics. Mean per patient per year (PPPY) HCRU and costs were compared within subgroups of liver disease severity. Descriptive statistics were summarized, and comparisons were made via generalized linear models. **Results:** Among 12,317 patients identified with HDV or HBV only, 756 met all inclusion criteria (HDV, n = 126; HBV only, n = 630). Patients' mean (SD) age was 41.7 (11.8) vs 41.2 (9.9) years in patients with HDV vs HBV only; 89.7% of patients in each group were male. Significantly greater proportions of patients with HDV vs patients with HBV only had compensated cirrhosis (CC; 25.4% vs 9.5%, $p < 0.0001$) or decompensated cirrhosis (DCC; 51.6% vs 20.6%, $p < 0.0001$). Mean time spent in each liver disease state was significantly shorter for patients with HDV vs HBV only. Mean (SD) length of hospital stay (days) was longer for patients with HDV vs HBV only for patients with CC (6.6 [2.7] vs 4.3 [1.8], $p = 0.04$), DCC (11.7 [4.7] vs 6.9 [3.8], $p = 0.03$), and liver transplantation (11.8 [3.0] vs 9.1 [3.4], $p = 0.04$). Mean pharmacy, inpatient, outpatient, and total costs PPPY were significantly higher for those with HDV vs HBV only and increased with disease state severity. **Conclusion:** In Spain, mean inpatient length of stay and total costs associated with HDV were higher than for patients with HBV only and increased with greater liver disease severity. These findings underscore the need for effective screening, diagnosis, and treatment of HDV to help reduce the clinical and economic burden of disease.

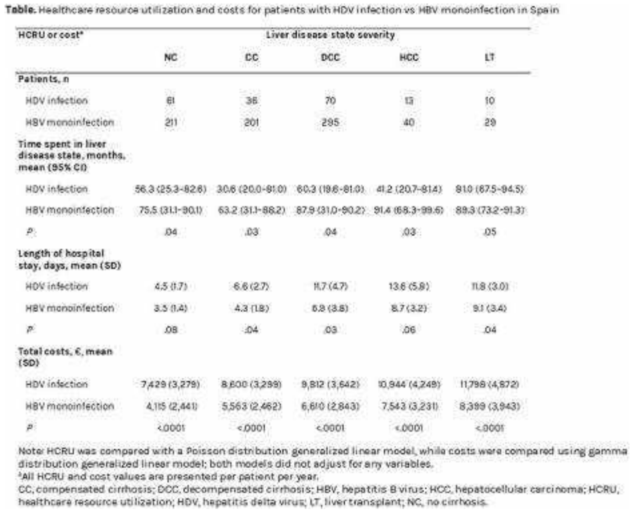


Table. Healthcare resource utilization and costs for patients with HDV infection vs HBV monoinfection in Spain

HCRU or cost[a]	Liver disease state severity				
	NC	CC	DCC	HCC	LT
Patients, n					
HDV infection	61	36	70	13	10
HBV monoinfection	211	201	295	40	29
Time spent in liver disease state, months, mean (95% CI)					
HDV infection	56.3 (25.3-82.6)	30.6 (20.0-81.0)	60.3 (19.6-81.0)	41.2 (20.7-81.4)	81.0 (67.5-94.5)
HBV monoinfection	75.5 (31.1-90.1)	63.2 (31.1-88.2)	87.9 (31.0-90.2)	91.4 (68.3-99.6)	89.3 (73.2-91.3)
P	.04	.03	.04	.03	.05
Length of hospital stay, days, mean (SD)					
HDV infection	4.5 (1.7)	6.6 (2.7)	11.7 (4.7)	13.6 (5.8)	11.8 (3.0)
HBV monoinfection	3.5 (1.4)	4.3 (1.8)	6.9 (3.8)	8.7 (3.2)	9.1 (3.4)
P	.08	.04	.03	.06	.04
Total costs, €, mean (SD)					
HDV infection	7,429 (3,279)	8,600 (3,299)	9,812 (3,642)	10,944 (4,249)	11,798 (4,872)
HBV monoinfection	4,115 (2,441)	5,563 (2,462)	6,610 (2,843)	7,543 (3,231)	8,399 (3,943)
P	<.0001	<.0001	<.0001	<.0001	<.0001

Note: HCRU was compared with a Poisson distribution generalized linear model, while costs were compared using gamma distribution generalized linear model; both models did not adjust for any variables.
[a]All HCRU and cost values are presented per patient per year.
CC, compensated cirrhosis; DCC, decompensated cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCRU, healthcare resource utilization; HDV, hepatitis delta virus; LT, liver transplant; NC, no cirrhosis.

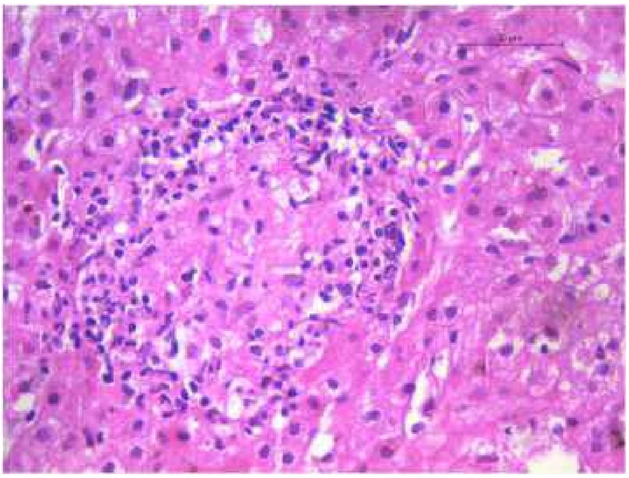
Disclosures: Maria Buti – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, Yes; GSK: Advisor, Yes, No;
Marvin Rock – Gilead Sciences, Inc.: Employee, No, No;
Chong Hoon Kim – Gilead Sciences, Inc.: Employee, No, No;
Disclosure information not available at the time of publication: Meritxell Ascanio, Josep Darba

1221-C | HEPATIC TUBERCULOSIS: REAL WORLD EXPERIENCE FROM A TERTIARY CARE CENTRE

Souveek Mitra[1], Ranajoy Ghosh[1], Dipankar Mondal[1], Srijan Mazumdar[1], Kishalaya.[1] and Abhijit Chowdhury[2], (1)Iilds, (2)Institute of Post Graduate Medical Education & Research

Background: In developing countries, like India, where tuberculosis is endemic, diagnosis of hepatic tuberculosis often remains a challenge. Due to the lack of specific presenting symptoms and characteristic imaging findings, diagnosis is challenging. Invasive methods like liver biopsy, for detection of granuloma, classical for tuberculosis, often aids in the diagnosis. Another challenge, lies in the therapy of these patients, as often they have altered liver function tests, which preclude the uses of first line antitubercular therapy. We retrospectively reviewed, a series of hepatic tuberculosis, diagnosed in our institute. **Methods:** Between September of 2018 to January of 2023, we reviewed all cases that were diagnosed as a case of hepatic tuberculosis at our institute. Diagnosis of hepatic tuberculosis was made if the subjects fulfilled any of the following criteria 1) Liver biopsy showing classical caseating granuloma, pathognomic for tuberculosis 2) Identification of acid fast positive bacilli from liver tissue 3) Positive culture for tuberculosis. **Results:** During the period, we identified twenty two (22) subjects, fulfilling our diagnostic criteria. 16 of the total subjects (72.73%) were male. Mean age was 53 years. 28% of the subjects were diabetic. 23% of them were diagnosed cirrhotic beforehand. Of the cirrhotic subjects, 20% was hepatitis B positive, and 40% were having alcohol use disorder (AUD). Presenting symptoms of 27% of subjects were pyrexia of unknown origin (PUO), among them 33% had isolated elevation of alkaline phosphatase (ALP). 14% of the total subjects were asymptomatic, and was identified via histopathology. Indications for liver biopsies in two of them were isolated elevation of ALP, one of them underwent liver biopsy during work up for non

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



Disclosures: The following people have nothing to disclose: Souveek Mitra, Abhijit Chowdhury
Disclosure information not available at the time of publication: Ranajoy Ghosh, Dipankar Mondal, Srijan Mazumdar, Kishalaya.

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

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

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

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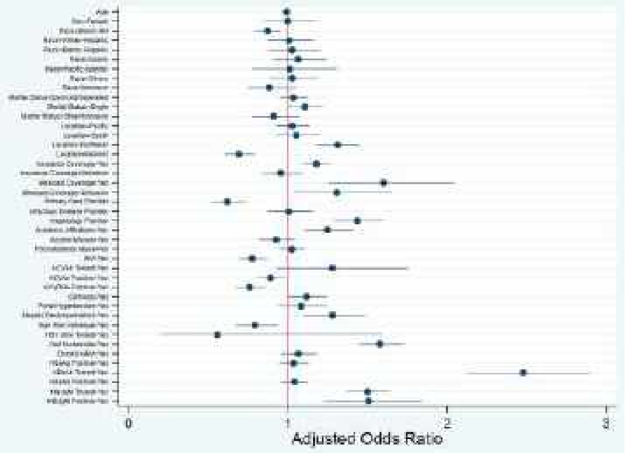
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

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



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Robert J. Wong – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Exact Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Thera Technologies: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bausch Health: Consultant, No, No; Salix Pharmaceuticals: Consultant, No, No;

Donna M. Evon – HighTide Therapeutics: Consultant, No, Yes;

Bassam Dahman – Exact Sciences: Consultant, No, Yes;

The following people have nothing to disclose: Mahmoud Manouchehri Amoli

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

Segolene Brichler, CHU Avicenne, Pascale Trimoulet, CHU Pellegrin, Anne-Marie Roque-Afonso, CHU Paul Brousse, Jacques Izopet, CHU Purpan, Vincent Thibault, CHU Pontchaillou, Caroline Scholtès, CHU Croix-Rousse and Stephane Chevaliez, Service De Virologie, Hôpital Henri Mondor

Background: Infection with Hepatitis delta virus (HDV) leads to the most severe form of chronic viral hepatitis; unfortunately, screening rates are scarce in most areas and patients are often diagnosed at an advanced clinical stage. International guidelines recommend either a systematic HDV screening for all HBsAg-positive patients (EASL) or a risk-based approach (AALSD). In addition to perform HDV serology on medical prescription, some laboratories have implemented a "HDV reflex testing" protocol, consisting of the addition of a serological HDV test on all samples with a first HBsAg positive result. The aim of this cross-sectional study was to analyse the different strategies implemented in seven French university hospital laboratories and to compare their efficiency for HDV antibody (HDV-Ab) and viral load (HDV-VL) screening. **Methods:** All individual's with a positive HBsAg test referred for the first time between January 2018 and October 2022 were included. Patients replicate requests were removed. Total or IgG HDV-Abs were assayed with commercial tests, HDV-VL with in-house or commercial tests, and HDV genotype with partial sequencing (R0 region). **Results:** Of 459,644 consecutive individual's, 6,772 were tested HBsAg-positive for the first time (mean age 38.7, sex ratio 2.03). Testing for HDV-Abs was conducted on 5,749 patients (84.9%) and 364 of them were positive (6.3%, CI 95%: 5.7-7.0, mean age 40.9, sex ratio 2.36). HDV-VL was determined in 285 (78.3%) patients and 167 (58.6%, CI 95%: 52.8-64.2) had an active HDV infection. HDV-1 genotype was predominant (77%), followed by HDV-5 (19%). The screening rate was 46.6% in one centre (pre-reflex testing period), varied from 65.2% to 96.4% in laboratories with a manual add-on strategy (i.e. biologist-driven, 5 centres), and reached up to 99.2% when the HDV-Ab reflex testing is automatically set in the local information system (2 centres). **Conclusion:** Even in this university hospital context, in a country with a recommendation to screen all HBsAg-positive patients, HDV is underdiagnosed with a prescription-only strategy. Both manual and automatic reflex testing are highly effective. Early identification of HBV-HDV infected patients allows a faster referral to hepatologists for adequate clinical management, especially in this era of new HDV treatments. This work strongly argues for changing public health policies and allowing laboratory-driven HDV reflex testing.

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The following people have nothing to disclose: Stephane Chevaliez

Disclosure information not available at the time of publication: Pascale Trimoulet, Anne-Marie Roque-Afonso, Jacques Izopet, Vincent Thibault, Caroline Scholtès

1224-C | HEPATITIS E RNA RESPONSE-GUIDED RIBAVIRIN TREATMENT IMPROVES SUSTAINED VIROLOGIC RESPONSE RATE COMPARED WITH A STANDARD 12-WEEK REGIMEN IN IMMUNOSUPPRESSED PATIENTS

Guan-Huei Lee[1,2]*, Haoxing Lai*[2]*, Zera Yingrui Te*[2] *and Margaret Li Peng Teng*[3]*, (1)National University Hospital, (2)National University of Singapore, (3) National University Health System (NUHS)*

Background: Hepatitis E virus (HEV) causes chronic hepatitis in immunosuppressed patients. Our earlier study revealed that the sustained virologic response rate (SVR) of 12-week ribavirin therapy for HEV infection was lower than expected. This study aims to compare the outcome of the standard 12-week of ribavirin treatment against a response-guided ribavirin treatment in immunosuppressed patients infected with HEV. **Methods:** We performed a retrospective analysis of all patients who had persistence of plasma HEV RNA for more than 3 months in NUH between 2012 to 2022. The study protocol is approved by NHG DSRB (reference: 2016/00250). Initially, most patients received standard 12-week ribavirin therapy, and subsequent patients were given response-guided ribavirin regimen, during which HEV RNA was monitored 4 weekly, and continued until it became undetectable for at least 8 weeks. Rapid virologic response (RVR) is defined as undetectable HEV RNA after 4 weeks of ribavirin therapy. SVR is defined as undetectable HEV RNA 24 weeks after completing treatment. Statistical analysis was carried out using OpenEpi online software. **Results:** Fifty immunosuppressed patients with HEV infection were reviewed. Thirteen were excluded due to spontaneous recovery or loss to follow-up before confirmation of SVR. Thirty-seven patients are included in the final analysis (6 liver transplant, 18 kidney transplant, 5 bone marrow transplant, and 8 steroid/chemotherapy). Thirteen patients received 12 weeks of ribavirin therapy, but only 8 patients achieved SVR (61.5%, all achieved RVR), and 5 relapsed, who then undergo retreatment. Remaining 24 patients required 12 weeks or more of treatment under response-guided regimen, of which 7 had prolonged viremia on continuous ribavirin for more than one year. Response-guided therapy results in all 24 patients achieving SVR, (100 % vs. 61.5%, Fisher exact test, $p = 0.006$), with 1 relapsed after > 6 months. Two-thirds (16 out of 24 patients) had positive HEV RNA at week 12, indicating a certainty of relapse if they had received the 12-week regimen. Achieving RVR followed by 8 weeks of consolidation predicts a good response for 12-week ribavirin regimen, whilst kidney transplant recipient, ribavirin dose reduction, and non-adherence to treatment contribute to longer treatment duration and relapse. **Conclusion:** HEV RNA response-guided treatment results in a higher treatment success rate than a fixed 12-week ribavirin regimen in immunosuppressed patients.

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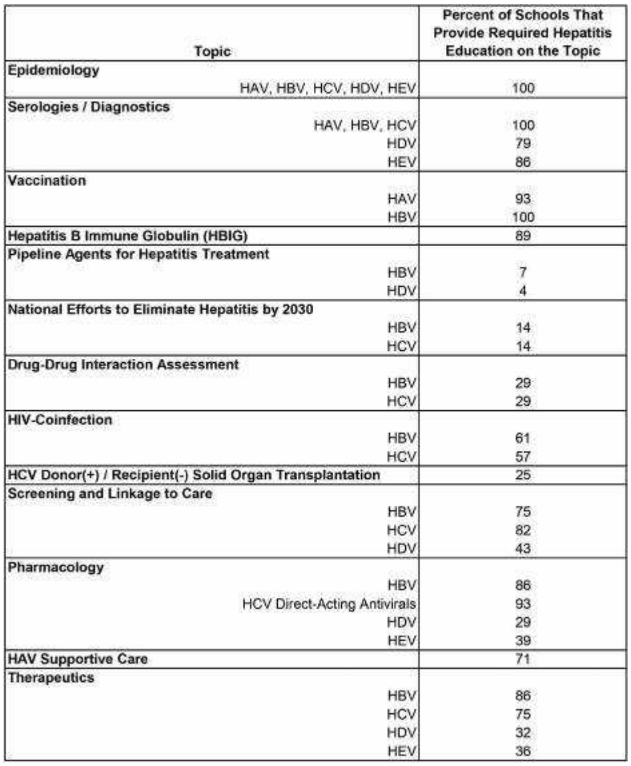
Disclosure information not available at the time of publication: Haoxing Lai, Zera Yingrui Te, Margaret Li Peng Teng

1225-C | HEPATITIS EDUCATION IN THE UNITED STATES' MEDICAL SCHOOL CURRICULA

Michelle Martin[1,2]*, Gerda Lescinskaite*[2]*, Alexander Pan*[1,3]*, Zeba Saiyad*[2] *and Adam E. Mikolajczyk*[1,3]*, (1)UI Health, (2)UIC College of Pharmacy, (3)UIC College of Medicine*

Background: The Viral Hepatitis National Strategic Plan documents the value of a collaborative provider workforce trained in the provision of hepatitis treatment and prevention to facilitate the United States' 2030 viral hepatitis elimination efforts. Physicians play a crucial role in viral hepatitis management, yet the Liaison Committee on Medical Education (LCME) does not mandate minimum requirements for hepatitis content in medical curricula in the United States. **Methods:** Investigators developed a 19-item Qualtrics survey, validated by 6 colleagues, sent survey links to curricula content experts at 157 LCME-accredited medical colleges/schools in April-May 2023, and allotted 28 days for survey completion. Survey questions assessed the type, amount, and topics of viral hepatitis instruction provided to Doctor of Medicine students, and the hepatitis instructors' training/experience. We used descriptive statistics for analysis. Results: By 5/24/2023, 29 medical institutions across 20 states responded; 93% were 4-year programs, 52% public, with an average enrollment of 154 ± 56 students/class. 76% use both lecture and discussion for provision of hepatitis education, 14% use small group discussion only, and 10% lecture only. 90% of institutions provide required hepatitis education with 2.5 ± 1.1 lecture hours/program and 2.7 ± 1.5 discussion hours/program, while 10% of institutions also offer elective hepatitis coursework averaging 4.5 ± 1.5 lecture hours/program. The table lists the percent of schools who provide required hepatitis education on the listed topics. All schools teach hepatitis A-E epidemiology, hepatitis A-C serologies/diagnostics, and HBV vaccination. Nearly all teach HAV vaccination and HBIG. Instruction on HDV and HEV pharmacology and therapeutics was less than half the rates for HBV and HCV, and screening/linkage to care was more commonly taught for HBV and HCV than HDV. Over half of schools teach about HBV and HCV/HIV-coinfection. Drug interaction assessment instruction for HBV and HCV is provided at fewer than one-third of programs. A quarter of programs teach HCV donor(+) / recipient(-) solid organ transplantation. Few programs teach about the 2030 national hepatitis elimination goals and pipeline agents for HBV and HDV. Responders stated 70% of primary hepatitis instructors had at least one board certification (58% each Gastroenterology and Internal Medicine, 26% Infectious Disease, 21% Transplant Hepatology), 96% were full-time faculty, and 41% of the 17 instructors with clinical appointments spent 20-39% time on patient care. **Conclusion:** Survey results show similarities, variability, and gaps in topics devoted to hepatitis education across United States medicine curricula. Our data offer knowledge about the viral hepatitis education provided to Doctor of Medicine students who will soon be able to assist with nationwide hepatitis elimination efforts.



Topic	Percent of Schools That Provide Required Hepatitis Education on the Topic
Epidemiology	
HAV, HBV, HCV, HDV, HEV	100
Serologies / Diagnostics	
HAV, HBV, HCV	100
HDV	79
HEV	86
Vaccination	
HAV	93
HBV	100
Hepatitis B Immune Globulin (HBIG)	89
Pipeline Agents for Hepatitis Treatment	
HBV	7
HDV	4
National Efforts to Eliminate Hepatitis by 2030	
HBV	14
HCV	14
Drug-Drug Interaction Assessment	
HBV	29
HCV	29
HIV-Coinfection	
HBV	61
HCV	57
HCV Donor(+) / Recipient(-) Solid Organ Transplantation	25
Screening and Linkage to Care	
HBV	75
HCV	82
HDV	43
Pharmacology	
HBV	86
HCV Direct-Acting Antivirals	93
HDV	29
HEV	39
HAV Supportive Care	71
Therapeutics	
HBV	86
HCV	75
HDV	32
HEV	36

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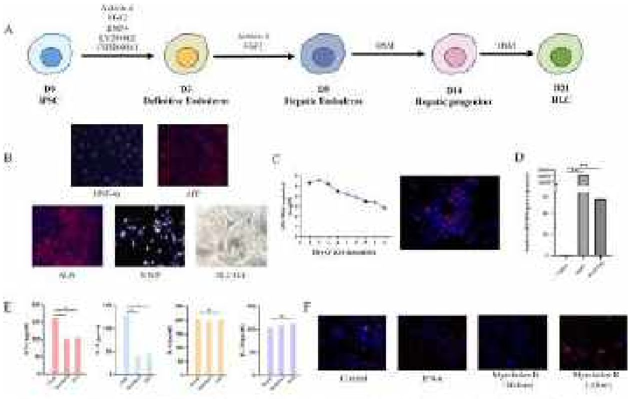
The following people have nothing to disclose: Gerda Lescinskaite, Alexander Pan, Zeba Saiyad, Adam E. Mikolajczyk

1226-C | HUMAN iPSC DERIVED HEPATOCYTE-LIKE CELLS SEEDED INTO INVERTED COLLOID CRYSTAL SCAFFOLDS AS A NOVEL ORGANOID MODEL FOR HEPATITIS D VIRUS INFECTION

Leer Shen, Qingxin Guo and Xiaohua Chen, Shanghai Sixth People's Hospital

Background: Hepatitis D virus (HDV) super-infection with Hepatitis B virus (HBV) is considered the most severe form of viral hepatitis, affecting 4.5% of HBV-positive patients. However, current in vivo and in vitro models provided limited information about HDV infection and replication, which has impeded the development of effective therapies. Thus, we aimed to develop an HDV infected model on the basis of a novel liver organoid platform using human induced pluripotent stem cell (iPSC) and 3-D inverted colloid crystal (ICC) to study the HDV infection mechanism and antiviral drug responses. **Methods:** We first fabricated ICC following NG Soon Seng's protocol. Under proper culture conditions iPSCs can be differentiated to hepatocyte-like cells (HLCs) in the 21th day in vitro (Fig A), which were later cultured in the 3-dimensional ICC scaffolds. HLCs were inoculated with concentrating HBV and HDV supernatants in the presence of 4% Polyethylene Glycol 8000 (PEG8000) and 2% dimethyl sulfoxide (DMSO). Myrcludex B (100 nM) were administrated before and after HDV inoculation, and IFN-± (1000UI/ml) were administrated after HDV inoculation to evaluate their antiviral effects. **Results:** After the iPSC-derived HLCs were generated and seeded into ICC scaffolds, the function and transcriptomic characteristics of the organoid model were confirmed resembling human liver characteristics by immunofluorescence (Fig B). HDV antigen was assessed by quantitative RT-PCR and immunofluorescence after HDV inoculation (Fig C). HDV RNA was highly expressed in Huh7 overexpressed with NTCP after inoculated with the supernatant HDV particles collected from the HDV infected model (Fig D). The change of HDV RNA, IL-2, IL-4, IL-10, TNF-± and IFN-γ were shown in Figure E. We further found that Myrcludex B treatment before HDV inoculation demonstrated the most effective antiviral therapy compared with Myrcludex B and IFN-± administration after HDV inoculation (Fig F). **Conclusion:** This novel HDV infected model presents a valuable platform for the study of HDV infection mechanisms and antiviral drug responses.



(A) iPSC differentiation protocol to HLCs in 21th day in vitro. (B) Immunofluorescence of hepatocyte marker protein after HLCs cultured into ICC. (C) Supernatant of the model was harvested for immunofluorescence and qRT-PCR. (D) HDV particles in supernatant of the model were inoculated to infected NTCP-Huh7. (E) Cytokine level in different intervention group. (F) HDV infected model were treated with Myrcludex B and IFN-α.

Disclosures: The following people have nothing to disclose: Leer Shen, Qingxin Guo, Xiaohua Chen

1227-C | IMPACT OF HYPERGLYCEMIA ON HOSPITAL ADMISSIONS DUE TO PYOGENIC LIVER ABSCESS: A NATIONWIDE STUDY

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Background: Liver abscesses are one of the most common types of visceral abscess. Pyogenic liver abscesses usually develop in the context of biliary disease, portal pyemia of various causes, through arterial hematogenous seeding, or via direct spread. It is associated with high mortality and morbidity. In this study we aimed to determine the impact of hyperglycemia on clinical outcome, inpatient mortality and hospital stay of patients admitted with pyogenic liver abscess. **Methods:** Methods: All adult patients (age > 18 y) old with pyogenic liver abscess with or without hyperglycemia during hospital admission from 2016-2020 were identified from the Nationwide Inpatient Sample (NIS). Data on demographic information, baseline clinical characteristics, and outcome variables such as mortality, hospital length of stay, and total hospital charges were collected and analyzed. Statistical analysis was performed by using the survey procedures function in STATA v.17. Statistical significance was defined by the two-sided t-test with a p value < 0.05. **Results:** A total of 4,895 patients were included in the analysis, of which 445 (10%) had hyperglycemia at the time of admission. Patients with hyperglycemia were found to have a significantly higher prevalence of chronic kidney disease (16% vs. 8%, $p = 0.01$), hyperlipidemia (50% vs. 35%, $p = 0.009$), obesity (22% vs. 14%, $p = 0.03$), and biliary and pancreatic disease (34% vs. 24%, $p = 0.03$). Furthermore, patients with hyperglycemia had a higher incidence of septic shock (6.74% vs. 1.01%, $p < 0.001$) and a greater need for mechanical ventilation (6.74% vs. 1.12%, $p = 0.0001$) compared to those without hyperglycemia. However, there was no significant difference between the two groups in terms of mortality, mean length of hospital stays, and total hospital charges. **Conclusion:** The presence of hyperglycemia in patients admitted with pyogenic liver abscess is associated with an increased risk of developing septic shock and requiring mechanical ventilation. However, it does not appear to impact hospital mortality rates, the duration of hospitalization, or the financial costs associated with the hospital stay.

Disclosures: The following people have nothing to disclose: Sajana Poudel, Ayusha Poudel, Karun

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

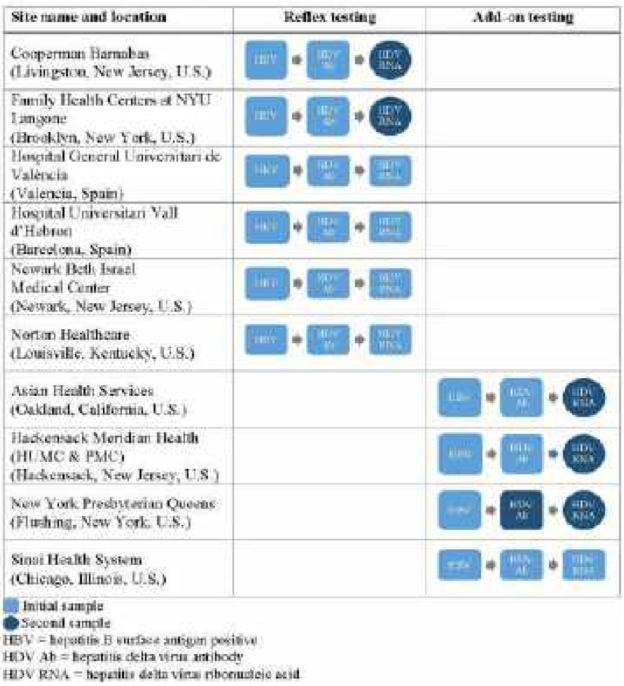
Shrestha, Kalpana Ghimire, Prakriti Subedi, Sumina Rai, Anurag Adhikari, Manoj Ghimire

1228-C | IMPLEMENTATION CONSIDERATIONS FROM A MULTI-SITE PILOT OF HEPATITIS DELTA VIRUS SCREENING AMONG HEPATITIS B SURFACE ANTIGEN POSITIVE PATIENTS IN THE UNITED STATES OF AMERICA AND SPAIN

Bijou Hunt[1], Bindu Balani[2], Maggie Li[3], Nancy Glick[1], Chinwe Ogedegbe[2], Peter Gordon[4], Michelle Rose[5], Joshua Hayden[5], Su Wang[6], Christopher Co[7], Victor Liang[7], Sandeep Bhat[8], Anita Chang[7], Miguel Garcia-Deltoro[9], Enrique Ortega Gonzalez[9] and Maria Buti[10], (1)Sinai Chicago, (2)Hackensack Meridian Health, (3) Northwestern University, (4)Newyork-Presbyterian Queens, (5)Norton Healthcare, (6)Cooperman Barnabas, (7)Asian Health Services, (8)Family Health Centers at NYU Langone, (9)Hospital General Universitari De València, (10)Hospital Universitari Vall d'Hebron, Department of Medicine of the UAB (Universitat Autònoma de Barcelona), Spain

Background: Hepatitis Delta virus (HDV) screening has been recommended for individual's with chronic hepatitis B (HBV), though guidelines differ on universal (EASL, APASL) vs. risk-based approaches (AASLD, WHO). Uptake of these recommendations, however, has been suboptimal. In 2022, 8 sites based in the United States of America (US) and 2 based in Spain implemented universal HDV screening among patients testing positive for HBV surface antigen (HBsAg). We describe the process of implementing HDV screening across various settings and identify challenges to and recommendations for making changes to workflows. **Methods:** The ten sites (hospital (7); community health center (3)) are in urban areas across the contiguous US and eastern Spain (Figure 1). While the primary populations served varied in terms of race/ethnicity and socio-economic status, all sites served large immigrant populations and had robust, policy-driven HBV screening and linkage to care programs. **Results:** Sites fell into two categories when considering their laboratory processes (Figure 1). Reflex testing meant that all HBsAg positive results were automatically tested for HDV antibody (Ab) and in 4 of the 6 reflex sites, HDV Ab positive results were automatically tested for HDV ribonucleic acid (RNA). Add-on testing required manual orders for HDV Ab and RNA tests for HBsAg positive results. Between 4/22-2/23, across all sites, a total of 68,536 patients were tested for HBsAg with 514 (1.0%) testing positive in the US and 371 (2.1%) in Spain. Among them, 63% (n = 326) in the US and 99% (n = 369) in Spain were tested for HDV Ab with 3.4% HDV Ab positive and 1.2% (n = 4) HDV RNA positive in the US and 7.3% HDV Ab positive and 2.4% (n = 9) HDV RNA positive in Spain. **Conclusion:** A lack of HDV reflex testing at certain sites presented more potential for disruptions in workflow and may have resulted in HBV patients not being tested for HDV, possibly missing the opportunity for diagnosis. Additionally, for all sites, regardless of reflex status, insufficient samples often resulted in missed HDV testing if additional tubes were not collected. Though early in implementation process, recommendations for HDV screening may include a double reflex from HBsAg positive results to HDV Ab and subsequent HDV RNA testing. Additionally, laboratories should consider instituting reflex confirmatory testing, as is best practice for hepatitis C testing. Sufficient sample availability will be an important consideration.

Figure 1. Site names, locations, and laboratory testing procedures



Site name and location	Reflex testing	Add-on testing
Cooperman Barnabas (Livingston, New Jersey, U.S.)	HBV → HDV Ab → HDV RNA	
Family Health Centers at NYU Langone (Brooklyn, New York, U.S.)	HBV → HDV Ab → HDV RNA	
Hospital General Universitari de València (Valencia, Spain)	HBV → HDV Ab → HDV RNA	
Hospital Universitari Vall d'Hebron (Barcelona, Spain)	HBV → HDV Ab → HDV RNA	
Newark Beth Israel Medical Center (Newark, New Jersey, U.S.)	HBV → HDV Ab → HDV RNA	
Norton Healthcare (Louisville, Kentucky, U.S.)	HBV → HDV Ab → HDV RNA	
Asian Health Services (Oakland, California, U.S.)		HBV → HDV Ab → HDV RNA
Hackensack Meridian Health (HUMC & PMC) (Hackensack, New Jersey, U.S.)		HBV → HDV Ab → HDV RNA
New York Presbyterian Queens (Flushing, New York, U.S.)		HBV → HDV Ab → HDV RNA
Sinai Health System (Chicago, Illinois, U.S.)		HBV → HDV Ab → HDV RNA

■ Initial sample
● Second sample
HBV = hepatitis B surface antigen positive
HDV Ab = hepatitis delta virus antibody
HDV RNA = hepatitis delta virus ribonucleic acid

Disclosures: Su Wang – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;
Maria Buti – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, Yes; GSK: Advisor, Yes, No;
The following people have nothing to disclose: Bijou Hunt, Chinwe Ogedegbe
Disclosure information not available at the time of publication: Bindu Balani, Maggie Li, Nancy Glick, Peter

Gordon, Michelle Rose, Joshua Hayden, Christopher Co, Victor Liang, Sandeep Bhat, Anita Chang, Miguel Garcia-Deltoro, Enrique Ortega Gonzalez

1229-C | IMPLEMENTATION OF A DOUBLE REFLEX STRATEGY FOR HEPATITIS DELTA DIAGNOSIS IN SOUTHERN SPAIN: A STORY OF SUCCESS

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Background: Hepatitis delta constitutes a global health problem affecting between 15 and 20 million people worldwide; with the recent introduction of Bulevirtide, the first antiviral for its treatment, and the imminent arrival of new antivirals against B virus, therapeutic options are expanded and may facilitate elimination strategies. Our aim has been to analyze the current status of undiagnosed hepatitis Delta in the South of Spain (Andalusia), and evaluate the efficacy and feasibility of hepatitis delta reflex testing. **Patients and Methods:** Ambispective (retro- and prospective) multicentre study in 17 hospitals in Andalusia. In the retrospective phase, we have analysed hepatitis delta diagnostic cascade, searching for HBsAg-positive patients, those in whom anti-delta antibody detection was performed, and those in whom HDV RNA detection was performed, extracting data from the laboratory information systems (LIS) of the participating centres (January 2018 to June 2022). From October 2022 to March 2023, all centres initiated the prospective phase in which reflex hepatitis delta (testing for anti-HDV in all HBsAg positive patients without a prior test) was implemented. **Results:** Regarding the retrospective phase, a total of 17872 HBsAg positive patients were analyzed; of those, anti-HDV was performed in 3287 (18%), and was positive in 178 patients (5,4%); HDV RNA was tested in 131 patients and, finally, 36 patients (1.1%) were identified as HDV-RNA positive. Data from the prospective phase are as follow: from a total of 3504 HBsAg positive patients, 927 had already been tested for anti-HDV; from the remaining 2577, 2150 (83%) were tested for anti-HDV, and from these 103 (4,8%) tested anti-HDV positive; HDV RNA was tested in 92/103 (89%) patients and, finally, 28 patients (1.3% of all HBsAg positive, 30,5% of HDV-RNA tested) were identified as HDV-RNA positive. **Conclusion:** Our retrospective data indicated an infra-diagnosis of HDV in Southern Spain: only a fifth of HBsAg positive patients had been screened for anti-HDV through the years 2018 to early 2022. We show here that implementing double reflex HDV testing is feasible and results in a very important increase in the detection of patients with HDV chronic infection. We believe this implementation will facilitate finding the “missing” hepatitis delta patients.

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1230-C | IMPROVING ACCESS TO HDV TESTING USING DRY BLOOD SPOTS

Valerian Delagarde, Athenaïs Gerber, Samira Dziri, Dominique M Roulot, Emmanuel Gordien, Frederic Le Gal and Segolene Brichler, CHU Avicenne

Background: Hepatitis Delta Virus (HDV) is a small satellite virus infecting about 5% of HBV carriers that increases the risk of serious liver complications. New treatment options are now available but limited testing facilities in areas of high prevalence means most infections remain undiagnosed and patients receive suboptimal care. Developing local expertise is key but meanwhile tools such as Dry Blood Spots (DBS, *i.e.* filter paper used as a non-infectious transport and storage medium) can provide an easy and cheap way to link patients and testing facilities. This study aimed at defining new matrix specific thresholds for HDV virological tests on DBS. **Methods:** We conducted two complementary studies. Using our large collection, representative serum and plasma samples were put on DBS before being tested respectively for total anti-HDV antibodies (Diasorin Liaison XL) and for HDV viral load (VL, Abbott m2000/Eurobio EBX-004). Multiple storage conditions (2 weeks ambient, 2 weeks at -20°C and 5 weeks ambient) were tested, and two resuspension buffers were compared for RNA recovery. In parallel, other DBS were prospectively prepared using whole peripheral blood samples from patients attending our hepatology clinic, and the same analyses were performed. **Results:** The evaluation of the two resuspension solutions showed a slight advantage for PBS/0.01% NP40 (*vs* the Abbott m2000 lysis buffer) especially in samples with low VL. The finalized DBS protocol was set: 50µL of matrix/circle, dried for 2 hours and stored in opaque bags with desiccants. Each circle was resuspended in 500µL PBS/0.01% NP40 and agitated for 1 hour at room temperature. The serum arm had a 100% specificity and a good antibody titer correlation between paired serum/DBS for high positive samples. The reduced sensitivity noted for weak positive samples led to redefining the signal cut-off around 0.15 (to be adapted locally according to background noise). Similarly, plasma samples on DBS showed a 100% specificity and a good capacity in detecting and quantifying HDV RNA. However, sensitivity dropped to 50% for samples with low VL, 1000 IU/mL being the observed limit. The prospective whole peripheral blood study provided similar results. **Conclusion:** DBS can be useful for patient's management and epidemiological studies. Both serological and molecular testing showed high sensitivity and specificity when antibody titers and VL are high. A general reduction in signal means adapted cut-offs need to be used and specific care needs to apply for very early infections and patients under medication. Testing capillary blood on DBS will be critical to further develop this tool.

Disclosures: Dominique M Roulot – Gilead Sciences, Inc.: Speaking and Teaching, No, No;
Segolene Brichler – Eurobio Scientific: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, Yes;
The following people have nothing to disclose: Athenaïs Gerber, Emmanuel Gordien
Disclosure information not available at the time of publication: Valerian Delagarde, Samira Dziri, Frederic Le Gal

1231-C | INDEPENDENT ONLINE MEDICAL EDUCATION SIGNIFICANTLY IMPROVES PHYSICIAN KNOWLEDGE REGARDING THE BURDEN OF HEPATITIS DELTA VIRUS INFECTION AND BEST PRACTICE IN SCREENING AND DIAGNOSIS

Julia Duffey[1], Gillian Griffiths[1], Tatyana Kushner[2], Juan Mendive[3], Fabien Zoulim[4] and Maria Buti[5], (1)Webmd Global, (2)Icahn School of Medicine at Mount Sinai, New York, NY, (3)La Mina Primary Care Academic Centre Catalan Health Institute, (4)Hépatologie Unit, Hospices Civils De Lyon, Lyon University, Inserm, (5) Hospital Vall D'hebrón, and Ciberehd Del Instituto Carlos III, Barcelona, Spain

Background: Many patients infected with hepatitis delta virus (HDV), experience disease progression to cirrhosis and HCC more rapidly than mono-infected HBV patients.[1] Data regarding the burden and epidemiology of HDV are varied[2] due to the lack of screening of all patients with HBV. We assessed whether two online independent medical education activities could improve the knowledge and confidence of gastroenterologists regarding the burden of HDV and best practices in screening and diagnosis. **Methods:** For both activities the educational effect was assessed using a repeated-pairs design with pre-/post-assessment. Six multiple choice questions assessed knowledge, and two questions assessed confidence. Statistical tests to assess significance included: Paired samples t-test for overall average number of correct responses and confidence. McNemar's test for individual questions and learning objectives ($p < 0.05$). Cohen's d estimated the effect size impact on number of correct responses (< 0.20 modest, .20-.49 small, .59-.79 moderate, e .80 large). **Results:** From a total audience of 2450 gastroenterologists there were 317 assessment completers. Overall, there were significant knowledge gains ($p < 0.001$) for both educational activities. Specifically, there was a significant gain in knowledge regarding the prevalence of HDV in patients with HBV with a 289% relative change in the proportion of gastroenterologists answering the question correctly following education (pre 9%; post 35%; $p < 0.001$). Another notable gain in knowledge was reported for awareness of HDV screening guideline recommendations (relative change 104%; pre 27%; post 55%; $p < 0.001$). A significant increase in confidence was observed in gastroenterologist's ability to identify patients who should be screened for possible HDV infection with 51% increasing their confidence (confidence shift 113%; $p < 0.001$). **Conclusion:** With therapies for HDV either available or in late phase clinical trials it is important to understand the burden of HDV and best practice in screening and diagnosis so that more patients can benefit from treatment. Online medical education significantly improved gastroenterologist's knowledge and confidence regarding data on epidemiology, patient risk factors, diagnostic tests and screening guidelines recommendations. These findings highlight the importance of independent online medical education to facilitate best practice in screening and diagnosis to increase understanding of HDV epidemiology and reduce the disease burden.

Disclosures: Tatyana Kushner – Bausch: Consultant, No, Yes; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; AbbVie: Consultant, No, Yes; Eiger: Advisor, No, No;

Juan Mendive – Reckitt: Advisor, No, Yes;

Fabien Zoulim – Janssen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Beam Therapeutics: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Assembly Biosciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Assembly Biosciences, Inc.: Consultant, No, Yes; Aligos: Consultant, No, Yes; Gilead Sciences, Inc.: Consultant, Yes, No; GlaxoSmithKline: Consultant, No, No; Antios: Consultant, No, No;

Maria Buti – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, Yes; GSK: Advisor, Yes, No;

The following people have nothing to disclose: Julia Duffey, Gillian Griffiths

1232-C | IS LIVER DISEASE A RISK FACTOR FOR SARS-COV-2 INFECTION? INSIGHTS FROM A RETROSPECTIVE COHORT STUDY

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Background: Previous studies have already demonstrated the thrombogenic effect of inflammatory cascade in COVID-19 disease. Due to this and their fragility, patients with Chronic Liver Disease (CLD), were considered at increased risk of SARS-CoV-2 infection and developing a more severe COVID-19 disease than the general population. This study aims to evaluate if the prevalence of SARS-CoV-2 infection among CLD patients is higher than the general population, and to assess potential risk factors of SARS-CoV-2 infection and severe COVID-19 disease among CLD patients. **Methods:** A retrospective analysis was conducted on a cohort of 1000 patients with CLD of different etiology, attending the Hepatology outpatient clinics of the Molinette University Hospital of Turin, Italy, from August 2022 to April 2023. Demographic characteristics, anthropometric measurements, biochemical values, etiology and severity of liver disease, comorbidities, anti-SARS-CoV-2 vaccination and COVID-19 severity with related symptoms and therapy were analyzed by multivariate logistic and ordered logistic regression analyses. These parameters were compared with those of a population of subjects without liver disease living in Turin. **Results:** The mean age of the cohort was 61.7 (Standard deviation (SD) ± 13.3), 44.1% were females. Patients with CLD had a lower prevalence of infection than the general population of Piedmont (27.5% vs 43.8%). The results showed that vaccinated patients had a lower likelihood of getting SARS-CoV-2 (adjusted Odds Ratio (adjOR) 0.45, 95% Confidence Interval (CI) 0.31; 0.64) and of developing a severe disease (adjOR 0.28, 95% CI 0.15; 0.50). After adjusting for anti-SARS-CoV-2 vaccine status, patients with high-stage liver fibrosis or cirrhosis did not show a significant higher predisposition of SARS-CoV-2 infection or a symptomatic form, whereas hepatic steatosis was correlated with a higher probability of infection (adjOR 1.58, 95% CI 1.18; 2.13) and diabetes with a higher likelihood of severe disease (adjOR 4.55, 95% CI 1.77; 11.69). Conversely, the presence of ascites is a risk factor for SARS-CoV-2 infection (adjOR 2.59, 95% CI 1.09; 6.16). **Conclusion:** Unlike previous studies, this preliminary work suggests that, after adjusting for anti-SARS-CoV-2 vaccine status, liver cirrhosis is not associated with a higher risk of SARS-CoV-2 infection or the development of severe COVID-19 disease. Further studies are needed to validate the results and contribute to the comprehension of the potential linkage between COVID-19 and CLD.

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1233-C | LABORATORY-CONFIRMED HEPATITIS DELTA VIRUS PREVALENCE AND PATIENT CHARACTERISTICS AMONG COMMERCIALLY INSURED PATIENTS IN THE US

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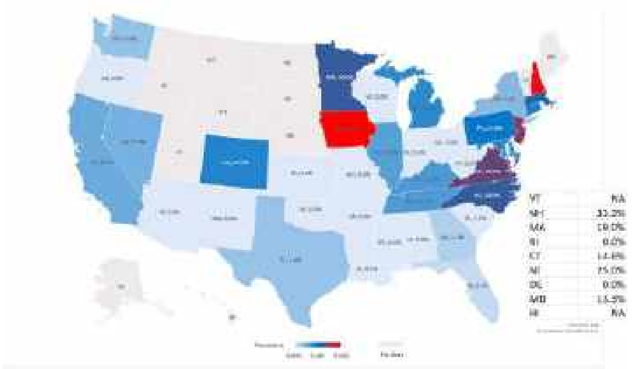
Background: Patients with hepatitis delta virus (HDV) infection have significantly increased risks of liver-related morbidity and mortality vs those with hepatitis B virus (HBV) monoinfection, yet data describing HDV epidemiology, particularly in the US, are limited. This study aims to evaluate the prevalence and incidence of laboratory-confirmed HDV infection among commercially insured adults with HBV in the US. **Methods:** Adults (e 18 y old) diagnosed with HBV infection (*ICD-9/10-CM*) or who had an HDV RNA test completed between Jan 1, 2015, and Dec 31, 2022 from the HealthVerity Database linked with Quest laboratory data were included. Overall, yearly, and state-level prevalence of lab-confirmed HDV infection, based on RNA test, were determined among all adults with HBV; incidence was calculated among patients who had HDV RNA− or anti-HDV− results prior to HDV RNA+ result. Annual prevalence was calculated based on the lifetime prevalence approach; adults with HDV RNA+ on or before the year of assessment were included. HDV RNA and anti-HDV test rates among HBV patients were reported. Baseline (12 mo pre-index) characteristics of laboratory-confirmed HDV or HBV only patients with at least 12 months pre- and post-index continuous enrollment were compared. **Results:** Among 1,217 commercially insured adults with lab-confirmed HBV infection between 2015–2022, 95 were HDV RNA+, corresponding to a prevalence of 7.8%; yearly prevalence ranged from 6.3%–11.3%. New lab-confirmed HDV infections accounted for 68 cases, an overall incidence of 5.7%; yearly incidence ranged from 0.5%–6.4%. When evaluated by state-level prevalence, the highest prevalence and incidence of HDV among patients with HBV was observed in New Hampshire and Iowa. Only 1.8% had RNA testing, while 11.3% had either RNA test or anti-HDV test among the HBV patients. Laboratory-confirmed adults with HDV and continuous enrollment (n = 15) were on average 44 years old; 47% were females, mean Charlson Comorbidity Index Score was 1.3, and 86.7% did not have any cirrhosis, hepatocellular carcinoma, or liver transplant during the baseline. **Conclusion:** Lab-confirmed HDV prevalence and incidence among US adults with HBV was 7.8% and 0.5% in 2022. Overall low rates of HDV testing among adults with HBV emphasize the need for increased efforts in screening, diagnosis, linkage to care, and timely treatment of HDV infection.

Figure. HDV Prevalence Among Adult HBV Patients With Commercial Insurance Between 2015–2022



HBV, hepatitis B virus; HDV, hepatitis delta virus.

Disclosures: Robert J. Wong – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Exact Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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Robert G. Gish – Abbott: Consultant, No, No; Abbvie: Speaking and Teaching, No, No; Altimmune: Consultant, No, No; Antios: Consultant, No, No; Arrowhead: Consultant, No, No; Dynavax: Consultant, No, No; Eiger: Advisor, No, No; Enyo: Consultant, No, No; Genentech: Consultant, No, No; Genlantis: Consultant, No, No; GLG: Consultant, No, No; Gilead Sciences: Consultant, Yes, No; Helios: Consultant, No, No; HepaTx: Advisor, No, No; HepQuant: Advisor, No, No; Intercept: Speaking and Teaching, No, No; Janssen: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Topography Health: Consultant, No, No; Venatorx: Consultant, No, No; Prodigy: Advisor, No, No; Eiger: Stock – privately held company (individual stocks and stock options), No, No; Ganlantis: Stock – privately held company (individual stocks and stock options), No, No; HepQuantum: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; Abbott: Consultant, No, No; Eisai: Consultant, No, No; Gilead Sciences: Consultant, No, No; CymaBay: Advisor, No, No; Durect: Advisor, No, No; AstraZeneca: Speaking and Teaching, No, No; BMS: Speaking and Teaching, No, No; Eisai: Speaking and Teaching, No, No; Hepquant: Stock – privately held company (individual stocks and stock options), No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

Ira M. Jacobson – AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Assembly Biosciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Eli Lilly: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Enanta: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Janssen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Novo Nordisk: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Aligos: Consultant, No, No; Arbutus: Consultant, No, No; Arrowhead: Consultant, No, No; Assembly Biosciences: Consultant, No, No; Galmed: Consultant, No, No; Gilead Sciences, Inc.: Consultant, No, No; GSK: Consultant, No, No; Intercept: Consultant, No, No; Janssen: Consultant, No, No; Merck: Consultant, No, No; Roche: Consultant, No, No; Takeda: Consultant, No, No; VBI Vaccines: Consultant, No, No;

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Joseph K. Lim:

Disclosure information not available at the time of publication: Gary Leung

1234-C | LIVER-RELATED COMPLICATIONS IN PATIENTS WITH HDV HIGHER THAN IN HBV MONO-INFECTED PATIENTS: A REGIONAL NYC BASED ASSESSMENT

Lauren Alpert[1], Xiaotao Zhang[1], Theresa Worthington[1], Marcia Lange[1] and Tatyana Kushner[2], (1)Icahn School *of Medicine at Mount Sinai, (2)Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Hepatitis delta virus (HDV) is the most severe form of viral hepatitis, as it is associated with the most rapid progression to cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Although New York City (NYC) has among the highest reported prevalence of HDV in the US, there is limited data on testing patterns, positivity rates, and disease outcomes in the NYC population. We evaluated the prevalence of liver-related health outcomes in NYC patients with HDV and HBV co-infection compared to patients with HBV mono-infection. **Methods:** This was a retrospective, longitudinal cohort study using data from the INSIGHT Clinical Research Network, a PCORNET database of approximately 19 million patients from 5 institutions across New York City. Individual's included in the study were identified based on a diagnosis code of HBV and/or HBsAg positive laboratory status. Among these patients, individual's with either a diagnosis code of HDV or positive HDV Ab and/or HDV RNA laboratory status were identified to indicate HDV co-infection. Multivariable logistic regression models were employed to evaluate adjusted OR of HDV infection on outcomes of cirrhosis, hepatocellular carcinoma, and liver transplantation. **Results:** We identified 36,494 patients with either laboratory evidence and/or diagnosis code evidence of HBV and 1637 patients with HDV. Patients with HDV were median age 50.2 (IQR:37.0, 62.0) at time of testing, 44% Asian, and 12% Hispanic ethnicity. Patient with HDV were more likely to have liver-related comorbidities including fatty liver (21.7% vs. 11.8%, $p < 0.0001$) and hepatitis C virus (HCV) (9.4% vs. 6.7%, $p < 0.0001$) (Table 1). Compared to patients mono-infected with HBV, patients co-infected with HDV had a higher prevalence of cirrhosis (23.5% vs. 5.6%, $p < 0.0001$), ascites (12.3% vs. 6.2%, $p < 0.0001$), and liver transplant (14.2% vs. 2.5%, $p < 0.0001$). In a multivariable regression analysis adjusted for age, gender, and liver-related comorbidity (i.e. fatty liver and HCV) co-infection with HDV was associated with cirrhosis (OR = 5.90, 95% CI: 5.00, 6.97), HCC (OR = 5.53, 95% CI: 4.49, 6.82) diagnoses, and liver transplant (OR = 7.47, 95%CI: 6.10, 9.15). **Conclusion:** In this diverse U.S. based cohort, ~5% of patients with HBV were co-infected with HDV. Patients with HDV were more likely to also have other liver-related comorbidities, including HCV and NAFLD. Patients co-infected with HDV had significantly increased risk of liver-related health outcomes, including cirrhosis, HCC, hepatic decompensation, and liver transplantation compared to those mono-infected with HBV. There is a clear need for HDV therapies in order to prevent progression of liver disease in patients with HDV.

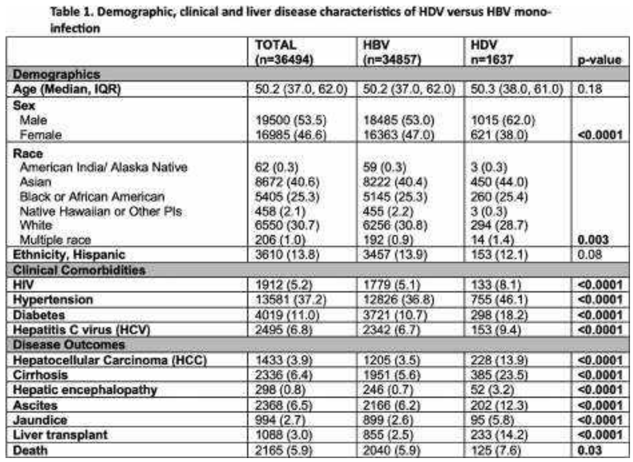

Table 1. Demographic, clinical and liver disease characteristics of HDV versus HBV mono-infection

	TOTAL (n=36494)	HBV (n=34857)	HDV n=1637	p-value
Demographics				
Age (Median, IQR)	50.2 (37.0, 62.0)	50.2 (37.0, 62.0)	50.3 (38.0, 61.0)	0.18
Sex				
Male	19500 (53.5)	18485 (53.0)	1015 (62.0)	
Female	16985 (46.6)	16363 (47.0)	621 (38.0)	**<0.0001**
Race				
American India/ Alaska Native	62 (0.3)	59 (0.3)	3 (0.3)	
Asian	8672 (40.6)	8222 (40.4)	450 (44.0)	
Black or African American	5405 (25.3)	5145 (25.3)	260 (25.4)	
Native Hawaiian or Other PIs	458 (2.1)	455 (2.2)	3 (0.3)	
White	6550 (30.7)	6256 (30.8)	294 (28.7)	
Multiple race	206 (1.0)	192 (0.9)	14 (1.4)	**0.003**
Ethnicity, Hispanic	3610 (13.8)	3457 (13.9)	153 (12.1)	0.08
Clinical Comorbidities				
HIV	1912 (5.2)	1779 (5.1)	133 (8.1)	**<0.0001**
Hypertension	13581 (37.2)	12826 (36.8)	755 (46.1)	**<0.0001**
Diabetes	4019 (11.0)	3721 (10.7)	298 (18.2)	**<0.0001**
Hepatitis C virus (HCV)	2495 (6.8)	2342 (6.7)	153 (9.4)	**<0.0001**
Disease Outcomes				
Hepatocellular Carcinoma (HCC)	1433 (3.9)	1205 (3.5)	228 (13.9)	**<0.0001**
Cirrhosis	2336 (6.4)	1951 (5.6)	385 (23.5)	**<0.0001**
Hepatic encephalopathy	298 (0.8)	246 (0.7)	52 (3.2)	**<0.0001**
Ascites	2368 (6.5)	2166 (6.2)	202 (12.3)	**<0.0001**
Jaundice	994 (2.7)	899 (2.6)	95 (5.8)	**<0.0001**
Liver transplant	1088 (3.0)	855 (2.5)	233 (14.2)	**<0.0001**
Death	2165 (5.9)	2040 (5.9)	125 (7.6)	**0.03**

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The following people have nothing to disclose: Lauren Alpert, Theresa Worthington

Disclosure information not available at the time of publication: Xiaotao Zhang, Marcia Lange

f 1235-C | LOWER INCIDENCE OF HCC AND OTHER MAJOR ADVERSE LIVER OUTCOMES IN PEOPLE LIVING WITH HIV AND CHRONIC LIVER DISEASE: A POPULATION-BASED COHORT STUDY

Maurice Michel[1,2], Hannes Hagström[3,4], Linnea Widman[3], Piotr Nowak[3,5], Ying Shang[3], Jorn Schattenberg[2,6] and Axel Wester[3], (1)University of Mainz, (2)I. Department of Medicine, University Medical Centre Mainz, Germany, (3)Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden, (4) Unit of Hepatology, Department of Upper GI Diseases, Karolinska University Hospital, Stockholm, Sweden, (5) Unit of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden, (6)Metabolic Liver Research Program, I. Department of Medicine, University Medical Centre Mainz, Germany

Background: Chronic liver disease (CLD), including non-alcoholic fatty liver disease (NAFLD) and viral hepatitis, is common in people living with HIV (PLWH). However, there are limited data on whether HIV is associated with a different risk of major adverse liver outcomes (MALO) in patients with CLD. Therefore, the aim of this study was to examine the association

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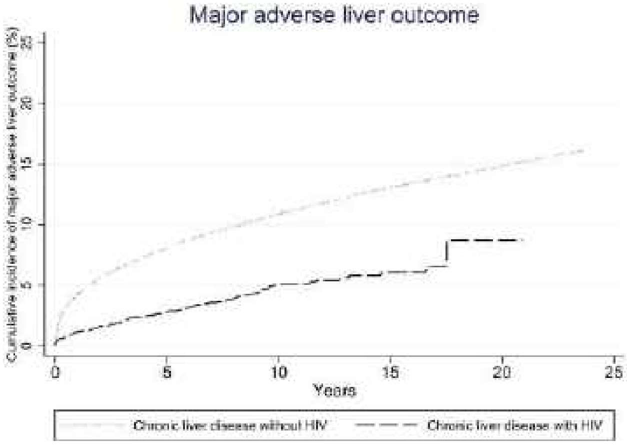
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

between HIV and MALO in patients with CLD. **Methods:** In this nationwide population-based cohort study, data were retrieved from the Swedish National Patient Register based on ICD-codes from patients with CLD and HIV (n = 2,375) or CLD without HIV (n = 144,346) between 1997 and 2020. MALO were defined according to the following diagnoses: ascites, bleeding varices, hepatorenal syndrome, portal hypertension, hepatocellular carcinoma (HCC), or liver transplantation. The cumulative incidence at 10 years follow-up was calculated while accounting for competing risks (non-MALO death). Incidence rates per 1000 person-years were compared between the exposure groups (HIV vs. no HIV) with Cox regression to estimate adjusted hazard ratios (aHR) and their 95% confidence intervals (CIs). Adjustments were made for age, sex, inclusion year, education, country of birth, cirrhosis, liver disease etiology, COPD, cancer, and metabolic comorbidities. **Results:** The majority of individual's in both groups were male, and the median age at baseline was lower in PLWH compared to HIV-negative individual's (41 y vs. 49 y). In both groups, the main etiology of CLD was viral hepatitis (PLWH: 91.7% vs. no HIV: 50.5%) followed by alcohol-related liver disease and NAFLD. At baseline, the prevalence of liver cirrhosis was lower in PLWH (2.9% vs. no HIV: 14.9%). The cumulative incidence of MALO:s at 10 years follow-up was lower in PLWH (5.0%, 95% CI 4.1-6.1 vs. 10.9%, 95% CI 10.7-11.0) (Figure). The incidence rate of MALO:s was significantly lower in PLWH (5.1, 95% CI 4.2-6.1) in comparison to those without HIV (13.1, 95% CI 12.9-13.3; aHR: 0.77, 95% CI 0.64-0.93). The incidence of the individual components of MALO were consistently lower in PLWH, with a significantly lower incidence of HCC in PLWH (1.5, 95% CI 1.1-2.1) than without HIV (3.4, 95% CI 3.3-3.5; aHR: 0.61, 95% CI: 0.43-0.86). **Conclusion:** The incidence of MALO was lower in PLWH and CLD, primarily due to a lower rate of HCC. These results may indicate that the close surveillance and improved treatment options of PLWH and CLD have affected liver-related outcomes.



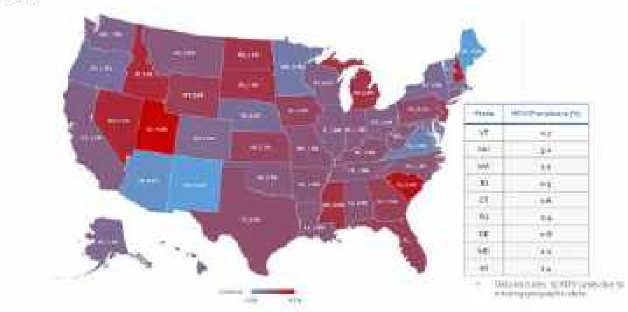
Disclosures: The following people have nothing to disclose: Maurice Michel, Hannes Hagström, Linnea Widman, Piotr Nowak, Ying Shang, Jorn Schattenberg, Axel Wester

1236-C | NATIONAL AND REGIONAL PREVALENCE OF HEPATITIS DELTA VIRUS AMONG COMMERCIALLY INSURED PATIENTS IN THE US

Robert J. Wong[1,2], Robert G. Gish[3], Ira M. Jacobson[4], Joseph K. Lim[5], Chong Hoon Kim[6] and Marvin Rock[6], (1)VA Palo Alto Healthcare System, (2)Stanford University School of Medicine, (3)Hepatitis B Foundation, La Jolla, CA, (4)NYU Grossman School of Medicine, (5)Yale School of Medicine, New Haven, CT, (6)Gilead Sciences, Inc.

Background: Patients with hepatitis delta virus (HDV) infection have increased risk of liver-related morbidity and mortality vs those with hepatitis B virus (HBV) monoinfection, yet data describing HDV epidemiology, particularly in the US, are sparse. This study aims to evaluate national and regional prevalence and incidence of HDV infection among commercially insured adults in the US. **Methods:** Adults (e 18 y old) diagnosed with HBV or HDV infection (*ICD-9/10-CM*) between Jan 1, 2014, and Dec 31, 2021, with continuous enrollment for e 12 months before and after first diagnosis and e 1 inpatient claim or e 2 outpatient claims, each e 30 days apart, were identified from the PharMetrics Database. Yearly and state-level prevalence of HDV infection were determined among (1) all commercially insured adults (Total) and (2) all adults with HBV; incidence was calculated among adults with no HDV infection diagnoses prior to the date of their first HDV claim. Annual prevalence was calculated based on the lifetime prevalence approach; adults diagnosed on or before the year of assessment were included. Comparisons between HDV and HBV cohorts used Mann-Whitney U tests for continuous and chi-square tests for categorical variables. **Results:** Among 74,937 commercially insured adults with HBV infection between 2015–2020, 1,422 had concurrent HDV infection identified, translating into a prevalence of 1.9%; the HDV prevalence among all commercially insured adults was 18.7 per million. Yearly HDV prevalence among patients with HBV ranged from 1.3%–1.9%. Newly diagnosed HDV infections among HBV patients accounted for 1,312 cases, with an overall incidence of 1.8%; the HDV incidence among all commercially insured adults was 17.3 per million. Yearly HDV incidence among HBV patients ranged between 0.2%–0.6%. The highest prevalence of HDV among adults with HBV was observed in Utah (4.1%), followed by New Hampshire (3.7%) and South Carolina (3.6%). Incidence was highest in Utah (4.1%), South Carolina (3.6%), and New Hampshire (3.2%). **Conclusion:** In a nationally representative US commercial claims database, the HDV prevalence among adults with HBV was 1.9%, and the prevalence of HDV among all commercially insured adults was 18.7 per million from 2015 to 2020. We observed significant regional differences in HDV prevalence, which was highest in Utah. Better describing HDV epidemiology will help guide healthcare resource planning and health policy as it relates to screening, diagnosis, and management of HDV.

Figure. HDV Incidence Among Adult HBV Patients With Commercial Insurance Between 2015–2020



HBV, hepatitis B virus; HDV, hepatitis delta virus.

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Robert G. Gish – Abbott: Consultant, No, No; Abbvie: Speaking and Teaching, No, No; Altimmune: Consultant, No, No; Antios: Consultant, No, No; Arrowhead: Consultant, No, No; Dynavax: Consultant, No, No; Eiger: Advisor, No, No; Enyo: Consultant, No, No; Genentech: Consultant, No, No; Genlantis: Consultant, No, No; GLG: Consultant, No, No; Gilead Sciences: Consultant, Yes, No; Helios: Consultant, No, No; HepaTx: Advisor, No, No; HepQuant: Advisor, No, No; Intercept: Speaking and Teaching, No, No; Janssen: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Topography Health: Consultant, No, No; Venatorx: Consultant, No, No; Prodigy: Advisor, No, No; Eiger: Stock – privately held company (individual stocks and stock options), No, No; Ganlantis: Stock – privately held company (individual stocks and stock options), No, No; HepQuantum: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; Abbott: Consultant, No, No; Eisai: Consultant, No, No; Gilead Sciences: Consultant, No, No; CymaBay: Advisor, No, No; Durect: Advisor, No, No; AstraZeneca: Speaking and Teaching, No, No; BMS: Speaking and Teaching, No, No; Eisai: Speaking and Teaching, No, No; Hepquant: Stock – privately held company (individual stocks and stock options), No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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Chong Hoon Kim – Gilead Sciences, Inc.: Employee, No, No;

Marvin Rock – Gilead Sciences, Inc.: Employee, No, No;

Joseph K. Lim:

1237-C | NO DETECTABLE RESISTANCE TO BULEVIRTIDE MONOTHERAPY THROUGH 96 WEEKS TREATMENT IN PATIENTS WITH CHRONIC HEPATITIS D

Soo Aleman[1], Yang Liu[2], Simin Xu[2], Silvia Chang[2], Ross Martin[2], Thomas Aeschbacher[2], Lindsey May[2], Savrina Manhas[2], Dong Han[2], Tahmineh Yazdi[2], Clarissa Martinez[2], Pui Yan Ho[2], Christopher Richards[2], Caleb Marceau[2], Dmitry Manuilov[2], John F. Flaherty[2], Evguenia Maiorova[2], Hongmei Mo[2], Heiner Wedemeyer[3] and Pietro Lampertico[4], (1)Karolinska University Hospital/Karolinska Institutet, Department of Infectious Diseases, (2)Gilead Sciences, Inc., (3) Hannover Medical School, (4)CRC "a. M. and a. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan

Background: Bulevirtide (BLV) is a novel entry inhibitor that binds to the HDV entry receptor, sodium taurocholate cotransporting polypeptide (NTCP). Virologic resistance analyses at Week (WK) 24 and WK48 show no resistance to BLV in MYR301 (NCT03852719), an ongoing Phase 3 study in patients with chronic hepatitis D (CHD). Here, we describe the WK96 resistance analyses of this study. **Methods:** In this study, 49 and 50 participants with CHD were randomized to receive BLV 2 mg or 10 mg given subcutaneously once daily for 96 weeks, respectively, as monotherapy. Results for the delayed treatment for 48 weeks followed by BLV 10 mg/day for 48 weeks group are not included herein. Deep sequencing of the BLV-corresponding region in HBV preS1 and HDV antigen (HDAg), and phenotypic analysis using a primary human hepatocyte based in vitro infection inhibition assay were attempted for virologic non-responders (NR; HDV RNA decrease < 1 log$_{10}$ IU/mL from baseline [BL] at WK96) and for participants with virologic breakthrough (VB; a e 2 log$_{10}$ IU/mL decrease in HDV RNA from BL for e 2 consecutive visits followed by a e 2 log$_{10}$ increase from nadir for e 2 consecutive visits; or e 2 consecutive HDV RNA e LLOQ if previously < LLOQ for e 2 consecutive visits). Virologic responder (VR) was defined as an undetectable HDV RNA or a decline in HDV RNA e 2 log$_{10}$ IU/mL from BL at WK96, and virologic partial responder (PR) was defined as a e 1 but < 2 log$_{10}$ IU/mL in HDV RNA from BL at WK96. **Results:** At WK96, of the 10 NRs that were observed at WK48, 1 became VR and achieved undetectable HDV RNA, 3 became PRs, and the remaining 6 NRs remained NRs. At WK96, there were 8 VBs, including 1 VB at WK48. In total, 14 of 99 (14%; BLV 2 mg, n = 10; BLV 10 mg, n = 4) participants qualified for resistance analysis at WK96, 6 of which were NRs and 8 which were VBs. By deep sequencing, no identical amino acid changes were identified in the BLV-corresponding region or HDAg from BL through WK96 in NRs/VBs. By phenotypic analysis, no change in sensitivity to BLV was observed in WK96 isolates versus BL isolates. Variants in the BLV-corresponding region and HDAg detected at BL were similarly present in NRs/VBs and VRs, and all remained susceptible to BLV in vitro. The BLV EC$_{50}$ values from 116 BL samples in this study were similar across NRs/VBs, PRs, and VRs. **Conclusion:** There was no genotypic or phenotypic resistance to BLV monotherapy through 96 weeks of treatment.

Disclosures: Soo Aleman – Gilead Sciences, Inc.: Speaking and Teaching, Yes, No; Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; AbbVie: Speaking and Teaching, No, No; AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; MSD and Biogen: Speaking and Teaching, No, No;

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1238-C | NON-INVASIVE FIBROSIS MARKERS FOR ASSESMENT OF LIVER FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS DELTA

Emin Bodakci, Muhammed Fatih Karakaya, Digdem Kuru Oz, Dilara Turan Gokce, Serkan Duman, Zeynep Melekoglu Ellik, Mesut Gumussoy, Sevinc Tugce Guvenir, Volkan Yılmaz, Ramazan Erdem Er, Hale Gökcan, Ayse Erden and Ramazan Idilman, Ankara University, Ankara, Turkey

Background: Non-invasive biochemical-based biomarkers and imaging methods are widely used to assess liver fibrosis in routine clinical practice. The accuracy of blood-based tests varies according to the underlying etiology of chronic liver disease. Magnetic resonance elastography (MRE) is significantly more accurate in assessing hepatic fibrosis in patients with chronic liver disease than other non-invasive techniques. However, data on patients with chronic delta hepatitis (CDH) are scarce. The aims of the present study were to evaluate the accuracy of MRE, vibration-controlled transient elastography (VCTE), and fibrosis-4 (FIB-4) in the assessment of liver fibrosis in patients with CDH. **Methods:** Between September 10, 2019 and March 9, 2023, 42 consecutive patients with CDH were included in the study. MRE, FIB-4, and TE were performed for liver stiffness measurements. **Results:** All 42 patients were Caucasian, their mean age was 51.8 ± 11.1 years, and their gender was predominantly female (60%). Among the patients, 52.4% of the patients were compensated, and 3 of them were decompensated. Median Child-Pugh and MELD scores were 5.0 and 6.5, respectively. The mean FIB-4 and APRI scores were 3.32 ± 2.92 and 1.15 ± 1.32, respectively. FIB-4 and APRI were calculated on the day when MRE was performed. The median liver stiffness values of VCTE and mean MRE were 10.95 kPa, (IQR: 5.20 - 15.7 kPa) and 3.98 ± 1.51 kPa, respectively. A significant positive correlation was found between MRE and VCTE ($r_s = 0.617$, $p < 0.001$). There was also a significant positive correlation between FIB-4 and the APRI ($r = 0.713$, $p < 0.001$). However, a moderate correlation existed between MRE and the FIB-4 ($r = 0.376$, $p = 0.014$) and between MRE and the APRI ($r = 0342$, $p = 0.026$). MRE and VCTE demonstrated a significant accuracy in the detection of clinical cirrhosis with an area under the ROC curve (AUC) of 0.855 (95% confident interval [CI]: 0.733 - 0.976, $p < 0.001$) and 0.841 (95%CI: 0.723 - 0.959, $p < 0.001$), respectively. **Conclusion:** In conclusion, MRE and TE accurately determine clinical cirrhosis in patients with CDH. These imaging methods can eliminate or reduce the number of liver biopsies for liver fibrosis assessments in such patients.

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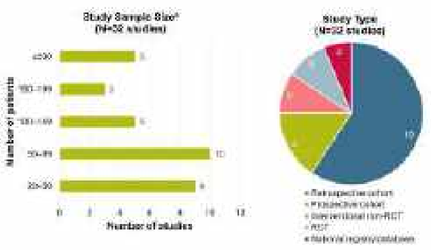
1239-C | OCCURRENCE OF LIVER-RELATED EVENTS IN INDIVIDUALS WITH HEPATITIS DELTA VIRUS: A SYSTEMATIC LITERATURE REVIEW

Laura E. Telep[1], Dominique M Roulot[2,3], Amanda W. Singer[1], Alice Stead[1], Ben L. Da[1], Grace Chee[1], Emily Kaiser[4], Max Lee[4], Patrick S. Reilly[4], Anand P. Chokkalingam[1] and Ira M. Jacobson[5], (1)Gilead Sciences, Inc., (2)Unité D'hépatologie, Assistance Publique-Hôpitaux De Paris, Hôpital Avicenne, (3) Université Paris-Est, U955, Inserm, (4)Costello Medical, (5)NYU Grossman School of Medicine

Background: Hepatitis delta virus (HDV) results in the most severe form of viral hepatitis and is associated with high risk of liver-related complications and mortality. We conducted a systematic literature review (SLR) to identify studies for a meta-analysis analyzing the incidence of liver-related events among patients with HDV infection. **Methods:** We searched online databases (MEDLINE, Embase, the Cochrane Library, and the University of York Center for Reviews and Dissemination) from Jan 1, 2000, to Dec 14, 2022, and relevant congress proceedings from 2021 and 2022. Bibliographies of identified SLRs and meta-analyses were also searched. Randomized controlled trials (RCTs), interventional non-RCTs, and observational studies reporting incidence of cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), liver transplant (LT), and liver-related death in ≥ 20 patients (≥ 18 y of age) with HDV infection (positive HDV RNA or ≥ 2 positive anti-HDV tests ≥ 6 mo apart) were included. Quality of included studies was assessed using the JBI Prevalence Checklist. Study and patient characteristics, cumulative incidence, and incidence rates were extracted. **Results:** From 2,227 records identified, 47 publications reporting on 37 studies were included; from these studies, 32 unique data sets were extracted. The 47 publications were published between 2004 and 2022, and 57% (n = 27) were published from 2019 to 2022. While most (n = 19; 59%) of the 32 studies included < 100 patients, 5 included ≥ 200 (Figure). The majority of studies were retrospective cohort studies (n = 19; 59%), and the remaining were prospective cohort (n = 5; 16%), interventional non-RCT (n = 3; 9%), RCT (n = 3; 9%), and registry/database studies (n = 2; 6%). The most commonly reported outcomes were hepatic decompensation (n = 21 studies) and HCC (n = 20 studies). LT was reported in 15 studies, liver-related death in 13, and cirrhosis in 9. Consistent with variable follow-up times across studies (12 weeks–13 y), a wide range of cumulative incidence values were observed (cirrhosis, 15.6%–51.9%; decompensation, 0.0%–50.4%; HCC, 0.0%–16.3%; LT, 0.8%–26.9%; liver-related death, 0.0%–22.2%); only 2 studies reported incidence rates. **Conclusion:** The number of studies describing the natural history of HDV infection has grown in recent years but remains limited. Quantifying the incidence of liver-related events can improve our understanding of disease progression and inform interventions and treatment strategies to reduce the burden of HDV infection.

Figure: Characteristics of studies included in the SLR



*The number of patients with HDV included in the study, regardless of whether they met the definition of HDV infection used for this SLR

HDV, hepatitis delta virus; RCT, randomized controlled trial; SLR, systematic literature review

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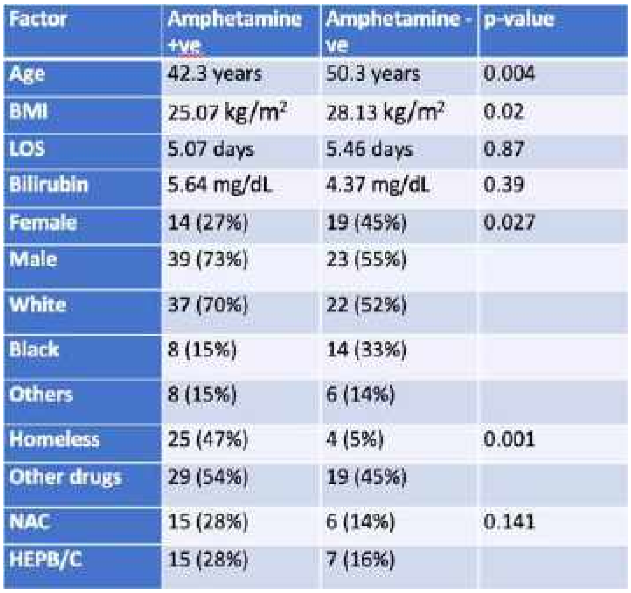
1240-C | PATTERN OF LIVER INJURY IN METHAMPHETAMINE USERS IN ACUTE HEPATITIS A AND UTILITY OF N-ACETYLECYSTEINE FOR TREATMENT

Ifrah Fatima[1], Vinay Jahagirdar[1], Noor Hassan[2], Islam Mohamed[1], Mohamed Ahmed[1], Jagadish Koyi[1], Jennifer Von Ende[1], Fouad Jaber[1], Kimberly Sanders[1] and Hassan Ghoz[1,3], (1)University of Missouri- Kansas City, (2)University of Missouri- Kansas City, Kansas City, MO, (3)University Health- Truman Medical Center

Background: Hepatitis A virus (HAV) is known to spread through the fecal-oral route from contaminated food, water, and person-to-person contact. The incidence of hepatitis A in the US has increased over the last decade, with the highest increase from 2017-2019. The total cases in Missouri were 1116 with 649 (58%) hospitalizations, during an outbreak from 09/01/2017 to 11/30/2022. Previous epidemiological studies from California, Kentucky, Michigan, and Utah have shown an association between Hepatitis A and drug use and homelessness. We aimed to identify the prevalence of drug use and its effect on outcomes in the Hepatitis A outbreak at our safety-net hospital. **Methods:** This a single-center retrospective study. Adult patients e 18 years with positive Hepatitis A IgM antibody were identified between March 2012-Feb 2022. Patients were classified into amphetamine-positive and negative groups. Patients with cirrhosis and hepatboiliary obstruction were excluded. Variables including age, total bilirubin, methamphetamine use, route of drug use, N-acetylcysteine use, length of stay, and mortality were identified. Chi-square and Fisher exact tests were used to compare categorical variables, and t-test for continuous variables. Multivariable logistic regression analysis was performed using Stata/SE 16.1. A two-tailed p value < 0.05 was considered statistically significant. **Results:** A total of 95 patients with acute Hepatitis A were identified. 55% (53) were found to have amphetamine use either by UDS or documented history. Among the amphetamine users, 73% were male and 70% were white. 54% (29) had concomitant use of other drugs and 28% (15) had an additional diagnosis of Hepatitis B or C. NAC was given to 28% (15) in the amphetamine users group vs 14%(6) in the non-users. Mean age (42.3 vs 50.3 years; $p = 0.01$) and BMI (25 vs 28; $p = 0.02$) were lower in the amphetamine positive group. Homelessness was higher and significant in the drug use group. (47% vs 5%; $p = 0.01$). The mean total bilirubin was comparable in the amphetamine-use group and non-users. (5.64 vs 4.37 g/dL; $p = 0.39$). On multivariate logistic regression, neither drug use ($p = 0.129$) nor use of NAC ($p = 0.9$) were significantly associated with length of stay or mortality. **Conclusion:** There is an increased prevalence of hepatitis A and

amphetamine use. Homelessness was significantly higher in the drug use group. The pattern of liver injury was similar and comparable in the two groups. Amphetamine use and treatment with NAC in acute hepatitis A did not significantly impact the length of stay or mortality. Future vaccination efforts towards these high-risk groups is needed.



Factor	Amphetamine +ve	Amphetamine -ve	p-value
Age	42.3 years	50.3 years	0.004
BMI	25.07 kg/m²	28.13 kg/m²	0.02
LOS	5.07 days	5.46 days	0.87
Bilirubin	5.64 mg/dL	4.37 mg/dL	0.39
Female	14 (27%)	19 (45%)	0.027
Male	39 (73%)	23 (55%)	
White	37 (70%)	22 (52%)	
Black	8 (15%)	14 (33%)	
Others	8 (15%)	6 (14%)	
Homeless	25 (47%)	4 (5%)	0.001
Other drugs	29 (54%)	19 (45%)	
NAC	15 (28%)	6 (14%)	0.141
HEPB/C	15 (28%)	7 (16%)	

Disclosures: The following people have nothing to disclose: Ifrah Fatima, Vinay Jahagirdar, Noor Hassan, Islam Mohamed, Mohamed Ahmed, Jagadish Koyi, Jennifer Von Ende, Fouad Jaber, Kimberly Sanders, Hassan Ghoz

1241-C | PREVALENCE CLINICAL CHARACTERISTICS OF HEPATITIS DELTA VIRUS (HDV) INFECTED INDIVIDUALS IN BRITISH COLUMBIA

Valeriya Oleksandrivna Zaborska, Ubc, Alnoor Ramji, Division of Gastroenterology, University of British Columbia, BC, Canada, Edward V. Tam, Pacific Gastroenterology Associates, Vancouver, BC, Canada and Hin Hin Ko, University of British Columbia

Background: Globally, HDV is reported in 4.5-13% of chronic hepatitis B (CHB) patients. HDV and HBV co-infection is associated with progression to cirrhosis and higher risk of hepatocellular carcinoma (HCC). HDV prevalence in Canada is not fully elucidated. The purpose of the study was to describe the prevalence and clinical characteristics of HDV infection in CHB patients in a tertiary care centre. **Methods:** Retrospective study of HBsAg-positive patients > 18 years of age tested for HDV Ab between April 2013 and October 2022. Data collected included HDV Ab status, patient demographics, comorbidities, alcohol use, fibrosis stage, and therapies utilized. **Results:** Among 663 HBsAg-positive patients tested for HDV Ab,10/663 (1.5%, 95% CI 0.58-2.44) wereHDV-Ab (+), with 8/10 (80%, 95% CI 0.55-1.05) of those confirmed HDV RNA (+). Average age of HDV patients was 57.8 (95% CI 52.7-62.9) years, similar to HBV patients. Compared to HBV mono-infected patients, HBV-HDV co-infected patients were more likely to be male (90.0% vs 57.6%; $p = 0.04$), have decompensated liver disease (30.0% vs 1.4%; $p < 0.0001$) and less likely to be Asian (50.0% vs 80.9%; $p = 0.014$). One HBV-HDV co-infected patient was also HIV/HCV co-infected, and two had cleared HCV. One HDV patient had a known history of IVDU (10%, 95% CI 0.09 – 0.28). Mean ALT in HDV patients was 55.9, vs. 34.3 in HBV mono group ($p = 0.0508$). 50% of HDV patients consumed any lifetime alcohol compared to 31.9% of HBV mono-infected patients ($p = 0.22$). HDV patients were more likely to have liver stiffness measurements > 9.0 kPa 30% vs 8.9%, $p = 0.02$), and equally likely to have HCC 10% vs 2.5% ($p = 0.13$). **Conclusion:** The prevalence of HDV positivity in CHB patients in this tertiary care centre was 1.5%. Persons with HDV were more likely to be male, and have decompensated liver disease and less likely to be Asian than those with HBV mono-infection. Further studies to understand the burden of disease in other regions are needed.

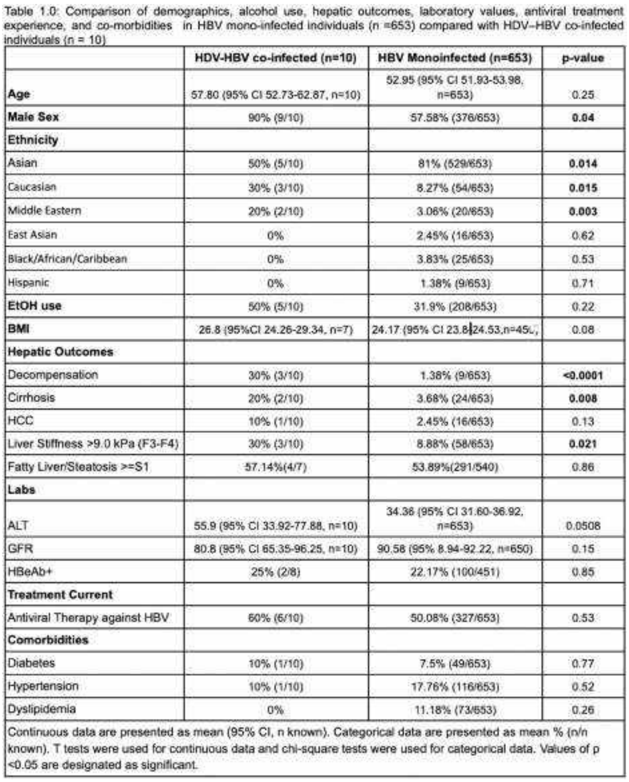


Table 1.0: Comparison of demographics, alcohol use, hepatic outcomes, laboratory values, antiviral treatment experience, and co-morbidities in HBV mono-infected individuals (n =653) compared with HDV–HBV co-infected individuals (n = 10)

	HDV-HBV co-infected (n=10)	HBV Monoinfected (n=653)	p-value
Age	57.80 (95% CI 52.73-62.87, n=10)	52.95 (95% CI 51.93-53.98, n=653)	0.25
Male Sex	90% (9/10)	57.58% (376/653)	**0.04**
Ethnicity			
Asian	50% (5/10)	81% (529/653)	**0.014**
Caucasian	30% (3/10)	8.27% (54/653)	**0.015**
Middle Eastern	20% (2/10)	3.06% (20/653)	**0.003**
East Asian	0%	2.45% (16/653)	0.62
Black/African/Caribbean	0%	3.83% (25/653)	0.53
Hispanic	0%	1.38% (9/653)	0.71
EtOH use	50% (5/10)	31.9% (208/653)	0.22
BMI	26.8 (95%CI 24.26-29.34, n=7)	24.17 (95% CI 23.8|24.53,n=45	0.08
Hepatic Outcomes			
Decompensation	30% (3/10)	1.38% (9/653)	**<0.0001**
Cirrhosis	20% (2/10)	3.68% (24/653)	**0.008**
HCC	10% (1/10)	2.45% (16/653)	0.13
Liver Stiffness >9.0 kPa (F3-F4)	30% (3/10)	8.88% (58/653)	**0.021**
Fatty Liver/Steatosis >=S1	57.14%(4/7)	53.89%(291/540)	0.86
Labs			
ALT	55.9 (95% CI 33.92-77.88, n=10)	34.36 (95% CI 31.60-36.92, n=653)	0.0508
GFR	80.8 (95% CI 65.35-96.25, n=10)	90.58 (95% 8.94-92.22, n=650)	0.15
HBeAb+	25% (2/8)	22.17% (100/451)	0.85
Treatment Current			
Antiviral Therapy against HBV	60% (6/10)	50.08% (327/653)	0.53
Comorbidities			
Diabetes	10% (1/10)	7.5% (49/653)	0.77
Hypertension	10% (1/10)	17.76% (116/653)	0.52
Dyslipidemia	0%	11.18% (73/653)	0.26

Continuous data are presented as mean (95% CI, n known). Categorical data are presented as mean % (n/n known). T tests were used for continuous data and chi-square tests were used for categorical data. Values of p <0.05 are designated as significant.

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1242-C | RECENT INCREASE IN HEPATITIS CASES (ACUTE HEPATITIS OF UNKNOWN ORIGIN IN CHILDREN/HEPATITIS A/OTHER FOOD BORNE HEPATITIS) WORLDWIDE: A POSSIBLE COVID19 LINKAGE

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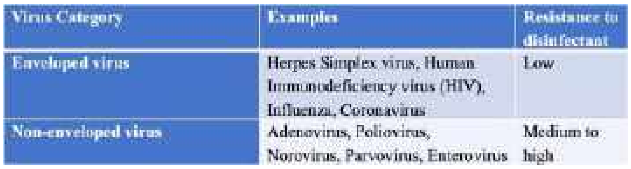
Background: In 2022, cases of acute hepatitis of unknown origin in children under 16 years, which are not associated with hepatitis viruses A-E, remained a cause for global concern and alarmed public health agencies. While the aetiology of these severe hepatitis cases is still under investigation, the leading hypothesis points to infection with a common adenovirus which was detected in 75% of confirmed cases with symptoms like abdominal pain, diarrhea and vomiting preceding severe acute hepatitis. In recent years, there has been also increase in enteric hepatitis infections in adults due to food borne viruses including hepatitis A virus, which led to serious public health problems worldwide. **Methods:** Concurrent and preceding to these reports, the emergence of novel SARS CoV2 virus led COVID 19 illness, a global pandemic as declared by World Health Organization (WHO) in early 2020, is accompanied by repeated and exuberant use of soap and alcohol-based sanitizers worldwide for cleaning the hands to curtail the virus transmission. Alcohol-based sanitizing agents considered as potent virucidal agents against enveloped viruses such as Hepatitis B virus, Herpes virus, SARS-CoV, and human immunodeficiency virus, whereas non-enveloped viruses like Adenovirus, Hepatitis A virus, Poliovirus and Norovirus exhibited medium to high level of resistivity against these disinfectants. Also, human innate cutaneous defense system i.e., RNases, an important barrier to prevent the entry of exogenous RNAs, may be compromised with these sanitizers and still be transmitting resilient non-enveloped enteric viruses such as adeno, hepatitis A virus and norovirus into the body. The children probably will be more prone for getting enteric viral infections because of typical playing/feeding habit and subsequent overreliance on alcohol-based sanitizers for cleaning the hands. **Results:** The possible linkage between COVID19 pandemic and emergence of frequent hepatitis A and acute hepatitis of unidentified etiology in children seems to be increased enteric viral infections in the wake of overuse and reliance on alcohol-based hand sanitizers which are considered less effective against non-enveloped viruses. **Conclusion:** In author's opinion, as SARS CoV2 infection is realized as an airborne infection, the unwarranted emphasis on alcohol-based sanitizers should now be guarded.



Virus Category	Examples	Resistance to disinfectant
Enveloped virus	Herpes Simplex virus, Human Immunodeficiency virus (HIV), Influenza, Coronavirus	Low
Non-enveloped virus	Adenovirus, Poliovirus, Norovirus, Parvovirus, Enterovirus	Medium to high

Disclosures: The following people have nothing to disclose: Arvind Tomar, Nishul Rani

1243-C | RECENT PREVALENCE AND CHARACTERISTICS OF PATIENTS WITH HEPATITIS DELTA VIRUS IN HOKKAIDO, JAPAN

Takashi Sasaki[1], Takashi Kitagataya[2], Masatsugu Ohara[1], Masato Nakai[3], Takuya Sho[1], Koji Ogawa[1], Goki Suda[1] and Naoya Sakamoto[1], (1)Hokkaido University Hospital, (2)Mayo Clinic, (3)Hokkaido University Hospital, Sapporo, Japan

Background: Approximately 300 million individual's worldwide carry the hepatitis B virus (HBV) infection, which remains a major cause of liver cirrhosis (LC) and hepatocellular carcinoma (HCC). Annually, 800,000 individual's die of HBV infection. Hepatitis delta virus (HDV) is an incomplete RNA virus that requires co-infection with HBV to replicate. Although HDV co-infection with HBV is a global health concern, the global prevalence of HDV infections remains unknown due to insufficient data in many countries. In Japan, HDV prevalence has not been updated for over 20 years. We aimed to investigate the recent prevalence of HDV infections in Japan. **Methods:** We screened 1,264 consecutive patients with HBV infection at the Hokkaido University Hospital between 2006 and 2022. Patients' serums were preserved and subsequently tested for HDV-antibody (immunoglobulin-G). Available clinical information was collected and analyzed. We compared the changes in liver fibrosis using the fibrosis-4 (FIB-4) index between propensity-matched patients with and without the evidence of anti-HDV antibodies and corrected for baseline FIB-4 index, nucleos(t)ide-analog administration, alcohol intake, sex, and age. **Results:** After excluding patients without properly stored serums and those lacking appropriate clinical information, 601 patients with HBV were included. Of these, 1.7% of patients had detectable anti-HDV antibodies. Patients with anti–HDV antibody serum positivity had a significantly higher prevalence of liver cirrhosis, significantly lower PT%, and a higher prevalence of human-immunodeficiency-virus co-infection than those who demonstrated serum anti-HDV antibody negativity. A propensity-matched longitudinal analysis revealed that liver fibrosis (FIB-4 index) progressed more rapidly in patients with positive results for anti–HDV antibody tests. Changes in FIB-4 index/year in patients tested positive for anti-HDV antibodies were more significant than in those with negative test results for anti-HDV antibodies (delta FIB-4 index/year were 0.22 and 0.03 in patients with and without anti-HDV antibody positive, respectively, $p = 0.006$). **Conclusion:** this study revealed that the recent prevalence of HDV infection in Japanese patients was 1.7% (10/601) among those with HBV infection. These patients experienced rapid progression of liver fibrosis. Therefore, a proper test for evaluating HDV infection in Japanese patients with HBV infection is required.

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1244-C | REFLEX TESTING FOR HEPATITIS DELTA SCREENING : DOES IT CHANGE THE PREVALENCE? CITYWIDE EXPERIENCE

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Background: The knowledge of Delta hepatitis prevalence is made difficult by the absence of reflex testing in the presence of a positive HBsAg. The aim of our study was to look at the prevalence of delta hepatitis (DH) in a city of 1.6 million inhabitants, between the university hospital (UH) where reflex testing was almost systematic (1) and two private structures (hospital with reference hepatology unit (HRH) and 25 city laboratories (CL)) where reflex testing was not systematic. **Methods:** From January 2019 to December 2022, we retrospectively analyzed in each facility the number of HBsAg tests requested, the prevalence of HBsAg, the number of delta serology tests requested in HBsAg-positive patients, the prevalence of DH, and the rate of delta RNA-positive patients and their characteristics (fibrosis, co-infection and treatment). **Results:** During the study period, 2,680,603 patients had blood test. 133,924 patients (5%) had HBsAg test (10% of patients in UH and HRH but 2,3% in CL). 3742 patients were HBsAg+ (2.8%) (2.7% in HU, 0,8% in HRH, 2% in CL). Among the 1792 newly HBsAg+ patients found in the study period, 998 patients (56%) had HDV antibody-(HDV-Ab) screening with huge variation according to site (84% in UH, 66% HRH, 21% in CL). 64 patients (6.4%) were HDV-Ab positive. The prevalence of varied according to site (7% in UH and HRH and 5% in CL $p = 0.6929$). 27 patients (2.7 %) were HDV RNA positive, 80% were male, mean age 44yo (SD15), 74% had advance fibrosis or cirrhosis and 3 patients (11%) were co infected by HIV. 4 patients died (2HCC and 1CCA), 9 patients were either loss of follow -up or refuse treatment and 15 patients have been treated by bulevirtide or NAPs. **Conclusion:** The prevalence of HDV was 6.4% among newly diagnosed HBsAg who had a HDV screening in our city with 15% of migrant's population. The prevalence did not change significantly according to the mode of Delta screening. Reflex testing

is therefore highly recommended in order to increase the number of patients who will need to be treated. 1) Colson Ph, Motte A, Dassetto C et al. Infections par le virus de l'hépatite delta dans
les hôpitaux universitaires de Marseille (2013-2022) RICAI 2022 p160.

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1245-C | SAFETY AND EFFICACY OF REP 2139-MG-BASED THERAPY IN AUSTRIAN PATIENTS WITH HBV / HDV COMPENSATED CIRRHOSIS WITH PRIOR FAILURE TO BULEVIRTIDE

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Background: REP 2139-Mg is a nucleic acid polymer (NAP) with demonstrated safety and antiviral efficacy in patients with HBV/HDV coinfection – including in compensated and decompensated cirrhosis (compassionate use program NCT05683548). **Methods:** REP 2139-Mg 250 mg s.c. qW and pegylated interferon (pegIFN) 90 μg s.c. qW were added to TDF/TAF in three patients with compensated HBV/HDV-induced cirrhosis and clinically significant portal hypertension (CSPH) who failed to respond to long-term BLV treatment. Weekly safety/antiviral efficacy evaluation was performed. Hepatic venous pressure gradient (HVPG) was measured at baseline and at week 12. **Results:** REP 2139-Mg was well tolerated with no related systemic adverse events. Injections were accompanied by grade 1 erythema and puritis in patient 2. Patient 1 is a Caucasian male (69 y.o., Child-A5, large varices, HVPG 17mmHg) with baseline HDV-RNA 3.28 log$_{10}$ copies/mL and qHBsAg 1202 IU/mL. At week 17, antiviral response was not yet observed, however, HVPG decreased by 18% to 14 mmHg at week 12. Patient 2 is a Caucasian female (51 y.o., Child-A5, large varices, HVPG 14mmHg) with baseline HDV-RNA 4.97 log$_{10}$ copies/mL and qHBsAg 626 IU/mL. Initial elevation of ALT (ALT$_{max}$ 683 U/L) and bilirubin (Bili$_{max}$ 6.9 mg/dL) but stable INR were noted - similar as during her previous pegIFN exposure. Upon halting pegIFN at week 7, ALT and bilirubin steadily declined during continued REP 2139-Mg therapy. HDV-RNA declined to 710 IU/mL (-2.11 log$_{10}$) and HBsAg declined to 8.29 IU/mL (-1.88 log$_{10}$) at week 13. However, HVPG increased by 29% to 18 mmHg, most likely related to the pegIFN-associated hepatitis flare. Patient 3 is a Caucasian male (38 y.o., Child-A5, large varices, HVPG 22mmHg) with baseline HDV-RNA 4.52 log$_{10}$ copies/mL and qHBsAg 922 IU/ml. An initial ALT flare (ALT$_{max}$ 659 U/L) was observed with stable bilirubin and INR. At week 13, HDV-RNA declined to 7700 IU/mL (-0.63 log$_{10}$) and HBsAg declined to 281 IU/mL. HVPG decreased by 19% to 18 mmHg at week 12. **Conclusion:** Subcutaneous weekly REP 2139-Mg in combination with TDF and low-dose pegIFN appears safe and effective against HBV/HDV infection in patients with compensated cirrhosis and CSPH, although the use of pegIFN warrants close clinical/laboratory monitoring. The reductions in HVPG observed in both patients with a hepatitis flare suggest a clinically meaningful amelioration of portal hypertension that may translate into a decreased risk of hepatic decompensation.

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Andrew Vaillant – Repicor Inc.: Employee, Yes, No; Replicor Inc.: Stock – privately held company (individual stocks and stock options), Yes, No;
The following people have nothing to disclose: Mathias Jachs, Michael Schwartz, Lorenz Balcar, Mattias Mandorfer

1246-C | SAFETY AND EFFICACY OF REP 2139-MG-BASED THERAPY IN FRENCH PATIENTS WITH PRIOR FAILURE TO PEGIFN AND OR BULEVIRTIDE

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Background: REP 2139 blocks HBV subviral particle assembly and hepatitis delta antigen function, driving HBsAg loss in HBV infection and HBsAg / HDV RNA loss in HBV / HDV co-infection. Compassionate access to REP 2139-Mg is being provided under the Replicor Compassionate Access Program (RCAP, NCT05683548). The safety and efficacy of weekly SC injection of REP 2139-Mg in combination therapy is currently being assessed in cirrhotic patients with chronic HBV / HDV co-infection after failure on bulevirtide (BLV). **Methods:** Compassionate access to REP 2139-Mg has been approved by the ANSM in 15 patients with compensated cirrhosis at baseline who had either no response or viral escape of HDV RNA during 2 or 10mg BLV. Existing TDF was supplemented with 48 weeks of QW SC 250mg REP 2139-Mg and 90 µg pegIFN. Weekly safety evaluations were accompanied by virologic assessment every 4 weeks. **Results:** Data is currently available for 11 patients with at least 4 weeks of REP 2139-Mg exposure. REP 2139-Mg administration has been well tolerated, with transient grade 1 erythema reported in 6/11 patients. ALT flares > 5X baseline have been observed in 1 patient. ALT elevation at baseline present in 7 patients has declined or normalized in 5 patients. No evidence of liver decompensation or other AEs has been observed. Esophageal varices present in one patient have disappeared. HDV RNA response is observed in 9/11 patients, 1 with HDV RNA > 2 $\log_{10}$ IU/mL decline from baseline and 3 with undetectable HDV RNA. HBsAg decline is observed in 6/11 patients with declines of 1 $\log_{10}$, and 2 $\log_{10}$ IU/mL from baseline in 1 and 1 patient respectively and undetectable HBsAg in an additional 2 patients (both with anti-HBs seroconversion). Undetectable HDV RNA and HBsAg and HBsAg seroconversion have been stable after withdrawal of REP 2139-Mg and pegIFN for 10 and 3 months respectively in 2 patients after completion of 48 weeks of therapy. One of these patients has now had TDF withdrawn with HBV DNA remaining additionally undetectable for 2 months. **Conclusion:** Subcutaneous REP 2139-Mg is safe, and effective against HBV and HDV infection in combination with TDF and low dose pegIFN in patients with compensated cirrhosis and can salvage failure from BLV therapy.

Disclosures: Marc Bourliere – Gilead Sciences, Inc.: Speaking and Teaching, Yes, No; AbbVie: Speaking and Teaching, No, No; Roche: Speaking and Teaching, No, No; Intercept: Speaking and Teaching, No, No;
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Segolene Brichler – Eurobio Scientific: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, Yes;
Andrew Vaillant – Repicor Inc.: Employee, Yes, No; Replicor Inc.: Stock – privately held company (individual stocks and stock options), Yes, No;

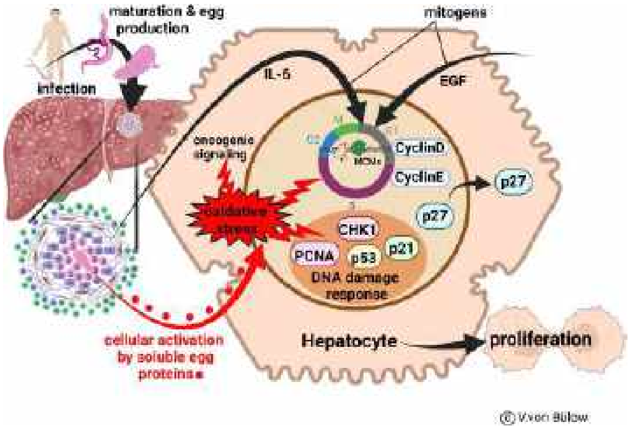
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

The following people have nothing to disclose: Veronique Loustaud-Ratti, Christiane Stern, Souad Benali, Edouard Bardou-Jacquet, Laurent Alric, Lea Colombain, Magdalena Meszaros, Sophie Métivier, Laurence Lecomte, Sandrine Francois, Cecilia De Freitas, Athenaïs Gerber, Emmanuel Gordien, Stephane Chevaliez

1247-C | SCHISTOSOMA MANSONI-INDUCED OXIDATIVE STRESS TRIGGERS HEPATOCELLULAR PROLIFERATION

Verena Von Bülow, Nicola Buss, Jakob Lichtenberger, Lukas Härle, Christoph Gero Grevelding, Martin Roderfeld and Elke Roeb, Justus-Liebig-University, Giessen

Background: Schistosomiasis is a parasitic infection which globally affects more than 250 million people. There is compelling evidence that schistosome eggs, but not the adult worms evoke major tissue damage. *S. mansoni* eggs induce metabolic exhaustion and a strong redox imbalance, which is critical for hepatocellular DNA integrity. However, the impact of egg-induced oxidative stress for the regulation of cell cycle remains elusive. In this study, we investigated, whether oxidative stress provokes hepatocyte proliferation upon *S. mansoni* infection. **Methods:** Cell cycle, replication stress response, and proliferation were analyzed in *S. mansoni*-infected hamsters. Functional experiments were performed in a human hepatic cell line using quantitative real-time PCRs, western blotting, and BrdU assays. Major results were validated by means of human biopsies. **Results:** *Schistosoma mansoni* infection promoted an induction of licensing factors of DNA replication and cell cycle checkpoint cyclins of the G1/S transition in parallel with a DNA damage response. *S. mansoni* egg antigen-induced oxidative stress triggered an upregulation of cyclin D1 in hepatocytes, thus driving G1/S phase transition. At the same time oxidative stress caused downregulation of the cell cycle inhibitor $p27^{KIP1}$. Together, these conditions led to hepatocyte proliferation overcoming the G1/S phase transition. Ultimately, there is an increase in hepatocyte proliferation, which was reversed by the administration of the ROS scavenger L-glutathione. Moreover, human liver biopsies from a patient infected with *S. mansoni* demonstrated elevation of nuclear cyclin D1 in hepatocytes. Furthermore, in a hamster model of *S. mansoni* infection, we confirmed SEA-induced cell cycle progression. **Conclusion:** Hepatocellular proliferation is triggered by *S. mansoni* egg-induced oxidative stress in addition to paracrine mitogenic signals induced by the eggs.The current study demonstrates that *S. mansoni* infection, and in particular the soluble egg antigens, promote hepatocellular proliferation by oxidative stress and subsequent modulation of cell cycle regulation. It appears that these mechanisms contribute to the parenchymal damage caused by *S. mansoni* eggs, and that they may even be associated with malignancy



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1248-C | SURGICAL MANIFESTATIONS OF HEPATOBILIARYPANCREATIC TUBERCULOSIS★

Daniel Ernest Laylay Florendo and Apolinario Ericson Berberabe, Philippine General Hospital

Background: Surgical hepatobiliary-pancreatic tuberculosis (HBPTB) has been documented in lieu of more effective therapies for tuberculosis. The documentation HBPTB is sporadic at most, with no large center studies to provide baseline data regarding this rare presentation of tuberculosis. A significant number of these studies draw conclusions based on clinical diagnosis alone with no histopathologic proof of tubercular involvement of the biliary tract and surrounding structures. This study aimed to determine the risk factors, diagnostic and therapeutic approach to surgical HBPTB patients at the Philippine General Hospital (UP-PGH) from January 1, 2014 to December 31, 2021 **Methods:** An institutional database was used to identify patients who underwent a surgical procedure for HBPTB. Patients were only included if there was biopsy or microbiologic proof of tuberculous involvement of the biliary tract or surrounding structures. Clinical data and corresponding outcomes were retrieved from the patient's medical

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

records. **Results:** Among the total 45 patients included in the study, the most common admitting diagnosis was either malignancy (35.6%) or tuberculosis (37.8%). The major risk factors identified include previous TB exposure (47.6%) and low albumin (60%). Most of the patients did not report any medical co-morbids (83.3%). The liver (37.8%) and the bile ducts (33.3%) were the most common organs involved. Six (6) patients presented with solid lesion and elevated tumor markers suspicious for malignancy; among these CA 19-9 was the most commonly elevated (5 out of 6). The most common surgical procedures done were 1) ultrasound-guided liver biopsy (26.7%), 2) biliary enteric anastomosis for diversion (22.2%) and 3) percutaneous transhepatic biliary drainage (15.6%). Most patients underwent a procedure with a therapeutic outcome (71.1%). There was a distinct preference for minimally invasive procedures such as ERCP or PTBD. Biliary enteric anastomosis was the most common procedure requiring a laparotomy. Average procedure time was 2 hours or less for 55.5%. Mean length of stay was 14.53 days with patients having a post-op stay of 7.47 days. There no mortalities but the identified morbidities were nosocomial pneumonia (6.67%), bacteremia (4.4%), surgical site infection and post-ERCP pancreatitis. **Conclusion:** Identifying which HBPTB patient requires surgery relies on recognition of the constellation of clinical, laboratory and imaging features. Minimally invasive approaches are the mainstay of treatment for surgical HBPTB, the goal of which may be to diagnose or provide symptom relief.

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1249-C | THE EFFECT OF METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE ON LIVER FIBROSIS PROGRESSION AND REGRESSION IN VIRUS-RELATED LIVER DISEASE: A MULTICENTER LONGITUDINAL STUDY

Felice Cinque[1], Jovana Milic[2], Stefano Renzetti[3], Federico Motta[2], Jenny Bischoff[4], Dana Kablawi[5], Wesal Elgretli[6], Giulia Besutti[2,7], Giuseppe Mancini[2,7], Sara Esperti[2,7], Marianna Menozzi[2,7], Stefano Calza[3], Cristina Mussini[2,7], Valentina Menozzi[2,7], Maria Daria Di Trapani[2,7], Juergen Rockstroh[4], Giovanni Guaraldi[2,7] and Giada Sebastiani[1,8], (1)Mcgill University Health Centre, Montreal, Canada, (2)University of Modena and Reggio Emilia, Modena, Italy, (3)University of Brescia, Brescia, Italy, (4)University Hospital Bonn, Bonn, Germany, (5)Mcgill University Health Centre, (6)Mcgill University, Montreal, Canada, (7)Policlinico of Modena, Modena, Italy, (8)Mcgill University

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a definition of fatty liver not requiring the exclusion of secondary causes of liver diseases, such as HIV and viral hepatitis. Liver fibrosis is a dynamic process recognized as the main predictor of liver disease progression and mortality. We aimed to investigate the effect of MAFLD on liver fibrosis progression and regression in virus-related liver disease. **Methods:** We included people with HIV with and without coinfection with HCV and HBV and with at least two transient elastography examinations with controlled attenuation parameters (CAP) from three prospective cohorts in Canada, Italy and Germany. MAFLD was defined according to Eslam criteria: presence of hepatic steatosis (CAP $>$ 248 dB/m), plus any among type 2 diabetes, overweight (BMI $>$ 25 Kg/m^2) or two other metabolic abnormalities. Fibrosis progression was defined as development of significant liver fibrosis, defined as liver stiffness measurement (LSM) $>$ 8 kPa, or transition to cirrhosis, defined as LSM $>$ 13 kPa, for those with LSM $>$ 8 but $<$ 13 kPa at baseline. Fibrosis regression was defined as transition to no liver fibrosis, defined as LSM $<$ 8 kPa, or to significant liver fibrosis for those with cirrhosis at baseline. Weight gain was defined as a 5% BMI increase in two consecutive visits. A continuous-time multi-state Markov model was used to describe transition across fibrosis stages. Cox regression model was used to identify predictors for liver fibrosis progression. **Results:** 1183 patients were included (median age 53 years, 77% males, median duration since HIV diagnosis 18 years, 25% HIV/HCV coinfected and 4% HIV/HBV coinfected). The baseline prevalence of MAFLD, significant liver fibrosis and cirrhosis was 47%, 14% and 6% respectively. During a median follow-up period of 3.5 years, two to six annual LSM were performed. The incidence rate of fibrosis progression and of fibrosis regression was 3.4 per 100 persons-year and 1.2 per 100 person-years, respectively. In Markov model, weight gain predicted fibrosis progression and prevented its regression (see Table). On multivariable Cox regression analysis, predictors of fibrosis progression were MAFLD (adjusted hazard ratio 2.50, 95% CI 1.06-5.89; $p = 0.036$) and weight gain (adjusted hazard ratio 2.65, 95% CI 1.32-5.26; $p = 0.006$), after adjusting for male sex, age, nadir CD4 cell count, coinfection with HBV and HCV and exposure to different classes of antiretroviral regimens. **Conclusion:** MAFLD and weight gain are the main drivers of liver fibrosis progression in virus-related liver disease, independently of HCV and HBV coinfection and antiretroviral therapy exposure. In the global effort for liver fibrosis screening in at-risk populations, metabolic health should be prioritized.

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

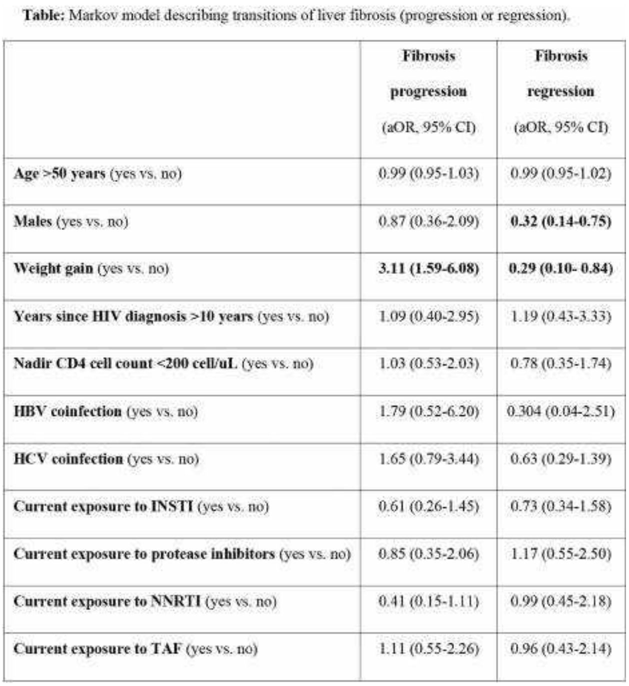

Table: Markov model describing transitions of liver fibrosis (progression or regression).

	Fibrosis progression (aOR, 95% CI)	**Fibrosis regression** (aOR, 95% CI)
Age >50 years (yes vs. no)	0.99 (0.95-1.03)	0.99 (0.95-1.02)
Males (yes vs. no)	0.87 (0.36-2.09)	**0.32 (0.14-0.75)**
Weight gain (yes vs. no)	**3.11 (1.59-6.08)**	**0.29 (0.10- 0.84)**
Years since HIV diagnosis >10 years (yes vs. no)	1.09 (0.40-2.95)	1.19 (0.43-3.33)
Nadir CD4 cell count <200 cell/uL (yes vs. no)	1.03 (0.53-2.03)	0.78 (0.35-1.74)
HBV coinfection (yes vs. no)	1.79 (0.52-6.20)	0.304 (0.04-2.51)
HCV coinfection (yes vs. no)	1.65 (0.79-3.44)	0.63 (0.29-1.39)
Current exposure to INSTI (yes vs. no)	0.61 (0.26-1.45)	0.73 (0.34-1.58)
Current exposure to protease inhibitors (yes vs. no)	0.85 (0.35-2.06)	1.17 (0.55-2.50)
Current exposure to NNRTI (yes vs. no)	0.41 (0.15-1.11)	0.99 (0.45-2.18)
Current exposure to TAF (yes vs. no)	1.11 (0.55-2.26)	0.96 (0.43-2.14)

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Giada Sebastiani – Merk: Speaking and Teaching, No, No; Gilead: Speaking and Teaching, No, No; Abbvie: Speaking and Teaching, No, No; Novonordisk: Speaking and Teaching, No, No; Pfizer: Speaking and Teaching, No, No; Pfizer: Advisor, No, No; Merk: Advisor, No, No; Novonordisk: Advisor, No, No; Gilead: Advisor, No, No; Theratec: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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1250-C | THE NEED FOR CAREGIVER SUPPORT IN PATIENTS WITH HEPATITIS D VIRUS INFECTION: DESCRIPTIVE RESULTS FROM A CROSS-SECTIONAL STUDY IN ITALY, GERMANY, SPAIN AND THE US

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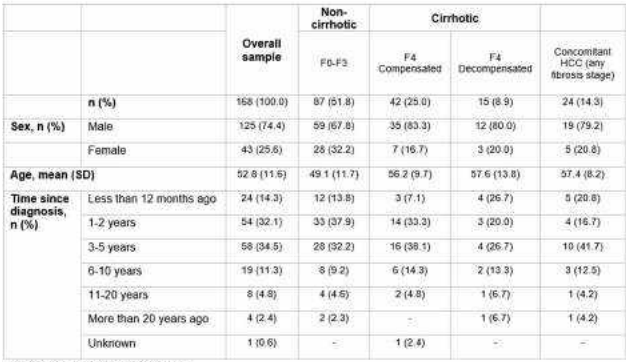
Background: Hepatitis D virus (HDV) is associated with accelerated progression to advanced liver disease compared to mono-infection with hepatitis B (Fattovich, et al. 2000). HDV may result in reduced health-related quality of life relative to other hepatitis infections (Buti et al., 2021). However, there is a lack of evidence regarding the caregiver burden associated with HDV. Novel questions were developed in this study to understand the need for caregiver support among patients living with chronic HDV who were not receiving any licensed HDV treatment. **Methods:** A cross-sectional survey was completed by adults with a physician confirmed diagnosis of chronic HDV in Italy, Germany, Spain, and the US between July-November 2022. The survey included questions that measured the impact of HDV including the need for caregiver support. Patients who were heavily immunocompromised, received interferon (IFN)/peg-IFN in the past six months, were diagnosed with human immunodeficiency virus or hepatitis C, or had received an organ transplant were excluded. Patients receiving any licensed HDV treatment were also excluded for this analysis. **Results:** Descriptive results were based on 168 patients who were not receiving treatment indicated for HDV

(demographics and clinical characteristics as per Table 1). Of these 168 patients 46 (27.4%) had received caregiver support. The percentage of patients who had received caregiver support rose to 62.5% in patients with a concomitant diagnosis of HCC, and 80.0% in patients with F4D cirrhosis. Most patients (93.5%) received care from people that lived with them; mainly the patient's spouse/partner (84.8%) as well as the patients' children (37.0%, 8.7% of whom were under 18) and other relatives (13.0%). The top 3 activities that patients received help with were preparing meals/cooking food (76.1%), emotional support (69.6%) and travelling out of home (65.2%). Some patients also received help with basic activities of daily living including getting dressed/washed (41.3%), getting in and out of bed (34.8%) and walking (28.3%). **Conclusion:** This study demonstrates a need for caregiver support in patients with HDV across a range of activities, with care mainly received from family members who live with them. The need for caregiver support is highest in patients at later stages of disease and in those with a concomitant HCC diagnosis. Newer treatment interventions which slow down disease progression could potentially ease the caregiver burden.

Table 1



		Overall sample	Non-cirrhotic	Cirrhotic		
			F0-F3	F4 Compensated	F4 Decompensated	Concomitant HCC (any fibrosis stage)
	n (%)	168 (100.0)	87 (51.8)	42 (25.0)	15 (8.9)	24 (14.3)
Sex, n (%)	Male	125 (74.4)	59 (67.8)	35 (83.3)	12 (80.0)	19 (79.2)
	Female	43 (25.6)	28 (32.2)	7 (16.7)	3 (20.0)	5 (20.8)
Age, mean (SD)		52.8 (11.6)	49.1 (11.7)	56.2 (9.7)	57.6 (13.8)	57.4 (8.2)
Time since diagnosis, n (%)	Less than 12 months ago	24 (14.3)	12 (13.8)	3 (7.1)	4 (26.7)	5 (20.8)
	1-2 years	54 (32.1)	33 (37.9)	14 (33.3)	3 (20.0)	4 (16.7)
	3-5 years	58 (34.5)	28 (32.2)	16 (38.1)	4 (26.7)	10 (41.7)
	6-10 years	19 (11.3)	8 (9.2)	6 (14.3)	2 (13.3)	3 (12.5)
	11-20 years	8 (4.8)	4 (4.6)	2 (4.8)	1 (6.7)	1 (4.2)
	More than 20 years ago	4 (2.4)	2 (2.3)	-	1 (6.7)	1 (4.2)
	Unknown	1 (0.6)	-	1 (2.4)	-	-

HCC: Hepatocellular carcinoma

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Robert G. Gish – Abbott: Consultant, No, No; Abbvie: Speaking and Teaching, No, No; Altimmune: Consultant, No, No; Antios: Consultant, No, No; Arrowhead: Consultant, No, No; Dynavax: Consultant, No, No; Eiger: Advisor, No, No; Enyo: Consultant, No, No; Genentech: Consultant, No, No; Genlantis: Consultant, No, No; GLG: Consultant, No, No; Gilead Sciences: Consultant, Yes, No; Helios: Consultant, No, No; HepaTx: Advisor, No, No; HepQuant: Advisor, No, No; Intercept: Speaking and Teaching, No, No; Janssen: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Topography Health: Consultant, No, No; Venatorx: Consultant, No, No; Prodigy: Advisor, No, No; Eiger: Stock – privately held company (individual stocks and stock options), No, No; Ganlantis: Stock – privately held company (individual stocks and stock options), No, No; HepQuantum: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; Abbott: Consultant, No, No; Eisai: Consultant, No, No; Gilead Sciences: Consultant, No, No; CymaBay: Advisor, No, No; Durect: Advisor, No, No; AstraZeneca: Speaking and Teaching, No, No; BMS: Speaking and Teaching, No, No; Eisai: Speaking and Teaching, No, No; Hepquant: Stock – privately held company (individual stocks and stock options), No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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

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1251-C | TREATMENT WITH REP 2139-MG IN ASSOCIATION WITH TDF IN HDV DECOMPENSATED CIRRHOSIS IS SAFE AND EFFECTIVE IN A REAL-LIFE SETTING

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Background: REP 2139-Mg blocks assembly and secretion of HBV subviral particles and hepatitis Delta antigen function, providing effects against both HBV and HDV infection. The objective of this study is to describe the safety and efficacy of REP 2139-Mg in CHD patients with decompensated cirrhosis. **Methods:** Compassionate use in three CHD patients with decompensated cirrhosis was approved by the ANSM in France. Scheduled therapy is 48 weeks of REP 2139-Mg 250 mg QW SC and TDF 245 mg QD PO. Clinical, biological, virological and imaging data were collected at baseline and every week for the first month, then every month. **Results:** SC administration of REP 2139-Mg has been well tolerated. No significant adverse events (including ALT elevation) have been observed to date. Patient 1 (Caucasian female, 56 y.o.) had portal hypertension and ascites (Child Pugh B8) with baseline HDV RNA 7.04 log$_{10}$ IU/mL and HBsAg 1177 IU/mL. Reversal of ascites occurred at week 4, HBsAg loss at week 10, anti-HBs seroconversion at week 14 (increasing to 559 mIU/mL at week 42) and HDV RNA has been undetectable since week 20. Improvement of liver function (to Child A6) occurred during therapy. REP 2139-Mg has now been withdrawn. Patient 2 (African female, 56 y.o.) was listed for liver transplantation due to hepatocellular carcinoma (HCC). She had portal hypertension and ascites (Child Pugh C12), baseline HDV RNA of 3.64 log$_{10}$ IU/mL and HBsAg of 4270 IU/mL. A significant reduction of ascites occurred at week 4 with marked reduction of edema and fatigue. Successful liver transplantation occurred after 10 weeks of therapy. HDV RNA became undetectable at week 6 and HBsAg was 1.75 IU/mL (anti-HBs 8 mIU/mL) prior to transplant. Explant histology was normal with well-differentiated HCC nodules and no vascular emboli. No ground glass hepatocytes were present. Patient 3 (African male, 47 y.o.) had portal hypertension, ascites, and hepatic encephalopathy (Child Pugh C10). Initial reversal of ascites relapsed with poor diet and diuretic discontinuation. Initial 2.7 log$_{10}$ IU/mL decline in HDV RNA at week 11 was followed by mild rebound concomitant with perfusion of albumin following paracentesis. **Conclusion:** REP 2139-Mg is safe and well tolerated in CHD patients with decompensated cirrhosis. HBV-HDV functional cure appears achievable for the first time in this special population, which could prevent the need for liver transplant.

Disclosures: Michel Bazinet – Replicor Inc.: Employee, Yes, No; Replicor Inc.: Stock – privately held company (individual stocks and stock options), Yes, No;
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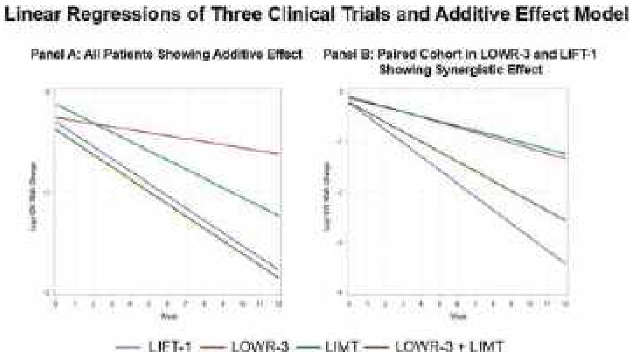
Andrew Vaillant – Repicor Inc.: Employee, Yes, No; Replicor Inc.: Stock – privately held company (individual stocks and stock options), Yes, No;
The following people have nothing to disclose: Christiane Stern, Cecilia De Freitas, Vincent Mackiewicz, Emmanuel Gordien, Stephane Chevaliez

1252-C | UNDERSTANDING THE ANTIVIRAL EFFECTS OF PEGINTERFERON LAMBDA WITH AND WITHOUT RITONAVIR BOOSTED LONAFARNIB IN CHRONIC HEPATITIS D INFECTION

Christina Park[1], *Julian Hercun*[1], *Harel Dahari*[2], *Ohad Etzion*[3], *Saeed S. Hamid*[4], *Edward J. Gane*[5], *Yoav Lurie*[6], *Farial Rahman*[1], *David Yardeni*[7], *Pallavi Surana*[1], *Colin Hislop*[8], *Ingrid Choong*[8], *Jeffrey Glenn*[9], *Theo Heller*[10] *and Christopher Koh*[11], *(1)National Institutes of Health, (2)The Program for Experimental and Theoretical Modeling, Division of Hepatology, Department of Medicine, Stritch School of Medicine, Loyola University Chicago, Maywood, Illinois, USA, Highland Park, IL, (3)Saroka University Medical Center, Beer-Sheba, Israel, Beer-Shiva, Israel, (4)Aga Khan University Hospital, Karachi, Pakistan, (5)University of Auckland, (6)Shaare Zedek Medical Center, (7)Soroka University Medical Center, Mishmar Hanegev, Israel, (8) Eiger BioPharmaceuticals, Inc., (9)Division of Gastroenterology and Hepatology, Departments of Medicine, Microbiology & Immunology, Stanford School of Medicine, Stanford, California, USA, (10) Translational Hepatology Section, Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, (11) National Institute of Diabetes and Digestive and Kidney Diseases, Nih*

Background: Hepatitis Delta Virus (HDV) infection causes the most aggressive form of human viral hepatitis and lacks an approved FDA therapy. Various investigative therapies are in the pipeline including interferon-based therapy and therapies targeting viral assembly. We aim to compare different combinations of novel HDV therapies and assess their anti-HDV effectiveness. **Methods:** Viral kinetic data was analyzed from three phase-2 clinical trials (LOWR-3 [NCT02511431], LIMT-1 [NCT02765802], and LIFT-1 [NCT03600714]). LOWR-3 employed Ritonavir (RTV-100mg) boosted Lonafarnib (LNF-50/75/100mg) for 12-24 weeks. LIMT-1 employed 180mcg of PEGylated lambda interferon (L-IFN) weekly for 48 weeks. LIFT-1 combined 180mcg of L-IFN with RTV-100mg and LNF-100mg for 24 weeks. 12 weeks of HDV RNA data were analyzed, and the Wilcoxon tests and linear regression were used to assess all three studies. In subgroup analysis, patients who participated in both the LOWR-3 and LIFT-1 studies were analyzed to further assess the combinatory effects of therapy. **Results:** The baseline HDV RNA levels were similar between cohorts in all three studies and not significantly different with a p-value of 0.075. At 12 weeks of therapy, the median HDV RNA decline from baseline in LOWR-3 (LNF 100mg + RTV) was 0.52 log IU/mL ($p = 0.181$), LIMT-1 was 1.14 log IU/mL ($p = 0.012$), and LIFT-1 was 1.72 log IU/mL ($p < 0.0001$). The coefficients of the LOWR-3 (100mg), LIMT-1, and LIFT-1 linear regressions were -0.030 ($R^2 = 0.045$), -0.093 ($R^2 = 0.335$), and -0.123 ($R^2 = 0.630$), respectively. A model of additive effect of L-IFN paired with LNF+RTV has the coefficient -0.1229, which comes from adding LOWR-3 and LIMT-1 coefficients. The LIFT-1 coefficient of -0.1231 is very close to the additive effect model, suggesting that the combination of L-IFN and LNF+RTV has an effect that is equal to the sum of their individual effects. In the individual patient analysis across LOWR-3 and LIFT-1 studies (n = 12), HDV RNA responses at week 12 differed by a mean of 0.97 log IU/mL (SD = 0.88). Additionally, the median HDV RNA decline from baseline after 12 weeks of therapy in LOWR-3 was 0.92 log IU/mL ($p = 0.003$) and LIFT-1 was 2.11 log IU/mL ($p = 0.001$). The coefficients of the LOWR-3 (100mg), LIMT-1, and LIFT-1 linear regressions were -0.104 ($R^2 = 0.703$), -0.093 ($R^2 = 0.335$), and -0.268 ($R^2 = 0.737$) respectively. The additive effect model of L-IFN and LNF+RTV has the coefficient -0.196, based on adding LOWR-3 and LIMT coefficients. However, the LIFT-1 coefficient of -0.268 is 1.37 times more suggesting a true synergistic effect of L-IFN plus LNF+RTV therapy. **Conclusion:** The combination of L-IFN plus LNF+RTV suggests a synergistic effect against HDV by 12 weeks after initiation of therapy. These findings have important implications for designing the optimal therapy to treat HDV.


Linear Regressions of Three Clinical Trials and Additive Effect Model

Panel A: All Patients Showing Additive Effect

Panel B: Paired Cohort in LOWR-3 and LIFT-1 Showing Synergistic Effect

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1253-C | UNSAFE SEXUAL PRACTICES PRIOR TO INCARCERATION, A HIGH-RISK FACTOR OF HEPATITIS B AND HIV INFECTION AMONG PRISONERS IN BLANTYRE, MALAWI

Shakira Chimberenga[1,2], Anastansia Mgawa[2], Grace James[3], Enock Jumbe[3], Marie-Claire Van Hout[4], Mulinda Nyirenda[2,5] and Isaac Thom Shawa[2,6], (1) Ministry of Health, Mzuzu Central Hospital, (2)Kamuzu University of Health Sciences, (3)Johns Hopkins Research Project, (4)Liverpool John Moore's University, (5)Ministry of Health, Queen Elizabeth Central Hospital, (6)University of Derby

Background: Hepatitis B and C viruses (HBV/HCV) are the major causes of liver diseases. Both HBV and HCV are primarily transmitted through contact with infected blood, and body fluids. Low and middle-income countries have a disproportionately high rate of chronic HBV and HCV especially in the HIV infected population. Prison settings are associated with substantial risk of HBV, HCV, and HIV acquisition and are a significant driver of blood-borne viruses among prisoners during detention and after release. The primary aim of this study was to assess the prevalence of HBV, HCV and HIV among those detained at Chichiri prison, that would provide insights into the highest risk factors associated with acquisition of hepatitis infection among prisoners in Malawi. **Methods:** 220 participants [86.4% males (n = 190/220), 13.6% females (n = 30/220) were enrolled at Chichiri prison. A structured questionnaire was used for collection of demographic details, assessment of knowledge, and risk factors for transmission of viral hepatitis in prison environment in Malawi. Serum samples were prepared and analyzed utilizing HBV, and HCV rapid assays. All positive samples were run on sandwich enzyme immunoassay (EIA). **Results:** The HBV prevalence was estimated at 8.6%; whereas HCV was not detected in the sample (0%). The HIV prevalence rate was 21%, and HBV/HIV co-infection prevalence was 11%. The majority (79.1%) of prisoners were incarcerated between 2017 and 2020. HBV/HIV co-infection was observed in 11% of the sample. **Conclusion:** This study confirms high prevalence of HBV among prisoners at Chichiri. Findings suggest that intra-prison viral hepatitis transmission was very minimal, possibly due to criminalisation of high-risk practices (injecting drug use, sex between men) for exposure to blood-borne viruses. Sexual transmission prior to incarceration was the highest risk factor for viral hepatitis and HIV. Prison environments present both challenges and opportunities for prevention and treatment of viral hepatitis and HIV infections. Absence of HCV markers reported in this study was expected since the HCV prevalence in general population was apparently very low. An exigent consideration of vertical and horizontal HBV transmission to be performed in future studies to provide further insights into the viral transmission dynamics.

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1254-C | USEFULNESS OF A UNIQUE PAN-GENOTYPIC PANEL OF HDV SAMPLES TO COMPARE HDV RNA QUANTIFICATION KITS

Athenaïs Gerber, Valerian Delagarde, Pascale Leloup, Emmanuel Gordien, Frederic Le Gal and Segolene Brichler, CHU Avicenne

Background: Hepatitis delta virus (HDV) infects a non-negligible fraction of HBV chronically infected patients, and worsens the clinical prognosis. Beyond HDV antibody screening with a serological test, RNA detection and quantification is required to identify patients with an active HDV infection, and further assess the efficacy of antiviral treatment. A few RT-qPCR commercial kits are now available worldwide, but despite the distribution of the First WHO International Standard, results are not yet standardized. Our objective was to compare the HDV quantification results obtained with pipelines (extraction device – RT-qPCR kit – thermocycler) from several manufacturers, on a unique HDV panel representative of circulating genotypes. **Methods:** A panel of 24 plasma samples of various viral loads (VL) and genotypes was established and multiples aliquots of 1mL each were stored at -80° C. We first compared four complete pipelines recommended by the manufacturers; then, the same amplification kit (EurobioPlex EBX-071 on a CFX96 thermocycler) was used after RNA extraction with four different automated devices. Volumes of plasma sample and eluate in each extraction technique were taken in account to calculate VL results in IU/mL. **Results:** The panel consisted of 2 negative, 8 HDV-1 (of both African and European origin), 3 HDV-2, 2 HDV-4, 3 HDV-5, 2 HDV-6, 2 HDV-7 and 2 HDV-8 positive samples, with VL ranging from 2 to 5 log IU/mL (as quantified with EurobioPlex EBX-071 kit). Qualitative results were concordant for all samples on the 4 pipelines. Quantitative results were very similar between the EurobioPlex EBX-071 (Eurobio), the RealStar HDV RT-PCR (Altona) and the RoboGene HDV RNA Quantification 3.0 (AG Roboscreen) kits, with a mean difference < 0.2 log IU/mL, whatever the genotype and VL, but the EurobioPlex EBX-004 (Eurobio) kit systematically overestimated the VL by 1 log IU/mL. Compared to the results obtained with the m2000sp, changing the extraction device led to a difference of -0.1, +0.2 and +0.5 log IU/mL (for EasyMag, Cobas 4800 and QiaSymphonySP respectively). **Conclusion:** Our results clearly show that standardized HDV VL results can be obtained with several RT-qPCR kits and pipelines now commercially distributed, but that not all kits are equivalent and that many factors can influence the final quantitative results. Using the same panel for comparison studies allows a rapid identification of concordant tests and participate to the ultimate goal of HDV quantification standardization.

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Disclosure information not available at the time of publication: Valerian Delagarde, Pascale Leloup, Frederic Le Gal

1255-C | VALIDATION OF PROGNOSTIC SCORES FOR PREDICTING ACUTE LIVER FAILURE AND IN-HOSPITAL DEATH IN PATIENTS WITH DENGUE-INDUCED SEVERE HEPATITIS

Tongluk Teerasarntipan[1], *Kessarin Thanapirom*[1], *Roongruedee Chaiteerakij*[1], *Piyawat Komolmit*[1] *and Sombat Treeprasertsuk*[2], *(1)Chulalongkorn University, (2)Chulalongkorn University, Bangkok, Thailand*

Background: Acute liver failure (ALF) in dengue is rare but fatal. MELD score was generally used in predicting liver-related prognosis. However, the complex calculation might limit its applicability. Recently, simple prognostic scores, including the ALBI, EZ-ALBI and PALBI scores, have been developed in determining prognosis in various aspects of liver injury. Therefore, we aimed to validate prognostic scores for predicting ALF and in-hospital mortality in patients with dengue-induced severe hepatitis (DISH). **Methods:** We retrospectively reviewed 2,532 serology-confirmed hospitalized adult dengue patients during the 16-year study period (2007-2022) at the King Chulalongkorn Memorial Hospital, Thailand. Patients with DISH [n = 193 (7.62%)], defined as transaminases > 10 times from the normal reference level, and DISH with subsequent ALF, defined by the EASL 2017 criteria, were included. Univariate regression analysis was used to identify potential factors associated with adverse outcomes. Youden's index in conjunction with receiver operating characteristics (ROC) analysis was used to determine the best cut-off value of prognostic scores in predicting ALF and in-hospital death and area under ROC (AUROC) curves were compared using a paired data nonparametric ROC curve estimation. **Results:** Of the 193 DISH patients, 20 patients developed ALF (0.79%). Mortality rates in patients with ALF and without ALF were 60.0% (12/20) and 0.58% (1/173), respectively. Regression analysis showed that INR, bilirubin, albumin, and creatinine were independent laboratory markers associated with ALF and death. Liver prognostic scores had excellent performance predicting adverse outcome from DISH; MELD score > 15 predicted ALF with AUROC of 0.917, (90.0% sensitivity, 88.4% specificity) and MELD score > 18 predicted in-hospital death with AUROC of 0.823, (86.9% sensitivity, 89.1% specificity); EZ-ALBI score > -30 predicted ALF and death with AUROC of 0.835, (80.0% sensitivity, 72.2% specificity), and AUROC of 0.808 (76.9% sensitivity, 69.3% specificity), respectively; ALBI score > -2 predicted ALF and death with AUROC of 0.806, (80.0% sensitivity, 77.4% specificity), and AUROC of 0.799 (76.9% sensitivity, 74.3% specificity), respectively. PALBI score had the lowest but still good performance predicting adverse DISH outcomes (AUROC of 0.786 and 0.699 for ALF and death, respectively). A paired sample ROC curve estimation showed non-different performance between MELD score and EZ-ALBI score, in predicting ALF (z = 1.688, *p* = 0.091, 95%CI of -0.014-0.194) and in-hospital death (z = 0.322, *p* = 0.747, 95%CI -0.141-0.197). **Conclusion:** MELD score was the best predictor of ALF and death in DISH patients. EZ-ALBI score, a simple and easy-to-use score, had excellent predictive performance and therefore might be considered as an alternative tool to predict prognosis in dengue patients.

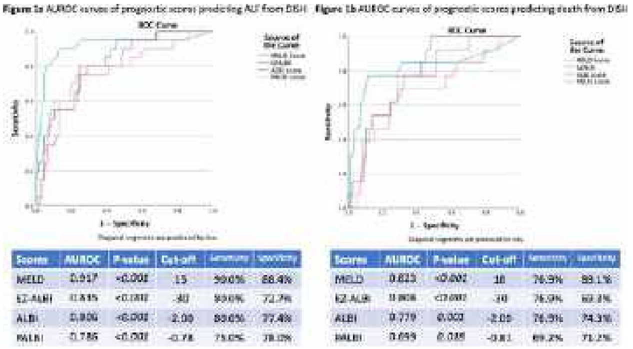

Figure 1a AUROC curves of prognostic scores predicting ALF from DISH

Figure 1b AUROC curves of prognostic scores predicting death from DISH

Scores	AUROC	P-value	Cut-off	Sensitivity	Specificity
MELD	0.917	<0.001	15	90.0%	88.4%
EZ-ALBI	0.835	<0.001	-30	80.0%	72.2%
ALBI	0.806	<0.001	-2.00	80.0%	77.4%
PALBI	0.786	<0.001	-0.78	75.0%	78.0%

Scores	AUROC	P-value	Cut-off	Sensitivity	Specificity
MELD	0.823	<0.001	18	76.9%	89.1%
EZ-ALBI	0.808	<0.001	-30	76.9%	69.3%
ALBI	0.779	0.002	-2.05	76.9%	74.3%
PALBI	0.699	0.038	-0.81	69.2%	71.2%

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Disclosure information not available at the time of publication: Piyawat Komolmit

f 1256-C | VASCULAR REMODELING AND LIVER REGENERATION BEGIN EARLY AND PERSIST IN CHRONIC HEPATITIS D PROGRESSION

Maleeha F Ahmad[1], Moumita Chakraborty[1], Adekanyinsola Onitiri[1], Rownock Afruza[1], Nicole San-Dee Minerva[1], David E Kleiner[2], Christopher Koh[3] and Theo Heller[1], (1)Translational Hepatology Section, National Institutes of Health, (2)Laboratory of Pathology, National Cancer Institute, National Institutes of Health, (3)National Institute of Diabetes and Digestive and Kidney Diseases, Nih

Background: Of all the viral hepatitides, delta virus is the most aggressive- carrying the highest risks for cirrhosis, decompensation, hepatocellular carcinoma, and mortality. Understanding chronic hepatitis delta's (CHD) ability to cause rapid and reproducible progression of liver disease will not only aid development of improved staging techniques and sorely needed therapeutics for CHD but will also allow for a deeper understanding of chronic liver disease (CLD) progression in general. Vascular and regenerative factors are of particular interest as potential key drivers of CLD progression. **Methods:** 42 treatment-naïve liver biopsies from CHD patients evaluated at the National Institutes of Health were staged according to the Ishak Fibrosis (IF) scale (IF 0-4: non-cirrhotic, IF 5-6: cirrhotic) and underwent immunofluorescent staining with vascular (Vascular Endothelial Growth Factor, VEGF; CD34) and regenerative markers (cytokeratins 7 and 19, CK7 and CK19; alpha-fetoprotein, AFP; CD133). Confocal microscopy was used to take images of each liver zone (Periportal, PP; Midlobular, ML; Pericentral, PC) and signal quantification was performed with FIJI. **Results:** Cirrhosis was significantly associated with male sex (11/12 cirrhotic patients, Fischer's exact $p=0.036$), increased aspartate aminotransferase (AST) (median 64 vs 44.5 U/L, $p=0.034$), decreased platelets (102 vs 174 K/mcL, $p=0.0009$), increased liver stiffness ($n=27$, 15.0 vs 9.95 kPa, $p=0.022$), and increased hepatic venous pressure gradients ($n=34$, 8.0 vs 4.5 mmHg, $p=0.0057$). Higher CD34 expression was noted in non-cirrhotic vs cirrhotic PC regions (median: 2.27 vs 1.45, $p=0.046$) and higher VEGF expression was observed in middle-stage (IF 3-4) vs cirrhotic PC zones (95.77 vs 41.64, $p=0.018$). Higher CD133 expression was seen in middle- compared to early-stage PC regions (2.83 vs 0.82, $p=0.037$). AFP expression was significantly higher in middle-stage vs cirrhotic ML regions (8.36 vs 2.18, $p=0.042$). Lower CK19 expression was detected in cirrhotic vs early-stage (IF 0-2) PP regions (164.2 vs 305.1, $p=0.044$). AFP and particularly CK7 were expressed notably in the PP zone, but did not statistically differ between disease stages, suggesting liver regeneration is occurring consistently throughout disease. CK7 and CK19 expression was also noted in the ML and PC regions, typically in middle-stage disease. **Conclusion:** CD34 and VEGF data suggest angiogenesis and vascular remodeling are prominent features even in early- and middle-stage CHD. CK7, CK19, CD133, and AFP results reveal that ductular reaction and liver regeneration take place in the PP region throughout the spectrum of CHD disease but that the ML and PC zones are also involved (most notably during middle-stage disease), indicating that liver regeneration begins earlier in the disease process and to a greater extent than perhaps was previously appreciated.

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1257-C | VIR-2218 AND VIR-3434 THERAPY IS EFFICACIOUS IN PRECLINICAL MODELS OF HEPATITIS DELTA VIRUS INFECTION

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Background: Chronic Hepatitis Delta Virus (HDV) infection represents the most severe form of viral hepatitis with limited treatment options. HDV is a satellite virus of Hepatitis B Virus (HBV) that depends on HBV-derived HBsAg for envelopment and viral dissemination. VIR-2218 is an investigational RNAi therapeutic that targets a highly conserved region within the HBV X open reading frame and demonstrates potent knockdown of all HBV transcripts, including HBsAg. VIR-3434 is an investigational monoclonal antibody targeting the antigenic loop of HBsAg, inhibiting viral entry, and reducing circulating HBsAg in preclinical models and in early-stage clinical trials. This study aims to investigate the antiviral effect of VIR-2218 and VIR-3434 on HDV infection in preclinical models. **Methods:** *In vitro* antiviral efficacy of VIR-2218 was determined in an HBV/HDV co-infection model of primary human hepatocytes (PHH). Secreted HBsAg was quantified using ELISA and secreted infectious HDV virions by re-infection of naïve Huh7-NTCP cells. *In vitro* neutralization potency of VIR-3434 was determined against HDV enveloped with HBsAg of eight different HBV genotypes. *In vivo*, efficacy of VIR-2218/VIR-3434 mono- and combination treatments were

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

evaluated in HBV/HDV co-infected liver-chimeric mice. **Results:** VIR-2218 treatment *in vitro* reduced HBsAg and secreted infectious HDV with picomolar efficacy. VIR-3434 neutralized HDV infection *in vitro* with > 10,000-fold higher potency than Hepatitis B Immunoglobulins. Neutralization activity was pan-genotypic as tested with HDV enveloped with HBsAg of HBV genotypes A-H. Combination treatment of co-infected PHH with VIR-2218 and VIR-3434 reduced levels of infectious HDV virions. *In vivo*, mono-treatment with VIR-2218 or VIR-3434 decreased HBsAg and HDV RNA serum levels by > 0.5 log and > 1 log, respectively. Combination treatment reduced HBsAg and HDV RNA serum levels by > 2 log. **Conclusion:** VIR-2218 and VIR-3434 have previously shown antiviral efficacy against HBV infection in multiple *in vitro* and *in vivo* models. Due to the shared use of HBsAg by HBV and HDV, targeting HBsAg also reduces concurrent HDV infection. VIR-2218 and VIR-3434 exert antiviral efficacy against HDV as single agents and in combination by reducing HBsAg secretion, circulating HBsAg and HDV virions, as well as by blocking entry into hepatocytes. These data support the clinical development of VIR-2218 and VIR-3434 for treatment of patients with chronic HDV infection.

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f 1258-C | YAP MEDIATES HIV-RELATED LIVER FIBROSIS

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Background: The successful implementation of antiretroviral therapy has shifted the focus of human immunodeficiency virus-1 (HIV-1) research towards the long-term effects of persistent, controlled infection. We and others have demonstrated that HIV accelerates liver fibrosis attributable to multiple etiologies, including HCV, HBV, and fatty liver disease. Evidence also suggests that HIV infection itself is associated with liver fibrogenesis. Recent studies have implicated Yes-Associated Protein 1 (YAP1) and the upstream lysophosphatidic acid (LPA)/PI3K/AKT pathway as critical regulators of hepatic fibrogenesis, and suggest a connection to HIV-related liver fibrosis. The aim of our study was to identify the relationship between YAP/PI3K/AKT pathway activation and HIV-related liver fibrosis. **Methods:** We examined the impact of HIV on the YAP pathway on serum samples as well as primary hepatic stellate cells (pHSC) and human hepatocytes (pHH) cultured directly from healthy donors. *Ex vivo* precision cut liver slices (PCLS) are also generated from patient samples which serve as transiently culturable tissue and facilitates the observation of HIV within the context of complete hepatic architecture. We also utilized a humanized mouse model (NRG-hu HSC mice) with both human liver tissue and immune system infected with HIV-1. The data was supplemented with both traditional *in vitro* models as well as a 3D spheroid system which supports crosstalk between hepatocytes and pHSCs. **Results:** Human serum samples analyzed via ELISA showed elevated levels of circulating YAP-related protein within HIV infected patients. PCLS and *in vitro* analysis of pHSCs, pHHs, and Huh7 cells (including mono and co-culture models (spheroids)) also showed that YAP-related and profibrotic genes were upregulated when exposed to HIV. In addition to upregulating YAP-regulated genes, the humanized mouse model developed histologically worsened fibrosis after infection with HIV. When Huh7 cells and pHSCs were each exposed to individual HIV proteins, gp120 was found to most closely reproduce the profibrotic program of the virus. Finally, lysophosphatidic acid receptor 1 (LPAR1), PI3K, and AKT inhibitors and knockout via siRNAs inhibitors abrogated the fibrotic effects of HIV exposure. **Conclusion:** We demonstrate through multiple lines of evidence that the LPAR/PI3K/AKT axis is vital for the activation of YAP and hepatic fibrogenesis due to HIV infection. This novel mechanistic insight suggests new pharmacologic targets for treatment of liver fibrosis in persons living with HIV.

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1300-C | A 20% DECREASE OF SERUM CHI3L1 INDICATES HISTOLOGICAL REGRESSION IN PATIENTS WITH CHRONIC HEPATITIS B DURING ANTIVIRAL TREATMENT

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Background: Chitinase 3-like 1 (CHI3L1) is a marker for staging of liver fibrosis, however its dynamic change and the potential application of CHI3L1 as a non-invasive surrogate marker for liver fibrosis regression in patients with chronic hepatitis B (CHB) during antiviral treatment is unknown. **Methods:** Serum CHI3L1 levels were tested in treatment-naïve patients with CHB who performed liver biopsy before and at 78 weeks of entecavir-based therapy. Histological change at 78 weeks were evaluated with the Ishak score as well as the P-I-R score. Liver fibrosis regression was defined as the Ishak score decreased by ≥ 1 point or predominantly regression by P-I-R score if there was no change in Ishak score. Kruskal-Wallis test was used to compare the differences in absolute values or changes of CHI3L1 levels from the baseline to 78 weeks, chi-square test was used to compare the proportion of patients with decreased CHI3L1 levels during treatment. **Results:** A total of 131 CHB patients were enrolled with a median age of 36 (29, 43) years and 77.9% of them were males. There were 41 (31.3%), 29 (22.1%), and 25 (19.1%) patients staged at significant fibrosis (Ishak 3), advanced fibrosis (Ishak 4), and cirrhosis (Ishak 5 and Ishak 6) before treatment according to the Ishak score system. Totally 83 (63.4%) of patients achieved histological regression at 78 weeks, and 48 (36.6%) were classified to the non-regression group. The baseline characters were comparable between two groups. Median levels of CHI3L1 seemed similar in both groups at baseline and at each visit during treatment [at baseline, 26 weeks, 52 weeks, and 78 weeks were 87.57 (66.42, 115.24), 67.52 (51.06, 91.66), 66.73 (45.20, 97.47), 69.41 (47.52, 88.56) *vs.* 91.29 (61.99, 136.85), 73.28 (53.70, 111.97), 84.39 (54.54, 131.59), 74.21 (54.41, 97.57) ng/ml, respectively; $p = 0.330\sim0.986$]. However, both groups showed a significant decrease in CHI3L1 levels during treatment compared with pre-treatment. Besides that, the decrease was more remarkable in the regression group at 52 weeks of treatment (the median difference in CHI3L1 levels: -19.09 ng/ml *vs.* -1.94 ng/ml, $p = 0.039$; the median rate of change: -26.85% *vs.* -3.05%, $p = 0.039$). Furthermore, we found that the proportion of patients with CHI3L1 decline during treatment was higher in the regression group than in the non-regression group at 52 and 78 weeks of treatment (79.5% *vs.* 54.2%, $p = 0.004$; 80.7% *vs.* 58.3%, $p = 0.010$). In addition, the proportion of patients with a ≥ 20% decrease in CHI3L1 was significantly higher in the regression group than in the non-regression group at 52 weeks of treatment (56.6% *vs.* 35.4%, $p = 0.031$). **Conclusion:** Serum CHI3L1 levels decreased significantly during antiviral therapy in treatment-naïve CHB patients with liver fibrosis, a ≥ 20% decrease at 52 weeks could be a potential non-invasive surrogate marker of liver fibrosis regression.

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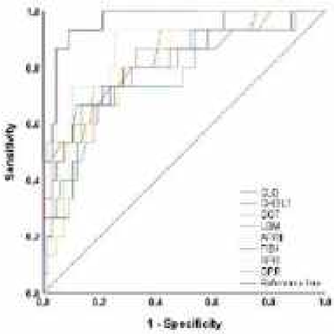
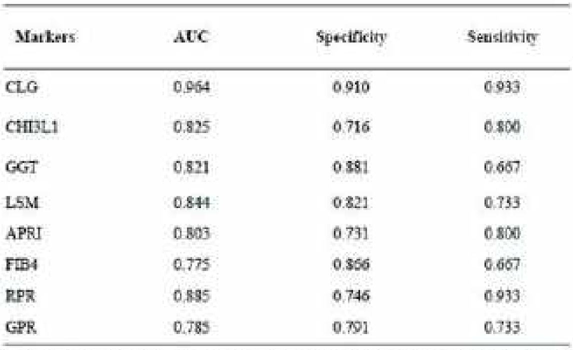
1301-C | A NONINVASIVE DIAGNOSTIC MODEL FOR LIVER CIRRHOSIS IN PATIENTS WITH HBV INFECTION BASED ON CHI3L1 AND ROUTINE CLINICAL PARAMETERS

Zhiwei Xie[1], Jinnian Lin[2], Chujing Li[1], Wenyu Wang[1], Songlian Liu[1], Honglian Bai[2], Jianping Li[1] and Yujuan Guan[1], (1)Guangzhou Eighth People's Hospital, Guangzhou Medical University, (2)The First People's Hospital of Foshan

Background: Chitinase-3 like-protein-1 (CHI3L1) is a chitinase-like protein that is expressed in various tissues, including the liver. This study aimed to investigate whether CHI3L1 could serve as a non-invasive diagnostic marker for assessing liver cirrhosis in patients with hepatitis B virus (HBV) infection. **Methods:** This study enrolled chronic hepatitis B (CHB) patients from Guangzhou Eighth People's Hospital and The First People's Hospital of Foshan. Inclusion criteria: age e 18 years, HBsAg (+) e 6 months, and HBV DNA (+). Patients with liver injury caused by factors such as HCV, HDV, or other etiologies were excluded. Serum CHI3L1 levels were measured using chemiluminescence enzyme-linked immunoassay. Liver biopsy was performed on patients who provided consent for liver puncture. Univariate and multivariate logistic regression analyses were conducted to identify independent predictors of liver cirrhosis and establish a diagnostic model. **Results:** Between November 2018 and July 2022, 152 patients with HBV infection were enrolled. They were divided into the CHB group (n = 115) and the liver cirrhosis (LC) group (n = 37). The median (interquartile) levels of serum CHI3L1 were 29.79 (21.68) ng/ml in the CHB group and 74.73 (75.66) ng/ml in the LC group. The difference between the two groups was statistically significant ($p < 0.001$). Among the 87 patients who underwent liver biopsy, the mean age was 38.14 ± 8.62 years; 58 (66.7%) were male; 28 (32.2%) were HBeAg (+); 69 were CHB and 18 were LC; 25 (28.7%) had fibrosis staging 0-1 (S0-1), 32 (36.8%) had S2, 11 (12.6%) had S3, and 19 (21.8%) had S4. CHI3L1 levels showed a gradual increase with the progression of fibrosis. Serum CHI3L1 expression levels were positively associated with liver stiffness measurement (LSM), aspartate aminotransferase-to-platelet ratio index (APRI), fibrosis-4 (FIB-4) index, gamma-glutamyl transferase-to-platelet ratio (GPR), and red cell distribution width-to-platelet ratio (RPR) ($p < 0.05$). The results of both univariate and multivariate logistic regression analyses indicated that CHI3L1, LSM, and GGT were independent predictors of liver cirrhosis in patients with HBV infection ($p < 0.05$). The diagnostic model was established as follows: CHI3L1/LSM/GGT (CLG) = 0.044 × CHI3L1 + 0.353 × LSM + 0.068 × GGT - 9.191. The receiver operating characteristic (ROC) curve demonstrated that CLG outperformed other non-invasive methods in diagnosing cirrhosis, with an area under the ROC curve (AUC) of 0.964 for liver cirrhosis diagnosis (Sensitivity: 0.933, Specificity: 0.910, cut-off value: -1.6314) (Figure 1). **Conclusion:** CHI3L1 levels were significantly higher in cirrhosis patients with HBV infection compared to non-cirrhosis patients. The CLG model exhibited a strong diagnostic efficacy for liver cirrhosis in patients with HBV infection, making it a precise non-invasive diagnostic index for clinical practice.





Markers	AUC	Specificity	Sensitivity
CLG	0.964	0.910	0.933
CHI3L1	0.825	0.716	0.800
GGT	0.821	0.881	0.667
LSM	0.844	0.821	0.733
APRI	0.803	0.731	0.800
FIB4	0.775	0.866	0.667
RPR	0.885	0.746	0.933
GPR	0.785	0.791	0.733

Figure 1. Diagnostic value of CLG, CHI3L1, LSM, GGT for distinguishing S0-S1 from S4 in patients with HBV infection. CLG(CHI3L1/LSM/GGT) = 0.044 × CHI3L1 + 0.353 × LSM + 0.068 × GGT-9.191; CHI3L1, Chitinase-3 like-protein-1; GGT, gamma-glutamyl transferase; LSM, liver stiffness measurement; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 index; RPR, red cell distribution width to platelet ratio; GPR, gamma-glutamyl transferase to platelet ratio.

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1302-C | ANALYSIS OF INTRAHEPATIC VIRAL RESERVOIR IN GAMBIAN CHRONICALLY INFECTED PATIENTS: CORRELATION WITH EMERGING SERUM VIRAL MARKERS AND FUNCTIONAL CHARACTERIZATION OF CLINICAL ISOLATES

Anaëlle Dubois[1,2], Sarah Heintz[1,2], Damien Cohen[1], Marie-Laure Plissonnier[1,3], Francoise Berby[1,2], Marintha Heil[4], Massimo Levrero[5], Fabien Zoulim[1,6,7,8], Yusuke Shimakawa[9], Maud Lemoine[10], Umberto D'Alessandro[11,12], Isabelle Chemin[1,2] and Barbara Testoni[1,3], (1)Cancer Research Center of Lyon (CRCL), Inserm U1052, Cnrs UMR5286, Lyon, France, (2) Institut D'hépatologie De Lyon, (3)Institut d'Hépatologie De Lyon, (4)Roche Molecular Diagnostics, (5) Department of Medicine Sciac and the Italian Institute of Technology (IIT) Center for Life Nanosciences (CLNS), University of Rome La Sapienza, Rome, Italy, (6) Hépatologie Unit, Hospices Civils De Lyon, Lyon University, Inserm, (7)Department of Hepatology, Croix Rousse Hospital, Hospices Civils De Lyon, France., (8) Hospices Civils De Lyon (HCL), Lyon, France, (9)Institut Pasteur, (10)Imperial College, London, (11)MRC Unit the Gambia, (12)School of Hygiene and Tropical Medicine, Banjul, the Gambia

Background: In Sub-Saharan Africa, hepatocellular carcinoma, one of the most common cancers in the region, is mainly attributable to HBV infection, which has a prevalence of 10% in the area. Mode of transmission, age of infection, and various genetic and environmental factors differ completely between Western, Asian and Sub-Saharan African populations. Therefore, data relating to the natural history of HBV infection in these patients are much needed. **Methods:** 96 untreated chronically HBV infected (CHB) patients were retrospectively selected from samples collected in The Gambia in the frame of the PROLIFICA program. Paired liver biopsy and serum samples were analyzed for serum HBV DNA, HBsAg, HBcrAg (Lumipulse CLEIA Assay) and alanine aminotransferase (ALT) levels. Liver total HBV DNA (tHBV DNA), cccDNA and 3.5Kb RNA were assessed by droplet digital PCR (ddPCR) and cccDNA transcriptional activity was calculated as 3.5Kb RNA/cccDNA ratio. Liver histology scores were also available. Serum HBV RNA (cirB-RNA) was quantified by the Roche HBV RNA investigational assay for use on the cobas® 6800 System (Scholtès, J Clin Virol 2022). **Results:** The large majority of patients were HBeAg(-), HBV genotype E and only 10% of them had ALT levels above twice the upper limit of normal. Median levels of serum HBV DNA were 2.9 (2.1-4.2) Log IU/ml and qHBsAg were 3.7 (2.5-4.9) Log IU/ml. All patients had quantifiable tHBV DNA in their liver, 90% had quantifiable cccDNA and 85% quantifiable 3.5Kb RNA. Results indicated the presence of two groups of patients with comparable cccDNA levels, but different transcriptional activity, which was not reflected in differences in the serum HBV DNA or qHBsAg levels. Eighty-five serum samples were available for HBcrAg and cirB-RNA quantification, which were detectable in 35 and 33 samples, respectively. Both markers were highly correlated with cccDNA levels which was confirmed also in the group of patients with low cccDNA transcriptional activity. Analysis of in vitro replicative capacity of clinical HBV isolates demonstrated a decreased HBsAg secretion associated with intracellular cytoplasmic accumulation at the endoplasmic reticulum. **Conclusion:** So far, this is the most comprehensive study evaluating the correlations between intrahepatic and serum HBV activity in people living with CHB in Sub-Saharan Africa. These data will contribute to a better understanding of the natural history of CHB and associated pathogenesis in this population.

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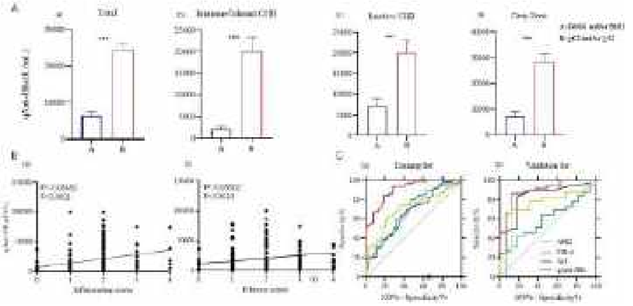
Disclosure information not available at the time of publication: Yusuke Shimakawa, Maud Lemoine, Umberto D'Alessandro

1303-C | ANTI-HBC QUANTIFICATION AS A BIOMARKER FOR IDENTIFYING SIGNIFICANT LIVER INJURY AMONG CHB PATIENTS WITH NORMAL ALT

Mingyang Feng, Xiaoyin Wang, Kehui Liu, Gangde Zhao, Weiliang Tang, Baoyan An, Lanyi Lin, Yezhou Ding and Hui Wang, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine

Background: Increased evidence demonstrates that there are still significant liver injuries in some CHB patients with normal ALT (CHB-NALT). In this study, we aim to investigate the correlation between hepatitis B core antibody quantification (qAnti-HBc) and the severity of hepatic pathological damage in CHB-NALT patients, as well as the feasibility of using it as a serum marker for identifying significant liver injury. **Methods:** CHB-NALT patients without antiviral therapy who underwent liver biopsy from Jan 2015 to Dec 2022 were retrospectively enrolled. The Scheuer scoring system was used to assess liver inflammation and fibrosis. The serum qAnti-HBc level was measured, using the newly developed double-sandwich immunoassay (Wantai, Beijing, China), calibrated in conjunction with the WHO standard (NIBSC, UK). **Results:** 212 CHB-NALT patients were enrolled for analysis. Based on the AASLD 2018 Hepatitis B guideline, 31% and 32% of these patients are in the Immune-Tolerant and inactive CHB phase respectively, whereas 37% were unable to be classified into any of the usual immune states, who were considered to be in the 'grey zone (GZ)'. 73% of these patients had significant liver injury. qAnti-HBc was significantly higher in CHB-NALT patients with significant liver injury than these without, regardless of the immune states (Fig. A). In addition, there was a positive correlation between liver injury scores and qAnti-HBc in these patients (Fig. B). In order to determine the feasibility of qAnti-HBc as a biomarker for identifying significant liver injury, these patients were randomly divided into two groups at a 3: 1 ratios, i.e., 159 subjects were assigned to the training cohort and the remaining 53 cases were assigned to the validation cohort. There was no significant difference in clinical characteristics between the two cohorts. In training cohort, the area under receiver operating characteristic curve (AUC) of qAnti-HBc level was 0.9037 (95% CI: 0.8498–0.9575, $p < 0.0001$) with a cut-off of 7585 IU/mL, the sensitivity and specificity were 0.8257 and 0.8056, respectively. By contrast, the AUC of ALT, FIB-4 and APRI was 0.6613, 0.6792 and 0.7101, respectively. In addition, similar results were obtained in the validation cohort (Fig. C). **Conclusion:** Serum qAnti-HBc level was associated with the severity of liver injury and might be served as a novel biomarker for identifying significant liver injury among CHB-NALT.



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1304-C | APPLICATION OF NOVEL HEPATITIS B CORE ANTIGEN-SPECIFIC IMMUNOASSAYS TO MONITOR TREATMENT RESPONSE IN HBEAG POSITIVE CHRONIC HEPATITIS B

Pir Shah^{1,2}, Rene Geissler^{3}, Megha Patel^{3}, Khawaja Hassam^{1}, Satinder Pal Kaur^{1}, Mark Anderson^{3}, Gavin A Cloherty^{3} and Daryl T. Y. Lau^{1}, (1)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (2)University of Texas San Antonio, Texas, USA, (3)Abbott Laboratories, IL

Background: Non-invasive surrogate markers to evaluate changes in HBV cccDNA levels and transcriptional activities are important in monitoring treatment response without the need for liver biopsy. Two novel hepatitis B core antigen (HBcAg) immunoassays that specifically detect HBV DNA-containing particles (HBcAg) and phosphorylated non-HBV DNA-containing particles (P-HBcAg) were recently developed. We examined the kinetics of HBcAg and P-HBcAg in relation to on-treatment HBV DNA and RNA levels in 22 HBeAg (+) patients who were treated for an average 4.4 (2.2-6.7) years with nucleos(t)ide analogs (NUCs). **Methods:** This is a single center, retrospective study that selected HBeAg(+) patients on prolonged NUC therapy with available serial stored sera from baseline. The HBcAg and P-HBcAg assays are chemiluminescent microparticle immunoassays (CMIA) performed on a fully automated platform (ARCHITECT i2000SR). Specific monoclonal antibodies were used to capture phosphorylated or non-phosphorylated HBcAg, but not HBeAg, in circulation. The limit of quantification (LOQ) is 14 pg/ml for HBcAg and 4 pg/ml for P-HBcAg. Serum HBV RNA was measured using the Abbott RealTime 0.2 HBV RNA Research assay (Sensitivity: 1.65 log U/ml). Quantitation of HBsAg (qHBsAg) was

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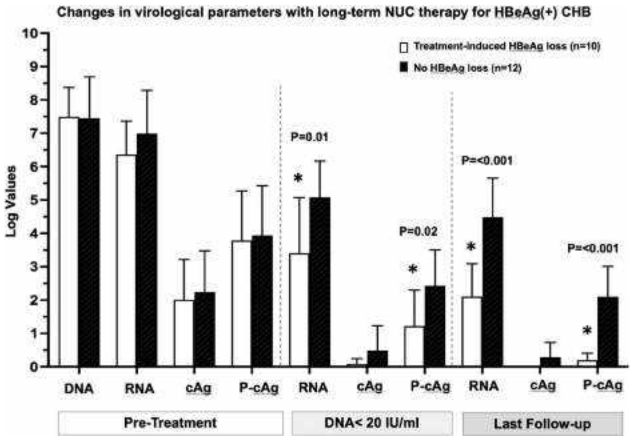
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

performed using ARCHITECT HBsAg assay (Sensitivity: 0.05 U/ml). **Results:** This was an Asian predominant (95%) cohort with HBV genotypes B and C. 10 (45%) achieved HBeAg loss after 2.7 (0.5-5) years of therapy and only 1 had HBsAg loss. Both groups with and without HBeAg loss had similar treatment duration (mean 4.5 vs. 4.3 y, $p = 0.4$) and pretreatment HBV DNA, RNA, HBcAg, P-HBcAg levels [Figure]. At baseline, HBV DNA correlated significantly with HBcAg ($r = 0.63$, $p < 0.001$); HBV RNA correlated equally well with HBcAg and P-HBcAg ($r = 0.79$ and 0.74 respectively, $p < 0.0001$). When HBV DNA was reduced to < 20 IU/ml in both groups, HBcAg was also suppressed to undetectable or low levels. At time of DNA < 20 IU/ml and at last follow up, both RNA and P-HBcAg levels were significantly lower for those who achieved HBeAg loss [Figure]. The on-treatment RNA and P-HBcAg (but not HBcAg) levels correlated closely at optimal DNA suppression ($r = 0.79$, $p < 0.0001$) and at last follow-up ($r = 0.87$, $p < 0.0001$). The qHBsAg levels were similar for those with and without HBeAg loss at baseline (3.4 vs. 3.5 log IU/ml, $p = 0.69$) and at last follow-up (3.3 vs. 3.4 log IU/ml, $p = 0.87$) excluding the single patient with HBsAg clearance. **Conclusion:** For HBeAg (+) patients with chronic hepatitis B, HBV DNA correlated significantly with HBcAg. Patients with treatment-induced HBeAg loss had differential differences in HBV RNA and P-HBcAg decline from those without, whereas the on-treatment qHBsAg titers cannot distinguish the 2 groups. P-HBcAg, together with HBV RNA, may serve as surrogate biomarker for HBV cccDNA and provides insight on its transcriptional status with prolonged NUC therapy or novel therapeutic agents.



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1305-C | BIOMARKER-BASED IDENTIFICATION OF HIGH-RISK GROUPS FOR PRIMARY HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS B PATIENTS UNDER THE NUCLEOS(T)IDE ANALOGUE TREATMENT

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Background: Although nucleos(t)ide analogues (NUCs) treatment for chronic hepatitis B (CHB) reduces the risk of developing hepatocellular carcinoma (HCC), it does not completely suppress developing HCC. Clinical characteristics of CHB patients who developed primary HCC under NUC treatment are not clear. Recently, we reported that serum GDF15 level may be a predictor of developing primary HCC after direct-acting antiviral therapy in chronic hepatitis C patients. The aim of this study was to identify high-risk groups for primary HCC in CHB patients under NUC treatment by retrospective analysis of biomarkers including serum GDF15. **Methods:** Two hundred forty-two CHB patients for whom stored sera were available, who had treated with NUC for at least 1 year at the time of stored serum collection, whose HBV DNA levels in sera were less than 3.0 log IU/mL, and who had no history of HCC were included. Stored sera were used to measure GDF15 using ELISA and HBcrAg using immunoassay for total antigen including complex by pretreatment (iTACT) technology. **Results:** The median age of the patient cohort was 55 years old, and 144 patients (60.0%) were male. The median observation period was 123.1 months. Seventy-three (30.3%) were hepatitis B envelope antigen (HBeAg) positive. The median hepatitis B surface antigen (HBsAg) was 3.2 log U/mL. HBcrAg (lower detection limit: 2.1 log U/mL) was quantified in 211 patients (87.2%) with the median of 4.2 log U/mL. GDF15 was quantified in 241 patients (99.6%) with the median of 0.86 ng/mL. During the observation period, 44 patients (18.2%) developed primary HCC, of which 13 were HBeAg positive. In multivariate analysis, gender (HR: 2.65 [1.18-5.96]), γ-GTP (HR: 1.01 per 1IU/L increase [1.003-1.011]), AFP (HR: 1.06 per 1ng/mL increase [1.02-1.09]), GDF15 (HR: 1.53 per 1ng/mL increase [1.04-2.12]), and FIB-4 index (HR: 1.27 per 1 increase [1.10-1.43]) were significant factors in the Cox proportional hazards model for factors related to the occurrence of primary HCC, while HBsAg, HBeAg, HBcrAg, and HBV DNA were not significant. When the median is defined as cut off value (0.858ng/mL), the cumulative HCC occurrence rate at 5/10 years was 12.4%/23.1% and 6.7%/9.2% in high GDF15 group and in low GDF15 group, respectively. **Conclusion:** Male sex, high γ-GTP, high AFP, high GDF15 and fibrosis progression were high risk factors for the occurrence of primary HCC in CHB patients under NUC treatment.

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The following people have nothing to disclose: Kazuhiro Murai, Hayato Hikita, Satoshi Tanaka, Jihyun Sung, Akiyoshi Shimoda, Makoto Fukuoka, Akira Nishio, Takahiro Kodama, Tomohide Tatsumi, Hidenori Toyoda, Tetsuo Takehara

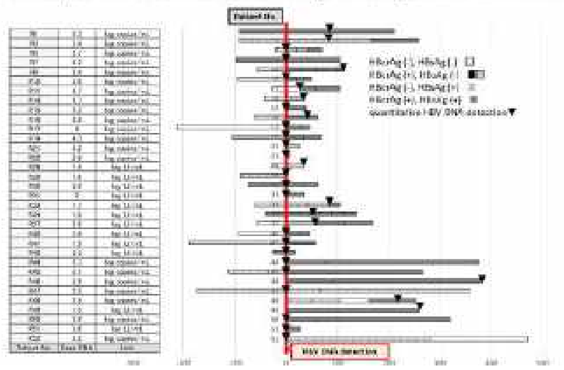
Disclosure information not available at the time of publication: Emi Sometani, Shinji Kuriki, Satoshi Shigeno

1306-C | CLINICAL APPLICATION OF NOVEL HIGHLY SENSITIVE HEPATITIS B SURFACE ANTIGEN AND HEPATITIS B CORE-RELATED ANTIGEN ASSAYS FOR MANAGEMENT OF HBV REACTIVATION

Takako Inoue[1], Takanori Suzuki[2], Takehisa Watanabe[3], Etsuko Iio[3], Katsuya Nagaoka[3], Hiroko Setoyama[3], Yoko Yoshimaru[3], Kentaro Matsuura[2] and Yasuhito Tanaka[3], (1)Nagoya City University Hospital, (2)Nagoya City University Graduate School of Medical Sciences, (3)Faculty of Life Sciences, Kumamoto University

Background: We developed a novel, highly sensitive hepatitis B core-related antigen assay (iTACT-HBcrAg) and described its utility for the diagnosis of HBV reactivation (J Hepatol, 2021). In Japan, iTACT-HBcrAg has gained pharmaceutical approval and is now available for clinical use. Meanwhile, hepatitis B surface antigen (HBsAg) assays with a higher sensitivity, such as iTACT-HBsAg, have also been developed as an alternative marker to HBV DNA. In this study, we examined the clinical application of iTACT-HBcrAg and iTACT-HBsAg to manage HBV reactivation. **Methods:** Between 2012 and 2022, 42 patients who were diagnosed with HBV-resolved infection before the introduction of systemic chemotherapy or immunosuppressive therapy were enrolled. Among them, the patients diagnosed with HBV reactivation and whose serial sera were stored were included in this study. Serial sera were measured with iTACT-HBcrAg (cut-off value: 2.1 log U/mL) and iTACT-HBsAg (cut-off value: 0.0005 IU/mL) and compared to the results of serum HBV DNA monitoring performed as the medical practice. The diagnostic criterion for HBV reactivation was detection of serum HBV DNA. This study was approved by the ethical review committee of our institute. **Results:** Thirty-three patients diagnosed with HBV reactivation during or after systemic chemotherapy or immunosuppressive therapy, and with quantitative detection of HBV DNA during the observation period, were selected. Their underlying diseases were hematopoietic malignancies in 22, non-hematopoietic malignancies in 4, autoimmune diseases in 5, and others in 2 patients. Of the 33 patients in which serum HBV DNA was detected quantitatively, iTACT-HBcrAg was detected early or simultaneously with the diagnosis of HBV reactivation in 85% (28/33), and was detected simultaneously or within 1 month of serum HBV DNA detection quantitatively in 94% (31/33). When iTACT-HBcrAg and iTACT-HBsAg were measured simultaneously, at least one of them was detected earlier or simultaneously with HBV DNA in 100% (33/33) (Figure). **Conclusion:** In this study, the usefulness of iTACT-HBcrAg for the diagnosis of HBV reactivation was reproduced, and the addition of iTACT-HBsAg provided a higher diagnostic performance. iTACT-HBcrAg and iTACT-HBsAg are rapid tests (within 30 min) with comparable sensitivity to quantitative HBV DNA detection. Because they serve as a guide for administration of nucleos(t)ide analogues, they are useful for monitoring of HBV reactivation among outpatients.

Figure Comparison of iTACT-HBcrAg and HBsAg for management of HBV reactivation



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Disclosure information not available at the time of publication: Kentaro Matsuura

1307-C | CLINICAL SIGNIFICANCE OF MAC-2 BINDING PROTEIN GLYCOSYLATION ISOMER IN KOREAN PATIENTS WITH CHRONIC HEPATITIS B: COMPARATIVE STUDY OF NON-INVASIVE MODALITY FOR DIAGNOSIS OF LIVER FIBROSIS

Jae-Sung Yoo[1], Hye Seon Kim[2], Jin Seoub Kim[2], Ji Min Kim[2], Ji Won Han[2], Pil Soo Sung[1], Si Hyun Bae[3], Jong Choi[1], Seung Kew Yoon[1] and Jeong Won Jang[1], (1) Seoul St Mary's Hospital, the Catholic University of Korea, Seoul, Republic of Korea, (2)The Catholic University of Korea, Seoul, Korea, (3)The Catholic University of Korea

Background: Mac-2 binding protein glycosylation isomer (M2BPGi), one of the novel, non-invasive fibrosis markers, has been evaluated for assessing liver fibrosis in a multitude of studies. Nevertheless, there is a scarcity of data on its diagnostic accuracy of M2BPGi for liver fibrosis in patients with chronic hepatitis B (CHB). The aim of this study is to investigate the clinical value of M2BPGi in assessing liver fibrosis in comparison with existing tools for liver fibrosis screening. **Methods:** A total of 367 patients diagnosed with chronic hepatitis B between June 2016 and January 2022, at our liver units were entered in this study. Patients' medical records at the time of liver biopsy were retrospectively reviewed for determining M2BPGi, transient elastography (TE, FibroScan®), fibrosis-4 (FIB-4) index, and aspartate aminotransferase to platelet ratio index (APRI). Liver fibrosis on pathology was assessed based on METAVIR fibrosis scores. **Results:** Pathological liver fibrosis grades of the 367 patients (216 males and 151 females; 163 without hemato-oncologic disease) were classified as F0 ($n=59$, 16%), F1 ($n=84$, 23%), F2 ($n=40$, 11%), F3 ($n=68$, 19%) and F4 ($n=116$, 32%). The median M2BPGi values for METAVIR fibrosis score F0, F1, F2, F3 and F4 were 1.9, 1.5, 1.4, 1.8, and 3.2 cutoff index (COI), respectively ($p<0.001$). M2BPGi levels weak correlated with the METAVIR scores ($r=0.295$, $p<0.001$). The area under receiver operating characteristic (AUROCs) with M2BPGi for e F2, e F3 and F4, were 0.6161, 0.6581 and 0.6908, respectively. To identifying significant fibrosis (F2-4), both M2BPGi and TE were significantly better than FIB-4 and APRI. The AUROCs with M2BPGi, TE, FIB-4, and APRI for diagnosing cirrhosis were 0.7208, 0.8085, 0.5051, and 0.6011, respectively. When analyzed without hemato-oncologic patients, the predictive value of M2BPGi for assessing liver fibrosis slightly increased (AUROC 0.6944 for significant fibrosis; 0.7837 for cirrhosis), which was significantly better than that of FIB-4 and APRI. With multivariate analysis with several other non-invasive fibrosis indices, M2BPGi didn't remain significant for diagnosing e F2, e F3, F4 (OR: 0.96, 95%CI: 0.77-1.20, $p=0.7$; OR: 1.05, 95%CI: 0.83-1.35, $p=0.7$; OR: 1.14, 95% CI: 0.93-1.44, $p=0.060$). However, M2BPGi Platelet ratio index (MPRI) was shown to be associated with e F3 and F4 (OR: 1.41, 95%CI: 1.09-2.06, $p=0.030$; OR: 1.43, 95% CI: 1.15-1.87, $p=0.03$) in multivariate analysis. **Conclusion:** Serum M2BPGi together with TE is a reliable non-invasive tool for assessing liver fibrosis and better performs than FIB-4 and APRI. Its performance for assessing fibrosis appears to be more efficient among non-hemato-oncologic patients. Additionally, markers combined with

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platelets and M2BPGi suggested the potential to enhance the capacity to predict liver fibrosis.

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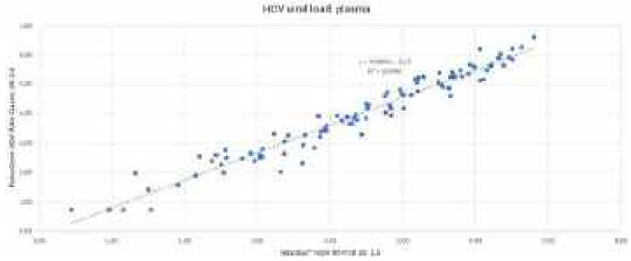
1308-C | COMPARISON OF ROBOGENE® 2.0 AND ALTOSTAR® ASSAYS FOR QUANTIFICATION OF PLASMA HDV RNA IN BULEVIRTIDE-TREATED PATIENTS WITH HDV RELATED CIRRHOSIS

Maria Paola Anolli[1], Sara Uceda Renteria[2], Elisabetta Degasperi[1], Floriana Facchetti[1], Dana Sambarino[1], Marta Borghi[1], Riccardo Perbellini[1], Roberta Soffredini[1], Sara Monico[1], Ferruccio Ceriotti[2] and Pietro Lampertico[1,3], (1)Division of Gastroenterology and Hepatology, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, (2)Virology Unit, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, (3)CRC "a. M. and a. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan

Background: Diagnosis and treatment of chronic hepatitis Delta (CHD) primarily depend on the quantification of HDV RNA, but there is considerable variability among different assays. The aim of this study was to compare two methods for measuring serum HDV RNA levels in Bulevirtide (BLV)-treated patients with HDV related cirrhosis. **Methods:** Frozen plasma from consecutive BLV treated-CHD patients were tested in a single-center retrospective study for HDV RNA levels by using two different quantification methods: Robogene® 2.0 (Roboscreen GmbH, Leipzig, Germany; CE-IVD-labeled; LOD 6 IU/mL) and AltoStar® HDV RT-PCR Kit 1.5 (Altona Diagnostics, Hamburg, Germany; RUO test, estimated LOD < 10 IU/mL). RNA extraction was performed according to the manufacturer indications: manual extraction with INSTANT Virus RNA/DNA kit (Analytik Jena AG, Jena, Germany) for Robogene® 2.0 and automated extraction with AltoStar® Purification Kit 1.5 (Altona Diagnostics GmbH) for AltoStar®. The extraction volume was 400 µl for Robogene® and 500 µl for AltoStar®. HDV genotype was determined by sequencing. **Results:** A total of 100 plasma samples collected from 44 BLV-treated CHD patients were analyzed: median age was 51 (29-77) years, 57% males, 93% of European origin, 100% with cirrhosis, 57% with gastroesophageal varices, 21% with hepatocellular carcinoma history, 100% under NUC, 98% HDV genotype 1, 95% HBeAg negative, 86% HBV DNA undetectable. Median ALT were 52 (12-310) U/L, HBsAg 3.7 (0.5-4.4) Log IU/mL. Median HDV RNA levels were 3.93 (0.70-6.60) *vs.* 4.49 (0.45-6.80) Log IU/mL by Robogene® 2.0 *vs.* AltoStar® ($p < 0.0001$). Correlation between the 2 tests was excellent (Figure, $R^2 = 0.9496$). HDV RNA levels were similar (Δ ± 0.5 Log) in 57 (57%) samples, while AltoStar® reported higher HDV RNA levels in 42 (42%) [Δ between +0.5 and +1 Log in 35; Δ between +1 and +2 Log in 7] samples. In one case AltoStar® reported lower HDV RNA levels (Δ < -0.5). Of the 6 (6%) target not detected (TND)/ < LOD samples by Robogene® 2.0, 3 tested > 10 IU/mL by AltoStar®. In contrast, all the 3 (3%) < 10 IU/mL samples by AltoStar® tested < LOD/TND by Robogene®. **Conclusion:** In BLV-treated patients, HDV RNA levels quantified by AltoStar® significantly correlated with those measured by Robogene® 2.0 but viremia resulted half a log IU/ml higher by the former assay.



Disclosures: Pietro Lampertico – BMS: Advisor, No, No; ROCHE: Advisor, No, No; GILEAD SCIENCES: Advisor, No, No; GSK: Advisor, No, No; ABBVIE: Speaking and Teaching, No, No; MSD: Advisor, No, No; ARROWHEAD: Advisor, No, No; ALNYLAM: Advisor, No, No; JANSSEN: Advisor, No, No; SBRING BANK: Advisor, No, No; MYR: Advisor, No, No; EIGER: Advisor, No, No; ANTIOS: Advisor, No, No; ALIGOS: Advisor, No, No; VIR: Advisor, No, No;

The following people have nothing to disclose: Maria Paola Anolli, Sara Uceda Renteria, Elisabetta Degasperi, Floriana Facchetti, Dana Sambarino, Marta Borghi, Riccardo Perbellini, Roberta Soffredini, Sara Monico, Ferruccio Ceriotti

1309-C | DIABETES MELLITUS IS AN INDEPENDENT PREDICTOR OF SIGNIFICANT INFLAMMATION AND FIBROSIS IN CHRONIC HEPATITIS B PATIENTS CONCURRENT WITH HEPATIC STEATOSIS

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Background: The coexistence of chronic hepatitis B (CHB) and hepatic steatosis (HS) is increasingly common, but the association of diabetes mellitus (DM) with hepatic inflammation and fibrosis is not well characterized. The aim of this study is to investigate the association of DM with significant hepatic inflammation and/or fibrosis in this population. **Methods:** This study consecutively enrolled CHB patients with concurrent HS who underwent liver biopsy from eight medical centers of China between April 2004 and October 2020. Univariable and multivariable logistic regression analyses were conducted to explore the association of DM with significant hepatic inflammation (Scheuer's system, grade [G] 2-4) and fibrosis (Scheuer''s system, stage [S] 2-4). **Results:** A total of 869 CHB patients with HS with available liver histology data were included in study analysis. The average age was 40.6 ± 10.4 years, 79.9% were male, and 8.2% (71 patients) had DM. The mean body mass index (BMI) was 24.9 ± 3.3 kg/m2 and the mean HBV-DNA was 5.3 ± 2.0 $\log_{10}$ IU/ml. About half (380 patients, 46.3%) were HBeAg-positive, and 5.9% (42 patients) were on antiviral therapy. Moderate and severe HS (grade 2-3) was present in 24.3% of patients (206 patients). The majority (529 patients, 60.9%) had significant inflammation (G2-4), and about half (431, 49.6%) had significant fibrosis (F2-4). Compared with non-DM patients, DM patients more likely had significant inflammation (76.1% vs 59.7%, $p = 0.02$) or significant fibrosis (76.1% vs 47.3%, $p < 0.001$). On multivariable logistic analysis adjusting for age, sex, BMI, HBV DNA, and HBeAg (model 1), DM was independently associated with significant inflammation (OR: 3.60; 95% CI: 1.56-8.33; $p = 0.003$) and significant fibrosis (OR: 4.08; 95% CI: 1.95-8.53; $p < 0.001$); We further adjusted for HS (model 2), and DM remained an independent factor associated with significant inflammation (OR: 3.38; 95% CI: 1.46-7.86; $p = 0.005$) and significant fibrosis (OR: 4.49; 95% CI: 2.08-9.72; $p < 0.001$) (Table). **Conclusion:** CHB patients with concurrent HS with DM was more than 3 times more likely to have significant hepatic inflammation and more than 4 times more likely to have significant fibrosis compared to non-DM patients, independent of the presence of HS, BMI, viral factors, and demographics. As liver inflammation and fibrosis are major predictors for future liver-related outcomes, collaboration between liver and metabolic specialists are needed to optimize the management of CHB patients with HS and DM. Keywords: chronic hepatitis B; nonalcoholic fatty liver diabetes; diabetes Mellitus; significant fibrosis; significant inflammation; risk factors

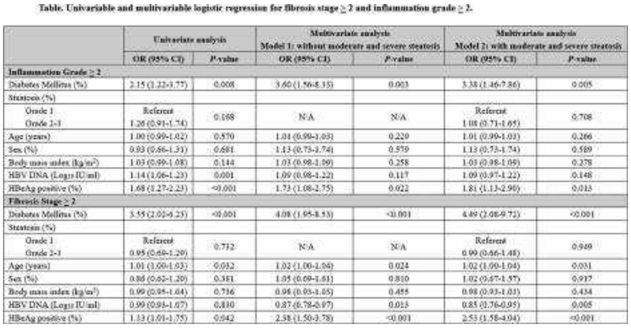

Table. Univariable and multivariable logistic regression for fibrosis stage ≥ 2 and inflammation grade ≥ 2.

	Univariate analysis		Multivariate analysis Model 1: without moderate and severe steatosis		Multivariate analysis Model 2: with moderate and severe steatosis	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Inflammation Grade ≥ 2						
Diabetes Mellitus (%)	2.15 (1.22-3.77)	0.008	3.60 (1.56-8.33)	0.003	3.38 (1.46-7.86)	0.005
Steatosis (%)						
Grade 1 Grade 2-3	Referent 1.26 (0.91-1.74)	0.168	N/A	N/A	Referent 1.08 (0.71-1.65)	0.708
Age (years)	1.00 (0.99-1.02)	0.570	1.01 (0.99-1.03)	0.220	1.01 (0.99-1.03)	0.266
Sex (%)	0.93 (0.66-1.31)	0.681	1.13 (0.73-1.74)	0.579	1.13 (0.73-1.74)	0.589
Body mass index (kg/m²)	1.03 (0.99-1.08)	0.144	1.03 (0.98-1.09)	0.258	1.03 (0.98-1.09)	0.278
HBV DNA (Log10 IU/ml)	1.14 (1.06-1.23)	0.001	1.09 (0.98-1.22)	0.117	1.09 (0.97-1.22)	0.148
HBeAg positive (%)	1.68 (1.27-2.23)	<0.001	1.73 (1.08-2.75)	0.022	1.81 (1.13-2.90)	0.013
Fibrosis Stage ≥ 2						
Diabetes Mellitus (%)	3.55 (2.02-6.23)	<0.001	4.08 (1.95-8.53)	<0.001	4.49 (2.08-9.72)	<0.001
Steatosis (%)						
Grade 1 Grade 2-3	Referent 0.95 (0.69-1.29)	0.732	N/A	N/A	Referent 0.99 (0.66-1.48)	0.949
Age (years)	1.01 (1.00-1.03)	0.032	1.02 (1.00-1.04)	0.024	1.02 (1.00-1.04)	0.031
Sex (%)	0.88 (0.62-1.20)	0.381	1.05 (0.69-1.61)	0.810	1.02 (0.67-1.57)	0.917
Body mass index (kg/m²)	0.99 (0.95-1.04)	0.736	0.98 (0.93-1.03)	0.455	0.98 (0.93-1.03)	0.434
HBV DNA (Log10 IU/ml)	0.99 (0.93-1.07)	0.830	0.87 (0.78-0.97)	0.013	0.85 (0.76-0.95)	0.005
HBeAg positive (%)	1.33 (1.01-1.75)	0.042	2.38 (1.50-3.78)	<0.001	2.53 (1.58-4.04)	<0.001

Disclosures: The following people have nothing to disclose: Jie Li, Fajuan Rui, Brian Nguyen, Qi Zheng, QingLei Zeng, Zebao He, Junping Shi, Chao Wu, Mindie H. Nguyen

1310-C | EVALUATION OF A FULLY AUTOMATED HIGH-THROUGHPUT SEROLOGY ASSAY FOR DETECTION OF HDV INFECTION

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Background: Hepatitis D virus (HDV) is a defective RNA virus requiring Hepatitis B virus (HBV) to produce infectious virus particles. Co-infection of HDV/HBV leads to increased mortality over HBV mono-infection. With new therapeutic drugs for HDV on the horizon, it has been suggested to expand current HDV screening efforts from risk based to universal screening of all HBsAg-positive individual's. Antibody to HDV is the serological marker of HDV infection and testing for HDV antibodies is recommended as the first line screening test of choice. Combining HDV antibody testing with reflex testing of HDV RNA can effectively identify patients with active infection for therapeutic treatments. The aim of this study is to evaluate the performance of a newly developed HDV antibody test, HDV Total Ig, on the fully automated and high-throughput Abbott ARCHITECT platform. **Methods:** An HDV panel, composed of 71 HDV RNA positive and 54 HDV RNA negative

Uganda/Cameroon samples previously determined using m2000 RealTi*m*e HDV RUO assay, was tested with both ARCHITECT HDV Total Ig (ARCHITECT HDV) and CE marked LIAISON XL Anti-HDV (LIAISON Anti-HDV). 600 healthy blood donors from the United States (US) were assessed with ARCHITECT HDV to determine assay specificity. A subset of 200 US donor samples was also tested with LIAISON Anti-HDV. **Results:** For the HDV panel, ARCHITECT HDV detected 67/71 RNA positive samples demonstrating comparable sensitivity ($p = 0.1336$) to the HDV RNA test with 94.4% positive agreement; sensitivity of LIAISON Anti-HDV was significantly lower ($p = 0.0412$) than the HDV RNA test with 91.5% (65/71) positive agreement. Notably, the 6 samples missed by either serology tests had low viral load ranged from 2.2-34.7 IU/ml, suggesting early seroconversion. For the 54 RNA negative samples, ARCHITECT HDV showed 76% (41/54) negative agreement with the RNA test, significantly greater ($p = 0.0003$) than the 43% (23/54) negative agreement of LIAISON Anti-HDV with the RNA test. Evaluation with the 600 US healthy blood donors showed 99.8% (599/600, 95%CI = 99.2-100.0) specificity for ARCHITECT HDV. Specificity of LIAISON Anti-HDV was 98.5% (197/200, 95%CI = 96.1-99.6) with the subset of 200 US donors. **Conclusion:** The newly developed ARCHITECT HDV Total Ig assay with enhanced sensitivity and specificity compared to current LIAISON Anti-HDV marketed in Europe offers a promising tool for universal screening of all HBsAg-positive persons.

Disclosures: Xiaoxing Qiu – Abbott Laboratories: Employee, Yes, No;

Mark Anderson – Abbott Diagnostics: Employee, Yes, No;

Gavin A Cloherty – Abbott Diagnostics: Employee, Yes, No;

Disclosure information not available at the time of publication: Abbas Hadji, Ana Olivo, Austin Hodges, Carla Beertsen, Mary Rodgers

1311-C | EVALUATION OF THE HEPATITIS B VIRUS CCCDNA LEVELS AND ACTIVITY COUPLING FINE NEEDLE ASPIRATES AND DROPLET DIGITAL PCR

Barbara Testoni[1,2], Armando Andrès Roca Suarez[1,2], Arianna Battisti[3,4], Marie-Laure Plissonnier[1,2], Marintha Heil[5], Thierry Fontanges[2,6], François Villeret[2,6], Yasmina Chouik[2,6], Massimo Levrero[1,2,6,7], Upkar Singh Gill[3,4], Patrick T. Kennedy[3,4] and Fabien Zoulim[1,2,8,9], (1)Cancer Research Center of Lyon (CRCL), Inserm U1052, Cnrs UMR5286, Lyon, France, (2)Institut d'Hépatologie De Lyon, (3)Barts Liver Centre, Immunobiology, Blizard Institute, Barts, (4)The London School of Medicine & Dentistry, Queen Mary University of London, London, UK, (5)Roche Molecular Diagnostics, (6)Department of Hepatology, Croix Rousse Hospital, Hospices Civils De Lyon, France, (7) Department of Medicine Sciac and the Italian Institute of Technology (IIT) Center for Life Nanosciences (CLNS), University of Rome La Sapienza, Rome, Italy, (8) Department of Hepatology, Croix Rousse Hospital, Hospices Civils De Lyon, France., (9)Universite Claude Bernard Lyon 1

Background: Available therapies against Hepatitis B virus (HBV) infection effectively limit viral replication but rarely lead to intrahepatic viral elimination. Likely, new treatment strategies will involve the combination of direct antiviral and host targeting agents to reach elimination or durable inactivation of intrahepatic covalently-closed circular (ccc)DNA. To assist drug development, it will be essential to define early predictive markers of clearance of the viral reservoir, assessing their value in reflecting intrahepatic cccDNA levels and transcriptional activity. Fine needle aspirates (FNA) have recently emerged as a less invasive alternative to core liver biopsy (CLB), having already shown to be useful for investigating intrahepatic immune responses. However, quantification of HBV replicative parameters using FNAs remains to be explored. **Methods:** We compared HBV cccDNA and 3.5Kb RNA quantification by droplet digital PCR in paired FNA/CLB samples from patients with hepatitis B e antigen (HBeAg)+ chronic hepatitis ($n = 4$), HBeAg- chronic hepatitis ($n = 4$) and HBeAg- chronic infection ($n = 1$). One HBeAg+ patient was undergoing tenofovir treatment. **Results:** Our results demonstrated that this method allowed cccDNA quantification in all but one FNA/CLB pair, showing the highest levels in untreated HBeAg+ subjects, except for the tenofovir-treated patient. Similarly, 3.5-kb RNA was detectable in all but one FNA sample and showed higher levels in HBeAg+ patients. When comparing cccDNA and 3.5-kb RNA quantification in FNA vs CLB samples, no statistically significant differences were identified either when values were normalized over the total number of cells or over the relative expression of NTCP RNA as an estimation of hepatocyte content. Correlation of cccDNA quantified in both CLB and FNA positively correlated with serum viral load and HBcrAg with similar statistical significance. **Conclusion:** Altogether, we demonstrate the feasibility of assessing cccDNA pool and transcriptional activity in HBV-infected patients by combining FNA and ddPCR, thus supporting the use of FNA in early-stage clinical trials to evaluate the intrahepatic viral reservoir during the development of new antivirals and immunomodulatory agents.

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1312-C | EXPLORING Mac2-BINDING PROTEIN GLYCOSYLATION ISOMER DIAGNOSTIC POTENTIAL FOR NON-INVASIVE TESTING OF LIVER DISEASE IN VIETNAMESE HBV PATIENTS

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Background: The study aims to explore the value driven care approach of utilizing serum based Mac2-binding Protein glycosylation isomer (M2BPGi) as a novel biomarker for the early detection of liver fibrosis and monitoring of anti-viral treatment response in patients with chronic hepatitis B (HBV). Non-invasive testing is patient friendly, and this work aims to fill critical gaps to derive clinical decision cut-offs for liver fibrosis staging and track responses of patients during treatment. **Methods:** This is a cross sectional study involving 334 mono-infected chronic HBV patients. The study receives ethical approval from Medic Medical Center, Ho Chi Minh City, Vietnam. Treatment naïve patients were recruited with baseline M2BPGi taken, and additional serial measurements at 3 and 6-month intervals. M2BPGi is measured via an automated chemiluminescence immunoassay (Sysmex, Japan) using residual serum samples. Kruskal-Wallis tests were used to ascertain the statistical significance of M2BPGi for fibrosis staging and variations at different serial measurements. Area under the receiver operating characteristics (AUROC) curve was computed comparing M2BPGi levels with different biomarkers. A *p*-value of < 0.05 was considered statistically significant. **Results:** Baseline M2BPGi median levels provided specific cut-offs relevant for liver fibrosis staging in comparison with classical biomarkers and transient elastography (TE). Baseline levels were found to be highly correlative to TE results (Pearson, $\rho = 0.71$, p-value < 0.0001). Median M2BPGi levels were 0.73, 0.92, 1.57 and 3.19 cut-off index (C.O.I.) across F0-1, F2, F3 and F4 cases respectively. To ascertain the diagnostic potential, AUROC was computed among these cases addresses early disease and cirrhosis. Between F2 and F3 cases, AUROC was 0.79, which presents strong performance measurements to discriminate early liver disease cases. Furthermore, AUROC between cirrhotic cases and F3 was 0.88, suggesting M2BPGi can be clinically useful in distinguishing advanced liver disease. Serial M2BPGi measurements showed monotonic decreasing trends among the patient cohorts across different fibrosis stages. Median levels reduced by 35% at 6-month for M2BPGi and 10% using TE. Interestingly, TE at 3-month were non-significant for the treated patients but observed a reduction of 25% using M2BPGi. **Conclusion:** Within the current HBV cases, M2BPGi displayed excellent discriminatory levels among different fibrosis stages prior to treatment. This work is the first in Vietnam that extensively validated the marker with specific decision limits. As a non-invasive test, M2BPGi can be easily integrated into existing testing programs for concurrent profiling of liver disease in chronic HBV. Early diagnosis of fibrosis adds value to reduce healthcare burden and prevents disease progression. In comparison with TE, we observed a better dynamic range using M2BPGi when tracking treated cases.

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

1313-C | HEPATIC EXOSOMAL miR122 DECLINES DURING NUCLEOTIDE THERAPY IN HBV/HIV COINFECTED PERSONS

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Background: New biomarkers of HBV infection provide additional insights into the biology of infection and treatment response. Circulating microRNA (miR) 122 enveloped in exosomes that are derived from the liver represents a potential novel biomarker of treatment response. **Methods:** ACTG 5127 was a Phase 2 treatment trial that enrolled HBV/HIV coinfected patients who were randomized to receive either tenofovir (TDF) or adefovir (ADV) for HBV suppression. Participants were followed for 48 weeks post-treatment initiation. Hepatic exosomal miR122 was isolated from serum using the Qiagen (Germantown, MD) miRNeasy Serum Advanced kit, with RNA spike-ins to monitor RNA isolation quality. RNA was then subjected to reverse transcription using the miRCURY LNA RT kit, including additional synthetic spike-ins to monitor cDNA synthesis and presence of inhibition. The resulting cDNA template was amplified by qPCR using the Qiagen miRCURY LNA SYBR Green kit and miRNA PCR assays for each target (spike-ins, reference miRNA [*C. eleg* miR39], and liver-specific miR122). Relative expression was determined using the $2^{-\Delta\Delta CT}$ method compared to the reference miRNA and reported as fold change from the healthy control group. Correlations were made with clinical characteristics, as well as HBV DNA, pgRNA, and qHBs antigen levels. **Results:** Baseline and week 48 timepoints were available for 35 study participants. The majority were male (91%), white non-Hispanic (52%), or black (33%). The groups were evenly randomized to receive either TDF or ADV. The mean baseline miR122 relative fold change was 49.5 ± 12.6. This declined to 10.9 ± 2.8 at week 48 post-treatment ($p < 0.003$ by paired t-test). The change negatively correlated with CD4 count (Pearson r = -0.422; $p = 0.021$) but not with HBV DNA, pgRNA, qHBsAg, or ALT. **Conclusion:** Liver-specific exosomal miR122 declines following HBV treatment in HBV/HIV coinfected persons but remains elevated compared to healthy controls. The correlation with CD4 suggests that immune status may be an independent predictor of hepatic miR122 in the setting of coinfection. Future studies will focus on the relationship between exosomal miR122 decline and functional cure status.

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The following people have nothing to disclose: Susan D Rouster

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1314-C | HEPATITIS B CORE-RELATED ANTIGEN (HBCRAG): A PROMISING BIOMARKER FOR LIVER DISEASE HISTORY

Rosa Claudia Stasio[1], Roberta Lasco[1], Elisabetta Bretto[1], Martina Marano[1], Marco Tizzani[1], Eleonora Ghessa[2], Yulia Troshina[2], Rossana Cavallo[2,3], Fabrizia Pittaluga[3], Giacomo Scaioli[4], Giulia Barbera[4], Giorgio Maria Saracco[1,2] and Alessia Ciancio[1,2], (1) Gastrohepatology Unit, Aou Città Della Salute e Della Scienza Di Torino, (2)University of Turin, (3) Microbiology Unit, Aou Città Della Salute e Della Scienza Di Torino, (4)Department of Public Health Sciences and Pediatrics, University of Turin

Background: Hepatitis B virus (HBV) infection remains a major public health problem. Several markers have been validated to monitor each phase of infection and its outcome. Hepatitis B core-related antigen (HBcrAg) is emerging as marker of virus replication. The aims of this study are to describe the variation of HBcrAg during each phase of HBV infection and its performance in predicting liver fibrosis levels and occurrence of hepatocellular carcinoma (HCC) compared to hepatitis B surface antigen (HBsAg) and HBV DNA in hepatitis B-e antigen (HBeAg) negative patients. **Methods:** among 273 HBV infected patients attending our center in the last year, 125 underwent HBcrAg dosage and represent our study population. In 33 of them the second determination was performed. Patients were classified according to the European Association for the Study of the Liver (EASL) phases of the HBV infection; we then compared HBeAg-negative chronically infected patients with those in other phases. For each patient we assessed demographics, virological data, comorbidities, stage of liver fibrosis, presence of HCC and antiviral treatment at the moment of the sampling. Equality of median test and multivariate linear regression analysis were performed to assess potential associations between HBcrAg levels and characteristics of the disease. **Results:** median age was 58 (IQR 45-66), 43% patients (n = 54) were female, 17% (n = 22) were cirrhotic, median liver stiffness was 6.4 kPa (IQR 4.6-10.7), 3% (n = 4) had HCC and 64% (n = 80) underwent NUC therapy. HBeAg-negative chronically infected patients (n = 83, 66%) showed significantly lower levels (median 2 log U/ml, IQR 1.9-3) of HBcrAg compared to the others (n = 42, 34%) (median 2.8 log U/ml, IQR 2-4.6; $p = 0.009$). HBcrAg levels did not differ significantly in patients with and without HCC (mean 2.2 log U/ml vs 2 log U/ml; $p = 0.347$). The multivariate linear regression analysis demonstrated that Fibroscan values were inversely related to HBcrAg ones ($p < 0.001$). After adjusting for age, sex and stage of fibrosis HBV DNA and HBsAg levels are directly related to HBcrAg ones ($p < 0.001$ each). **Conclusion:** in this ongoing study we demonstrate that the new HBcrAg biomarker can provide clinicians with reliable information on the HBV replication activity, especially in HBeAg negative chronic infected patients, in a non-invasive manner. In this prospective study HBcrAg seems to be useful to monitor the natural history of liver disease but further studies are needed to demonstrate if HBcrAg could predict occurrence of HCC or liver decompensation.

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1315-C | HEPATITIS B VIRUS SURFACE ANTIGEN GLYCAN ISOMER (HBSAGGI) AS A NEW GLYCO-BIOMARKER TO DETECT INFECTIOUS HBV VIRIONS

Kiyohiko Angata[1], Maki Sogabe[1], Hisashi Narimatsu[1], Murata Ayato[2] and Takuya Genda[2], (1)Rcmg Inc., (2) Juntendo University Shizuoka Hospital

Background: Hepatitis B virus surface antigen (HBsAg) gene generates L-, M-, and S-HBsAg. In HBV patients' sera, non-infectious particles are much dominant than infectious particles containing HBV DNA (Dane particles). Dane particles contain all HBsAgs, but non-infectious particles mainly contain S-HBsAg. Thus, general HBsAg test using antibodies recognizing S-HBsAg does not always distinguish infectious and non-infectious subviral particles. *O*-glycosylated M-HBsAg was determined by mass spectrometry, because a lectin recognizing *O*-glycans could enrich DNA-containing particle. This study aimed to develop a new marker to measure infectious particles which contain *O*-glycosylated M-HBsAg [HBsAg glycan isomer (HBsAgGi)]. **Methods:** To generate HBsAgGi antibodies, glycopeptides modified with *O*-glycans were generated. To analyze the HBsAgGi antibody, Western blotting, immunostaining, and ELISA were performed. To characterize target particles of HBsAgGi, immunoprecipitated (IP) particles by HBsAgGi antibody was analyzed by qPCR and reverse-transcription PCR for quantifying HBV DNA and HBV RNA, respectively. Furthermore, a new HBsAgGi ELISA system measured sera of chronic hepatitis B (CHB) patients before and after nucleos(t)ide analog (NA) treatment to investigate clinical utility of the HBsAgGi. **Results:** PreS2 peptide with or without glycans generated genotype specific antibodies. For genotype C, HBsAgGi antibody recognized M-HBs but not L-HBs that is not modified with *O*-glycan on the PreS2. Mutations in *O*-glycosylation site or removal of *O*-glycans resulted in decrease of the recognition by HBsAgGi antibody. HBsAgGi localized in ER to Golgi in MHBs-expressing cells, suggesting generation of HBsAgGi through glycosylation pathway. Immunoprecipitation experiments confirmed that both HBV DNA- and HBV RNA-containing particles were collected by HBsAgGi antibody. In treatment naïve CHB patients, serum HBsAgGi level was higher in HBe-positive patients than HBe-negative patients at baseline. HBsAgGi levels were significantly correlated with the HBV DNA level ($p = 0.002$, n = 32). **Conclusion:** New HBsAgGi antibodies recognize HBV particles in genotype specific manner dependent on the presence of *O*-glycans in PreS2 domain. HBsAgGi specifically presents in minor infectious fraction of HBV virions containing HBV DNA or HBV RNA. Taken together with ELISA analysis of patients' sera, HBsAgGi would be a new glyco-biomarker to monitor viral kinetics in CHB patients during therapy.

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1316-C | HIGH END-OF-TREATMENT HEPATITIS B CORE-RELATED ANTIGEN (HBCRAG) LEVELS PREDICT HEPATITIS FLARE AFTER STOPPING NA THERAPY: ANALYSIS OF THE AUSTRALIAN NA-STOP STUDY COHORT

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Background: Stopping nucleos(t)ide analogue (NA) therapy is associated with functional cure (HBsAg loss) in a significant minority of patients with chronic hepatitis B (CHB). Novel biomarkers are needed to predict those at high chance of HBsAg loss and low risk of hepatitis flare. Hepatitis B core-related antigen (HBcrAg) is a composite of three proteins: HBcAg, HBeAg and a truncated precore protein (p22cr). **Methods:** The predictive utility of end of treatment (EOT) and off-treatment HBcrAg level was evaluated amongst patients previously enrolled in the published HBV-STOP study with 96 weeks of follow-up (non-cirrhotic HBeAg-negative CHB patients). 68 of 110 patients in the original study had stored serum available and were included. HBcrAg levels were analysed using the Lumipulse® G System (Fujirebio, Japan). The lower limit of detection and quantification of HBcrAg were 2 and 3 log U/mL, respectively. EOT (at NA cessation) and longitudinal HBcrAg levels were used to predict clinical outcomes. **Results:** At EOT, the median [IQR] age was 54 years [48-60], 54% were male, 82% were Asian, the median [IQR] EOT HBsAg titre was 703 [245-1878] IU/mL and the median ALT was and 24 [17-33] U/L. At EOT, 10/68 (15%) had undetectable HBcrAg, 18/68 (26%) had a detectable HBcrAg below the lower limit of quantification, 30 (44%) had a level between 3 and 4 log U/mL and 10 (15%) had a level above 4 log U/mL. An EOT HBcrAg level of e 4 log U/mL strongly predicted biochemical relapse (80% vs 39%; OR = 6.55; $p < 0.05$) and hepatitis flare (80% vs 25%, OR = 11.47; $p < 0.005$; Figure 1). Longitudinal off-treatment HBcrAg levels also had predictive value with a HBcrAg level e 4 (compared to EOT HBcrAg d 2) demonstrating a strong association with subsequent hepatitis flare (HR = 31.9; $p < 0.005$). No patient who achieved HBsAg loss (n = 4) had a EOT HBcrAg level above 3 log U/mL (lower limit of quantification). **Conclusion:** High levels of HBcrAg (e 4 log U/mL) were present in 15% of patients at EOT and this was a marker of increased risk of hepatitis flare. In patients with low or undetectable levels at EOT, rising levels of HBcrAg (e 4 log U/mL) off-treatment were associated with subsequent hepatitis flare. HBcrAg is a clinically useful biomarker to predict patients who are at high risk of hepatitis flare after stopping NA and who should be encouraged to continue NA whilst awaiting new cure strategies.

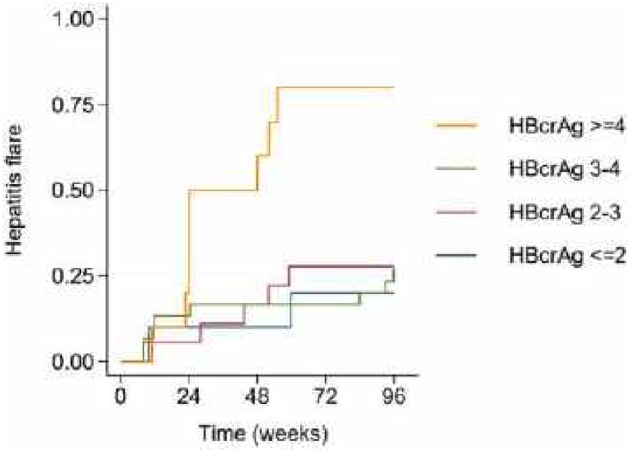

Figure 1. Cumulative incidence of hepatitis flare according to EOT HBcrAg level

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1317-C | IMPACT OF HBEAG LOSS ON HEPATOCELLULAR CARCINOMA RISK IN PATIENTS WITH HBEAG-POSITIVE CHRONIC HEPATITIS B: A MULTICENTER STUDY IN SOUTH KOREA

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Background: Antiviral treatment has been shown to reduce the risk of developing hepatocellular carcinoma (HCC) in patients with hepatitis B envelop antigen (HBeAg)-positive hepatitis. Nonetheless, whether the loss of HBeAg resulting from antiviral treatment has a beneficial effect on the risk of HCC remains uncertain. Our study aimed to investigate the impact of HBeAg loss timing on HCC development. **Methods:** HBeAg-positive chronic hepatitis B (CHB) patients who attended and were treated with antivirals at three tertiary centers in Korea from 2007 to 2021 were eligible for the study. Patients with cirrhosis, a normal alanine aminotransferase (ALT) level, HBeAg loss, or HCC occurrence within one year after initiation of

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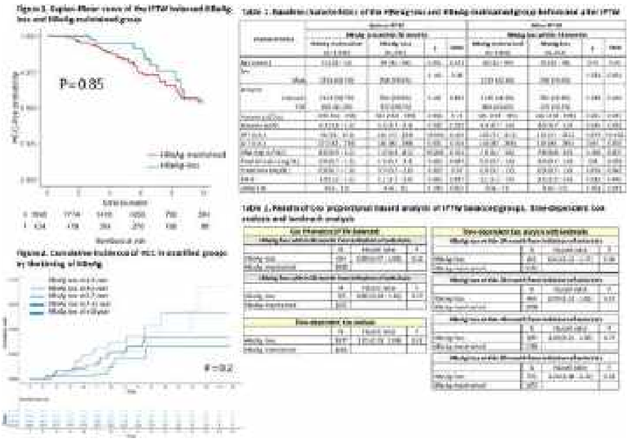
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

antiviral treatment were excluded from the study. The primary outcome of the study was the incidence of HCC, compared between the HBeAg-loss group and the HBeAg-maintained group using the inverse probability treatment weighting (IPTW) method. Landmark analysis and time-varying Cox analysis with multiple timepoints after the initiation of antiviral treatment were also performed as sensitivity analyses. **Results:** A total of 2,382 non-cirrhotic HBeAg-positive CHB patients were analyzed. Patients were followed for a median of 6.6 years, during which 64 patients (2.7%) developed HCC. In the IPTW-balanced population (Table 1), the HBeAg-loss group (HBeAg loss before 36 months after initiation of antiviral treatment) and the HBeAg-maintained group had a similar risk of developing HCC (hazard ratio [HR] = 0.89, 95% confidence interval [CI] = 0.47–1.68, $p = 0.72$ by Cox proportional hazard analysis, Table 1, $p = 0.85$ by log-rank test, Figure 1). Landmark analysis of HBeAg loss at different timepoints of 24 months (HR = 0.61, 95% CI = 0.21–1.77, $p = 0.36$), 36 months (HR = 0.99, 95% CI = 0.53–1.85, $p = 0.97$), 48 months (HR = 1.09, 95% CI = 0.61–1.96, $p = 0.77$), and 60 months (HR = 1.20, 95% CI = 0.68–2.10, $p = 0.53$) after initiation of antiviral treatment also showed an independent association with the development of HCC (Table 2). Stratification of groups by the timing of HBeAg loss also showed no difference of HCC development ($p = 0.2$ by log-rank test, Figure 2) **Conclusion:** This study implies that the timing of HBeAg loss was not associated with the risk of HCC in non-cirrhotic patients in the HBeAg-positive hepatitis phase. HBeAg positivity may be indicative of the early virologic phase of CHB, but it is not itself a substance associated with carcinogenesis.



Disclosures: The following people have nothing to disclose: Hyunjae Shin, Yunmi Ko, Youngsu Park, Jeayeon Park, Jeong-Hoon Lee, Won-Mook Choi, Seung Up Kim, Moon Haeng Hur, Min Kyung Park, Yun Bin Lee, Eun Ju Cho, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon

1318-C | KINETICS OF QUANTITATIVE HBsAg DECLINE IN CHRONIC HEPATITIS B PATIENTS RECEIVING NUCLEOS(T)IDE ANTIVIRAL THERAPY

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Background: Nucleos(t)ide analog therapy (NA) is the standard of care for patients with chronic hepatitis B (CHB) infection. However, NA rarely leads to HBsAg seroclearance, which is considered as ‘functional cure' and is associated with improved clinical outcomes. However, the optimal duration of NA among HBeAg-negative patients remains unclear and stopping NA as a strategy to cure HBV is controversial. The kinetics of HBsAg decline on NA has not been well studied in clinical trials but may help predict the duration of therapy required to achieve HBV cure. Therefore, the aim of this study was to determine the rate of HBsAg decline in order to predict time to functional cure in CHB patients on NA. **Methods:** Consecutive adult patients with CHB attending the Toronto General Hospital Liver Clinic from 2017-2022 who received NA as per current treatment guidelines were included. Baseline demographic, clinical and laboratory data including liver enzymes, quantitative HBsAg level (Abbott Architect, LLOQ 0.02 IU/ml), and HBV DNA (Roche TaqMan, LLOQ 10 IU/ml) were collected every 6 months during followup. Baseline HBsAg was compared with HBsAg level at the time of seroclearance or at last followup to analyze HBsAg kinetics and to estimate the rate of HBsAg loss. **Results:** Of 371 consecutive patients who were treated with NA (TDF 88%, ETV 9%, other 3%), the majority was male (67%), Asian (92%) with a mean age 57 yrs. Mean baseline HBsAg was 6754.6 IU/mL, 317 (86%) HBeAg-negative, and baseline HBV DNA 5.6 log IU/mL. Patients were divided into 3 categories according to HBsAg levels: low < 1000 IU/mL, 167 (45%) patients; intermediate 1000-10,000 IU/mL, 161 (44%); and high > 10,000 IU/mL, 43 (11%). Mean annual rate of HBsAg decline differed according to baseline HBsAg: low group declined 50.4 IU/mL; intermediate 446.8 IU/mL; and high 9851.5 IU/mL, ($p < 0.05$). Overall, annual average decline in HBsAg was 1034.7 IU/mL and HBsAg seroclearance was observed in 53 (14%) patients after a mean treatment duration of 5.2 years. Majority of HBsAg seroclearance occurred in patients in the low HBsAg group (87% low, 8% intermediate and 5% high). **Conclusion:** In this retrospective cohort study of CHB patients receiving long-term NA, the annual rate of HBsAg decline was slow but measurable at approximately 1000 IU/ml. The magnitude of HBsAg decline correlated with baseline HBsAg level. HBsAg seroclearance increased with prolonged duration of NA and was greatest among those with low HBsAg. These data demonstrate the utility of HBsAg kinetics and can predict time to functional cure for those receiving NA, although further studies are required.

Disclosures: Scott K. Fung – Gilead Sciences, Inc.: Speaking and Teaching, No, No; AbbVie: Speaking and Teaching, No, No; Lupin: Speaking and Teaching, No, No; Gilead Sciences, Inc.: Advisor, No, No; AbbVie: Advisor, No, No; Novo Nordisk: Advisor, No, No; Pfizer: Advisor, No, No; Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;

The following people have nothing to disclose: Yong Gyu Hyun

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

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

Background: Current criteria for defining immune-tolerant patients rely on serum ALT and HBV DNA levels. However, these markers can fluctuate, making it challenging to distinguish immune-tolerant patients from from immune-active individual's who may exhibit normal ALT levels temporarily. As viral quasispecies arise from the adaptation to selection pressure exerted by the host immune response, our objective was to investigate whether lower viral diversity could serve as an indicator to identify genuine immune-tolerant patients. **Methods:** We conducted a retrospective study involving 202 HBeAg-positive patients with HBV DNA levels exceeding 1 million IU/mL and ALT levels below the upper limits of normal defined by the AASLD guidelines. These patients were classified as immune-tolerant based on the AASLD criteria and were enrolled between 1985 and 1990. Throughout the HBeAg-positive stage, these patients remained untreated. The primary endpoint of the study was HBeAg seroclearance. Serum samples collected at enrollment were used to determine viral factors. Viral quasispecies of the hepatitis B core (HBc) gene were determined using deep sequencing, with the ability to detect viral variants as low as 0.1%. We defined high and low viral diversity using a cutoff of 0.005. **Results:** Among the 202 immune-tolerant patients, the mean age was 31.2 years, with 56.9% being male. A total of 13.3% of patients exhibited high HBc viral diversity. Over a mean follow-up period of 15.2 years, 88 patients achieved HBeAg seroclearance, resulting in an annual incidence of 2.9%. Univariable analysis demonstrated that older age and higher HBc diversity were associated with an increased probability of clearing HBeAg. Compared to patients with low HBc diversity, those with higher diversity had an elevated chance of clearing HBeAg, with a hazard ratio (HR) of 2.62 (95% CI: 1.58-4.36). Multivariable analysis revealed that higher HBc diversity remained an independent factor, with an HR of 2.32 (95% CI: 1.37-3.95), even after adjusting for age, sex, HBV DNA levels, and HBV genotype. This relationship remained significant, even when restricted to 165 immune-tolerant patients under the age of 40. **Conclusion:** In a cohort of immune-tolerant patients defined by HBV DNA and ALT levels according to the AASLD guideline, lower HBc viral diversity was associated with a reduced likelihood of clearing HBeAg. Deep sequencing-based determination of viral diversity may aid in the identification of genuine immune-tolerant patients.

Disclosures: The following people have nothing to disclose: Tai-Chung Tseng, Chun-Jen Liu, Tung-Hung Su, Hung-Chih Yang, Pei-Jer Chen, Jia-Horng Kao

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

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

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

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

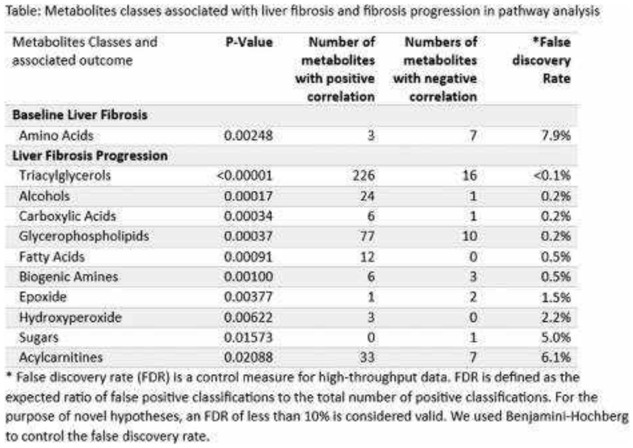

Table: Metabolites classes associated with liver fibrosis and fibrosis progression in pathway analysis

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

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

Disclosures: Keyur Patel – Gilead Sciences: Independent contractor (including contracted research), No, No; Novo-Nordisk: Advisor, No, No; Resalis: Consultant, No, No;

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Disclosure information not available at the time of publication: Joseph E Lucas, Wendy C King, Susanna Naggie

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

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Background: The development of hepatocellular carcinoma (HCC) due to hepatitis B is difficult to predict. One reason is that its pathogenesis is not due to a persistent accumulation of inflammation. The molecular changes that occur in cells persistently infected with hepatitis B virus (HBV) are not clear on a cell-by-cell basis. The impact of those HBV-infected cells on the pathogenesis of the disease is also unknown. In this study, single-cell RNA-seq (scRNA-seq) analysis of HBV-infected cells was performed to investigate changes in gene expression on a single-cell basis. The molecules relating to HCC were identified and their functions were analysed. **Methods:** After the infection of primary hepatocytes with HBV, their scRNA-seq analysis was performed. scRNA-seq data were compared between HBV RNA-positive and negative hepatocytes (cell populations in the same environment) in one dish. The miR-4461 levels of HuH7 and HepG2 cells with and without HBV were identified and analyzed for cell proliferation, invasion and migratory capacity. Target genes to which miR-4461 bound were explored by in vitro assay. miR-44661 was quantified in HCC and non-HCC areas using resected liver tissue of hepatitis B and non-B/non-C. **Results:** Primary hepatocytes were infected with HBV and then scRNA-seq was performed. miR-4461 was significantly reduced in HBV-infected hepatocytes. miR-4461 expression was reduced when HBV replication plasmids were transfected into HuH7 and HepG2 cells. siRNA knockdown of miR-4461 enhanced the proliferation, invasive and migratory capacity of HuH7 and HepG2 cells. miR-4461 expression levels were confirmed in liver tissues from hepatitis B and non-B/non-C HCC patients. In non-B/non-C specimens, no difference of the miR-4461 expression was observed in both HCC and non-HCC areas compared to normal liver tissue. On the other hand, in hepatitis B specimens, the expression of miR-4461 was lower than that of normal liver ($p < 0.05$). in addition, the expression in HCC areas was lower than non-HCC areas ($p < 0.05$). Target genes of miR-4461 were explored using database and in vitro assay. Then, the FGA gene was one of the targets of miR-4461. **Conclusion:** The miR-4461 pathway was suggested to be associated with the establishment and pathogenesis of HBV infection. miR-4461 levels were reduced in liver tissue derived from hepatitis B, and a more significant reduction was observed in HCC area, suggesting that this pathway could be a useful biomarker for HBV-derived HCC.

Disclosures: The following people have nothing to disclose: Aiko Sakai, Masaya Sugiyama

1322-C | NON-INVASIVE EXPLAINABLE MACHINE LEARNING MODELS FOR ASSESSMENT OF SIGNIFICANT FIBROSIS IN PATIENTS WITH AUTOIMMUNE HEPATITIS

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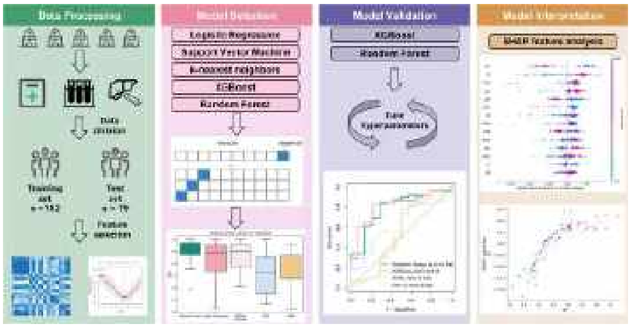
Background: Accurate assessment of significant fibrosis non-invasively is pivotal in managing patients with autoimmune hepatitis (AIH). This study aims to develop a non-invasive interpretable machine learning model for predicting significant fibrosis in AIH patients. **Methods:** A retrospective multi-center cohort of AIH patients who underwent liver biopsy was randomly divided, with 70% for model training and 30% for validation. Liver histology was assessed according to the Scheuer grading system and significant liver fibrosis was defined as stage S e 2. Five machine learning algorithms (logistic regression, support vector machine, k-nearest neighbors, XGBoost, random forest [RF]) underwent ten-fold cross-validation. Models with the highest area under the receiver operating characteristic curve (AUC) were fine-tuned using grid search. Better models were retrained with the optimized parameters, performance was compared with APRI and FIB-4 on a test dataset. SHapley Additive exPlanation (SHAP) analysis explained predictions and assessed feature contributions. **Results:** A total of 261 AIH patients were included. Among the five models, XGBoost (AUC: 0.856, 95% confidence interval [CI]: 0.775-0.938) and RF (AUC: 0.885, 95% CI: 0.811-0.960) exhibited superior predictive performance, demonstrating their robust discriminative capabilities. The grid-search identified optimal hyperparameters for these two models. Retrained models achieved an AUC of 0.813 (95% CI: 0.698-0.929) for XGBoost and 0.790 (95% CI: 0.661-0.919) for RF on test dataset, significantly surpassing the performance of APRI (AUC: 0.546, 95% CI: 0.345-0.747) and FIB-4 (AUC: 0.632, 95% CI: 0.476-0.788). SHAP feature analysis revealed platelets, prothrombin time, and cholinesterase as the most influential factors in predicting significant fibrosis. **Conclusion:** The non-invasive interpretable machine learning models hold promise for predicting significant fibrosis in AIH patients. These models can aid clinicians in early identification of significant fibrosis for better management in AIH patients.



Disclosures: The following people have nothing to disclose: Zhiyi Zhang, Huali Wang, Qun Zhang, Li Zhu, Shaoqiu Zhang, Yifan Pan, Jian Wang, Yuanwang Qiu, Chao Wu, Rui Huang, Jie Li

1323-C | O-GLYCOSYLATED MIDDLE-HEPATITIS B SURFACE ANTIGEN AS A NEW POTENTIAL BIOMARKER FOR CHRONIC HEPATITIS B: ASSOCIATION WITH HEPATOCELLULAR CARCINOMA AND QUANTITATIVE CHANGES WITH NUCLEOS(T)IDE ANALOG THERAPY

Taiki Okumura[1], Satoru Joshita[2], Takanobu Iwadare[1], Hiroyuki Kobayashi[1], Shunichi Wakabayashi[1], Yuki Yamashita[1], Takefumi Kimura[1] and Takeji Umemura[1], (1)Shinshu University Hospital, Matsumoto, Japan, (2) Yodakubo Hospital, Nagawa town, Chiisagata county, Japan

Background: A novel antibody recognizing O-glycosylated middle-hepatitis B surface antigen (HBsAgGi) can detect hepatitis B surface antigen (HBsAg) associated with hepatitis B virus (HBV) virions in patients with genotype C. This study investigated the association of HBsAgGi levels with clinical parameters, including other HBV markers and a history of hepatocellular carcinoma (HCC) development, in a cross-sectional cohort analysis (Study 1) in addition to the quantitative changes of HBsAgGi during nucleos(t)ide analog (NA) therapy in a longitudinal analysis (Study 2). **Methods:** HBsAgGi was measured by ELISA kits

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

(RCMG Inc.) using stored sera. A total of 124 patients were analyzed in Study 1. Among those, 36 patients receiving NA therapy were enrolled in Study 2 for quantitative comparisons between pre-treatment baseline and 48 weeks of NA treatment. **Results:** In Study 1, median age was 59 years, and 49 patients (39.5%) of subjects were male. Serum HBsAgGi was significantly associated with HBsAg ($r = 0.59$, $p < 0.001$). HBV DNA showed a higher correlation with HBsAgGi ($r = 0.29$, $p = 0.001$) than with HBsAg ($r = 0.28$, $p = 0.002$). After excluding 73 patients under NA treatment, HBV DNA continued to exhibit a higher correlation with HBsAgGi ($r = 0.43$, $p = 0.002$) than with HBsAg ($r = 0.39$, $p = 0.006$). Although HBsAgGi level was comparable between the HCC history (+) group (16 patients) and the HCC history (-) group (108 patients) ($p = 0.111$), the HBsAgGi/HBsAg ratio was significantly higher in the HCC history (+) group ($p = 0.011$). The patients were divided into 4 categories according to HBsAg and HBsAgGi titer according to the cut-off values of 3.0 log IU/mL and 3.0 log ng/mL, respectively. Multivariate testing using logistic regression analysis revealed low HBsAg and high HBsAgGi as an independent factor associated with HCC history (+) (hazard ratio: 4.20, 95% confidence interval: 1.34-13.12, $p = 0.014$). In Study 2, HBsAgGi was significantly decreased from baseline at 48 weeks of NA in the hepatitis B e antigen (HBeAg) (+) subgroup ($p = 0.005$), whereas HBsAg was comparable ($p = 0.051$). In contrast, HBsAgGi was similar between baseline and 48 weeks of NA in the HBeAg (-) subgroup ($p = 0.092$). **Conclusion:** In a cross-sectional analysis, HBsAgGi showed a stronger correlation with HBV DNA than did HBsAg, with the HBsAgGi/HBsAg ratio significantly associated with a history of HCC. Longitudinal analysis revealed that HBsAgGi was significantly decreased by 48-week NA therapy, suggesting its potential as a biomarker of HBV particles with HBV DNA.

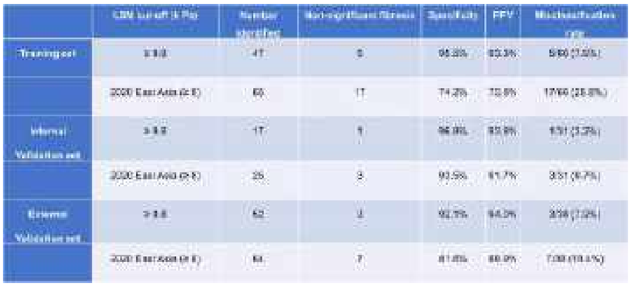
Disclosures: The following people have nothing to disclose: Taiki Okumura, Satoru Joshita, Takanobu Iwadare, Hiroyuki Kobayashi, Shunichi Wakabayashi, Yuki Yamashita, Takefumi Kimura, Takeji Umemura

1324-C | OPTIMIZED CUTOFF OF LIVER STIFFNESS MEASUREMENT FOR RULING IN SIGNIFICANT FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B

Zhiyi Zhang[1], *Li Zhu*[2], *Xingxiang Liu*[3], *Jian Wang*[4], *Shaoqiu Zhang*[4], *Xiaomin Yan*[4], *Yuanwang Qiu*[5], *Jie Li*[1,4], *Rui Huang*[1,4] *and Chao Wu*[1,4], *(1)Department of Infectious Diseases, Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China, (2)Department of Infectious Diseases, the Affiliated Infectious Diseases Hospital of Soochow University, Suzhou, Jiangsu, China, (3)Department of Clinical Laboratory, Huai'an No. 4 People's Hospital, Huai'an, Jiangsu, China, (4) Department of Infectious Diseases, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China, (5) Department of Infectious Diseases, the Fifth People's Hospital of Wuxi, Wuxi, Jiangsu, China*

Background: Accurate assessment of liver fibrosis is important in guiding therapeutic interventions and predicting prognosis in patients with chronic hepatitis B (CHB). Liver stiffness measurement (LSM) has emerged as a valuable non-invasive tool for evaluating the severity of fibrosis. However, the optimal cutoff of LSM values remains in debate. Therefore, we aim to identify the optimal cutoff value of LSM for ruling in/out significant fibrosis and cirrhosis among patients with CHB. **Methods:** We retrospectively collected the clinical data of a multi-center cohort of CHB patients who underwent liver biopsy along with LSM. Significant fibrosis and cirrhosis were defined as Scheuer fibrosis stage e 2 and Scheuer fibrosis stage 4, respectively. The diagnostic performance of LSM in differentiating between various fibrosis stages was evaluated using the areas under the receiver operating characteristic curve (AUC). Subsequently, new cutoff values of LSM were identified in the training set using the grid-search method, ensuring a specificity and positive predictive value (PPV) of over 90% for ruling in, sensitivity of at least 90% and negative predictive value (NPV) of more than 95% for ruling out. The new cutoff values of LSM were subsequently validated in an internal and an external validation set. **Results:** A total of 332 individual's were enrolled in this study, with the training set consisting of 145 patients, 79 of whom with significant fibrosis. The internal and external validation sets included 31 and 38 patients with significant fibrosis, respectively. A strong correlation between LSM and the severity of fibrosis was found. The AUCs of LSM for predicting significant fibrosis were 0.753 in the training set, 0.839 in the internal validation set, and 0.811 in the external validation set. The optimal cutoff value of LSM for ruling in significant fibrosis was determined to be 9.8 kPa, exhibiting a specificity of 95.5%, a PPV of 93.3% and a misclassification rate of 7.6% in the training set, which is significantly superior to the cutoff of LSM e 8 kPa recommended by the 2020 East Asia expert opinion with a specificity of 74.2%, a PPV of 73.8% and a misclassification rate of 25.8%. Furthermore, in the internal validation set, the optimal cutoff LSM value demonstrated a specificity of 96.8% and a PPV of 93.8%, while in the external validation set, it showed a specificity of 92.1% and a PPV of 94.0%. Importantly, the misclassification rate of the newly identified cutoff of LSM across all three datasets was below 10%.

However, the optimal cutoffs of LSM to rule out significant fibrosis or rule in/out liver cirrhosis could not be identified. **Conclusion:** The newly identified and validated cutoff value of e 9.8 kPa for LSM to rule in significant liver fibrosis, coupled with a low misclassification rate, provides invaluable guidance for risk stratification, treatment decision-making, and long-term prognosis for CHB patients.



Disclosures: The following people have nothing to disclose: Zhiyi Zhang, Li Zhu, Xingxiang Liu, Jian Wang, Shaoqiu Zhang, Xiaomin Yan, Yuanwang Qiu, Jie Li, Rui Huang, Chao Wu

1325-C | PREDICATION VALUE OF SERUM O-GLYCOSYLATED HEPATITIS B SURFACE ANTIGEN LEVELS IN CHRONIC HEPATITIS B PATIENTS DURING ANTIVIRAL THERAPY

Bilian Yao[1], Qi Xu[1], Kiyohiko Angata[2], Hisashi Narimatsu[2] and Xinxin Zhang[1], (1)Ruijin Hospital, Shanghai Jiaotong University School of Medicine, (2) Research Core for Medical Glycoscience (RCMG) Inc

Background: Recent research has revealed that hepatitis B surface antigen (HBsAg) of Hepatitis B virus (HBV) Dane particles and non-infectious subviral particles (SVPs) can be distinguished by their *O*-glycosylation of the PreS2 domain of the middle HBsAg protein. This study aimed to evaluate the changes of serum *O*-glycosylated HBsAg levels in chronic hepatitis B patients treated with entecavir (ETV) or pegylated interferon ± (Peg-IFN±) treatment. **Methods:** Eighty-six treatment-naïve patients with genotype C CHB were retrospectively enrolled. The *O*-glycosylated HBsAg, HBsAg, HBeAg, HBV DNA, HBV RNA at baseline, weeks 4, 12, 24 and 48 after ETV or Peg-IFN± treatment were determined. Serum *O*-glycosylated HBsAg levels were semi-quantified by immunoassay using a monoclonal antibody against the *O*-glycosylated PreS2 domain of middle HBsAg. **Results:** At baseline, the serum *O*-glycosylated HBsAg levels were significantly correlated with the HBsAg ($R = 0.719, p < 0.001$), HBV DNA ($R = 0.485$, $p < 0.001$), HBV-RNA ($R = 0.460$, $p < 0.001$), and HBeAg ($R = 0.403, p = 0.03$) as well as with the HBsAg ($R = 0.564, p < 0.001$), HBeAg ($R = 0.556, p < 0.001$) in patients($n = 68$) who achieved undetectable HBV DNA. Serum *O*-glycosylated HBsAg, HBsAg, HBV RNA, HBV DNA levels were decreased after 48 weeks of antiviral therapy. A total of 60 patients achieved virological response (VR) and the area under the ROC curve (AUC) of baseline O-glycosylated HBsAg levels was 0.841 in predicting VR, which was superior to HBsAg (AUC = 0.815), HBV RNA (AUC = 0.704) or HBV DNA (AUC = 0.694) during ETV treatment. Similarly, AUC of baseline *O*-glycosylated HBsAg levels in predicting VR was 0.762, which was also higher than that of HBV RNA (AUC = 0.755), HBV DNA (AUC = 0.667) or HBsAg (AUC = 0.556) during Peg-IFN± treatment. The AUC of baseline *O*-glycosylated HBsAg levels in predicting 1 log IU/L decline in serum HBsAg levels after 48 weeks of antiviral therapy was 0.900, which was also higher than that of HBV DNA (AUC = 0.839), HBsAg (AUC = 0.700) or HBV RNA (AUC = 0.515) during Peg-IFN± treatment. **Conclusion:** During antiviral therapy, changes in serum *O*-glycosylated HBsAg levels may be indicative of combined levels of serum HBV DNA and RNA virions. The baseline serum *O*-glycosylated HBsAg level might provide a novel predictor of VR during ETV or Peg-IFN± treatment in CHB genotype C patients.

Disclosures: The following people have nothing to disclose: Bilian Yao, Qi Xu, Kiyohiko Angata, Hisashi Narimatsu, Xinxin Zhang

1326-C | PREDICTORS OF TREATMENT INITIATION AMONG HIGH-RISK AND GREY AREA CHRONIC HEPATITIS B PATIENTS IN A REAL-WORLD CLINICAL PRACTICE SETTING IN THE UNITED STATES

Mark A Schmidt[1], Yihe G Daida[2], Sacha Satram[3], Teresa M Kimes[1], Ana Gabriela Rosales[1], Sixiang Nie[2], Richard T Meenan[1], Judy L Donald[1], Michael A. Chattergoon[4] and Norah Terrault[5], (1)Center for Health Research, Kaiser Permanente Northwest, (2)Center for Integrated Health Care Research, Kaiser Permanente Hawaii, (3)Vir Biotechnology, (4)Vir Biotechnology, Inc, (5)University of Southern California, Los Angeles, CA

Background: Antiviral treatment of chronic hepatitis B virus (cHBV) infection is recommended for those patients with active disease who are at high risk of severe, long-term consequences. We sought to describe the initiation of cHBV treatment among a cohort of real-world patients in the United States, by demographic characteristics and treatment recommendation category. **Methods:** This retrospective, cohort analysis utilized electronic health records from large, integrated

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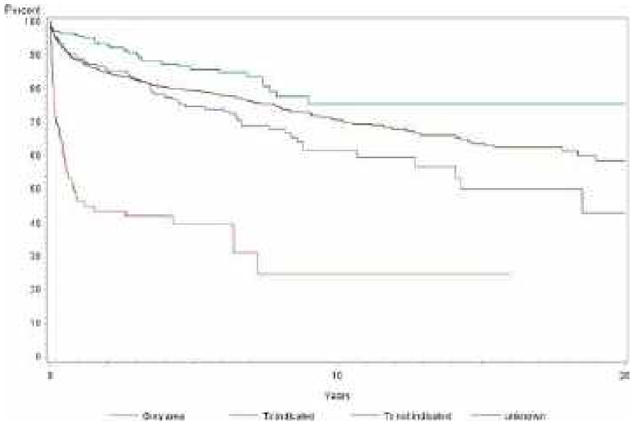
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

health delivery systems in the US. Patients were included if they had e 2 positive labs, or 1 positive lab and 1 diagnostic code for cHBV, at least 6 months apart, between January 1, 2000 – December 31, 2015. Patients were followed until treatment initiation, disenrollment from the health plan, death, or December 31, 2020. The 2018 AASLD Hepatitis B Guidance was used to define “high-risk treatment indicated,” “grey area,” and “treatment not indicated” categories. Kaplan-Meier survival curves and Cox proportional hazards regression with associated hazard ratios [HR] and 95% confidence intervals [CI] estimated the predictors of treatment initiation by treatment recommendation category, adjusting for baseline patient characteristics. **Results:** Of 1,946 total untreated cHBV patients, 1,008 (52%) were male and 938 (48%) were female. There were 96 (5%) high-risk, 356 (18%) grey area, 269 (14%) not treatment indicated, and 1,225 (63%) patients with unknown treatment recommendation category. Of all untreated patients, 452 (23%) initiated treatment during the study period, including 57 (59%) high risk and 89 (25%) grey area patients. Females were 22% less likely to initiate treatment than males (HR 0.78; 95% CI 0.64-0.95); with no significant differences found by age or race. Compared to patients who were not treatment indicated, high-risk (HR 7.7, CI 5.0-11.7) and grey area (HR 1.9, CI 1.3, 2.8) patients were significantly more likely to initiate treatment, with mean (median) time to treatment initiation of 0.7 (0.2) and 2.8 (2.1) years, respectively (Figure). **Conclusion:** We observed a higher likelihood and faster rate of high-risk treatment eligible patients initiating treatment than grey area or treatment not indicated patients. However, almost two-thirds of patients lacked information necessary to classify treatment eligibility and over one-third of high-risk patients remained untreated throughout the study period. Thus, there remains considerable room for improvement in treatment strategies among high-risk cHBV patients. Figure: Kaplan-Meier curve of time to treatment initiation among untreated cHBV patients, by treatment recommendation category



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Disclosure information not available at the time of publication: Teresa M Kimes, Ana Gabriela Rosales, Sixiang Nie, Richard T Meenan, Judy L Donald

1327-C | QUANTIFICATION OF PLASMA HDV RNA IN UNTREATED AND BULEVIRTIDE-TREATED PATIENTS WITH CHD: A COMPARISON BETWEEN ROBOGENE 2.0 AND EUROBIOPLEX

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Background: Accurate HDV RNA quantification is crucial for diagnosis and management of chronic hepatitis Delta, yet variability between assays exist. Aim of the study was to compare two methods to quantify HDV RNA in untreated and Bulevirtide (BLV)-treated CHD patients. **Methods:** Frozen plasma from consecutive untreated and BLV–treated CHD patients were tested in a single-center retrospective study with two quantification methods: Robogene HDV RNA Quantification Kit 2.0 (Roboscreen GmbH, Leipzig, Germany; LOD 6 IU/mL on 7500 Fast Real-Time PCR System [Applied Byosystem, Germany]) and EurobioPlex HDV PCR quantitative (Eurobio Scientific, France, LOD 100 IU/mL on CFX96™ real-time PCR detection system [Bio-Rad, USA]). RNA extraction was performed manually according to manufacturer indications: INSTANT Virus RNA/DNA kit (Roboscreen GmbH, Leipzig, Germany) for Robogene and NucleoSpin® Dx Virus Kit (Macherey-Nagel GmbH, Düren, Germany) for EurobioPlex. **Results:** 232 plasma samples from 127 CHD (69 untreated and 58 BLV-treated) patients were analyzed: age 52 (23-77) years, 54% males, 91% of European origin, 62% with cirrhosis, 75% under NUC, 96% HDV genotype 1, 87% HBeAg negative, 73% HBV DNA undetectable. ALT were 76 (6-743) U/L, HBsAg 3.8 (0.3-4.6) Log IU/mL. Overall, median HDV RNA levels were 3.78 (0.70-7.99) *vs.* 4.69 (2.00-8.19) Log IU/mL by Robogene 2.0 *vs.* EurobioPlex ($p < 0.0001$). Compared to Robogene 2.0, EurobioPlex reported similar HDV RNA levels ($\Delta \pm 0.5$ Log) in 66 (28%) patients, higher in 160 (69%) [Δ between +0.5 and +1 Log in 55; Δ between +1 and +2 Log in 98; $\Delta > 2$ in 7] and lower in 6 (3%) [Δ between -0.5 and -1 Log in all 6]. Among the 40 (17%) samples testing target not detected (TND) with Robogene 2.0, 73% tested TND with EurobioPlex, 13% tested < LOD, 15% tested positive (median HDV RNA 2.29 Log IU/mL). Of the 14 (6%) samples < LOD with Robogene 2.0, 79% were TND with EurobioPlex, 14% were < LOD and 1 positive (HDV RNA 3.03 Log IU/mL). 54 (23%) samples tested TND or < LOD with Robogene 2.0, 66 (28%) with EurobioPlex, respectively. In BLV-treated patients, virological response rates differed according to the assay: 25% of patients achieved HDV RNA < LOD/TND with Robogene 2.0, 33% with EurobioPlex. 14% of Robogene 2.0 negative patients tested positive with EurobioPlex (median HDV RNA 2.26 Log IU/ml). 33% of those negative with EurobioPlex tested positive with Robogene 2.0 (median HDV RNA of 1.91 Log IU/ml). We then tested 6 serum samples from the WHO standard: EurobioPlex read a median of 0.66 Log IU/mL more than the standard in 4/6 samples, Robogene 2.0 read a median of 0.20 Log IU/mL less than WHO standard in 5/6. **Conclusion:** HDV RNA quantification is significantly influenced by the assay, EurobioPlex reporting overall 1 Log higher viremia than Robogene 2.0. These results could significantly influence the clinical management of patients with CHD, being viral load a surrogate treatment endpoint in CHD.

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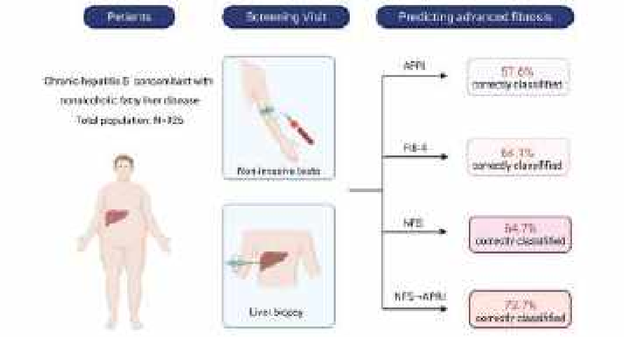
The following people have nothing to disclose: Maria Paola Anolli, Sara Uceda Renteria, Elisabetta Degasperi, Floriana Facchetti, Dana Sambarino, Marta Borghi, Riccardo Perbellini, Roberta Soffredini, Sara Monico, Ferruccio Ceriotti

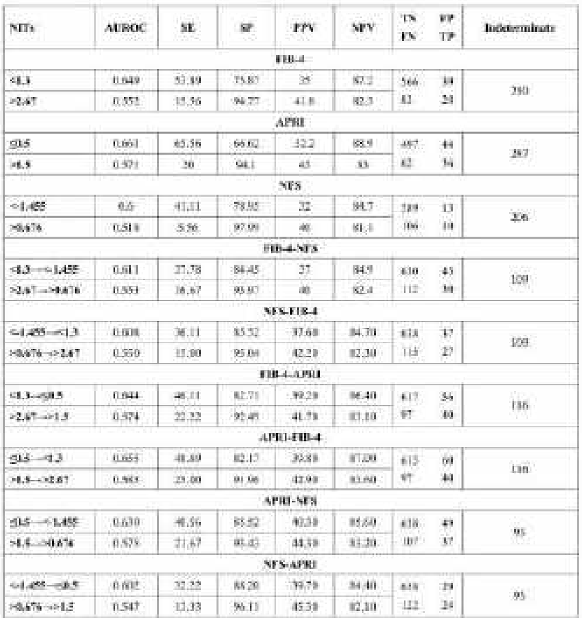
1328-C | STREAMLINING THE DIAGNOSIS OF LIVER FIBROSIS TO REDUCE PATIENTS WITH INDETERMINATE RESULTS: A NOVEL ALGORITHM FOR CHB PATIENTS WITH CONCURRENT NAFLD

Xiaoming Xu[1], Fajuan Rui[1], Wenjing Ni[1], Chao Wu[1,2], Jeff Liang[3], Junping Shi[4], Yee Hui Yeo[5] and Jie Li[1,2], (1)Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China, (2)Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China, (3)Cedars-Sinai Medical Center, Los Angeles, CA, (4)The Affiliated Hospital of Hangzhou Normal University, Hangzhou, Zhejiang, China, (5)Cedars-Sinai Medical Center, Culver City, CA

Background: Non-invasive tests (NITs) have been proposed as potential alternatives for the identification of patients at high risk of advanced fibrosis. However, they are limited by having a significant proportion of indeterminate results. Herein, we aimed to establish novel diagnostic algorithms to enhance the proportion of correct classification. **Methods:** From April 2004 to September 2021, treatment-naive patients with CHB patients with concurrent NAFLD, who underwent liver biopsies from nine medical centers in China, were consecutively enrolled in this study. Fibrosis index based on four factors (FIB-4), aspartate aminotransferase to platelet ratio index (APRI), and NAFLD fibrosis score (NFS), as well as their combinations, were used to predict advanced fibrosis. Area under receiver operating characteristic (AUROC), sensitivities, specificities, and positive and negative predicted values were calculated. Subsequently, we computed the proportion of patients with the correct classification (the sum of true positives and negatives) for different combinations of NITs. **Results:** Among 926 treatment-naive CHB patients with concurrent NAFLD, 180 (19.44%) patients had advanced fibrosis. At the lower cut-off values, APRI exhibited the highest sensitivity of 65.56%, followed by FIB-4 (53.89%) and NFS (41.11%). At the higher cut-off values, NFS had the highest specificity of 97.99%, followed by FIB-4 (94.77%) and APRI (94.1%). Notably, APRI displayed the highest indeterminate rate of 30.99% compared to other NITs. The proportions of patients to receive a correct classification according to a single test were 64.7% for NFS, 64.1% for FIB-4, and 57.6% for APRI. When combining the test, the algorithm with NFS followed by APRI enabled most patients to receive a correct classification (73.7%), compared to FIB-4-NFS (71.3%), NFS-FIB-4(71.8%), FIB-4-APRI (71.0%), APRI-FIB-4 (70.5%), APRI-NFS(71.8%) . **Conclusion:** Our study highlights the superior performance of the combined NFS-APRI model in improving the proportion of correct classification. The findings has implications for optimizing referral pathways and provide an invaluable tool for primary care to facilitate targeted screening for liver fibrosis in CHB patients with concurrent NAFLD. **Keywords:** chronic hepatitis B; nonalcoholic fatty liver disease; advanced fibrosis; combined models; non-invasive tests

Figure 1: Comparison of different non-invasive tests and combined model for predicting advanced fibrosis in chronic hepatitis B with concurrent nonalcoholic fatty liver disease patients.


Patients
Screening visit
Predicting advanced fibrosis
Chronic hepatitis B concomitant with nonalcoholic fatty liver disease
Total population: N=926
Non-invasive tests
Liver biopsy
APRI
57.6% correctly classified
FIB-4
64.1% correctly classified
NFS
64.7% correctly classified
NFS→APRI
72.7% correctly classified



NITs	AUROC	SE	SP	PPV	NPV	TN FN	FP TP	Indeterminate
				FIB-4				
<1.3	0.649	53.89	75.87	35	87.2	566	38	280
>2.67	0.552	15.56	94.77	41.8	82.3	82	23	
				APRI				
≤0.5	0.661	65.56	66.62	32.2	88.9	497	44	287
>1.5	0.571	30	94.1	45	83	82	34	
				NFS				
<-1.455	0.6	41.11	78.95	32	84.7	589	13	206
>0.676	0.518	5.56	97.99	40	81.1	106	10	
				FIB-4-NFS				
<1.3→<-1.455	0.611	27.78	84.45	27	84.9	630	45	109
>2.67→>0.676	0.553	16.67	93.97	40	82.4	112	30	
				NFS-FIB-4				
<-1.455→<1.3	0.608	36.11	85.52	37.60	84.70	618	37	109
>0.676→>2.67	0.550	15.00	95.04	42.20	82.30	115	27	
				FIB-4-APRI				
<1.3→≤0.5	0.644	46.11	82.71	39.20	86.40	617	56	116
>2.67→>1.5	0.574	22.22	92.49	41.70	83.10	97	40	
				APRI-FIB-4				
≤0.5→<1.3	0.655	48.89	82.17	39.80	87.20	613	60	116
>1.5→>2.67	0.563	25.00	91.96	42.90	83.60	97	40	
				APRI-NFS				
≤0.5→<-1.455	0.630	46.56	85.52	40.30	85.60	638	49	95
>1.5→>0.676	0.575	21.67	95.43	44.50	83.20	107	37	
				NFS-APRI				
<-1.455→≤0.5	0.602	32.22	88.20	39.70	84.40	658	29	95
>0.676→>1.5	0.547	13.33	96.11	45.50	82.10	122	24	

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1329-C | SURVEY TO EVALUATE THE IMPLEMENTATION OF THE RECOMMENDATIONS ON THE COMPREHENSIVE DIAGNOSIS OF VIRAL HEPATITIS IN A SINGLE EXTRACTION: WHERE ARE WE?

Joaquin Cabezas[1], Antonio Aguilera[2], Marina Berenguer[3], Maria Buti[4], María Eliecer Cano[5], Xavier Forns[6], Federico Garcia[7], Javier Garcia-Samaniego[8], Manuel Hernandez-Guerra[9], Francisco Jorquera[10], Jeffrey V. Lazarus[11], Sabela Lens[6], Elisa Martró[12], Juan Antonio Pineda[13], Martin Prieto[14], Francisco Rodriguez-Frias[15], Manuel Rodriguez[16], Miguel A. Serra[17], Juan Turnes[18], Araceli Casado[19], Raquel Domínguez-Hernández[19], Nerea Tejado Alsua[19], Miguel Angel Casado[19], Jose Luis Calleja[20] and Javier Crespo

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

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Background: The SEPD (Spanish Association for Digestive Diseases), AEEH (Spanish Association for the Study of the Liver), SEIMC (Spanish Society of Infectious Diseases and Clinical Microbiology), SEIMC-GEHEP (Work-group for Viral Hepatitis) and AEHVE (Spanish Viral Hepatitis Elimination Alliance) agreed on a document at the beginning of 2022 to carry out a comprehensive diagnosis of viral hepatitis (B, C and D): a positive result in serology to detect viral hepatitis (HBV, HCV and HDV), as well as HIV, would trigger the analysis of the rest of the virus, including the viral load when necessary, from the same blood sample. This process would increase the diagnosis rate and it would reduce the time to be evaluated. Aim: To evaluate the situation in Spain regarding the comprehensive diagnosis of viral hepatitis in a single blood draw. **Methods:** A panel of experts prepared a structured survey disseminated through the Google Forms platform to all Spanish hospitals, public or private with teaching accreditation, with 200 beds or more. The survey was sent on 20th Oct 2022 and the reception of the results closed on 1st Dec. 2022. **Results:** Of the 130 hospitals with inclusion criteria, 48 responded (37% response rate, 34 centers > 500 beds). All centers have tools for the determination of HBV surface antigen, anti-HCV and HIV serology. 92% have a PCR technique for HBV/HCV. Only 67% of the centers have capacity for the determination of anti-HDV, and this drops to 31% for the detection of HDV-RNA; 88%, who do not have this technique, outsource it. The availability of Point-of-Care (POC) tests is low (21% of centers), GenXpert HCV (38%) and dry blood spot (38%) being the most frequent. Most of the POCs (90%) are supervised by Microbiologists and are always included in the clinical records. Reflex-test diagnosis is performed simultaneously in 88% of centers for HCV, 62% for HBV, 50% for HDV, and only 41% for HBV-HDV. Although 90% of centers believe that HBV and HCV serology should be performed on HIV-positive patients in the same sample, it is only done on 18% of HBsAg-positive and/or anti-HCV-positive subjects. When there is an active infection, any communication strategy is used in 38/48 (79%) of the hospitals (38 hospitals for HCV, 18 for HBV and 10 for HDV). The automated appointment arrangement is only available in 19% of the centers. Only 44.2% of the respondents believe that the determinations to reach a definitive diagnosis must be made with a single blood sample. **Conclusion:** Although most hospitals have the procedures to carry out a comprehensive diagnosis of viral hepatitis in a single analytical sample, this is used in less than 50% of cases for HBV/HDV. Alerts to maintain continuity of care are widely available for hepatitis C, but they need to be increased for HBV and HDV. Likewise, it is necessary to implement the devices for decentralized diagnosis.

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Francisco Jorquera – Intercept Pharmaceuticals: Consultant, Yes, Yes;

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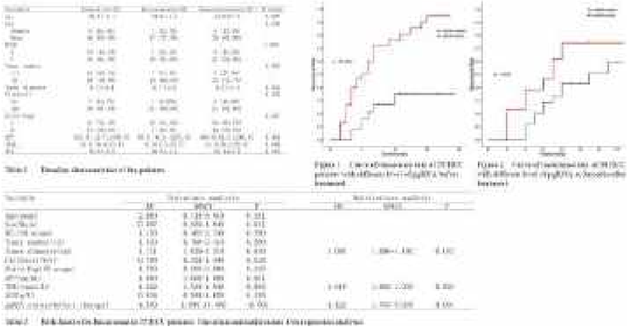
1330-C | THE ROLE OF PREGENOMIC RNA IN RECURRENCE OF ADVANCED HEPATOCELLULAR CARCINOMA

Yifan Han[1], Jiali Pan[1], Hongyu Chen[1], Zhan Zeng[1], Xiaoyuan Xu[1] and Wengang Li[2], (1)Peking University First Hospital, (2)Fifth Medical Center of Chinese PLA General Hospital

Background: Previous studies have suggested that pregenomic RNA (pgRNA) could serve as a potential prognostic marker for early-stage HBV-related hepatocellular carcinoma (HCC). However, the significance of pgRNA in advanced HCC is not yet fully understood. Therefore, the objective of our study is to investigate the potential role of pgRNA in predicting the recurrence of advanced HCC and to assess the prognostic value of dynamic changes in pgRNA levels. **Methods:** A total of 55 treatment-naïve patients with HBV-related HCC at BCLC stage B or C were included in this study. Following the diagnosis, all patients underwent systemic therapy, including stereotactic body radiation therapy (SBRT) and immunotherapy combined with anti-angiogenic drugs. Additionally, all patients received antiviral treatment for HBV infection, and their HBV-DNA levels were negative prior to HCC treatment. Serum levels of pgRNA were tested in all 55 patients before HCC treatment, and 38 of them underwent a retest after 3 months of treatment. The quantification of pgRNA was performed using quantitative polymerase chain reaction (qPCR) analysis. The cumulative probability of HCC recurrence was assessed using the Kaplan–Meier method, and univariate and multivariate analyses were conducted using Cox proportional hazard models. **Results:** Table 1 summarizes the clinical characteristics of 55 patients with HBV-related HCC. The average age of the patients was 54 years, with 46 male patients and 48 patients presenting with cirrhosis. The majority of patients had Child–Pugh A (74.5%) and BCLC Stage C (81.8%). There were no significant differences in age, gender, BCLC stage, and number of lesions between the recurrence and non-recurrence groups. The actuarial rates of overall recurrence at six months and one year were 34.5% (95% CI: 20.7–46.0%) and 58.6% (95% CI: 41.2–70.9%), respectively. The median time to recurrence was 8 months. Univariate and multivariate analyses (Table 2) revealed that the serum level of pgRNA before HCC treatment ($p = 0.001$, HR [4.122, 1.765–9.629]), maximum tumor diameter ($p = 0.037$, HR [1.095, 1.006–1.192]), and total bilirubin ($p = 0.024$, HR [1.019, 1.002–1.035]) were independent risk factors for recurrence. Patients with a positive baseline serum pgRNA had a worse prognosis and a higher cumulative recurrence rate after systemic treatment(Figure 1). Among the 38 patients tested for pgRNA levels after 3 months of systemic therapy, those who were pgRNA-positive also exhibited a worse prognosis and a higher recurrence rate(Figure 2). **Conclusion:** Our study demonstrates that pgRNA serves as a valuable predictor of recurrence in advanced HCC. Furthermore, our findings suggest that continuous monitoring of pgRNA levels after treatment may hold predictive value for the recurrence of advanced HCC.



Disclosures: The following people have nothing to disclose: Yifan Han, Jiali Pan, Hongyu Chen, Zhan Zeng, Xiaoyuan Xu, Wengang Li

1331-C | UNLEASHING THE POWER OF HBV QUASISPECIES CHARACTERISTICS: ENHANCING HCC PREDICTABILITY IN HBEAG-POSITIVE CHRONIC HEPATITIS B PATIENTS WITH REACH-B SCORE INTEGRATION

Chih-Jen Huang[1], Mei-Hung Pan[1], Rachel Wen-Juei Jeng[2], Yin-Han Chou[1], Pao-Chun Hsu[1], Ching-Yu Bao[1], Wenya Huang[3], Shiou-Hwei Yeh[4], Pei-Jer Chen[5], Chien-Jen Chen[1], Zhiwei Liu[6] and Hwai-I Yang[1], (1) *Genomic Research Center, Academia Sinica, (2)Linkou Chang Gung Memorial Hospital, (3)College of Medicine, National Cheng Kung University, (4)College of Medicine, National Taiwan University, (5)National Taiwan University Hospital, (6)National Cancer Institute*

Background: Hepatitis B virus (HBV) infection is a leading cause of hepatocellular carcinoma (HCC). Clinical seromarkers, including the seroclearence of HBeAg, HBV DNA, and HBsAg, are used to monitor disease progression among chronic hepatitis B (CHB) patients. These markers have been shown to be predictive to HCC risk. However, risk assessment during the early stage of infection, when HBeAg is still present, remains challenging. **Methods:** In this study, we utilized advanced long-read sequencing techniques to examine HBV quasispecies variants in 439 HBeAg-positive CHB patients enrolled in the REVEAL-HBV cohort. We investigated quasispecies characteristics within three major genomic variation categories: viral complexity (quantified by Shannon entropy [SE]) of the Core gene, proportion of a protective combination of SNVs associated with HCC (protective-SNVs), and proportion of a combination of splicing variants (SP combination). Risks associated with quasispecies characteristics were assessed by Cox proportional hazards models, with HCC as the primary end point, adjusting for covariates. These characteristics were defined and evaluated to assess their potential for predicting HCC risk. **Results:** During an average follow-up period of 21.5 years, a total of 133 HCC cases were identified. In models without mutual adjustment, HBV quasispecies characteristics (specifically SE of Core, protective-SNVs, and SP combination) were found to be associated with risk of HCC (adjusted hazard ratios [adj. HR] for the highest quartile compared to the lowest quartile = 3.3, 0.1, and 3.1 respectively; all p values < 0.05). These associations remained statistically significant in models with mutual adjustment and persisted when incorporating a previously established REACH-B score. In addition, a combined model of the quasispecies characteristics demonstrated good discriminative ability for HCC risk with high performance (area under the curve [AUC] = 0.780; 95% CI = 0.735-0.825), which was higher than that of using REACH-B score alone (AUC = 0.729; 95% CI = 0.676-0.783), albeit not statistically significant (p for difference = 0.0531). When integrating the quasispecies markers and the REACH-B score, the performance in predicting true positive HCC cases was significantly higher (AUC = 0.809; 95% CI = 0.765-0.853; p for difference < 0.001) than using the REACH-B score alone. **Conclusion:** Our study demonstrated the potential of HBV quasispecies characteristics for HCC risk assessment during the early stage of HBV infection. These findings could contribute to the development of more effective strategies for HCC prevention and treatment.

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Disclosure information not available at the time of publication: Mei-Hung Pan, Yin-Han Chou, Pao-Chun Hsu, Ching-Yu Bao, Wenya Huang, Shiou-Hwei Yeh, Chien-Jen Chen, Zhiwei Liu, Hwai-I Yang

1332-C | VALIDATION OF THE PAP MODEL PERFORMANCE FOR DIAGNOSING ADVANCED FIBROSIS AND CIRRHOSIS IN CHRONIC HEPATITIS B PATIENTS WITH CONCURRENT HEPATIC STEATOSIS ACROSS DIFFERENT SUBGROUPS

Wenjing Ni[1], Yee Hui Yeo[2], Fajuan Rui[1], Yayun Xu[3], Liang Xu[4], Qi Zheng[5], Xiaorong Tian[6], QingLei Zeng[7], Zebao He[8], Yuanwang Qiu[9], Chuanwu Zhu[10], Weimao Ding[11], Jian Wang[12], Rui Huang[13], Qi Xue[14], Xueqi Wang[3], Xiaolong Qi[15], Junping Shi[16], Vincent Wai-Sun Wong[17], Chao Wu[12], Jeff Liang[2] and Jie Li[13,18,19], (1) Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China, (2)Cedars-Sinai Medical Center, Los Angeles, CA, (3)Shandong Provincial Hospital, Shandong University, Jinan, Shandong, China, (4) Clinical School of the Second People's Hospital, Tianjin Medical University, Tianjin, China, (5)Hepatology Research Institute,the First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian, China, (6)School of Computer Science, China University of Geosciences, Wuhan, Hubei, China., (7)The First Affiliated Hospital of Zhengzhou University, Zhenghzhou, Henan, China, (8) Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Taizhou, Zhejiang, China, (9)The Fifth People's Hospital of Wuxi, Wuxi, Jiangsu, China, (10)The Affiliated Infectious Diseases Hospital of Soochow University, Suzhou, Jiangsu, China., (11) Huai'an No.4 People's Hospital, Huai'an, Jiangsu, China, (12)Department of Infectious Diseases, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China, (13)Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China, (14)Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China, (15)Zhongda Hospital, Medical School, Nanjing, Jiangsu, China., (16)The Affiliated Hospital of Hangzhou Normal University, Hangzhou, Zhejiang, China, (17)Chinese University of Hong Kong, Hong Kong, China, (18)Nanjing Drum Tower Hospital Clinical College of Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing, *Jiangsu, China, (19)Institute of Viruses and Infectious Diseases, Nanjing University, Nanjing, Jiangsu, China*

Background: Although the endemic phenomenon of the superimposed chronic hepatitis B (CHB) on hepatic steatosis (HS) has been observed, few non-invasive tools are suitable for CHB patients with concurrent HS to evaluate the severity of liver fibrosis. To address the clinical need, a diagnostic model named PAP was previously developed to assess advanced fibrosis and cirrhosis for these patients. The PAP model was built on Gaussian naive bayes (GNB) by including prothrombin time (PT), albumin(ALB) and platelet (PLT). However, the stability and reproducibility of the PAP model were not clear across different categories. Therefore, the study aimed to test the PAP model performance in five subgroups. **Methods:** The study used data from a previous population-based cohort of 1,427 patients from nine clinical centers in China (NCT05766449). Patients were divided into five groups according to age (e 40 y and < 40 y), sex (males and females), alanine transaminase (ALT) levels (normal and elevated ALT), hepatitis B e antigen (HBeAg) status (positive and negative) and hepatitis B virus deoxyribonucleic acid (HBV DNA) level ($< 10^5$ and e 10^5 IU/mL) in both the training and validation cohorts. A web page was developed to score the PAP model. **Results:** In the training cohort (n = 1,063), the PAP model had the highest area under curves (AUCs) in patients with HBV DNA e 10^5 IU/mL at 0.827 (95% CI 0.749-0.905) for diagnosing advanced fibrosis (e S3) and 0.864 (95% CI 0.794-0.934) in patients aged e 40 years for identifying cirrhosis (= S4), while it performed modestly in patients with normal ALT levels in diagnosing advanced fibrosis (e S3) and cirrhosis (= S4), with AUCs between 0.558 and 0.711. In the validation cohort (n = 364), the PAP model had the highest AUC of 0.824 (95% CI 0.765-0.883) in patients with HBV DNA e 10^5 IU/mL, and the lowest AUC of 0.687 (0.619-0.755) in patients aged < 40 years for diagnosing advanced fibrosis (e S3). In diagnosing cirrhosis(= S4), the PAP model performed best in female patients, with an AUC of 0.954 (95% CI 0.902-1.000), while showing the poorest performance in patients with HBV DNA $< 10^5$ IU/mL, with an AUC of 0.771 (0.708-0.834). A web-page for fibrosis score calculation of the PAP model is freely at http://py.reallife-liver.com/. **Conclusion:** In CHB patients with concurrent HS, the PAP model remained its reproducibility for diagnosing liver advanced fibrosis and cirrhosis across various groups, hoping to serve as a novel diagnostic tool.

Disclosures: Vincent Wai-Sun Wong – Sagimet: Consultant, No, Yes; Pfizer: Consultant, No, Yes; Novo Nordisk: Speaking and Teaching, Yes, Yes; Novo Nordisk: Consultant, Yes, Yes; Inventiva: Consultant, No, Yes; Intercept: Consultant, No, Yes; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences: Speaking and Teaching, No, No; Gilead Sciences: Consultant, No, Yes; Echosens: Consultant, Yes, Yes; Boehringer Ingelheim: Consultant, No, Yes; AbbVie: Speaking and Teaching, No, Yes; AbbVie: Consultant, No, Yes; Abbott: Speaking and Teaching, No, Yes; TARGET PharmaSolutions: Consultant, No, No; Unilab: Speaking and Teaching, No, Yes; Illuminatio Medical Technology Limited: Stock – privately held company (individual stocks and stock options), No, No;

The following people have nothing to disclose: Wenjing Ni, Yee Hui Yeo, Fajuan Rui, Yayun Xu, Liang Xu, Qi Zheng, Xiaorong Tian, QingLei Zeng, Zebao He, Yuanwang Qiu, Chuanwu Zhu, Weimao Ding, Jian Wang, Rui Huang, Qi Xue, Xueqi Wang, Xiaolong Qi, Junping Shi, Chao Wu, Jeff Liang, Jie Li

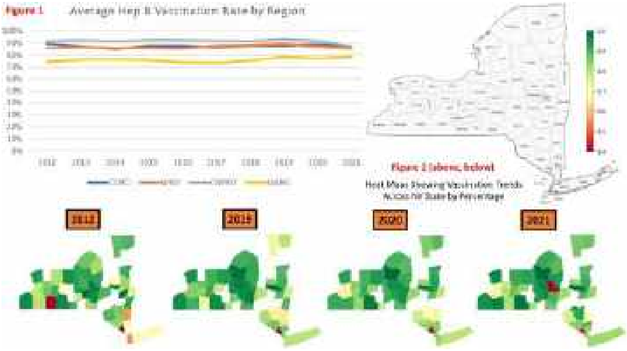
1333-C | A 10-YEAR STUDY OF PERINATAL HEPATITIS B VACCINATION TRENDS IN NEW YORK STATE AND THE IMPACT OF THE COVID-19 PANDEMIC

Clive Jude Miranda[1], Murad Hayatt Ali[2], Alexander Mark Carlson[3], Farhan Azad[2], Naren Srinath Nallapeta[2] and Anthony Dunning Martinez[4], (1)University at Buffalo, Buffalo, NY, (2)University at Buffalo, (3) University at Buffalo, Orchard Park, NY, (4)University of Buffalo

Background: Vaccination for hepatitis B virus (HBV) is recommended within 24-hours of birth for most neonates. The virus infects roughly 1000 neonates in the United States annually via vertical transmission from mother to infant. HBV vaccination is essential to prevent potentially lethal neonatal chronic infection. However, vaccination rates in the United States have been notably subpar, and the COVID-19 pandemic has further impaired timely and widespread vaccination initiatives. We aim to analyze trends in HBV vaccination in New York State over the past decade and investigate the extent to which the COVID-19 pandemic has influenced this. **Methods:** This retrospective cohort study investigated New York State neonates > 2000g who received birth hospitalization between 2012-2021. 143 hospitals in 45 counties were included. Counties were grouped into 4 Regional Offices (RO): Western (WRO); Capital District (CDRO); Metropolitan Area (MARO); Central New York (CYNRO). Annual HBV vaccination rates were analyzed in each county and trended over the 10-year period. The counties of Richmond, New York, Kings, Bronx, and Queens were absent in this study. **Results:** A total of 1,114,402

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

hospitalized births were accounted for between 2012-2021 in the healthcare facilities in our study. After adjusting for healthy infants weighing > 2000g, 1,084,315 neonates were included in the cohort analysis. Of these neonates, a total of 883,893 (81.5%) were vaccinated for HBV within 24-hours of life over the 10-year period. When grouping counties by Regional Offices, a steady rise in average HBV vaccination rates was noted in MARO from 74% in 2012 to 78% in 2021. Rates in CDRO stayed steady between 85-89%. Interestingly, both WRO and CNYRO reached a peak vaccination rate in 2019 of 89% and 93% respectively, before both plummeting to 85% and 87% in 2021 (Figure 1). This period correlated with the COVID-19 pandemic during which New York City was an infection epicenter with overcrowded healthcare facilities and dwindling resources. Individual counties showed wide discrepancy in their 10-year vaccination trends from 2012 to 2021, with some showing impressive rises (Allegany: 52% to 81%; Nassau: 63% to 82%) and some falling precipitously (Madison: 97% to 47%; Erie: 83% to 69%). Despite this, heat maps show an overall increase in vaccination rates in New York State between 2012-2021 despite the pandemic (Figure 2). **Conclusion:** Despite the COVID-19 pandemic impacting healthcare access, resources, and personnel in New York State, the overall trend of neonatal HBV vaccination rates has demonstrated a steady rise since 2012. However, it is still not up to target levels. Further work is needed on promoting medical education and developing neonatal HBV vaccination regimens in the state.



Disclosures: Anthony Dunning Martinez – gilead: Consultant, No, No; abbvie: Consultant, No, No; gilead: Speaking and Teaching, No, No; abbvie: Speaking and Teaching, No, No; antios: Consultant, No, Yes; eisai: Consultant, No, No; intercept: Consultant, No, Yes;
The following people have nothing to disclose: Clive Jude Miranda, Murad Hayatt Ali, Alexander Mark Carlson, Farhan Azad, Naren Srinath Nallapeta

1334-C | A 7th-YEAR INTERIM ANALYSIS OF PROSPECTIVE AND LONGITUDINAL KOREAN CHRONIC HEPATITIS B COHORT

Jae Seung Lee[1], Beom Kyung Kim[1], Hye Won Lee[1], Seung Up Kim[1], Do Young Kim[1], Sang Hoon Ahn[1], Sang Gyune Kim[2], Eun Young Cho[3], Young Mi Hong[4], Ki Tae Yoon[4], Yeon Seok Seo[5] and Jun Yong Park[1], (1) Yonsei University College of Medicine, Seoul, Republic of Korea, (2)Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Republic of Korea, (3)Wonkwang University College of Medicine, Iksan, Republic of Korea, (4)Pusan National University Hospital, Busan, Republic of Korea, (5)Korea University Anam Hospital, Korea University Medical College, Seoul, Korea, Republic of (South)

Background: We aimed to report the clinical outcome of Korean chronic hepatitis B (CHB) patients from a prospective longitudinal cohort. **Methods:** This cohort, supported by the Korea Disease Control and Prevention Agency (2022E190400), was established in 2015. Voluntarily enrolled patients with CHB serially provide their clinical data and blood samples during the ten-year follow-up. **Results:** From 2015 to 2022, 2949 patients (1812 male) with a mean age of 52.6 years participated in this study. Annual 16 mL of blood sampling was collected (median three times) from 1391 volunteers. Male patients had more smoking and hazardous alcohol intake ($p < 0.001$). At the enrollment, most patients were receiving antiviral therapy (AVT) (n = 2359, 80.0%), whereas 515 (17.4%) patients were AVT-naïve. Cirrhosis was noted in 646 (21.9%) patients. The most favored AVT regimen was tenofovir disoproxyl fumarate (TDF) (40.0%), followed by entecavir (33.0%). However, during the recent two years, an increasing proportion of patients are starting the first AVT with tenofovir alafenamide (5.9% to 13.5%) or besifovir dipivoxil maleate (2.8% to 7.5%). Most patients receiving AVT with a high-genetic barrier experienced a complete virologic response (more than 80% at week 48). Crudely, the incidence of an increase in chronic kidney disease stage e 1 was significantly higher in TDF users than ETV users (7.56 vs. 4.56 per 100 person-years, $p < 0.001$). Hepatocellular carcinoma occurred in 33 (1.9%) patients after 50.3 months of median follow-up, most of which were within Milan criteria. Cirrhosis was independently associated with hepatocellular carcinoma occur (adjusted hazard ratio, 5.005, $p = 0.002$). **Conclusion:** This cohort study will evaluate long-term liver-related outcomes among Korean CHB patients. Future research using the cohort data and blood samples after the data purification could reveal the unmet needs to manage CHB.

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

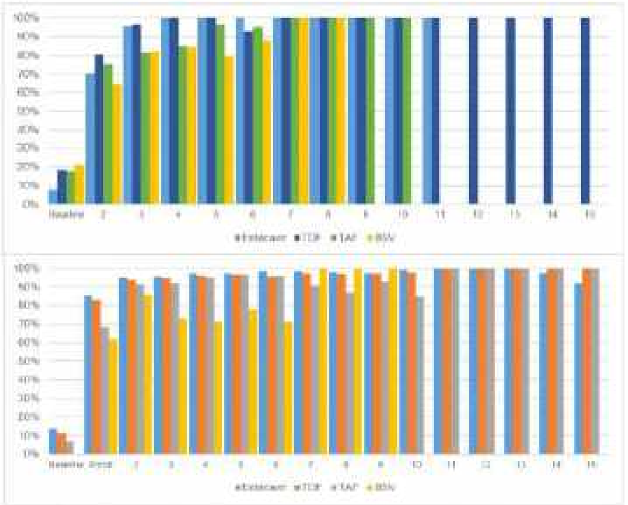


Figure. The proportion of patients who achieved HBV DNA <60 IU/mL after initiating entecavir, TDF, TAF, or BSV for treatment-naive CHB, (A) in whom initiated AVT after enrollment in this study, and (B) in whom initiated AVT before enrollment in this study

- The number of X-axis is at 6-month intervals.
- "Baseline" is a time point of initiating AVT. "Enroll" is a time point of the 1st visit for this study with receiving AVT.
- Abbreviation: CHB, chronic hepatitis B; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; BSV, besifovir dipivoxil maleate; AVT, antiviral therapy

Disclosures: Sang Hoon Ahn – Vir Biotechnology: Advisor, No, Yes; Vaccitech: Advisor, No, Yes; Abbvie: Advisor, No, Yes; Aligos: Advisor, No, Yes; Arbutus: Advisor, No, Yes; Assembly Biosciences: Advisor, No, Yes; Brii: Advisor, No, Yes; GeneOne Life Science: Advisor, No, Yes; Gilead Sciences Inc.: Advisor, Yes, No; GreenCross: Advisor, No, Yes; GSK: Advisor, No, Yes; Ildong: Advisor, No, Yes; Inovio: Advisor, No, Yes; Janssen: Advisor, No, Yes; Roche: Advisor, No, Yes; Samil: Advisor, No, Yes; SL Vaxigen: Advisor, No, Yes; Yuhan: Advisor, No, Yes;

The following people have nothing to disclose: Jae Seung Lee, Beom Kyung Kim, Hye Won Lee, Seung Up Kim, Do Young Kim, Sang Gyune Kim, Eun Young Cho, Young Mi Hong, Ki Tae Yoon, Yeon Seok Seo, Jun Yong Park

1335-C | A HEPATOCELLULAR CARCINOMA RISK PREDICTION MODEL IN PATIENTS ACHIEVING HBsAg SEROCLEARANCE

Jonggi Choi[1], *Hye Won Lee*[2], *Terry Cheuk-Fung Yip*[3], *Vincent Wai-Sun Wong*[4], *Young-Suk Lim*[5], *Henry Lik Yuen Chan*[6], *Sang Hoon Ahn*[2] *and Grace Lai-Hung C Wong*[7], *(1)Asan Medical Center, Seoul, Korea, Republic of (South), (2)Yonsei University College of Medicine, Seoul, Republic of Korea, (3)The Chinese University of Hong Kong, Hong Kong, 91, China, (4)The Chinese University of Hong Kong, Hong Kong, China, (5)Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South), (6) Chinese University of Hong Kong, Hong Kong, China, (7)Prince of Wales Hospital*

Background: The risk of hepatocellular carcinoma (HCC) decreases but remains present after HBsAg seroclearance in patients with chronic hepatitis B (CHB). The aim of this study was to determine the risk factors for HCC development and construct a prediction model to stratify the risk of HCC after HBsAg seroclearance. **Methods:** We analyzed CHB patients with confirmed HBsAg seroclearance, which was defined as HBsAg negativity by at least two consecutive tests, with a 6-month interval, regardless of hepatitis B surface antibody positivity. The primary outcome was the development of HCC following HBsAg seroclearance. A training cohort was derived from 3,476 patients at Asan Medical Center and Severance Hospital in Seoul, Republic of Korea, while 5,255 patients from the Chinese University of Hong Kong were used as an external validation cohort. A Cox model was used to determine the risk factors associated with HCC development in the training cohort. A prediction model for HCC risk with integer scores assigned to each risk factor based on the coefficient from the Cox model was built. The performance of the prediction model was evaluated using the time-dependent AUROC in predicting the 5- and 10-year risk of HCC. **Results:** In the entire cohort, 64.5% of the patients were male, the mean age at the time of HBsAg seroclearance was 55.4 years, and 17.1% had cirrhosis. During the 24,109 person-years (PYs) of follow-up, 102 patients developed HCC, resulting in an annual incidence of 0.43/100 PYs in the training cohort. Age ≥ 50 years (adjusted hazard ratio [AHR]: 2.8, $p < 0.001$), male gender (AHR: 3.81, $p < 0.001$), cirrhosis (AHR: 4.32, $p < 0.001$), and platelet count < 150,000 (AHR: 1.64, $p = 0.02$) were independently associated with an increased risk of HCC in multivariable analysis from the training cohort. Risk scores were assigned to age ≥ 50 years (2 points), male gender (3 points), cirrhosis (3 points), and low platelet count (1 point). Based on the sum of these points, the patients were categorized into low (0–3 points), intermediate (4–6 points), and high (≥ 7 points) risk groups, with incidences of HCC of 0.06, 0.41, and 1.37/100 PYs, respectively. The 5- and 10-year time-dependent AUROC of HCC in the training cohort were 0.782 and 0.827, respectively. In the validation cohort, 85 patients developed HCC with an annual incidence of 0.24/100 PYs. The incidences of HCC in the low-, intermediate-, and high-risk groups in the validation set were 0.07, 0.37, and 0.90/100 PYs, respectively. The 5- and 10-year time-dependent AUROC of HCC in the validation cohort were 0.785 and 0.771, respectively. **Conclusion:** Liver cirrhosis, age ≥ 50 years, male gender, and platelet < 150,000 at the time of HBsAg seroclearance were significantly associated with HCC development after HBsAg seroclearance. Our suggested model can be easily applied in the real world and aid in stratifying the risk of HCC after HBsAg seroclearance in patients with CHB.

Disclosures: Terry Cheuk-Fung Yip – Gilead Sciences: Consultant, No, No; Gilead Sciences: Speaking and Teaching, No, No;

Vincent Wai-Sun Wong – Sagimet: Consultant, No, Yes; Pfizer: Consultant, No, Yes; Novo Nordisk: Speaking and Teaching, Yes, Yes; Novo Nordisk: Consultant, Yes, Yes; Inventiva: Consultant, No, Yes; Intercept: Consultant, No, Yes; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences: Speaking and Teaching, No, No; Gilead Sciences: Consultant, No, Yes; Echosens: Consultant, Yes, Yes; Boehringer Ingelheim: Consultant, No, Yes; AbbVie: Speaking and Teaching, No, Yes; AbbVie: Consultant, No, Yes; Abbott: Speaking and Teaching, No, Yes; TARGET PharmaSolutions: Consultant, No, No; Unilab: Speaking and Teaching, No, Yes; Illuminatio Medical Technology Limited: Stock – privately held company (individual stocks and stock options), No, No;

Grace Lai-Hung C Wong – Gilead Sciences: Consultant, Yes, No; Gilead Sciences: Speaking and Teaching, Yes, No; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Abbvie: Speaking and Teaching, Yes, No; BMS: Speaking and Teaching, Yes, Yes; Echosens: Speaking and Teaching, Yes, Yes; Janssen: Consultant, Yes, No;

The following people have nothing to disclose: Jonggi Choi, Hye Won Lee, Young-Suk Lim, Henry Lik Yuen Chan, Sang Hoon Ahn

1336-C | ADHERENCE TO HEPATOCELLULAR CARCINOMA SURVEILLANCE IN PATIENTS WITH CHRONIC HEPATITIS B IN A LOW ENDEMIC COUNTRY

Lesley Ann Patmore[1], Warshan K. Katwaroe[1], Daniel Van Der Spek[1], Sylvia Brakenhoff[1], Laurens van Kleef[1], Adriaan J. Van der Meer[2], Harry L. A. Janssen[2,3], Rob J. De Knegt[1], Bettina E. Hansen[2], Robert A. De Man[1] and Milan J. Sonneveld[1], (1)Erasmus MC, University Medical Center, (2)Erasmus MC, University Medical Center Rotterdam, (3)Toronto General Hospital Research Institute

Background: Hepatocellular carcinoma (HCC) surveillance in high risk patients with chronic hepatitis B (CHB) is associated with improved long-term outcomes, and is therefore recommended in all guidelines. However, adherence to HCC surveillance recommendations is often suboptimal. We aimed to study adherence rates and predictors of non-adherence to HCC surveillance recommendations in a low endemic country. **Methods:** We conducted a single-center retrospective cohort study of all patients with HBV mono-infection attending the outpatient clinic of a tertiary care center in the Netherlands. We assessed the medical records to assess eligibility for HCC surveillance based on the Dutch guidelines. Patients were considered eligible for HCC surveillance in case of one of the following criteria (1) presence of cirrhosis (2) positive family history for HCC (3) Asian males e 40 years (4) Asian females e 50 years and (5) all Sub-Saharan African patients e 20 years. We compared adherence rates across risk groups (cirrhosis versus other indications) and across clinic types (dedicated viral hepatitis clinic versus general hepatology clinic). **Results:** A total of 480 patients were included, of whom 243 (50.6%) patients were considered eligible for HCC surveillance. Eligibility for HCC surveillance was based on presence of cirrhosis in 48 patients (10%). Of the 243 patients with an indication for HCC surveillance, 218 (89.7%) underwent surveillance. Adherence to surveillance was observed in all patients with cirrhosis, and in 87.2% of non-cirrhotic patients ($p = 0.009$). Among the chronic hepatitis B patients with a surveillance indication, 144 (59.3%) were seen at a dedicated viral hepatitis clinic. Dedicated viral hepatitis clinics had superior adherence rates to HCC surveillance guidelines compared to general hepatology clinics (95.1% versus 81.8%, $p < 0.001$), which was mostly accounted for by suboptimal adherence among non-cirrhotic patients (94.3% vs. 74.6% $p < 0.001$). **Conclusion:** The majority of patients with an indication for HCC surveillance were enrolled in an HCC surveillance program. Management at a dedicated viral hepatitis clinic was associated with superior adherence to HCC surveillance recommendations. These findings suggest that centralizing care for chronic hepatitis B in low incidence countries could potentially improve patient outcomes.

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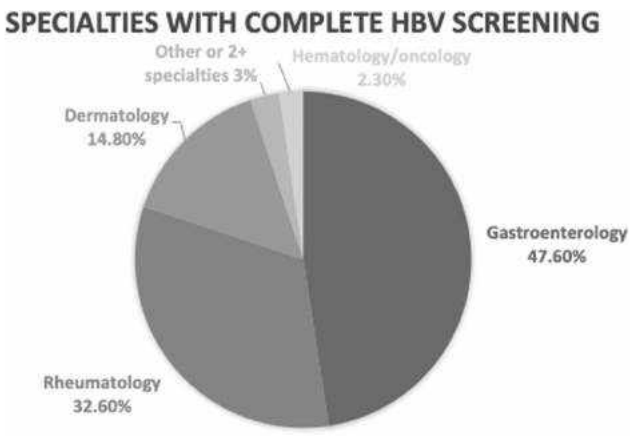
1337-C | ALL IN MODERATION: ASSESSING THE FREQUENCY OF GUIDELINE-BASED HEPATITIS B SCREENING IN THE MODERATE-RISK GROUP FOR HBV REACTIVATION PRIOR TO IMMUNOSUPPRESSIVE THERAPY

Joanne Lin, Humzah Iqbal, Jennifer Yoon, Alakh Gulati, Ratnali Jain and Marina M. Roytman, UCSF Fresno

Background: Hepatitis B virus reactivation (HBVr) is a syndrome associated with significant morbidity and mortality, reflecting the loss of immune control of the infection which can be due to stopping antiviral therapy or starting immunosuppressive medication. Immunosuppressive therapies are used to treat various conditions by many specialties including rheumatology, dermatology, oncology, and gastroenterology. Prior to starting immunosuppressive therapy, many clinical guidelines recommend screening for chronic hepatitis B (HBV). However, adherence in clinical practice varies. We sought to determine the frequency of complete guideline-based hepatitis B screening recommended by the American Gastroenterological Association (AGA) prior to the initiation of moderate-risk immunosuppressive therapy. **Methods:** Our retrospective study included 2443 patients over the age of 18 being treated with moderate-risk immunosuppressive therapy, which included tumor necrosis factor-alpha inhibitors, cytokine or integrin inhibitors, and tyrosine kinase inhibitors, from October 2020 to April 2021. Patients taking moderate-risk doses and duration of steroid therapy were not included. The following data were collected: gender, age, complete HBV serologies (hepatitis B surface antigen [HBsAg], hepatitis B core antigen [anti-HBc], hepatitis B surface antibody [anti-HBs]), the immunosuppressive regimen, and the indication for immunosuppression. **Results:** Of the 2443 patients, 33.2% were over the age of 65 and 63.2% were females. The most frequently used immunosuppressive therapy was adalimumab (33.8%), followed by etanercept (18.1%) and 2 or more medications (14.3%). The specialties that prescribed immunosuppressive therapies most often were rheumatology (51.6%), gastroenterology (23.4%), and dermatology (15.7%). Only 393 patients (16.1%) had complete HBV screening. Of the screening tests, HbsAg was tested in 44.8% of patients, anti-HBc in 33%, and anti-HBs in 20.6%. Gastroenterology completed HBV screening most frequently, followed by rheumatology, dermatology, other/mixed, and hematology/oncology. **Conclusion:** HBVr is a potentially life-threatening complication of immunosuppression but is preventable with appropriate pre-immunosuppression screening and antiviral therapy. Our study emphasizes the significant deficiencies in HBV screening even in moderate-risk patients and demonstrates that there are opportunities to improve provider adherence to HBV screening recommendations to prevent HBVr.



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Disclosure information not available at the time of publication: Jennifer Yoon, Alakh Gulati, Ratnali Jain

1338-C | AN INTEGRATED MODEL NURSE CLINIC TO PREVENT MOTHER-TO-CHILD TRANSMISSION (MTCT) OF HEPATITIS B VIRUS (HBV)

Amber C Yip[1], Cherry C Yung[1], Terry Cheuk-Fung Yip[2], Vincent Wai-Sun Wong[3] and Grace Lai-Hung C Wong[1], (1)The Chinese University of Hong Kong, (2)The Chinese University of Hong Kong, Hong Kong, 91, China, (3)The Chinese University of Hong Kong, Hong Kong, China

Background: Pregnant women with chronic hepatitis B virus (HBV) infection and high viral load (HBV DNA > 200,000 IU/mL) would be at higher risk to transmit the virus to their babies despite the universal HBV vaccination to neonates. An integrated model nurse clinic (IMNC) co-run by hepatologists and hepatitis nurses has been introduced since 2020 to prescribe perinatal tenofovir disoproxil fumarate (TDF) to mothers who are hepatitis B surface antigen (HBsAg) positive with high viral load (HBV DNA > 200,000 IU/mL) for the prevention of mother-to-child-transmission (MTCT) of HBV. We now report the outcomes of mothers who have attended this IMNC. **Methods:** This was a prospective single-center pilot programme in Prince of Wales Hospital, Hong Kong from February 2020 to December 2022. Pregnant women with HBV DNA > 200,000 IU/mL were identified. The uptakes of IMNC attendance and TDF use were captured. **Results:** We identified 284 women of childbearing age (18-40 y old) with HBV DNA > 200,000 IU/mL; 95 women (median age 34 y) were pregnant. 43 of 95 (45.3%) pregnant women attended IMNC during their pregnancy, and 77 of 95 (81.1%) pregnant women had received TDF during their pregnancy. The updates of IMNC attendance and TDF use increased from 67.7% and 87.1% respectively in 2020, to 76.2% and 90.9% respectively in 2021, but then dropped to 28.6% and 81.0% respectively in 2022 (when the outbreak of omicron variants of SARS-CoV-2 occurred in Hong Kong). **Conclusion:** The uptakes of IMNC attendance and hence TDF use increased in the first two years of the novel integrated model, but were significantly affected amid the omicron outbreak. Towards the end of the COVID-19 pandemics, this IMNC will keep playing an important role to prevent mother-to-child transmission of HBV in order to achieve hepatitis elimination.

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1339-C | ANTIVIRAL THERAPY AND RISK FOR HEPATOCELLULAR CARCINOMA AFTER HEPATITIS B SURFACE ANTIGEN SEROCLEARANCE

Han Ah Lee[1], Seung Up Kim[2], Beom Kyung Kim[2], Sang Hoon Ahn[2], Hyun Woong Lee[3], Ja Kyung Kim[4], Dong Hyun Sinn[5] and Yeon Seok Seo[6], (1)Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, South Korea, (2)Severance Hospital, Seoul, Republic of Korea, (3)Gangnam Severance Hospital, (4)Yonsei University, (5)Samsung Medical Center, (6)Korea University Anam Hospital, Korea University Medical College, Seoul, Korea, Republic of (South)

Background: The association between prior antiviral therapy (AVT) and the risk of hepatocellular carcinoma (HCC) after HBsAg seroclearance has not been confirmed. This study aimed to assess the relationship between AVT and HCC risk and develop a prediction model to determine the likelihood of HCC occurrence after HBsAg seroclearance. In addition, long-term incidence of HCC and hepatic decompensation after HBsAg seroclearance was investigated. **Methods:** Patients with chronic hepatitis B who achieved HBsAg seroclearance between 2003 and 2022 were retrospectively reviewed for eligibility. Exclusion criteria for this study included patients who developed HCC before HBsAg seroclearance, or had a follow-up duration less than 6 months. The primary endpoint of the study was the occurrence of HCC, while the secondary endpoint was hepatic decompensation. Baseline characteristics of the patient groups were balanced using inverse probability of treatment weighting (IPTW). **Results:** Among 1,521 patients selected for statistical analysis, 84.2% (n = 1,280) achieved HBsAg seroclearance without AVT (spontaneous clearance group), while the remaining 15.8% (n = 241) achieved it after AVT (AVT-induced clearance group). During a median follow-up of 4.3 years, 37 patients (2.4%) developed HCC. AVT-induced clearance group had a significantly larger number of patients with alcohol consumption and cirrhosis, a lower platelet count, and a ALBI grade compared to the spontaneous clearance group (all $p < 0.05$). The incidence rate of HCC was comparable between the two groups ($p = 0.727$ by log-rank test). However, after IPTW, that was significantly higher in the spontaneous clearance group compared to the AVT-induced clearance group ($p = 0.014$ by log-rank test). In multivariate analysis, older age (aHR = 1.054), cirrhosis (aHR = 5.022), lower platelet count (aHR = 0.992), ALBI grade e 2 (aHR = 5.340), and no previous AVT (aHR = 0.461) were independent predictors for the higher risk of HCC (all $p < 0.05$). The prediction model developed using these variables had AUC of 0.828 (95% CI 0.724-0.933) in the training group, and 0.801 (95% CI 0.719-0.882) in the validation group. The cumulative incidence of HCC was consistent 0-5 and 5-10 years after HBsAg seroclearance ($p = 0.30$). In total, 98 patients (6.5%) developed decompensation after HBsAg seroclearance, and the cumulative incidence of decompensation was persistent 0-5 and 5-10 years after HBsAg seroclearance ($p = 0.47$). In multivariable analysis, HBsAg loss for over 5 years was not associated with the risk of HCC (adjusted subdistribution hazard ratio [aSHR] 0.85, 95% CI 0.48-1.51, $p = 0.580$) or decompensation (aSHR 0.79, 95% CI 0.52-1.19, $p = 0.250$). **Conclusion:** The novel prediction model based on age, cirrhosis, platelet count, ALBI grade, and history of AVT is beneficial for determining the risk of HCC after HBsAg seroclearance. The risk of HCC and decompensation is consistent over time after HBsAg seroclearance.

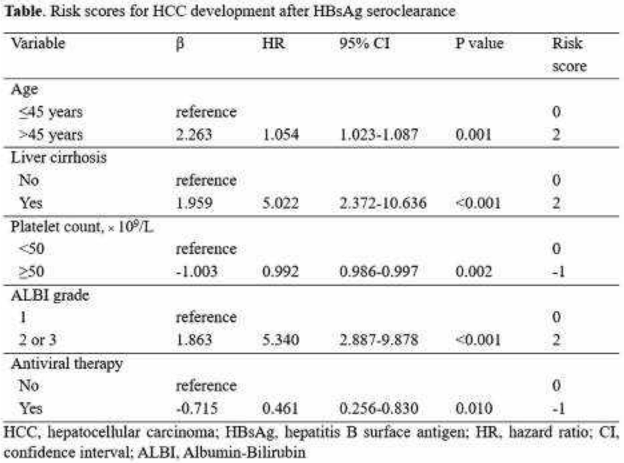

Table. Risk scores for HCC development after HBsAg seroclearance

Variable	β	HR	95% CI	P value	Risk score
Age					
≤45 years	reference				0
>45 years	2.263	1.054	1.023-1.087	0.001	2
Liver cirrhosis					
No	reference				0
Yes	1.959	5.022	2.372-10.636	<0.001	2
Platelet count, × 10^9/L					
<50	reference				0
≥50	-1.003	0.992	0.986-0.997	0.002	-1
ALBI grade					
1	reference				0
2 or 3	1.863	5.340	2.887-9.878	<0.001	2
Antiviral therapy					
No	reference				0
Yes	-0.715	0.461	0.256-0.830	0.010	-1

HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HR, hazard ratio; CI, confidence interval; ALBI, Albumin-Bilirubin

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1340-C | ASSOCIATION BETWEEN VIRAL LOAD AND HEPATOCELLULAR CARCINOMA RISK IN UNTREATED CHRONIC HEPATITIS B PATIENTS : A MULTINATIONAL COHORT STUDY

Gi-Ae Kim[1], Young-Suk Lim[2], Seungbong Han[3], Gwang Hyeon Choi[4], Won-Mook Choi[5], Jonggi Choi[6], Dong Hyun Sinn[7], Yong-Han Paik[7], Jeong-Hoon Lee[8], Yun Bin Lee[9], Ju-Yeon Cho[10], Nae-Yun Heo[11], Man-Fung Yuen[12], Vincent Wai-Sun Wong[13], Stephen Lam Chan[14], Hwai-I Yang[15] and Chien-Jen Chen[15], (1) Kyung Hee University Hospital, (2)Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South), (3)Korea University, (4) Seoul National University Bundang Hospital, (5)Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, Seoul, South Korea, (6)Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, (7)Samsung Medical Center, (8) Seoul National University College of Medicine, Seoul, South Korea, (9)Seoul National University College of

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

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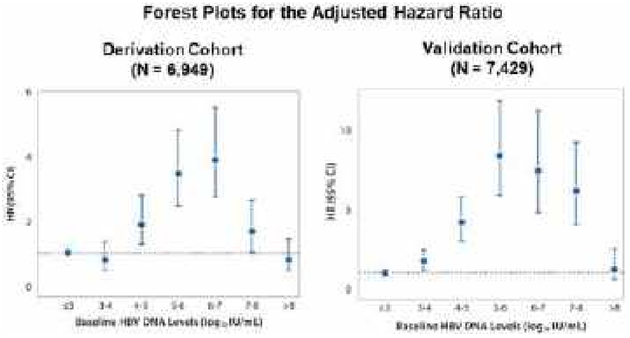
Background: This study aimed to investigate and validate the relationship between serum hepatitis B virus (HBV) DNA levels and hepatocellular carcinoma (HCC) risk in non-cirrhotic chronic hepatitis B (CHB) patients without significant elevation in alanine aminotransferase (ALT) levels, for whom antiviral treatment is typically not recommended despite high HBV viremia. **Methods:** A total of 7,429 CHB patients from the Taiwanese REVEAL-HBV cohort and 7 centers in Hong Kong and Korea (validation cohort) were used to validate findings from 6,949 patients at a Korean center (derivation cohort). All were non-cirrhotic adults with ALT levels < 2x the upper limit of normal, not indicated for antiviral treatment. **Results:** During a median follow-up of 10.0 and 12.2 years in the derivation and validation cohorts, 435 and 467 incident HCC cases were identified, respectively. The relationship between baseline HBV DNA levels and HCC risk was linear in HBeAg-negative patients, inverse in HBeAg-positive patients, and non-linear parabolic in the entire population for both cohorts. The highest HCC risk was observed with moderate viral loads (around 6 $\log_{10}$ IU/mL). Compared to viral load d 3.0 $\log_{10}$ IU/mL, the adjusted HCC risk was 3.97 times higher with viral load 6.0-7.0 $\log_{10}$ IU/mL in the derivation cohort (95% CI, 2.80–5.63; $p < 0.001$) and 8.36 times higher with viral load 5.0-6.0 $\log_{10}$ IU/mL in the validation cohort (95% CI, 5.89–11.87; $p < 0.001$). These findings were consistent in patients with normal ALT levels and in a nested case-control study. **Conclusion:** HCC risk was highest with moderate HBV viral load (around 6 $\log_{10}$ IU/mL) in untreated, non-cirrhotic, adult CHB patients without significant ALT elevation. Antiviral treatment should be considered for these patients to reduce HCC risk.



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Disclosure information not available at the time of publication: Gwang Hyeon Choi, Nae-Yun Heo, Hwai-I Yang, Chien-Jen Chen

1341-C | BENEFITS OF HEPATITIS B VIRUS (HBV) VACCINATION IN PATIENTS WITH CHRONIC LIVER DISEASES

Kaicen Wang[1], Timo Itzel[1], Jimmy Daza[1], Thomas Falconer[2], George Hripcsak[2], Jimyung Park[3], Jae Youn Cheong[3], Rae Woong Park[3], Matthias Ebert[1] and Andreas Teufel[1], (1)Medical Faculty Mannheim, Heidelberg University, (2)Columbia University Irving Medical Center, New York, NY, (3)Ajou University Graduate School of Medicine

Background: Hepatitis B vaccine has proven highly successful in preventing hepatitis B virus (HBV) infection and reducing consequential hepatitis B-related disease burden in the countries where vaccination has been implemented. However, few studies have reported the impacts of the hepatitis B vaccination in overall survival, particularly on patients with chronic liver disease (CLD) other than chronic hepatitis B. **Methods:** To investigate the efficacy of the hepatitis B vaccine on patients with chronic liver disease, a large USA cohort of 57.306 patients between 2000 and 2020 was obtained through the Observational Health Data Sciences and Informatics (OHDSI) consortium. **Results:** In the 20-year cohort of the Columbia University, 2.79% (1601/57306) of patients with chronic liver disease were reported as vaccinated. Overall, HBV-vaccinated patients with chronic liver disease had a significantly better survival ($p = 0.000$). Patients with liver cirrhosis also showed a significantly improved survival ($p = 0.000$). By investigating subgroups, particularly patients with chronic hepatitis C ($p = 0.000$), chronic non-alcoholic liver disease ($p = 0.000$), or both alcoholic and non-alcoholic-induced cirrhosis (both $p = 0.000$) all shared significant benefits from HBV vaccination ($p = 0.000$). These benefits showed no differences between gender. **Conclusion:** Our results demonstrated that vaccinated patients with different kinds of chronic liver diseases generally had significantly better survival when the use of Hepatitis B Surface Antigen vaccine was verified. However, as 97.21% (55706/57306) of the population were not reported as immunized, further efforts to improve the quality and comprehensiveness of medical records in chronic liver disease patients must be implemented.
Disclosures: The following people have nothing to disclose: Kaicen Wang, Timo Itzel, Jimmy Daza, Thomas Falconer, George Hripcsak, Jimyung Park, Jae Youn Cheong, Rae Woong Park, Matthias Ebert, Andreas Teufel

1342-C | CHARACTERIZING CHRONIC HEPATITIS B VIRUS INFECTION PREVALENCE, GEOGRAPHIC DISTRIBUTION, AND FOLLOW-UP TESTING, ALAMEDA COUNTY, CALIFORNIA, 2017–2021

Emily Yette[1], Rachel Marusinec[1], Craig Conlon[1], Robert J. Wong[2] and Amit S. Chitnis[1], (1)Alameda County

Public Health Department, (2)VA Palo Alto Healthcare System

Background: In the United States, chronic hepatitis B (CHB) virus infection predominantly affects ethnic minorities and vulnerable populations. We analyzed surveillance data to describe CHB prevalence, geographic distribution, and follow-up testing to guide prevention efforts in Alameda County. **Methods:** CHB cases from 2017–2021 were identified by > 2 positive hepatitis B virus (HBV) surface antigen (HBsAg), HBV e antigen (HBeAg), or HBV DNA tests > 6 months apart using data from the California Reportable Disease Information Exchange. CHB cases were stratified by age, race/ethnicity, census tract, zip code-based healthy places index (HPI), and federally-designated medically underserved areas (MUA). Lower HPI values represent less advantaged areas. Among CHB cases, we evaluated engagement with HBV care, which was defined as having at least annual testing with HBsAg, HBeAg, or HBV DNA, and stratified analyses by MUA status. Comparisons of CHB prevalence between groups utilized z-test; comparisons between MUA regions utilized chi-square testing. **Results:** Among a population of 1.53 million, 8122 CHB cases were identified; 5-year CHB prevalence was 0.53% (95% CI: 0.52%–0.54%). CHB prevalence was significantly higher among persons aged 50–69 years old than persons aged 30–49 years old (0.99%, 0.78%;$p < 0.01$) and Asians compared to Native Hawaiian/Pacific Islanders and African-Americans (1.21%, 0.56%, 0.18%;$p < 0.01$). CHB prevalence in the two lowest HPI quartiles was significantly higher than in the two highest quartiles (0.55% and 0.68%, 0.37% and 0.42%;$p < 0.01$). Geographic distribution of CHB prevalence by census tract and MUA identified areas within Alameda County that had < 1.0- to > 2.0-times overall County CHB prevalence is presented in the Figure. The 1933 CHB cases in MUA, compared to 5878 non-MUA cases, were significantly more likely to be African-American (7%, 3%;$p < 0.01$) and from the lowest HPI quartile (79%, 19%;$p < 0.01$). Among 6897 CHB cases eligible for e 1 year of follow-up, only 21% received annual testing, regardless of MUA status. **Conclusion:** CHB prevalence in Alameda County was 1.5-times higher than national estimates, and prevalence was highest among Asians and persons in more disadvantaged areas, with a high proportion of cases occurring in MUA. Only 21% of persons with CHB had annual testing, suggesting low engagement in CHB care. Analysis of local CHB surveillance data can guide public health efforts to improve outreach, CHB testing, and care.

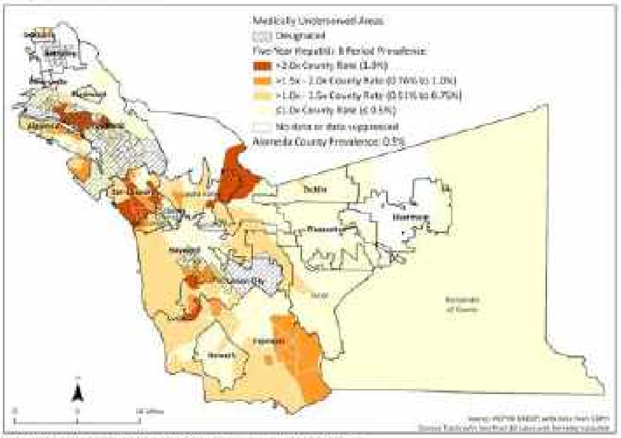

Figure: Chronic Hepatitis B Virus Infection Five-Year Prevalence* by Census Tract and Medically Underserved Areas, Alameda County**, California, 2017-2021

Medically Underserved Areas:
Designated
Five-Year Hepatitis B Period Prevalence:
>2.0x County Rate (1.0%)
>1.5x - 2.0x County Rate (0.76% to 1.0%)
>1.0x - 1.5x County Rate (0.51% to 0.75%)
≤1.0x County Rate (≤0.5%)
No data or data suppressed
Alameda County Prevalence: 0.5%
Berkeley
Oakland
Piedmont
Alameda
San Leandro
Dublin
Livermore
Pleasanton
Hayward
Union City
Sunol
Remainder of County
Fremont
Newark

Disclosures: Robert J. Wong – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Exact Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Thera Technologies: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bausch Health: Consultant, No, No; Salix Pharmaceuticals: Consultant, No, No;

The following people have nothing to disclose: Emily Yette, Rachel Marusinec, Craig Conlon, Amit S. Chitnis

1343-C | CHRONIC HBV INFECTION: IMPACT OF HDV COINFECTION AND IFN TREATMENT ON LIVER RELATED OUTCOMES AND MORTALITY IN THE MULTICENTER, PROSPECTIVE, OBSERVATIONAL ANRS CO22 HEPATHER FRENCH COHORT

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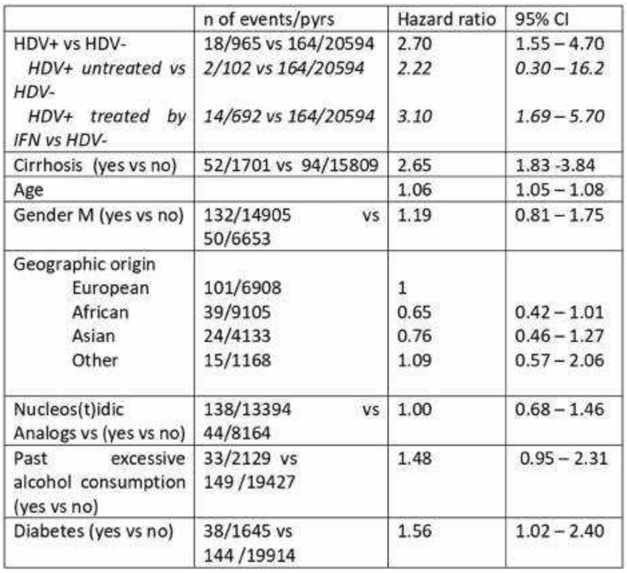
Background: The HBV-HDV coinfection is the most severe viral hepatitis, with the higher rate of morbidity and mortality. New drugs available for HDV treatment will change the natural history of HBV-HDV coinfected patients. We aimed to analyze the prognosis of HBV-HDV coinfected patients and the impact of IFN on liver related outcomes and mortality. **Methods:** We conducted a multicenter, national, prospective, observational cohort study between August 2012 and April 2023. The incidences of liver related complications (decompensation of cirrhosis and HCC), liver transplantation and mortality were measured according to HDV status and IFN treatment in patients with chronic HBV infection. Relative risks (HR) were calculated with multivariate analysis. **Results:** Among 3,958 HBsAg-positive patients with a known HDV status, 205 (5.2%) were HDV positive; 135 (66 %) HBV-HDV coinfected patients were male with a median age of 43 (35-52) years, 151 (73.6%) were treated by IFN. Compared to mono-infected patients, HBV-HDV coinfected patients were younger (43 vs 45 years, $p = 0.01$), more often Africans (58 vs 43%, $p < 0.0001$) and cirrhotic (39 vs 13%, $p < 0.0001$). A history of HCC (6 vs 3 %, $p = 0.03$) and of cirrhosis decompensation (10 vs 3 %, $p < 0.0001$) was more prevalent in coinfected than in mono-infected patients at the inclusion. After a median follow-up of 5.9 (3.9 ;7.2) years, the incidences of death, liver transplantation, HCC and cirrhosis decompensation in HBV-HDV coinfected vs mono-infected patients were 1.6 (0.9-2.5) vs 0.9 (0.8-1.1)/100pyr ($p = 0.04$), 1.1 (0.55-1.86) vs 0.12 (0.08-0.18)/100pyr ($p < 0.0001$), 1.7 (1.0-2.6) vs 0.6 (0.5-0.7)/100pyr ($p = 0.0002$), 1.36 (0.76-2.24) vs 0.23 (0.17-0.30)/100pyr ($p < 0.0001$), respectively. Treatment by IFN in HBV-HDV coinfected was not associated with any of the outcomes. In multivariable analysis, the HBV-HDV coinfection (HR 2.70, 95%CI (1.55-4.70)) w/o effect modification by IFN, cirrhosis (HR 2.65, 95%CI (1.83-3.84), older age (HR 1.06, 95%CI (1.05-1.08) and diabetes (HR 1.56, 95%CI (1.02-2.40) were significantly associated with the occurrence of liver related complications, liver transplantation and mortality (Table 1). **Conclusion:** HDV coinfection increases the risk of liver-related complications, transplantation and death in HBV-infected patients. IFN did not improve significantly the outcomes of these patients, underlying the need of efficacious therapy in this population.



	n of events/pyrs	Hazard ratio	95% CI
HDV+ vs HDV-	18/965 vs 164/20594	2.70	1.55 – 4.70
HDV+ untreated vs HDV-	*2/102 vs 164/20594*	*2.22*	*0.30 – 16.2*
HDV+ treated by IFN vs HDV-	*14/692 vs 164/20594*	*3.10*	*1.69 – 5.70*
Cirrhosis (yes vs no)	52/1701 vs 94/15809	2.65	1.83 -3.84
Age		1.06	1.05 – 1.08
Gender M (yes vs no)	132/14905 vs 50/6653	1.19	0.81 – 1.75
Geographic origin			
European	101/6908	1	
African	39/9105	0.65	0.42 – 1.01
Asian	24/4133	0.76	0.46 – 1.27
Other	15/1168	1.09	0.57 – 2.06
Nucleos(t)idic Analogs vs (yes vs no)	138/13394 vs 44/8164	1.00	0.68 – 1.46
Past excessive alcohol consumption (yes vs no)	33/2129 vs 149 /19427	1.48	0.95 – 2.31
Diabetes (yes vs no)	38/1645 vs 144 /19914	1.56	1.02 – 2.40

Disclosures: The following people have nothing to disclose: Lucia Parlati

1344-C | CHRONIC HEPATITIS B INFECTION IN PREGNANCY ASSOCIATED WITH IMPAIRMENT OF PATIENT-REPORTED OUTCOMES AND QUALITY OF LIFE

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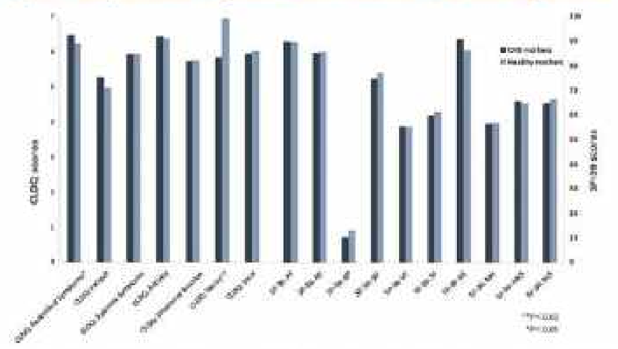
Background: The health-related quality of life (HRQoL) during pregnancy has not been well-elucidated in mothers with chronic hepatitis B (CHB). We aim to evaluate patient-reported outcomes (PROs) in CHB mothers and compare them with those of PROs from healthy mothers during pregnancy. **Methods:** We prospectively enrolled mothers from 4/1/2023 to 5/30/2023 at the outpatient clinic of a university medical center in China. Consecutive compensated CHB mothers and healthy mothers were invited to participate and complete the 36-item Short Form Survey (SF-36) and the Chronic Liver Disease Questionnaire (CLDQ). Covariates included pregnancy profiles, comorbidities or complications, laboratory parameters, and HBV virological variables. Data were compared between groups and risk factors for worse PROs were further analyzed by the multiple linear regression model.

Results: Among 131 participants including 61 CHB and 70 healthy mothers, the mean (SD) age was 29.3 ± 3.7, median (range) gestational week 23 (16 - 39), 42% had health insurance, 39.7 % had gravidity count > 1, and 3.1 % had comorbidities. When comparing variables between CHB and healthy mothers, there were statistically significant differences in the mean (SD) age (29.4 ± 4.35 vs 27.1 ± 3.03, $p = 0.01$), percentage of full-time workers (59% vs 75%, $p = 0.04$), and median (IQR) gestational week when reporting the PROs (32 [24, 35] vs 23 [16.25, 32], $p = 0.001$). Other variables including the frequency of comorbidities or pregnancy complications, spouse's support, gravidity counts, insurance status, and living condition did not differ between the two groups. Their scores for PROs are shown in Figure 1. CHB mothers had a significant impairment of the PROs ($p < 0.05$) in CLDQ domains with abdominal symptoms and worry. However, the PROs based on SF-36 measurements of eight scales did not differ between groups, which included T-scores from the mental and physical component summary. In the multivariate analysis model, independent predictors of worse PROs in pregnant women were CHB infection, younger age, and lack of full-time employment. **Conclusion:** Pregnant mothers with CHB reported a significant HRQoL impairment from abdominal symptoms and worry when compared to healthy mothers. CHB infection, younger age, and lack of full-time employment are independent risk factors for worse PROs during pregnancy. Further interventions with consultation and patient support are warranted.

Figure 1. Comparison of CLDQ and SF-36 scores between CHB and healthy mothers



PF: Physical functioning; RP: Role-Physical; BP: Bodily Pain; GH: General Health; VT: Vitality; SF: Social Functioning; RE: Role-Emotional; MH: Mental Health; MCS: Mental component summary; PCS: Physical component summary

Disclosures: Calvin Pan Pan – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Yueying Deng, Yawen Geng, Shi Ouyang

1345-C | CLINICAL IMPACT OF CONTINUATION VERSUS CESSATION OF ANTIVIRAL THERAPY IN HEPATITIS B "E" ANTIGEN-NEGATIVE CHRONIC HEPATITIS B: A MODELING STUDY WITH IMPLICATIONS FOR HEPATITIS B CURE

Amir M Mohareb[1], Ghideon Ezaz[2], Arthur Y Kim[3], Kenneth A. Freedberg[1], Anders Boyd[4] and Emily P Hyle[1], (1)Massachusetts General Hospital, (2)Mount Sinai Hospital, (3)Massachusetts General Hospital and Harvard Medical School, (4)Public Health Service of Amsterdam

Background: The AASLD HBV guidelines differ from other international HBV guidelines in recommending against stopping antiviral therapy in people with HBeAg-negative infection. Our objectives were to project long-term outcomes of treatment continuation versus cessation and to determine the threshold of HBsAg loss needed to counter the risks of cessation. **Methods:** We developed a Markov model of HBeAg-negative people with undetectable DNA receiving antiviral therapy in the US (age at model start, 51y). We simulated 4 strategies: (1) treatment continuation (Continue) and 3 cessation strategies in which treatment is stopped and then reinitiated within 5y for: (2) virologic relapse (Restart_VR); (3) clinical relapse (Restart_CR); or (4) hepatitis flare (Restart_HF). We simulated virologic relapse as an exponential decay function fit to observational data (65% incidence in 5y) with subsequent risk of clinical relapse and hepatitis flare. We estimated annual incidence on/off antiviral therapy of cirrhosis (0.3%/0.6%) and HCC (0.1%/0.25%) among people who remain HBsAg-positive. Following cessation, HBsAg loss occurs in 6-8% within 5y. Individual's with HBsAg loss have lower age-adjusted mortality and are assumed to have no incident cirrhosis or HCC. We projected cumulative incidence of HBsAg loss, cirrhosis, HCC, and life years from model start. We conducted one-way sensitivity analyses on cirrhosis/HCC incidence among people who remain HBsAg-positive off antiviral therapy (range, 0.4–1.5x base case) and incidence of HBsAg loss following antiviral cessation (range, 6-70% within 5y). **Results:** Treatment continuation would result in 13.0% cumulative incidence of HBsAg loss and an average of 28.41 life-years gained from model start (Table). Antiviral cessation strategies would more than double lifetime HBsAg loss compared with Continue. However, the cumulative incidence of cirrhosis and HCC would be higher following cessation. Survival would be lower at all time points with each of the antiviral cessation strategies compared with continuation. In sensitivity analysis, Continue would be preferred over Restart_VR unless off-therapy cirrhosis/ HCC incidence for people who remain HBsAg-positive is less than 0.6x the base case (i.e., approaching the on-therapy incidence). In sensitivity analysis, Restart_VR would be preferred to Continue only when the probability of HBsAg loss surpasses a threshold of 46% among people stopping treatment, given other base case estimates. **Conclusion:** Continuing antiviral therapy would result in improved survival in people with HBV despite lower rates of HBsAg loss. These results support current AASLD guidelines, which generally discourage treatment cessation in chronic HBV. Novel therapies aimed at HBV cure would need to provoke higher rates of HBsAg loss than currently observed following cessation to have a survival benefit over treatment continuation.

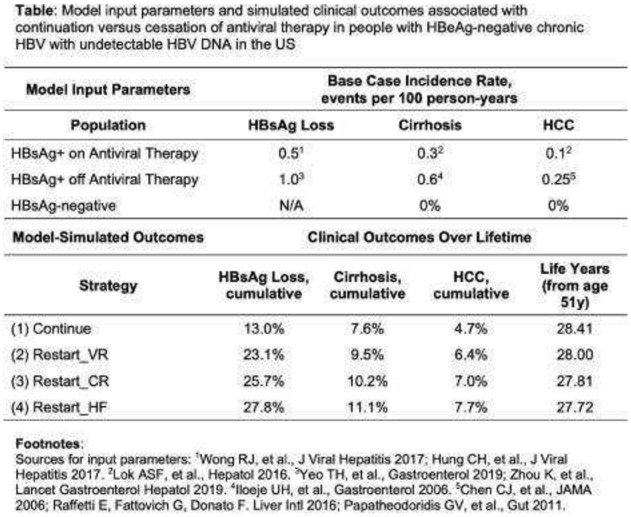


Table: Model input parameters and simulated clinical outcomes associated with continuation versus cessation of antiviral therapy in people with HBeAg-negative chronic HBV with undetectable HBV DNA in the US

Model Input Parameters	**Base Case Incidence Rate, events per 100 person-years**		
Population	**HBsAg Loss**	**Cirrhosis**	**HCC**
HBsAg+ on Antiviral Therapy	0.5[1]	0.3[2]	0.1[2]
HBsAg+ off Antiviral Therapy	1.0[3]	0.6[4]	0.25[5]
HBsAg-negative	N/A	0%	0%

Model-Simulated Outcomes	**Clinical Outcomes Over Lifetime**			
Strategy	**HBsAg Loss, cumulative**	**Cirrhosis, cumulative**	**HCC, cumulative**	**Life Years (from age 51y)**
(1) Continue	13.0%	7.6%	4.7%	28.41
(2) Restart_VR	23.1%	9.5%	6.4%	28.00
(3) Restart_CR	25.7%	10.2%	7.0%	27.81
(4) Restart_HF	27.8%	11.1%	7.7%	27.72

Footnotes:
Sources for input parameters: [1]Wong RJ, et al., J Viral Hepatitis 2017; Hung CH, et al., J Viral Hepatitis 2017. [2]Lok ASF, et al., Hepatol 2016. [3]Yeo TH, et al., Gastroenterol 2019; Zhou K, et al., Lancet Gastroenterol Hepatol 2019. [4]Ilоeje UH, et al., Gastroenterol 2006. [5]Chen CJ, et al., JAMA 2006; Raffetti E, Fattovich G, Donato F. Liver Intl 2016; Papatheodoridis GV, et al., Gut 2011.

Disclosures: The following people have nothing to disclose: Amir M Mohareb, Ghideon Ezaz, Arthur Y Kim, Kenneth A. Freedberg, Anders Boyd, Emily P Hyle

1346-C | CONCURRENT NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) IN CHRONIC HEPATITIS B (CHB) HAS NO ADDITIVE EFFECT ON FIBROSIS PROGRESSION AND HEPATOCELLULAR CARCINOMA (HCC) DEVELOPMENT

Ngai-Moh Law, Yong Loo Lin School of Medicine, National University of Singapore; Changi General Hospital

Background: Concurrent Non-Alcoholic Fatty Liver Disease (NAFLD) among patients with Chronic Hepatitis B (CHB) is becoming a significant clinical problem with increasing NAFLD prevalence. The direct fibrotic effect of NAFLD in CHB leading to cirrhosis and development of Hepatocellular Carcinoma (HCC) despite antiviral therapy remained unexplored. **Methods:** We studied the presence of NAFLD among our CHB patients who are on long term follow up for a period of ten years. We risk stratified CHB patients based on fibrosis score on Transient Elastography (TE) with liver function test and measurement of HBV viral load at point of entry. We examined the development of NAFLD during the follow up period and correlated with progression of fibrosis and development of HCC. All patients had baseline TE and liver function test done at entry point of screening. Those with TE cut-off reading of > =9.5 kPa were considered as significant fibrosis i.e.F2 and above with antiviral treatment initiated. All patients were on regular six monthly follow up with blood tests and ultrasound of liver for detection of NAFLD and HCC surveillance. Repeat TE measurement to assess progression of liver fibrosis if indicated. Detection of NAFLD was based on conventional ultrasound criteria. Detection of HCC was confirmed by radiological imaging and serum alpha-fetoprotein. **Results:** 486 patients were included (mean age 54, range 25 to 85). 78 patients had LSM > =9.5kPa i.e., significant liver fibrosis. Among these patients, 27 had developed superimposed fatty liver with 2 HCC detected. In contrast, 51 patients had significant fibrosis without NAFLD and 9 had HCC during the 10 years follow up period, Chi-square statistic = 1.528, p value = 0.22, (NS at $p < 0.05$). **Conclusion:** Our study showed that the prevalence of NAFLD among high risk CHB patients was 35%. Development of NAFLD did not increase the fibrosis staging if antiviral therapy was initiated. In addition, there is no increased risk of developing HCC even if patient has developed NAFLD during the follow up period.

Disclosures: The following people have nothing to disclose: Ngai-Moh Law

1347-C | COUNTRY-SPECIFIC SCREENING, PREVALENCE, AND IMMUNITY RATES FOR HEPATITIS B INFECTION IN THE UNITED STATES

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Background: Desegregated rates of hepatitis B virus (HBV) screening and prevalence in the United States (US) by birth country are largely unknown. This study provides current epidemiologic estimates of country- and region-specific HBV screening, prevalence, and immunity rates in a large US cohort enriched for foreign-born persons. **Methods:** Adults e 18 with at least two outpatient primary care visits and a self-reported country of birth in the Los Angeles County Department of Health Services healthcare system from 2017 to 2021 were included. Country- and region-specific HBV screening rates were estimated as the proportion tested for HBsAg from all eligible persons. Age-adjusted HBV prevalence rates were estimated as the proportion with a positive HBsAg among screened. Among those who tested negative for HBsAg between ages 19-59, we examined frequency of HBsAb testing and HBV immunity rates defined as a HBsAb titer e 12 U/L. Countries were grouped into six World Health Organization regions; countries with < 100 persons screened were only included in regional analyses. **Results:** The cohort included 202,868 adults from 174 unique countries; 86.2% from Region of the Americas, 6.8% from Western Pacific, 2.7% from European, 2.4% from Eastern Mediterranean, 1.1% from South-East Asian, and 0.8% from African Regions. Overall, 41.8% (41.5-42.0%) were screened for HBV and age-adjusted HBV prevalence was 0.9% (0.9-1.0%). 57.9% (57.6-58.3%) of uninfected had HBsAb testing, of which 29.9% (29.5-30.3%) were HBV immune. 40.3% (39.9-40.6%) of US-born were screened with HBV prevalence of 0.4% (0.3-0.5%) and immunity rates of 36.0% (35.3-36.7%); 42.7% of all foreign-born were screened with prevalence of 1.2% (1.1-1.3%) and immunity rates of 26.7% (26.2-27.2%). Rates of HBV screening were < 45% across all regions, with > 50% screened in only 2 countries. Prevalence varied from 0.3% in the Region of the Americas to 6.6% in the Western Pacific Region. e 5% prevalence was observed among immigrants from Cambodia, China + territories, Ethiopia, North Korea, Myanmar, Nigeria, Thailand, and Vietnam (Figure). HBV immunity rates ranged from 9.1% (0.2-42.3%) from Chile to 77.8% (57.7-91.4%) from Myanmar. **Conclusion:** Suboptimal HBV screening and immunity across countries of birth suggest that previous strategies of risk-based screening failed to adequately identify those with HBV infection. Our data supports the recent CDC guideline shift to universal HBV screening and vaccination.

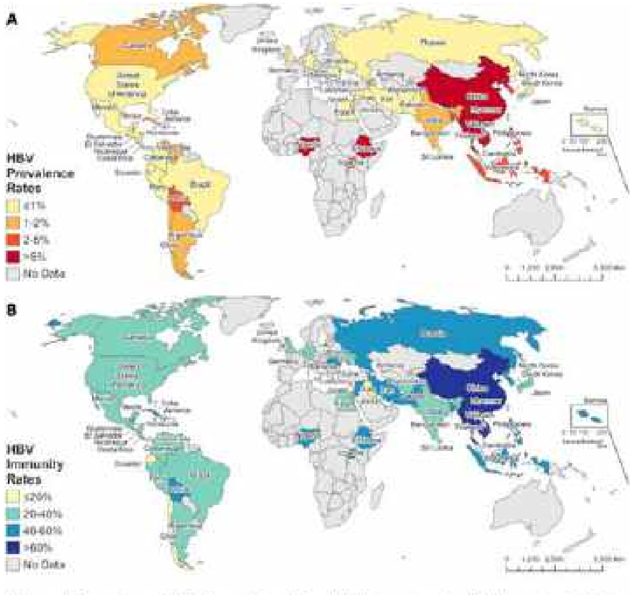


Figure 1. Prevalence of HBsAg positivity (A) and HBV immunity rates (B) by country of birth

Disclosures: Norah Terrault – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;

Kali Zhou – Gilead Inc: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Matt Sumethasorn

Disclosure information not available at the time of publication: Christopher Wong

1348-C | CROSS-CULTURAL COMPARISON OF DEMOGRAPHIC AND CLINICAL FACTORS OF KOREAN-AMERICAN AND KOREAN PATIENTS WITH CHRONIC HEPATITIS B

Hee-Soon Juon[1], Daniel Yang[1], Hie-Won L. Hann[2], Neung Hwa Park[3], Mimi Chang[4], Ho Bae[4] and Ann Klassen[5], (1)Thomas Jefferson University, (2)Thomas Jefferson University Hospital, Philadelphia, PA, (3) Ulsan University Hospital, (4)Coalition of Inclusive Medicine, (5)Drexel University

Background: Despite the high incidence of liver cancer related to hepatitis B virus (HBV) infection among foreign born Koreans, few studies have explored the differences in factors between immigrant Koreans and Koreans in host country. The purpose of this study is to describe and compare the sociodemographic and clinical characteristics between Korean American patients and Korean patients in South Korea living with chronic hepatitis B (CHB). **Methods:** We used data from two retrospective cohorts of CHB patients of Korean Americans (KAs) and South Koreans. Retrospective Medical Charts of the two cohorts were reviewed from 2016 to 2020. Categorical variables were compared using the Chi-square test and the Fisher test; continuous variables were compared using t-test. **Results:** Of a total of 1,194 patients (365 Korean Americans and 829 Koreans in South Korea), there were significant differences in age, gender, BMI, and health insurance status: KAs were older, were more likely to be female, and had a higher BMI than Koreans. About 92% of KAs had any types of health insurance, while all Koreans had national health insurance (100%). KAs were diagnosed with HBV for longer mean years compared to Koreans (28.43 years vs 14.35 years, $p < 0.001$). About 75% of KAs and 100% of Koreans had antiviral therapy ($p < 0.001$). KAs had higher rates of non-alcoholic fatty liver disease (NAFLD) than Koreans (34% vs. 21.6%, $p < 0.001$). KAs also had higher rates of hypertension (33.7% vs 13.5%, $p < 0.001$) and hyperlipidemia (35.6% vs 8.2%, $p < 0.001$) than Koreans. In contrast, Koreans had higher rates of liver cirrhosis than KAs (40% vs. 13.7%, $p < 0.001$). **Conclusion:** Intra-ethnic differences in demographic and clinical characteristics were found between KAs and South Koreans. Because unfamiliar sociocultural and clinical factors may influence the treatment of CHB, cultural differences and language barriers should be considered in CHB management strategies for Asian immigrants in the United States.

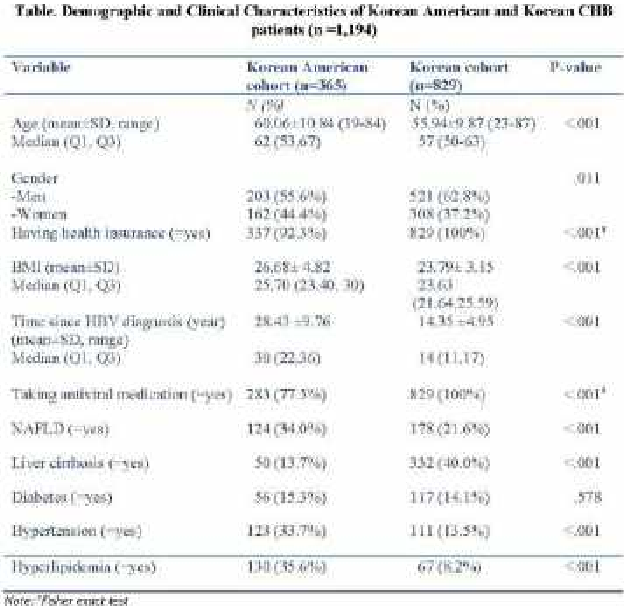


Table. Demographic and Clinical Characteristics of Korean American and Korean CHB patients (n =1,194)

Variable	Korean American cohort (n=365)	Korean cohort (n=829)	P-value
	N (%)	N (%)	
Age (mean±SD, range)	60.06±10.84 (19-84)	55.94±9.87 (23-87)	<.001
Median (Q1, Q3)	62 (53,67)	57 (50-63)	
Gender			.011
-Men	203 (55.6%)	521 (62.8%)	
-Women	162 (44.4%)	308 (37.2%)	
Having health insurance (=yes)	337 (92.3%)	829 (100%)	<.001†
BMI (mean±SD)	26.68± 4.82	23.79± 3.15	<.001
Median (Q1, Q3)	25.70 (23.40, 30)	23.63 (21.64,25.59)	
Time since HBV diagnosis (year) (mean±SD, range)	28.43 ±9.76	14.35 ±4.95	<.001
Median (Q1, Q3)	30 (22,36)	14 (11,17)	
Taking antiviral medication (=yes)	283 (77.5%)	829 (100%)	<.001†
NAFLD (=yes)	124 (34.0%)	178 (21.6%)	<.001
Liver cirrhosis (=yes)	50 (13.7%)	332 (40.0%)	<.001
Diabetes (=yes)	56 (15.3%)	117 (14.1%)	.578
Hypertension (=yes)	123 (33.7%)	111 (13.5%)	<.001
Hyperlipidemia (=yes)	130 (35.6%)	67 (8.2%)	<.001

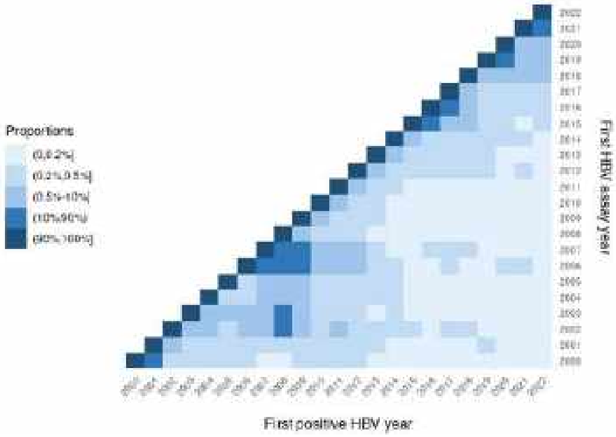
Note: †Fisher exact test

Disclosures: The following people have nothing to disclose: Hee-Soon Juon, Daniel Yang, Hie-Won L. Hann, Neung Hwa Park, Mimi Chang, Ho Bae, Ann Klassen

1349-C | DELAYED DIAGNOSIS OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION INCREASES THE RISK OF HEPATOCELLULAR CARCINOMA (HCC): A TERRITORY-WIDE STUDY

Grace Lai-Hung C Wong[1], Vicki Wing Ki Hui[1], Yee-Kit Tse[1], Vincent Wai-Sun Wong[2] and Terry Cheuk-Fung Yip[1], (1)The Chinese University of Hong Kong, (2)The Chinese University of Hong Kong, Hong Kong, China

Background: World Health Organization (WHO) proposes to reduce of chronic viral hepatitis incidence and mortality of 90% and 65% respectively by 2030. Early diagnosis of chronic hepatitis B virus (HBV) infection is one of the cornerstones to reduce mortality by offering timely antiviral treatment and surveillance for complications. We aimed to incidence of delayed HBV diagnosis and the clinical outcomes of such patients. **Methods:** This was a territory-wide retrospective observational cohort study in Hong Kong. We identified subjects who had hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and HBV DNA checked in 2000-2022. Patients who had negative HBV results initially, then positive HBV results later were defined to have delayed HBV diagnosis. Incidence of hepatocellular carcinoma (HCC) was compared in patients who did or did not have delayed HBV diagnosis. **Results:** We identified 1,684,821 subjects who had HBV checked in 2000-2022, and 256,822 (15.2%) had positive results; of whom 10,015 (3.9%) had delayed HBV diagnosis. Delayed HBV diagnosis was more commonly observed in patients who had their first HBV assay performed in 2000-2010 compared to whose done in 2011-2022 (Figure). The patients were younger (median age 51 vs. 56 y), more likely to be men (49.9% vs.43.7%) and had higher 10-year incidence rate of HCC was 41.6% (95% CI 40.3%-42.9%) vs. 34.4% (95% CI 34.2%-34.7%) in patients who had delayed HBV diagnosis compared to those who did not have delayed HBV diagnosis (all $p < 0.001$). **Conclusion:** A small yet non-negligible proportion of patients had delayed HBV diagnosis, which is linked to higher risk of HCC. Repeated tests with more sensitive HBV assays should be offered to patients who are at risk of chronic HBV infection, in order to achieve early diagnosis, timely antiviral treatment and reducing HCC and hence mortality.



Disclosures: Vincent Wai-Sun Wong – Sagimet: Consultant, No, Yes; Pfizer: Consultant, No, Yes; Novo Nordisk: Speaking and Teaching, Yes, Yes; Novo Nordisk: Consultant, Yes, Yes; Inventiva: Consultant, No, Yes; Intercept: Consultant, No, Yes; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences: Speaking and

Teaching, No, No; Gilead Sciences: Consultant, No, Yes; Echosens: Consultant, Yes, Yes; Boehringer Ingelheim: Consultant, No, Yes; AbbVie: Speaking and Teaching, No, Yes; AbbVie: Consultant, No, Yes; Abbott: Speaking and Teaching, No, Yes; TARGET PharmaSolutions: Consultant, No, No; Unilab: Speaking and Teaching, No, Yes; Illuminatio Medical Technology Limited: Stock – privately held company (individual stocks and stock options), No, No;

Terry Cheuk-Fung Yip – Gilead Sciences: Consultant, No, No; Gilead Sciences: Speaking and Teaching, No, No;

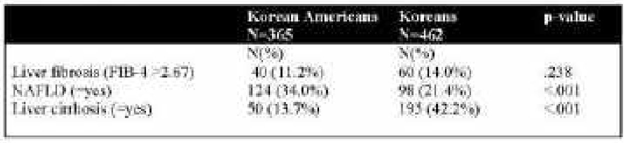
The following people have nothing to disclose: Grace Lai-Hung C Wong, Vicki Wing Ki Hui, Yee-Kit Tse

1350-C | DIFFERENCES IN LIVER DISEASE PROGRESS OF CHRONIC HEPATITIS B PATIENTS OF TWO COHORTS OF KOREAN AMERICAN AND SOUTH KOREAN

Hee-Soon Juon[1], *Hie-Won L. Hann*[2], *Neung Hwa Park*[3], *Mimi Chang*[4], *Ho Bae*[4], *Daniel Yang*[1] *and Ann Klassen*[5], *(1)Thomas Jefferson University, (2)Thomas Jefferson University Hospital, Philadelphia, PA, (3) Ulsan University Hospital, (4)Coalition of Inclusive Medicine, (5)Drexel University*

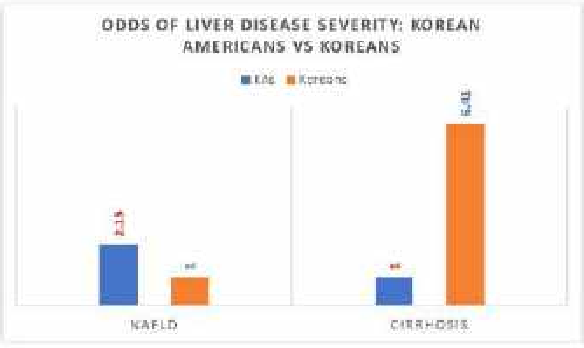
Background: In the treatment of chronic hepatitis B, patients were closely monitored their liver disease progress such as liver fibrosis, liver cirrhosis, or non-alcoholic fatty liver disease (NFALD). We aimed to describe and compare disease progression with two cohorts with chronic hepatitis B (CHB): Korean Americans and Koreans in South Korea. **Methods:** We used data from two cohorts of CHB patients: Korean Americans (KAs) and Koreans in South Korea. Retrospective medical histories from 2016-2020 of the two cohorts were reviewed. The binary outcomes of liver disease severity were included liver fibrosis (measured by FIB-4 > 2.67), diagnosis of liver cirrhosis, and NAFLD. Multiple logistic regression was used to examine the differences of cohort after controlling age, gender, education, marital status, current drinking, BMI, time since HBV diagnosis (years). **Results:** Among 827 CHB patients (365 Korean Americans and 462 Koreans), KAs had higher rates of NAFLD than Koreans (34% vs. 21.4%, $p < 0.001$). In contrast, Koreans had higher rates of liver cirrhosis than KAs (42.2% vs. 13.7%, $p < 0.001$). There were no differences in FIB-4. In multivariate analysis, KAs had higher odds of having NAFLD than Koreans (aOR = 2.15, 95% CI: 1.34-3.47). In contrast, Koreans had higher odds of having liver cirrhosis than KAs (aOR = 6.41, 95% CI: 3.65-11.24). In addition, BMI and education were associated with NAFLD, while age and current drinking were associated with liver cirrhosis. **Conclusion:** Intra-ethnic differences in liver disease progress were found between KAs and Koreans. Because these differences in clinical characteristics may influence the treatment of CHB, clinicians should consider different CHB management strategies for KA cohort and Korean cohort.

Table 1. Comparison of liver disease severity of two cohorts of chronic hepatitis B patients: Korean Americans and Koreans in South Korea (n=827)



	Korean Americans N=365	Koreans N=462	p-value
	N(%)	N(%)	
Liver fibrosis (FIB-4 >2.67)	40 (11.2%)	60 (14.0%)	.238
NAFLD (=yes)	124 (34.0%)	98 (21.4%)	<.001
Liver cirrhosis (=yes)	50 (13.7%)	193 (42.2%)	<.001

Figure 1. Comparison of two cohorts: results from multivariate analysis (n=827), 2020



Note. Adjusting age, gender, education, marital status, drinking, BMI, time since HBV diagnosis

Disclosures: The following people have nothing to disclose: Hee-Soon Juon, Hie-Won L. Hann, Neung Hwa Park, Mimi Chang, Ho Bae, Daniel Yang, Ann Klassen

1351-C | EFFICACY AND SAFETY OF TENOFOVIR ALAFENAMIDE FUMARATE VERSUS TENOFOVIR DISOPROXIL FUMARATE IN PREVENTING MOTHER-TO-CHILD TRANSMISSION OF HBV: A PROSPECTIVE COHORT STUDY

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Background: Tenofovir disoproxil fumarate (TDF) is most commonly used for pregnant women in preventing mother-to-child transmission (MTCT) of HBV in the world. However, tenofovir alafenamide fumarate (TAF) has been gradually initiated for preventing MTCT due to its better safety profile. This head-to-head study aimed to compare the efficacy and safety of TAF and TDF for the prevention of MTCT of HBV. **Methods:** Pregnant women with chronic HBV infection and high viral load (HBV DNA e 200,000 IU/ml) were enrolled from January 2019 to January 2022 in The Third People's

Hospital of Shenzhen. They could choose to receive TDF 300 mg/d or TAF 25 mg/d from gestational weeks 24–32 until delivery. Infants received immunoprophylaxis. All mothers and infants were followed up at postpartum month 1, 7, 12. The primary efficacy endpoints were the decrease in viral load and MTCT rates at month 7~12. The primary safety endpoints were the changes in liver and renal function of mothers, the infants' growth parameters. **Results:** There were 66 mothers in TAF group and 115 mothers in TDF group respectively. A total of 181 infants were delivered, all of whom were single births. 137 mothers and infants completed 12 months follow-up. The levels of HBV-DNA decline in TDF-treated mothers were compared with those in TAF-treated mothers before delivery (3.56 log10IU/ml vs 3.13 log10IU/ml, $p > 0.05$). The HBsAg positive rate was 0% in all infants. The TAF group was well tolerated during treatment. No adverse events such as cholestasis or renal impairment, and none of them reported drug related nausea and vomiting. However, 10 cases of gastrointestinal discomfort were reported in TDF group, but they did not discontinue or switch until delivery. In TAF group, 6 mothers had ALT elevation after delivery and restarted TAF treatment; in TDF group, 10 mothers had ALT elevation after delivery and 8 of them restarted TAF treatment. All mothers returned to normal ALT. Additionally, no significant differences were observed for serum creatinine levels between two groups. No congenital defects, malformations or neurodevelopmental disorders occurred in the infants of both groups. There was no significant difference in height, weight and head circumference between the two groups at postpartum month 12 and all were in the normal range. **Conclusion:** The efficacy and safety of TAF for the prevention of MTCT of HBV were similar with TDF.

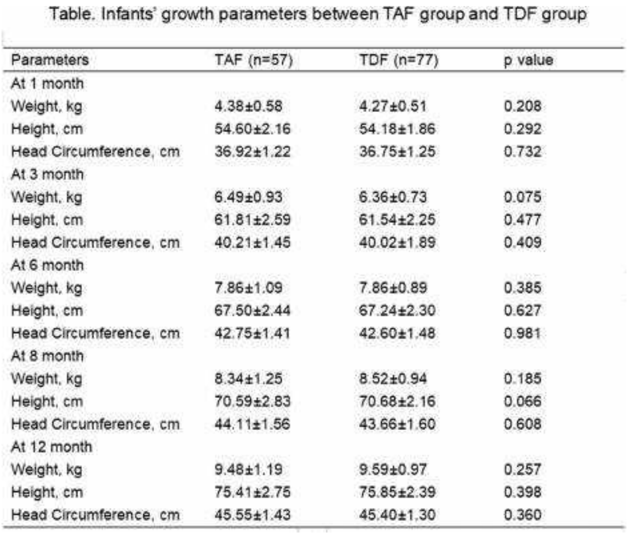

Table. Infants' growth parameters between TAF group and TDF group

Parameters	TAF (n=57)	TDF (n=77)	p value
At 1 month			
Weight, kg	4.38±0.58	4.27±0.51	0.208
Height, cm	54.60±2.16	54.18±1.86	0.292
Head Circumference, cm	36.92±1.22	36.75±1.25	0.732
At 3 month			
Weight, kg	6.49±0.93	6.36±0.73	0.075
Height, cm	61.81±2.59	61.54±2.25	0.477
Head Circumference, cm	40.21±1.45	40.02±1.89	0.409
At 6 month			
Weight, kg	7.86±1.09	7.86±0.89	0.385
Height, cm	67.50±2.44	67.24±2.30	0.627
Head Circumference, cm	42.75±1.41	42.60±1.48	0.981
At 8 month			
Weight, kg	8.34±1.25	8.52±0.94	0.185
Height, cm	70.59±2.83	70.68±2.16	0.066
Head Circumference, cm	44.11±1.56	43.66±1.60	0.608
At 12 month			
Weight, kg	9.48±1.19	9.59±0.97	0.257
Height, cm	75.41±2.75	75.85±2.39	0.398
Head Circumference, cm	45.55±1.43	45.40±1.30	0.360

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1352-C | EPIDEMIOLOGY OF HEPATITIS B VIRUS INFECTION IN ENDEMIC AREA OVER THE PAST 15 YEARS AND THE INFLUENCE OF COVID-19 INFECTIONS

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Background: The purpose of this study is to investigate the epidemiological changes of chronic hepatitis B (CHB) and the impact of COVID-19 over the past 15 years in Korea, an HBV endemic area. **Methods**: We used the National Health Insurance Service claims data on hepatitis B patients from 2007 to 2021. In addition, in order to compare the characteristics of the hepatitis B group, a 4-fold control group adjusted for age and gender was set using the propensity score matching analysis. **Results**: Excluding the COVID period, the number of patients with CHB has continuously increased for 15 years. The average age of the CHB patient group increased every year, and the male dominance pattern gradually decreased. In addition, the proportion of patients taking antiviral drugs increased in both men and women. When classified according to the severity of liver disease, the proportion of hepatocellular carcinoma (HCC), liver cirrhosis, and decompensation showed a decreasing trend, while the proportion of liver transplants continuously increased. Patients with CHB had significantly higher medical and drug costs than the control, especially when they developed decompensation, HCC, or liver transplantation. Patients with CHB had more comorbidities such as osteoporosis, chronic kidney disease, and diabetes than the control, and the rate of taking concomitant medication was significantly higher. During the COVID period, the number of outpatient visits and overall medical costs in the HBV group significantly decreased compared with control. **Conclusion**: The epidemiology of chronic hepatitis B in HBV endemic area has changed over the past 15 years in terms of prevalence, severity, medical costs, and comorbidities. In addition, COVID-19 showed an effect of reducing healthcare utilization in patients with chronic hepatitis B compared to controls.

Disclosures: The following people have nothing to disclose: Jeong-Ju Yoo, Dong Hyeon Lee, Jae Young Jang, Log Young Kim

1353-C | EPIDEMIOLOGY, TREATMENT PATTERN, AND SURVIVAL IN CANADIAN PATIENTS WITH CHRONIC HEPATITIS B RELATED HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the second-most frequent cause of malignancy-associated death. Chronic hepatitis B (CHB) infection is the leading cause of developing HCC. We aimed to describe and evaluate the outcomes of CHB-HCC patients in Canada, addressing a paucity of such data in large North American patient populations. **Methods:** Data was collected from January 1, 2012, to December 31, 2022, from a cross-sectional cohort of subjects mono-infected with CHB and HCC (per AASLD guidance) from the Canadian HBV Network - a national consortium involving 10 Canadian provinces and 19 academic and community hospitals. Descriptive analysis and Chi-square modeling were used to develop statistical outcomes for the comparison of cohorts. Statistical analyses were done in R (version 4.1.1). **Results:** Of the 6711 CHB patients who met inclusion criteria, 232 (3.5%) developed HCC. The median age for the HCC cohort was 65 years (IQR 57-73) with a population of 80% male and 71% Southeast Asian (SEA) patients. The HCC cohort had a median HBV DNA of log 3.67 IU (IQR1.86-5.62), and 16% of HCC patients had a positive HbeAg status (vs 47% in the CHB group, $p < 0.0001$). Relative to the CHB cohort, the CHB-HCC cohort had a higher proportion of male (80% vs 55%; $p < 0001$) and SEA patients (71% vs 55%; $p < 0001$). A greater number of HCC patients were born in an endemic region (63% vs 40%; $p < 0001$). 92% of HCC patients had advanced liver disease (minimum Fibrosis Stage 3 or known diagnosis of cirrhosis). A greater proportion of HCC patients underwent antiviral treatment with Tenofovir (50.9% vs 19.7%; $p < 0.0001$), Lamivudine (19.8% vs 12.2%; $p = 0.0012$), and Entecavir (23.3% vs 5.8%, $p < 0.0001$). HCC patients were followed for a median 15 months (IQR 2-69) prior to diagnosis, and a median 41 months (IQR 19-87) post-diagnosis. 53% of patients were diagnosed with HCC as part of surveillance protocols. The median lesion number was 1(IQR 1-1), with a median lesion size of 2.5cm (IQR 1.7-4.0). HCC diagnoses skewed towards early-stage BCLC 0-A disease (81%). There was an overall 84% survival rate post-HCC diagnosis during follow-up. Overall, 38% of patients received ablation, 16% received TACE, 25% underwent resection, 17% underwent a liver transplant, 8% required systemic therapy, and 6% received palliative therapy. Patient treatment was compared to recommendations per BCLC with an 82% treatment concordance. **Conclusion:** In this large multi-ethnic cohort of patients with CHB-HCC, the majority of patients were detected with early-stage HCC and received treatment with curative intent, resulting in excellent survival rates, likely driven by surveillance practices in tertiary centers.

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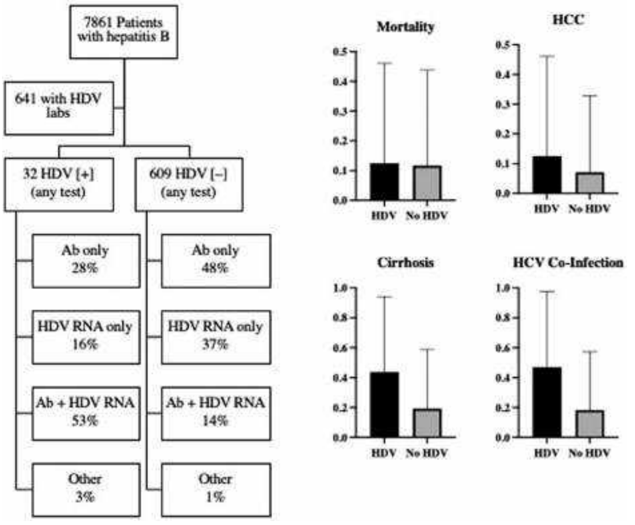
1354-C | EVALUATION OF HEPATITIS D SCREENING PATTERNS AND OUTCOMES AMONG HEPATITIS B PATIENTS IN AN ACADEMIC MEDICAL CENTER

Dilara Hatipoglu, Massachusetts General Hospital, Philadelphia, PA and Raymond T. Chung, Massachusetts General Hospital and Harvard Medical School

Background: Coinfection of hepatitis D virus (HDV) and hepatitis B virus (HBV) is associated with more severe outcomes compared to monoinfection. Consistent screening and care are essential to identify this patient population, especially in light of recent treatment advancements. **Methods:** This study utilized data from the Mass General Brigham Research Patient Data Registry, focusing on a cohort of patients with hepatitis B who were screened for hepatitis D at Massachusetts General Hospital between 2011 and 2021. Manual chart review was conducted to collect relevant data, and statistical analysis was performed using unpaired t-tests. **Results:** Among 7,861 patients with chronic hepatitis B; only 737 (9.4%) were screened for hepatitis D. Of 641 reviewed patients, 48% were tested for HDV antibody only, 37% for HDV RNA only, 14% for both antibody and RNA, and the remainder tested with IgM antibody and antigen. There were 32 (4.9%) patients diagnosed with hepatitis D. Screening strategies used in this group included 28% HDV antibody only, 16% HDV RNA only, 53% antibody and RNA, and 3% for IgM antibody and RNA. Among those tested for HDV antibody and RNA, 44% tested positive for both. Interferon treatment was administered to five patients (16%), two had sustained response, 1 failed treatment, and two discontinued due to side effects. Comparing outcomes between HDV positive and negative patients, no significant difference in mortality (12.5% vs. 11.7%, $p = 0.89$, CI -0.12 to 0.11) or rates of hepatocellular carcinoma (12.5% vs. 7%, $p = 0.26$, CI -0.15 to 0.039) was observed. However, higher rates of cirrhosis (43.8% vs. 19.4%, $p = 0.0009$, CI -0.39 to -0.10) and hepatitis C co-infection (46.9% vs. 18.4%, $p < 0.0001$, CI -0.43 to -0.14) were found in patients with chronic hepatitis D. Interestingly, patients with HDV were less likely to fit HDV screening recommendations outlined by the AASLD guidelines (75% vs. 92%, $p = 0.0013$, CI 0.065 to 0.27). Fibrosis screening rates, including liver biopsy, elastography, or Fibrotest, were similar between the two groups (50.0% vs. 49.9%, $p = 0.99$, CI -0.18 to -0.178). **Conclusion:** This study highlights the lack of screening for HDV and variability in screening decision-making and serology selection for hepatitis D within a single hospital system. Given the disparity in outcomes among patients with HDV infection, the establishment of more standardized screening guidelines is crucial to facilitate effective screening and subsequent treatment for individual's with hepatitis D.



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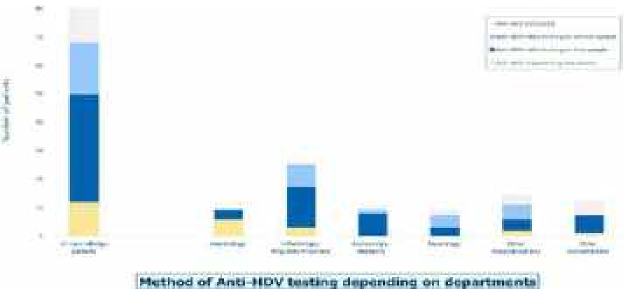
1355-C | FEASIBILITY AND EFFECTIVENESS OF REFLEX TESTING IN PERFORMING HEPATITIS DELTA SEROLOGY IN HBSAG+ PATIENTS

Albert Tran, Anne De Monte, Valerie Giordanengo, Regine Truchi and Laurence Ollier, Archet Hospital

Background: Several studies have shown that screening for the hepatitis Delta virus (HDV) was not optimal: between 30 and 50% in HBsAg positive patients (HBsAg+). The virology laboratory of the Nice University Hospital Center (CHU) has been carrying out HDV reflex testing (HDV RT) for several years in patients with HBsAg+ screening. **Methods:** This work assesses the feasibility and effectiveness of HDV RT within the different departments of our University Hospital. HDV RT consists of systematically adding HDV serology to HBsAg+ patients if the latter was not requested by the prescriber. In the event of an insufficient quantity of sample, the virology laboratory contacts the clinical department to obtain a second sample in order to carry out HDV screening. **Results:** From 01/01/2021 to 12/31/2021, 17364 HBsAg screenings were carried out at the CHU. 182 HBsAg screenings were positive, corresponding to 138 patients (58 F and 80 M). 80 among 138 patients (58%) were screened for the first time at the CHU and 58 patients (42%) were already known to be positive. Among the 80 HBsAg+ patients screened for the first time in our center, HDV serology was immediately prescribed by the department for 12 patients (15%). HDV serology could be added to the first sample for 38 patients (47%) and performed after obtaining a second sample for 18 patients (23%). Thus, 68 of the 80 HBsAg+ patients (85%) had an HDV serology result available, including 56 following reflex testing carried out by the virology laboratory. The operating procedure of the HDV serology is carried out by the different CHU departments is shown in the figure below. Among these 68 HBsAg+ screened for HDV, HDV serology was positive for 4 patients (6%), with HDV replication detected in 3 of them. Concerning the 58 patients already known to be HBsAg+ at the CHU, HDV serology was already available or prescribed from the outset for 49 patients (85%). The reflex testing made it possible to search for co-infection with HDV for 7 additional patients (12%), with a total of 97% of patients screened for HDV. **Conclusion:** HDV reflex testing is feasible at the level of an university establishment and makes it possible to optimize the search for HDV co-infection in different departments, including departments not specialized in the management of viral hepatitis.



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1356-C | GLOBAL DIFFERENCES IN THE EVALUATION AND TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS B: A REAL-B STUDY

Sahith Kudaravalli[1,2], Daniel Q Huang[3], Leslie Yeeman Kam[4], Vy H. Nguyen[1,5], Huy N. Trinh[6], Yao-Chun Hsu[7], Jiayi Li[8], Jianqing Zhang[9], Eiichi Ogawa[10], Dong Hyun Lee[11], Takanori Ito[12], Tsunamasa Watanabe[13], Masaru Enomoto[14], Carmen Preda[15], Yasuhito Tanaka[16], Man-Fung Yuen[17], Masanori Atsukawa[18], Sebastian Marciano[19], Maria Buti[20], Son T. Do[21], Christopher Wong[8], Haruki Uojima[22], Hirokazu Takahashi[23], Sabrina Quek[24], Htet Htet Toe Wai Khine[24], Masatoshi Ishigami[12], Norio Itokawa[25], Min Seok Go[11], Raluca Marin[15], Irina Sandra[15], Takanori Suzuki[26], Yoko Yoshimaru[16], Michael KI Ko[27], Rex Wan-Hin Hui[28], Clifford Wong[8], Dang Kh Vo[29], Ana Barreira[30], Cheng-Hao Tseng[31], Chul-Jin Lee[11], Kaori Inoue[32], Mayumi Maeda[1], Joseph Hoang[1], Lindsey Trinh[1], Angela Chau[1], Wan Long Chuang[33], Chia-Yen Dai[33], Jee-Fu Huang[34], Chung-Feng Huang[35], Ming-Lun Yeh[36], Adrián Gadano[19], Ramsey Cheung[4], Seng Gee Lim[24,37], Hidenori Toyoda[38], Ming-Lung Yu[33] and Mindie H. Nguyen[4], (1)Stanford University Medical Center, (2)Duke University, (3)National University Health System (NUHS), (4)Stanford University Medical Center, Palo Alto, CA, (5)Harvard Medical School, (6) San Jose Gastroenterology, (7)E-Da Hospital, (8)Wong Clinics, (9)Chinese Hospital, (10)Kyushu University Hospital, Fukuoka, Japan, (11)Good Gang-an Hospital, (12)Nagoya University Graduate School of Medicine, (13)St. Marianna University School of Medicine, (14) Osaka Metropolitan University Graduate School of Medicine, (15)Clinic Fundeni Institute, (16)Faculty of Life Sciences, Kumamoto University, (17)State Key Laboratory of Liver Research, the University of Hong Kong, Hong Kong, Hong Kong, China, (18)Nippon Medical School Hospital, (19)Hospital Italiano De Buenos Aires, (20)Hospital General Universitari Valle, Barcelona and Ciberehd Del Instituto Carlos III, Spain, (21)Texas GI Alliance, (22)National Center for Global Health and Medicine, (23)Division of Metabolism and Endocrinology, Faculty of Medicine, (24)National University Health System, (25)Nippon Medical School, (26)Nagoya City University Graduate School of Medical Sciences, (27)Queen Mary Hospital, (28)Department of Medicine, School of Clinical Medicine, the University of Hong Kong, Hong Kong SAR, (29)Digestive Health Associates of Texas, Garland, TX, (30)Hospital Universitari Valle d'Hebron, (31)E-Da Cancer Hospital, (32)Saga University Hospital, (33)Kaohsiung Medical University, (34)Kaohsiung Medical University, Kaohsiung, Taiwan, (35)Kaohsiung Medical University Hospital, (36)National Sun Yat-Sen University, (37)Yong Loo Lin School of Medicine, (38)Ogaki Municipal Hospital

Background: Antiviral therapy is effective in suppressing hepatitis B virus (HBV) replication and reducing hepatocellular carcinoma risk. However, studies on adherence to guidelines for HBV treatment globally are sparse. We aimed to determine the treatment evaluation, eligibility, and initiation rates of patients with chronic hepatitis B (CHB) in a real-world multinational patient cohort using the American Association for the Study of Liver Diseases (AASLD) guidelines for HBV. **Methods:** We performed a retrospective cohort study of treatment-naïve patients with CHB in the REAL-B registry, an observational chart review registry at 26 study centers (Japan, Korea, Hong Kong, Taiwan, Singapore, US, Spain, Romania, and Argentina). We then determined the proportions of patients who received complete evaluation (HBV DNA, ALT, and HBeAg), subsequently met AASLD treatment criteria, and initiated treatment at any time during the study period. We also identified factors associated with receiving complete evaluation and treatment using multivariable Cox regression analysis. **Results:** We included 12,692 adult patients with treatment-naïve CHB: 58.3% male, mean age 47.1 ± 13.7 years, 95.0% Asian, 50.2% from Asia, and 8.6% with baseline cirrhosis. Overall, 28.7% (3641 patients) of the cohort received complete evaluation. Among those with complete evaluation, 22.8% (831 patients) met AASLD treatment criteria, and 78.5% of these treatment-eligible patients initiated antiviral therapy. Notably, there were significant disparities in both the evaluation and treatment rates by geographic region and ethnicity, with patients from non-Asia less likely to have complete evaluation compared to those from Asia (21.3% vs. 36.0%, $p < 0.001$) but more likely to initiate treatment (85.0% vs. 75.4%, $p = 0.001$). However, Asia Asian had a higher rate of complete evaluation compared to US Asian (36.0% vs. 18.6%, $p < 0.001$) but a lower rate of treatment initiation (75.4% vs. 84.5%, $p = 0.010$) (Figure 1). In

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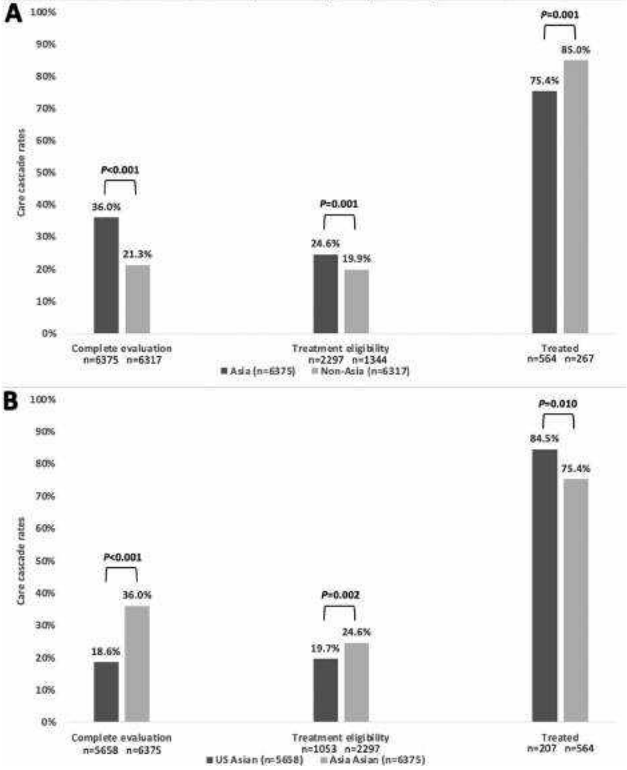
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

multivariable analysis adjusting for age, sex, and geographic region, patients from non-Asia were about 60% less likely than those from Asia to have complete evaluation (adjusted hazards ratio [aHR]: 0.44, 95% CI: 0.41-0.48, $p < 0.001$), but there was no significant association in antiviral therapy initiation by region (aHR: 1.08, 95% CI: 0.91-1.27, $p = 0.390$). **Conclusion:** In this multinational real-world study, we found significant geographic and ethnic differences in the treatment evaluation and initiation rates, likely reflecting differences in local practice and reimbursement policies. Additional studies with a larger geographic representation are needed to assess global CHB treatment landscape.

Figure 1. Treatment evaluation, eligibility, and initiation rates by (A) Asia and Non-Asia regions and (B) US Asian and Asia Asian at any time during study follow-up.



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1357-C | HBV TREATMENT CAN REDUCE RISK OF KIDNEY DISEASE AMONG PATIENTS WITH HEPATITIS B, YET TREATMENT IN THE US REFLECTS INEQUITIES IN CARE

Kaori L Ito[1], *Yuqing Zhang*[1], *Biao Li*[1], *Jinfeng Liu*[1], *Andrew King*[2], *Leland J. Yee*[1], *Frida Abramov*[1], *Catherine Frenette*[1], *John F. Flaherty*[1] *and Vladislav A*

Malkov[1], (1)Gilead Sciences, Inc., (2)Scripps Clinic Torrey Pines

Background: Kidney disease (KD) can be comorbid with chronic hepatitis B virus (HBV) infection, and untreated HBV is associated with increased risk of KD (Ning et al., 2017). We used a large electronic medical record (EMR) database to examine whether patients with HBV are at greater risk for developing KD vs those without HBV and identified factors placing patients at risk. We also explored the effect of using oral antiviral (OAV) treatment on the risk of developing KD. **Methods:** Data were queried from the IQVIA Ambulatory EMR (2006–2020). Propensity score matching and Cox proportional hazards were performed for all comparisons. Time to development of KD was assessed in patients with/without HBV, where age of KD onset served as a proxy for time to KD. KD was defined as worsening of eGFR/UACR or e 1 ICD code. Hypertension, diabetes, and obesity were evaluated as concomitant risk factors for KD. The association between KD and cirrhosis in untreated patients aged e 55 years was evaluated using FIB-4 (e 3.25) and cirrhosis ICD codes. The risk of KD with OAV use was assessed in patients with HBV age e 55 with HBV DNA, ALT, or liver disease codes. **Results:** Compared with matched controls, patients with HBV were more likely to develop KD (hazard ratio [HR], 2.18 [95% CI, 1.89, 2.50]). Most events occurred after age 55. Patients with HBV with comorbid risks were more likely to develop KD (HR, 1.99 [1.71, 2.30]; Figure). Neither cirrhosis nor FIB-4 score e 3.25 was associated with KD (cirrhosis HR, 1.18 [0.65, 2.15]; FIB-4 HR, 1.21 [0.59, 2.52]). Treated patients were at lower risk of developing KD (HR, 0.61 [0.42, 0.88]) compared with untreated patients; however, only 17% of patients with HBV received treatment. Stratification analyses showed that African American (AA) patients were more likely to have at least 1 risk factor for KD (Figure) yet were underrepresented in the treated group; only 10% of AA and 11% of White patients with HBV received treatment, whereas 20% of Asian patients with HBV received treatment. **Conclusion:** Patients with HBV, especially older patients with comorbid risks, were at higher risk of developing KD relative to matched controls. KD was observed even in the absence of cirrhosis, suggesting that HBV infection may directly induce renal tissue injury. Our results show that OAVs may decrease the risk of developing KD in patients with HBV, yet inequities in treatment were observed. These results require further investigation.

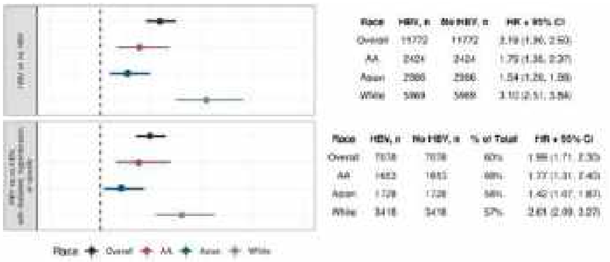

Figure. Hazard ratios for kidney disease in patients with and without chronic HBV by race. Patients with chronic HBV, particularly those with hypertension, diabetes, or obesity, were more likely to develop kidney disease.
AA, African American; HBV, hepatitis B virus; HR, hazard ratio. % in Total calculated as number of patients with hypertension, diabetes, or obesity within each race divided by total number of patients within each race category.

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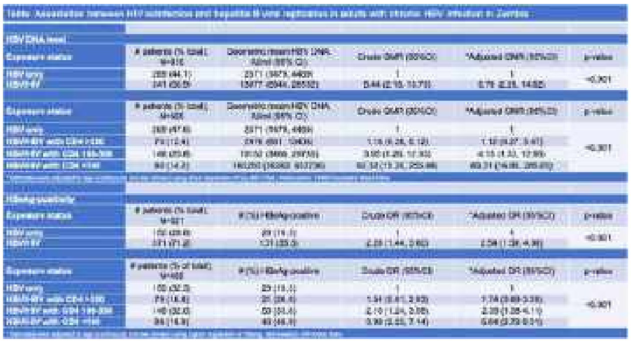
1358-C | HBV VIRAL REPLICATION MARKERS AND HEPATIC FIBROSIS IN UNTREATED CHRONIC HBV INFECTION WITH AND WITHOUT HIV COINFECTION IN ZAMBIA

Michael Vinikoor[1,2], Samuel Bosomprah[1], Edford Sinkala[3], Bright Nsokolo[4], Taonga Musonda[3], Kalongo Hamusonde[5], Debika Bhattacharya[6], Georg M. Lauer[7], Raymond T. Chung[8], Lloyd Mulenga[9], Gilles Wandeler[5] and Guy Muula[1], (1)Centre for Infectious Disease Research in Zambia, (2)University of Alabama at Birmingham, (3)University of Zambia, (4)Levy Mwanawasa Medical University, (5)University of Bern, (6)University of California, Los Angeles, (7) Massachusetts General Hospital and Harvard Medical School, (8)Massachusetts General Hospital, Harvard Medical School, (9)Zambian Ministry of Health

Background: To inform novel curative therapies for patients with HBV/HIV coinfection, a more nuanced understanding is needed of HIV's impact on hepatitis B virus (HBV) natural history. Prior analyses of HBV/HIV coinfection had small and selected groups of patients or occurred in the context of HIV cohorts with limited focus on liver endpoints. Because HBV and HIV care is often siloed, direct comparisons between people with coinfection and HBV monoinfection have been scarce. In adults in Zambia, we analyzed pre-therapy viral and liver markers of chronic HBV with and without HIV coinfection across a range of CD4 counts. **Methods:** In Lusaka, Zambia, where adult HIV prevalence is 12% and chronic HBV prevalence is 6%, we analyzed baseline data from an HBV clinical cohort study. Adults (18+ years) with chronic HBV infection, with and without HIV, prior to the start of antiviral therapy were included in analysis. To reduce selection bias created by later diagnosis (i.e., with advanced liver disease) of HBV versus HIV in Africa, we excluded participants with HBV diagnosed on clinical suspicion. We assessed HBV DNA levels, hepatitis B e antigen, CD4 (if coinfection), and liver disease (transient elastography [TE], serum alanine aminotransferase). In multivariable analyses, we evaluated the association of HIV overall and then we considered the level of CD4 count to assess heterogeneity. **Results:** Among 713 adult (> 18 y) participants analyzed, the median age was 33 years, 63.0% were male, and 433 had HBV/HIV coinfection. HBV DNA was > 2,000 IU/ml for 311 (51.0%) and 227 (32.5%) were HBeAg-positive. 15.5% had advanced fibrosis or cirrhosis. In coinfection, the median CD4 count was 200 cells/mm^3. HIV coinfection was overall associated with 5-fold increased HBV DNA levels (adjusted geometric mean ratio, 5.78; 95% confidence interval, 2.29-14.62) and 2 times the odds of HBeAg-positivity (adjusted odds ratio, 2.54; 95% CI, 1.59-4.08). However, these associations were significant only at CD4 counts 100-350 and < 100 cells/mm^3 but not at CD4 > 350. HIV was not associated with markers of fibrosis or ALT, either overall or by CD4 strata. **Conclusion:** In the context of HIV, acceleration of HBV natural history likely depends on the degree and duration of immune suppression. Thus, HBV immunity may be less affected in patients with HBV/HIV coinfection who started antiretroviral therapy at high CD4 count. A better understanding is needed of mechanisms of increased liver-related mortality in people with HBV/HIV coinfection.



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1359-C | HEPATITIS DELTA VIRUS SUPERINFECTION INCREASES THE RISK OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC HEPATITIS B VIRUS

Mohamed I Elsaid[1], Khalid Mumtaz[2], Na Li[2], Demond Handley[1], Joanna Jianing[1], Bipul Gnyawal[1] and Vinod K. Rustgi[3], (1)The Ohio State University College of Medicine, (2)The Ohio State University, Wexner Medical Center, (3)Rutgers Robert Wood Johnson School of Medicine

Background: Hepatocellular Carcinoma (HCC) incidence and mortality continue to rise in the United States despite the declining trends in numerous other cancers. While the hepatitis delta virus (HDV) has been shown to increase the risk of adverse hepatic manifestations, research on the association between HDV and HCC risk has yielded mixed results. In addition, most of the research on this topic has focused on Chronic Hepatitis B Virus CHBV/HDV coinfection, with limited studies on HBV-HDV superinfection. We aim to examine the association between CHBV-HDV superinfection and the risk of HCC in patients with CHBV. **Methods:** Using the MarketScan® Commercial Claims databases from January 1, 2008, to December 31, 2017, we combine claims data from the inpatient admissions and outpatient services records to identify patients with CHBV using ICD-9 and 10 codes. HBV-HDV superinfected patients were defined as new HDV diagnoses over 90 days from the first date of CHBV diagnosis. HDV status was modeled as a time-varying covariate to account for the effects of the wait time between the date of CHBV diagnosis and the first record for HDV diagnosis. Inverse probability of treatment weighted Cox proportional hazard models were used to assess the adjusted risks of HCC for CHBV mono-infection versus CHBV-HDV superinfection. **Results:** The study included 36,689 adults with CHBV (53.7% males, average age 45 y), of which 1,633 had CHBV-HDV superinfection. The average time from CHB diagnosis to HBV-HDV superinfected was 26.2 months. During the study period, 201 patients developed HCC. The median follow-up was 19 months. The risk of HCC was significantly higher in super- vs. mono-infected patients (1.4% vs. 0.5%; $p < 0.001$). The incidence rate of HCC was more than 2.5-fold higher in super- vs. mono-infected patients (6.7 vs. 2.3 per 1000 Person-years %; $p < 0.001$). The adjusted risk of cirrhosis was significantly higher super- vs. mono-infected patients hazard ratio (HR) of 2.64 (95% CI 2.11–3.28). In the fully adjusted models, HDV superinfection was associated with a 93% increase in the risk of HCC (HR, 1.93; 95% CI, 1.20–2.97) relative to CHBV mono-infection. **Conclusion:** Our comprehensive analysis of a large commercial claims database suggests a markedly increased risk of HCC in patients with CHBV-HDV superinfection compared to those with CHBV mono-infection. These findings underscore the crucial importance of early diagnosis, surveillance, and targeted intervention strategies for HBV-HDV superinfected patients.

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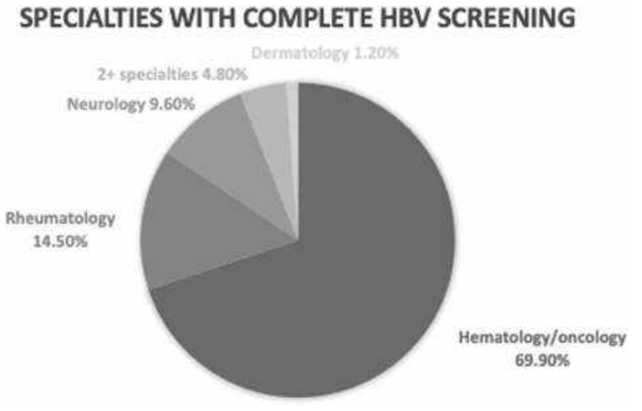
1360-C | HIGH RISK, HIGH REWARD: EVALUATING THE FREQUENCY OF GUIDELINE-BASED HEPATITIS B SCREENING IN THE HIGH-RISK GROUP FOR HBV REACTIVATION PRIOR TO IMMUNOSUPPRESSIVE THERAPY

Joanne Lin[1,2], Humzah Iqbal[1], Jennifer Yoon[1], Alakh Gulati[1], Ratnali Jain[1] and Marina M. Roytman[1], (1) UCSF Fresno, (2)Temple University

Background: Hepatitis B virus reactivation (HBVr) is a syndrome associated with significant morbidity and mortality, reflecting the loss of immune control of the infection which can be due to stopping antiviral therapy or starting immunosuppressive medication. Immunosuppressive therapies are used in the management of many rheumatologic and dermatologic conditions, malignancies, and inflammatory bowel diseases. Multiple guidelines recommend screening for chronic hepatitis B (HBV) prior to initiating immunosuppressive drug therapy. Adherence to these guidelines in clinical practice is variable. We sought to determine the frequency of complete guideline-based HBV screening prior to the initiation of immunosuppressive therapy in patients in the high-risk group based on the American Gastroenterological Association (AGA) classification. **Methods:** Our retrospective study included 305 patients over the age of 18 taking high-risk immunosuppressive therapy, which included B cell-depleting agents and anthracycline derivatives, from October 2020 to April 2021. Patients prescribed high-risk doses and duration of steroid therapy were not included. The following data were collected: gender, age, complete HBV serologies (hepatitis B surface antigen [HBsAg], hepatitis B core antigen [anti-HBc], hepatitis B surface antibody [anti-HBs]), the immunosuppressive regimen, and the indication for immunosuppression. **Results:** Of the 305 patients, 45.6% were over the age of 65 and 68.9% were females. The most frequently used immunosuppressive therapy was rituximab (64.3%), followed by doxorubicin (26.2%), 2 or more medications (8.2%), ofatumumab (1%) and epirubicin (0.3%). The specialties that prescribed immunosuppressive therapies most often were hematology/oncology (63.3%), rheumatology (22.6%), neurology (7.9%), dermatology (3.3%), and 2 or more specialties (3%). Only 83 patients (27.2%) had complete HBV screening. Of the screening tests, HBsAg was tested in 66.9% of patients, anti-HBc in 48.5%, and anti-HBs in 31.8%. Hematology/oncology completed HBV screening most frequently, followed by rheumatology, neurology, two or more specialties, and dermatology. **Conclusion:** HBVr is a potentially life-threatening complication of immunosuppression but is preventable with appropriate pre-immunosuppression screening and antiviral therapy. Our study highlights the stark deficiencies in HBV screening in high-risk patients and emphasizes the opportunities to improve provider adherence to HBV screening recommendations to prevent HBVr.



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1361-C | IMPACT OF COVID-19-RELATED PUBLIC HEALTH MEASURES ON TESTING FOR HEPATITIS B IN BRITISH COLUMBIA, CANADA: AN INTERRUPTED TIME SERIES ANALYSIS

Richard L Morrow[1,2], Sofia R. Bartlett[2], Mike Irvine[1], Mawuena Binka[3], Jean Damascene Makuza[1], Dahn Jeong[2], Jason Wong[1], Amanda Yu[1], Julia Li[1], Stanley Wong[1], Maria Jose Alvarez[1], Mel Krajden[1] and Naveed Zafar Janjua[1,2], (1)BC Centre for Disease Control, (2) University of British Columbia, (3)British Columbia Centre for Disease Control

Background: Public health measures implemented in response to the coronavirus disease 2019 (COVID-19) pandemic disrupted healthcare services internationally. We aimed to assess the impact of COVID-19-related public health policies on hepatitis B (HBV) testing among residents of British Columbia (BC), Canada. **Methods:** We used interrupted time series analysis with administrative health data from the province's COVID-19 Cohort to estimate changes in testing for HBV following an initial phase of COVID-19-related public health policies. The study period included a pre-policy period (January 2017 to February 2020), a 3-month transition period during restrictive early COVID-19-related public health measures (March to May 2020), and 3 follow-up periods (June to December 2020, January to December 2021, and January to December 2022). Models with a linear trend term and adjustment for seasonality and autocorrelation were used to estimate the absolute and percentage difference between actual and predicted monthly HBV surface antigen testing, HBV DNA testing, and HBV e-antigen testing during each follow-up period. **Results:** We observed both short-term and sustained impacts on HBV testing. The monthly rate of HBV surface antigen testing was 15.6% lower than predicted in June to December 2020 (73 fewer individual's tested each month per 100,000 population; 95% CI 61 to 86) and declined further to 24.1% lower than predicted in 2022. However, this decrease was attenuated among women 19 to 44 years of age, which may reflect prenatal HBV testing. The monthly rate of HBV DNA testing was 12.0% lower than predicted in June to December 2020 (7 fewer individual's tested each month per 100,000 population; 95% CI 5 to 8) and was 11.9% lower than predicted in 2022. The number of individual's with an e-antigen test was 5.3% lower than predicted in June to December 2020 (27 fewer individual's tested each month; 95% CI 4 to 52) and was 7.4% lower than predicted in 2022. **Conclusion:** The period following the introduction of public health measures related to COVID-19 has been associated a decrease in HBV testing relative to the predicted level in the short term and over a longer period. It is important to better understand and develop strategies to address this sustained impact on HBV testing.

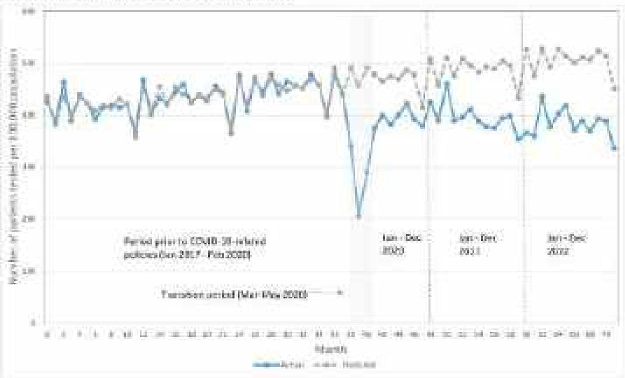

Figure 1. Actual vs predicted rate of hepatitis B surface antigen testing per 100,000 population in British Columbia following initial of phase of COVID-19 related policies

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Disclosure information not available at the time of publication: Mike Irvine, Jean Damascene Makuza, Jason Wong, Julia Li

1362-C | IMPACT OF FATTY LIVER (FL) ON VIROLOGIC (VR), BIOCHEMICAL (BR), AND COMPLETE RESPONSE (CR) AMONG PATIENTS WITH CHRONIC HEPATITIS B (CHB) TREATED WITH NUCLEOS(T)IDE ANALOGS (NA): A REAL-B STUDY

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Background: NA therapy can reduce disease progression in chronic hepatitis B (CHB) patients. However, there is limited data on treatment response among patients with concurrent fatty liver (FL) and CHB, including viral suppression (VR), biochemical response (BR), and complete response (CR) rates. Therefore, we aimed to compare the outcomes of NA therapy between FL-CHB and non-FL CHB groups. **Methods:** A retrospective real-world cohort study of adult CHB patients treated with either entecavir or tenofovir from 12 sites (U.S., Taiwan, and Japan) was conducted. FL was diagnosed by imaging. Propensity score matching (PSM) was used to balance the FL-CHB and non-FL CHB groups. The Kaplan-Meier method was used on the matched cohort to compare 5-year cumulative rates of VR, BR, and CR, stratified by FL-CHB vs. non-FL CHB. Univariable Cox proportional hazard regression was performed on the matched cohort to identify independent factors associated with VR, BR, and CR. **Results:** We analyzed 1693 adult CHB patients (452 FL-CHB; 1241 non-FL CHB). The mean (± SD) follow-up was 4.1 (± 3.8) years before PSM and 3.5 (± 2.8) years after PSM. At baseline before PSM, FL-CHB patients had higher BMI (25.6 vs. 23.9, $p < 0.001$), platelet count (240.7 vs. 203.9 10^3/ L, $p < 0.001$), and ALT (103 vs. 87 IU/L, $p = 0.004$). FL-CHB patients were more likely to be HBeAg-positive (32.8% vs. 25.9%, $p = 0.007$), and were less likely to have cirrhosis (9.6% vs. 34.1%, $p < 0.001$) or high FIB-4 (25.2% vs. 37.5%, $p < 0.001$). Baseline characteristics between the FL and non-FL CHB groups became similar after matching on age, BMI, diabetes mellitus, cirrhosis, platelets, ALT, HBV DNA, HBeAg positive, and FIB-4. On follow-up before PSM, FL-CHB patients had a lower 5-year cumulative VR rate (84.4% vs. 89.9%, $p = 0.0017$) and

5-year cumulative CR rate (80.2% vs. 85.1%, $p = 0.020$), as well as a slightly lower 5-year cumulative BR rate (90.3% vs. 92.3%, $p = 0.068$) (Table 1). However, after PSM with the two groups balanced well, FL and non-FL CHB patients had similar 5-year cumulative VR (91.5% vs. 89.9%, $p = 0.21$), BR (97.7% vs. 96.9%, $p = 0.34$), and CR rates (89.9% vs. 86.8%, $p = 0.099$) (Table 1). We found no statistically significant association between FL and VR (HR = 1.14, CI: 0.93-1.40, $p = 0.22$), BR (HR = 1.09, CI: 0.90-1.32, $p = 0.37$), or CR (HR = 1.19, CI: 0.96-1.47, $p = 0.11$) in the PSM-matched cohort. **Conclusion:** Among diverse real-world NA-treated CHB patients, while FL patients had higher baseline ALT levels than non-FL patients, FL was not independently associated with response to NA therapy.

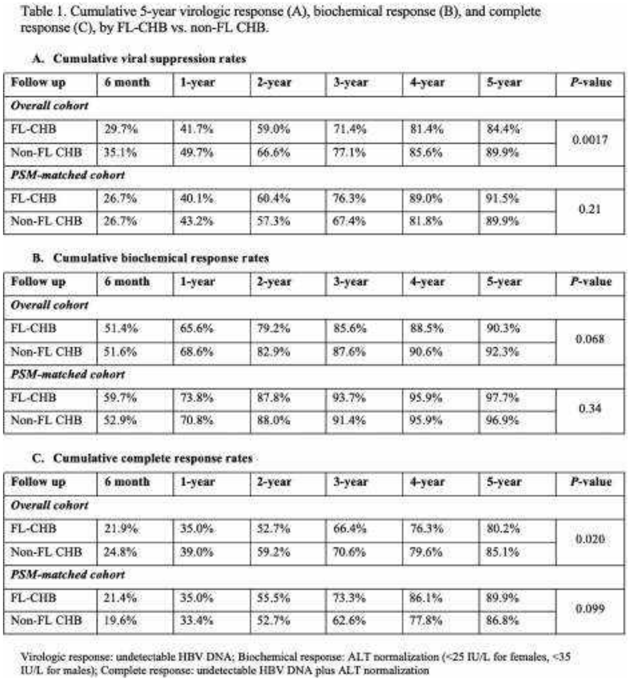

Table 1. Cumulative 5-year virologic response (A), biochemical response (B), and complete response (C), by FL-CHB vs. non-FL CHB.

A. Cumulative viral suppression rates

Follow up	6 month	1-year	2-year	3-year	4-year	5-year	*P*-value
Overall cohort							
FL-CHB	29.7%	41.7%	59.0%	71.4%	81.4%	84.4%	0.0017
Non-FL CHB	35.1%	49.7%	66.6%	77.1%	85.6%	89.9%	
PSM-matched cohort							
FL-CHB	26.7%	40.1%	60.4%	76.3%	89.0%	91.5%	0.21
Non-FL CHB	26.7%	43.2%	57.3%	67.4%	81.8%	89.9%	

B. Cumulative biochemical response rates

Follow up	6 month	1-year	2-year	3-year	4-year	5-year	*P*-value
Overall cohort							
FL-CHB	51.4%	65.6%	79.2%	85.6%	88.5%	90.3%	0.068
Non-FL CHB	51.6%	68.6%	82.9%	87.6%	90.6%	92.3%	
PSM-matched cohort							
FL-CHB	59.7%	73.8%	87.8%	93.7%	95.9%	97.7%	0.34
Non-FL CHB	52.9%	70.8%	88.0%	91.4%	95.9%	96.9%	

C. Cumulative complete response rates

Follow up	6 month	1-year	2-year	3-year	4-year	5-year	*P*-value
Overall cohort							
FL-CHB	21.9%	35.0%	52.7%	66.4%	76.3%	80.2%	0.020
Non-FL CHB	24.8%	39.0%	59.2%	70.6%	79.6%	85.1%	
PSM-matched cohort							
FL-CHB	21.4%	35.0%	55.5%	73.3%	86.1%	89.9%	0.099
Non-FL CHB	19.6%	33.4%	52.7%	62.6%	77.8%	86.8%	

Virologic response: undetectable HBV DNA; Biochemical response: ALT normalization (<25 IU/L for females, <35 IU/L for males); Complete response: undetectable HBV DNA plus ALT normalization

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Disclosure information not available at the time of publication: Keigo Kawashima, Akito Nozaki, Yuichiro Eguchi, Hiroshi Abe

1363-C | INFLUENCE OF VIRAL LOAD AND FIBROTIC BURDEN ON HEPATOCELLULAR CARCINOMA RISK AT PHASE CHANGE TO IMMUNE-ACTIVE PHASE IN CHRONIC HEPATITIS B

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Background: Recent studies reported that moderate hepatitis B virus (HBV) DNA levels are significantly associated with hepatocellular carcinoma (HCC) risk in hepatitis B e antigen (HBeAg)-positive, non-cirrhotic patients with chronic hepatitis B (CHB). We assessed

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

the association of baseline viral load and fibrotic burden with the risk of HCC development in CHB patients entering the immune-active (IA) phase. **Methods:** This multicenter cohort study recruited 3,589 HBeAg-positive, non-cirrhotic CHB patients who started antiviral treatment with entecavir or tenofovir disoproxil fumarate at IA phase transitioned from immune-tolerant (IT) phase in twenty-three tertiary university-affiliated hospitals of South Korea (2012–2020). Significant liver fibrosis was defined as fibrosis-4 index (FIB-4) > 3.25. Multivariable analysis using the Cox proportional hazards model was performed. **Results:** Sixty (1.7%) patients developed HCC (median follow-up, 5.4 y). Patients who developed HCC were significantly older and showed a significantly higher proportion of diabetes, lower platelet counts, and higher FIB-4 levels than those who did not (n = 3,525, 98.3%) (all $p < 0.05$). The HCC risk was highest at moderate HBV DNA levels (5.00–7.99 $\log_{10}$ IU/mL) and significant liver fibrosis. In multivariable analysis, moderate HBV DNA levels was independently associated with the increased risk of HCC development (adjusted hazard ratio [aHR] = 2.55, 95% confidence interval [CI] = 1.32–4.91, $p = 0.005$). After adjustment for FIB-4 levels, similar result was maintained (moderate HBV DNA levels: aHR = 2.68, 95% CI = 1.40–5.13; FIB-4 > 3.25: aHR = 7.63, 95% CI = 3.05–19.09; all $p < 0.05$). **Conclusion:** Moderate HBV DNA levels and significant liver fibrosis at the time of phase change from IT to IA phase was significantly associated with the risk of HCC development during potent antiviral therapy in patients with CHB.

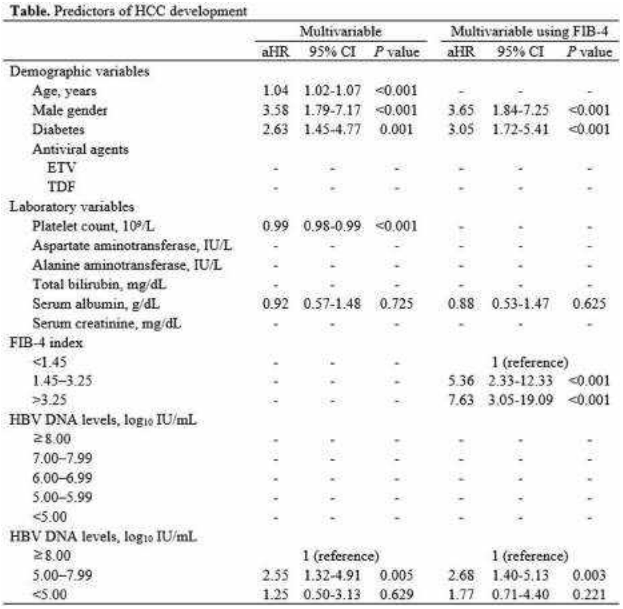


Table. Predictors of HCC development

	Multivariable			Multivariable using FIB-4		
	aHR	95% CI	P value	aHR	95% CI	P value
Demographic variables						
Age, years	1.04	1.02-1.07	<0.001	-	-	-
Male gender	3.58	1.79-7.17	<0.001	3.65	1.84-7.25	<0.001
Diabetes	2.63	1.45-4.77	0.001	3.05	1.72-5.41	<0.001
Antiviral agents						
ETV	-	-	-	-	-	-
TDF	-	-	-	-	-	-
Laboratory variables						
Platelet count, 10^9/L	0.99	0.98-0.99	<0.001	-	-	-
Aspartate aminotransferase, IU/L	-	-	-	-	-	-
Alanine aminotransferase, IU/L	-	-	-	-	-	-
Total bilirubin, mg/dL	-	-	-	-	-	-
Serum albumin, g/dL	0.92	0.57-1.48	0.725	0.88	0.53-1.47	0.625
Serum creatinine, mg/dL	-	-	-	-	-	-
FIB-4 index						
<1.45	-	-	-		1 (reference)	
1.45–3.25	-	-	-	5.36	2.33-12.33	<0.001
>3.25	-	-	-	7.63	3.05-19.09	<0.001
HBV DNA levels, $\log_{10}$ IU/mL						
≥8.00	-	-	-	-	-	-
7.00–7.99	-	-	-	-	-	-
6.00–6.99	-	-	-	-	-	-
5.00–5.99	-	-	-	-	-	-
<5.00	-	-	-	-	-	-
HBV DNA levels, $\log_{10}$ IU/mL						
≥8.00		1 (reference)			1 (reference)	
5.00–7.99	2.55	1.32-4.91	0.005	2.68	1.40-5.13	0.003
<5.00	1.25	0.50-3.13	0.629	1.77	0.71-4.40	0.221

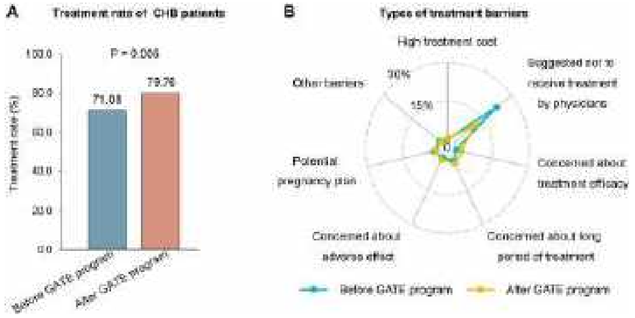
Disclosures: The following people have nothing to disclose: Ho Soo Chun, Minjong Lee, Hye Ah Lee, Jihye Kim, Han Ah Lee, Hwi Young Kim, Tae Hun Kim, Eileen L. Yoon, Dae Won Jun, Sang Hoon Ahn, Seung Up Kim, Yoon Jun Kim

1364-C | INTERIM RESULTS OF A PROGRAM TO NARROW GAP BETWEEN IN ACCORDANCE WITH GUIDELINES AND CONSENT TO TREAT CHB POPULATION IN EAST OF CHINA (GATE STUDY)

Shaoqiu Zhang[1], Jian Wang[1,2], Xiaomin Yan[1], Li Wang[1], Zhaoping Zhang[1], Sufang Lu[1], Yuxin Chen[3], Jie Li[1,2], Rui Huang[1,2] and Chao Wu[1,2], (1)Department of Infectious Diseases, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China, (2)Institute of Viruses and Infectious Diseases, Nanjing University, Nanjing, Jiangsu, China, (3)Department of Laboratory Medicine, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China

Background: Antiviral treatment may decrease risk of cirrhosis, liver failure, and hepatocellular carcinoma in patients with chronic hepatitis B (CHB). However, the rates of antiviral treatment are suboptimal in treatment-eligible CHB patients. We aimed to dissect the barriers to antiviral treatment and conduct a program to increase the treatment rate of treatment-eligible CHB patients. **Methods:** We established a retrospective cohort and a prospective cohort of treatment-naïve CHB patients from January 2019 to October 2021 and from November 2021 to February 2023, respectively. Treatment-naïve patients who fulfilled with indications for antiviral treatment according to Chinese 2019 CHB guidelines were recommended to initiating antiviral treatment. A standardized questionnaire survey was conducted via telephone or clinic follow-up visit to learn treatment status of patients and discover the possible treatment barriers. A program with integrated intervention strategies, including the development of online medical education and the design of follow-up alert system, was implemented to narrow Gap between in Accordance with guidelines and consent to Treat CHB population in East of China (GATE) and improve the treatment uptake. **Results:** Before the implement of integrated intervention strategies, 1134 treatment-eligible CHB patients were included in the retrospective cohort and 71.08% of patients received antiviral treatment. Of the treatment-eligible patients, 22.05% patients were not suggested to receive treatment by their physicians; 6.88% patients refused the treatment due to varying personal concerns, including concerns about long period of treatment, treatment efficacy and adverse effects and high cost, and potential pregnancy plan. After the GATE program with integrated strategies implemented, 252 patients were enrolled in the prospective cohort and there was an 8.68% (from 71.08% to 79.76%, $p = 0.005$) increase in rate of antiviral treatment. The proportion of patients

not suggested to receive treatment by their physicians decreased from 22.05% to 10.71% ($p < 0.001$). **Conclusion:** One of the major treatment barriers was a lack of adherence to guidelines for CHB in physicians. There remains a need to educate physicians regarding guidelines for CHB. The integrated intervention strategies achieved increased antiviral treatment rate in treatment-eligible CHB patients. This approach could be an important strategy to improve treatment uptake of CHB patients.



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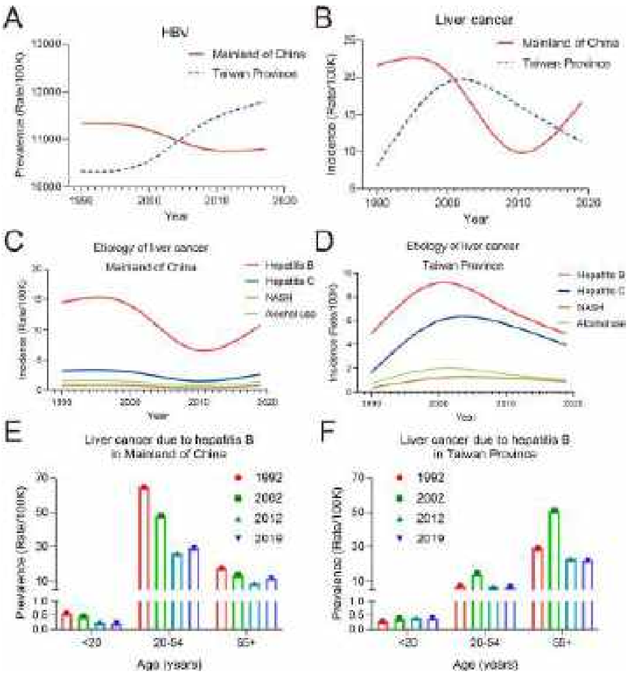
1365-C | IS NASH THE FASTEST GROWING CAUSE OF LIVER CANCER IN CHINA?

Liying Ren, Dongbo Chen, Shaoping She, Pu Chen, Guixin Li, Yao Yang and Hongsong Chen, Peking University People's Hospital, Peking University Hepatology Institute, Beijing Key Laboratory of Hepatitis C and Immunotherapy for Liver Disease

Background: Although NASH, progressing from non-alcoholic fatty liver disease (NAFLD), has become an important component of the etiology of liver cancer worldwide. However, in many countries and regions, viral hepatitis, particularly hepatitis B virus (HBV), remains the dominant cause of liver cancer. **Methods:** We collected the data from the GBD 2019, which includes mainland of China and Taiwan Province, prevalence and incidence rate per 100,000 person-years were calculated. **Results:** Data from mainland of China and Taiwan Province from 1990 to 2019 showed that HBV is still the most common cause of liver cancer in these regions, and the incidence is still high. Compared to HBV, the proportion of liver cancer cases caused by HCV, NASH, and alcohol in mainland of China has remained relatively stable. This suggests HBV is currently still the main cause of liver cancer. However, the incidence of HBV-related liver cancer in mainland of China has not decreased despite effective control of hepatitis B. From 2000 to 2019, the incidence of hepatitis B in mainland of China presented a downward trend, which may be closely related to the widespread use of the hepatitis B vaccine. Although the incidence of liver cancer in mainland of China showed a downward trend from 1990 to 2010 with the control of hepatitis B, the incidence of liver cancer has been increasing since 2010. Through the analysis of the etiology of liver cancer, we found that the incidence of HBV-related liver cancer in mainland of China has been on the rise since 2010, and its rate of increase far exceeds that caused by hepatitis C, alcohol, or NASH. In Taiwan Province, the incidence of liver cancer caused by various etiologies has decreased yearly. Moreover, the results stratified by age showed that the number of HBV-related liver cancer cases among individual's under 20 years of age remains very low in both mainland of China and Taiwan Province; in mainland of China, the number of cases among individual's over 20 years of age has continued to increase over the past decade, but in Taiwan Province, it has remained relatively stable over time. Therefore, the population mainly affected by the rising incidence of HBV-related liver cancer in mainland of China is hepatitis B patients older than 20. **Conclusion:** In summary, the widespread use of the hepatitis B vaccine has undoubtedly played an outstanding role in liver cancer prevention and control, especially among children and adolescents. However, the incidence of HBV-related liver cancer among adults in mainland of China has continued to rise, which may be the reason for the continuous increase in the total number of liver cancer cases. Although the popularization of liver cancer screening methods and the extension of life expectancy make this growth reasonable to some extent, we still need to increase public awareness and prevention of hepatitis B and carry out health education and monitoring for populations in high-risk countries and regions such as China.



Disclosures: The following people have nothing to disclose: Liying Ren, Dongbo Chen, Shaoping She, Pu Chen, Guixin Li, Yao Yang, Hongsong Chen

1366-C | LONG TERM HEPATITIS B CARE IN TORONTO, CANADA: A SINGLE CLINICIAN EXPERIENCE

David Kah Heng Wong, University of Toronto

Background: There is debate about whether clinical care of patients with chronic HBV should be simplified such that most, if not all, patients are treated indefinitely. The Liver Clinic in Toronto, Canada was first established by Jenny Heathcote in 1979. The patients in this clinic had universal free access to healthcare providers and investigations including all blood tests and medical imaging. An electronic medical record (EMR) on QuadraMed platform that was used from 2007. At the time, all patient records were individually reviewed and transferred from paper records to electronic records. Blood tests from Jan 2010 performed at labs in Ontario were accessible by Connecting Ontario. DW philosophy of care for hepatitis B: 1. Not all with HBV would benefit from antiviral treatment and 2. antiviral therapy need not be indefinite - stopping treatment might be beneficial. On June 4, 2022, the clinic moved to a commercial EMR (Epic). **Methods:** All current patient records were individually reviewed by DW and migrated to Epic EMR since June 4, 2022. Specific diagnoses were recorded in Medical History using ICD-10 codes that allowed analyses using the SlicerDicer module of Epic. **Results:** From Jun 4, 2022 to May 21, 2023, 2443 patients have been assessed by DW. From this clinic, 1115 had chronic HBV infection (HBsAg positive > 6 mo) and 1 had acute HBV infection. Of those with chronic HBV infection, mean age was 54 (range 18 to 97). N = 30 were co-infected with HIV. Self-identified racial identity was as follows: Chinese 528, White 145, Vietnamese 129, Black 71, Filipino 53, Indian 31, Korean 27, Middle-East 14, Other Asian 54. Of those with chronic infection, only 37 (3.3%) were HBeAg positive,19 (1.7%) were in the Immune Tolerant phase. An additional 79 had functional cure of chronic HBV infection. Antiviral treatment included Tenofovir based therapies 232 (includes N = 12 on TAF), Entecavir 220, Lamivudine 20, No treatment 650 (58.3%). Severity: history of HCC 65, ascites 11. Two individual's died during this time period: first was an Asian man at age 78, presented Mar 2023 with hypotension and large HCC and new diagnosis of hepatitis B, passed on Apr 2023. Second was a Tibeten woman at age 82, who presented with ascites in 2020 from untreated hepatitis B. Entecavir started in Aug 2020, aggressive HCC detected in Oct 2022, passed April 2023. **Conclusion:** Chronic HBV infection is a lifelong infection. Only 41.7% of this cohort were on antiviral therapy. With regular monitoring in a specialty clinic, mortality risk is low and predominately from advanced age-related comorbidity (personal observation). Only 2 deaths were noted in this study period, both referred to the clinic with end stage disease. The required monitoring was facilitated through electronic resources that are not universally available to most in Ontario, creating healthcare disparity even within the same health district.

Disclosures: The following people have nothing to disclose: David Kah Heng Wong

1367-C | LONG-TERM FOLLOW-UP OF PATIENTS WITH INCIDENTALLY DETECTED ASYMPTOMATIC HEPATITIS B

Mithun Sharma[1], Anand V. Kulkarni[1], Nagaraja Rao Padaki[2], Sowmya T R[1], Shantan Venishetty[1], Manasa Alla[1], Rajesh Gupta[1] and Nageshwar D Reddy[1], (1)Aig Hospitals, Hyderabad, India, (2)Asian Institute of Gastroenterology, Hyderabad, Telangana, India

Background: Incidentally detected asymptomatic hepatitis B (IDAHB) is found in 2.3% of subjects in India during routine screening, with an overall prevalence of 1.46%. Labeling these patients of chronic hepatitis B infection as inactive carriers have long

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

resulted in misinformation to patients leading to laxity in follow-up. This study was designed to find out the natural history of these patients who presented to a tertiary care center **Methods:** All patients with IDAHB were counseled with written documentation on the need to follow up with alanine aminotransferase(ALT), ultrasound abdomen (USG), and alpha-fetoprotein every six months and to report if there is an elevation of ALT > 70 for males and > 50 for females or if there are any abnormalities on the USG. The research coordinator will make a call if there is no update for greater than six months. **Results:** 740 patients were enrolled for follow-up from 2014 to 2017 and were followed up till January 2023. The mean duration of follow-up was 8.6 ± 3.8 years. 230(32.67%) patients defaulted in follow-up at a mean of 2.4 ± 1.2 years. 98 (13.24%) of the patients at the end of the follow-up term had converted to chronic hepatitis B requiring anti-viral therapies with a mean duration of 4.8 ± 2.1 years. The incidence of onset of hepatocellular carcinoma(HCC) was 13(1.75%) in patients on regular screening and was found in 11/240(4.58%) of those who did not follow the screening protocol. On inquiry, the majority of patients (45%) who defaulted in regular follow-up reported a belief that the disease would not spread, while an additional 21.2% reported unwillingness to spend money on conditions that did not cause symptoms. **Conclusion:** IDAHB patients become eligible for antiviral therapy on follow up, and lack of awareness of the disease despite proper counseling may hinder the detecting these patients. In addition, HCC develops more patients of even IDAHB who are not on the screening program.

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1368-C | NATURAL HISTORY OF CHRONIC HBEAG NEGATIVE INFECTION AMONG THE ANRS CO22 HEPATHER COHORT

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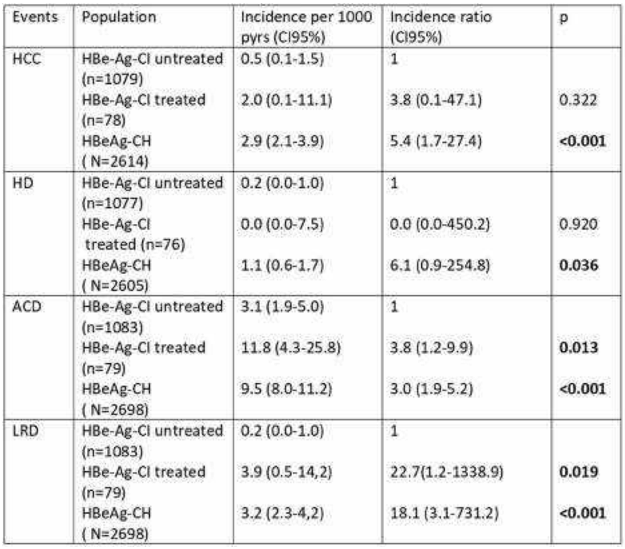
Background: Natural history of patients with HBeAg-negative chronic infection (HBeAg-CI) remains unclear regarding the loss of HBsAg, the need for treatment and their outcome. **Methods:** Among the 5174 HBs patients enrolled in the ANRS CO22 Hepather French national prospective cohort between Q3 2012 and Q4 2015, 1162 patients with HBeAg-CI were studied with a median follow-up of 5.8 years (IQR 4-7.2). At inclusion all patients had normal ALT < 40 IU/ml and HBV DNA < 2000 IU/ml. All patients were untreated and never treated by NUCs or Interferon during their past history. At inclusion, the median age was 41.9 yo (33.6-53,4). 50.4% were male. 54.8% were from African origin, 9.4% from Asia, 27.1% from Europe and 8.8% from other origins. 95% had F0-F2 fibrosis stage, 5.2% had past or current excessive alcohol consumption, 14.6% had obesity and 6.0% had diabetes. **Results:** 66 patients (5.6%) lost HBsAg. No clinical liver complications were observed. Geographical origins were not associated with HBsAg loss (7.0% for European, 5.4% for Africans, 5.5% for Asians and 4.0% for other origins). During follow-up, 1083 patients remained untreated and 79 patients (7.0%) started treatment with NUCs. Among the 1083 untreated patients, 18 died, including one death from liver end-stage disease in a patient with other cofactors alcohol and obesity. 3 patients had a hepatocellular carcinoma, 2 of them with other cofactors (overweight, diabetes and alcohol). Among the 79 patients treated, 6 died, two of them of hepatic causes, one of them with other cofactors (alcohol and HCC). The cumulative incidence per 1000 person-years (pyrs) (CI95%) of HCC, hepatic decompensation (HD), all cause of deaths (ACD), and liver related deaths (LRD), are given in the table and compared with those of 2698 chronic HBeAg negative hepatitis (HBe-Ag-CH) patients followed in the Hepather cohort. **Conclusion:** In this large cohort of HBeAg negative infection patients followed for more than 6 years, 5.6% lost HBsAg, 93% remained untreated with very low incidence of adverse events confirming the current EASL and AASLD guidelines recommendations.



Events	Population	Incidence per 1000 pyrs (CI95%)	Incidence ratio (CI95%)	p
HCC	HBe-Ag-CI untreated (n=1079)	0.5 (0.1-1.5)	1	
	HBe-Ag-CI treated (n=78)	2.0 (0.1-11.1)	3.8 (0.1-47.1)	0.322
	HBeAg-CH (N=2614)	2.9 (2.1-3.9)	5.4 (1.7-27.4)	**<0.001**
HD	HBe-Ag-CI untreated (n=1077)	0.2 (0.0-1.0)	1	
	HBe-Ag-CI treated (n=76)	0.0 (0.0-7.5)	0.0 (0.0-450.2)	0.920
	HBeAg-CH (N=2605)	1.1 (0.6-1.7)	6.1 (0.9-254.8)	**0.036**
ACD	HBe-Ag-CI untreated (n=1083)	3.1 (1.9-5.0)	1	
	HBe-Ag-CI treated (n=79)	11.8 (4.3-25.8)	3.8 (1.2-9.9)	**0.013**
	HBeAg-CH (N=2698)	9.5 (8.0-11.2)	3.0 (1.9-5.2)	**<0.001**
LRD	HBe-Ag-CI untreated (n=1083)	0.2 (0.0-1.0)	1	
	HBe-Ag-CI treated (n=79)	3.9 (0.5-14,2)	22.7(1.2-1338.9)	**0.019**
	HBeAg-CH (N=2698)	3.2 (2.3-4,2)	18.1 (3.1-731.2)	**<0.001**

Disclosures: The following people have nothing to disclose: Lucia Parlati

1369-C | NATURAL HISTORY OF DISEASE PROGRESSION IN PATIENTS WITH CHRONIC HEPATITIS B USING A LARGE NATIONWIDE POPULATION-BASED DATABASE

Nobuharu Tamaki, Masayuki Kurosaki, Yutaka Yasui, Kaoru Tsuchiya, Hiroyuki Nakanishi and Namiki Izumi, Musashino Red Cross Hospital

Background: Disease progression in patients with chronic hepatitis B remains unclear, especially in untreated patients. In this study, we aimed to investigate disease progression (hepatocellular carcinoma [HCC] development and decompensation) in patients with chronic hepatitis B using a large nationwide database. **Methods:** We used a large claims database established by the Japan Medical Data Center (JMDC Co., Ltd. Tokyo, Japan). The database consists of claims from medical institutions and annual health checkup data. Annual health checkup results consist of age, gender, physical examination, medical history, blood test results, and questionnaire information for smoking and alcohol habits. Claims data contains diagnostic ICD code, prescription, procedure/treatment code, etc. The database contains records of approximately 14 million insured persons. Among these patients, 3 million patients who have health checkup data from 2016 to 2021 were examined. Of these, 16,676 persons with chronic hepatitis B disease (based on ICD code) were included. The occurrence of new decompensation (encephalopathy, ascites, variceal bleeding) and HCC during the observation period was examined. **Results:** The mean age of the 16676 patients was 51.4 years and 69.2% were male. 3575 (21.4%) were taking nucleic acid analogs (NA). New decompensation occurred in 503 patients (3.0%) and new HCC in 116 patients (0.7%) during the observation period. The 3- and 5-year HCC incidence rates were 0.9% and 1.1%, and the 3- and 5-year decompensation rates were 2.1% and 2.9%. The 5-year HCC incidence was 3.1% and 0.6% in patients with and without NA, respectively. Although patients with NA had a significantly higher incidence of HCC, HCC was also observed in patients without NA. Age, male gender (hazard ratio [HR]:1.7), NA administration (HR:5.3), and alanine aminotransferase (ALT) every 10 IU/L (HR:1.12) were significant factors associated with the development of HCC. The 3- and 5-year decompensation rates were 4.1% and 5.2% in patients with NA and 1.5% and 2.1% in patients without NA, respectively. The significant factors associated with decompensation were age, male gender (HR: 1.4), NA administration (HR: 2.4), and ALT every 10 IU/L (HR: 1.16). In patients without NA, HCC development rates were equivalent in patients with ALT > 30, 20-30, and < 20 IU/L. Regarding the development of decompensation in patients without NA, the decompensation development was significantly higher in patients with ALT > 30 IU/L than those with ALT 20-30, and < 20 IU/L ($p < 0.01$). **Conclusion:** NA was introduced in high-risk cases for the prevention of HCC and decompensation, while a small number of cases without NA also developed HCC and decompensation, suggesting the need for further verification of the identification of high-risk groups and the criteria for NA administration.

Disclosures: Masayuki Kurosaki – Gilead: Speaking and Teaching, No, No;
Namiki Izumi – Gilead: Speaking and Teaching, No, No;
The following people have nothing to disclose: Nobuharu Tamaki, Yutaka Yasui, Kaoru Tsuchiya, Hiroyuki Nakanishi

1370-C | NEXT-GENERATION SEQUENCING OF HBV GENOTYPES CIRCULATING IN CHILE AMONG HAITIAN IMMIGRANTS AND CHILEAN PATIENTS; IDENTIFICATION OF POTENTIAL ESCAPE MUTANTS

Javier Uribe[1], Ruth Núñez[1], Karla Pino[1], Jorge Vera[1], Marcelo Lopez-Lastra[1], Alejandro Soza[1] and Francisco Fuster[2], (1)Pontificia Universidad Católica De Chile, (2) Hospital Gustavo Fricke

Background: Hepatitis B virus (HBV) infection presents different genotypes, viral variants, and escape mutants that can influence disease progression and vaccination response. HBV's prevalence and molecular characteristics in Haitian immigrants to Chile are poorly understood. This study aimed to describe the specific HBV genotypes infecting Haitian immigrants in Chile and compare them with Chilean isolates using next-generation sequencing (NGS). **Methods:** A total of 32 subjects were included in the study, comprising 8 Haitian immigrants and 24 Chileans. HBV viral DNA was sequenced using NGS, with a mean Phred score > 32, indicating high precision (> 99.9%). The raw FASTQ files were taxonomically classified using Kraken2, aligned with BWA, and variant detection was performed with LoFreq. Variants were annotated using SnpEff, and escape mutations were identified using geno2pheno. Genotyping, sub-genotyping, and serotyping were conducted using geno2pheno, HBVseq, and HBV Serotyper tools. **Results:** Chilean patients were predominantly infected with HBV genotype F1 (23 subjects) and genotype D4 (1 subject). In contrast, Haitian immigrants presented genotypes A1 (1 subject), E (1 subject), and F1 (3 subjects). Mutations were identified in preS1, preS2, S, P, X, preC, and C genes, with some representing previously reported escape mutations. Specifically, in the 'a' determinant (codons

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

121-147 of the S gen), the immunodominant portion of the HBsAg, 50 different mutations were found, and they were equally detected in the Haitian and Chilean populations (75%). **Conclusion:** This study revealed distinct HBV genotypes and potential viral escape mutants among Haitian immigrants and Chilean patients, highlighting the importance of understanding the molecular dynamic of HBV infection in different populations within a country. These findings could inform public health policies and optimize vaccination strategies for marginalized groups, such as Haitian immigrants in Chile.

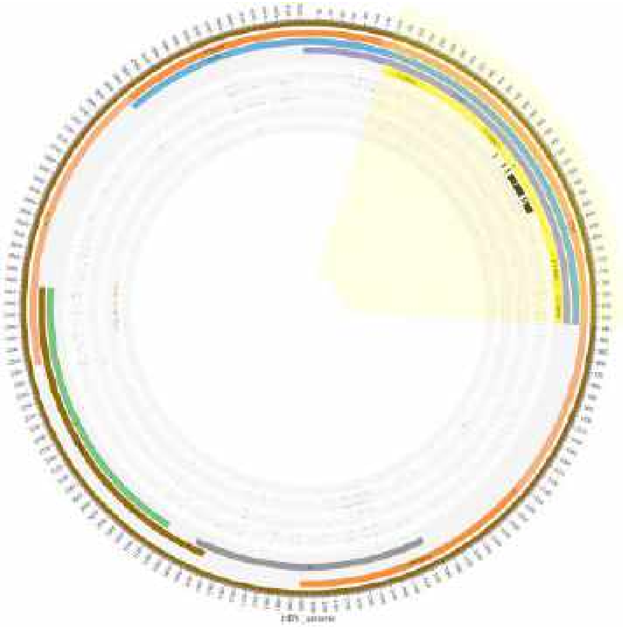

Figure 1. Variations found along the Hepatitis B virus genome in samples from Haitian individuals. The concentric circles represent, from the inside out, the variants (red stripes) found for samples 456, 413, 401, 357, 351, 204, and 75; the codons where an escape variant has been described (black stripes); the annotation of the virus proteins; and the positions along the genome. The variations shown (red stripes) are a sub-selection of the total variants, with a frequency ≥ 1% and excluding synonymous variations, insertions, and deletions. P-TP, polymerase terminal domain; P-Spacer, polymerase spacer domain; P-RT, reverse transcriptase domain; P-RNaseH, ribonuclease H activity; S-TMM, transmembrane sites 1,2,3,4 of the S protein.

Disclosures: Alejandro Soza – Gilead: Independent contractor (including contracted research), Yes, No; MSD: Independent contractor (including contracted research), No, No;

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Disclosure information not available at the time of publication: Ruth Núñez, Karla Pino, Jorge Vera, Marcelo Lopez-Lastra, Francisco Fuster

1371-C | NON-ALCOHOL FATTY LIVER DISEASE IN A PROSPECTIVE NATIONAL COHORT OF HEPATITIS B PATIENTS WITH SUBOPTIMAL RESPONSE TO ANTIVIRAL THERAPY

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Background: The non-alcohol fatty liver disease (NAFLD) had been reported in 27% of Chinese adults with chronic hepatitis B (CHB). Although coexisting NAFLD was associated with a significantly higher frequency of HBsAg seroclearance in virologically quiescent CHB, the risk of dual etiologies on outcomes and the efficacy of antivirals have not been fully characterized in CHB with persistent viremia on antiviral therapy. We aimed to compare the differences in clinical features between CHB with and without NAFLD in this subpopulation. **Methods:** In a cross-sectional prospective study from 9/3/2021 to 3/20/2023, CHB adults with a suboptimal response (SOR) to antivirals (who met the 2017 EASL guideline definition for the SOR) were enrolled from 11 centers (Hepatitis B Research Network) in China. NAFLD was identified by fibroscan with the controlled attenuation parameter (CAP) e 238 dB/m. We explored the possible roles of NAFLD in these patients by comparing clinical characteristics between the two sub-groups (presence *vs.* absence of NAFLD), including disease activity (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] as a surrogate), virological profile, and fibrosis. **Results:** Among 90 patients enrolled (Table 1), all were viremic and currently adhered to the antiviral therapy without genotypic resistance (96% taking entecavir, 1% tenofovir-DF, and 3% second-line antivirals), the median age was 39 years, 64% male, 82% HBeAg (+), and 47% had significant viremic levels (HBV DNA > 2000 IU/mL). Only 6% and 1% of them reported a history of NAFLD and diabetes, respectively. At enrollment, 43% (39/90) of them had CAP ≥ 238 dB/m and received the NAFLD diagnosis (38.5% [15/39], 46.1% [18/39], and 15.4% [6/39] were mild, moderate, and severe steatosis, respectively). CHB patients with NAFLD had a significantly higher mean body mass index (BMI: 25.5 *vs.* 21.9 kg/m^2; $p < 0.001$), higher median ALT levels (34.7 *vs.* 24.0 U/L; $p = 0.004$), higher median AST levels (23.7 *vs.* 21.0 U/L; $p = 0.02$), and higher frequency of HBV DNA > 2000 IU/mL (64.1% *vs.* 33.3%; $p = 0.04$). **Conclusion:** We observed a high frequency of NAFLD (43%) in CHB patients with SOR to antiviral therapy. The presence of NAFLD was associated with high levels of ALT or AST, BMI > 25 Kg/m^2, and HBV DNA > 2000 IU/mL. Because of the association between NAFLD and death from cancer or cardiovascular events, identifying NAFLD and managing adverse metabolic profiles are critically important in CHB patients with viremia on antiviral therapy, which already carries a high risk for liver cancer. Grant support: Gilead Science, Inc.

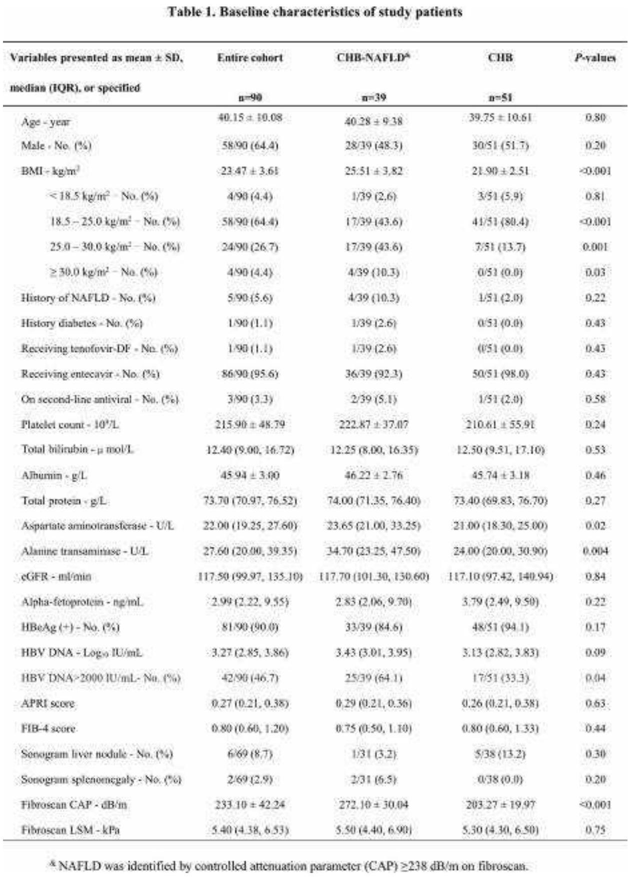


Table 1. Baseline characteristics of study patients

Variables presented as mean ± SD, median (IQR), or specified	Entire cohort n=90	CHB-NAFLD^a n=39	CHB n=51	P-values
Age - year	40.15 ± 10.08	40.28 ± 9.38	39.75 ± 10.61	0.80
Male - No. (%)	58/90 (64.4)	28/39 (48.3)	30/51 (51.7)	0.20
BMI - kg/m^2	23.47 ± 3.61	25.51 ± 3.82	21.90 ± 2.51	<0.001
< 18.5 kg/m^2 - No. (%)	4/90 (4.4)	1/39 (2.6)	3/51 (5.9)	0.81
18.5 – 25.0 kg/m^2 - No. (%)	58/90 (64.4)	17/39 (43.6)	41/51 (80.4)	<0.001
25.0 – 30.0 kg/m^2 - No. (%)	24/90 (26.7)	17/39 (43.6)	7/51 (13.7)	0.001
≥ 30.0 kg/m^2 - No. (%)	4/90 (4.4)	4/39 (10.3)	0/51 (0.0)	0.03
History of NAFLD - No. (%)	5/90 (5.6)	4/39 (10.3)	1/51 (2.0)	0.22
History diabetes - No. (%)	1/90 (1.1)	1/39 (2.6)	0/51 (0.0)	0.43
Receiving tenofovir-DF - No. (%)	1/90 (1.1)	1/39 (2.6)	0/51 (0.0)	0.43
Receiving entecavir - No. (%)	86/90 (95.6)	36/39 (92.3)	50/51 (98.0)	0.43
On second-line antiviral - No. (%)	3/90 (3.3)	2/39 (5.1)	1/51 (2.0)	0.58
Platelet count - 10^9/L	215.90 ± 48.79	222.87 ± 37.07	210.61 ± 55.91	0.24
Total bilirubin - μ mol/L	12.40 (9.00, 16.72)	12.25 (8.00, 16.35)	12.50 (9.51, 17.10)	0.53
Albumin - g/L	45.94 ± 3.00	46.22 ± 2.76	45.74 ± 3.18	0.46
Total protein - g/L	73.70 (70.97, 76.52)	74.00 (71.35, 76.40)	73.40 (69.83, 76.70)	0.27
Aspartate aminotransferase - U/L	22.00 (19.25, 27.60)	23.65 (21.00, 33.25)	21.00 (18.30, 25.00)	0.02
Alanine transaminase - U/L	27.60 (20.00, 39.35)	34.70 (23.25, 47.50)	24.00 (20.00, 30.90)	0.004
eGFR - ml/min	117.50 (99.97, 135.10)	117.70 (101.30, 130.60)	117.10 (97.42, 140.94)	0.84
Alpha-fetoprotein - ng/mL	2.99 (2.22, 9.55)	2.83 (2.06, 9.70)	3.79 (2.49, 9.50)	0.22
HBeAg (+) - No. (%)	81/90 (90.0)	33/39 (84.6)	48/51 (94.1)	0.17
HBV DNA - Log$_{10}$ IU/mL	3.27 (2.85, 3.86)	3.43 (3.01, 3.95)	3.13 (2.82, 3.83)	0.09
HBV DNA>2000 IU/mL- No. (%)	42/90 (46.7)	25/39 (64.1)	17/51 (33.3)	0.04
APRI score	0.27 (0.21, 0.38)	0.29 (0.21, 0.36)	0.26 (0.21, 0.38)	0.63
FIB-4 score	0.80 (0.60, 1.20)	0.75 (0.50, 1.10)	0.80 (0.60, 1.33)	0.44
Sonogram liver nodule - No. (%)	6/69 (8.7)	1/31 (3.2)	5/38 (13.2)	0.30
Sonogram splenomegaly - No. (%)	2/69 (2.9)	2/31 (6.5)	0/38 (0.0)	0.20
Fibroscan CAP - dB/m	233.10 ± 42.24	272.10 ± 30.04	203.27 ± 19.97	<0.001
Fibroscan LSM - kPa	5.40 (4.38, 6.53)	5.50 (4.40, 6.90)	5.30 (4.30, 6.50)	0.75

[a] NAFLD was identified by controlled attenuation parameter (CAP) ≥238 dB/m on fibroscan.

Disclosures: Calvin Pan Pan – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

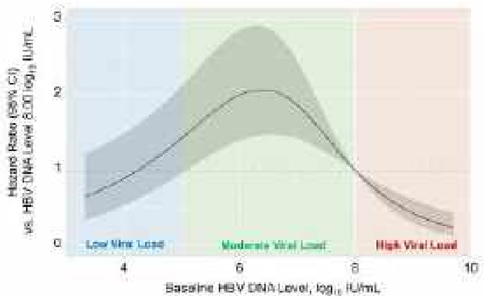
The following people have nothing to disclose: Wen Xie, Lihua Cao, Shuangsuo Dang, Liying Zhu, Dongliang Yang, Yueyong Zhu, Xiaoguang Dou, Zhiliang Gao, Binbin Chen, Xinxin Zhang, Yuming Wang, Yan Liu, Ting Zhang

1372-C | NON-LINEAR ASSOCIATION OF BASELINE VIRAL LOAD WITH ON-TREATMENT HEPATOCELLULAR CARCINOMA RISK IN CHRONIC HEPATITIS B★

Won-Mook Choi[1], *Gi-Ae Kim*[2], *Jonggi Choi*[3], *Gwang Hyeon Choi*[4], *Yun Bin Lee*[5], *Dong Hyun Sinn*[6] *and Young-Suk Lim*[1], *(1)Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South), (2)Kyung Hee University School of Medicine, (3)Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, (4)Seoul National University Bundang Hospital, Seoul National University College of Medicine, (5)Seoul National University College of Medicine, (6)Samsung Medical Center*

Background: The association between baseline pretreatment serum hepatitis B virus (HBV) DNA levels and on-treatment hepatocellular carcinoma (HCC) risk remains controversial in chronic hepatitis B (CHB) patients. We aimed to investigate the association between baseline HBV viral load and on-treatment HCC risk in non-cirrhotic CHB patients. **Methods:** Using a multicenter historical cohort study including 4,693 non-cirrhotic adult patients with HBeAg-negative and HBeAg-positive CHB who initiated antiviral treatment, HCC risk was estimated by baseline HBV viral load as a categorical variable. **Results:** During a median of 7.6 years of antiviral treatment, 193 patients developed HCC (0.53 per 100 person-years). Baseline HBV DNA level was independently associated with on-treatment HCC risk in a non-linear, parabolic pattern. Patients with moderate baseline viral loads (5.00–7.99 log$_{10}$ IU/mL) exhibited the highest HCC risk (adjusted hazard ratio [aHR], 2.60; 95% confidence interval [CI], 1.61–4.22; $p < 0.001$), followed by those with low viral loads (3.30–4.99 log$_{10}$ IU/mL; aHR, 1.66; 95% CI, 0.88–3.12; $p = 0.11$). Patients with high viral loads (≥ 8.00 log$_{10}$ IU/mL) presented the lowest HCC risk. Particularly, patients with baseline HBV DNA levels 6.00–6.99 log$_{10}$ IU/mL had the highest on-treatment HCC risk (aHR, 3.36; 95% CI, 2.00–5.65; $p < 0.001$) compared to those with baseline HBV DNA levels ≥ 8.00 log$_{10}$ IU/mL. These findings were more prominent among younger patients (< 45 y) and those with less advanced hepatic fibrosis. **Conclusion:** Patients with moderate baseline viral load, particularly around 6 $\log_{10}$ IU/mL, demonstrated the highest on-treatment HCC risk, despite long-term antiviral treatment. Early initiation of antiviral treatment, tailored to viral load, should be considered to minimize HCC risk in non-cirrhotic adult CHB patients.

Figure. Adjusted hazard ratio for the on-treatment HCC risk by baseline HBV DNA levels in CHB patients treated with entecavir or TDF.
Hazard ratio plot adjusted for age, sex, platelet count, HBeAg-positivity, levels of ALT, and FIB-4 index with HBV DNA level of 8.00 $\log_{10}$ IU/mL as a reference.
The black line represents the point estimates, and the grey zone indicates 95% confidence intervals.
ALT, alanine aminotransferase; CHB, chronic hepatitis B; FIB-4, fibrosis-4; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TDF, tenofovir disoproxil fumarate.



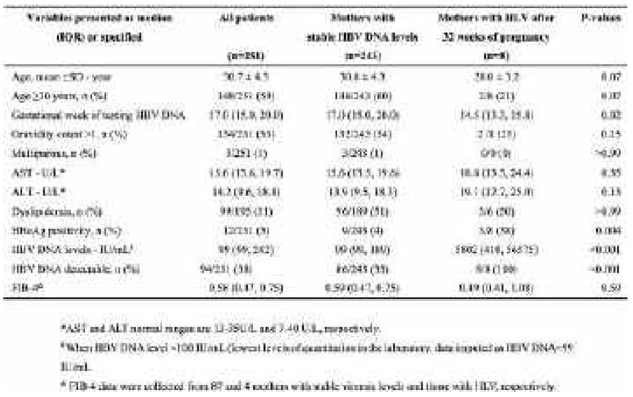
Disclosures: The following people have nothing to disclose: Won-Mook Choi, Gi-Ae Kim, Jonggi Choi, Gwang Hyeon Choi, Yun Bin Lee, Dong Hyun Sinn, Young-Suk Lim

1373-C | PREDICTORS FOR HIGH LEVELS OF VIREMIA AT DELIVERY IN CHB MOTHERS WITHOUT INDICATIONS FOR ANTIVIRAL PROPHYLAXIS UP TO GESTATIONAL WEEK 32

Shi Ouyang[1], Yawen Geng[1,2], Tingting Peng[1] and Calvin Pan Pan[1,3], (1)The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhuo, China, (2) North China University of Technology, Tangshan, China, (3)NYU Grossman School of Medicine

Background: International guidelines recommend antiviral prophylaxis initiated at gestational weeks of 24-28 for chronic hepatitis B (CHB) mothers with high levels of viremia (HLV), i.e., HBV DNA > 200,000 IU/mL to prevent vertical transmission. In mothers without HLV during the first and second trimesters, the frequency of developing HLV at delivery and missing the opportunity for antiviral prophylaxis has not been elucidated. We aimed to study the incidence of HLV before delivery and predictors in mothers without HLV before gestational week 32. **Methods:** In a retrospective cohort study at a university medical center in China from 1/2020 to 9/2022, consecutive CHB mothers who had HBV DNA tested before and after gestational week 32 were eligible. We excluded those with HLV before or at gestational week 32, or taking antiviral therapy at any time during pregnancy. Mothers with and without HLV after gestational week 32 were identified and compared for their baseline parameters obtained at the earliest visit with virological tests during pregnancy. We analyzed the frequency and predictors for HLV occurring after gestational week 32 until delivery. **Results:** We enrolled 251 mothers. At baseline, the mean (SD) age was 30.7 (±4.3) years, the median (range) gestational week was 17 (12-24), five percent was HBeAg (+), and the median (IQR) HBV DNA was 99 (99, 242) IU/mL (Table 1). All mothers had HBV DNA < 200,000 IU/mL before or at gestational week 32, and three percent (8/251) of them presented with HBV DNA > 200,000 IU/mL after gestational week 32. When comparing mothers with and without HLV before delivery, there were statistically significant differences in several baseline variables including HBV DNA tests performed at the time of median (IQR) gestational weeks (14.5 [13.3, 15.8] vs 17.0 [15.0, 20.0]; $p = 0.02$), HBeAg positive status (38% [3/8] vs 4% [9/243], $p = 0.004$), and median (IQR) HBV DNA levels (5,802 [410; 56,575] vs 99 [99,189] IU/mL; $p < 0.001$). **Conclusion:** Three percent of CHB mothers without HLV before or at 32 weeks of pregnancy progressed to the status of HBV DNA > 200,000 IU/mL before delivery, which increased the risk for HBV vertical transmission. HBeAg positive status, HBV DNA levels ranging from 2 to 4 $\log_{10}$ IU/mL, and testing HBV DNA in the 1st trimester without repeating it thereafter were the risk factors. Close monitoring of mothers with these features or considering preemptive antiviral prophylaxis before gestational week 32 might be necessary to reduce the risk of transmission.

Table 1. Baseline characteristics of mothers at the time of the first HBV virological testing



Variables presented as median (IQR) or specified	All patients (n=251)	Mothers with stable HBV DNA levels (n=243)	Mothers with HLV after 32 weeks of pregnancy (n=8)	P-values
Age, mean ±SD - year	30.7 ± 4.3	30.8 ± 4.3	28.0 ± 3.2	0.07
Age ≥30 years, n (%)	148/251 (59)	146/243 (60)	2/8 (21)	0.07
Gestational week of testing HBV DNA	17.0 (15.0, 20.0)	17.0 (15.0, 20.0)	14.5 (13.3, 15.8)	0.02
Gravidity count >1, n (%)	139/251 (55)	132/243 (54)	2/8 (25)	0.15
Multiparous, n (%)	3/251 (1)	3/243 (1)	0/8 (0)	>0.99
AST - U/L*	15.6 (13.6, 19.7)	15.6 (13.5, 19.6)	18.8 (13.5, 24.4)	0.35
ALT - U/L*	14.2 (9.6, 18.8)	13.9 (9.5, 18.3)	19.1 (12.7, 25.0)	0.13
Dyslipidemia, n (%)	99/195 (51)	96/189 (51)	3/6 (50)	>0.99
HBeAg positivity, n (%)	12/251 (5)	9/243 (4)	3/8 (38)	0.004
HBV DNA levels - IU/mL†	99 (99, 242)	99 (99, 189)	5802 (410, 56575)	<0.001
HBV DNA detectable, n (%)	94/251 (38)	86/243 (35)	8/8 (100)	<0.001
FIB-4‡	0.58 (0.47, 0.75)	0.59 (0.47, 0.75)	0.49 (0.41, 1.08)	0.59

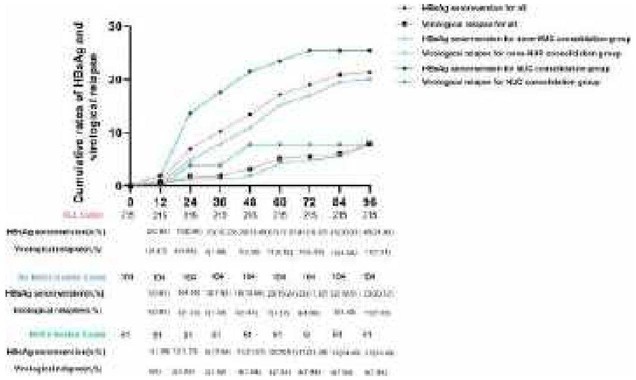
*AST and ALT normal ranges are 13-35 U/L and 7-40 U/L, respectively.
†When HBV DNA level <100 IU/mL (lowest level of quantitation in the laboratory, data imputed as HBV DNA=99 IU/mL.
‡ FIB-4 data were collected from 87 and 4 mothers with stable viremia levels and those with HLV, respectively.

Disclosures: Calvin Pan Pan – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
The following people have nothing to disclose: Shi Ouyang, Yawen Geng, Tingting Peng

1374-C | PREDICTORS OF HBsAg SEROREVERSION IN PATIENTS ACHIEVING SERUM HBsAg LOSS WITH PEGYLATED INTERFERON-BASED THERAPY

Na Gao[1], Haishi Wu[1], Huiying Yu[1], Jing Zhang[1], Zhishuo Mo[1], Qiyi Zhao[1,2,3] and Zhiliang Gao[1,2,3], (1) Department of Infectious Diseases, Third Affiliated Hospital of Sun Yat-Sen University, (2)Guangdong Key Laboratory of Liver Disease Research, the Third Affiliated Hospital of Sun Yat-Sen University, (3)Key Laboratory of Tropical Disease Control (Sun Yat-Sen University)

Background: HBsAg loss is a well-accepted treatment endpoint for chronic hepatitis B. However, it is unclear whether nucleos(t)ide analogue (NUC) consolidation confers clinical benefits after HBsAg seroclearance with pegylated interferon-based therapy, especially in HBsAg seroreversion and HBsAb production. **Methods:** Patients with CHB who achieved serum HBsAg loss with pegylated interferon (PEG-IFN)-based therapy were enrolled and followed up 96 weeks. HBsAg loss was confirmed by two or more consecutive negative-qualitative HBsAg results. The primary endpoint was HBsAg seroreversion. Secondary endpoint was virological relapse. Using multivariable logistic regression analysis, we determined factors associated with HBsAg seroreversion. **Results:** 215 patients achieving HBsAg seroclearance were enrolled in the present study including 164 and 51 patients in the none-NUC consolidation group and NUC consolidation group, respectively. In NUC consolidation group, patients received (quartile [Q] 1, Q3, 23.00, 96.00) weeks oral NUCs therapy. There were no significant difference of gender, treatment time of PEG-IFN to attain HBsAg loss ($p = 0.744$), consolidation treatment time of PEG-IFN ($p = 0.658$), serum ALT ($p = 0.681$), serum HBsAb($p = 0.052$), compensated cirrhosis ($p = 0.064$) at the baseline of follow-up and also the HBsAg level before PEG-IFN treatment ($p = 0.979$). The age in NUC consolidation group was older than none-NUC consolidation group[(44.61 ± 7.84) vs. (39.89 ± 8.33), $p < 0.001$]. At week 96, the rate of HBsAg seroreversion (20.12% vs. 24.49%, $p = 0.414$) and virological relapse (7.83% vs 7.84%, $p = 1.000$) were similar between the none-NUC consolidation group and NUC consolidation group. Furthermore, HBsAb production rate during 96-week follow-up in patients with negative HBsAb at ceasing time of PEG-IFN did not display statistical discrepancies between the none-NUC consolidation and NUC consolidation groups(62.86% vs. 58.82%, $p = 0.779$). For patients with positive serum HBsAb at ceasing time of PEG-IFN, sustainable positive HBsAb rate during 96-week follow-up showed no statistical significance between the two groups (77.17% vs. 69.70%, $p = 0.373$). HBsAb titer at ceasing PEG-IFN therapy was independent predictors of HBsAg seroreversion (odds ratio [OR] 0.419, 95% confidence interval [CI]: 0.272–0.645, $p < 0.001$). **Conclusion:** NUC consolidation therapy were not significantly associated with HBsAb production and HBsAg seroreversion in patients achieving serum HBsAg loss with PEG-IFN-based therapy.

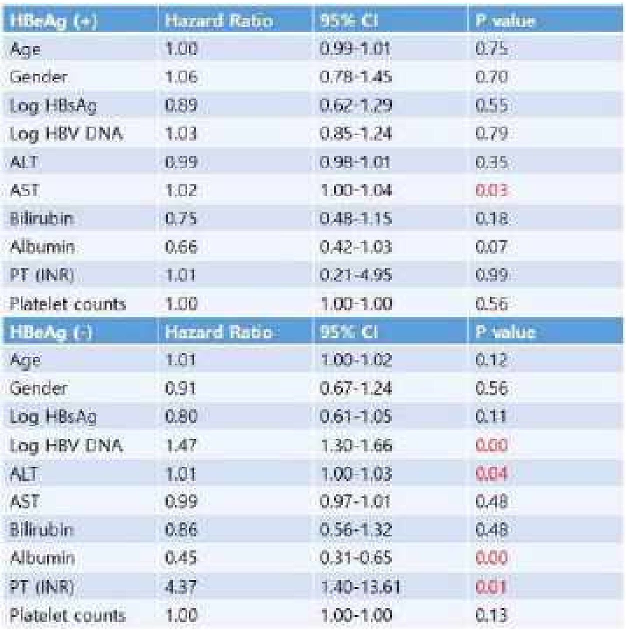


Disclosures: The following people have nothing to disclose: Na Gao, Haishi Wu, Huiying Yu, Jing Zhang, Zhishuo Mo, Qiyi Zhao, Zhiliang Gao

1375-C | PREDICTORS OF HEPATITIS FLARE AND INITIATION OF ANTIVIRAL THERAPY IN NUCLEOS(T)IDE-NAÏVE CHRONIC HEPATITIS B IN GREY ZONE

Yunjeong Lee and Jin-Wook Kim, Seoul National University Bundang Hospital

Background: Chronic hepatitis B (CHB) patients without significant liver inflammation, i.e., immune-tolerant or HBeAg-negative inactive carrier phase, are followed without nucleos(t)ide analogs (NAs) until transaminase level elevates. A substantial number of patients show low/normal transaminase with persistent viremia, known as "grey zone" phase. It is unclear, however, which patients in grey zone have high probability of hepatitis-flare. This study aimed to investigate the clinical and laboratory characteristics which may predict the hepatitis flare and becoming initiated of antiviral therapy in nucleos(t)ide-naïve patients with low/normal transaminase level (both AST/ALT < 80 U/L), along with HBV DNA levels > 2,000 IU/mL in HBeAg-negative and > 20,000 IU/mL in HBeAg-positive CHB. **Methods:** We reviewed nucleos(t)ide analogue-naïve, noncirrhotic CHB patients with low/normal transaminase level (both AST/ALT < 80 U/L) seen at our hospital between April 2003 and April 2023. 467 HBeAg-positive patients with HBV DNA level > 20,000 IU/mL and 2,008 HBeAg-negative patients with HBV DNA level > 2,000 IU/mL were included in our analysis. The Cox regression model was used to identify the factors associated with initiation of antiviral therapy throughout the follow-up period in each group. Age, gender, serum AST, ALT, albumin, prothrombin time (INR), bilirubin, platelet counts, HBsAg level as well as the HBV DNA level were tested. **Results:** In the HBeAg-negative CHB, lower serum albumin (hazard ratio [HR] = 0.45, 95% confidence interval [CI]: 0.31–0.65, p value = 0.00) and prolonged prothrombin time (HR = 4.37, 95% CI: 1.40–13.61, p value = 0.01) along with higher serum ALT and HBV DNA level were associated with the initiation of antiviral therapy. In contrast, there were no statistically significant independent factors associated with initiation of antiviral therapy other than higher baseline serum AST levels in HBeAg-positive CHB. **Conclusion:** Decreased serum albumin level and prolonged prothrombin time along with high baseline HBV DNA levels were predictive of the hepatitis flare and initiation of NA therapy in HBeAg-negative grey zone CHB patients. In HBeAg-positive grey zone, only elevated baseline AST levels were associated with hepatitis flare.



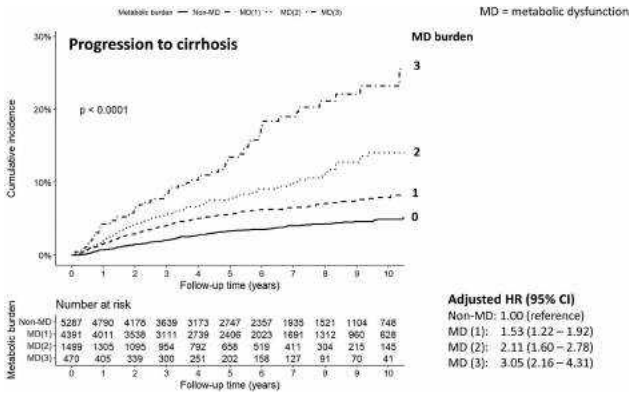
HBeAg (+)	Hazard Ratio	95% CI	P value
Age	1.00	0.99-1.01	0.75
Gender	1.06	0.78-1.45	0.70
Log HBsAg	0.89	0.62-1.29	0.55
Log HBV DNA	1.03	0.85-1.24	0.79
ALT	0.99	0.98-1.01	0.35
AST	1.02	1.00-1.04	0.03
Bilirubin	0.75	0.48-1.15	0.18
Albumin	0.66	0.42-1.03	0.07
PT (INR)	1.01	0.21-4.95	0.99
Platelet counts	1.00	1.00-1.00	0.56
HBeAg (-)	**Hazard Ratio**	**95% CI**	**P value**
Age	1.01	1.00-1.02	0.12
Gender	0.91	0.67-1.24	0.56
Log HBsAg	0.80	0.61-1.05	0.11
Log HBV DNA	1.47	1.30-1.66	0.00
ALT	1.01	1.00-1.03	0.04
AST	0.99	0.97-1.01	0.48
Bilirubin	0.86	0.56-1.32	0.48
Albumin	0.45	0.31-0.65	0.00
PT (INR)	4.37	1.40-13.61	0.01
Platelet counts	1.00	1.00-1.00	0.13

Disclosures: The following people have nothing to disclose: Yunjeong Lee, Jin-Wook Kim

1376-C | PRE-EXISTING AND NEWLY-DEVELOPED METABOLIC DYSFUNCTIONS INCREASE THE RISKS OF CIRRHOSIS AND ITS COMPLICATIONS IN CHRONIC HEPATITIS B PATIENTS

Shang-Chin Huang[1,2,3], Tung-Hung Su[4], Tai-Chung Tseng[2], Chi-Ling Chen[3], Shih-Jer Hsu[2], Chen-Hua Liu[4], Sih-Han Liao[5], Chun-Ming Hong[4], Ting-Yuan Lan[6], Hung-Chih Yang[2], Chun-Jen Liu[4], Pei-Jer Chen[4] and Jia-Horng Kao[4], (1)National Taiwan University Hospital Bei-Hu Branch, Taiwan, (2)National Taiwan University Hospital, Taiwan, (3)National Taiwan University College of Medicine, (4)National Taiwan University Hospital, (5) National Taiwan University Cancer Center, Taipei City, Taiwan, (6)National Taiwan University Hospital Hsin-Chu Branch

Background: Cirrhosis is the major adverse outcome of chronic hepatitis B (CHB). We aimed to explore the impact of pre-existing and newly-developed metabolic comorbidities on the risks of cirrhosis and its complications in CHB patients. **Methods:** Patients with CHB were consecutively recruited at the National Taiwan University Hospital. The presence of metabolic dysfunction (MD) was based on the criteria of type 2 diabetes mellitus (DM), overweight/obesity, or e two other metabolic risk abnormalities. Patients were categorized into MD and non-MD groups based on these criteria. **Results:** From 2006 to 2021, 11,647 treatment-naïve non-cirrhotic CHB patients were included with a median follow of 5.2 years. Patients in the MD group (n = 6,360) had older age and lower HBV DNA levels than non-MD patients (n = 5,287). After adjustment for clinical and viral factors, MD patients had significantly higher risks of cirrhosis (adjusted hazard ratio [aHR]: 1.75, 95% confidence interval [CI]: 1.42 – 2.16, $p < 0.001$) and cirrhotic complications (aHR: 2.51, 95% CI: 1.31 – 4.84, $p = 0.006$) than non-MD patients, with a dose-dependent effect of MD on cirrhosis (aHR: 1.45 per MD increase, 95% CI: 1.31 – 1.60, $p < 0.001$) and the complications (aHR: 1.63 per MD increase, 95% CI: 1.24 – 2.14, $p < 0.001$). Furthermore, in patients without pre-existing DM, the newly-developed DM during the follow-up additively increased the risk of cirrhotic complications (aHR: 2.13, 95% CI: 1.04 – 4.37, $p = 0.040$). The MD group with hepatic steatosis had a higher risk of cirrhosis than the steatosis-only non-MD group in a dose-dependent manner (aHR: 1.46 per MD increase, 95% CI: 1.23 – 1.72, $p < 0.001$). Sensitivity analyses, including the inverse probability of treatment weighting (IPTW) and multiple imputation, confirmed the robustness of these results. **Conclusion:** Concurrent and newly-developed metabolic dysfunctions increase the risks of cirrhosis and cirrhotic complications in CHB patients, independent of hepatic steatosis. Identifying and managing metabolic comorbidities in CHB are thus critical to prevent liver disease progression.



Disclosures: The following people have nothing to disclose: Shang-Chin Huang, Tung-Hung Su, Tai-Chung Tseng, Chi-Ling Chen, Shih-Jer Hsu, Chen-Hua Liu, Sih-Han Liao, Chun-Ming Hong, Ting-Yuan Lan, Hung-Chih Yang, Chun-Jen Liu, Pei-Jer Chen, Jia-Horng Kao

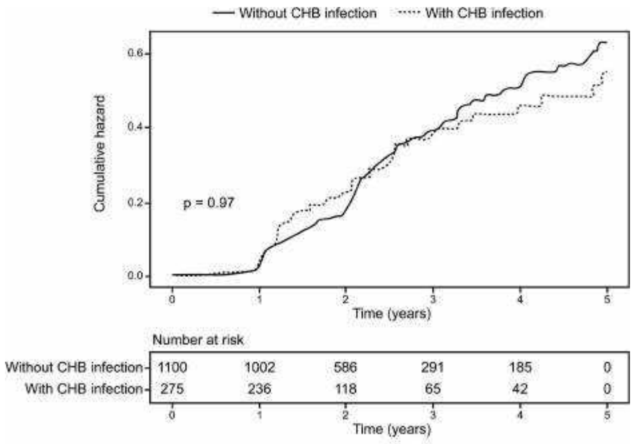
1377-C | PREVALENCE AND INCIDENCE OF OSTEOPENIA AND OSTEOPOROSIS IN PATIENTS WITH CHRONIC HEPATITIS B: A COHORT STUDY IN SOUTH KOREA

Hye Won Lee[1,2,3], Sungshin Kwon[4], Yeo Rae Moon[5], Hyunjung Ahn[5], Juyeon Lee[5] and Sang Hoon Ahn[1,2,3], (1)Yonsei Liver Center, Severance Hospital, Seoul, South Korea, (2)Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea, (3)Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, South Korea, (4) Gilead Sciences Korea, Ltd., Seoul, South Korea, (5) Kakao Healthcare Corp., Seoul, South Korea

Background: Despite recent findings that patients with chronic hepatitis B (CHB) had higher risk of osteoporosis/fracture,[1] awareness of metabolic bone diseases in patients with CHB is low among hepatologists. Assessment of bone health may be beneficial in evaluating and monitoring treatment plans for patients with CHB. Here, we report the epidemiology and risk factors associated with osteopenia/osteoporosis in CHB patients in South Korea. **Methods:** This retrospective cohort study included patients ≥ 19 years with or without CHB who went through bone mineral density (BMD) testing at least twice and with their first BMD test date in 2005–2021 at Severance Hospital. Patients with liver cancer prior to the first BMD test, hepatitis C infection at baseline, or a follow-up observation period of < 6 months from the first BMD test were excluded. Demographic factors (i.e., age, sex), and comorbidities for CHB and non-CHB patients were matched at a 1:4 ratio based on propensity scores. Univariate and multivariate Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and their 95% confidence intervals (CI) for assessing the risk of osteoporosis. **Results:** Overall, the incidence rate of osteopenia/osteoporosis in CHB and non-CHB patients was 25.8% and 28.7%, respectively. After propensity matching, 275 CHB patients (mean age: 57.8 y) and 1,100 non-CHB patients (mean age: 57.9 y) who had normal BMD in the first BMD test were further analyzed. In the second BMD test, 73.8%, 24.7%, and 1.5% of CHB patients and 70.7%, 26.5% and 2.8% of non-CHB patients, had normal BMD, osteopenia, and osteoporosis, respectively. Significant risk factors (HR [95% CI]) for osteoporosis in CHB patients were age (1.00 [1.00–1.00]), body mass index (BMI) ≥ 25 (0.65 [0.50–0.84]), chronic kidney disease (2.10 [1.50–2.80]), and proton pump inhibitor use (0.78 [0.62–0.99]) based on the multivariate analysis. The difference between the cumulative hazard for patients with or without CHB was not statistically significant ($p = 0.97$; Figure 1). **Conclusion:** In this cohort, CHB patients showed similar risks of osteopenia/osteoporosis compared to non-CHB patients. In addition to providing closer monitoring for CHB patients with greater bone disease risk, further studies of bone disease in CHB patients may help to understand the factors that impact bone health in CHB patients.

References:

1. Oh H, et al. Aliment Pharmacol Ther 2020;52: 371–381.



CHB: chronic hepatitis B

Disclosures: Sungshin Kwon – Gilead Sciences Inc.: Employee, Yes, No; Gilead Sciences Inc.: Stock – privately held company (individual stocks and stock options), Yes, No;

Sang Hoon Ahn – SL Vaxigen: Advisor, No, Yes; Samil: Advisor, No, Yes; Roche: Advisor, No, Yes; Janssen: Advisor, No, Yes; Inovio: Advisor, No, Yes; Ildong: Advisor, No, Yes; GSK: Advisor, No, Yes; GreenCross:

Advisor, No, Yes; Gilead Sciences Inc.: Advisor, Yes, No; GeneOne Life Science: Advisor, No, Yes; Brii: Advisor, No, Yes; Assembly Biosciences: Advisor, No, Yes; Arbutus: Advisor, No, Yes; Aligos: Advisor, No, Yes; Abbvie: Advisor, No, Yes; Vaccitech: Advisor, No, Yes; Vir Biotechnology: Advisor, No, Yes; Yuhan: Advisor, No, Yes;

The following people have nothing to disclose: Hye Won Lee, Yeo Rae Moon, Hyunjung Ahn, Juyeon Lee

1378-C | PREVALENCE OF HDV INFECTION AND LIVER DISEASE SEVERITY IN A LARGE COHORT OF HBsAg POSITIVE PATIENTS IN TWO BIG URBAN ÁREAS IN SPAIN

Pablo Ryan[1,2], Sabela Lens[3,4], Antonio Madejon[4,5], Jorge Valencia[1,2], Ana Martínez-Alcocer[3,4], Guillermo Cuevas[1,2], Xavier Forns[3,4] and Javier Garcia-Samaniego[4,5], (1)Hospital Universitario Infanta Leonor, Madrid, Spain, (2)Ciber De Enfermedades Infecciosas (CIBERINFEC), (3)Idibaps - Hospital Clínic, Barcelona, Spain, (4)Ciber De Enfermedades Hepáticas y Digestivas (CIBEREHD), (5)Hepatology Unit, Hospital Universitario La Paz, Spain

Background: The prevalence of hepatitis delta virus (HDV) infection in patients with chronic HBV infection varies across studies. The aims of the study were to assess the prevalence of HDV and to investigate the impact of HDV viremia in the severity of hepatic disease. **Methods:** A retrospective study was conducted in 3 hospitals from the two biggest cities in Spain (Madrid and Barcelona). Sociodemographic data was collected, and the medical records of patients with hepatitis B were also reviewed. All participants had a positive hepatitis B surface antigen (HBsAg). The prevalence of HDV was calculated and a descriptive analysis of patients with HDV infection was performed. The data were collected using REDCap. **Results:** Of 2241 HBsAg-positive participants, the prevalence of HDV coinfection was 4.5% (103/2241) and 39% of HDV-positive individual's had active HDV replication (detectable HDV-RNA). The median age was 54 (47-61) years, 65 (63%) were male and 35% were non-native. Main risk factors for HBV/HDV were unknown route (64%), intrafamilial transmission (18%), intravenous drug use (14%) and men who had sex with men who engaged in unsafe sexual behaviors (3%). Of the 103 patients with HBV/HDV coinfection, 16 (16%) had been exposed to HCV and 14 (14%) were coinfected with HIV. Regarding liver disease severity, 11% had advanced liver fibrosis (F3) and 51 (50%) had cirrhosis (F4), based on transient elastography or liver biopsy. Of those with liver cirrhosis and according to the Child-Pugh score, patients were classified as: A (26%), B (34%) and C (40%). Of these patients, 19 (18%) were on the waiting list for liver transplantation and 10 (10%) had been diagnosed with a hepatocellular carcinoma. Ten patients (14%) had received pegylated interferon, but of these, 7 patients still had detectable HDV-RNA. In a multivariate regression analysis, the only variable associated with liver cirrhosis was the presence of detectable HDV-RNA (OR 8.1 [95% CI, 2.9-22.7] $p < 0.001$). **Conclusion:** The prevalence of HDV infection in HBsAg positive patients in a large urban Spanish cohort was 4.5 %. The presence of cirrhosis was very common, particularly in patients with detectable HDV-RNA. Only a minority had had past exposure to IFN-based therapies.

Disclosures: Pablo Ryan – AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; MSD: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Consultant, No, No; Abbvie: Speaking and Teaching, No, No; Gilead: Speaking and Teaching, No, No; ViiV: Speaking and Teaching, No, No;

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The following people have nothing to disclose: Sabela Lens, Antonio Madejon, Jorge Valencia, Ana Martínez-Alcocer, Guillermo Cuevas, Xavier Forns

1379-C | PREVALENCE OF HEPATITIS B AND D VIRUS AMONG A NATIONALLY REPRESENTATIVE INSURED POPULATION IN THE UNITED STATES

Norah Terrault[1], Sacha Satram[2], Michael A. Chattergoon[3], Christopher Dieyi[4], Jason Maynard[4], Radhika Trivedi[4], Richard Coppola[4] and Nancy Reau[5], (1)University of Southern California, (2)Vir Biotechnology, (3)Vir Biotechnology, Inc, (4)Statinmed, LLC, (5)Rush Medical College, Chicago, IL

Background: Hepatitis D virus (HDV) is an incomplete human RNA virus that requires chronic hepatitis B (HBV) infection for replication. HDV is the most severe form of viral hepatitis and presents as a co-infection (simultaneous infection) or superinfection (acquired infection) with HBV. The true prevalence of HBV and HDV remains unclear in the United States (US), given that HBV is not a nationally reportable condition, and many prevalence estimates rely on small studies from special high-risk subpopulations. The aim of this study is to provide updated prevalence estimates for HBV and HDV using a large, population-based administrative claims database. **Methods:** This cross-sectional, prevalence study used data from an all-payer claims database, from January 1, 2014 to December 31, 2022. The database contains information on 80% of the US insured population. Prevalence of HBV was defined among all patients in the database (N = 278,679,590), while prevalence of HDV was defined among patients with HBV. Patients with HBV and HDV were identified by the presence of e 2 International Classification of Diseases 9th/10th Clinical Revision (ICD-9/-10-CM) diagnoses codes, at least 1 month apart to exclude rule out diagnoses (i.e. patients screened but not diagnosed). Baseline demographic characteristics (age at diagnosis, sex, US residential region, and race) were assessed. **Results:** The prevalence of HBV was 0.2% (n = 548,722). The majority of HBV patients were adults (aged 18+ years; 99%), male (54%), located in the Northeast (36%), and enrolled under Medicaid (42%). Where race information was available (34%), most were White (48%) or Asian (36%). Among the patients with HBV, the prevalence of HDV was 2.8% (n = 15,065), with the majority being adults (97%), male (52%), located in the North central region (42%), and enrolled under Medicaid (56%). Among those with available race information (38%), most were White (43%) or Black (34%). **Conclusion:** This is the largest study to date on the diagnosed prevalence of HBV and HDV in the US and provides further support of a previously reported 3% overall prevalence of HDV among HBV patients. A robust definition of HBV and HDV that required confirmation of at least 2 diagnostic codes on medical claims is a strength of this study and adds to the existing sparse literature on disease burden of HDV in the US.

Disclosures: Norah Terrault – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;

Sacha Satram – Vir Biotechnology: Employee, Yes, No; Vir Biotechnology: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Michael A. Chattergoon – Vir Biotechnology, Inc.: Employee, Yes, No; Vir Biotechnology, Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Christopher Dieyi – Vir Biotechnology: Consultant, Yes, No;

Jason Maynard – Vir Biotechnology: Consultant, Yes, No;

Radhika Trivedi – Vir Biotechnology: Consultant, Yes, No;

Richard Coppola – Vir Biotechnology: Consultant, Yes, No;

Nancy Reau – Gilead Sciences: Consultant, Yes, No;

1380-C | PREVALENCE, CLINICAL AND VIROLOGICAL CHARACTERISTICS AND SHORT-TERM PROGNOSIS OF HEPATITIS DELTA INFECTION AMONG HIV/HBV COINFECTED PATIENTS IN NOUAKCHOTT, MAURITANIA

Hélène Le Guillou-Guillemette[1,2], Adeline Pivert[1,2], Ahmed ElBara[3], Mazouz Vall[4], Cindy Ng Wing Sang[1], Pascal Veillon[1], Alexandra Ducancelle[1,2], Mohamed Abdallahi Bollahi[3], Francoise Anne Caroline Lunel-Fabiani[1,2] and Mohamed Hemeyine[5], (1)Angers University Hospital, Angers, France, (2)Angers University, Angers, France, (3)Institut National De Recherche En Santé Publique, Nouakchott, (4)Centre De Traitement Ambulatoire, Nouakchott, (5)Institut National D'hépato-Virologie, Nouakchott

Background: Patients living with HIV infection (PLWH) are at risk of acquiring HBV and HDV. The present study aimed to determine the prevalence and characteristics of HIV-HDV-HBV tri-infection in comparison with HIV-HBV coinfection and to estimate severities and outcomes of associated liver diseases in Mauritanian PLWH. **Methods:** 292 consecutive HBsAg-positive PLWH were included. Anti-HDV antibodies (Ab) and HBV and HDV viral loads were determined. APRI, FIB-4 and FibroScan were used to evaluate liver disease. **Results:** The anti-HDV Ab prevalence was 37% and HDV RNA was positive in 40.7% of patients. At inclusion, for almost all variables studied, including FIB-4 and APRI scores, no significant differences were found between anti-HDV-Ab positive or negative patients. Significant differences were also absent at end-of-follow-up FibroScan examinations. However, after a mean follow-up of 24.55 ± 8.01 months, a highly significant worsening of APRI and FIB-4 scores was found in the group of patients with follow-up (n = 217). Moreover, patients with HDV showed more severe liver disease progression. **Conclusion:** In a substantial Mauritanian cohort of PLWH, we found high HDV prevalence and worsening liver disease. In high-risk countries, screening for HDV and providing appropriate treatment and follow-up are warranted in PLWH.

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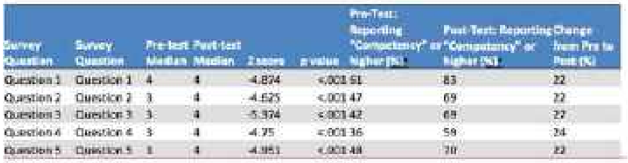
1381-C | PROJECT ECHO IMPLEMENTING CASE BASED PROVIDER TRAINING FOR HEPATITIS B TO REDUCE HEALTH DISPARITIES

Catherine Freeland[1], John Bruckbauer[2], Evangeline Wang[1], Anousha Qureshi[1], Katherine Huynh[3], Myra Rutland[4], Jonathan M. Fenkel[5], Jessie Torgersen[6], Kenneth D. Rothstein[7], Robert G. Gish[8] and Chari Cohen[1], (1)Hepatitis B Foundation, (2)Thomas Jefferson University College of Population Health Science, (3)Fairmount Primary Care Center Gmc, (4) Spectrum Health Services, (5)Thomas Jefferson University Hospital, (6)University of Pennsylvania Perelman School of Medicine, (7)University of Pennsylvania Health System, (8)Hepatitis B Foundation, La Jolla, CA

Background: In the United States, 2.4 million people are living with chronic hepatitis B, but less than 20% are aware of their status. Screening and vaccination uptake remains low among adult U.S. populations. Comprehensive hepatitis B education and testing remains low at the primary care level. The Project ECHO (Extension for Community Health Outcomes) seeks to simplify complex hepatitis B epidemiology and enhance medical knowledge competency on hepatitis B testing, treatment, and management among primary care providers and public health professionals through case-based learning modules, best practices, and interactive discussions delivered by experts in the field. This study assesses the impact of the ECHO sessions on provider training to deliver efficient and specialized care to test, treat, and manage hepatitis B. **Methods:** The hepatitis B ECHO uses the ECHO model (all teach all learn) collaborative learning model of case-based learning. Hepatitis B Project ECHO hosts monthly hour-long sessions for an international audience. Each session features a didactic session followed by a case presentation with feedback and discussion. Sessions are evaluated through pre- and post-test surveys to assess provider knowledge and confidence gained following each session. Qualitative data is also captured to assess provider satisfaction. To assess provider knowledge and satisfaction, survey results from the 2021 and 2022 sessions were used to report the mean change in reported scores from survey participants. The Wilcoxon signed-rank test was performed to evaluate the change in scores from pre- to post-session survey results. SPSS statistical software was used for analysis. **Results:** A total of 20 Hepatitis B ECHO sessions took place in 2021 and 2022 with an average attendance of 40 participants in each session. From the statistical analysis, average scores from post testing demonstrate a significant growth in confidence and hepatitis B related knowledge following each session (Figure 1). Results of the Wilcoxon Rank Test indicated a statistically significant difference in the scores from pre to post. Analysis of scores before and after each session identified increased competency, with changes from pre to post ranging between 22% to 27% in growth (Table 1). Qualitative data demonstrated positive feedback from attendees who completed the survey describing it as “a great source for learning” and “a wonderfully diverse participant group that lends well to comprehensive discussion.” **Conclusion:** Hepatitis B provider training is limited in its availability and gaps in provider knowledge related to hepatitis B have been demonstrated within the literature. The Hepatitis B ECHO fills the gap in provider training and demonstrates the value of mentored, case-based, didactic learning as well as an interest and need for ongoing support for primary care providers to improve testing, treatment and management for hepatitis B.

Table 1. Change in scores before and after using Wilcoxon Rank Test from the HBV Provider ECHO evaluation.



Survey Question	Survey Question	Pre-test Median	Post-test Median	Z score	p value	Pre-Test: Reporting "Competency" or higher (%)	Post-Test: Reporting "Competency" or higher (%)	Change from Pre to Post (%)
Question 1	Question 1	4	4	-4.874	<.001	61	83	22
Question 2	Question 2	3	4	-4.525	<.001	47	69	22
Question 3	Question 3	3	4	-5.374	<.001	42	69	27
Question 4	Question 4	3	4	-4.75	<.001	36	59	24
Question 5	Question 5	3	4	-4.951	<.001	48	70	22

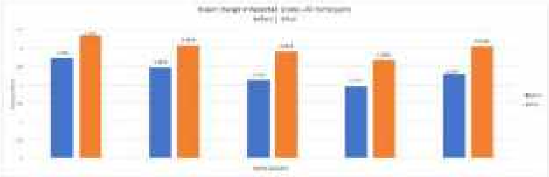


Figure 1. Mean change in reported scores for all participants before and after attending the HBV ECHO sessions.

Disclosures: Jonathan M. Fenkel – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Abbvie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Alexion: Consultant, No, No;

Robert G. Gish – Abbott: Consultant, No, No; Abbvie: Speaking and Teaching, No, No; Altimmune: Consultant, No, No; Antios: Consultant, No, No; Arrowhead: Consultant, No, No; Dynavax: Consultant, No, No; Eiger: Advisor, No, No; Enyo: Consultant, No, No; Genentech: Consultant, No, No; Genlantis: Consultant, No, No; GLG: Consultant, No, No; Gilead Sciences: Consultant, Yes, No; Helios: Consultant, No, No; HepaTx: Advisor, No, No; HepQuant: Advisor, No, No; Intercept: Speaking and Teaching, No, No; Janssen: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Topography Health: Consultant, No, No; Venatorx: Consultant, No, No; Prodigy: Advisor, No, No; Eiger: Stock – privately held company (individual stocks and stock options), No, No; Ganlantis: Stock – privately held company (individual stocks and stock options), No, No; HepQuantum: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; Abbott: Consultant, No, No; Eisai: Consultant, No, No; Gilead Sciences: Consultant, No, No; CymaBay: Advisor, No, No; Durect: Advisor, No, No; AstraZeneca: Speaking and Teaching, No, No; BMS: Speaking and Teaching, No, No; Eisai: Speaking and Teaching, No, No; Hepquant: Stock – privately held company (individual stocks and stock options), No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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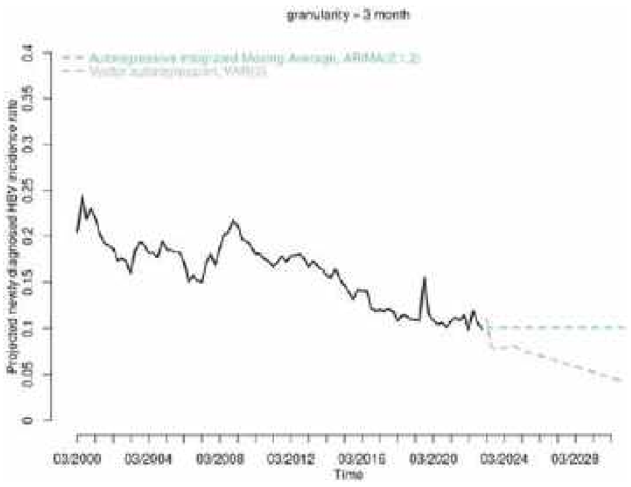
1382-C | PROJECTED BURDEN OF NEWLY DIAGNOSED CHRONIC HEPATITIS B IN HONG KONG TOWARDS 2030

Vicki Wing-Ki Hui[1], Grace Lai-Hung C Wong[1], Yee-Kit Tse[1], Vincent Wai-Sun Wong[2] and Terry Cheuk-Fung Yip[3], (1)The Chinese University of Hong Kong, (2)The Chinese University of Hong Kong, Hong Kong, China, (3)The Chinese University of Hong Kong, Hong Kong, 91, China

Background: Chronic Hepatitis B (CHB) is a major public health concern, particularly in Hong Kong, where approximately 7% of the population is affected. The World Health Organization (WHO) aims to eliminate hepatitis B by 2030, making it essential to understand the disease burden and treatment adoption among CHB patients. In this study, we sought to estimate the disease burden in Hong Kong from 2023 to 2030. **Methods:** This territory-wide retrospective observational cohort study was conducted in Hong Kong. We identified subjects who had hepatitis B surface antigen, hepatitis B e antigen, and Hepatitis B virus (HBV) DNA tested between 2000 and 2022. Vector autoregression and autoregressive integrated moving average were utilized to forecast the HBV incidence rate, with the optimal granularity identified as a three-month interval. Health expenditure per capita, total visitor arrivals, and death counts were considered in forecasting. The yearly HBV incidence rate is approximated by the number of patients with the first HBV positive case divided by the number of patients with the first HBV assay checked. **Results:** Between 2000 and 2022, 1,684,821 patients who had undergone HBV testing were identified, with 256,822 (15.2%) yielding positive results. Over the 23-year period, newly diagnosed HBV patients between 2011-2022 had a higher average age of 57.3 ± 14.7, compared to 44.9 ± 17.1 for those diagnosed between 2000-2004. The majority of patients were male (129,367, 57%). Projections indicate that the incidence rate of HBV is expected to decrease by 36% from 0.11 to 0.04 between March 2023 and December 2030. **Conclusion:** Our study suggests that Hong Kong is on track to achieve the WHO's goal of hepatitis B elimination by 2030, leading to improved public health and reduced healthcare costs. The projected decrease in the incidence rate of HBV highlights the effectiveness of public health measures and increased awareness of the disease. The government-sponsored hepatitis B vaccination program in Hong Kong has played a significant role in reducing the prevalence of HBV among younger generations, which is consistent with the observation that newly diagnosed patients are older. Figure: Projected HBV incidence rate from 2023 to 2030.



Disclosures: Vincent Wai-Sun Wong – Sagimet: Consultant, No, Yes; Pfizer: Consultant, No, Yes; Novo Nordisk: Speaking and Teaching, Yes, Yes; Novo Nordisk: Consultant, Yes, Yes; Inventiva: Consultant, No, Yes; Intercept: Consultant, No, Yes; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences: Speaking and Teaching, No, No; Gilead Sciences: Consultant, No, Yes; Echosens: Consultant, Yes, Yes; Boehringer Ingelheim: Consultant, No, Yes; AbbVie: Speaking and Teaching, No, Yes; AbbVie: Consultant, No, Yes; Abbott: Speaking and Teaching, No, Yes; TARGET PharmaSolutions: Consultant, No, No; Unilab: Speaking and Teaching, No, Yes; Illuminatio Medical Technology Limited: Stock – privately held company (individual stocks and stock options), No, No;
Terry Cheuk-Fung Yip – Gilead Sciences: Consultant, No, No; Gilead Sciences: Speaking and Teaching, No, No;
The following people have nothing to disclose: Vicki Wing-Ki Hui, Grace Lai-Hung C Wong, Yee-Kit Tse

1383-C | RECOMPENSATION TIMEFRAME AND STABILITY IN TREATMENT-NAÏVE HBV-RELATED DECOMPENSATED CIRRHOSIS

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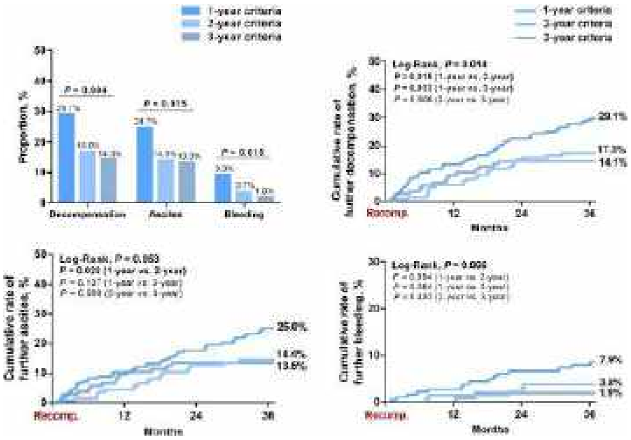
Background: Recompensation could be achieved by effective etiological treatment in patients with HBV-related decompensated cirrhosis. However, the timeframe criteria to define recompensation and its stability has not been well clarified. **Methods:** In this retrospective multicenter study, treatment-naïve HBV-related decompensated patients were enrolled at first decompensating event of ascites and/or variceal bleeding in 8 participating hospitals. Further complications and clinical characteristics were collected every 6 months to 6 years of antiviral treatment. Recompensation was defined as maintaining free of decompensation for at least 1 year, along with stable improvement of liver function within Child-Pugh A and/or MELD < 10. The timeframe criteria for recompensation were further subclassified according to the different time interval within the first 3 years since first decompensation: 1 year (1-year criteria), 2 years (2-year criteria) and 3 year (3-year criteria). Stablility of recompensation was determined as free of decompensation and maintenance of liver function following recompensation. **Results:** A total of 243 patients were included for analysis with a median follow-up duration of 64.8 months. Among them, there were 192 (79.0%), 147 (60.5%) and 110 (45.3%) patients met the criteria for recompensation according to 1-year, 2-year and 3-year criteria ($p < 0.001$), respectively. In recompensated patients, the 5-year cumulative rate of second decompensation was significant higher in the 1-year criteria group compared to the 2-year and 3-year criteria groups (35.0% vs. 22.9% and 12.3%, $p < 0.05$). During an extended 3-year follow-up period after recompensation in recompensated patients, the rate of further decompensation was highest in 1-year criteria group with a rate of 29.1%, which was 17.3% and 14.1% in 2-year and 3-year criteria groups (1-year vs. 2- and 3-year criteria, $p < 0.05$; 2-year vs. 3-year criteria: $p > 0.05$), respectively. The proportion of stable recompensation was lower in 1-year criteria group compared to 2-year and 3-year criteria (52.7% vs. 63.2% vs. 68.6%), and the difference was only observed between the 1-year and 3-year criteria groups ($p = 0.009$). Thus, compared to 1-year criteria recommended in Baveno VII

consensus, using 2- or 3-year criteria resulted in a higher proportion of stable recompensation. **Conclusion:** In treatment-naïve HBV-related decompensated patients, maintaining free of decompensation for at least 2 years was highly recommended to define recompensation.



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1384-C | REGIONAL DIFFERENCES IN HEPATITIS DELTA SEROPREVALENCE AND EPIDEMIOLOGY IN PORTUGAL: DATA FROM THREE CENTERS

Mariana Ferreira Cardoso[1], Isabel Garrido[2], Verónica Gamelas[3], Henrique Coelho[1], Maria Inês Canha[3], Guilherme Macedo[2], Filipe Calinas[3] and Alexandra Martins[1], (1)Hospital Professor Doutor Fernando Fonseca, (2)Centro Hospitalar Universitário S. João, (3) Centro Hospitalar Universitário Lisboa Central

Background: Data about seroprevalence and clinical features of hepatitis delta virus (HDV) infection in Portugal are scarce. We aimed to perform a combined analysis of three cohorts of patients followed in Hepatology clinics for hepatitis B virus (HBV) infection regarding HDV seroprevalence, to characterize seropositive patients, and to compare their epidemiology in the 3 groups. **Methods:** We included data from two hospitals in Lisbon metropolitan area, including one in the city center (HSAC) and one serving the districts of Amadora and Sintra (HFF), as well as a third hospital in Porto (CHUSJ). The cohort from HSAC refers to consecutive patients followed for chronic HBV infection between January 2018 and December 2019. In HFF, patients followed for HBV between 2012 and 2022 were included. In CHUSJ, all HBV patients who had been tested for HDV between 2010 and 2020 were studied. SPSS was used for statistical analysis. Fischer exact test and t-student test were used to compare groups ($p < 0.05$ was considered significant). **Results:** HDV serology data were available in 196/349 (56%) HBV patients from HSAC, 665/835 (80%) from HFF and 580 from CHUSJ, adding up to 1441 patients. HDV seroprevalence was 28/196 (14.3%) in HSAC, 43/665 (6.5%) in HFF and 20/580 (3.4%) in CHUSJ, resulting in a pooled seroprevalence of 91/1441 (6.3%). Considering the group of 91 seropositive patients, 68% were male and mean age was 43 ± 11 [20-68] years. A high proportion of patients originated from African countries (47%), 88% of which from Guinea-Bissau, while 38% originated from Portugal, 12% from Central and Eastern Europe, and 3% from American and Asian countries. Most patients were HBeAg negative at diagnosis (91%). RNA data was available in 43 patients and was positive in 11 (26%), of which 8 had been genotyped: 7 patients as GT5 and one as GT1. Advanced chronic liver disease was present in 36% of patients and 5 (6%) presented liver cancer (hepatocellular carcinoma: 4; cholangiocarcinoma: 1). When comparing Lisbon area (HSAC and HFF) to Porto (CHUSJ), HDV seroprevalence was higher in Lisbon (8.3% vs 3.4%, $p < 0.0001$). A higher proportion of seropositive patients were immigrants from endemic areas in Lisbon than in Porto (70% vs 30%, $p = 0.002$), while intravenous drug use (IDU) was more common in the cohort from Porto (55% vs 14%, $p < 0.0001$). In Lisbon area, HFF had the strongest influence of immigration, with 84% of seropositive patients originating from endemic areas, compared to 46% in HSAC ($p = 0.001$). Age (43.3 vs 41.8 y, $p = 0.582$) and gender (65% vs 80% male, $p = 0.154$) did not differ in Lisbon and Porto. **Conclusion:** Pooled HDV seroprevalence in 1441 patients followed for HBV in three portuguese centers was 6.3%. Seroprevalence was higher in Lisbon than in Porto. In Porto, IDU was the most common source of HDV transmission, while in Lisbon, and particularly in HFF, immigration from endemic countries played a major role.

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1385-C | RELATIONSHIP BETWEEN PRESENCE OF METABOLIC DYSFUNCTION ASSOCIATED FATTY LIVER DISEASE AND CHANGE IN LIVER STIFFNESS IN INDIVIDUALS WITH CHRONIC HEPATITIS B

Lesley Ann Patmore[1], Kirsi Van Eekhout[2], Ozgur Mustafa Koc[3], Rob J. De Knegt[1], Harry L. A. Janssen[4,5], Matthijs Kramer[3], Willem Pieter Brouwer[6], Pieter Honkoop[7], Joep De Bruijne[8], Greet Boland[8], Robert A. De Man[6], Bart Takkenberg[2] and Milan J. Sonneveld[1], (1)Erasmus MC, University Medical Center, (2)Amsterdam University Medical Center, Amsterdam, Netherlands, (3)Maastricht University Medical Center, (4)Erasmus MC, University Medical Center Rotterdam, (5)Toronto General Hospital Research Institute, (6)Erasmus MC, University Medical Center, Rotterdam, Netherlands, (7)Albert Schweitzer Hospital, (8)Utrecht Umc

Background: Recent studies suggest that presence of metabolic dysfunction associated fatty liver disease (MAFLD) is associated with an increased risk for liver-related events in individual's with chronic hepatitis B (CHB). This might be due to more rapid progression of liver fibrosis in individual's co-affected by CHB and MAFLD. Therefore, we studied the association between presence of MAFLD and change in liver stiffness over time in individual's with CHB. **Methods:** We conducted a multicenter retrospective cohort study of mono-infected individual's with CHB who underwent at least two liver stiffness measurements (LSM) with FibroScan. MALFD was defined as presence of hepatic steatosis (based on histology, controlled attenuation parameter or ultrasound) in combination with metabolic dysfunction (diabetes, overweight or hypercholesterolemia and hypertension). We studied the change in LSM from the first LSM to the most recent LSM and defined a significant increase/decrease of e 1 kPa from baseline. **Results:** We analyzed 1376 individual's with a median age of 40 years (interquartile range [IQR] 31-49). MAFLD was present in 359 (26.1%) individual's. The median LSM at baseline was and at last follow-up was 5.6 kPa (IQR: 4.4–7.4) and 5.1 kPa (IQR 4.1–6.5); with a median follow-up time of 4.7 years (IQR 2.6–7.7). Individual's co-affected by MAFLD had a significantly higher LSM compared to individual's without MAFLD (8.0 kPa vs. 6.6 kPa $p = 0.003$). An increase in LSM was observed in 283 (20.5%) individual's, with a significantly higher proportion among individual's with MAFLD versus those without MAFLD (25% vs. 18%, $p = 0.008$). 682 (49.6%) individual's initiated antiviral therapy, of whom 181 (26.5%) had MAFLD ($p = 0.707$). Antiviral therapy was associated with a significant decrease in LSM (72.1% vs. 53.1% $p < 0.001$). Individual's with MAFLD were significantly less likely to achieve a decrease in LSM (57.9% vs 67.8%, $p = 0.001$). An increase in LSM was observed in 128 individual's (18.7%) who initiated antiviral therapy. MAFLD was associated with a significantly higher risk of LSM increase (27% vs. 15%, $p < 0.001$), and the absolute increase in LSM was also higher among individual's with MAFLD (4.9 vs. 3.5 kPa, $p = 0.01$). In multivariable logistic regression analysis, adjusting for duration of follow-up, baseline HBV DNA and ALT levels, higher age (odds ratio [OR] 1.02, $p = 0.008$), higher LSM at baseline (OR 1.302, $p < 0.001$) and MAFLD (OR 1.516, $p = 0.010$) were significantly associated with an increased risk of LSM progression. **Conclusion:** Individual's with CHB co-affected by MAFLD are more likely to experience an increase in LSM during follow-up. While initiation of antiviral therapy was associated with a decline in LSM in the overall population, such a decrease was less frequently observed among individual's with CHB and MAFLD, and MAFLD was an independent risk factor for liver stiffness increase despite initiation of antiviral therapy.

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Harry L. A. Janssen – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GlaxoSmithKline: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Janssen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Vir Biotechnology Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Aligos: Consultant, No, No; Gilead Sciences: Consultant, No, No; GlaxoSmithKline: Consultant, No, No; Janssen: Consultant, No, No; Roche: Consultant, No, No; Vir Biotechnology Inc.: Consultant, No, No; Precision Biosciences: Consultant, No, No;

Milan J. Sonneveld – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Fujirebio: Grant/ Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;

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1386-C | RE-VACCINATION AGAINST HEPATITIS B IN PREVIOUS NON-RESPONDERS FOLLOWING HEPATITIS C ERADICATION

Jesse Powell[1], Spencer Goble[1] and Jose D. Debes[2], (1)Hennepin Healthcare, (2)University of Minnesota

Background: Rates of immunization against hepatitis B virus (HBV) among individual's with chronic hepatitis C virus (HCV) are low and patients with chronic HCV infection do not respond to HBV vaccination as efficiently as non-infected patients. We assessed if HCV treatment resulted in improved response after re-vaccination for HBV. **Methods:** Adult patients who previously did not respond to HBV vaccine were prospectively recruited for re-vaccination after HCV eradication with direct acting antivirals (DAAs). Vaccine response was evaluated by obtaining hepatitis B surface antibody (HBsAb) one month following completion of either the ENGERIX-B or HEPLISAV-B vaccine series. **Results:** A total of 34 patients were enrolled. The median age at time of re-vaccination was 61.5 years (IQR 55-65 y). The majority of patients were male (68%) and Black (59%). The median time from completed HCV treatment to first dose of re-vaccination was 18 months (IQR 8-30 mo). HBsAb testing was performed in 31/34 re-vaccinated patients with 21 reactive (67.7%), 8 non-reactive (25.8%) and 2 equivocal results (6.5%). There were no significant differences in HBsAb reactivity based on age, sex, race, or ethnicity. Presence of advanced fibrosis, being on hemodialysis, HIV co-infection and presence of hepatitis B core antibody also did not significantly impact development of HBsAb following re-vaccination. **Conclusion:** Most prior HBV vaccine non-responders responded to re-vaccination after treatment of HCV. We suggest considering HBV re-vaccination in individual's post DAA treatment. Our results have important public health implications.

Disclosures: The following people have nothing to disclose: Spencer Goble, Jose D. Debes

Disclosure information not available at the time of publication: Jesse Powell

1387-C | RISK FACTORS FOR THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA AFTER ANTIVIRAL THERAPY FOR CHRONIC HEPATITIS B PATIENTS

Junjie Chen[1], Tienan Feng[2] and Xinxin Zhang[1], (1) Ruijin Hospital, Shanghai Jiaotong University School of Medicine, (2)Shanghai Jiao Tong University School of Medicine

Background: It is widely believed that antiviral therapy can reduce the occurrence of hepatocellular carcinoma (HCC) related to chronic hepatitis B (CHB). However, there are still some CHB patients developing HCC during or after antiviral treatment. This study aims to investigate the risk factors for the development of HCC after antiviral therapy in CHB patients. **Methods:** We selected CHB patients who received their first antiviral therapy and completed follow-up from April 2006 to March 2023 in our hospital. All patients were divided into two groups: the HCC group (patients who developed HCC) and the control group (patients who did not develop HCC). Baseline data, including age, gender, initial liver cirrhosis status, routine blood biochemistry, virological examinations, and imaging results (ultrasound, CT, MRI, etc.) were collected. Univariate and multivariate analyses were performed, and a regression model was established using a nomogram for prediction. **Results:** A total of 1450 patients were included, with a median follow-up time of 60 months and a maximum follow-up time of 144 months. During the follow-up period, 32 cases of HCC occurred. The HCC group had significantly lower baseline platelet (PLT) counts, older age, and a higher proportion of pre-existing liver cirrhosis compared to the control group ($p < 0.001$). The levels of γ-glutamyl transferase(γ-GT) and alpha-fetoprotein (AFP) at baseline were higher in the HCC group than in the control group ($p < 0.01$). The HCC group also had a higher proportion of males, higher HBeAb-positive rate, lower albumin (ALB) levels, higher alkaline

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

phosphatase (ALP) levels, and higher total bilirubin (TBil) levels ($p < 0.05$). There were no significant differences between the two groups in terms of HBeAg-positive rate, HBV DNA levels, HBsAg levels, HBcAb levels, and alanine transaminase (ALT) levels. Multivariate analysis revealed that pre-existing liver cirrhosis, male gender, and older age were independent risk factors for HCC development ($p < 0.05$). Besides, higher levels of γ-GT and lower PLT counts at baseline were also identified as risk factors for HCC occurrence ($p < 0.05$). A predictive model for HCC was constructed using baseline liver cirrhosis status, gender, age as independent risk factors, and ALB, HBeAb, γ-GT, TBil, and PLT count as covariates. The model had an area under the curve (AUC) of 0.85 [0.77-0.92], sensitivity of 0.78 [0.60-0.91], and specificity of 0.78 [0.76-0.80]. **Conclusion:** These findings suggest that pre-existing liver cirrhosis, the male and older age at baseline were risk factors associated with HCC, clinicians should monitor closely and intervene early to reduce the incidence of HCC in those CHB patients. Additionally, in high-risk patients for HCC, attention should be given to γ-GT and PLT counts.

Disclosures: The following people have nothing to disclose: Junjie Chen, Tienan Feng, Xinxin Zhang

1388-C | SCREENING FOR ISOLATED HEPATITIS B CORE ANTIBODIES IN GREATER PHILADELPHIA

Catherine Freeland[1], Vivek Sreepathi[2], Evangeline Wang[1], Jonathan M. Fenkel[3], Richard W Hass[2], Kenneth D. Rothstein[4], Jessie Torgersen[5], Robert G. Gish[1] and Chari Cohen[1], (1)Hepatitis B Foundation, (2) Thomas Jefferson University College of Population Health Science, (3)Thomas Jefferson University Hospital, (4)University of Pennsylvania Health System, (5)University of Pennsylvania Perelman School of Medicine

Background: Approximately 2.4 million individual's are living with chronic hepatitis B in the U.S., but less than 20% are diagnosed. Isolated anti-hepatitis B core (IAHBc) antibodies indicate serology in an individual that is positive for anti-HBc antibodies, while negative for surface antigen (HBsAg) and surface antibodies (anti-HBs). Excluding anti-HBc from HBV screening tests makes interpreting screening results challenging and fails to identify a population of patients at risk for hepatitis B reactivation and increased liver cancer risk. This study assesses the prevalence and risk factors associated with anti-HBc and IAHBc among people at high risk for hepatitis B in Philadelphia at community-based screening events. **Methods:** Individual's from communities at high risk for HBV were offered free hepatitis B triple panel screening (HBsAg, anti-HBc, and anti-HBs) between September 2022 and December 2022. Individual's were recruited through community partners and social service organizations serving known high-risk communities. Participants completed an informed consent and brief demographic survey to assess risk factors, followed by a blood draw. Participants received results within two weeks and were provided linkage to care according to test results. Chi-square tables and Firth logistic regression were used to define demographic factors associated with positive anti-HBc and IAHBc. **Results:** Participants (n = 177) were screened for HBsAg, anti-HBs, and anti-HBc. This study detected anti-Hbs in 58.2% (n = 103) of participants, of whom 63.1% also had detectable anti-HBc. Overall, 50.8% of participants had detectable anti-Hbc (63.1% prior exposure (65/103), 12.6% IAHBc (13/103), and 11.7% (12/103) current infection). The prevalence of IAHBc was 7.3% (n = 13). Participants born in the Western Pacific (5.5) and Africa (12.1) have increased odds of anti-HBc versus American-born participants. Individual's born in Africa had 7.93 greater odds for IAHBc than those born in American and odds that were multiplied by 1.01 for every 1-year increase in age. There were no differences in odds based on whether an individual reported being vaccinated, had health insurance, or had a primary care provider. **Conclusion:** Our data show a high burden of IAHBc within high-risk and often hard-to-reach communities. Much of Philadelphia's high-risk HBV population may have been missed due to IAHBc during screening programs, implying an increased risk of reactivation as well as HCC. Triple panel screening should be incorporated into all HBV screening programs, in accordance with current universal screening guidelines, to ensure a comprehensive picture of the disease burden and reduce the risk of misdiagnosis or further liver complications. This recommendation is within the currently updated hepatitis B universal screening guidelines from March of 2023 and should be implemented within practice, particularly in communities at high-risk for HBV.

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Robert G. Gish – Abbott: Consultant, No, No; Abbvie: Speaking and Teaching, No, No; Altimmune: Consultant, No, No; Antios: Consultant, No, No; Arrowhead:

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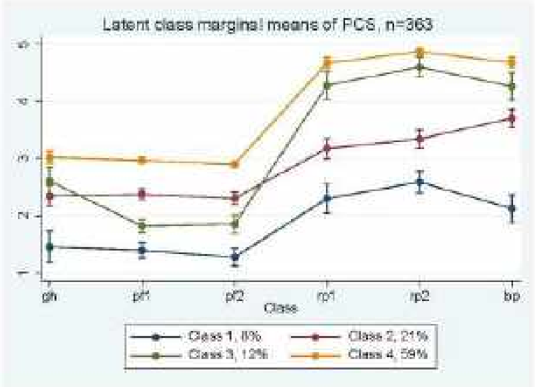
1389-C | SOCIODEMOGRAPHIC, BEHAVIORAL, AND CLINICAL CHARACTERISTICS DIFFERENTIATED IN PHYSICAL FUNCTION AMONG CHRONIC HEPATITIS B PATIENTS OF KOREAN AMERICANS

Hee-Soon Juon[1], Ann Klassen[2], Mimi Chang[3], Julia Katcher[1] and Hie-Won L. Hann[4], (1)Thomas Jefferson University, (2)Drexel University, (3)Coalition of Inclusive Medicine, (4)Thomas Jefferson University Hospital, Philadelphia, PA

Background: Although physical function is an important patient outcome, little is known about physical function in chronic hepatitis B (CHB) patients. The purpose of this study to identify subgroups of Korean American CHB patients based on their level of physical function; determine which sociodemographic, behavioral, and clinical factors were associated with subgroup membership; and determine if these subgroups differed on moderate physical activity. **Methods:** Latent class analysis was used to identify groups of CHB patients ($n = 365$) with distinct physical function profiles. Patients were assessed using the Physical Component Summary (PCS) score from the Short Form 12. Differences, among the groups, in factors were evaluated using multinomial logistic regression. ANOVA was used to examine the differences in moderate physical activity by subgroup. **Results:** Four groups of CHB patients with distinct functional classes were identified: Well Below (8%), Below (21%), Above (12%), well Above (59%) normative PCS scores. Compared with those in the Well Above class, those in the Well Below class were more likely to being older, being female, not married, having poor spoken English proficiency, current smoker, and having a higher level of comorbidity. Two characteristics differentiated Below class and Well Above class: being older and having a higher level of comorbidity. Compared with the Well Above class, patients in the other three classes had significantly lower regular exercise ($p < 0.017$). **Conclusion:** This is the first study to use a person-centered analytic approach to identify subgroups of Korean American CHB patients with distinct physical function profiles. About one third of CHB patients reported significant decrements in physical function which led to lack of regular exercise. Clinicians can assess for those characteristics associated with poorer functional status to identify high-risk patients and initiate appropriate interventions.

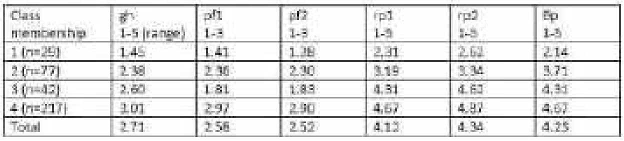
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Figure 1. Class membership of Physical Component Summary (PCS) among Korean Americans with chronic hepatitis B (CHB)



Note. PCS score from the Medical Outcome Study-Short Form 12 (SF-12)
gh=general health; pf=physical function; rp=role-physical; bp=bodily pain

Mean of each physical function by class membership, n=365



Class membership	gh 1-5 (range)	pf1 1-3	pf2 1-3	rp1 1-5	rp2 1-5	Bp 1-5
1 (n=29)	1.45	1.41	1.28	2.31	2.62	2.14
2 (n=77)	2.38	2.36	2.30	3.19	3.34	3.71
3 (n=42)	2.60	1.81	1.83	4.31	4.62	4.31
4 (n=217)	3.01	2.97	2.90	4.67	4.87	4.67
Total	2.71	2.56	2.52	4.12	4.34	4.25

Disclosures: The following people have nothing to disclose: Hee-Soon Juon, Ann Klassen, Mimi Chang, Julia Katcher, Hie-Won L. Hann

1390-C | STATUS OF ANTI-HEPATITIS B ANTIBODY TITER IN ADULTS AND FACTORS ASSOCIATED WITH LOW TITER LEVEL: A RETROSPECTIVE STUDY IN A TERTIARY HOSPITAL IN WV, U.S.A.

Tewodros Ayele, *Marshall University*

Background: Hepatitis B (HBV) vaccine programs have reduced the global incidence of hepatitis B & hepatocellular carcinoma. Immunity lasts for about 35 years, however there are patients who either remain unimmune or lose immunity over time, putting them at risk for infection. In this study, we examined post-vaccination HBs antibody level & factors associated with low titers in adult patients. **Methods:** A cross sectional study was used to assess the status of hepatitis B antibody titer in patients who were tested between 2018 & 2022 in a tertiary hospital. A total of 2248 patients with antibody titer test results were retrieved. In depth chart review of 800 randomly selected patients was done. Descriptive & logistic regression analysis were used to find possible risk factors for low titers. **Results:** In 2248 patients, the median age was 40 (18-89). 2043 (90.9%) where White. The mean anti-HBs antibody titer level was 165.99 (0.10-4000); 1170 (52%) had titers < 10 mIU/mL. In patients aged 18-35, 402 (44.1%) had titers < 10 mIU/mL. Out of the 800 randomly selected patients, median age was 40 (18-85); 488 (61.5%) Female; 761 (95.8%) White. In patients aged 18-35, 113 (45.6%) had titers < 10 mIU/mL. Median BMI was 29.0 (13.3-141.0). 501 (63.1%) had e 1 comorbidity. 502 (63.2%) used tobacco, 227 (28.6%) used alcohol, & 337 (42.4%) used other substances. 241 (30.4%) had documented HBV vaccination. 228 (28.7%) patients had hepatitis C; 36 (4.5%) had HIV. HIV was significantly associated with immunity (OR = 0.221 95%CI 0.049-0.999). Four other factors had clinically significant but not statistically significant association with antibody titer: substance abuse (OR = 2.393 95%CI 0.917-6.246), alcohol abuse (OR = 1.792 95%CI 0.852-3.769), obesity (OR = 1.782 95%CI 0.801-3.963), & female gender (OR = 0.503 95% CI 0.248-1.020). **Conclusion:** A large portion of young adults have low antibody titers. Those with levels < 3.2 were likely unexposed to the vaccine, while those with levels 3.2 & 10 were likely vaccinated, however lost immunity over time. HIV was associated with higher antibody titers likely due to guideline recommendations for boosters while substance use, alcohol use, & obesity were associated with low titers. These factors may become statistically significant with increased sample sizes. Larger studies may be beneficial, as some of these groups, particularly substance use, are not part of current recommendations for assessing post-vaccination immunity.

Disclosures: The following people have nothing to disclose: Tewodros Ayele

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

1391-C | TENOFOVIR ALAFENAMIDE FUMARATE WAS EFFECTIVE AND SAFE IN PREVENTING MOTHER-TO-CHILD TRANSMISSION OF HEPATITIS B VIRUS: A MULTICENTER PROSPECTIVE COHORT STUDY IN SOUTHWEST CHINA(INTERIM ANALYSIS)

Yan Zhu[1], Dan Wang[2], Jie Xia[1], Guohong Deng[3], Qiong Tan[2], Fang Chen[1], Yi Wu[3], Shilian Li[1], Xuqing Zhang[4], Baofang Zhang[5], Fang Zeng[6] and Qing Mao[3], (1)Department of Infectious Diseases, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China, (2)Department of Obstetrics and Gynecology, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China, (3)Department of Infectious Diseases, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China., (4)Department of Infectious Diseases, the Third Affiliated Hospital of Chongqing Medical University, China, (5)Department of Infectious Diseases, Affiliated Hospital of Guizhou Medical University, Guiyang, China, (6)Department of Infectious Diseases, Wushan County People's Hospital of Chongqing, China

Background: Evidence of Tenofovir alafenamide fumarate(TAF) for the prevention of HBV mother-to-child transmission(MTCT) is limited. Our study aimed to evaluate the effectiveness and safety of TAF in preventing MTCT in Southwest China. **Methods:** In this multicenter prospective study, chronic HBV infected pregnant women with HBsAg(+), HBeAg (+) and HBV DNA > 200,000 IU/ml were enrolled in 4 hospitals in Southwest China. TAF was given to all the pregnant mothers from 24-29 weeks' gestation until 4 to 6 weeks postpartum, and then followed up to 7 to 9 months after infants were born. All the infants received standard immunoprophylaxis with Hepatitis B hyper-immune globulin(HBIG) within 12 hours of birth and hepatitis B vaccination at birth, 1 month and 6 months old. The primary endpoint was HBsAg positive rate at 7-9 months of age in the infants. **Results:** From Apr. 2021 to Apr. 2022, a total of 128 pregnant women were enrolled and 69 mothers and 69 infants completed 7 to 9 months postpartum follow-up. Basic characteristics are showed in Table 1. The HBsAg positive rate was 0% at 7-9 months in all children who completed immunoprohylaxis. Body weight, height and head circumferences were comparable with national standards. No infant had congenital defects and growth retardation. At delivery, maternal mean HBV DNA levels were significantly reduced (from baseline 7.22 ± 1.20 $\log_{10}$ IU/mL to 3.76 ± 0.91 $\log_{10}$ IU/mL, $p = 0.000$) and 95.7%(66/69) of mothers had HBV DNA < 200,000 IU/mL, including 46.4%(32/69) with HBV DNA < 500 IU/mL. ALT, AST, serum creatinine maintained normal before and after TAF treatment. TAF was well tolerated during mean duration of 24-29 weeks of TAF treatment. The most common AEs were weakness(1%) and fatigue(3%). No pregnant woman discontinued TAF treatment due to AE. **Conclusion:** TAF was determined to be effective and safe for both mothers and infants and the MTCT rate is 0%. Therefore, TAF will be an appropriate choice for HBV infected pregnant women for preventing MTCT.

Figure 1. Follow-up of enrolled patients

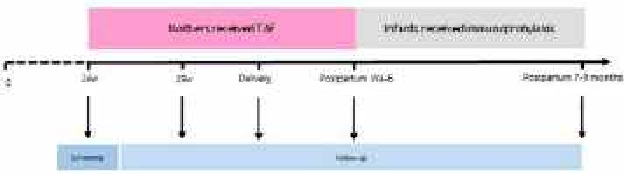
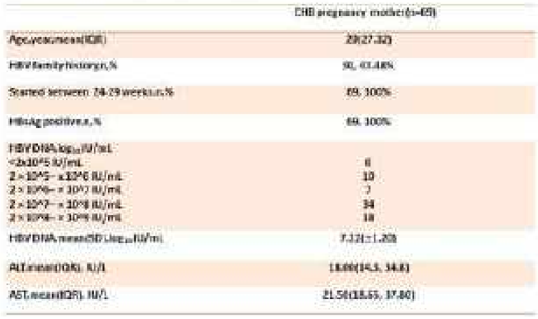


Table 1. Characteristics of the Mothers at Treatment Initiation



	CHB pregnancy mother(n=69)
Age,years,mean(IQR)	29(27,32)
HBV family history,n,%	30, 43.48%
Started between 24-29 weeks,n,%	69, 100%
HBeAg positive,n,%	69, 100%
HBV DNA $\log_{10}$ IU/mL $<2\times10^5$ IU/mL $2\times10^5 - \times10^6$ IU/mL $2\times10^6 - \times10^7$ IU/mL $2\times10^7 - \times10^8$ IU/mL $2\times10^8 - \times10^9$ IU/mL	 0 10 7 34 18
HBV DNA,mean±SD,$\log_{10}$ IU/ml	7.22±1.20
ALT,mean(IQR), IU/L	18.00(14.5, 34.8)
AST,mean(IQR), IU/L	21.50(18.65, 37.80)

Disclosures: The following people have nothing to disclose: Yan Zhu, Dan Wang, Jie Xia, Guohong Deng, Qiong Tan, Fang Chen, Yi Wu, Shilian Li, Xuqing Zhang, Baofang Zhang, Fang Zeng, Qing Mao

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1392-C | THE APPLICATION OF RISK SCORES IN PREDICTION OF HCC IN CHRONIC HEPATITIS B PATIENTS WITH HBsAg SEROCLEARANCE

Rachel Wen-Juei Jeng[1,2], Mei-Hung Pan[3], Chien-Jen Chen[3], Hwai-I Yang[3] and REVEAL-HBV team, (1) Chang Gung Memorial Hospital, Linkou Medical Center, (2)College of Medicine, Chang Gung University, Taiwan, (3)Genomic Research Center, Academia Sinica

Background: Several scores were developed and validated based on HBsAg-positive chronic hepatitis B patients (CHB). However, their ability to predict hepatocellular carcinoma (HCC) development after HBsAg seroclearance (SC) remains unknown. This study aims to compare the REACH-B, CAG, CAMD, RWS, and NGM scores with Yang's score (*J Hepatol. 2022 Sep;77(3):632-641*), derived from Korean CHB patients who experienced SC, to predict subsequent HCC occurrence. Additionally, we will investigate whether changes in the REACH-B score at SC, compared to the score upon entry to the REVEAL cohort, impact HCC development after HBsAg seroclearance. **Methods:** The REACH-B score, CAG score, CAMD score, RWS score, and NGM score were calculated for a total of 632 REVEAL-CHB patients who experienced HBsAg seroclearance. These scores were estimated using the patients' characteristics at the time of entry into the REVEAL study as well as at the time of SC. On the other hand, Yang's score was only estimated at the time of SC. To assess the predictability of HCC, the area under the reciprocal operating curve (AUROC) was calculated. HCC diagnosed was ascertained using National Cancer Registry database. A *p*-value of less than 0.05 was considered statistically significant. **Results:** Out of 632 CHB patients who achieved SC, 29 patients were diagnosed with HCC over a median follow-up of 17.5 years. The AUROC values for predicting overall, 5-year, 10-year, and 15-year HCC using Yang's score were 0.6207, 0.8883, 0.7261, and 0.7004, respectively. These values were comparable to those obtained using the REACH-B score, which was estimated either at study entry (0.6491, 0.7856, 0.6985, and 0.6865, respectively) or at the time of seroclearance (0.5903, 0.8040, 0.7171, and 0.6973, respectively). Similar predictive performance was observed for the GAG score, CAMD score, RWS score, and NGM score, except for the RWS score at study entry, which was less effective than Yang's score for predicting HCC at 5 years (AUROC: 0.6389 vs. 0.8883, $p = 0.0118$). When comparing the REACH-B scores at the time of cohort entry and seroclearance, it was found that 83.5% of the 540 patients with an initial score < 9 remained in the low-risk group (group 0), while 16.5% progressed to the intermediate-risk group at the time of seroclearance (group 1). Among the 92 patients with an initial score between 9 and 17, 51.1% transitioned to the low-risk group (group 2), while 48.9% remained in the intermediate-risk group (group 3). The occurrence of HCC was highest in group 3 (15.6%), followed by group 2 (6.4%), group 1 (4.5%), and lowest in group 0 (3.3%). **Conclusion:** The risk prediction scores derived from HBsAg seropositivity cohort has comparable HCC predictability as that derived from HBsAg loss cohort. Patients whose REACH-B score reduced at time of SC also have reduced HCC risk.

Disclosures: The following people have nothing to disclose: Rachel Wen-Juei Jeng

Disclosure information not available at the time of publication: Mei-Hung Pan, Chien-Jen Chen, Hwai-I Yang

f 1393-C | THE EFFECT OF ANTIVIRAL TREATMENTS IN PATIENTS WITH CHRONIC HEPATITIS B OF NEAR-CUTOFF ALT LEVELS: A REGRESSION DISCONTINUITY DESIGN STUDY

Hyunjae Shin[1], Yunmi Ko[2], Youngsu Park[2], Jeayeon Park[2], Moon Haeng Hur[1], Min Kyung Park[2], Yun Bin Lee[1], Eun Ju Cho[2], Su Jong Yu[2], Yoon Jun Kim[3], Jung-Hwan Yoon[2] and Jeong-Hoon Lee[4], (1)Seoul National University Hospital, (2)Seoul National University College of Medicine, (3)Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, South Korea, (4)Seoul National University College of Medicine, Seoul, South Korea

Background: Antiviral treatment reportedly reduces the risk of hepatocellular carcinoma (HCC) development in patients with chronic hepatitis B (CHB). However, it is controversial whether antiviral treatment would be beneficial for patients with high serum HBV DNA and modestly elevated alanine aminotransferase (ALT) levels. We aimed to examine the effect of antiviral treatments on patients with serum ALT levels around 80 U/L, which is the Asian-Pacific treatment threshold. **Methods:** Consecutive non-cirrhotic CHB patients with serum HBV DNA **e** 2,000 IU/mL and an ALT level around the threshold (i.e., 60–100 U/L) were included from a tertiary hospital in Korea. With an ALT cutoff of 80 U/L, regression discontinuity design (RDD), a quasi-experimental impact evaluation method, was utilized. Patients were classified into two groups: those with ALT levels of 80–100 U/L who initiated antiviral treatment within a year (the early treatment group) and those with ALT levels of 60–80 U/L of ALT level who did not begin antiviral treatment within a year (the delayed treatment group). The primary outcome was the HCC development. According to the assumptions of RDD, two groups were assumed to have comparable characteristics, including unmeasured confounders, except for ALT level and timing of antiviral initiation. Inverse probability treatment weighting (IPTW) method of two groups were applied to rebalance the remaining unbalanced baseline characteristics. **Results:** A total of 781 non-cirrhotic CHB patients were analyzed. During a median of 7.1 (interquartile range = 3.2–11.8) years of follow-up, 24 patients (3.1%) developed HCC. Baseline ALT levels were lower in the delayed treatment group (median = 68 U/L, interquartile range = 64–73 U/L) than in the early treatment group (median = 89 U/L, IQR = 84–94 U/L). After employing IPTW, baseline characteristics except for ALT level were well-balanced (Table 1). In the IPTW-balanced population, the early treatment group had a significantly lower risk of HCC than the delayed treatment group (hazard ratio [HR] = 0.23, 95% confidence interval [CI] = 0.08–0.73, *p* = 0.02 by log-rank test; Figure 1). In the subgroup analysis, the HRs of the HBeAg-negative (HR = 0.29, 95% CI = 0.08–1.05, *p* = 0.06; Figure 2) and HBeAg-positive (HR = 0.19, 95% CI = 0.02–1.87, *p* = 0.15) subgroups were similar, although neither result reached statistical significance. **Conclusion:** This finding of RDD study suggests that antiviral treatments is associated with lower of HCC development among patients with near-cutoff ALT levels and active HBV replication. Further study is warranted to lower the treatment threshold of ALT level in CHB patients.

Figure 1. Kaplan-Meier curve After IPTW

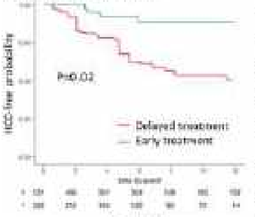

Figure 2. Kaplan-Meier curve After IPTW in HBeAg-negative subgroup

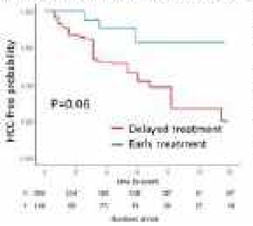

Table 1. Baseline characteristics before and after IPTW

Disclosures: The following people have nothing to disclose: Hyunjae Shin, Yunmi Ko, Youngsu Park, Jeayeon Park, Moon Haeng Hur, Min Kyung Park, Yun Bin Lee, Eun Ju Cho, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon, Jeong-Hoon Lee

1394-C | THE IMPACT OF CHANGING HBV TREATMENT ELIGIBILITY ON PORTION ELIGIBLE FOR TREATMENT BY REGION, 2024

Devin Razavi-Shearer, Ivane Gamkrelidze, Kathryn Razavi-Shearer, Alexis Voeller and Homie Razavi, Center for Disease Analysis Foundation

Background: As countries and regions begin to expand eligibility guidelines for hepatitis B virus (HBV) it is important to understand the potential impact that this will have on healthcare systems. We aimed to quantify the portion of HBV infections eligible for treatment under different guidelines at the regional level in 2024. **Methods:** The Polaris Observatory maintains and annually updates 170 country specific PRoGReSs Models. The PRoGReSs Model is a fully dynamic HBV disease burden and transmission Markov model. This model considers the impact of diagnosis, treatment, and all prophylaxis measures on the incidence and disease burden of hepatitis B. The models were then used to estimate the impact of 10 different scenarios altering cut-offs for viral load, ALT, and age. **Results:** Models were populated for 170 countries, 97 of which received feedback from country experts, 54 were based on published data, and 19 used extrapolated prevalence data. Lowering the eligible age has little impact on the portion of HBV-positive individual's eligible for treatment in EURO, PAHO, and WPRO (Table 1). However, lowering the age cut-off had the largest impact in the AFRO. When the viral load threshold for eligibility was lowered it had a large impact on the total number and proportion eligible in every region. Lowering the viral load cut-off from **e** 20,000 IU/mL to **e** 2000 IU/mL increased eligibility by 37% in the AFRO region whereas the same change would increase eligibility by only 18% in the WPRO region (Table 1). Removing ALT (greater than upper limit of normal) from eligibility criteria had the largest impact on proportion eligible. Removing ALT > ULN increased the number of HBV infections eligible for treatment in 75–100% across the regions analysed (Table 1). **Conclusion:** Expanding treatment eligibility will result in many more individual's being eligible for treatment. However, there is great variation on the impact of changing specific thresholds will have by region dependent on the historical vaccination coverage, current age structure, and HBV genotype. Even with expansion in treatment criteria the biggest hurdles yet to overcome remain increasing the share of infected individual's who are diagnosed and linked to care. This will require an increase in awareness regarding HBV, including that it is a virus that cause liver cancer, and a mobilization of resources centring primary health care workers on all fronts.

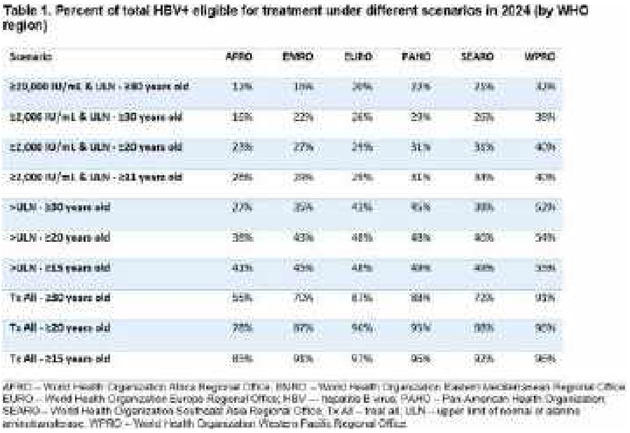

Table 1. Percent of total HBV+ eligible for treatment under different scenarios in 2024 (by WHO region)

Disclosures: The following people have nothing to disclose: Devin Razavi-Shearer, Alexis Voeller
Disclosure information not available at the time of publication: Ivane Gamkrelidze, Kathryn Razavi-Shearer, Homie Razavi

1395-C | THE IMPACT OF HEPATIC STEATOSIS ON RESPONSE OF ANTIVIRAL THERAPY IN CHB PATIENTS: A META-ANALYSIS

Lili Liu[1], Hong Li[1], Daqiong Zhou[1], Xiaofei Du[1], Lixia Qiu[1], Shan Liang[1], Xiaohui Liu[1], Lixia Ma[1], Xinhuan Wei[1], Haiqing Guo[1], Shanshan Xu[1], Yang Zhang[1], Yali Liu[1], Jing Zhang[2] and Zhenhuan Cao[1], (1)Beijing Youan Hospital Capital Medical University, Beijing, China, (2) Beijing Youan Hospital, Capital Medical University

Background: Hepatitis B virus (HBV) infection combined with nonalcoholic fatty liver disease (NAFLD) is very common. However, it remains unclear whether hepatic steatosis affects the antiviral efficacy in patients with chronic hepatitis B (CHB). **Methods:** We searched the literature from PubMed, EMBASE, Cochrane library and Web of Science from inception to July 22, 2022. Data were collected and meta-analysis was performed using fixed or random models. **Results:** A total of 14 studies with 2591 CHB patients were included. CHB patients combined with steatosis had lower alanine transaminase (ALT) normalization rates when treated with nucleoside analog (NA) at 48 and 96 weeks (60% vs. 72% and 62% vs. 74%, $p < 0.001$), but the difference was not statistically significant with pegylated interferon (PEG-IFN) treatment. HBV DNA suppression rates were lower in patients with hepatic steatosis treated with NA and PEG-IFN at week 48 (64% vs. 76%, $p < 0.001$ and 39% vs. 45%, $p = 0.043$), while there was no significant difference at week 96 treated with NA. The clearance rates of hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) were higher with PEG-IFN than with NA. There were no significant differences in HBeAg and HBsAg clearance rates between CHB patients with and without steatosis treated with NA or PEG-IFN at week 48. **Conclusion:** Hepatic steatosis did not impose a significant effect on NA and PEG-IFN treatment efficacy. Perhaps hepatic steatosis reduced HBV DNA suppression in the short time with NA therapy, but this effect disappeared with longer treatment duration. Studies on the antiviral efficacy of hepatic steatosis on PEG-IFN are rare and more studies are needed, especially for long-term treatment.

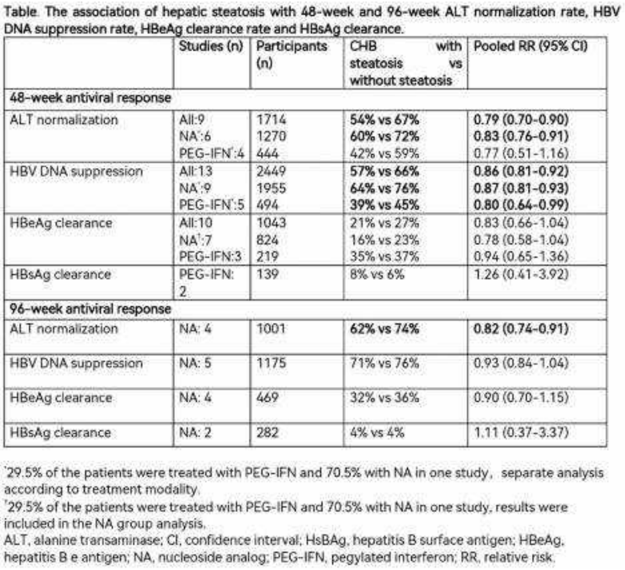

Table. The association of hepatic steatosis with 48-week and 96-week ALT normalization rate, HBV DNA suppression rate, HBeAg clearance rate and HBsAg clearance.

	Studies (n)	Participants (n)	CHB with steatosis vs without steatosis	Pooled RR (95% CI)
48-week antiviral response				
ALT normalization	All:9 NA[*]:6 PEG-IFN[*]:4	1714 1270 444	**54% vs 67%** **60% vs 72%** 42% vs 59%	**0.79 (0.70-0.90)** **0.83 (0.76-0.91)** 0.77 (0.51-1.16)
HBV DNA suppression	All:13 NA[*]:9 PEG-IFN[*]:5	2449 1955 494	**57% vs 66%** **64% vs 76%** **39% vs 45%**	**0.86 (0.81-0.92)** **0.87 (0.81-0.93)** **0.80 (0.64-0.99)**
HBeAg clearance	All:10 NA[†]:7 PEG-IFN:3	1043 824 219	21% vs 27% 16% vs 23% 35% vs 37%	0.83 (0.66-1.04) 0.78 (0.58-1.04) 0.94 (0.65-1.36)
HBsAg clearance	PEG-IFN: 2	139	8% vs 6%	1.26 (0.41-3.92)
96-week antiviral response				
ALT normalization	NA: 4	1001	**62% vs 74%**	**0.82 (0.74-0.91)**
HBV DNA suppression	NA: 5	1175	71% vs 76%	0.93 (0.84-1.04)
HBeAg clearance	NA: 4	469	32% vs 36%	0.90 (0.70-1.15)
HBsAg clearance	NA: 2	282	4% vs 4%	1.11 (0.37-3.37)

[*] 29.5% of the patients were treated with PEG-IFN and 70.5% with NA in one study, separate analysis according to treatment modality.
[†] 29.5% of the patients were treated with PEG-IFN and 70.5% with NA in one study, results were included in the NA group analysis.
ALT, alanine transaminase; CI, confidence interval; HsBAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; NA, nucleoside analog; PEG-IFN, pegylated interferon; RR, relative risk.

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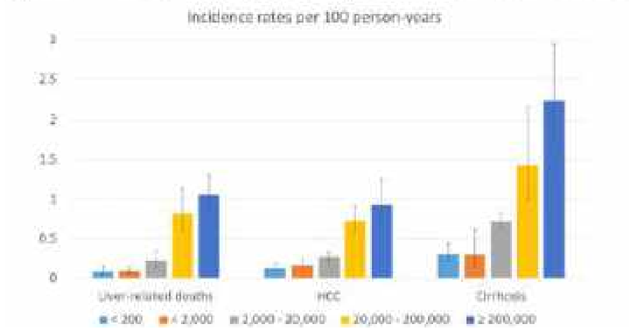
1396-C | THE NATURAL HISTORY OF CHRONIC HBV INFECTION ACCORDING TO HBV DNA & ALT LEVELS AT BASELINE: A GLOBAL SYSTEMATIC REVIEW & META-ANALYSIS

Zakary Ismail Warsop[1], Arthur Rakover[2], Daniela Yucuma[2], Yu Ri Im[3], Si Emma Chen[2], Rukmini Jagdish[4], Roger Chou[5], Philippa Easterbrook[6] and Yusuke Shimakawa[2], (1)Imperial College London, (2) Institut Pasteur, (3)University of Oxford, (4)St George's Hospital, (5)Oregon Health & Science University, (6) World Health Organization

Background: The World Health Organisation (WHO) has set global viral hepatitis elimination targets, emphasizing the urgent need for expanding testing and antiviral therapy coverage, especially in resource-

limited settings. A crucial milestone is achieving 80% treatment coverage among eligible individual's. Currently, high risk of disease progression determines antiviral treatment eligibility for chronic hepatitis B virus (HBV). In order to inform the updating of the 2015 WHO recommendations on who to treat, a systematic review and meta-analysis was undertaken to estimate the incidence rate of clinical outcomes in untreated, noncirrhotic people with HBV, stratified by HBV DNA levels and alanine transaminase (ALT) levels at baseline. **Methods:** We searched PubMed, Embase, Web of Science, and the Cochrane Library for cohort studies published up to 6th Feb 2023. Two reviewers independently screened the titles and abstracts and extracted data from full-text articles. Outcomes included cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality. The pooled incidence rates of each outcome were stratified by the baseline viral load (<2,000, 2,000-20,000, 20,000-200,000, and **e** 200,000 IU/mL) or ALT levels (1x, 1-2x, **e** 2x ULN). A meta-analysis using a generalized linear mixed model was performed. **Results:** Of 13,124 identified and screened studies, 80 were included. In low viral load strata - HBV DNA < 200 IU/mL and < 2,000 IU/mL, the pooled incidence of HCC (per 100 person-years) was low: 0.129 (95% CI: 0.090-0.183) and 0.161 (0.103-0.253) respectively. In viral load strata above 2,000 IU/mL, there was a clear dose-response relationship: 0.267 (0.213-0.334), 0.732 (0.592-0.905), and 0.923 (0.679-1.256) when HBV DNA were 2,000-20,000, 20,000-200,000, and **e** 200,000 IU/mL, respectively ($p < 0.01$, Figure). A similar relationship was observed for the incidence of cirrhosis and liver-related mortality. HCC incidence was low (0.094 (0.045-0.196)) in individual's with persistently normal ALT. There were only 12 studies in children, and we did not observe any clear association between viral loads at baseline and clinical outcomes. **Conclusion:** This represents the most comprehensive global systematic review and meta-analysis to date of the natural history of chronic HBV infection. The incidence rates of cirrhosis and HCC were low in those with HBV DNA < 2000 IU/ml. There was paucity of data for the natural history of chronic HBV in the paediatric population, and this is a priority for further research.

Figure. Incidence rates of liver-related deaths, HCC, and cirrhosis by baseline HBV DNA levels.



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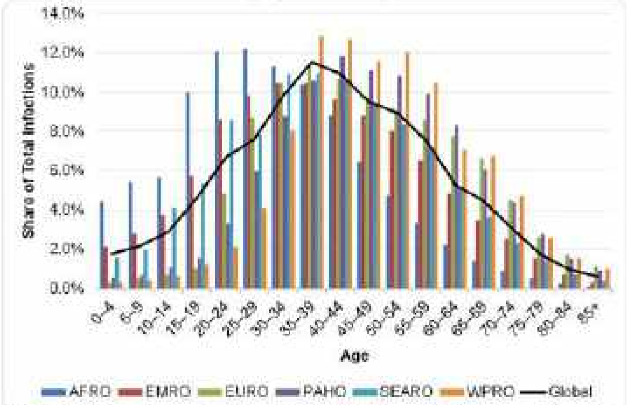
1397-C | THE SHARE OF TOTAL HBV INFECTIONS BY AGE AT THE GLOBAL AND REGIONAL LEVEL, 2022

Devin Razavi-Shearer, Ivane Gamkrelidze, Kathryn Razavi-Shearer, Alexis Voeller and Homie Razavi, Center for Disease Analysis Foundation

Background: As we move closer to the 2030 date set for the elimination of viral hepatitis as a public health threat, information is needed to guide countries towards strategies that will be most impactful. Due to the diversity of nations, their historical and current programs, there exists great heterogeneity in the burden of hepatitis B virus (HBV). One way this can be understood, and targeted is through the share of infections by age. This provides insights into what has worked and what still needs to be done. We aimed to quantify the share of HBV infections at the global and regional level in 2022. **Methods:** The Polaris Observatory maintains and annually updates 170 country specific PRoGReSs Models. The PRoGReSs Model is a fully dynamic HBV disease burden and transmission Markov model. This model considers the impact of diagnosis, treatment, and all prophylaxis measures on the incidence and disease burden of hepatitis B. **Results:** Models were populated for 170 countries, 97 of which received feedback from country experts, 54 were based on published data, and 19 used extrapolated prevalence data. Globally, just over 11% of all HBV infections were found to be among those aged **d** 20 years of age, with over 50% of cases being among those aged 30-54 (Figure 1). The AFRO region stands out with 25% of all HBV infections being in ages **d** 20 years and 14.4% in the EMRO region, compared to 2.5% in the WPRO and EURO regions. On the other hand, the WPRO and EURO regions show a very low number of HBV infections in younger age groups with a peak of infections among those aged 35-39 due to a long history of birth- and three-dose HBV vaccinations. The peak share of infections in the oldest population is in the PAHO region with the 40-44 age group representing 11.9% of all infections in that region. **Conclusion:** These data provide evidence for policy makers to use on multiple fronts. In the regions in which there remains a high burden of pediatric HBV infections, it is clear that more needs to be done to support prevention programs, particularly elimination of mother to child transmission. These regions will also face large burdens of HBV-related morbidity and mortality for years to come. However, regions with a higher share of prevalence among older individual's have been successful in prevention but will still have a large number of individual's in need of screening and treatment to prevent liver cancer and mortality in the shorter term.

Figure 1. Share of Total HBV Infections by Age Group and Region, 2022



AFRO – World Health Organization Africa Regional Office; EMRO – World Health Organization Eastern Mediterranean Regional Office; EURO – World Health Organization Europe Regional Office; HBV — hepatitis B virus; PAHO – Pan-American Health Organization; SEARO – World Health Organization Southeast Asia Regional Office; WPRO – World Health Organization Western Pacific Regional Office

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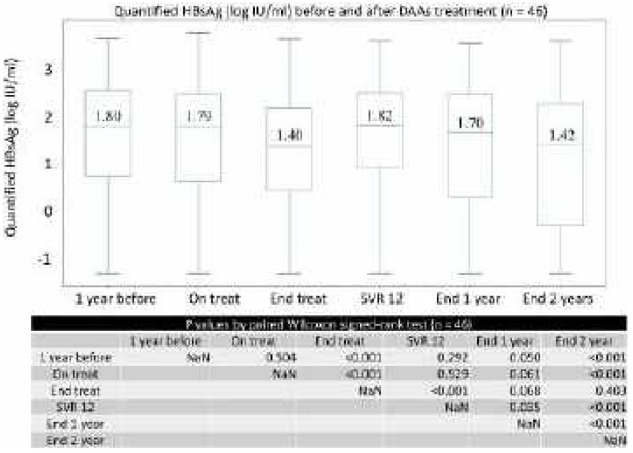
Disclosure information not available at the time of publication: Ivane Gamkrelidze, Kathryn Razavi-Shearer, Homie Razavi

1398-C | VIGOROUSLY DYNAMIC CHANGES OF HEPATITIS B SURFACE ANTIGEN AFTER DIRECT-ACTING ANTIVIRALS TREATMENT AMONG HEPATITIS C VIRUS AND HEPATITIS B VIRUS CO-INFECTED PATIENTS

Chenger Hsu[1], *Yen-Chun Liu*[1], *Ya-Ting Cheng*[2], *Yi-Chung Hsieh*[3], *Rachel Wen-Juei Jeng*[3], *Chun-Yen Lin*[3], *Rong-Nan Chien*[3] *and I-Shyan Sheen*[3], *(1)Chang Gung Memorial Hospital, Linkou Medical Center, (2)Linkou Chang Gung Memorial Hospital, Linkou Branch, Taiwan, (3)Linkou Chang Gung Memorial Hospital*

Background: Direct-acting antivirals (DAAs) achieved high sustained virologic response (SVR) rate in patients co-infected with hepatitis C virus (HCV) and hepatitis B virus (HBV). Whether HBsAg level reduction will be accelerated after SVR remained unknown. This study aims to investigate this issue by comparing the longitudinal dynamic changes of quantitative HBsAg (qHBsAg) level before, during and after DAAs treatment. **Methods:** CHC patients with HBV co-infection who received DAA treatment and achieved SVR12 between March 2015 and December 2019 in Chang Gung Memorial Hospital, Linkou branch were prospectively enrolled. qHBsAg level was assayed at 1 year before DAA, at start of DAA, end-of-treatment, SVR and 1, 2 years after DAA treatment. The qHBsAg was quantified by Roche Elecsys HBsAg II quantitative assay detection range 0.05 - 52000 IU/mL. **Results:** A total of 46 CHC patients with SVR and with all timepoint qHBsAg assessment available were included in the analysis. The median age was 63.2 years, 25 patients (54.3%) were male. The kinetics of qHBsAg level before DAA to start of DAA (SOT), during DAA (from end-of-treatment(EOT) to SOT) and from EOT to SVR 12 were -0.01, -1, and 0.9 $\log_{10}$ IU/mL/year, respectively. Rapid decline of HBsAg (>1 $\log_{10}$IU/mL/year) was observed in 50% of patients during DAA treatment but the phenomenon is not sustained and 19 of these 23 (83%) rapid HBsAg decline patients rebound from nadir while the rest remain declining and 2 patients achieved HBsAg<0.05 by EOT and sustained till SVR 12. Interestingly, HBsAg median level drop from 1.82 $\log_{10}$ IU/mL (SVR 12) to 1.70 $\log_{10}$ IU/mL by EOT 1-year and 1.42 $\log_{10}$ IU/mL by EOT 2-year. Rapid HBsAg decline was observed in 6.5% of the CHC/CHB-SVR patients (Figure 1). By 2-year follow-up after EOT, 7 patients (16%) achieved HBsAg loss. **Conclusion:** Eradication of HCV by DAA leads to a temporal rapid reduction of HBsAg level during DAA therapy and rebound in most patients by SVR12. HBsAg decline appeared to be increased after SVR 12 than that before SVR 12. This phenomenon may reflect the different durability of the restored anti-HBV immunity during DAA and after SVR12.



P-values by paired Wilcoxon signed-rank test (n = 46)

	1 year before	On treat	End treat	SVR 12	End 1 year	End 2 year
1 year before	NaN	0.504	<0.001	0.292	0.050	<0.001
On treat		NaN	<0.001	0.529	0.061	<0.001
End treat			NaN	<0.001	0.068	0.403
SVR 12				NaN	0.035	<0.001
End 1 year					NaN	<0.001
End 2 year						NaN

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Disclosure information not available at the time of publication: Yen-Chun Liu, Yi-Chung Hsieh

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

1399-C | A MEDIATION ANALYSIS OF DYNAMIC PROCESS OF HEPATOCELLULAR CARCINOMA DEVELOPMENT IN CHRONIC HEPATITIS B PATIENTS WITH ANTIVIRAL TREATMENT

Minjoo Cho[1], Jonggi Choi[1], Yeojin Lee[1], Hyeyeon Hong[1], Jiwon Yang[1], Sung Won Chung[1], Won-Mook Choi[1], Danbi Lee[1], Ju Hyun Shim[2], Kang Mo Kim[2], Young-Suk Lim[3], Han Chu Lee[1] and Seungbong Han[4], (1)Asan Medical Center, Seoul, Korea, Republic of (South), (2)Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, (3)Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South), (4)Korea University

Background: Antiviral treatment in chronic hepatitis B (CHB) patients without cirrhosis is determined by ALT levels and HBV DNA levels to prevent disease progression. We performed a mediation analysis to examine the dynamic process of hepatocellular carcinoma (HCC) development in CHB patients treated with antiviral treatment. **Methods:** A total of 4,832 patients with CHB who received with entecavir or tenofovir disoproxil fumarate at Asan Medical Center, Seoul, Korea were analyzed retrospectively. The association between HBV DNA levels and the on-treatment ALT normalization or VR were analyzed by multiple logistic regression. A mediation analysis was conducted to see whether these on-treatment ALT normalization or VR mediate the association between the pre-treatment HBV DNA levels and the HCC risk. **Results:** The mean age was 48.3 years, and 62.0% were men. HBeAg was positive in 59.3% and cirrhosis was present in the 52.5% of the patients. On-treatment ALT normalization was achieved in 4,635 (95.9%) patients during the study period. At 1 year of antiviral treatment, patients with pre-treatment HBV DNA levels **e** 8 log10 IU/mL showed the highest rate of on-treatment ALT normalization (81.8%), whereas those with pre-treatment HBV DNA levels of 6.0-6.99 log IU/mL showed the lowest rate of on-treatment ALT normalization (69.9%). A total of 4,511(93.4%) achieved VR during the overall treatment period. The rate of VR at 1 year of antiviral treatment was proportionally increased as the pre-treatment serum HBV DNA level decreases. HCC occurred in 455 patients with an annual incidence of 1.61/100 person-years. Pre-treatment HBV DNA levels of 6.0-6.99 (adjusted hazard ratio: 2.08, 95% CI: 1.43–3.04, $p < 0.001$) showed the highest risk of HCC development after adjusting for confounders. Indirect effect of the 6.00–6.99 log IU/mL HBV DNA group or the HBV DNA group (<5 log IU/mL) through the on-treatment ALT normalization were statistically significant, which was smaller than direct effect. This indicates that indirect mediation effect of on-treatment ALT normalization on the risk of HCC is negligible. Regarding the association between the pre-treatment HBV DNA level, VR, and the HCC risk, indirect and direct effect of the pre-treatment HBV DNA groups through the VR were also negligible. **Conclusion:** The present study demonstrated three important aspects; 1) CHB patients with pre-treatment serum HBV DNA levels of 6-7 had the highest risk of HCC development. 2) this group of patients showed the lowest rate of on-treatment ALT normalization at 1 year of antiviral treatment. 3) the risk of HCC development in patients with CHB was mainly determined by the pre-treatment serum HBV DNA levels rather than achievement of intermediate outcomes by antiviral treatment.

Disclosures: The following people have nothing to disclose: Minjoo Cho, Jonggi Choi, Yeojin Lee, Hyeyeon Hong, Jiwon Yang, Sung Won Chung, Won-Mook Choi, Danbi Lee, Ju Hyun Shim, Kang Mo Kim, Young-Suk Lim, Han Chu Lee, Seungbong Han

1400-C | ACUTE HEPATITIS FLARES AFTER CESSATION OF NUCLEOS(T)IDE ANALOGUES ARE ASSOCIATED WITH LOWER RATES OF HBsAg SEROCLEARANCE IN PATIENTS WITH CHRONIC HEPATITIS B

Ying-Nan Tsai[1,2], Jia-Ling Wu[3], Cheng-Hao Tseng[1,2], Yi Ling Wu[4], Jaw-Town Lin[4], Mindie H. Nguyen[5] and Yao-Chun Hsu[1,2], (1)E-Da Cancer Hospital, I-Shou University, (2)I-Shou University, (3)National Cheng Kung University, (4)E-Da Hospital, I-Shou University, (5) Stanford University Medical Center, Palo Alto, CA

Background: Patients with hepatitis B virus (HBV) infection frequently experience acute hepatitis flares after stopping nucleos(t)ide analogue (NA) treatment. These flares could precipitate liver failure but they are also thought to promote hepatitis B surface antigen (HBsAg) seroclearance, which is one of the major rationales for NA cessation. We aimed to evaluate and clarify the association between acute hepatitis flares and subsequent HBsAg seroclearance following NA cessation in patients with chronic hepatitis B (CHB). **Methods:** This retrospective, multi-center cohort study systematically reviewed all CHB patients who received NA treatment in a healthcare system in Taiwan. We included adults who discontinued NA therapy between April 01, 2004, and May 24, 2022, who had at least one year of continuous treatment before discontinuation. Patients with malignancy, hepatic insufficiency (defined by jaundice and coagulopathy), or viral coinfections were excluded. A hepatitis flare was defined as a serum level of alanine aminotransferase (ALT) > 5 times the upper limit of normal (ULN; 40 U/L). The primary outcome was HBsAg seroclearance during the post-NA cessation period. We estimated the incidence of HBsAg seroclearance using a competing risk analysis, factoring in death or retreatment as informative censoring events. The occurrence of ALT flares was evaluated as a time-dependent variable in the multivariable-adjusted sub-distribution hazard regression models. **Results:** A total of 854 eligible patients (median age of 53.2 y, 74.6% male) were enrolled. The median duration of NA therapy was 34.7 (interquartile range [IQR], 31.0-38.5) months and the majority (63.4%) of patients used entecavir. During a median post-NA cessation follow-up of 3.7 years (IQR, 1.4-6.3), HBsAg seroclearance occurred in 51 patients, at an average annual rate of 1.48% (95% confidence interval [CI], 1.10-1.95%) and a cumulative incidence of 13.8% (95% CI, 10.20-18.05%) at 10 years. Of the 175 patients who experienced acute ALT flares, 6 (3.43%) subsequently cleared HBsAg. Conversely, 45 of 679 patients (6.63%) without ALT flares achieved HBsAg seroclearance. In the multivariable-adjusted model, occurrence of ALT flares was associated with a lower incidence of HBsAg seroclearance (sub-distribution hazard ratio, 0.24; 95% confidence interval, 0.09-0.64). Furthermore, the peak serum ALT level post NA cessation was significantly lower in patients achieving HBsAg seroclearance (median, 77 U/L; IQR, 42-136) compared to those who did not achieve HBsAg seroclearance (median, 127 U/L; IQR, 47-341; $p < 0.0001$) (Figure 1). **Conclusion:** Acute ALT flares are associated with a lower incidence of subsequent HBsAg seroclearance in CHB patients who discontinued NA therapy. Therefore, ALT flares following NA cessation should not be viewed as a “desirable” event and treatment cessation should be avoided in patients at risk of withdrawal flares.

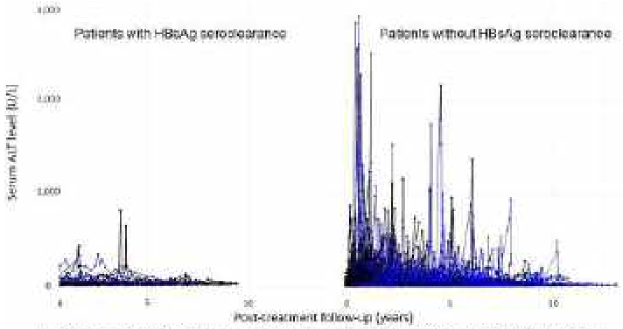

Figure 1. The trajectories of serum ALT levels in patients with and without achieving HBsAg seroclearance following NA cessation (patients who resumed treatment were indicated in blue).

Disclosures: The following people have nothing to disclose: Ying-Nan Tsai, Jia-Ling Wu, Cheng-Hao Tseng, Yi Ling Wu, Jaw-Town Lin, Mindie H. Nguyen, Yao-Chun Hsu

1401-C | AIR POLLUTION MIGHT IMPEDE ALT NORMALIZATION IN CHRONIC HEPATITIS B PATIENTS TREATED WITH NUCLEOTIDE/ NUCLEOSIDE ANALOGUES

Tyng-Yuan Jang, Kaohsiung Medical University

Background: Biochemical response is an important prognostic indicator in chronic hepatitis B (CHB) patients receiving nucleotide/nucleoside analogues (NAs). However, the effects of air pollution in alanine aminotransferase (ALT) normalization remain elusive. **Methods:** This longitudinal study recruited 80 hepatitis B e antigen (HBeAg)–negative CHB patients who received NAs. ALT levels were measured during the first year of anti-HBV therapy. Normal ALT levels were defined as < 19 U/L for females and < 30 U/L for males, and the risk factors associated with ALT abnormalities were analyzed. The daily estimations of air pollutants (particulate matter **d** 2.5 μm in diameter ($PM_{2.5}$), nitrogen dioxide (NO_2), ozone (O_3), and benzene) were aggregated into the mean estimation for the previous month based on the date of recruitment (baseline) and 1 year later. **Results:** Sixteen patients (20.0%) had a baseline ALT > 40 U/L; overall, 41 (51.6%) had an abnormal ALT (**e** 19 U/L for females and **e** 30 U/L for males). After 1 year of NA therapy, 75 patients (93.8%) had undetectable HBV DNA levels. Mean post-treatment ALT levels were significantly lower than mean pre-treatment levels (21.3 U/L vs 30.0 U/L, respectively; $p < 0.001$). The proportion of patients with a normal ALT was also significantly higher after versus before treatment (71.2% vs. 51.2%, respectively; $p = 0.001$). The strongest factors associated with ALT abnormality after 1 year of NA treatment were body mass index (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.05–1.54; $p = 0.01$). and ozone level (OR, 1.11; 95% CI, 1.02–1.22; $p = 0.02$). **Conclusion:** Among HBeAg-negative CHB patients with relatively low viral loads, 1 year of NA treatment improved ALT levels after the adjustment for confounding factors and increased the proportion of patients with normal ALT levels. Air pollution affects the efficacy of ALT normalization.

Disclosures: The following people have nothing to disclose: Tyng-Yuan Jang

1402-C | ASSOCIATION BETWEEN ON-TREATMENT HBSAG DECLINE AND OFF-TREATMENT OUTCOMES AFTER NUCLEO(S)TIDE ANALOGUE CESSATION

Milan J. Sonneveld[1], S.-M. Chiu[2], Jun Yong Park[3], Sylvia Brakenhoff[1], Apichat Kaewdech[4], Wai-Kay Seto[5], Yasuhito Tanaka[6], Ivana Carey[7], Margarita

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

Papatheodoridi[8], Piero Colombatto[9], Florian Van Bömmel[10], Harry L. A. Janssen[11,12], Thomas Berg[13], Fabien Zoulim[14], Sang Hoon Ahn[15], George N. Dalekos[16], Nicole S. Erler[12], Maurizia R. Brunetto[17], Heiner Wedemeyer[18], Markus Cornberg[18], Mf Yuen[19], K Agarwal[20], Andre Boonstra[21], Maria Buti[22], Teerha Piratvisuth[23], George V. Papatheodoridis[24], Chien Hung Chen[2], Benjamin Maasoumy[18] and CREATE study group, (1)Erasmus MC, University Medical Center, (2) Koahsiung Chang Gung Memorial Hospital, (3)Yonsei University College of Medicine, (4)Prince of Songkla University, (5)Department of Medicine, School of Clinical Medicine, the University of Hong Kong, (6) Graduate School of Medical Sciences, Kumamoto University, (7)Institute of Liver Studies, Kings College Hospital, London, United Kingdom, (8)Medical School of Athens University, (9)University Hospital of Pisa, (10) University Hospital Leipzig, (11)Toronto General Hospital Research Institute, (12)Erasmus MC, University Medical Center Rotterdam, (13)University Hospital of Leipzig, (14)Universite Claude Bernard Lyon 1, (15)Yonsei Liver Center, Severance Hospital, Seoul, South Korea, (16)University of Thessaly, (17) Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, Reference Center of the Tuscany Region for Chronic Liver Disease and Cancer, University Hospital of Pisa, (18)Hannover Medical School, (19)The University of Hong Kong, (20) King's College Hospital, (21)Erasmus University Medical Center, Rotterdam, Netherlands, (22)Hospital Universitari Vall d'Hebron and Ciberehd Del Intituto Carlos III De Barcelona, (23)Nkc Institute of Gastroenterology and Hepatology, Songkhla, Thailand, (24)Medical School of National & Kapodistrian University of Athens, Athens, Greece

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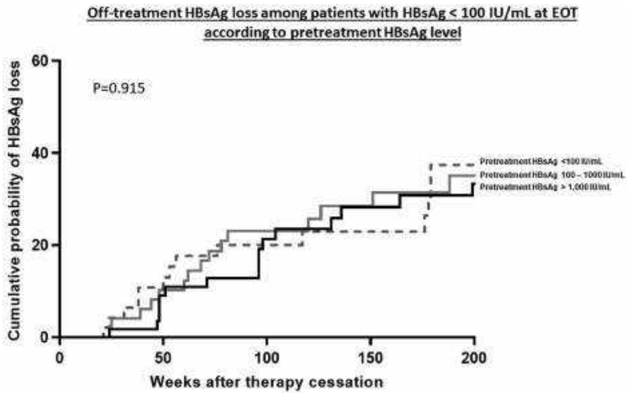
Background: End of treatment (EOT) HBsAg levels <100 IU/mL identify patients most likely to achieve a favorable outcomes after nucleo(s)tide analogue (NUC) withdrawal. Various strategies are being explored to increase the number of patients achieving HBsAg levels below this threshold, but it is unclear whether the outcomes of patients who achieved on-treatment HBsAg decline to <100 IU/mL are comparable to outcomes in patients who already had low HBsAg levels at the start of antiviral treatment. **Methods:** We identified chronic hepatitis B patients who discontinued NUC monotherapy and had available information on pretreatment and EOT HBsAg levels in an international multicentre database. We studied the association between pretreatment HBsAg levels and on-treatment HBsAg decline with the cumulative probability of clinical relapse (defined as the occurrence of either HBV DNA $>2{,}000$ IU/mL with ALT >2x the upper limit of normal) and HBsAg loss at 192 weeks of post-treatment follow-up. **Results:** We enrolled 746 patients, the majority of whom were Asian (92%), HBeAg negative at start of treatment (69.6%) and treated with entecavir (61%). Pretreatment HBsAg levels were <100/100-1000/>1000 IU/mL in 68/198/480 patients. Patients with higher pretreatment HBsAg levels had a higher risk of clinical relapse (HR 1.224, $p<0.001$) and a lower chance of off-treatment HBsAg loss (HR 0.473, $p<0.001$). After a median of 157 (IQR: 156 - 165) weeks of treatment, HBsAg decline from pretreatment to EOT was <1 log IU/mL in 545 (73%), 1-2 log IU/mL in 149 (20%) and >2 log IU/mL in 52 (7.0%). Patients who had achieved >2 log decline from pretreatment to EOT had a significantly lower probability of post-treatment clinical relapse (38% vs 59%, $p<0.001$) and a significantly higher chance of HBsAg loss (32.5% vs 4.6%; $p<0.001$) when compared to patients who experienced <1 log on-treatment decline. Among the 678 patients with a pretreatment HBsAg level >100 IU/mL, 106 (15.6%) achieved HBsAg <100 IU/mL at EOT. Patients who achieved an EOT HBsAg level <100 IU/ml had a significantly lower risk of clinical relapse (33.4% vs 62.1%; $p<0.001$) and a significantly higher chance of HBsAg loss (31.1% vs 2.4%; $p<0.001$). Finally, outcomes at 192 weeks of follow-up were similar for patients with high pretreatment HBsAg levels who achieved a decline to <100 IU/mL during treatment when compared to patients who already had HBsAg levels <100 IU/mL at start of treatment (clinical relapse: 26.1% versus 33.4% [$p=0.202$] and HBsAg loss: 36.5% versus 32.6% [$p=0.915$], see figure).
Conclusion: An on-treatment decline of HBsAg levels to <100 IU/mL was associated with excellent outcomes after NUC cessation. These findings support the exploration of novel strategies to reduce viral antigen levels in order to facilitate safe NUC withdrawal.



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1403-C | ASSOCIATION OF LOW-DOSE ASPIRIN USE WITH RISK OF HEPATOCELLULAR CARCINOMA AND GASTROINTESTINAL BLEEDING IN PATIENTS WITH HBV-RELATED CIRRHOSIS: A LANDMARK ANALYSIS

Mi Na Kim[1], Geun U Park[2], Jae Seung Lee[1], Hye Won Lee[1], Beom Kyung Kim[1], Seung Up Kim[1], Jun Yong Park[1], Do Young Kim[1] and Sang Hoon Ahn[1], (1)Yonsei University College of Medicine, Seoul, Republic of Korea, (2)Clinical and Translational Hepatology Laboratory, Seongnam, Seongnam, Korea, Republic of (South)

Background: The use of aspirin in hepatocellular carcinoma (HCC) prevention is still uncertain in patients with hepatitis B virus (HBV)-related cirrhosis. In addition, results regarding whether the risk of gastrointestinal (GI) bleeding is associated with aspirin use in patients with HBV related cirrhosis are controversial. Accordingly, we investigated the association between aspirin use and the risks of HCC and GI bleeding in HBV-related cirrhosis patients using a nationwide cohort. **Methods:** We conducted a 3-year landmark analysis using nationwide cohort data from the National Health Insurance Service of South Korea. Patients with diagnosed with compensated HBV-related cirrhosis in 2005-2017 were included. Patients who were prescribed aspirin for at least 90 days consecutively during the 3-year exposure period were classified as the aspirin-treated group. A propensity-score matching analysis was applied to balance the aspirin-treated and untreated groups. Using Cox proportional hazard regression analysis, we estimated the risks of HCC and GI bleeding, accounting for competing events. **Results:** A total of 12,687 patients (608 aspirin-treated and 12,079 untreated) were included in the analysis. During a median of 7.6 years of follow-up, HCC developed in 219 (36.0%) patients of the aspirin-treated group and 4,265 (35.3%) patients of the untreated group. After multivariate adjustment, the aspirin-treated group showed a significantly lower risk of HCC than the untreated group (adjusted hazard ratio [aHR] = 0.84, 95% confidence interval [CI] = 0.73-

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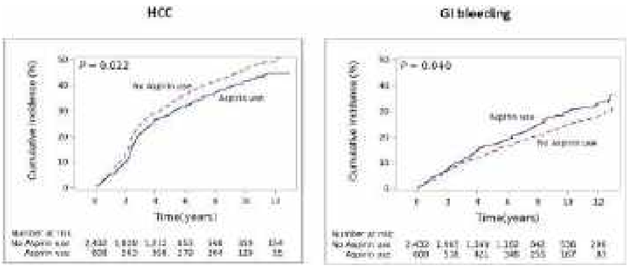
0.96; $p = 0.013$). GI bleeding developed in 157 (25.8%) of the aspirin-treated group and 2,072 (17.2%) of the untreated group. The aspirin-treated group showed a significantly higher risk of GI bleeding than the untreated group (aHR = 1.21, 95% CI = 1.03-1.43; $p = 0.021$). After propensity-score matching, the cumulative incidence rate of HCC was significantly lower in the aspirin-treated group than the untreated group ($p = 0.022$, log-rank test). Whereas, the cumulative incidence rate of GI bleeding was significantly higher in the aspirin-treated group than the untreated group ($p = 0.040$, log-rank test). The aspirin-treated group showed a significantly lower risk of HCC and higher risk of GI bleeding than the untreated group after propensity-score matching (both $p < 0.05$). **Conclusion:** In patients with HBV-related cirrhosis, the aspirin-treated group showed a significantly lower risk of HCC than the untreated group, whereas the risk of GI bleeding was significantly higher in the aspirin-treated group.



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1404-C | BASELINE PREDICTORS OF VIROLOGICAL AND BIOCHEMICAL RESPONSES IN HDV COMPENSATED CIRRHOTIC PATIENTS TREATED WITH BULEVERTIDE MONOTHERAPY (HEP4Di STUDY)

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Background: Bulevirtide (BLV) has been approved by EMA for treatment of chronic compensated hepatitis D virus (HDV) infection, however predictors of response are still unknown. **Methods:** Consecutive compensated HDV cirrhotic patients treated with BLV 2 mg/day monotherapy were retrospectively enrolled in a multicenter Italian real-life study (HEP4Di). Clinical, biochemical and virological features at BLV start and during treatment were collected. Virological response (HDV RNA undetectable or **e** 2-log decline *vs.* baseline), biochemical response (ALT < 40 U/L) and combined response (biochemical + virological) were assessed. HDV RNA was quantified locally (Robogene 2.0 [LOD 6 IU/mL] in 71% of the patients). **Results:** 97 HDV cirrhotic patients receiving BLV monotherapy up to 96 weeks were included: at BLV start, median age was 52 (29-77) years, 53% males, 100% CPT score A, 9% HIV-positive, 52% with oesophageal varices, 19% with history of previous ascites, 11% with active HCC, 97% on NUC. Median ALT were 80 (26-1,074) U/L, liver stiffness measurement (LSM) 17.4 (6.4-68.1) kPa, platelets 83 (17-330) x10^3/mm^3, HBsAg 3.7 (0.8-4.5) Log IU/mL and HDV RNA 5.1 (1.2-7.6) Log IU/mL. At BLV treatment weeks (W) W24, W48, W72 and W96, rates of virological response were 53%, 70%, 75% and 80%, respectively, and HDV RNA was undetectable in 16%, 15%, 38% and 33% patients. Biochemical response was achieved by 65%, 74%, 81% and 67% at W24, W48, W72 and W96, respectively, while rates of combined response were 38%, 59%, 63% and 67%. By univariate logistic regression analysis, baseline viremia was the only factor associated with the achievement of virological response: indeed, HDV RNA levels < 5 LogIU/mL predicted HDV RNA < 1000 IU/mL (OR 3.33, 95% CI 1.19-9.26, $p = 0.02$) and < 100 IU/mL (OR 7.30, 95% CI 2.49-21.41, $p = 0.0003$) at week 24, while HDV RNA levels < 4 LogIU/mL were associated with HDV RNA < 100 IU/mL at week 24 (OR 7.37, 95% CI 2.21-24.60, $p = 0.001$). Conversely, none of the other baseline clinical features (age, sex, albumin, platelets, presence of varices, ALT values, bile acids) were associated with virological response, and none of the baseline clinical/virological features predicted biochemical or combined response. **Conclusion:** In HDV compensated cirrhotic patients treated with BLV monotherapy, baseline viremia is the only factor associated with early virological response at week 24. Week 48 data will be presented at the meeting.

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1405-C | BONE AND RENAL SAFETY OF TENOFOVIR ALAFENAMIDE (TAF) AT 8 YEARS IN CHRONIC HBV (CHB) PATIENTS WITH UNDERLYING RISK FACTORS FOR USE OF TENOFOVIR DISOPROXIL FUMARATE (TDF)

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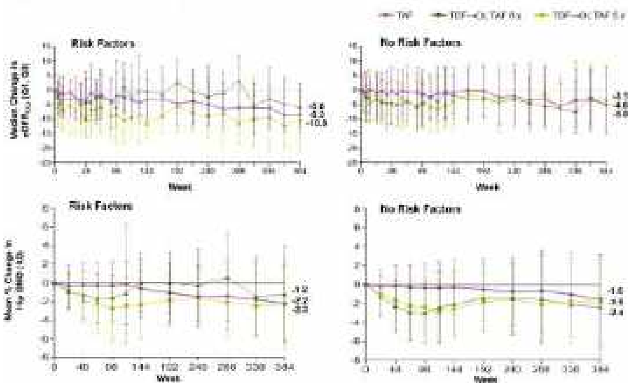
Background: Current guidelines recommend using TAF or entecavir as alternative first-line therapy in patients with risk factors for TDF-associated toxicities. We evaluated the safety of TAF, including in patients switched from TDF to TAF, who were considered to be at risk for adverse bone and/or renal effects from TDF based on EASL guidelines. **Methods:** In two similarly designed Phase 3 studies, HBeAg-positive ($N = 873$) and HBeAg-negative ($N = 425$) patients were initially randomized (2:1) to TAF 25 mg QD vs TDF 300 mg QD in a double-blind (DB) phase for up to 3 years, after which all patients received TAF during the open-label (OL) extension phase (ie, TAF vs TDF→TAF). Safety results were pooled for bone (serial DXA scans at hip/spine and serum bone biomarkers) and renal (eGFR by Cockcroft-Gault [eGFR$_{CG}$] and urinary biomarkers of tubular function) parameters assessed over 8 years in the subsets with or without baseline risk factors for TDF use: age > 60 y, osteoporosis at hip/spine by t-scores, eGFR$_{CG}$ < 60 mL/min, urine albumin-to-creatinine ratio > 30 mg/g, or serum phosphorus < 2.5 mg/dL. **Results:** Of 1298 randomized and treated patients, 239 (18%; 151 TAF and 88 TDF→TAF) had at least 1 risk factor. Baseline demographics were similar between treatment groups: 29% with age > 60 y, 60% male, 40% with eGFR$_{CG}$ $<$ 90 mL/min, and 6% and 36% with osteoporosis at hip and spine, respectively. A greater median decline in eGFR was seen in TAF-treated patients with risk factors at Year 8 (−8.3 vs −4.6 ml/min) compared to those without. In the TDF→TAF groups, a greater degree of recovery was noted in those with risk factors switched at Year 2 vs Year 3 (Figure). In the TAF group, mean % decline in hip BMD at Year 8 was small regardless of risk factor status. In the TDF→TAF groups, mean % increases occurred after switching to TAF with changes that were similar to the TAF group at Year 8, supporting sustained reversibility of TDF-associated bone loss. Consistent changes were seen in proteinuria markers and serum bone biomarkers. **Conclusion:** Long-term TAF treatment showed favorable renal and bone tolerability in patients with and without baseline risk factors for TDF use supporting guideline recommendations.

Figure. Bone and Renal Changes Over 8 Years in CHB Patients With/Without TDF Risk Factors



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1406-C | CHRONIC HEPATITIS B (CHB) PATIENTS WITH NORMAL ALT MAY HAVE IMPROVED LONG-TERM OUTCOMES AFTER ANTIVIRAL THERAPY

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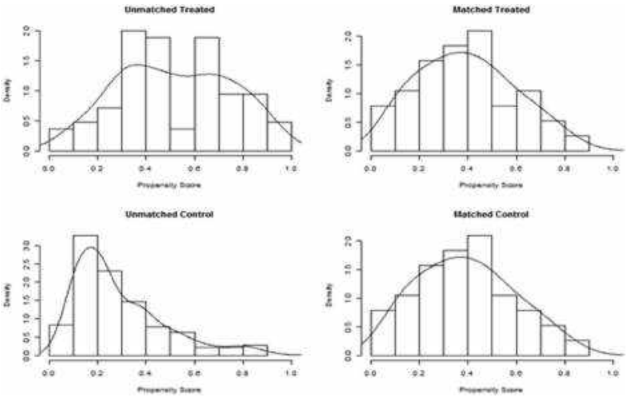
Background: With the improved efficacy and accessibility of antiviral agents as well as the concerns about disease progression, there is a hot discussion on whether HBeAg-negative chronic hepatitis B (CHB) patients with normal alanine aminotransferase (ALT) and positive HBV DNA should be treated. However, studies on long-term outcomes of antiviral therapy in CHB patients with normal ALT are still lacking. **Methods:** 256 cases of HBV infection in the antiviral therapy group of our study cohort from January 2008 to January 2021 were retrospectively enrolled. Patients with normal ALT at baseline were assigned to the study group (n = 61), alT1-2 ×ULN at baseline were assigned to the control group 1 (n = 62), ALT > 2×ULN were assigned to the control group 2 (n = 58), and were recieved NAs antiviral therapy. The above three groups were incorporated into the treatment group, and 256 subjects who were not treated with antiviral therapy were included in the historical control group by propensity score matching with gender, age and baseline HBeAg as factors. The occurrence of cirrhosis or liver cancer was the endpoint, and no endpoint event was observed until the last follow-up. SPSS 20.0 software package was used for statistical analysis, and lifetime table method was used to calculate the cumulative progression rate and the annual incidence of end-point events (cirrhosis, liver cancer, death). Analysis of variance was used to compare measurement data between the three groups. **Results:** 182 (71.1%) of the 256 patients in the study group were male. The mean follow-up time was 3.13 years. In the historical control group, there were 190 males (74.2%) with a mean follow-up of 3.63 years. The annual incidence of cirrhosis was 2.24% in the treatment group and 5.6% in the historical control group ($p < 0.05$). The annual incidence of liver cancer in the treatment group and the historical control group was 0.4% and 3.2%, respectively ($p < 0.05$).The annual incidence of cirrhosis in the study group,the control group 1 and the control group 2 were 1.97%, 1.56% and 1.09%, respectively ($p > 0.05$). **Conclusion:** Patients with positive serum HBV DNA, regardless of ALT level, active antiviral therapy is beneficial to delay and reduce the occurrence of liver failure, cirrhosis, HCC and other complications, improve the patients' quality of life , and prolong their survival time.



Disclosures: The following people have nothing to disclose: Zhihong Liu, Jianning Jiang, Cailian Cai

1407-C | COMPARABLE RISK OF RENAL DYSFUNCTION BETWEEN ENTECAVIR AND TENOFOVIR ALAFENAMIDE IN PATIENTS WITH CHRONIC HEPATITIS B

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Background: A previous study suggested a higher higher risk of renal function decline with entecavir (ETV) compared to tenofovir alafenamide (TAF) in treatment-naïve patients with chronic hepatitis B (CHB). However, the sample size was limited. This study aimed to compare the risk of renal dysfunction between ETV and TDF in a large-scale hospital cohort of treatment-naïve CHB patients. **Methods:** A total of 3,343 treatment-naïve patients with CHB who received with ETV or TAF at Asan Medical Center, Seoul, Republic of Korea were included. The primary outcome was chronic kidney disease (CKD) progression, defined as an increase in CKD stage by at least one stage. CKD stage was based on the estimated glomerular filtration rate (GFR), determined using the CKD-EPI equation. Patients below 18 years old, with a history of hepatocellular carcinoma or other malignancies, baseline eGFR < 60 ml/min, or follow-up duration < 3 months were excluded. Multivariable Cox models were used to evaluate factors associated with CKD progression. Propensity score (PS) matching was conducted to minimize baseline characteristic differences and compare the primary outcome. **Results:** Of the 3,343 patients, 2,635 (78.8%) received ETV and 708 (21.2%) received TAF. The mean age was 49.0 years in the ETV group and 49.3 years in the TAF group. Cirrhosis was present in 52.4% of the ETV group and 38.1% of the TAF group. Baseline median eGFR was significantly lower in the ETV (81.0 mL/min) than TAF group (90.0 mL/min). The prevalence of hypertension and diabetes was higher in the ETV group (5.9% and 7.9%) than TAF group (4.0% and 4.4%). Over 18,806 person-years (PYs) of observation, 207 patients experienced CKD progression, resulting in an annual incidence of 1.10 / 100 PYs. Multivariable analysis identified hypertension, diabetes, and increasing age as significant factors for CKD progression. However, treatment with TAF compared to ETV was not independently associated with the risk of CKD progression (adjusted hazard ratio: 0.87, 95% confidence interval: 0.46–1.66, $p = 0.68$). PS matching generated 586 matched pairs and baseline characteristics were comparable between the two groups. CKD progression occurred in 36 patients treated with ETV (3,358 PYs of observation) and in 10 patients treated with TAF (1,008 PYs of observation). The annual incidence of CKD progression was 1.10 / 100 PYs in the ETV group and 0.99 / 100 PYs in the TAF group, without a statistically significant difference ($p = 0.08$). **Conclusion:** In contrast to previous report, the risk of renal dysfunction did not significantly differ between ETV and TAF in this larger historical cohort with sufficient long-term follow-up period.

Disclosures: The following people have nothing to disclose: Jiwon Yang, Yeojin Lee, Hyeyeon Hong, Sung Won Chung, Minjoo Cho, Won-Mook Choi, Danbi Lee, Ju Hyun Shim, Kang Mo Kim, Young-Suk Lim, Han Chu Lee, Jonggi Choi

1408-C | COMPARABLE SAFETY AND EFFICACY OF TENOFOVIR ALAFENAMIDE WITH TENOFOVIR DISOPROXIL FUMARATE IN PREGNANT WOMEN: SYSTEMATIC REVIEW WITH META-ANALYSIS

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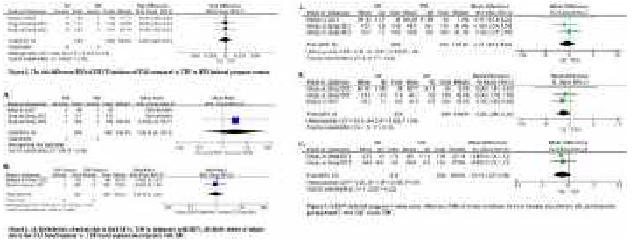
Background: Tenofovir alafenamide (TAF) has been administered extensively in patients with hepatitis B virus (HBV) or human immunodeficiency virus (HIV). Mother-to-child transmission (MTCT) is one of the main transmission routes for HBV and HIV. Whereas, data about TAF in pregnant women was insufficient. To further evaluated the safety and effectiveness of TAF during pregnancy and direct clinical practice, we conducted a review and meta-analysis. **Methods:** Two reviewers independently searched randomized controlled trials and nonrandomized trials concerning peripartum TAF administered in MEDLINE (PubMed), Embase, Cochrane library, Clinical Trials.gov, Wanfang, and Chinese National Knowledge Infrastructure (CNKI), without language restriction, published from inception to March 10, 2023. The search terms covered HBV (or HIV), TAF, and pregnancy. We enrolled the studies concerning pregnant women with HBV or HIV infection receiving TAF during pregnancy. The following outcomes should be reported: the MTCT rate, the incidence of congenital malformations in new-borns, and the changes in serum creatinine levels during and after treatment. **Results:** Nine studies involving 1359 pregnant women were included for final analyses. Among the 6 studies of HBV infected pregnant women, the pooled rate of MTCT was zero in pregnant women administered with TAF (N = 513). Similarly, the pooled MTCT rate was also zero in the study of pregnant women with HIV infection receiving antiviral therapy containing TAF regimen. Further compared with pregnant women receiving tenofovir disoproxil fumarate (TDF), risk differences of TAF for congenital malformations was 0.00 (-0.01-0.02, $p = 0.61$) in HBV-infected pregnant women receiving TAF. Among all HBV-infected pregnant women treated with TAF, only one case of congenital malformations was reported. Additionally, among HIV-infected pregnant women, the odds ratio of birth defects for the TAF-containing antiviral regimens compared with the TDF-containing antiviral regimens was 1.02 (0.46, 2.27, $p = 0.96$). Moreover, among HBV-infected pregnant women, the mean difference of serum creatinine level between TAF group and the TDF group were comparable, -1.22 (-0.28, 0.36, $p = 0.13$) at delivery and -1.11 (-2.87, 0.65, $p = 0.22$) at 6 months after delivery, respectively. **Conclusion:** In pregnant women with HBV or HIV infection, the administration of TAF or TAF-containing antiviral regimens can effectively prevent MTCT. Compared with TDF or TDF-containing regimen, TAF or TAF-containing regimen presents comparable safety in mothers and infants.

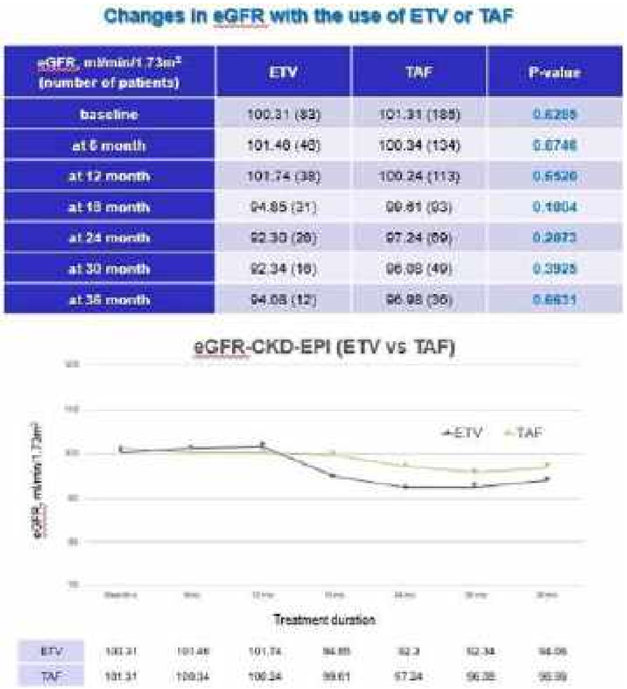


Disclosures: The following people have nothing to disclose: Ruojing Wang, Xiaoli Zhang, Shan Fu, Yali Feng, Yingren Zhao, Jinfeng Liu, Tianyan Chen

1409-C | COMPARISON OF THE EFFECTS OF ENTECAVIR AND TENOFOVIR ALAFENAMIDE ON KIDNEY FUNCTION IN CHRONIC HEPATITIS B: PROPENSITY SCORE MATCHED RETROSPECTIVE COHORT STUDY

Eunjee Lim and Jin-Wook Kim, Seoul National University Bundang Hospital

Background: Since the treatment of chronic hepatitis B involves long-term medication, it is crucial to take into account the potential negative effects of the drugs when choosing the appropriate treatment. Long-term treatment with nuleos(t)ide analogues (NAs) such as adefovir or tenofovir disoproxil fumarate (TDF) may impair renal function in chronic hepatitis B (CHB). Entecavir (ETV) and tenofovir alafenamide (TAF) are known to be safer than adefovir or TDF for renal function, but insufficient research has been conducted comparing the renal effects of these two drugs. Therefore, we retrospectively investigated the effect of TAF or ETV on estimated glomerular filtration rate (eGFR) in chronic hepatitis B patients. **Methods:** This study evaluated propensity score (PS)-matched 268 treatment-naive patients with CHB who had been treated with either ETV (n = 83) or TAF (n = 185) between 2017 and 2021. Changes in renal functions were monitored over a period of 36 months (at baseline, 6, 12, 18, 24, 30 and 36 mo). Patients were excluded if they had used any nucleotide analogue other than those two specific drugs, received preemptive therapy for drug treatment, had a baseline HBV DNA level below 27 unit/ml confirmed as negative, had no previous HBV DNA or eGFR data before starting the drug, had a follow-up duration of less than 90 days, had experienced sepsis or received an organ transplant, had a history of alcohol-related liver disease or cancer including HCC, had HCV co-infection or were diagnosed with ESRD. Propensity score matching was conducted using age, sex, baseline HBV DNA level, baseline creatinine (Cr) level, baseline eGFR-CKD-EPI level, systolic blood pressure (SBP), platelet count (PLT), total bilirubin, prothrombin time (PT, INR), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) and presence of portal systemic encephalopathy (PSE)/ascites/diabetes mellitus (DM)/dyslipidemia (DL). **Results:** The baseline mean eGFR was 100.31 ml/min/1.73 m2 vs. 101.31 ml/min/1.73 m2 in the ETV and TAF groups, respectively (*p* = 0.63). Comparison of eGFR between ETV group and TAF group during follow-up showed no significant differences at 6 months (101.46 vs 100.34, *p* = 0.67), 12 months (101.74 vs 100.24, *p* = 0.65), 18 months (94.85 vs 99.61, *p* = 0.18), 24 months (92.30 vs 97.24, *p* = 0.21), 30 months (92.34 vs 96.08, *p* = 0.39) and 36 months (94.08 vs 96.98, *p* = 0.66), respectively. Furthermore, there was no significant difference in annual changes in eGFR (ETV -1.38 vs TAF -2.04, *p* = 0.5708) and 1-stage progression of CKD stage at study endpoints between the two treatment groups (ETV 10.8% vs TAF 18.8%, *p* = 0.21). **Conclusion:** There was no significant difference in eGFR-CKD-EPI between the ETV and TAF treatment groups over a 36-month period in NAs-naive CHB patients. Further research is required to establish the long-term effect of ETV and TAF on kidney function.



Changes in eGFR with the use of ETV or TAF

eGFR, ml/min/1.73m² (number of patients)	ETV	TAF	P-value
baseline	100.31 (83)	101.31 (188)	0.6285
at 6 month	101.46 (46)	100.34 (134)	0.6746
at 12 month	101.74 (38)	100.24 (113)	0.6520
at 18 month	94.85 (31)	99.61 (93)	0.1804
at 24 month	92.30 (26)	97.24 (69)	0.2073
at 30 month	92.34 (16)	96.08 (49)	0.3925
at 36 month	94.08 (12)	96.98 (36)	0.6631

eGFR-CKD-EPI (ETV vs TAF)

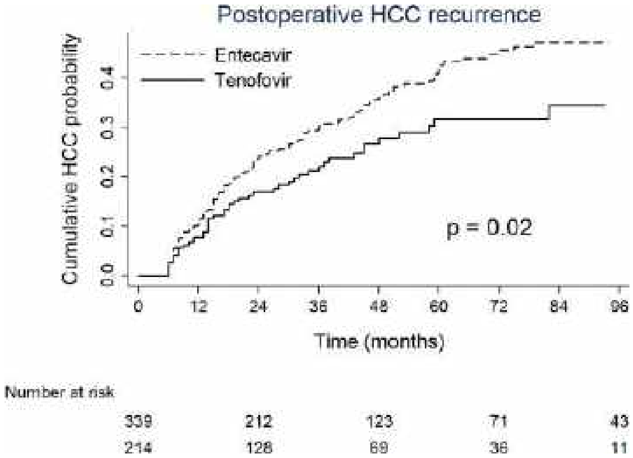
ETV	100.31	101.46	101.74	94.85	92.3	92.34	94.08
TAF	101.31	100.34	100.24	99.61	97.24	96.08	96.98

Disclosures: The following people have nothing to disclose: Eunjee Lim, Jin-Wook Kim

f 1410-C | COMPARISON OF THE EFFECTS OF ENTECAVIR AND TENOFOVIR DISOPROXIL FUMARATE ON RECURRENCE OF HEPATOCELLULAR CARCINOMA AFTER CURATIVE RESECTION IN CHRONIC HEPATITIS B

Eunjee Lim and Jin-Wook Kim, Seoul National University Bundang Hospital

Background: Antiviral therapy with nuleos(t)ide analogues (NAs) may reduce the risk of hepatocellular carcinoma (HCC) recurrence after curative resection in patients with chronic hepatitis B (CHB). However, it is not fully elucidated whether entecavir (ETV) or tenofovir disoproxil fumarate (TDF) provide a comparable beneficial effect on postoperative recurrence of HCC. Therefore, we investigated the effect of TDF or ETV on recurrence of HCC after curative surgery in chronic hepatitis B patients. **Methods:** This retrospective cohort study analyzed 553 patients who received either ETV (n = 339) or TDF (n = 214) after curative resection of HCC. The curative surgery included hepatectomy, lobectomy, sectionectomy, segmentectomy, and tumorectomy. The recurrence was confirmed based on positive imaging studies. We used Kaplan-Meier estimation to assess HCC recurrence, and used a multivariable-adjusted Cox proportional hazard model to adjust covariates between the two groups. **Results:** The median age of patients was 61 years (ETV group 62 y, TDF group 59 y) and 78% were male (ETV group 76%, TDF group 82%). The median follow-up duration was 32 months (ETV group 33 mo, TDF group 32 mo). The cumulative HCC recurrence rate was 9, 21, 27 and 38% after 12, 24, 36 and 60 months, respectively. By multivariable-adjusted analysis, more recurrence was observed with younger patients (hazard ratio[HR] = 0.970, 95% CI = 0.955-0.986, *p* value = 0.000), male (HR = 1.704, 95% CI = 1.117-2.600, *p* value = 0.013), lower albumin level (HR = 0.543, 95% CI = 0.389-0.757, *p* value = 0.000) and use of TDF compared to ETV (HR = 0.612, 95% CI = 0.434-0.864, *p* value = 0.005). **Conclusion:** This study showed that TDF treatment was associated with a significantly lower risk of HCC recurrence following curative surgery compared to ETV treatment among patients with CHB.



Disclosures: The following people have nothing to disclose: Eunjee Lim, Jin-Wook Kim

1411-C | EFFECTIVENESS AND SAFETY OF SWITCHING TENOFOVIR DISOPROXIL FUMARATE AND ENTECAVIR TO TENOFOVIR ALAFENAMIDE FUMARATE (TAF) IN VIROLOGICALLY SUPPRESSED CHRONIC HEPATITIS B VIRUS-INFECTED PATIENTS WITH ONE-MINUTE OSTEOPOROSIS RISK TEST

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Background: Long-term antiviral treatment is necessary for chronic hepatitis B (CHB) patients and treatment safety is imperative for these patients. However, there is still lack of a rapid and convenient method to identify CHB patients at high risk of osteoporosis before initiating antiviral treatment. One-minute osteoporosis risk test(Figure 1) was recommended to screen early high-risk patients by international osteoporosis foundation (IOF). Previous studies showed tenofovir alafenamide (TAF) has shown efficacy non-inferior to that of tenofovir disoproxil fumarate (TDF) with improved renal and bone safety. We aimed to evaluate the feasibility of the one-minute osteoporosis risk test as well as the effectiveness and safety among virologically suppressed CHB patients switching to TAF. **Methods:** In this multiple, prospective study, CHB patients who had been receiving TDF or ETV for at least 48 weeks with HBV DNA less than 20 IU/ml for more than 6 months were screened by one-minute osteoporosis risk test. Patients at high risk of osteoporosis and then diagnosed with osteopenia or osteoporosis by dual-energy X-ray absorptiometry (DEXA) were enrolled. Safety in bone and bone turnover markers and antiviral efficacy of TAF were assessed respectively at 24 and 48 weeks. **Results:** 84.95% (175/206) CHB patients screened by one-minute osteoporosis risk test were at risk of osteoporosis. 85.71% (150/175) of them were diagnosed with osteopenia by DEXA. A total of 138 patients were included for analysis.92(62.3%) patients were male, and 46 (37.7%) patients were female, with a mean age of 45 years old. HBV DNA was suppressed at 48 weeks with 88% (35/40) in the prior ETV group, and 90% (88/98) in the prior TDF group. BMD of the lumbar spine (L1-L4) in patients switching from TDF to TAF was improved at 24 weeks (1.03 ± 0.11 vs 0.97 ± 0.12, $p = 0.001$) than baseline. Serum Propeptide of type I procollagen (PINP) and serum beta-C-terminal telopeptides of type 1 collagen (CTX) declined at 24 weeks after switching from TDF to TAF compared with baseline (50.35 ± 18.90 vs 63.65 ± 19.17, $p = 0.016$ and 0.21 ± 0.13 vs 0.32 ± 0.10, $p = 0.017$). BMD, PINP, and CTX in the prior ETV group maintained stable compared with baseline (Table 1). **Conclusion:** Osteoporosis risk should be paid closely attention to during lone-term nucleot(s)ide analogue treatment. One minute test of osteoporosis risk could rapidly identify most CHB patients at risk of osteoporosis. It is convenient and we recommend this test for early screening in CHB patients before initiating antiviral treatment. Our results also demonstrated that there is improvement in bone safety after switching to TAF in virologically suppressed CHB patients with osteoporosis.

Figure 1. One-minute osteoporosis risk test

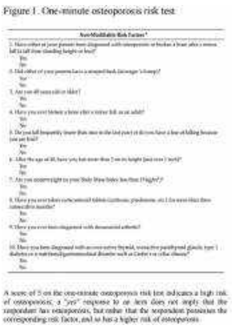
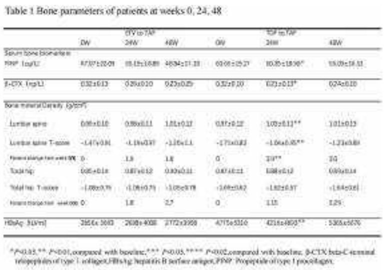


Table 1 Bone parameters of patients at weeks 0, 24, 48



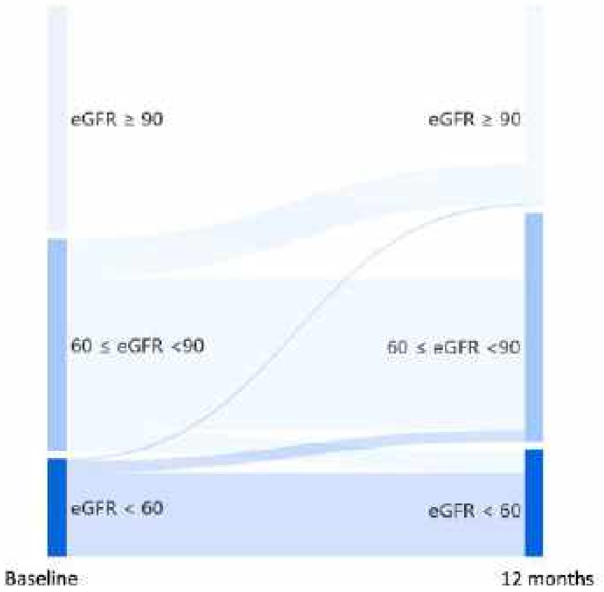
Disclosures: The following people have nothing to disclose: Hui Li, Chunmei Li, Jia Wei, Yunhua Liu, Ming Gong, Ruyi Zhang, Jiawei Geng, Hongyan Wang, Zhijian Yu, Zi Wang, Xiang Liu

1412-C | EFFICACY AND RENAL SAFETY IN CHRONIC HEPATITIS B PATIENTS ON TENOFOVIR ALAFENAMIDE

Lilian Yan Liang[1], Vicki Wing Ki Hui[1], Terry Cheuk-Fung Yip[2], Jimmy Che-To Lai[1], Yee-Kit Tse[1], Henry Lik Yuen Chan[1], Vincent Wai-Sun Wong[1] and Grace Lai-Hung C Wong[3], (1)The Chinese University of Hong Kong, (2) The Chinese University of Hong Kong, Hong Kong, 91, China, (3)Medical Data Analytics Centre (MDAC), the Chinese University of Hong Kong

Background: Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir. We aimed to evaluate the antiviral effectiveness and renal safety in those chronic hepatitis B (CHB) patients on TAF treatment during the first 12 months of follow-up. **Methods:** This is a retrospective cohort study. TAF-treated CHB patients who were previously treated naïve were included. The baseline was defined as the start date of TAF treatment. Chronic kidney disease (CKD) progression was defined as an increase in the CKD stage of at least one stage for at least three consecutive months. **Results:** We analyzed 296 treatment-naïve CHB patients on TAF treatment, among whom 181 (61.1%) patients are males and their mean age was 59 ± 14 years old. The median TAF treatment duration was 17 months. The proportion of patients with undetectable hepatitis B virus (HBV) DNA increased from 37.9% to 78.1% ($p < 0.001$). The majority of patients achieved alanine transaminase (ALT) normalization at 12 months (71.1%) compared with that of baseline (50.3%) ($p < 0.001$). The number of patients with estimated glomerular filtration rate (eGFR) **e** 90, between 60 and 90, and < 60 mL/min/1.73 m^2 were 97 (42.4%), 91 (39.6%) and 42 (18.3%) at baseline and 86 (37.4%), 98 (42.6%) and 46 (20.0%) at 12 months, respectively ($p = 0.067$) (Figure). 28 (9.4%) patients experienced CKD progression during the first 12 months of follow-up. **Conclusion:** The use of TAF improves the virological and biochemical responses with comparable kidney function during the first 12 months of follow-up.

Figure. The dynamic changes of eGFR levels at baseline and 12 months.



Disclosures: Terry Cheuk-Fung Yip – Gilead Sciences: Consultant, No, No; Gilead Sciences: Speaking and Teaching, No, No;

Henry Lik Yuen Chan – Aligos: Advisor, No, No; GSK: Advisor, No, No; Gilead Sciences, Inc.: Advisor, No, No; Roche: Advisor, No, No; Vaccitech: Advisor, No, No; Vir Biotechnology: Advisor, No, No; Virion Therpeutics: Advisor, No, No; Gilead Sciences, Inc.: Speaking and Teaching, No, No; Roche: Speaking and Teaching, No, No; Viatris: Speaking and Teaching, No, No;

Grace Lai-Hung C Wong – Gilead Sciences, Inc.: Advisor, No, No; Janssen: Advisor, No, No; Abbott Diagnostics: Speaking and Teaching, No, No; AbbVie: Speaking and Teaching, No, No; Ascletis: Speaking and Teaching, No, No; Bristol Myers Squibb: Speaking and Teaching, No, No; Echosens: Speaking and Teaching, No, No; Gilead Sciences, Inc.: Speaking and Teaching, No, No; Janssen: Speaking and Teaching, No, No; Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;

The following people have nothing to disclose: Lilian Yan Liang, Vicki Wing Ki Hui, Jimmy Che-To Lai, Yee-Kit Tse, Vincent Wai-Sun Wong

1413-C | EFFICACY AND SAFETY OF PEGYLATED INTERFERON ALPHA-2b IN HBV POSTPARTUM WOMEN WITH LOW HBsAg LEVELS: AN EXPLORATORY STUDY IN SOUTHWEST CHINA

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Background: To date, there is limited data on the efficacy and safety of pegylated interferon alpha-2b (Peg-IFN α-2b) treatment for postpartum women with hepatitis B virus infection. In this exploratory study, we assessed the virological and serological responses of Peg-IFN α-2b alone or in combination with tenofovir disoproxil fumarate (TDF) therapies for HBV postpartum women with low HBsAg level. **Methods:** Postpartum patients received TDF during pregnancy or treatment-naïve with HBsAg **d** 3000 IU/mL were included in this study (No.ChiCTR 2200058096). All of them received at least 48 weeks of Peg-IFN α-2b therapy after delivery. The primary endpoint was HBsAg clearance rate at the end of the treatment (EOT). Clinical and laboratory data and adverse events (AEs) were collected. **Results:** A total of 42 HBV postpartum women were included and half of them had already received TDF during pregnancy. The mean age was 32.4 (± 3.4) years and 38 (90.5%) patients were HBeAg-negative. The mean initial treatment time of Peg-IFN α-2b was 9.4 (± 4.3) months after delivery. Till now, 34 (81.0%) patients completed treatment, and the data of these patients were analyzed. At EOT, 41.2% (14/34) patients achieved HBsAg clearance and 35.3% (12/34) achieved HBsAg seroconversion. The median treatment time for HBsAg clearance was 24.5 (14.5-39.5) weeks and the median HBsAb level in patients with HBsAg seroconversion was 339.3 (107.2-633.2) IU/L. The median baseline HBsAg level in patients with HBsAg clearance was significantly lower than those without HBsAg clearance (271.6 IU/mL vs. 956.9 IU/mL, $p = 0.002$), and the decline degrees of HBsAg at 12th and 24th week from baseline were significantly higher than those without HBsAg clearance (99.8% vs. 43.0%, $p = 0.000$; 100% vs. 70.1%, $p = 0.000$), while the baseline ALT and HBV DNA levels were not significantly different. 90.0% (9/10) patients with HBV DNA-positive at baseline converted to HBV DNA-negative at EOT. Three patients discontinued Peg-IFN α-2b therapy due to AEs, which included abnormal thyroid function (2/3) and thrombocytopenia (1/3). **Conclusion:** Peg-IFN α-2b monotherapy or combined with TDF treatment in HBV postpartum women with low HBsAg levels can obtain relatively high HBsAg clearance rate. The baseline HBsAg level and on-treatment HBsAg declines at 12/24 weeks might be valuable predictors of HBsAg clearance at EOT.

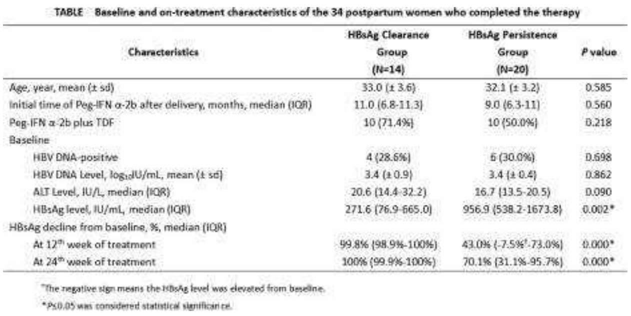

TABLE Baseline and on-treatment characteristics of the 34 postpartum women who completed the therapy

Characteristics	HBsAg Clearance Group (N=14)	HBsAg Persistence Group (N=20)	P value
Age, year, mean (± sd)	33.0 (± 3.6)	32.1 (± 3.2)	0.585
Initial time of Peg-IFN α-2b after delivery, months, median (IQR)	11.0 (6.8-11.3)	9.0 (6.3-11)	0.560
Peg-IFN α-2b plus TDF	10 (71.4%)	10 (50.0%)	0.218
Baseline			
HBV DNA-positive	4 (28.6%)	6 (30.0%)	0.698
HBV DNA Level, $\log_{10}$IU/mL, mean (± sd)	3.4 (± 0.9)	3.4 (± 0.4)	0.862
ALT Level, IU/L, median (IQR)	20.6 (14.4-32.2)	16.7 (13.5-20.5)	0.090
HBsAg level, IU/mL, median (IQR)	271.6 (76.9-665.0)	956.9 (538.2-1673.8)	0.002*
HBsAg decline from baseline, %, median (IQR)			
At 12th week of treatment	99.8% (98.9%-100%)	43.0% (-7.5%[†]-73.0%)	0.000*
At 24th week of treatment	100% (99.9%-100%)	70.1% (31.1%-95.7%)	0.000*

[†] The negative sign means the HBsAg level was elevated from baseline.

*P≤0.05 was considered statistical significance.

Disclosures: The following people have nothing to disclose: Yan Guo, Li Jiang, Ming Liu, Yi Wu, Jie Xia, Guohong Deng, Qing Mao

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1414-C | EFFICACY AND SAFETY OF TENOFOVIR ALAFENAMIDE (TAF) AT 2 YEARS IN CHILDREN AND ADOLESCENTS WITH CHRONIC HEPATITIS B (CHB)

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Background: TAF, a novel prodrug of tenofovir, has shown noninferior efficacy with superior bone and renal safety compared to tenofovir disoproxil fumarate in randomized trials in adults with CHB. The US FDA has recently approved TAF for treatment of CHB in patients aged 12 and older and weighing **e** 35 kg with compensated liver disease, based on Week (W) 24 findings from a randomized, double-blind, placebo (PBO)-controlled trial (GS-US-320-1092; NCT02932150) in children and adolescents. Here we report W96 (2 y) findings from this study. **Methods:** CHB patients 12 to < 18 y and **e** 35 kg body weight (Cohort 1; adolescents) and 6 to < 12 y weighing **e** 25 kg (Cohort 2, Group 1; children), with HBV DNA **e** 2×10^4 IU/mL, ALT **e** 1.5 × ULN (30 U/L), and creatinine clearance (eGFR; Schwartz method) **e** 80 mL/min/1.73m^2 were randomized (2:1) to TAF 25 mg or matching PBO once daily (QD) for 24 weeks followed by an open-label (OL) extension phase where all patients received TAF 25 mg

QD through W240 (ie, TAF vs PBO→TAF). At W96, efficacy was assessed by proportion with HBV DNA < 20 IU/mL, serologic, and biochemical responses. Safety assessments included adverse events (AEs) and serious AEs (SAEs) during OL and changes in bone mineral density (BMD) by DXA, eGFR, and resistance surveillance. **Results:** 88 patients were randomized and treated (adolescents: n = 70 [TAF 47, PBO 23]; children: n = 18 [TAF 12, PBO 6]). Overall, mean (range) age and BMI were 14 (7-17) y, and 20.0 (13.6-29.4) kg/m^2; 58% male, 66% Asian, 99% HBeAg-positive, 68% with HBV DNA **e** 8 log$_{10}$ IU/mL; median (Q1, Q3) ALT was 66 (52,103) U/L, and 22% had prior nucleos(t)ide use. Forty-four percent were HBV genotype (GT) D, with 24%, 23%, and 7% being GT C, B, and A, respectively. Results at W96 vs W48 showed increasing proportions with HBV DNA < 20 IU/mL in both groups: TAF (61% vs 37%) and PBO→TAF (48% vs 21%). In the TAF group, there was a trend for higher viral suppression in adolescents vs children at W96: 64% vs 50%. Most AEs were mild-moderate; no patient had a Grade 3 or 4 AE or serious AE related to study treatment, and none discontinued TAF due to an AE. At W96, changes from baseline in BMD and in eGFR for the TAF vs PBO→TAF groups were similar (Table), and no participant had eGFR < 90 mL/min/1.73m^2. Resistance to TAF was not detected through W96. **Conclusion:** Increasing rates of viral suppression were seen in pediatric CHB patients treated with TAF for 2 years, while the safety profile remained favorable.

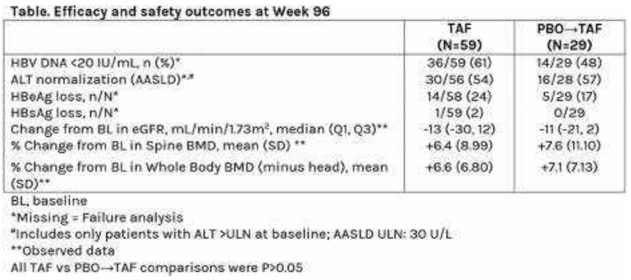

Table. Efficacy and safety outcomes at Week 96

	TAF (N=59)	PBO→TAF (N=29)
HBV DNA <20 IU/mL, n (%)*	36/59 (61)	14/29 (48)
ALT normalization (AASLD)*ª	30/56 (54)	16/28 (57)
HBeAg loss, n/N*	14/58 (24)	5/29 (17)
HBsAg loss, n/N*	1/59 (2)	0/29
Change from BL in eGFR, mL/min/1.73m^2, median (Q1, Q3)**	-13 (-30, 12)	-11 (-21, 2)
% Change from BL in Spine BMD, mean (SD) **	+6.4 (8.99)	+7.6 (11.10)
% Change from BL in Whole Body BMD (minus head), mean (SD)**	+6.6 (6.80)	+7.1 (7.13)

BL, baseline
*Missing = Failure analysis
ªIncludes only patients with ALT >ULN at baseline; AASLD ULN: 30 U/L
**Observed data
All TAF vs PBO→TAF comparisons were P>0.05

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1415-C | EFFICACY AND SAFETY OF TENOFOVIR ALAFENAMIDE FOR 48 WEEKS IN HBEAG-POSITIVE CHB PATIENTS: A REAL-WORLD, MULTICENTER COHORT STUDY

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Background: There is a limited number of real-world studies investigating the efficacy of tenofovir alafenamide (TAF) in China. Nucleotide analogues (such as tenofovir disoproxil fumarate) have been reported to exhibit additional immunoregulatory effects compared to nucleoside analogues. But there are few clinical studies to explore the immunoregulatory effects of TAF, and a lack of prospective cohort studies evaluating serum cytokine changes during treatment. We conducted a multicenter prospective cohort study to assess the efficacy and safety of TAF, HBsAg and cytokines profile was also conducted during 48-week TAF treatment for chronic hepatitis B virus (HBV) infection. **Methods:** We performed a multicentre, prospective real-world study in China, which enrolled 98 HBeAg positive, treatment-naïve CHB patients with baseline HBV DNA > 2×10^4/mL. The enrolled patients were treated with TAF for 48 weeks. Blood samples were collected at 0, 12, 24 and 48 weeks to detect HBsAg level, cytokines (IFN-λ3, IP-10, IL-12, IL-21, IL-10) in patient serum. **Results:** A total of 98 patients were included. The medium levels of baseline HBV DNA and HBsAg were 7.7 $\log_{10}$ IU/mL and 4.3 $\log_{10}$ IU/mL, respectively. After 48 weeks of TAF treatment, HBsAg declined significantly by a median level of 0.53 log10 IU/mL. Among the patients, 28.6% experienced a decline in HBsAg of more than 1 $\log_{10}$ IU/mL, while no patient achieved HBsAg clearance. Additionally, 12 patients (12.2%) achieved HBeAg clearance, 52 patients (53.1%) achieved the complete virological response (HBV DNA **d** 20 IU/mL), and ALT normalization (the American Association for the Study of Liver Diseases criteria) in 56.5% of patients after 48 weeks of treatment. Compared with baseline, there were small mean increases in serum creatinine at week 48 (mean change 0.03 mg/dL [0.01-0.05], $p = 0.006$), with almost no change in blood phosphorus and calcium. During the 48-week treatment, IP-10 declined significantly from baseline to 48 weeks (0W, 12W, 24w, 48w median: 671.3 vs 431.3 vs 287.3 vs 269.5 pg/mL, $p < 0.001$). Similarly, IFN-λ3 slightly decreased during 48-week treatment. IL-12, IL-21 and IL-10 remained stable and did not show significant changes. Based on multivariate analysis, it was found that the baseline IP-10 > 1000 pg/mL was an independent predictor of complete virological response at 48 weeks (OR = 5.26, 95% CI:1.27-21.71, $p = 0.022$). Moreover, baseline HBsAg > 4.6 $\log_{10}$ IU/mL , ALT > 299 U/L and IP-10 > 680 pg/mL were independently related with the decline in HBsAg of more than 1 $\log_{10}$ IU/mL after 48 weeks. **Conclusion:** HBsAg declined significantly after 48-week TAF treatment. TAF demonstrated good renal safety during the 48-week treatment period. Moreover, baseline IP-10 level may be related with antiviral efficacy.

Disclosures: The following people have nothing to disclose: Jiajia Han, Jiming Zhang, Yongmei Zhang, Yao Zhang, Yifei Guo, Feifei Yang, Richeng Mao, Xueyun Zhang

1416-C | EFFICACY AND SAFETY OF TENOFOVIR ALAFENAMIDE IN THE TREATMENT OF DECOMPENSATED CIRRHOTIC PATIENTS WITH CHRONIC HEPATITIS B

You Deng[1], Shuqian Zhang[1], Wenya Chen[1], Jiashuo Li[1], Mengqi Li[1], Qi Wang[1], Hong Zhao[1], Bing Qiao[2] and Wen Xie[1], (1)Center of Liver Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, China, (2) Qingdao Sixth People's Hospital

Background: Hepatitis B viral (HBV) infection is a leading cause of liver cirrhosis and hepatocellular carcinoma (HCC) worldwide. Tenofovir alafenamide (TAF) is a new antiviral drug approved for the treatment of chronic HBV (CHB) infection. However, the effect of TAF therapy on viral suppression and hepatic function in CHB patients with decompensated cirrhosis remains unknown. This study aims to evaluate the efficacy and safety of TAF treatment in CHB patients with decompensated cirrhosis. **Methods:** Decompensated CHB patients with ascites were enrolled and provided 25 mg/day of TAF. Treatment outcomes were evaluated after 24 weeks of treatment, including clinical events, virological, serological, and biochemical responses. **Results:** Among the 182 recruited patients, 126 have completed the 24-week study thus far. At week 24, an undetectable HBV-DNA level was achieved in 56.3% (71/126) of patients, and ALT normalization was observed in 76.2% (96/126) of patients. Additionally, 69 (54.8%) patients experienced resolution of ascites. During the study, one patient died, three patients developed HCC, six patients developed gastroesophageal variceal bleeding, and five patients

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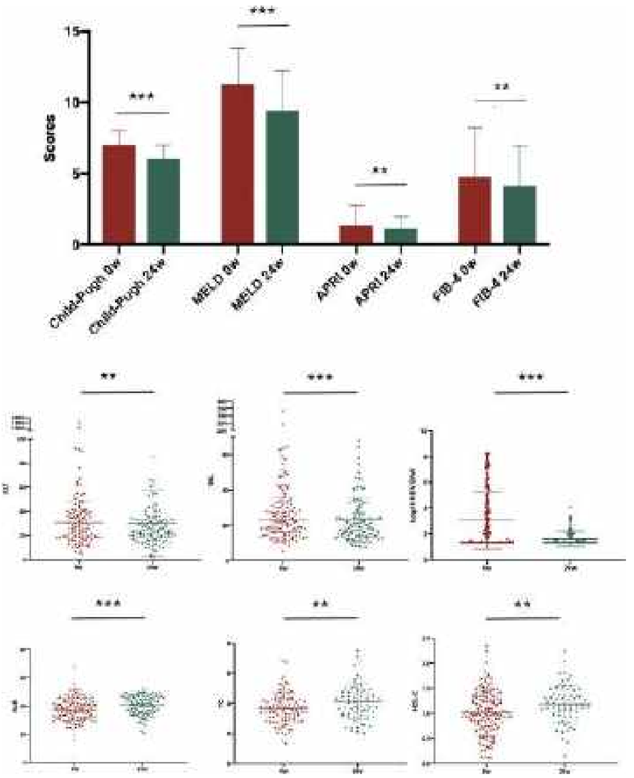
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

developed hepatic encephalopathy. After 24 weeks of TAF treatment, significant improvements were observed in CTP [7.0 (6.0-9.0) vs. 6.0 (5.0-7.0), $p < 0.001$], MELD [11.4 (9.2-13.8) vs. 9.4 (8.3-12.3), $p < 0.001$], FIB-4 [5.2 (2.8-8.5) vs. 4.1 (2.2-7.0), $p = 0.003$], bilirubin [23.9 (16.5, 34.8) μmol/L vs. 18.9 (14.1, 25.8) μmol/L, $p < 0.001$], INR [1.31 (1.20, 1.51) vs. 1.21 (1.13, 1.33), $p = 0.001$], albumin (36.8 ± 7.74 g/L vs. 40.6 ± 6.69 g/L, $p < 0.001$), and ALT [30.3 (19.0, 51.6) IU/L vs. 24.8 (18.5, 33.7) IU/L, $p = 0.009$]. Meanwhile, TAF treatment was associated with a significant increase in blood lipid levels (total cholesterol: 3.64 ± 0.97 vs. 4.10 ± 1.18, $p = 0.004$; high density lipoprotein cholesterol: 1.02 ± 0.43 vs. 1.19 ± 0.37). There was no significant difference in eGFR (102.0 (88.5, 110.6) mL/min vs. 103.6 (91.8, 111.0) mL/min, $p = 0.364$). **Conclusion:** TAF treatment demonstrates efficacy in improving virological and liver function outcomes in CHB patients with decompensated cirrhosis. Further studies are needed to confirm the long-term efficacy and safety of TAF in this patient population.



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1417-C | EFFICACY COMPARISON OF HIGH GENETIC BARRIER NUCLEOS(T)IDE ANALOGUES IN TREATMENT-NAÏVE CHRONIC HEPATITIS B PATIENTS: A NETWORK META-ANALYSIS

Hyun Yang[1], Si Hyun Bae[1], Jaejun Lee[2], Ahlim Lee[1], Pil Soo Sung[3], Jeong Won Jang[3], Jong Choi[2] and Seung Kew Yoon[3], (1)The Catholic University of Korea, (2) College of Medicine, the Catholic University of Korea, (3)Seoul St Mary's Hospital, the Catholic University of Korea, Seoul, Republic of Korea

Background: Chronic HBV infection is a major cause of liver cirrhosis that may progress to hepatocellular carcinoma (HCC). Four high genetic barrier nucleos(t)ide analogues (NA) for CHB, namely entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and besifovir dipivoxil maleate (BSV) have been established. The aim of this study is to investigate the efficacy of four high genetic barrier NAs using a network meta-analysis of randomized trials and propensity score matched cohorts. **Methods:** Systematic search was performed using PubMed, Cochrane library, and EMBASE and included randomized controlled trials and cohort studies that used propensity score matching. Studies on treatment-naïve CHB patients treated with ETV, TDF, TAF, or BSV were included. Outcomes included alanine aminotransferase normalization and HBeAg seroclearance at week 48 and undetectable HBV DNA at week 48 and 96. The ROB2.0 and ROBANS-I tools were used for quality assessment of included studies. Network meta-analysis was performed to synthesize the results. **Results:** In total, 13,822 patients from 15 studies were included. In terms of 48- and 96-week virologic response, TDF was ranked best and outperformed ETV with statistical significance (odds ratio 1.46, $p < 0.001$). ETV was ranked first for 48-week biochemical response and outperformed TDF (odds ratio 0.76, $p = 0.028$). In the sensitivity analyses, 48-week virologic responses from randomized-controlled trials were compiled, and the same trend toward the superiority of TDF over ETV was found (odds ratio = 1.51, $p = 0.030$). **Conclusion:** Four high genetic barrier NAs were compared and TDF and TAF were more likely to achieve a virologic response after 48 weeks and ETV provided a superior biochemical response after 48 weeks. Additional studies with longer treatment durations and large-sample studies are needed to determine the benefit of each of these drugs.

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1418-C | FACTORS ASSOCIATED WITH A LACK OF VIRAL SUPPRESSION IN CHRONIC HBV (CHB) PATIENTS AFTER 8 YEARS OF TREATMENT WITH TENOFOVIR ALAFENAMIDE (TAF) OR TENOFOVIR DISOPROXIL FUMARATE (TDF) FOLLOWED BY TAF TREATMENT

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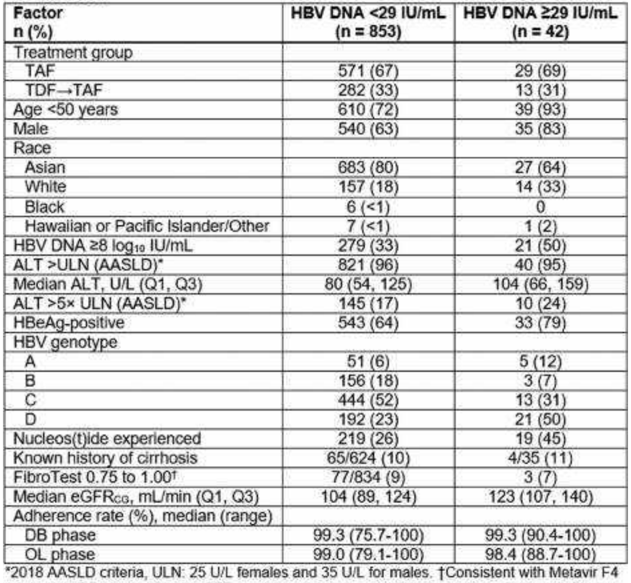
Background: We have previously shown that in CHB patients treated with TAF, or with TDF followed by rollover to TAF, high rates of viral suppression (≥91%) were achieved and maintained at Week 384 (Year 8), with no emergence of antiviral resistance. Although only a small proportion of patients did not suppress, we sought to characterize factors associated with virologic failure after 8 years of treatment in a cohort of patients enrolled in two large Phase 3 studies. **Methods:** Pooled on-treatment data from two similarly designed Phase 3 studies (GS-US-320-0108; HBeAg-negative) and (GS-US-320-0110; HBeAg-positive) were included in this analysis. Briefly, patients were randomized (2:1) to TAF 25 mg QD vs TDF 300 mg QD in a double-blind (DB) phase for up to 3 years, after which all patients received TAF during the open-label (OL) extension phase (ie, TAF and TDF→TAF groups). Patients were assessed by the proportions with or without HBV DNA < 29 IU/mL (COBAS® AmpliPrep/ COBAS® TaqMan® HBV Test, v2.0) at Week 384. Demographic and disease characteristics and other factors potentially influencing treatment response (eg, adherence) were evaluated by univariate and multivariate logistic regression analyses. **Results:** Of 1298 randomized and treated patients, 895 (69%) remained on study treatment at Week 384. Forty-two of 895 (4.7%; TAF 29/600 [4.8%] and TDF→TAF 13/295 [4.4%]) had HBV DNA ≥29 IU/mL at Week 384, and of these, 38 (90%) had achieved HBV DNA < 29 IU/mL, and 4 (10%) had achieved HBV DNA between 29 and < 2000 IU/mL at least once; no patient had a viral nadir ≥2000 IU/mL. Characteristics of patients with HBV DNA < 29 vs ≥29 IU/mL at Week 384 are shown in the Table. Disproportionally more nonsuppressed patients were younger in age, male, White, HBeAg-positive, genotype (GT) A or D, nucleos(t)ide-experienced, and baseline viral load and serum ALT were higher. Treatment assignment and study drug adherence (by pill count) did not differ between groups. By multivariate analysis, predictors of HBV DNA ≥29 IU/mL were: GT A infection (OR 95% CI, 3.24 [1.13, 9.26]; *p* = 0.028); GT D infection (4.03 [2.06, 7.91]; *p* < 0.001), and age < 50 y (4.78 [1.45, 15.71]; *p* = 0.010). **Conclusion:** After 8 years of TAF or sequential TDF and TAF treatment, virologic failures were uncommon. HBV GT A or D infection and younger age were independently associated with lack of suppression.

Table. Characteristics of CHB Patients With/Without Viral Suppression at Week 384



Factor n (%)	HBV DNA <29 IU/mL (n = 853)	HBV DNA ≥29 IU/mL (n = 42)
Treatment group		
TAF	571 (67)	29 (69)
TDF→TAF	282 (33)	13 (31)
Age <50 years	610 (72)	39 (93)
Male	540 (63)	35 (83)
Race		
Asian	683 (80)	27 (64)
White	157 (18)	14 (33)
Black	6 (<1)	0
Hawaiian or Pacific Islander/Other	7 (<1)	1 (2)
HBV DNA ≥8 $\log_{10}$ IU/mL	279 (33)	21 (50)
ALT >ULN (AASLD)*	821 (96)	40 (95)
Median ALT, U/L (Q1, Q3)	80 (54, 125)	104 (66, 159)
ALT >5× ULN (AASLD)*	145 (17)	10 (24)
HBeAg-positive	543 (64)	33 (79)
HBV genotype		
A	51 (6)	5 (12)
B	156 (18)	3 (7)
C	444 (52)	13 (31)
D	192 (23)	21 (50)
Nucleos(t)ide experienced	219 (26)	19 (45)
Known history of cirrhosis	65/624 (10)	4/35 (11)
FibroTest 0.75 to 1.00†	77/834 (9)	3 (7)
Median $eGFR_{CG}$, mL/min (Q1, Q3)	104 (89, 124)	123 (107, 140)
Adherence rate (%), median (range)		
DB phase	99.3 (75.7-100)	99.3 (90.4-100)
OL phase	99.0 (79.1-100)	98.4 (88.7-100)

*2018 AASLD criteria, ULN: 25 U/L females and 35 U/L for males. †Consistent with Metavir F4 (cirrhosis). DB, double-blind; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault method; OL, open-label.

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1419-C | FDA APPROVED DRUG LIBRARY SCREENING TO IDENTIFY COMPOUNDS THAT REDUCE HBS ANTIGEN

Akiyoshi Shimoda[1], Hayato Hikita[1], Kazuhiro Murai[1], Shinji Kuriki[1], Emi Sometani[1], Jihyun Sung[1], Makoto Fukuoka[1], Satoshi Shigeno[1], Akira Nishio[1], Takahiro Kodama[2], Tomohide Tatsumi[2], Hiroshi Suemizu[3] and Tetsuo Takehara[2], (1)Osaka University, Graduate School of Medicine, (2)Osaka University Graduate School of Medicine, (3)Central Institute for Experimental Animals

Background: Hepatitis B surface antigen (HBsAg), a component protein of hepatitis B virus (HBV), is suspected to be related to liver carcinogenesis or immune exhaustion that contributes to persistent infection. Current anti-HBV therapy, nucleos(t)ide analogue (NUC) have little effect on HBsAg. In this study, it is aimed to search for novel treatment to reduce HBsAg by FDA approved drug library screening and to elucidate its mechanism. **Methods:** Library screening with FDA approved drugs consisting of 1134 compounds was performed on HepG2.2.15.7 cells, HBV genome-integrated cells. The screening was conducted at a concentration of 9.9µM for 7 days. After 7 days incubation, the level of HBsAg in the supernatant and cell viability were measured. Compounds that reduced cell viability by more than 1 standard deviation (SD) were excluded. The compounds that decreased the level of HBsAg in the supernatant by more than 1.5 SD were selected as candidate compounds. The candidate compounds were validated at concentrations of 5 and 0.5 µM with the same time course. Compounds that significantly reduced the supernatant HBsAg at both concentrations were selected as final candidate compounds. To elucidate the mechanism of HBsAg reduction, HepG2.2.15.7 cells and HBV-inoculated (1000 genome equivalent/cell) primary human hepatocytes isolated from humanized liver chimeric TK-NOG mice (HepSH cells) were treated with final candidate compounds. **Results:** Total 126 compounds were excluded because their cell viability was below 1 SD. Out of the remaining 1008 compounds, 6 compounds were identified as candidate compounds with HBsAg levels decreased by more than 1.5 SD. Among them, only ethacridine and auranofin significantly decreased HBsAg in the supernatant at the both concentrations of 5 and 0.5 µM. Using HBV-inoculated HepSH cells, while ethacridine did not decrease HBsAg, auranofin decreased HBsAg. Hepatitis B envelope antigen (HBeAg), HBV-DNA in the supernatant or intracellular pregenomic RNA (pgRNA) was not decreased by auranofin. In addition, Western blotting did not show intracellular HBsAg decrease by auranofin. In a transmission electron microscopy image, many vesicles in the endosome were detectable in auranofin-treated HepSH cells inoculated with HBV, but not in untreated HepSH cells inoculated with HBV, suggesting that auranofin suppresses HBsAg secretion from the endosome. **Conclusion:** FDA approved drug library screening identified auranofin which suppresses HBsAg levels.

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f 1420-C | FIBROSIS REGRESSION CONFERS LONG-TERM CLINICAL BENEFITS IN PATIENTS ON ANTI-HBV THERAPY: AN EXTENSION ASSESSMENT BY P-I-R SCORE

Yameng Sun[1], Wei Chen[1], Shuyan Chen[2], Xiaoning Wu[3], Xinxin Zhang[4], Lingyi Zhang[5], Hong Zhao[6], Mingyi Xu[7], Yongpeng Chen[8], Hongxin Piao[9], Ping Li[10], Lei Li[11], Wei Jiang[12], Xiaodong Li[13], Huichun Xing[14], Xudong Liu[15], Yuxi Zhang[16], Bingqiong Wang[3], Jialing Zhou[3], Tongtong Meng[17], Xinyan Zhao[3], Chen Shao[18], Yuanyuan Kong[19], Xinyu Zhao[20], Xiaojuan Ou[3], Chenghai Liu[21], Jidong Jia[3] and Hong You[1], (1)Liver Research Center, Beijing Friendship Hospital, Capital Medical University, (2)Beijing Friendship Hospital, Capital Medical University, Beijing, China, (3)Liver Research Center, Beijing Friendship Hospital, Capital Medical University, National Clinical Research Center of Digestive Diseases, Beijing, China, (4)Department of Infectious Diseases, Research Laboratory of Clinical Virology, National Research Center for Translational Medicine (Shanghai), Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, (5)Department of Hepatology, Second Hospital, Lanzhou University, Lanzhou, China, (6)National Center for Infectious Diseases, Beijing, China, (7)Department of Gastroenterology and Hepatology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, (8)Nanfang Hospital of Southern Medical University, (9)Infectious Department, Affiliated Hospital of Yanbian University, Yanji, Jilin, China, (10) Department of Hepatology, Tianjin Second People's Hospital, Tianjin, China, (11)Department of Gastroenterology and Hepatology, Beijing Youan Hospital, Capital Medical University, Beijing, China, (12) Shanghai Institute of Liver Diseases, Fudan University Shanghai Medical College, Shanghai 200032, China, (13)Hepatic Disease Institute, Hubei Key Laboratory of Theoretical and Applied, Research of Liver and Kidney in Traditional Chinese Medicine, Hubei Provincial

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Background: Liver fibrosis in patients with chronic hepatitis B (CHB) could be regressed with successful antiviral therapy. However, the long-term clinical benefits of fibrosis regression have not been fully elucidated. This study investigated the association between biopsy-proven fibrosis regression by P-I-R score with liver-related events (LREs) in CHB patients. **Methods:** Patients with on-treatment liver biopsy and significant fibrosis/cirrhosis (Ishak **e** stage 3) were enrolled in this study. Fibrosis regression was evaluated according to the P-I-R score of the Beijing Classification. LREs was defined as decompensations, hepatocellular carcinoma (HCC), liver transplantation, or death. Cox proportional hazards model was used to determine associations of fibrosis regression with LREs. **Results:** A total of 733 patients with Ishak stage 3/4 ($n=456$, 62.2%) and cirrhosis (Ishak stage 5/6, $n=277$, 37.8%) by on-treatment liver biopsy were enrolled. According to P-I-R score, fibrosis regression, indeterminate and progression were observed in 314 (42.8%), 230 (31.4%) and 189 (25.8%) patients, respectively. The 7-year cumulative incidence of LREs was 4.1%, 8.7% and 18.1% in regression, indeterminate and progression, respectively (Log-rank, $p<0.001$). Compared with progression, patients with fibrosis regression had a lower risk of LREs (adjusted HR = 0.40, 95%CI: 0.16-0.99, $p=0.047$), followed by indeterminate (adjusted HR = 0.86, 95%CI: 0.40-1.85, $p=0.691$). Specifically, this favorable association was also observed in patients with cirrhosis or low-level platelet counts ($<150\times10^9$/L). **Conclusion:** Antiviral therapy-induced liver fibrosis regression assessed by P-I-R score is associated with reduced liver-related events. This study strengthened the utility of histologic fibrosis regression assessed by on-treatment P-I-R score as surrogate endpoints for clinical events in patients with HBV-related fibrosis or early cirrhosis.

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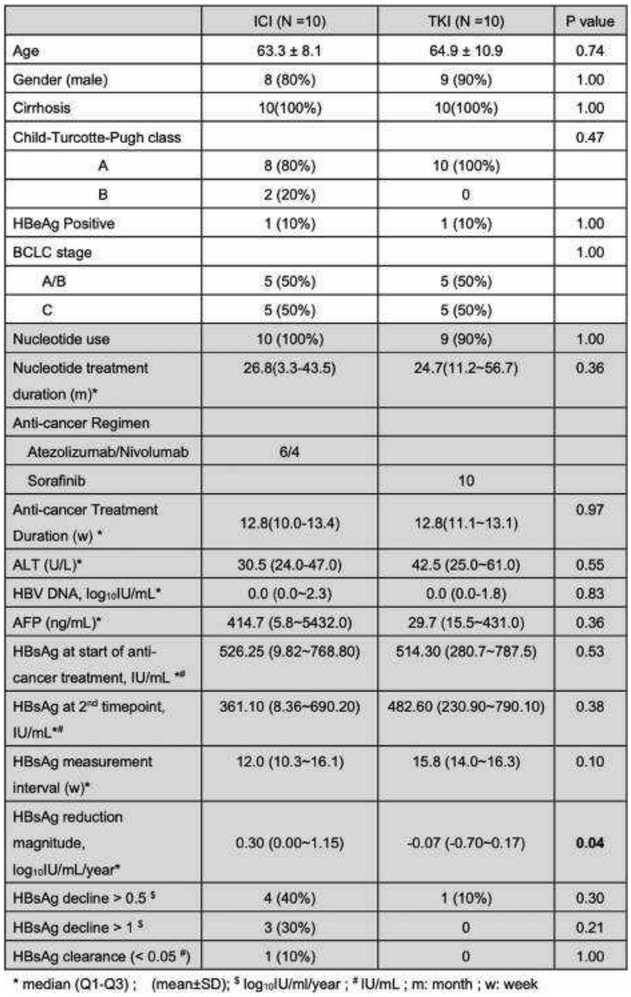
1421-C | Immunotherapy Impact on HBsAg Reduction in Chronic Hepatitis B with HCC: Diminished by Corticosteroid Co-administration

TeWei Tseng[1], Wei Teng[1,2], Po-Ting Lin[1,2], Chung-Wei Su[1,2], Rachel Wen-Juei Jeng[1,2] and Chun-Yen Lin[1,2], (1)Linkou Chang Gung Memorial Hospital, (2)College of Medicine, Chang Gung University, Taiwan

Background: In a recent phase I clinical trial, chronic hepatitis B (CHB) patients treated with 0.3 mg/kg/dose of Nivolumab, a PD1 inhibitor, showed a mean decline of 0.30 $\log_{10}$ IU/ml in HBsAg levels at week 12 and a 4.5% loss of HBsAg after 6 months. However, our study reported in ILC 2023 found that using anti-cancer doses of ICI did not result in greater HBsAg reduction or higher HBsAg loss compared to CHB patients with HCC (CHB-HCC) who received TKIs. Importantly, the common use of corticosteroids among HCC patients undergoing immunotherapy, which can increase HBV replication and reactivation, may influence the inconsistent decline/loss rate of HBsAg between clinical trials and real-world ICI treatment in CHB-HCC patients. To investigate this further, we aim to compare HBsAg kinetics between CHB-HCC patients receiving ICI or TKI anti-cancer treatment, while excluding patients prescribed steroids. **Methods:** Retrospectively enrolled were CHB-HCC patients who received Nivolumab (2-3 mg/kg/dose) or Atezolizumab (1200 mg/dose) plus Bevacizumab (5-10 mg/kg/dose) as ICI therapy, or Sorafenib (400-800 mg/day) as TKI therapy, between 2012 and 2023. Only patients with a follow-up > 8 weeks were included, while those with prior systemic cancer treatments or concurrent steroid administration during ICI or TKI therapy were excluded. Propensity score matching (PSM) was employed to balance baseline differences (age, gender, ALT, BCLC stage, HBV DNA level, and NUC coadministration status) between the two groups in a 1:1 ratio.

HBsAg levels were measured and compared at the initiation of anti-cancer therapy and the second timepoint > 8 weeks post-treatment. HBsAg reduction magnitude was estimated using the formula [$\log_{10}$ (HBsAg level at second timepoint) – $\log_{10}$ (HBsAg level at the start of anti-cancer treatment)] / (HBsAg estimated interval, in years). **Results:** After PSM, there were 10 patients in each group. The median duration of ICI or TKI treatment was 12.8 weeks and 12.8 weeks, respectively. The median interval of two timepoints HBsAg measurement were 12.0 vs. 15.8 weeks in ICI versus TKI arms ($p = 0.10$). Characteristics at study entry including HBsAg levels at the start of treatment were comparable between both groups (Table). The ICI group had higher HBsAg reduction magnitude than TKI [median: 0.30 vs -0.07 ($\log_{10}$IU/ml/year), $p = 0.04$)], with a numerically higher proportion of rapid HBsAg decline (> 0.5 $\log_{10}$IU/ml/year) 4/10 vs 1/10, $p = 0.30$) and HBsAg loss rate (1/10 vs 0/10, $p = 1.00$). **Conclusion:** Upon excluding the influence of corticosteroids, a notable reduction in HBsAg was observed in CHB-HCC patients receiving ICI, compared to those treated with TKI. The administration of corticosteroids during anti-cancer therapy may hinder the impact of ICI on HBsAg reduction.



	ICI (N =10)	TKI (N =10)	P value
Age	63.3 ± 8.1	64.9 ± 10.9	0.74
Gender (male)	8 (80%)	9 (90%)	1.00
Cirrhosis	10(100%)	10(100%)	1.00
Child-Turcotte-Pugh class			0.47
A	8 (80%)	10 (100%)	
B	2 (20%)	0	
HBeAg Positive	1 (10%)	1 (10%)	1.00
BCLC stage			1.00
A/B	5 (50%)	5 (50%)	
C	5 (50%)	5 (50%)	
Nucleotide use	10 (100%)	9 (90%)	1.00
Nucleotide treatment duration (m)*	26.8(3.3-43.5)	24.7(11.2~56.7)	0.36
Anti-cancer Regimen			
Atezolizumab/Nivolumab	6/4		
Sorafinib		10	
Anti-cancer Treatment Duration (w) *	12.8(10.0-13.4)	12.8(11.1~13.1)	0.97
ALT (U/L)*	30.5 (24.0-47.0)	42.5 (25.0~61.0)	0.55
HBV DNA, $\log_{10}$IU/mL*	0.0 (0.0~2.3)	0.0 (0.0-1.8)	0.83
AFP (ng/mL)*	414.7 (5.8~5432.0)	29.7 (15.5~431.0)	0.36
HBsAg at start of anti-cancer treatment, IU/mL *#	526.25 (9.82~768.80)	514.30 (280.7~787.5)	0.53
HBsAg at 2nd timepoint, IU/mL*#	361.10 (8.36~690.20)	482.60 (230.90~790.10)	0.38
HBsAg measurement interval (w)*	12.0 (10.3~16.1)	15.8 (14.0~16.3)	0.10
HBsAg reduction magnitude, $\log_{10}$IU/mL/year*	0.30 (0.00~1.15)	-0.07 (-0.70~0.17)	**0.04**
HBsAg decline > 0.5 $	4 (40%)	1 (10%)	0.30
HBsAg decline > 1 $	3 (30%)	0	0.21
HBsAg clearance (< 0.05 #)	1 (10%)	0	1.00

* median (Q1-Q3) ; (mean±SD); $ $\log_{10}$IU/ml/year ; # IU/mL ; m: month ; w: week

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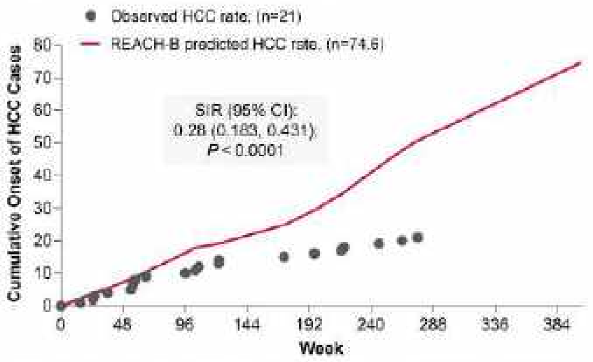
1422-C | IMPACT OF LONG-TERM TREATMENT WITH CONTINUOUS TENOFOVIR ALAFENAMIDE (TAF) OR AFTER SWITCH FROM TENOFOVIR DISOPROXIL FUMARATE (TDF) ON HEPATOCELLULAR CARCINOMA (HCC) INCIDENCE IN PATIENTS WITH CHRONIC HEPATITIS B (CHB)

Young-Suk Lim[1], Grace Lai-Hung C Wong[2], Sang Hoon Ahn[3], Wai-Kay Seto[4], Kosh Agarwal[5], Harry L. A. Janssen[6,7], Calvin Q. Pan[8], Wan Long Chuang[9], Scott K. Fung[10], Dr Shalimar[11], Maurizia R. Brunetto[12], Aric Josun Hui[13], Ting-Tsung Chang[14], Seng Gee Lim[15], Frida Abramov[16], John F. Flaherty[16], Hongyuan Wang[16], Leland J. Yee[16], Jia-Horng Kao[17], Patrick Marcellin[18], Edward J. Gane[19] and Maria Buti[20], (1) Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South), (2)Medical Data Analytics Centre (MDAC), the Chinese University of Hong Kong, (3)Department of Internal Medicine, Yonsei University College of Medicine, (4)Department of Medicine, School of Clinical Medicine, the University of Hong Kong, (5)Institute of Liver Studies, King's College Hospital, (6)Toronto Centre for Liver Disease, University Health Network, (7)Erasmus Medical Center, (8)NYU Langone Health, New York University Grossman School of Medicine, (9)Kaohsiung Medical University Hospital, Kaohsiung Medical University, (10) Department of Medicine, University of Toronto, Toronto, ON, Canada, (11)All India Institute of Medical Sciences, India, (12)Azienda Ospedaliero-Universitaria Pisana, (13)Alice Ho Miu Ling Nethersole Hospital, (14)National Cheng Kung University Hospital, (15)National University Health System, Singapore, Singapore, (16) Gilead Sciences, Inc., (17)National Taiwan University College of Medicine, (18)Hôpital Beaujon, Aphp, University of Paris, (19)University of Auckland, (20) Hospital Universitario Vall D'hebron and Ciberehd Del Instituto Carlos III

Background: Antiviral therapy reduces HCC risk in patients with CHB, particularly with TDF or entecavir. TAF, a novel prodrug of tenofovir, is a first-line recommended treatment for CHB and has shown efficacy comparable to TDF with higher rates of ALT normalization and no resistance. In an integrated analysis of 2 global Phase 3 studies, we evaluated HCC incidence and risk at 8 years (Week 384) in CHB patients treated solely with TAF and those treated initially with TDF and then switched to TAF for up to

6 years (y). **Methods:** In 2 similarly designed studies, HBeAg-positive (n = 859) and -negative (n = 439) CHB patients with HBV DNA **e** 20,000 IU/mL and ALT > 60 U/L (males) or > 38 U/L (females) were randomized (2:1) to TAF 25 mg or TDF 300 mg given once daily in a double-blind (DB) phase for up to 3 y, followed by open-label (OL) TAF through Y8. HCC was assessed by local standards of care and by hepatic ultrasonography introduced after Week 96 and performed at 6-month intervals. Three validated models (REACH-B, aMAP, and mPAGE-B) were utilized to assess HCC risk by initial treatment assignment and collectively. Using the REACH-B model, standard incidence ratios (SIRs) for HCC (observed vs model-predicted HCC rates) were calculated; for aMAP and mPAGE-B, shifts in baseline risk for HCC were determined at Week 384. **Results:** Through Y8, HCC was diagnosed in 21/1298 patients (1.6%; TAF 1.4% [12/866]; TDF→TAF 2.1% [9/432]; $p = 0.33$ by logrank test)—11 in DB/10 in OL phase. Eight of 21 HCC cases were in cirrhotic patients. Median (Q1, Q3) time to HCC onset was 729 (388, 1373) days (TAF 1291 [397, 1629], TDF→TAF 460 [180, 729] days). Advanced age, male gender, and cirrhosis (defined as FibroTest **e** 0.75) were more common in HCC vs non-HCC patients ($p < 0.05$). Proportionately more HCC patients were HBV genotype C (76% vs 47%) and had BL HBV DNA between 6 to **d** 8 $\log_{10}$ IU/mL (57% vs 38%). With treatment over 8 y, by REACH-B, HCC incidence was significantly reduced (21 observed vs 74.6 predicted; SIR [95% CI] 0.28 [0.183-0.431]; $p < 0.0001$; Figure). Of patients predicted to be low risk for HCC at BL, nearly all remained low risk at Y8 by aMAP (98%) and mPAGE-B (97%), and substantial proportions estimated to be medium or high risk at BL shifted to a lower risk at Y8 (aMAP: 45% and 72%; mPAGE-B: 27% and 51%, respectively). **Conclusion:** CHB patients treated with TAF alone or switched from TDF to TAF for up to 8 y showed a reduced observed vs predicted risk for HCC development.

Observed vs Predicted HCC Cases in Patients Treated With Continuous TAF or Being Switched From TDF to TAF Through Year 8



HCC, hepatocellular carcinoma; SIR, standardized incidence ratio for observed cases vs predicted cases based on the REACH-B model; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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1423-C | IMPROVEMENT OF NON-INVASIVE FIBROSIS TESTS IN HDV CIRRHOTIC PATIENTS WITH CLINICALLY SIGNIFICANT PORTAL HYPERTENSION RESPONDING TO BULEVERTIIDE MONOTHERAPY

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Background: In patients with chronic hepatitis B or C, non-invasive fibrosis tests (NITs) have demonstrated significant improvement following antiviral treatment, whereas little is known about patients with chronic hepatitis Delta treated with Bulevirtide (BLV) monotherapy. **Methods:** Consecutive HDV patients with compensated cirrhosis and clinically significant portal hypertension (CSPH) according to Baveno VII criteria with a virological response (**e** 2 Log HDV RNA decline *vs.* baseline) to BLV monotherapy 2 mg/day up to 96 weeks were enrolled in this single-center study. HDV RNA was quantified by Robogene 2.0 (LOD 6 IU/mL). AST to Platelet Ratio Index (APRI), Fibrosis-4 (FIB-4) Index and liver stiffness-spleen size-to-platelet ratio score (LSPS) were calculated from clinical variables recorded on-therapy. Liver (LSM), spleen (SSM) stiffness measurement performed both by transient elastography (Fibroscan®) and point shear-wave elastography (ElastPQ) were also assessed on-treatment every 24 weeks. **Results:** 46 HDV cirrhotic patients with a virological response to BLV were included: pre-treatment, median age was 52 (30-77) years, 59% males, ALT 98 (30-1,074) U/L, platelets 78 (17-217) $x10^3/mm^3$, 54% with varices, spleen 15 (9-25) cm, CPT-A 100%, HDV RNA 5.2 (2.4-6.9) Log IU/mL. During BLV monotherapy [median 48 (range 8-96) weeks], serological NIT significantly improved at all timepoints, APRI decreasing from baseline 3.5 (0.6-16.5) to 1.2 (0.3-4.5) at week 96 ($p < 0.001$), and FIB-4 from 6.1 (1.3-28.1) to 4.1 (1.2-9.0) ($p = 0.003$). LSM decreased from baseline 17.2 (6.4-68.1) to 13.8 (5.4-54.3) kPa at week 48 ($p = 0.001$) and LSPS from baseline 4.1 (0.5-23.7) to 3.8 (0.3-14.3) at week 48 ($p = 0.001$), whereas no other significant changes were observed throughout weeks 48 and 96. Conversely, other NITs did not significantly modify from baseline to week 96: liver ElastPQ 14.3 (4.2-35.2) *vs.* 10.9 (7.0-22.3) kPa ($p = 0.54$); SSM 50.3 (19.7-100) *vs.* 47.9 (21.2-97.9) kPa ($p = 0.69$), Spleen ElastPQ 36.9 (12.8-114) *vs.* 30.6 (17.4-51.8) kPa ($p = 0.31$). Five patients underwent liver transplantation (HCC n = 3; liver decompensation n = 2) and one patient died of liver unrelated causes. **Conclusion:** In HDV compensated cirrhotic patients with CSPH and a virological response to BLV monotherapy, long-term treatment led to a statistically significant improvement of serological fibrosis NITs, liver stiffness and LSPS.

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Pietro Lampertico – BMS: Advisor, No, No; ROCHE: Advisor, No, No; GILEAD SCIENCES: Advisor, No, No; GSK: Advisor, No, No; ABBVIE: Speaking and Teaching, No, No; MSD: Advisor, No, No; ARROWHEAD: Advisor, No, No; ALNYLAM: Advisor, No, No; JANSSEN: Advisor, No, No; SBRING BANK: Advisor, No, No;

MYR: Advisor, No, No; EIGER: Advisor, No, No; ANTIOS: Advisor, No, No; ALIGOS: Advisor, No, No; VIR: Advisor, No, No;
The following people have nothing to disclose: Elisabetta Degasperi, Maria Paola Anolli, Sara Uceda Renteria, Dana Sambarino, Marta Borghi, Riccardo Perbellini, Floriana Facchetti, Sara Monico, Mirella Fraquelli, Ferruccio Ceriotti

1424-C | INCIDENCE AND RISK FACTORS FOR LOW LEVEL VIREMIA IN CHRONIC HEPATITIS B PATIENTS RECEIVING ANTIVIRAL TREATMENT

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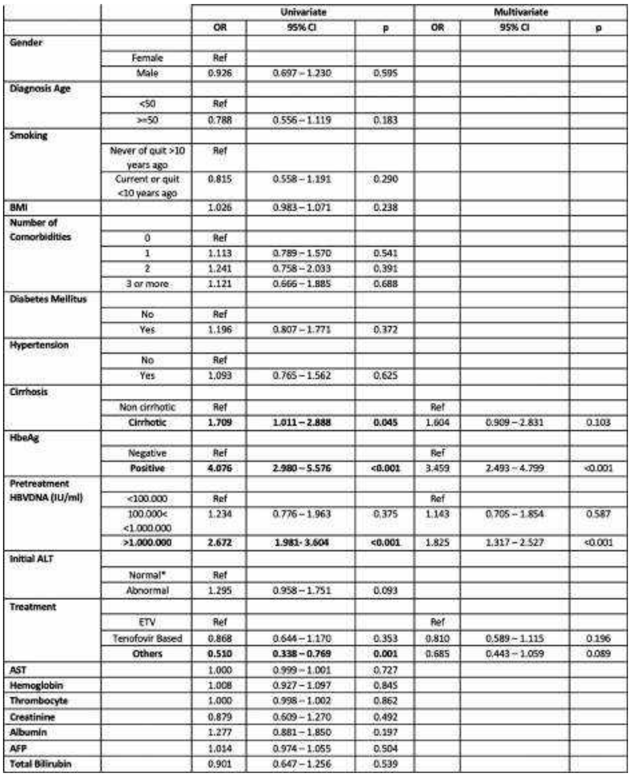
Background: Although there may not be many options in the treatment of chronic hepatitis B (CHB), the available antiviral agents have demonstrated the ability to suppress HBV DNA replication and reduce the risk of liver-related complications. Nevertheless, despite long-term antiviral therapy, some patients continue to experience low-level viremia (LLV) which is defined as HBV DNA < 2000 IU/ml. In this study, we aimed to evaluate the incidence and the factors that influence low-level LLV in patients with CHB receiving antiviral treatment. **Methods:** This multicenter retrospective observational study included clinical data from CHB patients who had received antiviral treatment for at least one year from January 2010 to April 2023. Univariate and multivariate logistic regression analyses were conducted to investigate the risk factors for LLV. **Results:** A total of 1826 patients from 32 centers included in the study. At the end of 1 year, incidence of LLV was 14.2%. To evaluate the risk factors for LLV, patients were divided into two groups as LLV and sustained virological response (SVR). Results of the univariate and multivariate logistic regression analyses are given in are given in Table 1. Multivariate logistic regression analyses showed that patients with HBeAg positive serostatus and pretreatment HBV DNA levels > 1.000.000 IU/ml has increased risk for LLV. No significant difference was observed between patients receiving entecavir and tenofovir in terms of LLV. **Conclusion:** Studies have demonstrated that a significant proportion of CHB patients, ranging from 20.0% to 40, maintain LLV. Results of this study emphasize that patients with HBeAg positive serostatus or pretreatment HBV DNA > 1.000.000 IU/ml has higher risk for LLV and should carefully monitored and the incidence of LLV was similar in entecavir and tenofovir treatments.



		Univariate			Multivariate		
		OR	95% CI	p	OR	95% CI	p
Gender							
	Female	Ref					
	Male	0.926	0.697 – 1.230	0.595			
Diagnosis Age							
	<50	Ref					
	>=50	0.788	0.556 – 1.119	0.183			
Smoking							
	Never of quit >10 years ago	Ref					
	Current or quit <10 years ago	0.815	0.558 – 1.191	0.290			
BMI		1.026	0.983 – 1.071	0.238			
Number of Comorbidities							
	0	Ref					
	1	1.113	0.789 – 1.570	0.541			
	2	1.241	0.758 – 2.033	0.391			
	3 or more	1.121	0.666 – 1.885	0.688			
Diabetes Mellitus							
	No	Ref					
	Yes	1.196	0.807 – 1.771	0.372			
Hypertension							
	No	Ref					
	Yes	1.093	0.765 – 1.562	0.625			
Cirrhosis							
	Non cirrhotic	Ref			Ref		
	Cirrhotic	**1.709**	**1.011 – 2.888**	**0.045**	1.604	0.909 – 2.831	0.103
HbeAg							
	Negative	Ref			Ref		
	Positive	**4.076**	**2.980 – 5.576**	**<0.001**	3.459	2.493 – 4.799	<0.001
Pretreatment HBVDNA (IU/ml)							
	<100.000	Ref			Ref		
	100.000< <1.000.000	1.234	0.776 – 1.963	0.375	1.143	0.705 – 1.854	0.587
	>1.000.000	**2.672**	**1.981- 3.604**	**<0.001**	1.825	1.317 – 2.527	<0.001
Initial ALT							
	Normal*	Ref					
	Abnormal	1.295	0.958 – 1.751	0.093			
Treatment							
	ETV	Ref			Ref		
	Tenofovir Based	0.868	0.644 – 1.170	0.353	0.810	0.589 – 1.115	0.196
	Others	**0.510**	**0.338 – 0.769**	**0.001**	0.685	0.443 – 1.059	0.089
AST		1.000	0.999 – 1.001	0.727			
Hemoglobin		1.008	0.927 – 1.097	0.845			
Thrombocyte		1.000	0.998 – 1.002	0.862			
Creatinine		0.879	0.609 – 1.270	0.492			
Albumin		1.277	0.881 – 1.850	0.197			
AFP		1.014	0.974 – 1.055	0.504			
Total Bilirubin		0.901	0.647 – 1.256	0.539			

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1425-C | INTERFERON-BASED THERAPIES ARE BENEFICIAL IN CIRRHOTIC HEPATITIS B PATIENTS WITH GOOD LIVER FUNCTION RESERVE: REAL-WORLD EVIDENCE FROM OASIS PROJECT 2.5-YEAR DATA

Qiran Zhang[1], Feng Sun[1], Yiqi Yu[1], Shulan Sui[1], Tingting Zhao[1], Ying Guo[2], Wanhua Ren[3], Jiming Zhang[4], Yuxian Huang[1] and Wenhong Zhang[1], (1) Huashan Hospital, Shanghai Medical College, Fudan

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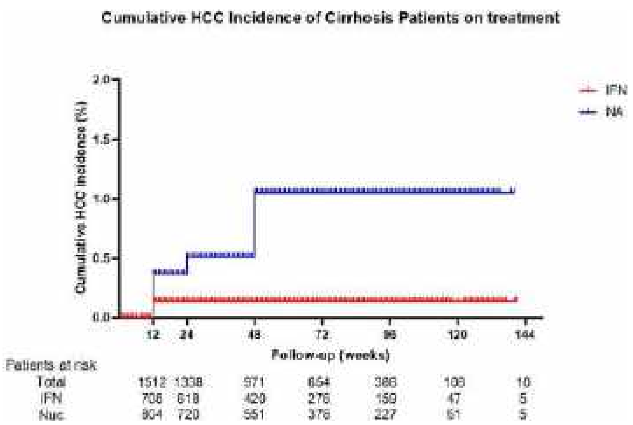
Background: Interferon (IFN)-based therapies are considered effective in functional cure and reducing hepatocellular carcinoma (HCC) risks in patients with chronic hepatitis B (CHB). However, in practice, IFN-based therapies are less used in cirrhotic patients and have limited evidence. We aimed to evaluate the safety and effects of interferon-based therapy in CHB patients with cirrhosis, based on large scale real-word data from China. **Methods:** The analysis was conducted in the data from a multi-center, prospective real-world study (OASIS Project) from China. This project recruited patients with CHB from 32 provinces in China. Participants in OASIS Project received either IFN-based therapy or Nuc therapy, and would be followed up for five years. We made this analysis at the time-point of 2.5 years from project initiation, and in the subgroup of patients with cirrhosis. **Results:** A total of 1944 cirrhotic patients with complete baseline information was included in this analysis, of which 920 received IFN-based therapies and 1024 received Nuc therapy. Most of patients (897, 97.5%) in IFN group are classified as Child–Pugh class A at baseline, and the rest (23, 2.5%) are classified as Child–Pugh class B, while in Nuc group, there are 930 (90.8%), 79 (7.7%) and 15 (1.5%) patients in Child–Pugh class A, B and C, respectively. In IFN group, 72 (7.8%) patients had ALT elevation above 3 ULN, significantly higher than that in Nuc group (15[1.5%], $p < 0.0001$), and 17 (1.8%) had bilirubin elevation over 2ULN. None of them resulted in irreversible injury or liver failure yet. Up to this analysis, 2(8.7%) patients in IFN group child-pugh classification improved from B class to A class, and all those originally classified as A class stayed the same. No progression or decompensation happened in either group. A total of 971 participants reached 48-week follow-up visit and 386 reached 96-week follow-up study at the timepoint of analysis. In participants with HBsAg < 1500IU/ml, the HBsAg loss rates of IFN-based therapy were higher than in Nuc group at 48 weeks (11.2% vs 2.9%, $p = 0.008$) and 96 weeks (19.4% vs 4.8%, $p = 0.047$). However, in patients with HBsAg **e** 1500IU/ml, IFN-based therapies could not improve HBsAg loss rates significantly from Nuc either at 48 weeks (2.7% vs 1.4%, $p = 0.62$) or 96 weeks (6.7% vs 3.7%, $p = 0.366$). For HBV DNA suppression and HBeAg loss, patients in two group had no significant difference. There were 8 cases developed HCC within 144 weeks. The cumulative HCC incidence was lower in IFN-based treatment group than Nuc treatment group (0.14% vs 1.05 %) but not statistically significant after adjusting covariates including age, gender and baseline HBsAg level ($p = 0.0612$), and the HR of IFN-based therapy for HCC was 0.264 (95%CI 0.065-1.065) compared with Nuc therapy (Figure 1). **Conclusion:** IFN-based therapies are safe in CHB patients with child-pugh A cirrhosis, and more effective in terms of functional cure and HCC risk reduction.



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1426-C | LONG-TERM EFFECTIVENESS AND SAFETY OF TENOFOVIR ALAFENAMIDE FOR TREATMENT-NAÏVE AND EXPERIENCED PATIENTS WITH CHRONIC HEPATITIS B: RESULTS FROM A REAL-WORLD, MULTICENTER STUDY

Eiichi Ogawa[1], Makoto Nakamuta[2], Motoyuki Kohjima[2], Toshimasa Koyanagi[3], Aritsune Ooho[4], Norihiro Furusyo[5], Eiji Kajiwara[6], Kazufumi Dohmen[7], Akira Kawano[8], Takeaki Satoh[9], Kazuhiro Takahashi[10], Koichi Azuma[11], Rie Sugimoto[12], Hiromasa Amagase[13], Takeshi Senju[14], Yasunori Ichiki[15], Chie Morita[16], Masatake Tanaka[17], Hideyuki Nomura[18] and Jun Hayashi[18], (1)Kyushu University Hospital, Fukuoka, Japan, (2)National Hospital Organization Kyushu Medical Center, (3)Fukuoka City Hospital, (4)Steel Memorial Yawata Hospital, (5)Taihaku Avenue Clinic, (6)Kajiwara Clinic, (7)Chihaya Hospital, (8)Kitakyushu Municipal Medical Center, (9)National Hospital Organization Kokura Medical Center, (10) Hamanomachi Hospital, (11)Kyushu Central Hospital, (12)National Hospital Organization Kyushu Cancer Center, (13)Amagase Clinic, (14)Kyushu Rosai Hospital, (15)Jcho Kyushu Hospital, (16)Kyushu Railway Memorial Hospital, (17)Graduate School of Medical Sciences, Kyushu University, (18)Haradoi Hospital

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

Background: Tenofovir alafenamide (TAF) has similar efficacy and fewer safety concerns than tenofovir disoproxil fumarate (TDF) in the treatment of patients with chronic hepatitis B (CHB). Switching from TDF to TAF improves biochemical response and renal safety; however, long-term real-world data are limited. The aim of this study was to assess the effectiveness and safety outcomes for both treatment-naïve and experienced CHB patients treated with TAF for up to four years. **Methods:** This multicenter, retrospective, observational cohort study consisted of consecutive CHB patients aged 18 years and older who from March 2017 initiated or switched to a fixed dose of TAF, 25mg orally once daily. Primary outcomes were viral suppression (VR: HBV DNA $<$ 10 IU/mL), ALT normalization (BR: ALT $<$ 35/25 U/L men/women), and complete response (CR: viral plus biochemical response) within four years. Safety assessments included changes in estimated glomerular filtration rate (eGFR) and serum phosphorus level. **Results:** We enrolled 578 eligible patients: 115 treatment-naïve and 463 treatment-experienced. In the treatment-naïve group, the mean age was 56.5 ± 13.1, 53.0% were male, 25.2% were HBe-antigen positive, and 13.9% had cirrhosis. In the four-year follow-up, the proportions of VR and BR were 77.5%/66.3%, 87.7%/75.3%, 89.8%/78.5%, 92.5%/80.6%, and 94.3%/83.3% at month 6, year 1, year 2, year 3, and year 4, respectively. The proportions of CR also longitudinally increased, to 59.0%, 70.7%, 71.6%, 73.5%, and 75.6%, at month 6, year 1, year 2, year 3, and year 4, respectively ($p < 0.01$). eGFR significantly decreased during the first 6 months (79.3 to 77.0 mL/min/1.73m^2, $p < 0.01$); however, it did not change significantly after 6 months of TAF therapy. Moreover, 9.3% of treatment-naïve patients experienced hypophosphatemia ($<$ 2.5 mg/dL). In the treatment-experienced group, the mean age was 57.9 ± 12.6, 62.0% were male, and 14.9% had cirrhosis. All had been treated with entecavir (n = 200), TDF (n = 135), or a combination of nucleos(t)ide analogues (n = 128) before switching to TAF. Sixty-five (14.0%) had HBV DNA $>$ 20 IU/mL at baseline. In the four-year follow-up, the proportions of VR and BR increased, to 95.7%/81.1%, 96.3%/80.9%, 97.8%/83.2%, 97.8%/82.1%, and 98.9%/83.5% at month 6, year 1, year 2, year 3, and year 4, respectively. The proportions of CR also significantly increased, to 81.4%, 81.4%, 83.8%, 82.7%, and 84.6%, at month 6, year 1, year 2, year 3, and year 4, respectively ($p < 0.01$, compared to baseline). For patients who switched from a TDF-containing regimen to TAF, eGFR significantly improved during the first 6 months (+3.1 mL/min/1.73m^2) ($p < 0.01$). **Conclusion:** In this 4-year real-world cohort, TAF had a potent virological and biochemical effect for treatment-naïve and experienced patients with CHB. Moreover, patients who switched from TDF to TAF can benefit from TAF therapy in terms of improvement of renal function.

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1427-C | LONG-TERM FOLLOW-UP OF WOMEN RECEIVING TENOFOVIR ALAFENAMIDE DURING PREGNANCY TO PREVENT MATERNAL HBV TRANSMISSION

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Background: Tenofovir alafenamide (TAF), a newer generation of tenofovir with less renal and bone toxicity, has been demonstrated to have a favorable effectiveness and safety profile in preventing maternal HBV transmission in studies with a follow-up duration of no longer than 12 months. Long-term data is lacking. This study reports on the long-term liver outcomes of women who received TAF during pregnancy to prevent maternal HBV transmission. **Methods:** Women included in this study were the participants in our prospective cohort (ClinicalTrials.gov, NCT 03695029) on TAF treatment in pregnancy from 3rd trimester until 2 weeks postpartum. At baseline, all pregnant women were hepatitis B e antigen (HBeAg)-positive and had a viral load above 6.0 log10 IU/mL. Serum alanine aminotransferase (ALT) and HBV viral load were measured at baseline, delivery, 1, 2, 4, 6, and 12 months postpartum, and subsequently at 12-month intervals. HBeAg was checked at delivery, 6, and 12 months postpartum, followed by 12-month intervals thereafter. The hazard ratios for HBeAg clearance with 95% confidence intervals (CI) were determined using a Cox proportional hazards model adjusted with multiple covariates. **Results:** The analysis included 78 women. The median follow-up duration after delivery was 23.8 months (range, 12 to 50.6 mo). Postpartum, 21 (26.9%) women continued or resumed antiviral nucleos(t)ide analog (NA) treatment, including two who received short-term TAF treatment for subsequent pregnancies. At baseline, six (7.7%) pregnant women had ALT elevations above 40 U/L. During the follow-up period, ALT elevations above 40 U/L were observed in 7.7%, 56.4% and 16.7% of the women at delivery, during 1-6 months postpartum, and at 1 year postpartum. Of the 78 subjects, 9 (11.5%) cleared HBeAg, including one became HBeAg negative at the time of delivery, while 8 cleared HBeAg during the postpartum follow-up period. After adjustment for maternal age, baseline ALT, ALT flare within 6 months postpartum, ALT flare at one year postpartum, and NA treatment during follow-up, we found that mothers with ALT $>$ 40 IU/L at delivery were more likely to clear HBeAg than mothers with normal ALT at delivery (hazard ratio, 16.80; 95% CI, 2.38 to 118.71; $p = 0.005$). None of these women experienced progression to liver failure, cirrhosis, or cancer. **Conclusion:** Highly viremic women receiving TAF during pregnancy to prevent maternal HBV transmission had high rates of ALT elevations during 1-6 months postpartum, and some continued or resumed antiviral therapy. An ALT flare greater than 40 IU/L at delivery serves as an independent predictor of HBeAg clearance.

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1428-C | MATHEMATICAL MODELING OF HBV KINETICS IN HUMANIZED MICE SUGGESTS THAT NA BLOCKS NOT ONLY RCDNA PRODUCTION BUT ALSO PGRNA SYNTHESIS

Ashish Goyal[1], Yuji Ishida[2,3], Chise Tateno[3,4], Andrew Vaillant[5], Scott J. Cotler[1], Kazuaki Chayama[3,6,7] and Harel Dahari[1], (1)Loyola University Chicago, (2)R&D, Phoenixbio Co., Ltd., (3)Hiroshima Institute of Life Sciences, (4)Phoenixbio Co., Ltd., (5)Replicor Inc., Montreal, Canada, Montreal, QC, Canada, (6)Riken Center for Integrative Medical Sciences, (7) Collaborative Research Laboratory of Medical Innovation, Hiroshima University

Background: Nucleos(t)ide analogue therapy (NA) for hepatitis B was recently suggested to be multifunctional based on the observed decline of both serum HBV DNA and pregenomic RNA (pgRNA) in patients (Hepatology. 2021;74(3):1708-1709). We aim to provide insights into NA modes of action in chimeric urokinase type plasminogen activator (uPA)/severe combined immunodeficiency (SCID) mice reconstituted with humanized livers using a mathematical modeling approach. **Methods:** We first employed a modeling selection approach to identify a mathematical model that best reproduced the observed multiphasic serum HBV kinetics from de-novo infection to a steady state of viremia in humanized mice (Hepatology. 2018;68(2):473-484). Models that were explored assumed: (1) basic viral dynamic model without intracellular dynamics, (2) extended models that included intracellular covalently closed circular DNA (cccDNA; accumulation up to 5 cccDNA per infected cell), and relaxed circular DNA (rcDNA) with or without pgRNA and with or without saturation (i.e., Michaelis–Menten equation) in pgRNA and/or rcDNA production. The best model found in Fig. 1A was then used to fit the viral kinetics observed in 21 humanized mice (Fig. 1B) that were treated with lamivudine (LAM) for 14 days after reaching viral steady state (J Virol.2021;24;95(14):e0049220). We fit the models to the observed serum viral data using a population, nonlinear mixed-effects approach. **Results:** The multiphasic serum viral kinetics from de-novo infection to steady state were successfully recapitulated using an extended model that included pgRNA synthesis in a saturated manner from cccDNA and the synthesis of rcDNA from pgRNA by HBV reverse transcriptase, (RT) [Fig. 1A, solid line]. When we assumed that LAM inhibits both RT and pgRNA synthesis, the model fit the observed viral kinetics during LAM treatment better (Fig.1B, solid line) than when we assumed that LAM inhibits RT alone (Fig. 1B, dashed line). The estimated dual LAM inhibition efficacy of rcDNA and pgRNA synthesis which best fit the viral kinetics following LAM treatment were 81% (95% CI: 80%-83%) and 93% (95% CI: 89%-95%), respectively. **Conclusion:** Modeling suggests that intracellular saturated pgRNA synthesis plays a pivotal role in reproducing the observed multiphasic viral kinetics from infection to steady state in humanized mice. The use of a model that includes intracellular HBV dynamics to reproduce viral kinetics under LAM treatment predicts potential upstream NA interactions affecting intracellular pgRNA synthesis in addition to rcDNA synthesis.

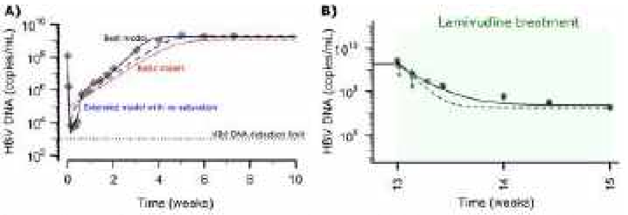

Figure 1: (A) Model fitting with the observed HBV kinetics (diamonds) from de-novo infection to steady state in a representative humanized mouse inoculated with 10^{8} HBV genome equivalents. Models shown are the basic model (dashed-dotted line) and extended models with (solid line) or without saturation (dashed line) in pgRNA synthesis. (B) The best extended model then was fit (lines) with the mean observed HBV DNA response to LAM treatment (markers) assuming that LAM solely inhibits RT with efficacy 98.7% (95% CI: 98.6%-99.0%) (dashed line) or inhibits both HBV reverse transcriptase RT and pgRNA synthesis (solid line). Vertical arrows represent the 95%CI (n=21) in serum HBV DNA.

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1429-C | NO DETECTED RESISTANCE TO TENOFOVIR ALAFENAMIDE (TAF) THROUGH 96 WEEKS OF TREATMENT IN CHILDREN AND ADOLESCENTS WITH CHRONIC HEPATITIS B

Philip Rosenthal[1], Mei-Hwei Chang[2], Jorge A. Bezerra[3], Yang Liu[4], Dong Han[4], Simin Xu[4], Caleb Marceau[4], Tahmineh Yazdi[4], Lindsey May[4], Robert Li[4], Savrina Manhas[4], Pui Yan Ho[4], Clarissa Martinez[4], Nadine Peinovich[4], Silvia Chang[4], Ross Martin[4], Evguenia Maiorova[4], Hongmei Mo[4], Frida Abramov[4], John F. Flaherty[4] and Kathleen B. Schwarz[5], (1)University of California San Francisco, (2)National Taiwan University, College of Medicine, (3)University of Texas Southwestern Medical Center, (4)Gilead Sciences, Inc., (5)University of California San Diego, Rady Children's Hospital San Diego

Background: Tenofovir alafenamide (TAF) is approved for use in adults with chronic hepatitis B (CHB) and no resistance has been detected through 8 years of treatment. Here, we describe the resistance analyses at Week 96 of a Phase 2 study evaluating TAF for the treatment of children and adolescents aged 6 to < 18 years with CHB. **Methods:** A total of 88 adolescents (n = 70) and children (n = 18) with CHB were randomized (2:1) to receive TAF 25 mg once daily or matching placebo (PLB) in Cohort 1 (aged 12 to < 18 years weighing ≥ 35kg) and Cohort 2 Group 1 (aged 6 to < 12 years weighing ≥ 25kg) in a double-blind fashion for 24 weeks followed by open-label TAF through Week 240 (ie TAF or PLB-TAF). HBV pol/RT deep sequencing was conducted for participants with HBV DNA ≥ 69 IU/mL at Week 96. Virologic breakthrough (VB) was defined as HBV DNA ≥ 69 IU/mL after achieving < 69 IU/mL or a ≥ 1.0-log$_{10}$ increase from nadir for 2 consecutive visits; participants meeting these criteria at only 1 visit were classified as having a virologic blip. Viremia was defined as having persistent HBV DNA ≥ 20 IU/mL over the course of treatment. Phenotypic analysis using recombinant HBV in HepG2 cells was performed for those with VB, conserved site substitutions, or same polymorphic substitutions emergent in > 1 participant. **Results:** At Week 96, 24 of 88 (27%) participants (TAF 8, PLB-TAF 9 in Cohort 1; TAF 4, PLB-TAF 3 in Cohort 2 Group 1) qualified for resistance analysis due to persistent viremia (n = 19) or VB (n = 5). The number of participants who qualified for resistance analysis decreased compared to Week 48 (43 of 88, 49%). Of the 24 participants who qualified for sequencing at Week 96, 1 had conserved site substitution, 3 had polymorphic site substitutions, 15 had no change from baseline, and 5 were unable to be sequenced due to low level HBV DNA. At Week 96, 2 participants qualified for phenotypic analysis due to conserved site change (n = 1) or virologic breakthrough (n = 1) and both the baseline as well as the Week 96 isolates remained sensitive to TAF in vitro. **Conclusion:** Fewer participants qualified for resistance analysis with continued TAF treatment. The majority of participants qualified for sequence analysis due to persistent viremia (79%) and most had no sequence change from baseline. No substitutions associated with resistance were detected in children and adolescents with CHB treated with TAF for up to 96 weeks.

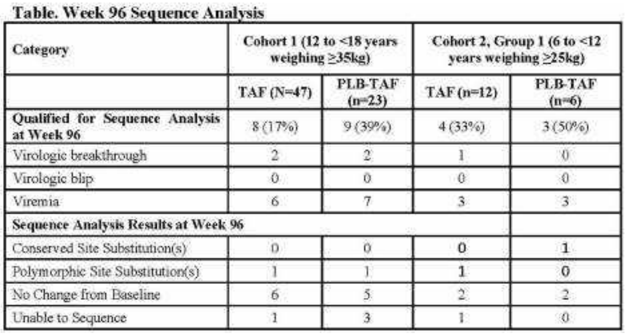

Table. Week 96 Sequence Analysis

Category	Cohort 1 (12 to <18 years weighing ≥35kg)		Cohort 2, Group 1 (6 to <12 years weighing ≥25kg)	
	TAF (N=47)	PLB-TAF (n=23)	TAF (n=12)	PLB-TAF (n=6)
Qualified for Sequence Analysis at Week 96	8 (17%)	9 (39%)	4 (33%)	3 (50%)
Virologic breakthrough	2	2	1	0
Virologic blip	0	0	0	0
Viremia	6	7	3	3
Sequence Analysis Results at Week 96				
Conserved Site Substitution(s)	0	0	0	1
Polymorphic Site Substitution(s)	1	1	1	0
No Change from Baseline	6	5	2	2
Unable to Sequence	1	3	1	0

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1430-C | NO RESISTANCE TO TENOFOVIR ALAFENAMIDE (TAF) IN ADULT, HBEAG-POSITIVE AND HBEAG-NEGATIVE PARTICIPANTS WITH CHRONIC HEPATITIS B INFECTION TREATED WITH TAF FOR UP TO 8 YEARS.

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Background: Tenofovir alafenamide (TAF) has shown similar efficacy and improved safety profiles for treatment of patients with chronic hepatitis B (CHB) compared to tenofovir disoproxil fumarate (TDF). We have previously shown no resistance to TDF after 8 years, and TAF resistance has not been detected after up to three years of treatment in CHB patients. Here we report results from annual resistance surveillance from years 3 through 8 of TAF treatment. **Methods:** Two randomized, double-blind (DB), active-controlled trials to evaluate TAF treatment of hepatitis e antigen (HBeAg)-negative (Study GS-US-320-0108) and HBeAg-positive (Study GS-US-320-0110) participants with CHB were conducted over 8 years (384 weeks). Sequence analysis of the pol/RT region was attempted for any participant who experienced a viral breakthrough, viral blip, or persistent viremia with HBV DNA **e** 69 IU/mL at annual intervals and for any participant who discontinued study drug with HBV DNA **e** 69 IU/mL. Participants that developed substitutions at conserved pol/RT sites or at polymorphic residues (if observed in **e** 2 participants within the study) were also phenotyped against TAF. **Results:** Out of 1298 participants enrolled in both studies, the percentage of participants who qualified for resistance analysis annually from Week 144 (Year 3) to Week 384 (Year 8) remained low (range 1.7 – 8.4%). Among those qualifying for sequencing, the proportions with persistent viremia progressively declined with time, with only 3 participants being persistently viremic by Year 8. The viral load of these 3 participants at baseline was $>10^8$ $\log_{10}$ IU/mL and declined over time but did not reach 69 IU/mL. During the 5-year open-label period where all participants received TAF, conserved site substitutions in the HBV viral pol/RT were observed in 13 participants. Polymorphic site substitutions present in **e** 2 participants in the study were observed in 10, 6, 18, 8 and 6 participants at Weeks 192, 240, 288, 336 and 384, respectively. Phenotypic analysis showed that viruses containing those substitutions had TAF EC_{50} fold-change values in the range 0.21-1.85, compared to baseline (below the assay cut-off of 2-fold). **Conclusion:** Overall, no resistance to TAF was detected in adult CHB participants with positive or negative HBeAg who received TAF therapy for up to 8 years. These findings support the use of TAF as long-term viral suppressive therapy in patients chronically infected with HBV regardless of their HBeAg status.

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Maria Buti – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, Yes; GSK: Advisor, Yes, No;
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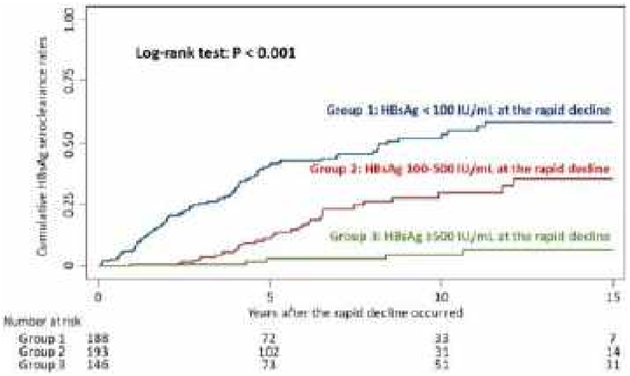
1431-C | NUC-INDUCED RAPID DECLINE IN HEPATITIS B SURFACE ANTIGEN BELOW LOW LEVELS LEADS TO SURFACE ANTIGEN SEROCLEARANCE IN PATIENTS TREATED WITH LONG-TERM AND CONTINUOUS NUCLEOS(T)IDE ANALOGUES.

Tetsuya Hosaka[1], Fumitaka Suzuki[1], Mariko Kobayashi[1], Shunichiro Fujiyama[1], Yusuke Kawamura[1], Hitomi Sezaki[2], Norio Akuta[1], Yoshiyuki Suzuki[1], Satoshi Saitoh[1], Yasuji Arase[1], Kenji Ikeda[1] and Hiromitsu Kumada[1], (1)Toranomon Hospital, (2) Toranomon Hospital, Tokyo, Japan

Background: Long-term nucleos(t)ide analogues (NUCs) treatment improve the prognosis in chronic hepatitis B (CHB) patients. However, hepatitis B surface antigen (HBsAg) seroclearance rates are still low by NUC treatment. Therefore, some new antiviral agents targeting the great reduction in HBsAg are now developing, combined with NUC treatment. It is important to investigate the underlying mechanisms of HBsAg reduction and seroclearance during long-term NUC treatment. **Methods:** We conducted a retrospective cohort study of 1696 patients who received nucleos(t)ide analogues (NUCs) including lamivudine, entecavir and tenofovir for more than three years in our institute. Almost all patients received continuous NUC treatment until HBsAg seroclearance. Serum HBsAg levels were quantified at annual time points from baseline to last visits by the commercial assay (lower limit of quantification = 0.05 IU/mL) in the regular visits or from their stored serum samples. "Rapid decline" in HBsAg levels was defined as over 0.3 log IU/mL/year reduction 3 years after starting with NUC. We examined the association between the kinetics of on-treatment HBsAg levels and subsequent HBsAg seroclearance in chronic hepatitis B (CHB) patients treated with long-term and continuous NUCs. **Results:** During follow-ups of median 12.6 years, 128 patients achieved HBsAg seroclearance (5.9/1,000 person-years), and rapid decline in HBsAg occurred in 527 patients (31%). Median time from baseline when rapid decline occurred was year 7. Cumulative incidences rates of rapid decline were 12% at year 5, 27% at year 10, 40% at year 15, and 49% at year 20, respectively. 36% of patients with rapid decline had HBsAg $<$ 100 IU/mL at the rapid decline, 37% had HBsAg **e** 100 and $<$ 500, and 28% had HBsAg **e** 500. Next, we evaluated HBsAg seroclearance rates since rapid decline occurred in patients with rapid decline stratified by HBsAg levels at the rapid decline. Cumulative HBsAg seroclearance rates from the rapid decline were significantly greater in patients with HBsAg **e** 100 IU/mL (group 1) than those with HBsAg **e** 100 and $<$ 500 (group 2), and **e** 500 (group 3) (Figure). 5-year HBsAg seroclearance rates from the rapid decline were 41% in group 1, 11% in group 2 and 3% in group 3, despite of continuous NUC treatment. Median reductions in HBsAg 3 years after the rapid decline were -0.55 log IU/mL in group 1, -0.30 in group 2, and -0.11 in group 3 (*p* trend $<$ 0.001). Median ALT levels at the rapid decline were 20 IU/L in group 1, 21 in group 2 and 25 in group 3 (*p* trend = 0.027). Factors with the occurrence of rapid decline below HBsAg $<$ 100 were baseline low HBsAg levels, baseline HBeAg negativity and male using multivariable Cox regression. **Conclusion:** When the rapid decline below HBsAg $<$ 100 occurred in continuous NUC, subsequent HBsAg seroclearance rates were relatively high, and HBsAg reduction was durable. Further investigation is needed to find out this mechanism.



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Hitomi Sezaki – Abbvie: Speaking and Teaching, No, Yes;
Norio Akuta – Abbvie: Speaking and Teaching, No, Yes;
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1432-C | NUCLEOS(T)IDE ANALOGUES HELP PRESERVE LIVER VOLUME IN CHRONIC HEPATITIS B PATIENTS WITH LOW VIRAL LOAD

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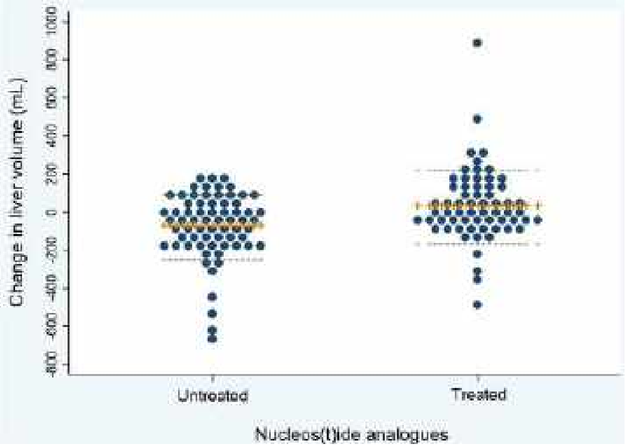
Background: The ultimate goal of treatment for chronic hepatitis B (CHB) is to halt progression of liver injury and to prevent the development of hepatocellular carcinoma. Since these long-term outcomes are not readily obtainable, surrogate markers, i.e., transaminase and viral load, are used both as a response marker and an indication of nucleos(t)ide analogue (NA) therapy. Hepatic volumetry has been used for the planning of liver transplantation and liver resection. Previous studies have also suggested that liver volume can predict prognosis in chronic viral hepatitis. This study aimed to test whether liver volume may serve as a response marker in CHB patients with low HBV DNA level (< 2000 IU/mL) and persistently low AST/ALT level (both < 80 U/L), for whom current guidelines do not recommend initiation of NA therapy. **Methods:** We retrospectively examined CHB patients with a low HBV DNA level (< 2000 IU/mL) and persistently low transaminase level (both ALT and AST < 80 U/L), either with or without maintenance of NA therapy, who underwent computed tomography (CT) scans seen between April 2003 and February 2023. A total of 131 were categorized into on-NA group (n = 63) and NA-untreated group (n = 68). Whole-liver volume quantification on their initial and latest follow-up CT images was performed using a semiautomatic 3-dimensional multiplanar reconstruction tool within the DICOM Viewer Pro edition 64-bit version (Inobitec, Moscow, Russia). We used the two-sample Wilcoxon rank-sum (Mann-Whitney) test to determine the effect of NUCs on the subsequent change in liver volume using Stata/SE 14.0. **Results:** At baseline, on-NA group had significantly lower HBV DNA level with higher serum AST/ALT level with more HbeAg positivity than NUC-untreated group. Otherwise, there was no statistically significant difference in age, gender, other laboratory data, initial liver volume or interval between the CT scans. Liver volumes in NA-untreated group decreased more with time than those in on-NA group (-71 ± 170 mL vs. +35 ± 193 mL, $p = 0.00$; Figure). When compared according to HBV DNA levels regardless of history of NUC use, patients with undetectable HBV DNA level (< 60 UL/mL, n = 64) showed more preserved liver volume than those with higher HBV DNA titers (60 ~ 2000 UL/mL, n = 67) (+1 ± 195mL vs. -40 ± 181 mL, $p = 0.02$). **Conclusion:** In CHB patients with low/normal transaminases and low HBV DNA, treatment with NUC therapy was associated with preservation of liver volume. Also, the loss of liver volume was significantly larger in low viremia patients (60 ~ 2000 IU/mL) than those with undetectable HBV DNA level (< 60 IU/mL). Our data suggests that liver volume may serve as a new response indicator to NA therapy, and that suppression of low viremia may contribute to preservation of liver volume in CHB with low/normal transaminases and low HBV DNA who are not currently indicated for NA therapy.



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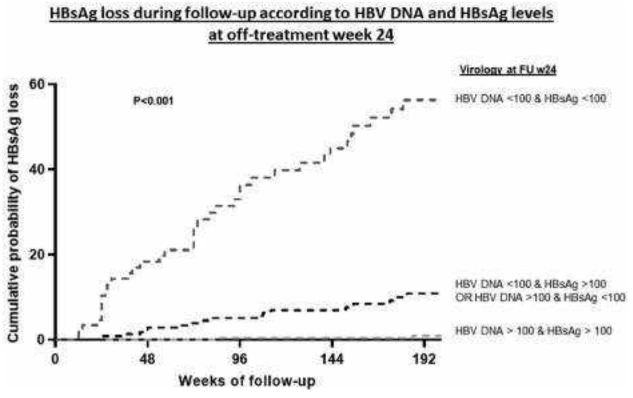
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

1433-C | OFF-TREATMENT HBSAG AND HBV DNA LEVELS PREDICT OUTCOMES AFTER THERAPY WITHDRAWAL AMONG PATIENTS WITH HIGH HBSAG LEVELS AT END OF TREATMENT

Milan J. Sonneveld[1], S.-M. Chiu[2], Jun Yong Park[3], Sylvia Brakenhoff[1], Apichat Kaewdech[4], Wai-Kay Seto[5], Yasuhito Tanaka[6], Ivana Carey[7], Margarita Papatheodoridi[8], Piero Colombatto[9], Florian Van Bömmel[10], Harry L. A. Janssen[11,12], Thomas Berg[13], Fabien Zoulim[14], Sang Hoon Ahn[15], George N. Dalekos[16], Nicole S. Erler[11], Maurizia R. Brunetto[17], Heiner Wedemeyer[18], Markus Cornberg[18], Mf Yuen[19], K Agarwal[20], Andre Boonstra[21], Maria Buti[22], Teerha Piratvisuth[23], George V. Papatheodoridis[24], Chien Hung Chen[2], Benjamin Maasoumy[18] and CREATE study group, (1)Erasmus MC, University Medical Center, (2) Koahsiung Chang Gung Memorial Hospital, (3)Yonsei University College of Medicine, (4)Prince of Songkla University, (5)Department of Medicine, School of Clinical Medicine, the University of Hong Kong, (6) Graduate School of Medical Sciences, Kumamoto University, (7)Institute of Liver Studies, Kings College Hospital, London, United Kingdom, (8)Medical School of Athens University, (9)University Hospital of Pisa, (10) University Hospital Leipzig, (11)Erasmus MC, University Medical Center Rotterdam, (12)Toronto General Hospital Research Institute, (13)University Hospital of Leipzig, (14)Universite Claude Bernard Lyon 1, (15) Yonsei Liver Center, Severance Hospital, Seoul, South Korea, (16)University of Thessaly, (17)Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, Reference Center of the Tuscany Region for Chronic Liver Disease and Cancer, University Hospital of Pisa, (18)Hannover Medical School, (19)The University of Hong Kong, (20)King's College Hospital, (21)Erasmus University Medical Center, Rotterdam, Netherlands, (22)Hospital Universitari Vall d'Hebron and Ciberehd Del Intituto Carlos III De Barcelona, (23)Nkc Institute of Gastroenterology and Hepatology, Songkhla, Thailand, (24)Medical School of National & Kapodistrian University of Athens, Athens, Greece

Background: Nucleo(s)tide analogue (NUC) withdrawal is being explored as a novel means of increasing HBsAg loss in patients with chronic hepatitis B, but has been associated with a significant risk of severe viral rebound and hepatitis flares. End-of-treatment (EOT) HBsAg levels < 100 IU/mL are associated with favorable outcomes after therapy withdrawal. Unfortunately, the majority of patients potentially eligible for therapy withdrawal do not have such low HBsAg levels. We studied whether off-treatment HBV DNA and HBsAg levels can be used to guide further management in these patients. **Methods:** Chronic hepatitis B patients with HBsAg levels > 100 IU/mL at the time of NUC cessation who were still HBsAg positive and without clinical relapse or retreatment at follow-up week 24 (FU W24) were identified in an existing multicenter database. The association between HBsAg and HBV DNA levels at FU W24 with subsequent clinical relapse (defined as HBV DNA > 2,000 IU/mL + ALT > 2x ULN or retreatment) and HBsAg loss was studied through univariable analyses using the Kaplan-Meier method, as well as multivariable Cox regression analysis adjusting for other potential predictors. **Results:** We enrolled 509 patients, 85% Asian, 29% pretreatment HBeAg positive, and 60% treated with entecavir. At 192 weeks of subsequent follow-up, the cumulative probability of clinical relapse and HBsAg loss were 56% and 5.1%. Patients with higher HBV DNA levels at FU W24 had a higher risk of clinical relapse (hazard ratio [HR] 1.550, $p < 0.001$) and a lower chance of HBsAg loss (HR 0.572, $p < 0.001$). Similarly, patients with higher HBsAg levels at FU W24 had a higher risk of clinical relapse (HR 1.379, $p < 0.001$) and a lower chance of HBsAg loss (HR 0.162, $p < 0.001$). Patients with both HBsAg < 100 IU/mL and HBV DNA < 100 IU/mL (n = 22) at FU W24 had excellent outcomes (13% clinical relapse and 53% HBsAg loss at 192 weeks of subsequent follow-up, see figure). Amongst patients with both HBsAg > 100 IU/mL and HBV DNA > 100 IU/mL (n = 308), clinical relapse rates were very high (68% at 192 weeks), and HBsAg loss rates were dismal (< 1% at 192 weeks). Findings were consistent in multivariable analysis.

Conclusion: Among CHB patients with HBsAg > 100 IU/mL at EOT, HBsAg and HBV DNA levels at FU W24 predict outcomes during subsequent follow-up. Presence of HBsAg < 100 IU/mL with HBV DNA < 100 IU/mL at FU W24 is associated with a low risk of subsequent clinical relapse and excellent chances of HBsAg loss. Retreatment should be considered for all patients with both HBsAg > 100 IU/mL and HBV DNA > 100 IU/mL due to high clinical relapse rates and virtually no chance of HBsAg loss.



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1434-C | PEGINTERFERON ALFA-2b PLUS TDF TREATMENT IN ADULTS WITH HBEAG-POSITIVE CHRONIC HEPATITIS B VIRUS INFECTION: A PILOT, OPEN-LABEL, PROSPECTIVE COHORT STUDY

Min Liu[1], Lili Zuo[1], Yuting Zhang[1], An Xiao[1], Yilan Wang[1], Bing Bu[1], Jiayi Chen[1], Ling Zhu[1], Wei Yue[1], Jiawei Geng[1] and Xueshan Xia[2], (1)The First People's Hospital of Yunnan Province, (2)Kunming University of Science and Technology

Background: Expanding antiviral therapy to benefit more patients with chronic HBV infection and optimizing treatment to improve prognoses are two main objectives in current guidelines. However, the guidelines do not recommend antiviral therapy for HBeAg-positive chronic HBV infection (immune-tolerant, IT) patients. Currently, existing literature is sparse on the clinical efficacy for IT adults. This study aims to evaluate the efficacy and safety of the combination of peginterferon alfa-2b (PEG-IFNα-2b) and Tenofovir disoproxil fumarate (TDF) in IT adults. **Methods:** This is a pilot, open-label, prospective cohort study from May 2019 to October 2022. Treatment-naive adults aged 18 to 60 years in immune-tolerant phase were recruited and divided to three groups as their willing. Patients in combination therapy group received PEG-IFNα-2b for 12 weeks followed by TDF "add-on" for 36 weeks, TDF monotherapy group received TDF for 48 weeks and control group received follow-up only (Figure 1A). The primary endpoints were HBeAg loss rate and the proportion of patients achieving qHBsAg $<$ 3000 IU/mL at the end of treatment (EOT). The secondary endpoints were HBsAg loss rate and proportion of patients with HBV DNA d 10 IU/mL at EOT. **Results:** 247 patients were enrolled. At baseline, there was no significant difference in the epidemiological, biochemical, serological and virological indicators among groups. The median age was 28 years, 34.82% were male, and nearly all were genotype B or C. Of the 73 patients in the combination therapy group, 5.48% achieved HBeAg loss, 46.58% achieved HBsAg $<$ 3000 IU/mL, 71.23% had HBV DNA d 10 IU/mL, and 4.11% achieved HBsAg loss at EOT. Of 121 patients in the TDF monotherapy group, only 0.83% achieved HBeAg loss, 2.48% achieved HBsAg < 3000 IU/mL, 52.07% obtained HBV DNA **d** 10 IU/mL, and none had HBsAg loss. In the control group, none met any endpoints (Figure 1B). No serious adverse events were observed in the study. **Conclusion:** A lead-in strategy of 12 weeks of PEG-IFNα-2b followed by TDF "add-on" for 36 weeks had good efficacy in IT adults. We emphasize the need for more multicenter large sample randomized trials in the future to verify whether the combination antiviral therapy strategy for IT patients is associated with good outcomes or reduced risk of end-stage liver disease.

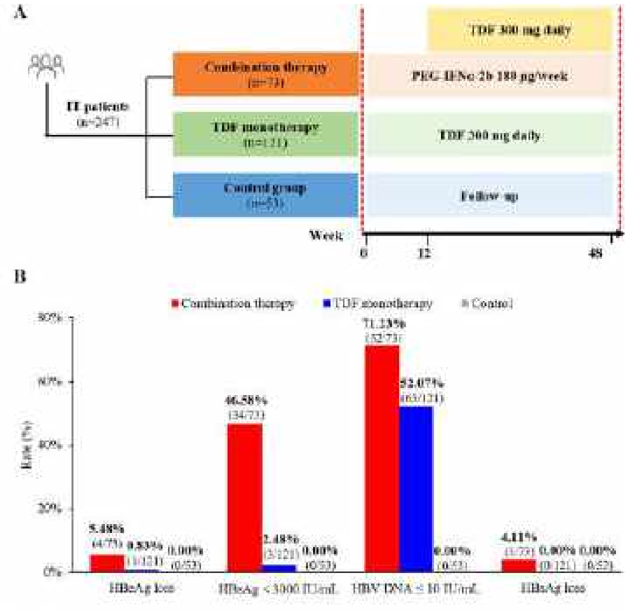

Figure 1

A. Study design.

B. Efficacy outcomes of different groups at EOT

Disclosures: The following people have nothing to disclose: Min Liu, Lili Zuo, Yuting Zhang, An Xiao, Yilan Wang, Bing Bu, Jiayi Chen, Ling Zhu, Wei Yue, Jiawei Geng, Xueshan Xia

1435-C | PEGINTERFERON ALFA-2b PLUS TDF TREATMENT OF HBEAG-NEGATIVE CHRONIC HEPATITIS B PATIENTS IN INDETERMINATE PHASE: A PILOT, OPEN-LABEL, PROSPECTIVE COHORT STUDY

Min Liu[1]*, Yuting Zhang*[1]*, Lili Zuo*[1]*, An Xiao*[1]*, Wei Yue*[1]*, Bing Bu*[1]*, Yilan Wang*[1]*, Jiayi Chen*[1]*, Ling Zhu*[1]*, Jiawei Geng*[1] *and Xueshan Xia*[2]*, (1)The First People's Hospital of Yunnan Province, (2)Kunming University of Science and Technology*

Background: Many chronic hepatitis B (CHB) patients cannot be clearly classified into natural history phases of chronic HBV infection, which were defined as "indeterminate phase (IP)" patients. However, it is unclear whether the antiviral treatment indications should be expanded for IP patients. This study aims to evaluate the efficacy and safety of the combination therapy of peginterferon alfa-2b (PEG-IFNα-2b) and Tenofovir disoproxil fumarate (TDF) in HBeAg-negative IP patients. **Methods:** This is a pilot, open-label, prospective cohort study from May 2019 to October 2022. Treatment-naïve CHB patients aged 18-60 years with HBeAg-negative, qHBsAg > 3000 IU/mL and normal ALT were enrolled and divided into three groups according to their willing. Combination therapy group received PEG-IFNα-2b for 12 weeks followed by TDF "add-on" for 36 weeks, TDF monotherapy group received TDF for 48 weeks and control group were followed-up without any antiviral treatment (Figure 1A) . The primary endpoint was the proportion of patients achieving qHBsAg < 1500 IU/mL at the end of treatment (EOT), and the secondary endpoint was HBsAg loss at EOT. **Results:** 261 IP patients were enrolled. At baseline, there was no significant difference in the epidemiological, biochemical, serological and virological indicators among the groups. In the combination therapy group, 55.06% (49/89) achieved HBsAg < 1500 IU/mL and 4.49% (4/89) achieved HBsAg loss at EOT. In the TDF monotherapy group and control group, none met these endpoints (Figure 1B). Patients achieving qHBsAg < 1500 IU/mL in the combination therapy group had significantly higher mean ALT levels at week 12/24 compared to those with qHBsAg **e** 1500 IU/mL ($p = 0.04$; $p = 0.002$, Figure 1C). Week 12/24 ALT > 2 × baseline were associated with higher rates of qHBsAg < 1500 IU/mL at EOT (97.96% and 73.47%, respectively). No serious adverse events were observed in the study. **Conclusion:** A lead-in strategy of 12 weeks of PEG-IFNα-2b followed by TDF "add-on" for 36 weeks had good efficacy in HBeAg-negative IP patients

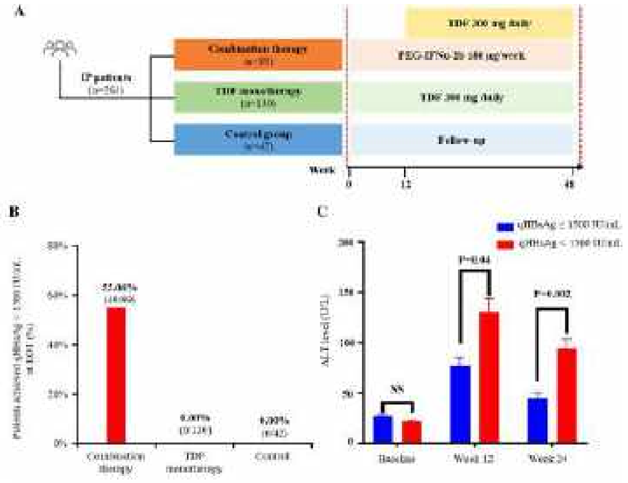

Figure 1

A. Study design.

B. The proportion of IP patients achieved qHBsAg < 1500 IU/mL at EOT.

C. Change of ALT levels of patients with qHBsAg < 1500 IU/mL or ≥1500 IU/mL in combination therapy group at EOT.

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

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1436-C | PREDICTIVE VALUE OF AGE ON LIVER HISTOLOGICAL CHANGES IN CHB PATIENTS WITH NORMAL ALT LEVELS

Xuefu Chen, Xiaodan Luo, Yifan Yang, Ren Chen, Xiaoping Chen and Xiaoming Chen, Guangdong Provincial People's Hospital

Background: The 2022 China HBV guideline recommends antiviral therapy for CHB with normal ALT levels, HBV DNA (+), and age > 30 years (B1). This study aimed to analyze the role of age in liver histological changes in CHB patients with normal ALT levels, using the presence of moderate to severe liver injury as an indication for initiating antiviral therapy. **Methods:** This retrospective study included CHB patients with normal ALT levels who were treatment naive and had undergone liver biopsy in Guangdong Provincial People's Hospital between Jan. 2010 and Dec. 2019. Inclusion criteria : age between 16 and 70 years (Y), HBsAg (+) > 6 months, ALT **d** 40 U/L, and HBV DNA > 20 IU/ml. Exclusion criteria: liver injury caused by HCV, HDV or other factors, and severe heart comorbidities et al. Patients were categorized as having either mild (G < 2 and/or S < 2) or moderate to severe (G **e** 2 and/or S **e** 2) liver injury based on liver histological changes. All patients have signed consent for liver puncture. The Wilcoxon rank-sum test and Pearson $\chi 2$ test were used to compare differences in quantitative and qualitative data between groups, respectively. The kappa coefficient was used to evaluate the sensitivity (SEN%) and specificity (SPE%) of each indicator for liver histological changes. Statistical analyses were performed using SAS 9.4 and MedCalc. **Results:** 648 CHB patients were included,375 (57.9%) were male, mean age was 37.7 ± 11.3 Y, 444 (68.5%) were > 30 Y, 316 (48.8%) were HBeAg (+), mean HBV DNA was 5.65 ± 1.84Log$_{10}$IU/mL, 581 (90.0%) had HBV DNA **e** 2000 IU/ml, mean ALT was 26.0 ± 7.6U/L, 365(56.3%) **e** 30 (male)/19(female)U/L ; 305 (47.1%) had moderate to severe liver injury. Comparing the mild and moderate to severe liver injury groups, the proportion of patients > 30 Y was higher in the moderate to severe group than in the mild group (72.5% vs. 65.0%, *p* = 0.042), and the proportion of patients with ALT **e** 30/19 U/L was higher in the moderate to severe group than in the mild group (61.0% vs. 52.2%, *p* = 0.024). When evaluating the SEN and SPE of clinical indicators for moderate to severe liver histological changes, the results were as follows: for age > 30 Y, SEN was 72.46, SPE was 34.99; for ALT **e** 30/19 U/L, SEN was 60.98, SPE was 47.81; for HBV DNA **e** 2000 IU/mL, SEN was 89.18, SPE was 9.91. Combining age > 30 Y with other indicators further increased the SEN. For age > 30 Y and ALT **e** 30/19 U/L, SEN and SPE is 87.54 and 17.78, respectively. For age > 30 Y and HBV DNA **e** 2000 IU/mL, SEN and SPE is 97.70 and 2.62, respectively. Three indicators combined, SEN 98.36, SPE 1.75. (Figure 1) **Conclusion:** Age > 30 Y can be a good predictor for the liver tissue damage in CHB patients with normal ALT levels, which is very meaningful for initiating antiviral treatment in this population. This study supports the use of ALT thresholds of 30 U/L for male and 19 U/L for female for antiviral therapy. Combining age > 30 Y with HBV DNA **e** 2000 IU/ml or ALT **e** 30/19 U/L can further improve the sensitivity of evaluating the degree of liver tissue damage.

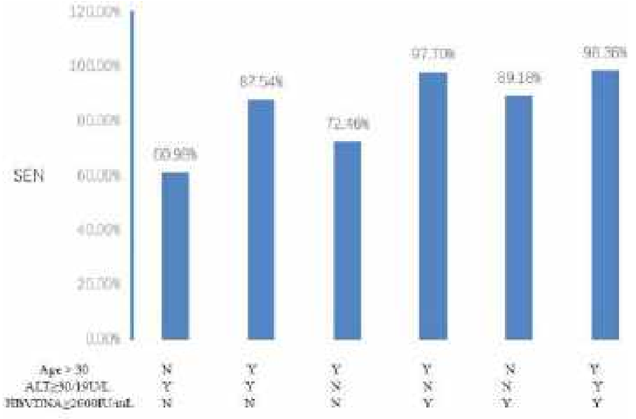

Figure 1: The SEN% of clinical indicators in evaluating moderate to severe liver histological changes

Disclosures: The following people have nothing to disclose: Xuefu Chen, Xiaodan Luo, Yifan Yang, Ren Chen, Xiaoping Chen, Xiaoming Chen

1437-C | PREDICTIVE VALUE OF HEPATITIS B CORE-RELATED ANTIGEN FOR CLINICAL CURE AND RELAPSE FOLLOWING PEGYLATED INTERFERON-ALPHA THERAPY IN PATIENTS WITH CHRONIC HEPATITIS B AND LOW HBsAg LEVELS

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

Background: Pegylated interferon-α (Peg-IFN-α) therapy is currently considered a promising treatment option for achieving clinical cure of chronic hepatitis B (CHB) patients. In this study, we aimed to identify biomarkers associated with clinical cure and off-treatment hepatitis B surface antigen (HBsAg) relapse in CHB patients with low HBsAg levels. **Methods:** Chronic hepatitis B patients with HBeAg-negative and HBsAg < 2000 IU/mL who were treated with Peg-IFN-α alone or in combination with nucleotide analogs for 48-96 weeks were enrolled in our study. The serum levels of hepatitis B core-related antigen (HBcrAg), HBsAg, and hepatitis B surface antibody (HBsAb) were dynamically examined. **Results:** A total of 101 patients were enrolled, 40.59% (41/101) achieved HBsAg clearance, and 33.66% (34/101) achieved HBsAg seroconversion at the end of treatment (EOT). The baseline HBsAg level was strongly associated with the probability of HBsAg clearance, specifically when HBsAg < 210.10 IU/mL, there will be a 69.8% conversion rate after 48 weeks of treatment with IFN. Additionally, for patients with baseline HBsAg > 210.10 IU/mL, baseline HBcrAg levels < 3.90 log10 U/mL predicted 69.3% of HBsAg clearance, with positive and negative predictive values of 38.71% and 87.88%, respectively. Nine of 41 patients who achieved HBsAg clearance experienced HBsAg relapse during a follow-up time of 114.00(49.00-217.00) weeks. There was a significant difference of EOT HBcrAg levels between the patients with HBsAg relapse and those without (3.96 ± 0.57 log10 U/mL vs 3.25 ± 0.65 log10 U/mL, $p < 0.05$). An EOT HBcrAg level > 3.8 log10 U/mL indicated a recurrence rate of 79.3%. When combined with HBsAb (**d** 51.50 IU/L) at EOT, predictive value for off-treatment HBsAg relapse was up to 84%, with positive and negative predictive values of 66.67% and 85.71%, respectively. **Conclusion:** HBcrAg and HBsAg can be used to predict the possibility of clinical cure, while HBcrAg and HBsAb are closely related to off-treatment HBsAg relapse following Peg-IFN-α therapy in patients with CHB and low HBsAg. Specifically, when the baseline level of HBsAg is less than 210.10 IU/mL, pegylated interferon-α is strongly recommended. When the baseline level of HBsAg is over 210.18 IU/mL, levels of HBcrAg should be tested, and patients should be treated if HBcrAg is less than 3.90 log10 U/mL. When levels of HBcrAg are over 3.8 log10 U/mL after treatment, close follow-ups are recommended to reduce relapse.

Disclosures: The following people have nothing to disclose: Ming Liu, Zhongwei Liu, Yan Guo, Hongmei Gong, Qing Mao

1438-C | RETREATMENT WITH TENOFOVIR ALAFENAMIDE FOR 48 WEEKS SIGNIFICANTLY REDUCES LIVER FIBROSIS, QUANTITATIVE HBsAg AND HBCRAG LEVELS

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Background: Achieving function cure and reducing liver fibrosis are important goals in management of chronic hepatitis B. Mac-2 binding protein glycosylation isomer (M2BPGi) is a novel marker for liver fibrosis. Hepatitis B core related antigen (HBcrAg) reflects intrahepatic cccDNA of HBV and its transcriptional activity. Little is known the dynamic change of these two markers after retreatment by tenofovir alafenamide (TAF) at hepatitis relapse after discontinuation of prior entecavir or tenofovir disoproxil fumarate (TDF) therapy. **Methods:** This prospective multicenter CHANGE (Chronic Hepatitis b patients switch to tAf after discontinuation of Nucleoside analoGuE) study (NCT04496882) is enrolling patients who experienced off-therapy (TDF or entecavir) clinical relapse and switch them to TAF for retreatment for 48 weeks in Taiwan. The primary endpoint was the rate of virological remission (HBV DNA < 20 IU/mL), and the secondary endpoints include the change of HBsAg, HBcrAg and M2BPGi levels. **Results:** As of April 30 2023, 47 patients were enrolled and 42 patients were included in this biomarker evaluation (discontinuation of prior TDF: entecavir = 21:21). At retreatment, the median age was 49 years and 5 were HBeAg positive. After 48-week of therapy, the virological remission and ALT normalization (< 41 U/L) rate were 77% and 88%, respectively. Among 30 patients who completed 48-week TAF therapy, there is a significant decline of HBsAg (0.6 $\log_{10}$ IU/mL, $p < 0.001$) and 6 patients (6/30, 20%) had achieved a favorable HBsAg response (**d** 100 IU/mL). There was a significant reduction of liver stiffness measured by M2BPGi (0.93 to 0.59 C.O.I., $p < 0.001$), FIB-4 index (1.62 to 1.20, $p < 0.001$) and HBcrAg levels (6.05 to 3.50 $\log_{10}$ IU/mL, $p < 0.001$), especially in HBeAg-negative patients (5.70 to 3.20 $\log_{10}$ IU/mL,

$p < 0.001$). **Conclusion:** Switching to TAF retreatment for 48 weeks after off-TDF or entecavir relapse is effective in viral suppression, reduction of quantitative HBsAg and HBcrAg levels, ALT normalization and liver stiffness improvement.

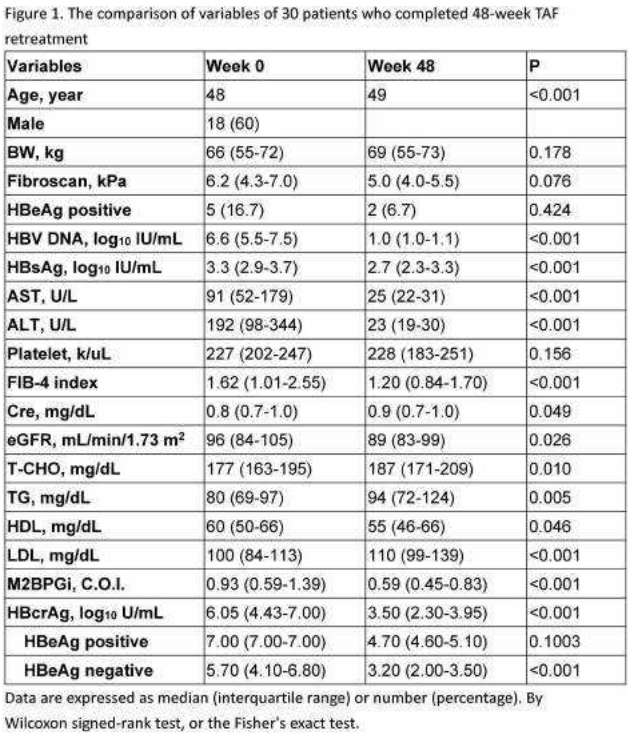

Figure 1. The comparison of variables of 30 patients who completed 48-week TAF retreatment

Variables	Week 0	Week 48	P
Age, year	48	49	<0.001
Male	18 (60)		
BW, kg	66 (55-72)	69 (55-73)	0.178
Fibroscan, kPa	6.2 (4.3-7.0)	5.0 (4.0-5.5)	0.076
HBeAg positive	5 (16.7)	2 (6.7)	0.424
HBV DNA, $\log_{10}$ IU/mL	6.6 (5.5-7.5)	1.0 (1.0-1.1)	<0.001
HBsAg, $\log_{10}$ IU/mL	3.3 (2.9-3.7)	2.7 (2.3-3.3)	<0.001
AST, U/L	91 (52-179)	25 (22-31)	<0.001
ALT, U/L	192 (98-344)	23 (19-30)	<0.001
Platelet, k/uL	227 (202-247)	228 (183-251)	0.156
FIB-4 index	1.62 (1.01-2.55)	1.20 (0.84-1.70)	<0.001
Cre, mg/dL	0.8 (0.7-1.0)	0.9 (0.7-1.0)	0.049
eGFR, mL/min/1.73 m^2	96 (84-105)	89 (83-99)	0.026
T-CHO, mg/dL	177 (163-195)	187 (171-209)	0.010
TG, mg/dL	80 (69-97)	94 (72-124)	0.005
HDL, mg/dL	60 (50-66)	55 (46-66)	0.046
LDL, mg/dL	100 (84-113)	110 (99-139)	<0.001
M2BPGi, C.O.I.	0.93 (0.59-1.39)	0.59 (0.45-0.83)	<0.001
HBcrAg, $\log_{10}$ U/mL	6.05 (4.43-7.00)	3.50 (2.30-3.95)	<0.001
HBeAg positive	7.00 (7.00-7.00)	4.70 (4.60-5.10)	0.1003
HBeAg negative	5.70 (4.10-6.80)	3.20 (2.00-3.50)	<0.001

Data are expressed as median (interquartile range) or number (percentage). By Wilcoxon signed-rank test, or the Fisher's exact test.

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Disclosure information not available at the time of publication: Chih-Lin Lin, Chia-Chi Wang

1439-C | SELF-DISCONTINUATION DURING NUC THERAPY IN HBEAG-NEGATIVE CHRONIC HEPATITIS B PATIENTS: A NOT UNCOMMON BUT PERILOUS SITUATION

Rachel Wen-Juei Jeng[1,2], Chenger Hsu[2], Chia-Ling Wu[2], Chung-Wei Su[1], Yen-Chun Liu[2], Rong-Nan Chien[1,2] and Yun-Fan Liaw[1,2], (1)College of Medicine, Chang Gung University, Taiwan, (2)Chang Gung Memorial Hospital, Linkou Medical Center

Background: In real-world practice, self-discontinuation and loss to follow-up (LTFU) during long-term antiviral treatment are not uncommon. Chronic hepatitis B (CHB) patients who self-discontinue treatment without proper monitoring face risks of delayed retreatment and hepatic decompensation/hepatic failure. Limited information exists on the incidence and factors associated with self-discontinuation/LTFU. This study explores the issue using a multi-institutional electronic medical record database (CGRD). **Methods:** We recruited HBeAg-negative CHB patients who received ETV or TDF for **e** 3 months between Jan 2004 and Nov 2021 at Chang Gung Memorial Hospital's branches in Taipei, Linkou, and Taoyuan, selected from CGRD. Exclusions included patients on Nuc for prophylaxis related to chemotherapy or immunosuppressants, with co-infections (HCV, HIV, or HDV), or diagnosed with HCC within 5 years before antiviral treatment. Self-discontinuation/LTFU was identified as patients failing to refill medication for **e** 2 consecutive months, verified through medical chart review. Logistic regression analysis identified factors associated with self-discontinuation. Hepatic decompensation (HD) was determined using ICD codes (ICD-9: 572.2, 789.5, 578.0, 578.9, 456.0, 456.2 or ICD-10: K72.9, K72.91, R18.8, K92, K92.2, I85.01, I85.11, I86.4). HD events after Nuc discontinuation in non-retreated patients or within 1 year during retreatment were considered associated with Nuc discontinuation. Comparison was made between self-discontinuation and scheduled withdrawal. **Results:** A total of 3358 HBeAg-negative CHB patients with 4217 treatment courses were included. Over a median treatment duration of 2.4 (IQR: 1.1-3) years, 341 self-discontinuation/LTFU events were identified, with annual incidence rates of 3.02% and cumulative rates of 8.61%, 13.23%, and 19.97% at 3, 5, and 10 years. Most self-discontinuation events (38.4%) occurred within the first year. Factors associated with self-discontinuation events included age (< 40 or **e** 70) [age 40-69 as referent: < 40, aOR: 2.10 ; **e** 70, aOR: 1.65], liver cirrhosis (aOR: 2.04), prior treatment experienced (aOR: 0.61), pretherapy ALT levels (< 2X ULN as referent, 2-5X ULN: aOR: 0.72, > 5X ULN: aOR: 0.78), and use of ETV (TDF as referent, aOR: 1.36). During median follow-up of 2.5 years (IQR: 1.3-5.4), 49 (2.1%) of 2,321 patients who stopped Nuc experienced off-Nuc HD events, primarily among cirrhosis patients (96%). Self-stop/LTFU patients had significantly higher HD incidence (7.3% vs. 1.2%, $p < 0.0001$) than scheduled stopped patients. **Conclusion:** Self-discontinuation/LTFU increased with the duration of Nuc therapy, reaching 8.61% and 19.97% within 3 and 10 years, respectively. Among these cases, 7.3% were complicated by HD. It is crucial to prioritize education and establish a tele-call back service to prevent such events and mitigate the associated adverse outcomes.

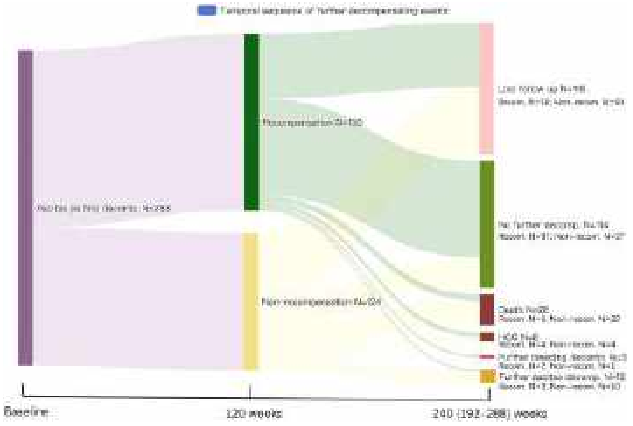
Disclosures: The following people have nothing to disclose: Rachel Wen-Juei Jeng, Chenger Hsu, Chung-Wei Su, Rong-Nan Chien

Disclosure information not available at the time of publication: Chia-Ling Wu, Yen-Chun Liu, Yun-Fan Liaw

f 1440-C | STABLE RECOMPENSATION IN ENTECAVIR-TREATED HEPATITIS B PATIENTS WITH DECOMPENSATED CIRRHOSIS★

You Deng[1], Haiyan Kang[2], Huiling Xiang[3], Yuemin Nan[4], Jinhua Hu[5], Qinghua Meng[6], Xiaoyuan Xu[7], Jilian Fang[8], Jie Xu[9], Xiaoming Wang[10], Hong You[10], Qi Wang[1], Hong Zhao[1], Jidong Jia[11] and Wen Xie[1], (1)Center of Liver Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, China, (2)Shijiazhuang Fifth Hospital, Shijiazhuang, China, (3)Tianjin Third Central Hospital, Tianjin, China, (4)Third Hospital of Hebei Medical University & Hebei Key Laboratory of Mechanism of Liver Fibrosis in Chronic Liver Disease, (5)The Fifth Medical Centre of Chinese PLA General Hospital, Beijing, China, (6)Beijing Youan Hospital Capital Medical University, Beijing, China, (7)Peking University First Hospital, (8)Peking University People's Hospital, Beijing, China, (9)Peking University Third Hospital, Beijing, China, (10)Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China, (11)Liver Research Center, Beijing Friendship Hospital, Capital Medical University, National Clinical Research Center of Digestive Diseases, Beijing, China

Background: Recompensation is achievable in certain chronic hepatitis B (CHB) patients with decompensated cirrhosis who are treated with nucleos(t)ide analogues (NAs).However, the understanding of stable recompensation in these patients remains limited. **Methods:** This study was based on a multicenter, prospective study of CHB patients with decompensated cirrhosis who were enrolled at the onset of ascites as the first decompensated event and treated with entecavir for 120 weeks. At week 120, out of the recruited 283 patients, 159 achieved recompensation and 124 did not. These patients were further followed up until the occurrence of a second decompensation event or until March 2023. Recompensation was defined by the Baveno VII definition and the criteria of stable improvement in liver function tests reported by us. **Results:** Out of the initial 283 patients, 165 patients were followed beyond week 120, with a further median follow-up time of 240 (192-288) weeks. Among the 101 patients who achieved recompensation by week 120, 87 (86.1%) did not experience any subsequent decompensated events; 4 patients were diagnosed with HCC, 2 patients developed variceal bleeding, 2 patients developed moderate-severe ascites, and 6 patients died. In contrast, among the 64 patients who did not achieve recompensation by week 120, 27 (42.2%) did not experience any further decompensated events (achieved recompensation); 4 patients were diagnosed with HCC,1 patient developed variceal bleeding, 10 patients developed moderate-severe ascites, and 22 patients died. **Conclusion:** In CHB patients with decompensated cirrhosis, approximately 86% of those who achieved recompensation by week 120 maintained stable recompensation during the next 120 (72-168) weeks of antiviral therapy. Furthermore, recompensation was attained in the next 120 (72-168) weeks in 42% of patients who did not achieve it by week 120. Besides, patients undergoing recompensation also need to pay attention to the monitoring of hepatocellular carcinoma.



Disclosures: Yuemin Nan – BMS, Gilead, and GSK: Speaking and Teaching, Yes, No;

Hong You – BMS, Gilead, and GSK: Speaking and Teaching, Yes, No;

The following people have nothing to disclose: You Deng, Haiyan Kang, Huiling Xiang, Jinhua Hu, Qinghua Meng, Xiaoyuan Xu, Jilian Fang, Jie Xu, Xiaoming Wang, Qi Wang, Hong Zhao, Jidong Jia, Wen Xie

1441-C | TENOFOVIR ALAFENAMIDE FOR TREATMENT-NAÏVE AND NUCLEOS(T)IDE-EXPERIENCED PATIENTS WITH HEPATITIS B VIRUS INFECTION—96-WEEK DATA FROM A REAL-WORLD STUDY (TRUE)

Di Wu[1], Peng Wang[2], Xiaoping Wu[3], Yan Huang[4], Youqin Yan[5], Liang Chen[6], Zhe Yu[7], Bing Pi[1], Weiming Yan[2] and Qin Ning[8], (1)State Key Laboratory for

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

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Background: Tenofovir alafenamide (TAF) has been approved for the treatment of chronic hepatitis B (CHB). We aimed to assess the effectiveness and safety of TAF-based therapy in treatment naïve (TN) or experienced (TE) CHB patients. **Methods:** This multicenter, prospective, real-word study included 500 CHB patients treated with TAF monotherapy or combining with entecavir (ETV) for 144 weeks. Virological and biochemical responses and safety were evaluated (clinicaltrial.gov: NCT03752658). **Results:** 404 patients (TN, 146; TE, 258) with available data were included in this interim analysis. 13.6% had cirrhosis at baseline. All TN patients and 164 TE patients received TAF alone, and 94 TE patients received TAF plus ETV. Of TN patients, 88.7% achieved virological response (HBV DNA < 20 IU/mL) at week 96. 81.8% achieved biochemical response (ALT < 40 U/L) at week 96. Among TE patients switching to TAF, virological response rate was significantly increased, from 67.8% at baseline to 91.7% at week 96 ($p < 0.05$), and biochemical response rate was 79.7% at baseline and 92.1% at week 96. Among TE patients receiving TAF+ETV, virological response rate was significantly increased from 42.0% at baseline to 91.3% at week 96 ($p < 0.05$), and biochemical response rate was significantly increased from 80.0% at baseline to 92.9% at week 96 ($p < 0.05$). Of 75 TE patients with low level viremia at baseline (HBV DNA < 2000 IU/mL), 61 achieved virologic response at week 96. Among patients with estimated glomerular filtration rate (eGFR) below 90 mL/min/1.73m^2 at baseline, eGFR was significantly improved at week 96 ($p < 0.05$). Total cholesterol levels significantly increased at week 96 ($p < 0.05$). TAF-based therapy was well-tolerated. **Conclusion:** TAF-based therapy was effective in both TN and TE CHB patients, as well as those with low level viremia. TAF therapy show a sustained improvement in renal glomerular function in patients with prior impaired renal function.

Disclosures: The following people have nothing to disclose: Di Wu, Peng Wang, Xiaoping Wu, Yan Huang, Youqin Yan, Liang Chen, Zhe Yu, Bing Pi, Weiming Yan, Qin Ning

1442-C | TENOFOVIR ALAFENAMIDE FUMARATE THERAPY IN HEALTHY HBsAg CARRIERS: PRELIMINARY RESULTS OF A RANDOMIZED CONTROLLED TRIAL

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Background: At present, antiviral therapy for healthy HBsAg carriers is still controversial. This study is to evaluate the safety and efficacy of tenofovir alafenamide fumarate (TAF) in these subjects. **Methods:** It is a prospective randomized controlled trial and the protocol has been published (BMJ Open. 2021;11: e048410). In brief, the subjects enrolled were healthy HBsAg carriers, defined as positive HBV DNA (> 20 IU/ml in HBeAg (+), and 20-2000 IU/ml in HBeAg (-)), normal ALT, Fibroscan < 5.8 KPa, without family history of cirrhosis or hepatocellular carcinoma. Participants were randomly divided into treatment group (treated with TAF) and control group in a 1:1 ratio. More details of the study protocol can be seen in the previous article mentioned above. **Results:** 122 patients were enrolled by May 15, 2023, including 61 HBeAg (+) cases (30 treated with TAF, 31 without treatment) and 61 HBeAg (-) cases (29 treated with TAF, 32 without treatment). 20 cases in TAF group and 17 in control group have been followed up to 24 weeks in HBeAg (+) cohort, while 22 and 17 cases in HBeAg (-) cohort. Baseline characteristics were similar between TAF group and control group in HBeAg (+) cohort, as well as in HBeAg (-). The mean HBV DNA values of TAF group and control group in HBeAg (+) cohort at baseline were 7.85 and 8.03 $\log_{10}$IU/ml respectively, while those in HBeAg (-) were 2.74 and 2.60 $\log_{10}$IU/ml. No severe adverse effects and no significant changes in ALT, Cr, CHI3L1 and Fibroscan were observed in each arm. HBV DNA was < 10 IU/ml in 2 out of 20 HBeAg (+) patients and 18 out of 22 HBeAg (-) patients after treatment for 24 weeks. The HBeAg (+) and HBeAg (-) TAF groups showed an average decrease of 4.24 and 2.57 $\log_{10}$IU/ml in HBV DNA at 12w after treatment, respectively. While at

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

24w, HBV DNA decreased by a mean of 5.24 $\log_{10}$IU/ml in the HBeAg (+) TAF group. The virological changes were shown in Figure 1. **Conclusion:** The preliminary results indicated that TAF was safe in healthy HBsAg carriers. HBV DNA decreased rapidly at the first 12 weeks of treatment in both HBeAg (+) and HBeAg (-) groups. HBsAg changed little in this study. However, HBsAg reduction from baseline was greater in the HBeAg (+) group than HBeAg (-). PgRNA increased in HBeAg (+) cases after 24 weeks of antiviral therapy, and this trend should be monitored during treatment extension. The number of patients followed up to 48 weeks was insufficient to make a valid statistic. More results will be reported in the near future.

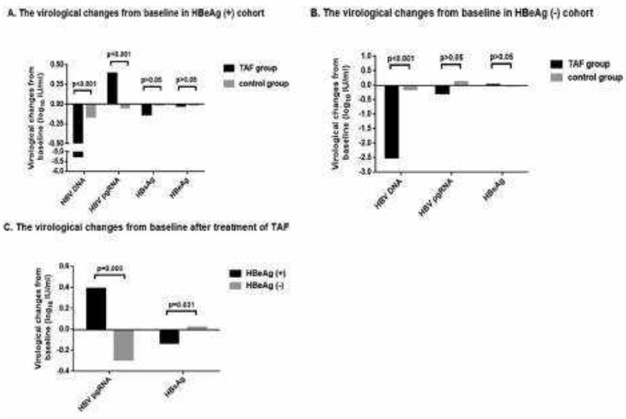


Figure 1. Changes in virological indices from baseline in each group at 24 weeks.

Disclosures: The following people have nothing to disclose: Qiumin Luo, Wenxiong Xu, Xiangyong Li, Chan Xie, Liang Peng

1443-C | TENOFOVIR ALAFENAMIDE FUMARATE WAS EFFECTIVE AND SAFE FOR CHB PATIENTS WITH LIVER CIRRHOSIS: A REAL-WORD EVIDENCE IN CHINA

Lufeng Li[1], Zhonglan You[1], Jing Wang[1], Guohong Deng[1], Baoyan Xu[1], Yan Zhu[2], Jie Xia[1] and Qing Mao[1], (1)Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China, (2) Department of Infectious Diseases, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China.

Background: Previous studies showed antiviral treatment(AVT) improves clinical outcomes in patients with chronic hepatitis B (CHB). However evidence of AVT for patients with liver cirrhosis or end-stage liver disease was limited. We aimed to evaluate the efficacy and safety of Tenofovir alafenamide fumarate(TAF) for CHB patients with liver cirrhosis (LC)or liver failure(LF). **Methods:** Cirrhotic CHB patients receiving TAF treatment were retrospectively enrolled(cirrhosis was diagnosed by imaging examinations and clinical symptoms). Complete virological response rate(CVR, (defined as serum HBV DNA $<$ 50 IU/mL), ALT normalization (defined as ALT $<$ 42 U/L) rate, AST level, FIB-4 and APRI score were also observed. Safety profiles including liver function and renal function were collected. **Results:** From Jan.2020 to Dec.2022, a total of 171 CHB patients with LC or LF receiving TAF were enrolled. The patients were divided into three groups: Group 1(n = 37) was treatment-naïve patients receiving TAF and group 2(n = 125) was treatment experienced patients receiving TAF. Group 3(n = 12) was treatment experienced patients receiving TAF in combination with ETV. 92%(157/171) of patients had compensated cirrhosis(CC), 6.4%(11/171) had decompensated cirrhosis(DCC) and 1.8%(3/171) of patients had LF. Baseline characteristics were showed in Table 1. 100% of the patients achieved CVR after 96 weeks of TAF or TAF +ETV treatment, regardless of treatment experience. A total of 10 patients with DCC and 1 patient with liver failure improved to CC after 96 weeks treatment. Mean ALT and AST level decreased during treatment in each group. And the rate of ALT normalization improved significantly in group 1 at 48 weeks compared with baseline(from 44.1% to 73.5%, $p = 0.013$). Other groups had numerically increase for ALT normalization rate after 48 weeks and 96 weeks treatment. Serum creatinine was significantly reduced after 48 weeks of TAF treatment in group 1(from 84.55 ± 45.87 μmol/L to 74.42 ± 38.77 μmol/L, $p = 0.006$) and remained stable in the other groups. Mean FIB-4 and APRI scores also decreased during treatment(Table 2). No drug-related AEs or SAEs were observed during the follow-up period. **Conclusion:** TAF was effective and safe for CHB patients with liver cirrhosis or liver failure, regardless of previous treatment.

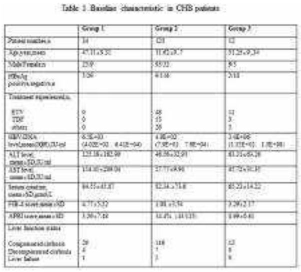


Table 1 Baseline characteristic in CHB patients

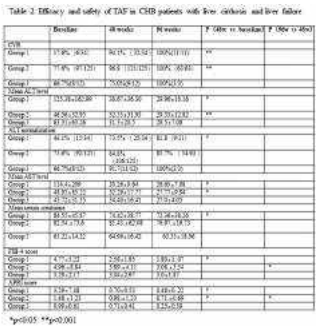


Table 2 Efficacy and safety of TAF in CHB patients with liver cirrhosis and liver failure

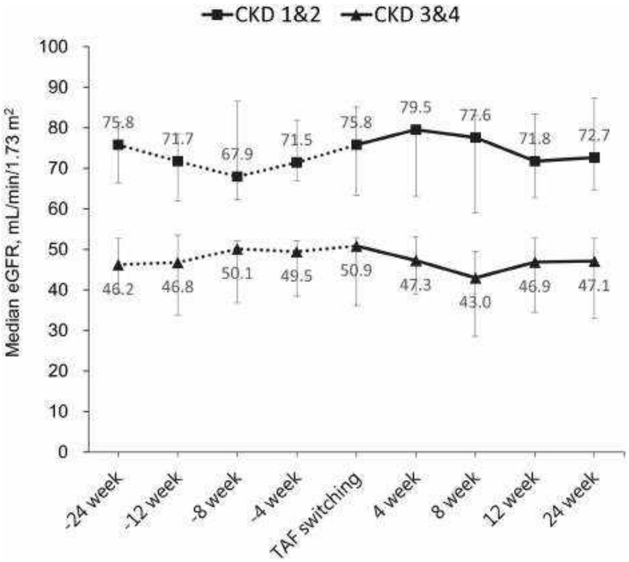
*p<0.05 **p<0.001

Disclosures: The following people have nothing to disclose: Lufeng Li, Zhonglan You, Jing Wang, Guohong Deng, Baoyan Xu, Yan Zhu, Jie Xia, Qing Mao

1444-C | TENOFOVIR ALAFENAMIDE SWITCHING THERAPY IN KIDNEY TRANSPLANT RECIPIENTS WITH CHRONIC HBV INFECTION – MIDTERM ANALYSIS OF A PROSPECTIVE STUDY

Teng-Yu Lee, Hsin-Ju Tsai, Cheng-Hsu Chen, Sheng-Shun Yang, Ming-Ju Wu, Tung-Min Yu, Chung-Hsin Chang, Szu-Chia Liao, Mu-Chi Chung and Hsien-Fu Chiu, Taichung Veterans General Hospital

Background: Kidney transplant recipients (TKRs) with chronic HBV infection may be indicated for tenofovir alafenamide (TAF) switching therapy, however the related studies remain limited. We aimed to assess the effects of TAF switching therapy in KTRs. **Methods:** In this prospective cohort study (ClinicalTrials.gov: NCT05410496), KTRs who were indicated for TAF switching therapy, such as concerns in virological response, biochemical response, drug compliance, or safety to the used HBV antivirals, were enrolled. Following conditions were excluded: (1) End stage renal disease (eGFR < 15 mL/min/1.73m^2); (2) Co-infected with HIV or HCV; (3) Any active malignancies; (4) Pregnant or breast-feeding women; (5) Known allergy to tenofovir-contained regimens. After switching to TAF therapy, any treatment-related adverse effects (TRAEs) and the changes in virological responses, renal function, bone mineral density, and drug adherence were prospectively recorded. **Results:** Until May 17, 2022, two patients early withdrew from this study due to non-TRAEs, and 31 patients who were followed up for more than 24 weeks were included for this mid-term analysis. In the per-protocol analysis, median age was 58.9 (IQR: 53.1-64.6) years, and 24 (77.4%) patients received entecavir before switching to TAF. Seventeen (54.8%) and 14 (45.2%) patients were classified in the chronic kidney disease stage 1&2 and 3&4, respectively. After 24-week TAF therapy, more patients achieved undetectable serum HBV DNA (96.8% vs. 77.4%; $p = 0.031$) and ALT normalization (80.6% vs. 67.7%; $p = 0.125$). The changes in renal parameters were not significant, including serum creatinine (1.18 [IQR: 0.97-1.52] vs. 1.15 [IQR: 0.95-1.42] mg/dL), eGFR (61.1 [IQR: 50.5-80.4] vs. 60.3 [IQR: 51.3-79.2] mL/min/1.73 m^2), urine fractional excretion of phosphate (17.6 [IQR: 13.2-23.4] vs. 16.4 [IQR: 12.5-20.8]), urine β2 microglobulin-to-creatinine ratio (3.1 [IQR: 1.3-11.1] vs. 4.0 [IQR: 1.3-27.1]), and urine albumin-to-creatinine ratio (21.6 [IQR: 11.2-205.0] vs. 22.6 [IQR: 7.2-102.8]). The changes in bone mineral density were not significant (Trabecular bone score: 1.37 [IQR: 1.28-1.44] vs. 1.36 [IQR: 1.30-1.43]). Evaluated by Morisky 8-item questionnaire at week 24, more patients achieved the full scores to HBV antivirals (100% vs. 77.4%; $p = 0.014$). **Conclusion:** TAF switching therapy is effective and safe to TKRs, and medication adherence can be significantly improved.



Disclosures: Teng-Yu Lee – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; AbbVie: Speaking and Teaching, No, Yes; BMS: Speaking and Teaching, No, Yes; Roche: Consultant, No, Yes; MSD: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;

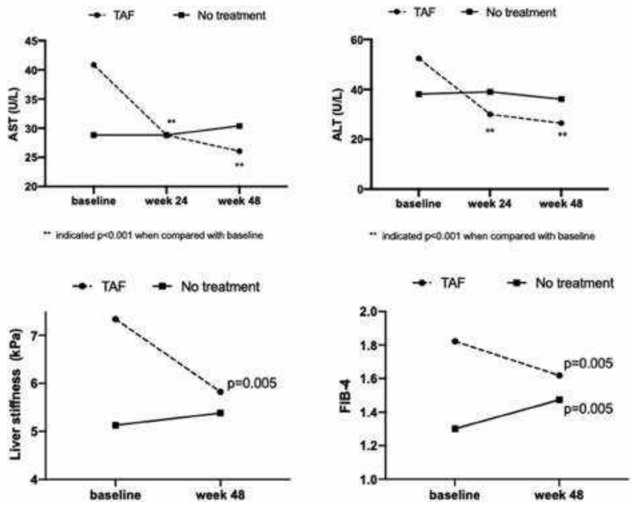
The following people have nothing to disclose: Hsin-Ju Tsai, Cheng-Hsu Chen, Sheng-Shun Yang, Ming-Ju Wu, Tung-Min Yu, Chung-Hsin Chang, Szu-Chia Liao, Mu-Chi Chung, Hsien-Fu Chiu

1445-C | THE CLINICAL EFFECTIVENESS AND SAFETY OF TENOFOVIR ALAFENAMIDE FOR HBV-INFECTED PATIENTS WITH SIGNIFICANT VIREMIA AND MILDLY ELEVATED ALANINE AMINOTRANSFERASE

Pin-Nan Cheng, National Cheng Kung University Hospital, Ming-Lung Yu, Kaohsiung Chang Gung Memorial Hospital, Yao-Chun Hsu, I-Shou University and Chun-Jen Liu, National Taiwan University Hospital

Background: Treatment for chronic hepatitis B virus (HBV) infected patients with significant viremia and mildly elevated alanine aminotransferase (ALT) is controversial. In this study, we aimed to investigate the efficacy and renal safety of tenofovir alafenamide (TAF) and also to evaluate the nature course of untreated patients. **Methods:** Patients with chronic HBV infection with HBV DNA > 2000 IU/mL of HBeAg negative or HBV DNA > 20000 IU/mL of HBeAg positive, naive to any antiviral treatment, and an ALT level between 1-2 folds of ULN within one year before entering study were enrolled in this phase IV study (NCT04674423). Liver biopsy was suggested and liver histology was assessed by histology activity index (HAI) of Knodell necroinflammation scoring system and fibrosis stage of Metavir scoring system. TAF treatment was commenced for those patients exhibited significant liver injury, which was defined as HAI > =4 or Metavir fibrosis stage 2 or 3. For patient with HAI < 4 or Metavir fibrosis stage < 2 or not agree to receive liver biopsy, periodic follow-up including biochemical, hematology, and virological tests were conducted. Liver stiffness measurement (LSM) by FibroScan at enrollment and at week 48 was performed for each patient. **Results:** In total, 62 patients with mean age of 55.5 years and 31 females were enrolled. Of these patients, 22 received TAF treatment and 40 patients received periodic follow-up. Baseline characteristics of the two groups were comparable except significantly higher values of AST, ALT, LSM, and FIB-4 score in TAF treated patients. Following a 48-week TAF treatment, 21 patients (21/22, 95.5%) achieved undetectable HBV DNA and 16 patients (16/22, 72.2%) had normal ALT. Comparing with baseline values, significant reduction of AST, ALT, LSM, and FIB-4 score were observed. In periodic follow-up group, AST, ALT, and LSM remained stationary while FIB-4 was significantly increased at week 48 (Fig.1). Impact of TAF on renal parameters were also examined and revealed that urine phosphate, urine protein, serum creatinine and phosphate, and eGFR (MDRD equation) at baseline and at week-48 were similar between two groups of patients. In TAF treatment group, no significant changes of these parameters were present before and after 48-week treatment. **Conclusion:** A 48-week TAF treatment could effectively suppress HBV replication, normalize ALT, improve liver stiffness and FIB-4 score, and maintain renal parameters in patients with significant HBV viremia and mildly elevated ALT.

Disclosures: Pin-Nan Cheng – Gilead Sciences: Grant/ Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

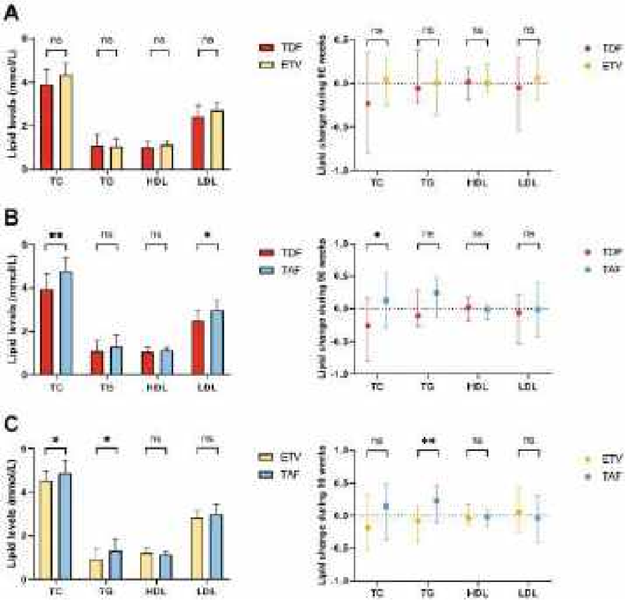


The following people have nothing to disclose: Ming-Lung Yu, Yao-Chun Hsu, Chun-Jen Liu

1446-C | THE EFFECTS OF NUCLEOS(T)IDE ANALOGUES ON LIPID PROFILES IN TREATMENT-NAÏVE CHRONIC HEPATITIS B PATIENTS

Mengqi Li[1,2], Lin Zhu[1,2], You Deng[1,2], Xiaoping Jiang[1,2], Shuqian Zhang[1,2], Ligai Liu[1,2], Hong Zhao[1,2], Qi Wang[1,2] and Wen Xie[1,2], (1)Center of Liver Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, China, (2)National Center for Infectious Diseases, Beijing, China

Background: International guidelines have approved entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF) as first-line oral antiviral nucleos(t)ide analogues (NA) for the treatment of chronic hepatitis B (CHB). However, there is still controversy surrounding the effects of these medications on lipid metabolism. This study aimed to clarify the impact of ETV, TDF, and TAF on lipid metabolism in patients with CHB. **Methods:** This retrospective cohort study included 156 patients with CHB who initiated treatment with ETV, TDF, or TAF after a minimum of 96 weeks between July 2020 and March 2023 at Beijing Ditan Hospital, Capital Medical University. To minimize selection bias, the effects of these treatments on the lipid profiles of the CHB patients were evaluated after propensity score matching (PSM). One-to-one pair matching was performed by nearest-neighbor matching without replacement. Propensity scores were estimated based on baseline characteristics, including age, sex, and lipid profiles. PSM was performed using a caliper width set at 0.2 times the standard deviation of the logit of the propensity score. **Results:** After PSM, the study cohorts were divided into three separate groups for analysis: 37:37 (TDF: ETV), 33:33 (TDF: TAF), and 48:48 (ETV: TAF). After 96 weeks of follow-up, the TAF group demonstrated significantly higher levels of total cholesterol (TC) and low-density lipoprotein (LDL) at 96 weeks compared to the TDF group (TC 4.76 [4.13, 5.39] vs. 3.93 [3.47, 4.63], $p = 0.004$; LDL 2.96 [2.44, 3.43] vs. 2.50 [1.92, 2.99], $p = 0.028$). Additionally, the TAF group exhibited significantly higher levels of TC and triglycerides (TG) at 96 weeks compared to the ETV group (TC: 4.89 [4.52, 5.45] vs. 4.54 [3.95, 4.97], $p = 0.016$; TG: 1.31 [0.92, 1.85] vs. 0.94 [0.75, 1.38], $p = 0.011$). However, no significant differences in lipid profiles were observed between the ETV and TDF groups after 96 weeks of follow-up. Furthermore, among the 156 patients, none of them exhibited e Grade 3 lipid abnormalities at 96 weeks. Additionally, there were only a few cases of Grade 2 lipid abnormalities, with one patient in the ETV group, one patient in the TDF group, and three patients in the TAF group. **Conclusion:** After 96 weeks of treatment, TAF may lead to increased lipid levels compared to ETV and TDF. The impact of such lipid metabolism abnormalities on the clinical outcomes of patients requires further exploration.

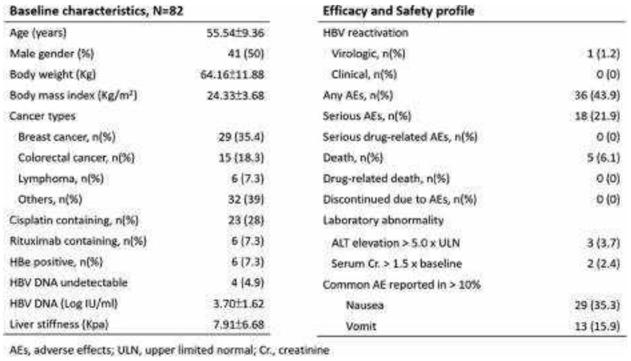


Disclosures: The following people have nothing to disclose: Mengqi Li, Lin Zhu, You Deng, Xiaoping Jiang, Shuqian Zhang, Ligai Liu, Hong Zhao, Qi Wang, Wen Xie

f 1447-C | THE EFFICACY AND SAFETY OF PROPHYLACTIC TENOFOVIR ALAFENAMIDE TO PREVENT HBsAg-POSITIVE CANCER PATIENTS UNDERGOING CHEMOTHERAPY FROM HBV REACTIVATION- AN INTERIM REPORT OF A PROSPECTIVE TRIAL

Po-Yueh Chen[1], Hung-Da Tung[2], Ching-Chu Lo[3], Jow-Jyh Huang[3], Kuo-Chih Tseng[4], Chih Wei Tseng[4], Yu-Jen Fang[5], Jyh-Jou Chen[2] and Chi-Yi Chen[1], (1) Ditmanson Medical Foundation Chiayi Christian Hospital, (2)Department of Internal Medicine, Chi Mei Medical Center, Liouying, Tainan, Taiwan, (3)St. Martin De Porres Hospital - Daya, Chiayi, Taiwan, (4) Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, (5) National Taiwan University Hospital, Yun-Lin Branch

Background: Hepatitis B reactivation had been noted in HBsAg-positive patients undergoing chemotherapy and could result in hepatic decompensation or even mortality. Prophylactic use of nucleos(t)ide analogues (NUCs) had been proved to lower the incidence of HBV reactivation in patients receiving highly risky immunosuppressants. We aim to prospectively evaluate the efficacy and safety of prophylactic tenofovir alafenamide (TAF) in HBsAg-positive cancer patients undergoing chemotherapy. **Methods:** This prospective trial was conducted in middle-south part of Taiwan and we aimed to enroll 150 patients. Individual's aged 20 years or more with positive HBsAg would be enrolled when scheduled systemic chemotherapy was confirmed. All participants would receive 25mg TAF daily for 48 weeks and the first dose would be given less than 7 days prior to start of chemotherapy. The HBV DNA level would be checked at baseline, week 4, 12, 24, 36, and 48 after TAF use. The primary endpoint is the rate of HBV reactivation during prophylactic use of TAF. HBV reactivation is defined as either HBV DNA increase 2 logs compared to the baseline level or 3 log of HBV DNA in patient with previously undetectable level. **Results:** One hundred and seven patients were screened from Jun 2021 to Apr 2023 and 82 patients were enrolled. The mean age of all patients was 55.5 years old and 41 (50%) patients were male. The baseline mean HBV DNA level was 3.7 (log IU/ml) and the mean value of liver stiffness was 7.49 kPa. Among the 82 patients, the most common cancer type was breast cancer (35.4%, 29/82). Cisplatin-containing regimens were prescribed in 23 patients (28.0%, 23/82) and 6 patients (7.3%, 6/82) ever received rituximab. Of 82 patients with a mean follow-up of 7.8 months, one patient (1.2%, 1/82) had experience of virologic HBV reactivation due to poor drug adherence. Among 30 patients with complete 48-weeks of TAF prophylaxis, 26 patients (86.7%, 26/30) were with undetectable HBV DNA and decreased liver stiffness from baseline to 48th week was also found (7.49 kPa to 6.89 kPa). Acute kidney injury (serum creatinine > 1.5 x baseline) was noted in 2 patients (2.4%, 2/82) and all of them received cisplatin-based regimens. The eGFR level and serum phosphate were stationary from baseline to 48th week of TAF treatment. The safety profiled show that 36 patients (43.9%, 36/82) had adverse effects. Five patients were expired due to progression of underlying malignancies. Serious adverse effects were found in 18 patients (21.9%, 18/82), however, none was resulted from TAF. No adverse effect induced drug discontinuity or death was found. The most common adverse effects were nausea (35.3%, 29/82) and vomit (15.9%, 13/82). **Conclusion:** Tenofovir alafenamide (TAF) is an effective and tolerable antiviral agent to prevent HBV reactivation in cancer patients with positive HBsAg undergoing chemotherapy.



Baseline characteristics, N=82	
Age (years)	55.54±9.36
Male gender (%)	41 (50)
Body weight (Kg)	64.16±11.88
Body mass index (Kg/m²)	24.33±3.68
Cancer types	
Breast cancer, n(%)	29 (35.4)
Colorectal cancer, n(%)	15 (18.3)
Lymphoma, n(%)	6 (7.3)
Others, n(%)	32 (39)
Cisplatin containing, n(%)	23 (28)
Rituximab containing, n(%)	6 (7.3)
HBe positive, n(%)	6 (7.3)
HBV DNA undetectable	4 (4.9)
HBV DNA (Log IU/ml)	3.70±1.62
Liver stiffness (Kpa)	7.91±6.68

Efficacy and Safety profile	
HBV reactivation	
Virologic, n(%)	1 (1.2)
Clinical, n(%)	0 (0)
Any AEs, n(%)	36 (43.9)
Serious AEs, n(%)	18 (21.9)
Serious drug-related AEs, n(%)	0 (0)
Death, n(%)	5 (6.1)
Drug-related death, n(%)	0 (0)
Discontinued due to AEs, n(%)	0 (0)
Laboratory abnormality	
ALT elevation > 5.0 x ULN	3 (3.7)
Serum Cr. > 1.5 x baseline	2 (2.4)
Common AE reported in > 10%	
Nausea	29 (35.3)
Vomit	13 (15.9)

AEs, adverse effects; ULN, upper limited normal; Cr., creatinine

Disclosures: The following people have nothing to disclose: Po-Yueh Chen, Hung-Da Tung, Ching-Chu Lo, Jow-Jyh Huang, Kuo-Chih Tseng, Chih Wei Tseng, Yu-Jen Fang, Jyh-Jou Chen, Chi-Yi Chen

f 1448-C | THE EFFICACY OF ANTIVIRAL THERAPY AT PREVENTING CLINICAL OUTCOMES IN HBV-INFECTED PEOPLE AT DIFFERENT BASELINE VIRAL LOAD AND ALT LEVELS: A GLOBAL SYSTEMATIC REVIEW & META-ANALYSIS★

Yu Ri Im[1], Si Emma Chen[2], Rukmini Jagdish[3], Daniela Yucuma[2], Arthur Rakover[2], Zakary Ismail Warsop[4], Roger Chou[5], Philippa Easterbrook[6] and Yusuke Shimakawa[2], (1)University of Oxford, (2)Institut Pasteur, (3)St George's Hospital, London, United Kingdom, (4)Imperial College London, (5)Oregon Health & Science University, (6)World Health Organization

Background: In 2015, the WHO issued its first clinical guidelines for management of chronic HBV infection (CHB), recommending antiviral therapy in non-cirrhotic people with a baseline viral load (VL) of **e** 20,000 IU/mL and abnormal alanine transaminase (ALT) levels. It is not known whether antiviral therapy is also efficacious in groups with lower VL. To inform the development of updated WHO guidelines and expanded treatment criteria, we conducted a systematic review and meta-analysis and provided summary estimates of the efficacy of antiviral therapy in groups stratified by baseline VL (< 2000, 2000-20,000, 20,000-200,000, **e** 200,000 IU/mL) and ALT levels. **Methods:** We searched PubMed, Embase, Web of Science, and the Cochrane Library for randomized controlled trials (RCTs) and non-randomized studies of anti-HBV therapy versus placebo or no treatment. Treatment efficacy needed to be reported in groups stratified by baseline VL for inclusion. Random-effects meta-analysis was performed to pool risk ratios from RCTs and adjusted hazard ratios (HR) from observational studies. Risk of bias was assessed with the Cochrane ROB2 and Newcastle-Ottawa scales and the quality of the evidence with GRADE. **Results:** Of 13,124 records identified, 30 RCTs and 12 observational studies met inclusion criteria. 22 (52%) studies were from Asia, 0 (0%) from Africa, 2 (5%) from North America, and 7 (17%) from Europe. 21 (50%) studies were in adults > 18 years and 13 (31%) in those < 18 years. Most studies (86%) only reported outcomes for groups with VL > 20,000 IU/mL. Only one RCT and five observational studies (14%) reported results for groups with VL < 20,000 IU/mL (n = 5 for < 2000, n = 1 for 2000-20,000). Overall, the pooled HR of HCC for treated vs. untreated groups was 0.72 (95%CI 0.43-1.20; only one study), 0.45 (0.14-1.46; only one study), 0.17 (0.06-0.50; only one study), 0.48 (0.26-0.91; 3 studies, I2 = 31.4%), 0.44 (0.19-1.03; only one study), and 0.40 (0.17-0.9; 2 studies) for the groups with baseline viral load < 2,000, 2,000-20,000, 20,000-200,000, 200,000-2M, 2M-20M, and 20M-200M IU/mL, respectively. These and other outcomes are summarised in table 1. The quality of evidence supporting treatment efficacy was very low or low for the lower VL strata (< 2000, 2000-20,000) and ranged from very low to high for the higher VL strata. **Conclusion:** Only one RCT evaluated the efficacy of antiviral therapy in patients with VL < 2000 IU/mL and only five non-randomized studies in patients with VL 2000-20,000 IU/mL. Within these limitations, we observed a tendency for an interaction between higher VL and higher treatment efficacy for a range of clinical, histological, virological, and biochemical outcomes. Our findings highlight the urgent need for RCTs of antiviral therapy to establish treatment

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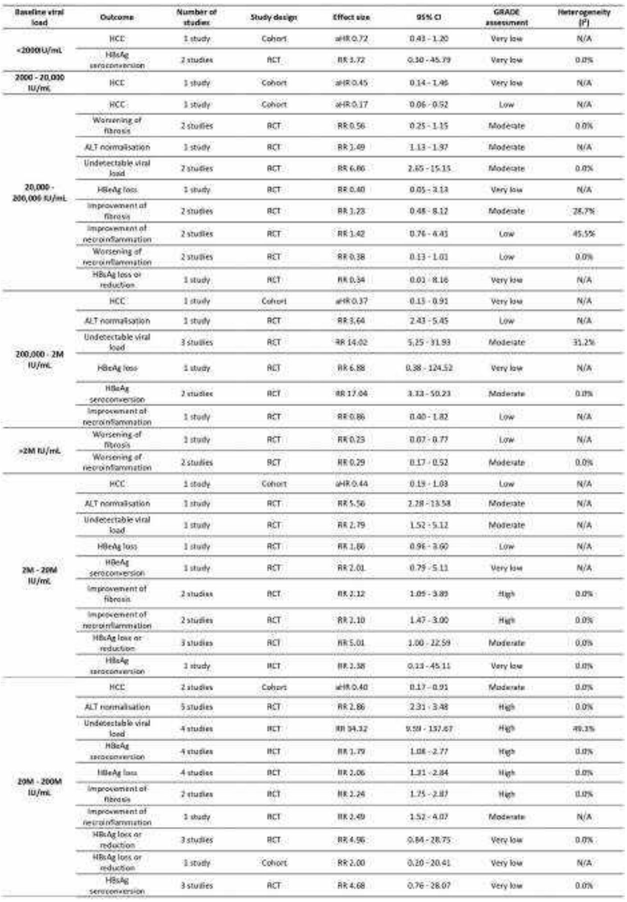
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

impact in patients with low-level viraemia and early fibrosis stages, especially in Sub-Saharan Africa.



Baseline viral load	Outcome	Number of studies	Study design	Effect size	95% CI	GRADE assessment	Heterogeneity (I^2)
<2000IU/mL	HCC	1 study	Cohort	aHR 0.72	0.43 - 1.20	Very low	N/A
	HBsAg seroconversion	2 studies	RCT	RR 3.72	0.30 - 45.79	Very low	0.0%
2000 - 20,000 IU/mL	HCC	1 study	Cohort	aHR 0.45	0.14 - 1.46	Very low	N/A
20,000 - 200,000 IU/mL	HCC	1 study	Cohort	aHR 0.17	0.06 - 0.52	Low	N/A
	Worsening of fibrosis	2 studies	RCT	RR 0.56	0.25 - 1.15	Moderate	0.0%
	ALT normalisation	1 study	RCT	RR 1.49	1.13 - 1.97	Moderate	N/A
	Undetectable viral load	2 studies	RCT	RR 6.86	2.65 - 15.15	Moderate	0.0%
	HBeAg loss	1 study	RCT	RR 0.40	0.05 - 3.13	Very low	N/A
	Improvement of fibrosis	2 studies	RCT	RR 1.23	0.48 - 8.12	Moderate	28.7%
	Improvement of necroinflammation	2 studies	RCT	RR 1.42	0.76 - 6.41	Low	45.5%
	Worsening of necroinflammation	2 studies	RCT	RR 0.38	0.13 - 1.01	Low	0.0%
	HBsAg loss or reduction	1 study	RCT	RR 0.34	0.01 - 8.16	Very low	N/A
200,000 - 2M IU/mL	HCC	1 study	Cohort	aHR 0.37	0.15 - 0.91	Very low	N/A
	ALT normalisation	1 study	RCT	RR 3.64	2.43 - 5.45	Low	N/A
	Undetectable viral load	3 studies	RCT	RR 14.02	5.25 - 31.93	Moderate	31.2%
	HBeAg loss	1 study	RCT	RR 6.88	0.38 - 124.52	Very low	N/A
	HBeAg seroconversion	2 studies	RCT	RR 17.04	3.33 - 50.23	Moderate	0.0%
	Improvement of necroinflammation	1 study	RCT	RR 0.86	0.40 - 1.82	Low	N/A
>2M IU/mL	Worsening of fibrosis	1 study	RCT	RR 0.23	0.07 - 0.77	Low	N/A
	Worsening of necroinflammation	2 studies	RCT	RR 0.29	0.17 - 0.52	Moderate	0.0%
2M - 20M IU/mL	HCC	1 study	Cohort	aHR 0.44	0.19 - 1.03	Low	N/A
	ALT normalisation	1 study	RCT	RR 5.56	2.28 - 13.58	Moderate	N/A
	Undetectable viral load	1 study	RCT	RR 2.79	1.52 - 5.12	Moderate	N/A
	HBeAg loss	1 study	RCT	RR 1.86	0.96 - 3.60	Low	N/A
	HBeAg seroconversion	1 study	RCT	RR 2.01	0.79 - 5.11	Very low	N/A
	Improvement of fibrosis	2 studies	RCT	RR 2.12	1.05 - 3.89	High	0.0%
	Improvement of necroinflammation	2 studies	RCT	RR 2.10	1.47 - 3.00	High	0.0%
	HBsAg loss or reduction	3 studies	RCT	RR 5.01	1.00 - 22.59	Moderate	0.0%
	HBsAg seroconversion	1 study	RCT	RR 2.38	0.13 - 45.11	Very low	0.0%
20M - 200M IU/mL	HCC	2 studies	Cohort	aHR 0.40	0.17 - 0.91	Moderate	0.0%
	ALT normalisation	5 studies	RCT	RR 2.86	2.31 - 3.48	High	0.0%
	Undetectable viral load	4 studies	RCT	RR 34.32	9.59 - 137.67	High	49.3%
	HBeAg seroconversion	4 studies	RCT	RR 1.79	1.08 - 2.77	High	0.0%
	HBeAg loss	4 studies	RCT	RR 2.06	1.31 - 2.84	High	0.0%
	Improvement of fibrosis	2 studies	RCT	RR 2.24	1.75 - 2.87	High	0.0%
	Improvement of necroinflammation	1 study	RCT	RR 2.49	1.52 - 4.07	Moderate	N/A
	HBsAg loss or reduction	3 studies	RCT	RR 4.96	0.84 - 28.75	Very low	0.0%
	HBsAg loss or reduction	1 study	Cohort	RR 2.00	0.20 - 20.41	Very low	N/A
	HBsAg seroconversion	3 studies	RCT	RR 4.68	0.76 - 28.07	Very low	0.0%

Disclosures: Yu Ri Im – ST & T Consulting Ltd: Consultant, No, Yes; SYSMED LTD: Consultant, No, No; The following people have nothing to disclose: Zakary Ismail Warsop, Philippa Easterbrook

Disclosure information not available at the time of publication: Si Emma Chen, Rukmini Jagdish, Daniela Yucuma, Arthur Rakover, Roger Chou, Yusuke Shimakawa

1449-C | THE EFFICACY OF ANTIVIRAL THERAPY FOR HBV-INFECTED CHILDREN: A MULTICENTER REAL-WORLD STUDY (SPROUT PROJECT) - AN INTERIM ANALYSIS

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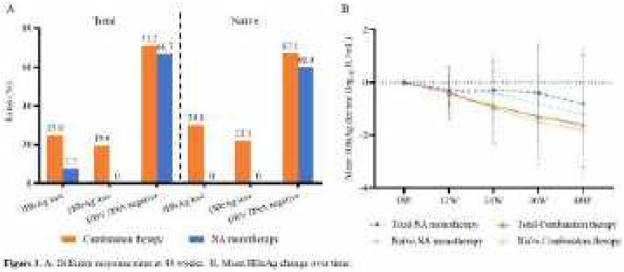
Background: In China, approximately 30% to 50% of HBV transmission occurs through the mother-to-infant, and nearly 2 million children are HBsAg-positive. Children infected with HBV, if not treated timely, not only affect their healthy growth, but also have a significant risk of disease progression, making them a huge additional population for adult chronic hepatitis B. We aimed to investigate the efficacy and safety of different antiviral strategies for HBV-infected children. **Methods:** This is a multicenter real-world study in China, three types of HBV-infected children were enrolled, including treatment-naïve, NA-treated and normal ALT level population. All patients were 3-18 years old and HBsAg positive, they received NA monotherapy or in combination with peginterferon α-2b for 96 weeks according to the willing of their own or guardian (NCT05792761). Data on those who have completed at least 48 weeks of treatment before April 13, 2023 were analyzed. **Results:** A total of 197 children who met the inclusion criteria and completed 48 weeks of treatment were analyzed (NA monotherapy group, n = 13; combination therapy group, n = 184). The average age was 7.7 years, and 56.9% were male, 89.8% were HBeAg positive and 90.3% were HBV DNA positive. The mean baseline HBsAg, HBV DNA and HBeAg were 3.59, 6.14 $\log_{10}$ IU/mL and 2.48 $\log_{10}$ COI, respectively. 50.8% (100/197) of patients were treatment-naïve chronic hepatitis B. In the total population, the HBsAg loss rate at 48 weeks was 25.0% in combination therapy group, while 7.7% in NA monotherapy group. In treatment-naïve patients, the HBsAg loss rates were 30.1% and 0% in combination therapy group and NA monotherapy group, respectively (Figure 1A). During the treatment course, the mean HBsAg gradually decline in both groups, but was significantly greater in combination therapy group, reaching 1.6 and 1.8 $\log_{10}$ IU/mL at 48 weeks in total and treatment-naïve population, respectively (Figure 1B). For the total population, 19.6% in combination therapy group and 0% in NA monotherapy group achieved HBeAg loss at 48 weeks, while 71.2% and 66.7% achieved HBV DNA negative. For treatment-naïve population, the HBeAg loss rates were 22.1% in combination therapy group and 0% in NA monotherapy group, while the HBV DNA negative rates were 67.1% and 60.0% (Figure 1A). Both therapies were well-tolerated. **Conclusion:** HBV-infected children can achieve significant higher HBeAg loss and HBsAg loss chance in peginterferon α-2b combination group, although HBV DNA negative can be well obtained in both groups. Therefore, peginterferon α-based strategies can help pediatric patients better pursue functional cure.



Disclosures: The following people have nothing to disclose: Hongfei Zhang, Hong Zhang, Wenxian Ouyang, Yilan Zeng, Shuangjie Li, Jia Shang, Qing He, Fang Wang, Hongxia Zhou, Lijuan Ouyang

1450-C | USEFULNESS OF FIB-4 INDEX AND ALT AT 1 YEAR OF NUCLEOS(T)IDE ANALOG TREATMENT FOR PREDICTION OF HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS B PATIENTS

Jun Inoue[1], Takehiro Akahane[2], Tomoo Kobayashi[3], Osamu Kimura[4], Kosuke Sato[5], Masashi Ninomiya[1], Tomoaki Iwata[1], Satoshi Takai[6], Norihiro Kisara[7], Toshihiro Sato[8], Futoshi Nagasaki[9], Masahito Miura[10], Takuya Nakamura[11], Teruyuki Umetsu[12], Akitoshi Sano[13], Mio Tsuruoka[1], Masazumi Onuki[1], Satoko Sawahashi[14], Hirofumi Niitsuma[1], Atsushi Masamune[1] and THERME Study Group, (1)Tohoku University Graduate School of Medicine, (2)Japanese Red Cross Ishinomaki Hospital, (3)Tohoku Rosai Hospital, (4) South Miyagi Medical Center, (5)Tohoku University Graduate School of Medicine, Sendai, Japan, (6)Iwaki City Medical Center, (7)Japan Community Health Care Organization Sendai South Hospital, (8)LC Clinic, (9) Sendai City Hospital, (10)Omagari Kousei Medical Center, (11)Yamagata City Hospital Saiseikan, (12) Kesennuma City Hospital, (13)Tohoku University Graduate School of Medicine, Sendai-shi, Japan, (14) Tohoku University Graduate School of Medicine, Sendai city, Miyagi, Japan

Background: Patients with chronic hepatitis B virus (HBV) infectionare at risk for liver cirrhosis and hepatocellular carcinoma (HCC). The incidence of HCC has been reported to be reduced with nucleos(t)ide analogs (NAs), but patients on such antiviral treatments are still at risk for HCC.The aim of this study was to evaluate the dynamics of a non-invasive marker of liver fibrosis, the FIB-4 index, for predicting the development of HCC. **Methods:** Among a total of 882 chronically HBV-infected patients who were treated with NAs (lamivudine, entecavir, tenofovir disoproxil fumarate or tenofovir alafenamide fumarate as a 1st line therapy), 472 patients without a history of HCC whose FIB-4 was obtained at baseline and 1 year of treatment were evaluated for the incidence of HCC. **Results:** The median age was 54 years and 303 (64.2%) were male. 147 patients (31.1%) were HBeAg positive and 350 patients (74.2%) were treated with entecavir as the 1st line NA. Of 417 patients whose HBV genotypes were determined, 36.9% and 61.2% were genotype B and C, respectively. The median FIB-4 index was 2.00 and the median observation period after starting NAs was 72 months. The median FIB-4 index at year 1 was 1.57 and had decreased significantly from the baseline ($p < 0.001$), but the reduction was small at 2 years or later. When a receiver operating characteristic (ROC) analysis of FIB-4 was performed to predict HCC within 5 years, the area under the curve of FIB-4 at 1 year was higher than that at baseline (0.676 vs. 0.599). The HCC incidence was significantly higher in patients with FIB-4 **e** 1.58 at 1 year than in those with FIB-4 < 1.58 (14.8% vs. 3.6% at 10 years, $p < 0.001$). In addition, alanine aminotransferase (ALT) at year 1 was included in the analysis. An ROC curve was plotted for the HCC incidence at year 5 and, based on the Youden index, the ALT cut-off was set at 31. When a FAL-1 score was evaluated as an applicable number of FIB-4 **e** 1.58 and ALT **e** 31 as 0, 1 and 2, the risk of HCC was significantly higher in patients with score 2 than in those with score 1 or score 0 (24.1% vs. 9.8% vs. 0.7% at 10 years, $p < 0.001$). **Conclusion:** This study showed that chronic hepatitis B patients with FIB-4 index **e** 1.58 and ALT **e** 31 at year 1 of NA had a high risk of HCC, and conversely, those with low FIB-4 index and low ALT at year 1 had a minimal risk. The FAL-1 score can stratify the HCC risk and may be useful for individualized HCC surveillance planning.

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1451-C | A HUMANIZED MONOCLONAL ANTIBODY 4G2 EXHIBITS ANTI-VIRAL ACTIVITY IN A MOUSE MODEL OF PERSISTENT HEPATITIS B VIRUS (HBV) INFECTION

Aditi Deshpande[1], Renae Walsh[2], Hans Netter[2], Chee Leng Lee[2], Rachel Hammond[2], Marcela Toro[2], Stephen

Locarnini[2] and Aileen Rubio[1], (1)Clearb Therapeutics, (2)Victorian Infectious Diseases Reference Laboratory

Background: We have previously identified a murine monoclonal antibody (mAb) 4G2 that binds specifically to a key loop 1 epitope within the Hepatitis B surface antigen (HBsAg) and demonstrates anti-viral activity in the hydrodynamic tail vein injection (HDI) mouse model of persistent HBV infection (EASL poster # 2543, 2023). This antibody was humanized onto human IgG1 backbone to support the clinical development of a therapeutic antibody approach in Chronic Hepatitis B (CHB) patients. **Methods:** Humanized versions of the 4G2 mAb were developed by grafting the CDRs from the murine 4G2 into human IgG1 acceptor to obtain three light and heavy chains. These were paired with each other to create nine humanized candidates which were recombinantly expressed and purified from CHO cells. Binding to CLB-405 (HBsAg with multiple loop1 epitopes) using SPR and ELISA methods identified the strongest binding candidate 4G2 (3-2) which was tested for anti-viral activity in the HDI model [Chou H-H et al. 2015. PNAS 112(7) pp2175]. These mice were administered a single 400 µg dose of 4G2 (3-2) by intravenous injection and monitored for serological markers of HBsAg and HBV DNA over time, as well as liver HBsAg and Hepatitis B core antigen (HBcAg) immunohistochemistry at the end of study. **Results:** The humanized candidates successfully bound CLB-405 thereby retaining the binding affinity of the murine 4G2 mAb. A single injection of 4G2 (3-2) at 400 µg resulted in an average reduction of 1.67 log IU/ml HBsAg at peak response (4 d post-dose antibody administration). The number of animals with undetectable HBsAg was 1/8 in placebo and 8/8 in 4G2 (3-2) groups. A rebound in HBsAg level was observed one week post dose in a subset of animals. Seroclearance of HBsAg resulted in clearance of HBsAg and HBcAg positive cells in the liver. This data was comparable with the effect observed from treatment with the parent murine 4G2 mAb (EASL poster # 2543, 2023), for which multiple dosing data showed enhanced efficacy in all treated mice. **Conclusion:** Serotherapy using humanized 4G2 (3-2) mAb was highly efficacious in the HDI HBV persistent murine model with rapid serum HBsAg decline and clearance in a subset of animals, followed by clearance of infected hepatocytes. Multiple injections of 4G2 (3-2) were not tested in this model due to likelihood of formation of anti-drug antibodies associated with species mismatch. These findings further support the clinical development of 4G2 (3-2) for the treatment of CHB.

Disclosures: The following people have nothing to disclose: Aditi Deshpande

Disclosure information not available at the time of publication: Renae Walsh, Hans Netter, Chee Leng Lee, Rachel Hammond, Marcela Toro, Stephen Locarnini, Aileen Rubio

1452-C | A RANDOMISED, DOUBLE-BLIND, PHASE 3, NON-INFERIORITY TRIAL OF PRADEFOVIR MESYLATE VERSUS TENOFOVIR DISOPROXIL FUMARATE FOR PAITENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION

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Background: Pradefovir is a liver-targeted prodrug of adefovir, a nucleoside/nucleotide analogue with antiviral activity against hepatitis B virus (HBV) DNA polymerase. From the Phase 2 trial, we had the results that Pradefovir and TDF exhibited comparable reductions in HBV DNA levels. All treatments were safe and well tolerated. This phase 3 study aimed to further confirm the efficacy and safety of pradefovir versus tenofovir disoproxil fumarate (TDF) of long-term drug use. **Methods:** This ongoing randomized, double-blind, non-inferiority, phase 3 study was conducted at 58 sites in China. Patients with chronic HBV infection were randomly assigned (2:1) to receive either 45 mg daily pradefoivr mesylate(PDV) or 300 mg daily TDF with matching placebo. Patients were stratified according to hepatitis B e-antigen (HBeAg) status and previous treatment experience. The patients with compensated cirrhosis were lower than 20% in over roll. The primary efficacy endpoint was defined as the proportion of patients who's HBV DNA level were less than 29 IU/mL at week 48. The pre-specified non-inferiority margin was 12%. All participants who received one dose of the study drug were included in the primary intention to treat efficacy and safety analyses with pre-specified renal and bone endpoints at the 48 weeks. **Results:** 1170 patients were screened ; 912 eligible patients were randomized and 908 patients received study drug. The baseline characteristics were well balanced between groups. In the HBeAg positive group, 444 patients received PDV and 222 patients received TDF; at week 48, 264 (59.5%) patients who received PDV and 136 (61.3%) patients who received TDF reached HBV DNA less than 29IU/ml; the virologic success rate was similar between the two groups with difference -1.8% [-9.7% to 6.1%]. In the HBeAg negative group, 162 patients received PDV and 80 patients received TDF. At week 48, 150 (92.6%) patients who received PDV and 72 (90.0%) who received TDF reached HBV DNA less than 29IU/ml; the virologic success rates were similar between the two groups with difference 2.6%[-5.1% to 10.3%]. Through 48 weeks, there were significantly less adverse events assessed related to the study drug by the investigator were reported (with differences of 62.9% *vs* 67.9% ($p = 0.0415$) of PDV *vs* TDF); the rates of the most common adverse events reported were similar between the two groups. Patients in PDV group demonstrated a significantly lower trend of decrease in bone mineral density at both hip and spine, and a smaller decrease in sCCR at week 48, especially in the elderly patients (older than 40 y) ; which suggested patients with PDV had a more favorable long-term renal and bone safety profile. **Conclusion:** These findings suggest that the efficacy of Paladofovir 45mg QD is equal to or better than TDF 300mg, and the safety of Paladofovir 45mg QD has significant advantages, which can be used in the treatment of HBeAg-positive or HBeAg-negative adult patients with chronic hepatitis B.

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Lu, Wenting Zeng, Qinming Hu, Dengke Zhang, Weili Jin, Daidi Wang, Xiuhong Wen, Yuan Wang, Nini Liu, Junqi Niu

1453-C | ADENINE BASE EDITING SILENCES HBsAg EXPRESSION AND INHIBITS HEPATITIS B VIRAL REPLICATION IN HBV MOUSE MODELS

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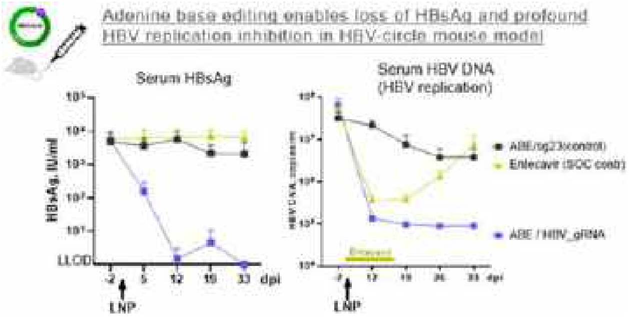
Background: The hepatitis B virus (HBV) covalently closed circular (ccc)DNA serves as a template for viral replication. It is not targeted efficiently by nucleos(t)ides analogues nor by small molecules in development. HBV DNA also integrates into the human genome. Integrated HBV DNA contributes to Hepatitis B surface antigen (HBsAg) expression, which inhibits HBV-specific immune responses. Adenine Base Editors (ABEs) can convert A™T to G™C within DNA in a guide RNA-dependent manner, and thus can directly modify the HBV genomic elements responsible for viral persistence. **Methods:** Guide RNAs (gRNAs) were designed such that, when paired with an ABE, they lead to missense mutations in HBV genes or disrupt regulatory elements in the HBV genome. Transfection of ABE-encoding mRNA and HBV-targeting gRNAs was performed to evaluate their antiviral efficacy *in vitro* in HBV-infected HepG2-NTCP cells and primary human hepatocytes (PHH), as well as in PLC/PRF/5 cells with naturally integrated HBV DNA. *In vivo* antiviral effect was assessed after lipid nanoparticle (LNP)-mediated delivery of the ABE mRNA and HBV targeting gRNAs in two animal models: HBV-circle mouse model and HBV-infected liver-humanized mice. **Results:** Adenine base editing enabled robust HBV cccDNA editing and reduction of the corresponding viral markers in HepG2-NTCP and PHHs. Furthermore, *HBs*-targeting gRNAs robustly inhibited HBsAg expression in PLC/PRF/5 cells. In the HBV-circle mouse model, intravenous injection with base editing reagents formulated in LNPs resulted in a complete loss of HBsAg and profound sustained reduction in the serum HBV DNA. In HBV-infected humanized mice, base editing enabled 1log (90%) sustained reduction in HBsAg and 1.3log (>90%) reduction in the serum HBV DNA. **Conclusion:** Combined, the data indicate that base editing can silence HBsAg expression and abrogate HBV replication *in vitro* and *in vivo*. Figure: Loss of HBsAg and HBV replication inhibition in HBV-circle mouse model. 3-4 log sustained HBsAg reduction in ABE / HBV gRNA treated group > 4 weeks after a single injection with LNP/ABE&gRNA; HBV replication is reduced in entecavir treated mice, and then rebounds when the treatment is discontinued (positive control); sustained reduction in serum HBV DNA in base editing treated groups; no HBV rebound.



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The following people have nothing to disclose: Anuj Kumar
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1454-C | AN EFFECTIVE STRATEGY TO REDUCE HBsAg LEVEL WITHOUT DIRECT INHIBITION OF INTRACELLULAR HBsAg SYNTHESIS IN HBV INFECTED HUMANIZED MICE

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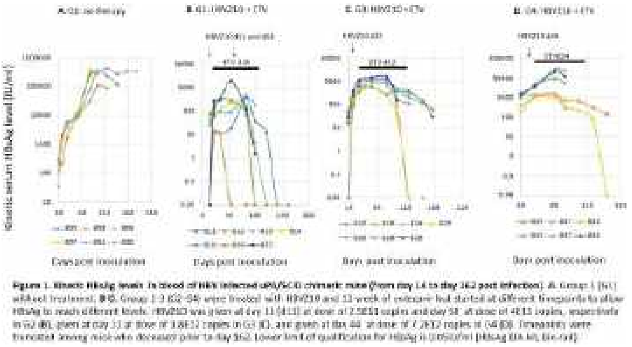
Background: The current strategy to reduce serum HBsAg is to inhibit cellular HBsAg synthesis using siRNA/ASO drugs that show an average < 2log serum HBsAg reduction. cccDNA is the major HBsAg transcription template. We have reported spontaneous cccDNA loss from infected cells in humanized livers of chimeric mice. Thus, cccDNA loss and ongoing HBsAg secretion could lead to clearing HBsAg in the infected cells. We hypothesize that an effective strategy to reduce serum HBsAg to an undetectable level is to block cccDNA replenishment with a sustained high level of anti-HBs antibody. We have developed a new HBV drug candidate HBVZ10 that uses an optimized AAV vector to deliver human anti-HBs antibody genes into muscle cells. HBVZ10 expresses sustained high levels of anti-HBs antibody after a single injection. We evaluated the efficacy in reducing cellular and serum HBsAg levels by blocking de novo infection-mediated cccDNA replenishment. **Methods:** HBV infected chimeric mice were divided into 4 groups, including 1 untreated control and 3 groups treated with HBVZ10 combined with 12-weeks of entecavir administered at different timepoints post infection. Serum HBsAg, HBeAg, HBV DNA, and anti-HBs were analyzed in serial blood samples. Average intrahepatic HBV DNA levels were determined using qPCR and dPCR after random sampling of each liver 20 times. **Results:** High Anti-HBs antibody levels were expressed by HBVZ10 and reached and sustained > 100,000mIU/ml in all treated mice during the experiment period. All HBVZ10 treated mice responded with serum HBsAg reduction. Baseline HBsAg in the 8 of 11 treated mice who survived long enough ranged from 2000 to 10,000IU/ml among 7 mice and was 58IU/ml in the last mouse, and became undetectable in all 8 mice after 3-5log progressive reduction by day 162 pi (Figure 1). Progressive serum HBsAg reduction was closely paralleled with progressive serum HBeAg decline, implying that progressive serum HBsAg reduction reflects progressive HBV clearance in the livers, which was confirmed by a 3-4 log lower intrahepatic HBsAg, rc, and cccDNA levels from mice who achieved undetectable serum HBsAg compared to untreated controls. **Conclusion:** HBsAg can be efficiently cleared from infected cells through secretion, provided the replenishment of depleted cccDNA pool is prevented. Blocking of cccDNA replenishment with HBVZ10 is more effective in reducing both cellular and serum HBsAg levels than the reported direct inhibition of cellular HBsAg synthesis in the same animal model.



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1455-C | ANALYSIS OF HBV GENOTYPE ASSOCIATION TO SEQUENTIAL BEPIROVIRSEN AND PEGYLATED INTERFERON TREATMENT RESPONSE IN PATIENTS WITH CHRONIC HBV INFECTION (PHASE 2b B-TOGETHER STUDY)

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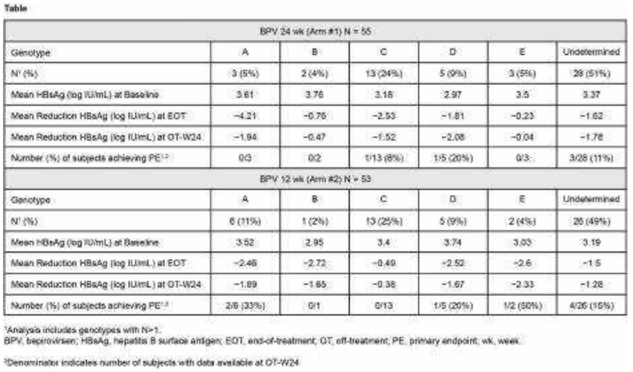
Background: Bepirovirsen (BPV; GSK3228836) is an antisense oligonucleotide that targets a conserved 20 nucleotide sequence within HBV pregenomic RNA and mRNAs. B-Together is a phase 2b trial (NCT04676724) assessing the efficacy and safety of sequential treatment of up to 24 wk BPV followed by up to 24 wk of pegylated interferon (PegIFN) in patients with CHB. We present the HBsAg response for patients by viral genotype. **Methods:** Multicenter, randomized, open-label study in patients with CHB who were receiving concomitant stable nucleos(t)ide analogue (NA) therapy. Patients were randomized (1:1) to receive BPV 300 mg weekly either for 24 wk (Arm 1) or 12 wk (Arm 2). A loading dose of BPV was given on days 4 and 11. For eligible patients, BPV treatment was followed by up to 24 wk of PegIFN. Patients were followed for 24 weeks (OT-WK24) after the planned end of treatment (EOT). B-Together recruited patients in 11 countries encompassing Asia, Europe, North America, and South Africa. Genotype was determined by HBV RNA sequencing and/or investigator report. **Results:** Six different genotypes (GT) were observed: A, B, C, D, E, and H, with GT-C (24%) and GT-D (9%) observed most frequently. All patients maintained concomitant NA therapy throughout the study, resulting in low/undetectable RNA/DNA and a high proportion of undetermined genotypes (51%, 28/55 for Arm 1; 49%, 26/53 for Arm 2). Arm 1: GT-C (24%, 13/55 patients) was most frequently observed, followed by GT-D (9%, 5/55), GT-A (5%, 3/55), GT-E (5%, 3/55), and GT-B (4%, 2/55). Patients with GT-D virus had the lowest mean HBsAg level at baseline (2.97 log IU/mL) and GT-B the highest (3.76 log IU/mL). Arm 2: GT-C (25%, 13/53 patients) was most frequently observed, followed by GT-A (11%, 6/53), GT-D (9%, 5/53), GT-E (4%, 2/53), and GT-B (2%, 1/53). The patient with GT-B virus had the lowest mean HBsAg level at baseline (2.95 log IU/mL) and GT-D the highest (3.74 log IU/mL). Treatment response: Treatment response 24 wk after planned EOT by GT is shown in Table 1. **Conclusion:** BPV treatment followed by PegIFN resulted in substantial HBsAg reduction (> 1log IU/mL) in all genotypes, and the primary endpoint (PE; HBsAg and HBV DNA < LLOQ for 24 wk after planned EOT, in the absence of rescue therapy) was achieved in GT-A, C, D, E. Few genotype differences were observed between Arm 1 and Arm 2, which may be attributed to the small sample size and low genotype data availability.

Funding: GSK (209348; NCT04676724)



Table

BPV 24 wk (Arm #1) N = 55						
Genotype	A	B	C	D	E	Undetermined
N[1] (%)	3 (5%)	2 (4%)	13 (24%)	5 (9%)	3 (5%)	28 (51%)
Mean HBsAg (log IU/mL) at Baseline	3.61	3.76	3.18	2.97	3.5	3.37
Mean Reduction HBsAg (log IU/mL) at EOT	−4.21	−0.76	−2.53	−1.81	−0.23	−1.62
Mean Reduction HBsAg (log IU/mL) at OT-W24	−1.94	−0.47	−1.52	−2.08	−0.04	−1.78
Number (%) of subjects achieving PE[1,2]	0/3	0/2	1/13 (8%)	1/5 (20%)	0/3	3/28 (11%)
BPV 12 wk (Arm #2) N = 53						
Genotype	A	B	C	D	E	Undetermined
N[1] (%)	6 (11%)	1 (2%)	13 (25%)	5 (9%)	2 (4%)	26 (49%)
Mean HBsAg (log IU/mL) at Baseline	3.52	2.95	3.4	3.74	3.03	3.19
Mean Reduction HBsAg (log IU/mL) at EOT	−2.46	−2.72	−0.49	−2.52	−2.6	−1.5
Mean Reduction HBsAg (log IU/mL) at OT-W24	−1.89	−1.65	−0.38	−1.67	−2.33	−1.28
Number (%) of subjects achieving PE[1,2]	2/6 (33%)	0/1	0/13	1/5 (20%)	1/2 (50%)	4/26 (15%)

[1] Analysis includes genotypes with N>1.
BPV, bepirovirsen; HBsAg, hepatitis B surface antigen; EOT, end-of-treatment; OT, off-treatment; PE, primary endpoint; wk, week.

[2] Denominator indicates number of subjects with data available at OT-W24

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Leigh Felton – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Thomas Greene – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Jill Walker – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

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Melanie Paff – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Susan Dixon – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

1456-C | APPARENT VIROLOGICAL CURE OF HBV INFECTION BY THE NOVEL CAPSID/CGAS BIFUNCTIONAL MOLECULE LW231 IN AAV-HBV MICE

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Background: Current cHBV treatment options have a low incidence of functional cure. Combination therapy including direct-acting antivirals and immunomodulators is a promising approach to achieve cHBV cure. Here, we present preclinical studies of a novel bifunctional molecule LW231, which can simultaneously modulate HBV capsid assembly and activate cGAS-STING pathway. **Methods:** The effect of LW231 on HBV capsid assembly and cGAS expression was studied *in vitro*. The activity of LW231 were tested both *in vitro* and *in vivo*. The AAV-HBV mice were randomly divided into six groups: vehicle, LW231 (bid at 50, 100, and 200 mg/kg), ETV (qd at 0.1 mg/Kg) and combination group (100 mg/Kg LW231 with ETV). HBV virological markers in blood and liver tissue were detected. **Results:** *In vitro* study: LW231 enhanced the formation of empty capsids. LW231 also dose-dependent promoted the expression of cGAS in HepG2.2.15 cells, but the effect was absent in HepG2 cells. LW231 demonstrated potent activity across HBV genotypes A-J ($EC_{50} = 8$ - 60 nM, $CC_{50} > 100$ μM). *In vivo* study: After treated with LW231 for 42 days in the AAV-HBV mice, the mean declines in HBV DNA was 0.2, 2.2 and 2.3 logs, in HBsAg was 0.3, 0.8, 0.5 logs, in HBeAg was 0.08, 1.1, 0.7 logs comparison to pretreatment levels in mice dosed with 50, 100 and 200 mg/kg LW231, respectively. LW231 (100 mg/Kg, the optimal dose for HBsAg and HBeAg reduction) single treatment continued to show a decrease in serum HBV DNA (-3.4 logs), HBsAg (-1.2 logs) and HBeAg (-1.9 logs) levels on day 112. LW231/ETV combination treatment synergistically reduced the HBV DNA level (-5.5 logs) but not HBsAg (-1.3 logs) and HBeAg (-1.9 logs) levels on day 112. In comparison, ETV treatment showed no effect on HBsAg and HBeAg levels despite its potent inhibition of HBV DNA. Encouragingly, the serum HBV DNA, HBsAg and HBeAg levels did not rebound after 8-weeks off-treatment in both LW231 treatment groups, while serum HBV DNA levels in the ETV-treated mice rapidly rebounded. Liver tissues analysis showed that LW231 treatment completely cleared of $HBcAg^+$ and $HBsAg^+$ hepatocytes and markedly decrease the level of liver HBV DNA (-2.8, -3.2 logs for single and combination groups respectively) on day 112, and there was no rebound following 8-weeks recovery period. **Conclusion:** These preclinical studies showed the bifunctional properties of LW231 and demonstrated that LW231 treatment achieve apparent virological cure of HBV infection in AAV-HBV mice.

Disclosures: The following people have nothing to disclose: Ning Zhang, Anran Qian, Zhe Wang

1457-C | ASSESSMENT OF REGIONAL IMPACT ON THE PHARMACOKINETICS OF VIR-2218 (BRII-835) IN SUBJECTS WITH CHRONIC HEPATITIS B VIRUS INFECTION

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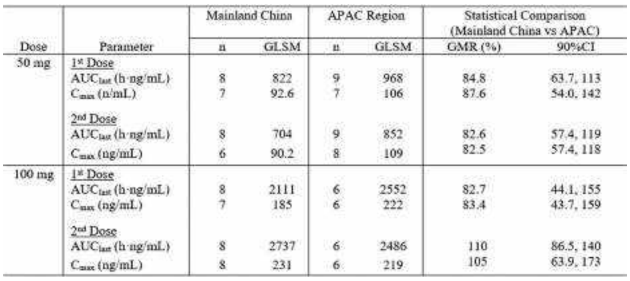
Background: VIR-2218 (also referred as BRII-835) is an investigational, N-acetylgalactosamine (GalNAc)–conjugated RNA interference (RNAi) therapeutic that targets a region of the hepatitis B virus (HBV) genome that is common to all HBV viral RNA transcripts. VIR-2218 is in clinical development for treatment of chronic HBV infection in multiple trials over different regions as a single agent or in combination with other treatment modalities. Here we report the potential effect of region on VIR-2218 pharmacokinetics (PK) via cross-study comparison. **Methods:** VIR-2218-1001 is a Phase 1/2 single and multiple ascending dose study at multiple sites in Asia-Pacific (APAC) region excluding mainland China. Parts B (HBeAg-) and C (HBeAg+) of the study evaluated 2 SC injections of 20 to 200 mg VIR-2218 4 weeks apart (Q4W) as a single agent in subjects with HBV infection. VIR-2218-1005 is a Phase 2 study in mainland China; each subject with HBV infection with HBeAg- (Part One) or HBeAg+ (Part Two) received 2 SC injections of 50 or 100 mg VIR-2218 Q4W. PK exposures at same dose levels (50, 100 mg) between the two studies were log-transformed and statistically analyzed using a mixed effects model, with study region as a fixed effect. For each dose level and dosing day separately, geometric least square mean (GLSM), geometric mean ratio (GMR), and 90%CI are calculated. **Results:** In study VIR-2218-1001, 24 subjects received VIR-2218 of which 23/24 (95.8%) were Asian ethnicity enrolled in the APAC region. In study VIR-2218-1005, all 16 subjects receiving VIR-2218 were of Asian ethnicity enrolled in mainland China. PK profiles in subjects with HBV infection are generally similar between APAC region and mainland China. No accumulation of BRII-835 in plasma was evident after a second dose. Subjects with HBeAg- or HBeAg+ had similar PK profiles, and thus were combined for each study. Statistical analysis demonstrated no clinically meaningful differences in PK exposure between the two study populations in different regions. The GMRs were 82.5-110% and 90%CIs for GMR encompass 100%, though with wide range due to small sample size and data variability. Comparable safety and HBsAg reduction profiles were also observed between the two studies. **Conclusion:** Chinese ethnic background from mainland China has no apparent impact on the PK of VIR-2218, which could serve as a bridge to support mainland China's participation in future global trials for further evaluation of VIR-2218.



Dose	Parameter	Mainland China		APAC Region		Statistical Comparison (Mainland China vs APAC)	
		n	GLSM	n	GLSM	GMR (%)	90%CI
50 mg	1st Dose						
	AUC_{last} (h·ng/mL)	8	822	9	968	84.8	63.7, 113
	C_{max} (n/mL)	7	92.6	7	106	87.6	54.0, 142
	2nd Dose						
	AUC_{last} (h·ng/mL)	8	704	9	852	82.6	57.4, 119
	C_{max} (ng/mL)	6	90.2	8	109	82.5	57.4, 118
100 mg	1st Dose						
	AUC_{last} (h·ng/mL)	8	2111	6	2552	82.7	44.1, 155
	C_{max} (ng/mL)	7	185	6	222	83.4	43.7, 159
	2nd Dose						
	AUC_{last} (h·ng/mL)	8	2737	6	2486	110	86.5, 140
	C_{max} (ng/mL)	8	231	6	219	105	63.9, 173

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1458-C | BASELINE CHARACTERISTICS OF HEPATITIS DELTA PATIENTS ENROLLED ACROSS PHASE 2 AND 3 STUDIES OF BULEVIRTIDE

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Background: Hepatitis delta (HDV) infection is the most severe form of viral hepatitis. Bulevirtide (BLV), a first-in-class entry inhibitor, is approved in Europe for the treatment of chronic hepatitis delta (CHD). Here we describe the baseline (BL) demographics and clinical characteristics of patients included in the BLV clinical program. **Methods:** A pooled analysis was conducted on BL data collected from 4 CHD trials that enrolled patients from 7 countries in Europe, including the Phase 2 studies MYR202 (NCT03546621), MYR203 (NCT02888106), and MYR204 (NCT03852433), and the Phase 3 study MYR301 (NCT03852719). Patients with compensated liver disease, alanine aminotransferase (ALT) > 1×ULN but < 10×ULN, with/without prior nucleos(t)ide analogue therapy were included. Key exclusion criteria included total bilirubin **e** 34.2 μmol/L, current or prior hepatic decompensation (history or within the last 2 y, depending on study), and recent interferon (IFN) use (duration depending on study). Patients were categorized into terciles based on BL ALT and HDV RNA for comparison. Fisher's exact test and ANOVA test were used for univariate analysis as appropriate. **Results:** 532 CHD patients were included; age, mean (SD) years, was 40 (9); 65% were male; 87% were White; 10% had BMI **e** 30 kg/m^2; and 10% were HBeAg+. 46% of patients (244 of 532) had prior IFN therapy. The BL mean (SD) HDV RNA viral load was 5.3 (1.3) $\log_{10}$ IU/mL, and 94% of the cohort was Genotype (GT) HDV-1. The majority of patients (95%) had elevated ALT, median (Q1, Q3), of 87 (60, 131) U/L. The mean liver stiffness (LS) was 13.8 (8.1) kPa with 38% of the cohort having cirrhosis. On subgroup analysis, those with higher BL ALT were more often of male sex ($p < 0.0001$) and had higher LS ($p = 0.0003$; Table). Further, those with higher BL HDV RNA were more often HBeAg+ ($p = 0.0052$) and had higher ALT ($p = 0.0313$) and HBsAg levels ($p < 0.0001$). 319

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

patients (60%) with CHD were treated with BLV monotherapy alone (92 BLV 2 mg; 32 BLV 5 mg; 195 BLV 10 mg), while 145 patients (27%) were treated with BLV + pegylated IFN (PEG; 65 [12%] BLV 2 mg + PEG; 15 [3%] BLV 5 mg + PEG; 65 [12%] BLV 10 mg + PEG). 68 patients (13%) were controls (no treatment) for the duration of the study. **Conclusion:** This is a large, pooled analysis including 532 CHD patients enrolled in past and ongoing BLV trials from Europe. The population identified here is predominantly male, White, and GT HDV-1. Those with higher BL ALT are more likely to be male with higher LS while those with higher HDV RNA are more likely to be HBeAg+ with higher ALT and HBsAg levels.

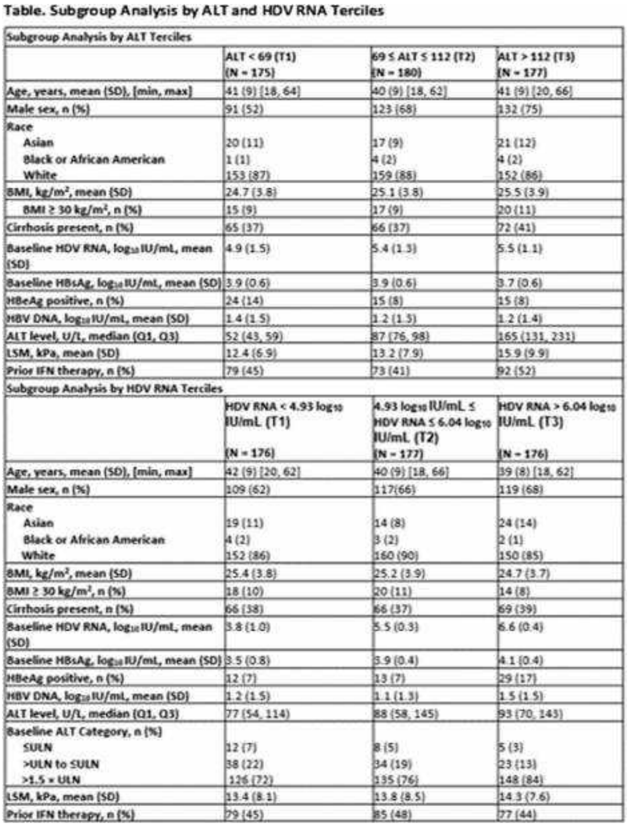

Table. Subgroup Analysis by ALT and HDV RNA Terciles

Subgroup Analysis by ALT Terciles			
	ALT < 69 (T1) (N = 175)	69 ≤ ALT ≤ 112 (T2) (N = 180)	ALT > 112 (T3) (N = 177)
Age, years, mean (SD), [min, max]	41 (9) [18, 64]	40 (9) [18, 62]	41 (9) [20, 66]
Male sex, n (%)	91 (52)	123 (68)	132 (75)
Race			
Asian	20 (11)	17 (9)	21 (12)
Black or African American	1 (1)	4 (2)	4 (2)
White	153 (87)	159 (88)	152 (86)
BMI, kg/m^2, mean (SD)	24.7 (3.8)	25.1 (3.8)	25.5 (3.9)
BMI ≥ 30 kg/m^2, n (%)	15 (9)	17 (9)	20 (11)
Cirrhosis present, n (%)	65 (37)	66 (37)	72 (41)
Baseline HDV RNA, log$_{10}$ IU/mL, mean (SD)	4.9 (1.5)	5.4 (1.3)	5.5 (1.1)
Baseline HBsAg, log$_{10}$ IU/mL, mean (SD)	3.9 (0.6)	3.9 (0.6)	3.7 (0.6)
HBeAg positive, n (%)	24 (14)	15 (8)	15 (8)
HBV DNA, log$_{10}$ IU/mL, mean (SD)	1.4 (1.5)	1.2 (1.3)	1.2 (1.4)
ALT level, U/L, median (Q1, Q3)	52 (43, 59)	87 (76, 98)	165 (131, 231)
LSM, kPa, mean (SD)	12.4 (6.9)	13.2 (7.9)	15.9 (9.9)
Prior IFN therapy, n (%)	79 (45)	73 (41)	92 (52)
Subgroup Analysis by HDV RNA Terciles			
	HDV RNA < 4.93 log$_{10}$ IU/mL (T1) (N = 176)	4.93 log$_{10}$ IU/mL ≤ HDV RNA ≤ 6.04 log$_{10}$ IU/mL (T2) (N = 177)	HDV RNA > 6.04 log$_{10}$ IU/mL (T3) (N = 176)
Age, years, mean (SD), [min, max]	42 (9) [20, 62]	40 (9) [18, 66]	39 (8) [18, 62]
Male sex, n (%)	109 (62)	117(66)	119 (68)
Race			
Asian	19 (11)	14 (8)	24 (14)
Black or African American	4 (2)	3 (2)	2 (1)
White	152 (86)	160 (90)	150 (85)
BMI, kg/m^2, mean (SD)	25.4 (3.8)	25.2 (3.9)	24.7 (3.7)
BMI ≥ 30 kg/m^2, n (%)	18 (10)	20 (11)	14 (8)
Cirrhosis present, n (%)	66 (38)	66 (37)	69 (39)
Baseline HDV RNA, log$_{10}$ IU/mL, mean (SD)	3.8 (1.0)	5.5 (0.3)	6.6 (0.4)
Baseline HBsAg, log$_{10}$ IU/mL, mean (SD)	3.5 (0.8)	3.9 (0.4)	4.1 (0.4)
HBeAg positive, n (%)	12 (7)	13 (7)	29 (17)
HBV DNA, log$_{10}$ IU/mL, mean (SD)	1.2 (1.5)	1.1 (1.3)	1.5 (1.5)
ALT level, U/L, median (Q1, Q3)	77 (54, 114)	88 (58, 145)	93 (70, 143)
Baseline ALT Category, n (%)			
≤ULN	12 (7)	8 (5)	5 (3)
>ULN to ≤ULN	38 (22)	34 (19)	23 (13)
>1.5 × ULN	126 (72)	135 (76)	148 (84)
LSM, kPa, mean (SD)	13.4 (8.1)	13.8 (8.5)	14.3 (7.6)
Prior IFN therapy, n (%)	79 (45)	85 (48)	77 (44)

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1459-C | BASELINE NUCLEOTIDE POLYMORPHISMS WITHIN HBV TARGET SITE IN CHRONIC HEPATITIS B SUBJECTS DO NOT IMPACT HBsAg REDUCTIONS MEDIATED BY RNA INTERFERENCE THERAPEUTIC AB-729

Christine Espiritu, Holly M Micolochick Steuer, Andrzej Ardzinski, Varun Sharma, Timothy Eley, Karen Sims, Amy C.H. Lee, Rene Rijnbrand, Andrea Cuconati, Nagraj Mani, Angela M. Lam, Michael J Sofia and Emily P Thi, Arbutus Biopharma, Warminster, PA

Background: AB-729 is a *N*-Acetylgalactosamine (GalNac) conjugated small interfering RNA (siRNA) currently being investigated for the treatment of chronic hepatitis B virus (HBV) infection. In clinical study AB-729-001, mean HBsAg declines from baseline ranged from 1.8 to 2.6 $\log_{10}$ across all cohorts by end of treatment. Here we report the characterization of AB-729 HBV target site variants identified from the HBVdb database as well as from sequence profiling of the AB-729 target site at baseline in chronic hepatitis B (CHB) subjects enrolled in AB-729-001. The impact of identified target site variants on HBV fitness and AB-729 activity was assessed in a transient transfection cell model of HBV. **Methods:** CHB subjects were administered single doses (60mg, 90mg, or 180mg) or multiple doses (60mg or 90mg every 4, 8 or 12 weeks) of AB-729. At baseline, prior to AB-729 administration, HBV RNA extracted from plasma was reverse transcribed, subjected to PCR amplification and ultra deep sequencing (UDS) of the HBx region. Additionally, sequences from the HBVdb database were screened for AB-729 target site variants. To determine the impact of identified AB-729 target site variants on viral fitness and AB-729 activity, point mutations were introduced into an HBV plasmid by site-directed-mutagenesis and transfected into HepG2 cells. Viral fitness and AB-729 activity were determined by comparing inhibitory activity in variants versus wildtype. **Results:** Analysis of HBV sequences from the HBVdb database identified changes in 8 nucleotide positions (G1577A, T1580A, C1582G, C1587T, G1588A/C/T, C1589A/G, T1590G and T1591C) with e 0.5% prevalence in any one HBV genotype or e 0.3% prevalence in at least two genotypes. UDS analysis from 31 subjects at baseline showed target site conservation in 23 subjects (74.2%). Single nucleotide polymorphisms (SNPs) were observed at positions 1590 and 1593 at > 15% read count frequency at baseline. *In vitro* analysis of these variants showed viral fitness to be > 50% of wildtype, with no decrease in sensitivity to AB-729. **Conclusion:** SNPs in the AB-729 HBV target site were identified in sequences obtained from a publicly available database and were observed at baseline in some CHB subjects in AB-729-001. *In vitro* testing in an HBV cell-based model confirm retention of AB-729 activity against tested variants, suggesting that these SNPs have no apparent influence on individual or mean HBsAg declines observed in subjects treated with AB-729.

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1460-C | BEPIROVIRSEN HAS INTRINSIC INNATE ACTIVITY, DISTINCT FROM THAT OF OTHER ANTI-SENSE OLIGONUCLEOTIDES

Megan Ermler[1], Kristen Jones[1], Amitabh Das[1], Anne DeHart[1], Nicholas Galwey[1], Melanie Paff[2] and Shihyun You[2], (1)GSK, (2)GSK, Collegeville, PA, USA

Background: Bepirovirsen (BPV) is an anti-sense oligonucleotide (ASO) that is in phase 3 clinical trials for chronic hepatitis B (CHB). Previously, we have reported that BPV induces innate immune activation in human PBMCs and also specific activity in transgenic hTLR8 mice (Shanghai Model Organisms Center, Inc.), but not in wild type mice. Here, we investigate whether bepirovirsen is unique in its mechanism for innate immune activation compared to other ASOs, and whether presence of HBV mRNA via infection alters innate activity in the hTLR8 transgenic mouse model. **Methods:** WT littermate control and transgenic hTLR8 mice were dosed with BPV, other ASOs (including a scrambled, a minimally inflammatory, and a TLR9 activating ASO), or control treatments. Mice were euthanized four hours after dosing and plasma protein and liver RNA cytokine levels were examined. To investigate the impact of HBV infection on innate immune response to bepirovirsen, WT littermate control and transgenic hTLR8 mice were infected with 1x10^11 viral genome per mouse of AAV-HBV for at least 30 days prior to study start. Mice were stratified based on HBsAg levels prior to dosing. **Results:** BPV had a distinct profile of innate immune activation compared to the other ASOs tested. Levels of TNF-α and IL-6 were significantly higher in hTLR8 mice dosed with BPV than in those dosed with scrambled ASO (TNFα: $p < 0.0001$; IL-6: $p = 0.0169$) or the non-inflammatory ASO 104838 ($p = 0.025$, $p = 0.0346$). BPV induced TNF-α and IL-6 in hTLR8 mice but not in WT mice, whereas ASO 421856 (activates through TLR9) induced TNF-α and IL-6 in

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

both hTLR8 and WT mice. Additionally, AAV-HBV infection of both WT and hTLR8 transgenic mice had no impact on cytokine protein production by BPV treatment within four hours post-dose. **Conclusion:** The innate immune activity of BPV in hTLR8 transgenic mice is distinct from that from another ASO known to induce TLR9 activity, suggesting that the BPV-mediated innate response is more specific to human TLR8. Interestingly, infection of either WT or hTLR8 transgenic mice with AAV-HBV does not impede, enhance, or alter the innate immune protein response observed with BPV treatment.

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1461-C | CHARACTERIZATION OF THE DIRECT ANTIVIRAL EFFECT OF REP 2139 ON HDV REPLICATION

Simone Fonte[1,2], Marie-Laure Plissonnier[1,3], Maud Michelet[1,2], Matthieu Blanchet[4,5], Patrick Labonte[6], Andrew Vaillant[7] and Massimo Levrero[1,3,8,9,10], (1) Cancer Research Center of Lyon (CRCL), Inserm U1052, Cnrs UMR5286, Lyon, France, (2)Institute d'Hépatologie De Lyon, Lyon, France, (3)Institut d'Hépatologie De Lyon, (4)Replicor Inc., (5)Inrs – Institut Armand Frappier, Institut National De La Recherche Scientifique, Laval, Canada, (6)Inrs-Centre Armand-Frappier Santé Biotechnologie, (7) Replicor Inc., Montreal, Canada, (8)Department of Hepatology, Croix Rousse Hospital, Hospices Civils De Lyon, France, (9)University of Lyon Claude Bernard 1 (UCLB1), Lyon, France, (10)Department of Medicine Sciac and the Italian Institute of Technology (IIT) Center for Life Nanosciences (CLNS), University of Rome La Sapienza, Rome, Italy

Background: REP 2139 blocks the assembly and secretion of HBV subviral particles, an effect which also blocks envelopment of the Hepatitis D Virus (HDV) ribonuclear protein (RNP) and secretion of HDV from infected cell. A previous phase II study and current compassionate use of REP 2139 in Hepatitis B Virus (HBV) / HDV infection have shown an early and more robust antiviral response toward HDV RNA than as compared to HBsAg, suggesting a second, upstream and direct acting antiviral mechanism. Here we have investigated the direct antiviral activity of REP 2139 in relevant HDV cell infection models *in vitro*. **Methods:** Restoration of REP 2139 endosomal release *in vitro* employed the UNC 7938-based method previously described (Blanchet et al., Antiviral Res 2019; 164: 97). Clinical supply of REP 2139-Mg (lot FAB-22-0001) was used for dosing in HDV infected HepG2-NTCP cells and primary human hepatocytes (PHH) at (10 genome equivalents/cell). REP 2139-Mg was diluted in normal saline before addition to tissue culture. Intracellular HDV viral genome levels were assessed in cell lysates by quantitative RT-PCR. The association of HDV RNA and Hepatitis Delta Antigen (HDAg) to form the HDV ribonucleoprotein (HDV RNP) was monitored by anti-HDAg RNA immunoprecipitation (RIP) followed by HDV specific RT-PCR (Abeywickrama-Samarakoon N et al., Nat Commun. 2020; 11: 419). **Results:** A single dose of REP 2139-Mg reduced intracellular HDV viral genome levels by ~1 $\log_{10}$ in HepG2-NTCP and PHH cells at 400nM and 600nM respectively. Loss of antiviral activity at higher doses could be recovered by increasing UNC 7938 concentration, indicating that the efficiency of endosomal release of REP 2139 into cells is a process influenced by endosomal concentration of REP 2139 and the dose of UNC 7938 used. A single dose of REP 2139-Mg also reduced the intranuclear association of HDV RNA with HDAg in both HepG2-NTCP and PHH by ~60% (@ 600nM) and 65% (@ 400nM), respectively. **Conclusion:** REP 2139 has a direct acting antiviral effect against HDV RNA replication which may involve blocking HDV RNA interaction with HDAg during the morphogenesis of HDV RNP. These antiviral effects bear further investigation and may explain the more rapid decline of HDV RNA versus HBsAg in human studies.

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The following people have nothing to disclose: Marie-Laure Plissonnier, Patrick Labonte, Massimo Levrero
Disclosure information not available at the time of publication: Simone Fonte, Maud Michelet, Andrew Vaillant

1462-C | CLASS A CAMS INDUCE CELL DEATH THROUGH HBV CORE PROTEIN AGGREGATION AND POTENTIALLY ACTIVATE THE INNATE IMMUNE RESPONSE

Valerio Taverniti[1], Hannah Vanrusselt[2], Dieudonné Kum[3], Yannick Debing[2], Eloi R. Verrier[1] and Thomas F.

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Background: Despite a preventive vaccine, almost 300 million people suffer from a chronic hepatitis B virus (HBV) infection. Therapies controlling HBV replication exist but do not lead to functional cure of chronic hepatitis B. HBV core protein (HBc) is the building block of the HBV nucleocapsid and it modulates almost every step of the HBV life cycle. Class A capsid assembly modulators (CAM-As) represent attractive direct antiviral agents (DAAs). These compounds impair HBV replication by blocking pgRNA encapsidation and inducing HBc aggregation due to aberrant nucleocapsid structures. We previously showed that CAM-A RG7907 treatment leads to an unexpected sustained HBsAg reduction and loss of infected hepatocytes via apoptosis in an AAV-HBV mouse model. In this study we present further insights into the mechanism of action of the CAM-A compound, RG7907 **Methods:** We investigated the impact of RG7907 treatment on HBc aggregation, cell survival, and transcriptomic reprogramming in HBc-expressing hepatoma cell lines (HepG2) and primary human hepatocytes (PHH) as well as in the HBV-replicating cell line HepAD38 **Results:** RG7907 induced extensive HBc-aggregation-dependent cell death both in hepatoma cells and in primary hepatocytes. Transcriptomic analyses revealed the activation of specific host pathways such as apoptosis, inflammation, and the interferon response. The induction of apoptosis-related gene expression was validated in HBc-expressing HepG2 and PHH as well as in HepAD38. We also observed activation of an interferon response in HepAD38 suggesting the potential activation of the innate immunity upon CAM-A treatment **Conclusion:** CAM-A-dependent HBc aggregation drives cell death via activation of host specific pathways such as apoptosis and the inflammatory and innate immunity responses. These results shed light on a previously unknown mechanism of action specific to CAM-A compounds.

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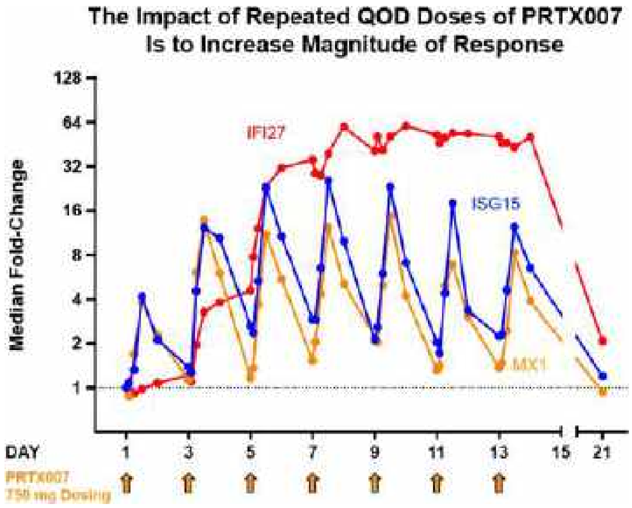
Thomas F. Baumert – Alentis Therapeutics: Advisor, No, No;

1463-C | CLINICAL VALIDATION OF AN ORALLY-DELIVERED, SYSTEMICALLY ACTIVATED TLR7 AGONIST TO BOOST HOST IMMUNE RESPONSE TO CHRONIC VIRAL DISEASES, INCLUDING HEPATITIS B VIRUS

Curtis L. Scribner[1], Charlotte R. Lemech[2], Christopher Argent[2], Richard Daniels[3] and James R Appleman[3], (1) Curtis L. Scribner, (2)Scientia Clinical Research, Ltd, (3) Primmune Therapeutics

Background: PRTX007 is a novel, clinical stage TLR7 agonist prodrug that can be used in multiple indications, including as part of a functional cure for chronic hepatitis B virus (HBV) infection. Using phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) healthy volunteer (HV) data, we show its safety profile and immunomodulatory activity are optimal for clinical use. All synthetic non-nucleoside TLR7 agonists activate NF-κB and have failed clinically in chronic viral infection settings. In contrast, nucleoside-based TLR7 therapies have shown benefit in clearing HBsAg. PRTX007 is an orally administered prodrug of PRX034, a nucleoside-based TLR7 agonist, that elicits an optimal pattern of systemic immune induction in non-human primates and in humans. There is no evidence of NF-kB-mediated systemic inflammation at drug levels that stimulate IFN-responsive pathways and corresponding downstream cellular processes. **Methods:** This was a phase 1, single-center, prospective, randomized, double-blind, placebo-controlled study of 9 SAD and 4 MAD cohorts of PRTX007 given orally every other day (QOD) to adult HVs. Primary objectives were safety and tolerability. Secondary objectives were evaluation of pharmacokinetics (PK) and pharmacodynamics (PD). In total, 104 of the 130 HVs received the study drug. **Results:** PRTX007 was well-tolerated with no grade 3 or higher AEs and no dose modifications or discontinuations due to treatment-related AEs. The PKs of PRTX007 and PRX034 are well-behaved, with a planned short half-life and exposure increasing proportionally with PRTX007 dose without accumulation upon repeated dosing (QOD) in the 300, 400, and 750 mg dose cohorts. Coordinated expression of IFN stimulated genes and genes known to be related to

TLR7 agonism was observed in immune cells in blood in all HVs. There was no change in expression of NF-kB regulated gene products. Increases in IL-1RA, MCP-1 and IP10 in plasma were observed. IL-6, TNFα, and IL- 1b remained essentially unchanged from pretreatment levels. **Conclusion:** PRTX007 was well tolerated, with mostly mild AEs and no SAEs. Activation of the innate and adaptive immune responses were observed without systemic increases in proinflammatory factors. Sustained immune pressure and extended PD response was demonstrated with oral QOD doses. These data demonstrate the suitability of PRTX007 for investigation in combination therapy for curative treatment of chronic HBV infection.



Disclosures: Curtis L. Scribner – Primmune Therapeutics: Consultant, Yes, No;
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Richard Daniels – Primmune Therapeutics: Executive role , Yes, No;
James R Appleman – Primmune Therapeutics: Executive role , Yes, No;

1464-C | DEEP IMMUNOPHENOTYPING ANALYSIS OF PBMC FROM THE BEPIROVIRSEN PHASE 2a STUDY

Jared Delahaye[1], Cory Knudson[1], Thea Hogan[2], Esther Perez Garcia[2], Irene Del Molino Del Barrio[2], Elizabeth Moore[1], Jennifer Singh[1], Dickens Theodore[3], Melanie Paff[1], Shihyun You[1] and Avijit Ray[1], (1)GSK, Collegeville, PA, USA, (2)GSK, Stevenage, UK, (3) GSK, Durham, NC, USA

Background: Bepirovirsen is an antisense oligonucleotide (ASO) targeting all hepatitis B virus (HBV) RNAs, and currently in Phase 3 development for chronic HBV infection. Phase 2 studies have demonstrated that bepirovirsen treatment induces loss of hepatitis B surface antigen (HBsAg) in a subset of participants (pts) as well as inducing serum immune activation. Here we sought to evaluate pts peripheral blood mononuclear cells (PBMC) post-hoc using deep immunophenotyping by high parameter flow cytometry from the Phase 2a study (NCT02981602), which included a 4-week treatment period. **Methods:** The samples included placebo-treated and bepirovirsen-treated pts (25 total pts) who experienced high (> 2.0log), partial (> 0.2 to **d** 2.0log) or no (**d** 0.2log) HBsAg reduction at a range of timepoints, which allowed us to detect changes in immune cells in blood during and following the treatment period. **Results:** During bepirovirsen treatment, pts with high HBsAg reduction had a greater proportion of PD1+ CD8 T cells compared with no HBsAg reduction pts, and there were also trends for elevated Granzyme B+ CD8 T cells at Day 15. After treatment, it was observed that high reduction pts had elevated TCF1+ CD4 and CD8 T cells, and there were trends for increased effector memory and Ki67+ CD4 T cells than no reduction pts. **Conclusion:** While the small sample size and high variation in this dataset limit our conclusions, this analysis provides a first glimpse of cellular immune characterization during bepirovirsen treatment. Our results suggest that pts with high HBsAg reduction may mount an enhanced T cell response with signs of superior proliferative potential after treatment. We will apply similar approaches to subsequent clinical studies to further elucidate immune responses in bepirovirsen-treated pts. Funding: GSK (study 205695; NCT02981602)

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

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1465-C | DEVELOPMENT OF ANTI-DRUG ANTIBODIES ON BULEVIRTIDE MONOTHERAPY IN CHD DOES NOT IMPACT BULEVIRTIDE EFFICACY, SAFETY OR PHARMACOKINETICS

Pietro Lampertico[1,2], Soo Aleman[3], Pavel Bogomolov[4], Viacheslav Morozov[5], Nina Mamonova[6], Dmitry Manuilov[7], Lei Ye[7], Ben L. Da[7], Renee-Claude Mercier[7], Audrey H. Lau[7], Grace Chee[7], Navita Mallalieu[7], Parag Kumar[7], Tatyana Stepanova[8], Vladimir Chulanov[6], Stefan Zeuzem[9], Heiner Wedemeyer[10], Marc Bourliere[11], Fabien Zoulim[12], Tarik Asselah[13], Maurizia R. Brunetto[14], Markus Cornberg[10] and Antje Blank[15], (1)CRC "a. M. and a. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, (2)Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, (3)Karolinska University Hospital/ Karolinska Institutet, Department of Infectious Diseases, (4)State Budgetary Institution of Health Care of Moscow Region "Moscow Regional Research Clinical Institute after M.F. Vladimirsky", (5)Hepatolog Medical Company, (6)Fsbi National Research Medical Center for Phthisiopulmonology and Infectious Diseases of the Ministry of Health of the Russian Federation, (7)Gilead Sciences, Inc., (8)Modern Medicine Clinic, (9)Goethe University Hospital, (10) Hannover Medical School, (11)Service Hépato-Gastro-Entérologie, Hôpital Saint-Joseph, (12)Hépatologie Unit, Hospices Civils De Lyon, Lyon University, Inserm, (13)Hôpital Beaujon Aphp, Université De Paris, Inserm, (14)Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, Reference Center of the Tuscany Region for Chronic Liver Disease and Cancer, University Hospital of Pisa, (15)Heidelberg University Hospital, Clinical Pharmacology and Pharmacoepidemiology

Background: Bulevirtide (BLV), a novel entry inhibitor, is approved in Europe for chronic hepatitis delta (CHD) treatment. Early results from a Phase 1b/2a study (MYR201) reported no correlation with antidrug antibody (ADA) development and the efficacy, safety, or pharmacokinetic (PK) profile of BLV. The potential for ADA development with BLV treatment was assessed in an integrated analysis of results from 2 Phase 2 studies (MYR203, MYR204) and 1 Phase 3 study (MYR301). **Methods:** The incidence of ADA development (ADA+) was defined as ADA negativity or missing at baseline with subsequent ADA positivity at any postbaseline visit and for this analysis was evaluated following BLV alone (2 or 10 mg) given subcutaneously once daily for 48W. Impact of ADA development on efficacy (virologic response [VR, defined as undetectable HDV RNA or decrease by **e** 2 $\log_{10}$ IU/mL from baseline], biochemical response [BR, defined as alanine aminotransferase (ALT) normalization], and combined response [CR; VR +BR]), safety, and PK were explored. W48 efficacy pooled data from MYR203 and MYR301, while adverse event and PK data were pooled across all 3 studies. **Results:** For the W48 efficacy analysis, 128 CHD patients showed similar incidences of ADA+ status among patients treated with BLV 2 or 10 mg (15/64 [23%] and 14/64 [22%]). VR for ADA+ vs ADA− patients was similar at BLV 2 mg (ADA+, 10/15 [67%] vs ADA−, 34/49 [70%]) and higher with BLV 10 mg (ADA+, 13/14 [93%] vs ADA−, 38/50 [76%]), respectively (Table). BR rates were similar by ADA status for both BLV 2 mg (ADA+, 9/15 [60%] vs ADA−, 27/49 [55%]) and BLV 10 mg (ADA+, 8/14 [57%] vs ADA−, 26/50 [52%]). Rates of CR among ADA+ and ADA− patients were similar among dose groups: BLV 2 mg, ADA+, 7/15 (47%) vs ADA−, 23/49 (47%); BLV 10 mg, ADA+, 7/14 (50%) vs ADA−, 23/50 (46%). BLV exposure (area under the plasma concentration-time curve [AUC]) between ADA+ and ADA− patients was similar for 2 mg, $\mathrm{AUC}_{\mathrm{ratio}}$ (90% CI) = 1.22 (1.00-1.51) and for 10 mg, 1.12 (0.96-1.32). Of 177 patients in the safety analysis, among ADA+ patients, the rates of Grade 3 or higher treatment-emergent adverse events (TEAE) or hypersensitivity TEAEs were not higher and did not lead to BLV discontinuation. **Conclusion:** Development of ADA to BLV monotherapy did not impact efficacy, safety, or PK of BLV in CHD patients. Effect of ADAs on efficacy and safety of BLV will continue to be monitored in ongoing studies.

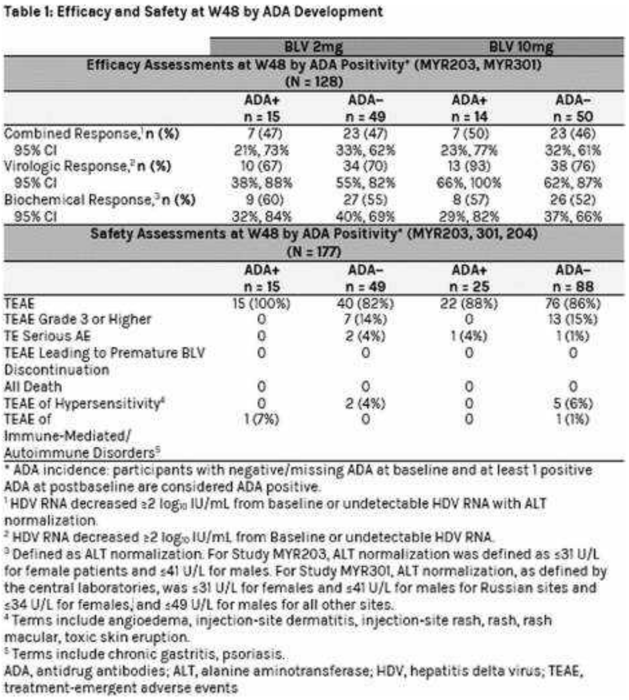

Table 1: Efficacy and Safety at W48 by ADA Development

	BLV 2mg		BLV 10mg	
Efficacy Assessments at W48 by ADA Positivity* (MYR203, MYR301) (N = 128)				
	ADA+ n = 15	**ADA− n = 49**	**ADA+ n = 14**	**ADA− n = 50**
Combined Response,[1] **n (%)**	7 (47)	23 (47)	7 (50)	23 (46)
95% CI	21%, 73%	33%, 62%	23%, 77%	32%, 61%
Virologic Response,[2] **n (%)**	10 (67)	34 (70)	13 (93)	38 (76)
95% CI	38%, 88%	55%, 82%	66%, 100%	62%, 87%
Biochemical Response,[3] **n (%)**	9 (60)	27 (55)	8 (57)	26 (52)
95% CI	32%, 84%	40%, 69%	29%, 82%	37%, 66%
Safety Assessments at W48 by ADA Positivity* (MYR203, 301, 204) (N = 177)				
	ADA+ n = 15	**ADA− n = 49**	**ADA+ n = 25**	**ADA− n = 88**
TEAE	15 (100%)	40 (82%)	22 (88%)	76 (86%)
TEAE Grade 3 or Higher	0	7 (14%)	0	13 (15%)
TE Serious AE	0	2 (4%)	1 (4%)	1 (1%)
TEAE Leading to Premature BLV Discontinuation	0	0	0	0
All Death	0	0	0	0
TEAE of Hypersensitivity[4]	0	2 (4%)	0	5 (6%)
TEAE of Immune-Mediated/ Autoimmune Disorders[5]	1 (7%)	0	0	1 (1%)

* ADA incidence: participants with negative/missing ADA at baseline and at least 1 positive ADA at postbaseline are considered ADA positive.

[1] HDV RNA decreased ≥2 $\log_{10}$ IU/mL from baseline or undetectable HDV RNA with ALT normalization.

[2] HDV RNA decreased ≥2 $\log_{10}$ IU/mL from Baseline or undetectable HDV RNA.

[3] Defined as ALT normalization. For Study MYR203, ALT normalization was defined as ≤31 U/L for female patients and ≤41 U/L for males. For Study MYR301, ALT normalization, as defined by the central laboratories, was ≤31 U/L for females and ≤41 U/L for males for Russian sites and ≤34 U/L for females, and ≤49 U/L for males for all other sites.

[4] Terms include angioedema, injection-site dermatitis, injection-site rash, rash, rash macular, toxic skin eruption.

[5] Terms include chronic gastritis, psoriasis.

ADA, antidrug antibodies; ALT, alanine aminotransferase; HDV, hepatitis delta virus; TEAE, treatment-emergent adverse events

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The following people have nothing to disclose: Pavel Bogomolov, Nina Mamonova

1466-C | DISCOVERY OF A LIVER TARGETED ORAL PD-L1 SMALL MOLECULE INHIBITOR FOR THE TREATMENT OF CHRONIC HEPATITIS B AND LIVER CANCER

Heleen Roose[1], Kristina Rekstyte-Matiene[1], Sarah K Stevens[2], Kusum Gupta[3], Sandra Chang[2], Cheng Liu[2], Vladimir Serebryany[2], Lillian Adame[2], Kha Le[2], Antitsa Stoycheva[2], Lawrence M. Blatt[2], Leonid N. Beigelman[2], Sushmita Chanda[2], David B. Smith[2], Julian Symons[2], Andreas Jekle[2,4] and Tongfei Wu[1], (1)Aligos Belgium BV, Leuven, Belgium, (2)Aligos Therapeutics, Inc., South San Francisco, CA, USA, (3)Aligos Therapeutics, Inc., (4)Aligos Therapeutics, Inc., South San Francisco, CA, USA, South San Francisco, CA, United States

Background: PD-1/PD-L1 antibody-based therapies have demonstrated success in the treatment of liver cancer and have exhibited potential for effecting functional cure of chronic hepatitis B (CHB). However, the systemic immune-related adverse events (irAEs) associated with PD-1/PD-L1 antibodies can be life threatening, due to their long half-lives. Our first-generation liver targeted PD-L1 small molecule inhibitor, ALG-093702, activated PBMC from an HBV-infected patient *ex vivo* with similar activity to durvalumab and demonstrated *in vivo* antitumor efficacy in a human PD-L1 MC38 subcutaneous mice model. Further optimization led to our next generation liver targeting PD-L1 small inhibitor, ALG-094103, which has similar *in vitro* potency to ALG-093702 with excellent oral bioavailability. **Methods:** Biochemical interaction of PD-1/PD-L1 and PD-L1 dimerization were assessed by AlphaLISA®. Cellular activity was measured using a co-culture assay of PD-1 expressing Jurkat NFAT luciferase T cells with PD-L1 expressing CHO cells. Pharmacokinetic (PK) and tissue distribution studies were performed in C57BL/6 mice. *In vivo* PD-L1 target occupancy was assessed at 6 hours of post single dose in the humanized-PDL1 MC38 subcutaneous mouse model. **Results:** ALG-094103 is a novel liver targeted oral PD-L1 small molecule which inhibits the PD-1/PD-L1 axis similarly to PD-L1 antibodies. ALG-094103 has *in vitro* potency similar to ALG-093702 and a non-liver targeted PD-L1 small molecule inhibitor, INCB086550. In mice, ALG-094103 exhibited significantly improved oral bioavailability compared to ALG-093702 and INCB086550. In a mouse tissue distribution study, ALG-094103 showed higher liver concentrations vs. other tested tissues (liver/lung ratio of 17) at 12 hours after a single dose. In the *in vivo* PD-L1 target occupancy model, oral dosing of ALG-094103 at 50 mg/kg demonstrated higher PD-L1 target occupancy than oral dosing of INCB086550 at 150 mg/kg and IV dosing of durvalumab at 5 mg/kg. **Conclusion:** We have discovered a novel liver targeted oral PD-L1 small molecule inhibitor, ALG-094103, with similar *in vitro* potency to ALG-093702 and INCB08655, and with significantly improved oral bioavailability. ALG-094103 will be further evaluated as a potential candidate for drug development.

Disclosures: Andreas Jekle – Aligos Therapeutics, Inc.: Employee, Yes, No; Aligos Therapeutics, Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

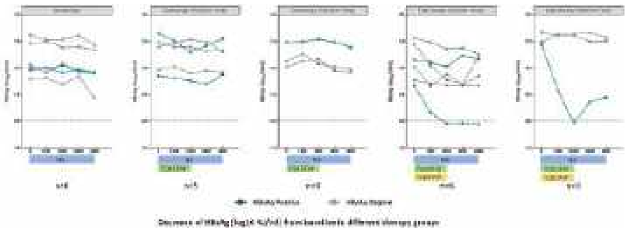
The following people have nothing to disclose: Heleen Roose, Kristina Rekstyte-Matiene, Sarah K Stevens, Kusum Gupta, Sandra Chang, Cheng Liu, Vladimir Serebryany, Lillian Adame, Kha Le, Antitsa Stoycheva, Lawrence M. Blatt, Leonid N. Beigelman, Sushmita Chanda, David B. Smith, Julian Symons, Tongfei Wu

1467-C | EFFICACY AND SAFETY OF COMBINATION TREATMENT OF TLR7 AGONIST TQA3334 AND ANTI-PD-L1 TQB2450 IN VIRALLY SUPPRESSED CHRONIC HEPATITIS B PATIENTS: A PILOT RCT PHASE II STUDY (OCEAN cure05 STUDY)

Ting Wu[1], Di Wu[1], Yuying Chen[1], Da Huang[1], Zhize Yuan[1], Peng Wang[2], Zhongnan Xu[3], Shuna Wang[3], Dandan Huo[3], Weiming Yan[1], Meifang Han[1], Qin Ning[4] and Xiaojing Wang[5], (1)State Key Laboratory for Diagnosis and Treatment of Severe Zoonotic Infectious Diseases, Department and Institute of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China, (2)State Key Laboratory for Diagnosis and Treatment of Severe Zoonotic Infectious Diseases, Department and Institute of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, (3)Chia Tai Tianqing Pharmaceutical Group Co., Ltd, (4)Institute and Department of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, (5)Tongji Medical College and State Key Laboratory for Diagnosis and Treatment of Severe Zoonostic Infectious Disease, Huazhong University of Science and Technology

Background: Curing chronic hepatitis B (CHB) relies on the orchestration of innate and adaptive immunity in addition to profound viral replication suppression. TQA3334 is a selective toll-Like Receptor-7 (TLR-7) agonist and activates innate immune to induce specific cytokines and chemokines to inhibit hepatitis B virus (HBV), such as IFN-α and IFN-inducible protein-10. TQB2450, a PD-L1 antibody, inhibits PD-1/PD-L1 axis and rouses adaptive immune response to HBV. This phase II study (OCEAN cure05 Study) aimed to evaluate the efficacy and safety of nucleos(t)ide analog (NA) and TQA3334 combined with/without TQB2450 in CHB patients. **Methods:** Totally 24 viral-suppressed (250 **d** IU/ml HBsAg **d** 5000 IU/ml, HBV DNA < 100 IU/ml) CHB patients were randomized to receive NA (monotherapy, n = 6), NA+TQA3334 (dual therapy, n = 9) or NA+TQA3334+TQB2450 (triple therapy, n = 9). In each cohort, the hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients were enrolled in a ratio of 1:2. TQA3334 (1.2mg or 1.5mg, QW) and TQB2450 (400mg, Q3W) were administrated for 24 weeks, and NA was given throughout 24-week treatment and 24-week follow-up. The HBsAg (Roche Elecsys, lower limit of quantification = 0.05 IU/ml) reduction and adverse events (AEs) were evaluated. **Results:** One patient in dual therapy arm withdrew at week 6 due to personal reasons, and

23 patients completed the study. At the end of treatment (EOT), 4 (66.67%), 5(62.5%) and 8 (88.89%) patients received NA monotherapy, dual therapy and triple therapy had a reduction in HBsAg from baseline. Compared to NA monotherapy and dual therapy, triple therapy was associated with greater HBsAg reduction at EOT (0.04 ± 0.08, 0.04 ± 0.16, and 0.37 ± 0.50 log10 IU/ml). HBsAg reduction > 0.5 log10 IU/ml (n = 3) and HBsAg declined to < 100 IU/ml (n = 2) were only observed in triple therapy arm. In triple therapy group, high dose TQA3334 administration had a prominent HBsAg reduction (0.46 vs 0.32 log10 IU/ml) at EOT. The maximum HBsAg reduction in this study was 1.4 log10 IU/ml with a baseline HBsAg of 2767 IU/ml and administration of 1.5mg TQA3334. After TQA3334 and TQB2450 discontinuation, HBsAg remained lower than those of EOT in 62.5% (5 of 8) and 66.6% (6 of 9) of patients received dual therapy and triple therapy respectively at the end of follow-up (EOF). Treatment related AEs were developed in 5 patients received dual therapy and 8 patients received triple therapy. The grade 1 thyroiditis was the most common immune-related AEs in patients received TQB2450. Two grade 3 AEs (neutropenia in dual therapy group and elevated creatine phosphokinase in triple therapy group) were reported. However, all the events were resolved before EOF. No serious AE or death reported in current study. **Conclusion:** The combination of NA, TQA3334 and TQB2450 induced greater and more durable HBsAg decline in viral-suppressed CHB patients with good safety and tolerability. Moreover, high dose of TQA3334 promoted HBsAg reduction in triple therapy.



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Dandan Huo – Chia Tai Tianqing Pharmaceutical Group Co., Ltd.: Employee, Yes, No;
The following people have nothing to disclose: Ting Wu, Di Wu, Yuying Chen, Da Huang, Zhize Yuan, Peng Wang, Weiming Yan, Meifang Han, Qin Ning, Xiaojing Wang

1468-C | EFFICACY AND SAFETY OF siRNA JNJ-73763989, CAPSID ASSEMBLY MODULATOR-E (CAM-E) JNJ-56136379, AND NUCLEOS(T)IDE ANALOGS (NA) WITH PEGYLATED INTERFERON ALPHA-2a (PEGIFN-α2a) ADDED IN IMMUNE-TOLERANT PATIENTS WITH CHRONIC HEPATITIS B VIRUS (HBV) INFECTION: INTERIM RESULTS FROM THE PHASE 2 REEF-IT STUDY

Patrick T. Kennedy[1], Scott K. Fung[2], Maria Buti[3], Gurdal Yilmaz[4], Wan Long Chuang[5], Tarik Asselah[6], Masayuki Kurosaki[7], John Jezorwski[8], Thierry Verbinnen[9], Thomas N. Kakuda[10], Oliver Lenz[9], Carine Guinard-Azadian[9] and Michal Biermer[9], (1)Barts and the London School of Medicine and Dentistry, London, United Kingdom, (2)University Health Network, Toronto, Ontario, Canada, (3)Hospital General Universitari Valle, Barcelona and Ciberehd Del Instituto Carlos III, Spain, (4)Trabzon Karadeniz Technical University Farabi Hospital, Trabzon, Turkey, (5)Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, (6)Université De Paris-Cité, Inserm UMR1149, Department of Hepatology, AP-HP Hôpital Beaujon, Clichy, France, (7)Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Musashino, Japan, (8)Janssen Research & Development, LLC, Titusville, NJ, USA, (9) Janssen Pharmaceutica NV, Beerse, Belgium, (10) Janssen Research & Development, LLC, Brisbane, CA, USA

Background: JNJ-73763989 (JNJ-3989) reduces hepatitis B surface antigen (HBsAg) in chronic hepatitis B (CHB) patients, but seroclearance remained rare; functional cure may require adding an immune modulator. Approved treatments have limited effects on HBsAg and hepatitis B e antigen (HBeAg) in immune-tolerant patients with CHB. The phase 2 REEF-IT study (NCT04439539) assessed the safety and efficacy of PegIFN-α2a add-on to JNJ-3989 ± JNJ-6379+NA in treatment naïve HBeAg+ CHB patients with alanine transaminase (ALT) < 2× upper limit of normal (ULN). **Methods:** Patients received JNJ-3989 200 mg Q4W +NA ± JNJ-6379 250 mg QD, for 36–52 weeks (induction phase) followed by 12 weeks of PegIFN-α2a 180 mcg QW add-on (consolidation phase). Primary endpoint is proportion of patients with HBsAg seroclearance after 24 weeks after stopping of all treatment (NA stopped based on criteria at end of treatment [EOT]) Changes in viral markers (HBsAg, HBV DNA, HBeAg) at EOT, with available Follow-up Week 24 (FU24) data, are presented. **Results:** 54 patients were enrolled (mean age 34 y; 69% with HBV DNA > 10^7 IU/mL and normal ALT); 49 (91%) completed EOT; 28 (52%) reached FU24. At EOT, mean (SE) HBsAg change from baseline (BL) was –3.61 (0.18) $\log_{10}$ IU/mL (Table). Mean (SE) HBV DNA change from BL was 6.24 (0.20) $\log_{10}$ IU/mL and 7/48 (15%) patients had HBeAg seroclearance. At FU24, mean (SE) HBsAg change from BL was –2.92 (0.37) $\log_{10}$ IU/mL (Table) and 21/28 (75%) patients on NA had HBV DNA < lower limit of quantitation. 10/54 (19%) patients had at least transient HBsAg sero-negativity; 7 remained HBsAg negative at the last available time point. Transient ALT and HBV DNA increases occurred during PegIFN-α2a add-on. Many patients showed increased HBsAg decline during or after PegIFN-α2a add-on. Treatments were generally safe and well tolerated with no serious adverse events (AEs) during treatment or, AEs leading to treatment discontinuation, or death; 3/49 (6%) and 0 patients experienced grade 3 and 4 AEs, respectively. **Conclusion:** In these treatment-naïve, HBeAg positive and mainly immune-tolerant patients, adding PegIFN-α2a increased HBsAg declines after levels were reduced by JNJ-3989. 19% of patients achieved transient HBsAg sero-negativity and 15% lost HBeAg.

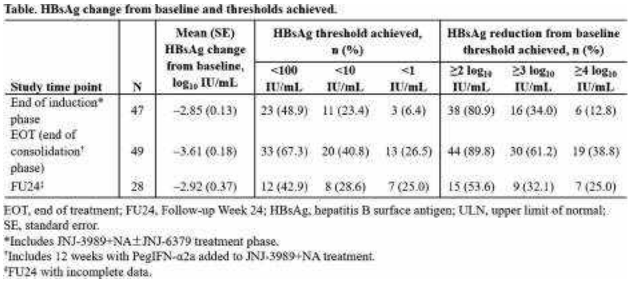

Table. HBsAg change from baseline and thresholds achieved.

Study time point	N	Mean (SE) HBsAg change from baseline, $\log_{10}$ IU/mL	HBsAg threshold achieved, n (%)			HBsAg reduction from baseline threshold achieved, n (%)		
			<100 IU/mL	<10 IU/mL	<1 IU/mL	≥2 $\log_{10}$ IU/mL	≥3 $\log_{10}$ IU/mL	≥4 $\log_{10}$ IU/mL
End of induction* phase	47	–2.85 (0.13)	23 (48.9)	11 (23.4)	3 (6.4)	38 (80.9)	16 (34.0)	6 (12.8)
EOT (end of consolidation† phase)	49	–3.61 (0.18)	33 (67.3)	20 (40.8)	13 (26.5)	44 (89.8)	30 (61.2)	19 (38.8)
FU24‡	28	–2.92 (0.37)	12 (42.9)	8 (28.6)	7 (25.0)	15 (53.6)	9 (32.1)	7 (25.0)

EOT, end of treatment; FU24, Follow-up Week 24; HBsAg, hepatitis B surface antigen; ULN, upper limit of normal; SE, standard error.

*Includes JNJ-3989+NA±JNJ-6379 treatment phase.

†Includes 12 weeks with PegIFN-α2a added to JNJ-3989+NA treatment.

‡FU24 with incomplete data.

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Scott K. Fung – Gilead Sciences, Inc.: Speaking and Teaching, No, No; AbbVie: Speaking and Teaching, No, No; Lupin: Speaking and Teaching, No, No; Gilead Sciences, Inc.: Advisor, No, No; AbbVie: Advisor, No, No; Novo Nordisk: Advisor, No, No; Pfizer: Advisor, No, No; Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;

Maria Buti – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, Yes; GSK: Advisor, Yes, No;

Tarik Asselah – AbbVie: Speaking and Teaching, No, No; Eiger Biopharmaceutical: Speaking and Teaching, No, No; Janssen: Speaking and Teaching, No, No; Gilead Sciences, Inc.: Speaking and Teaching, Yes, No; Myr Pharmaceutical: Consultant, No, No; Roche: Speaking and Teaching, No, No; Merck: Speaking and Teaching, No, No; AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Eiger Biopharmaceutical: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Janssen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Myr Pharmaceutical: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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1469-C | EVALUATING THE EFFICACY OF PEGYLATED IFN-LAMBDA AND IFN-ΑLFA TREATMENTS ON HBV AND HDV INFECTIONS IN HUMANIZED MICE

Sarah Duehren[1], Takuro Uchida[2,3], Masataka Tsuge[3,4], Nobuhiko Hiraga[3], Abu Fahad Abbasi[1], Ohad Etzion[5], Jeffrey Glenn[6], Christopher Koh[7], Theo Heller[7], Scott J. Cotler[1], Kazuaki Chayama[8,9,10] and Harel Dahari[1], (1) The Program for Experimental and Theoretical Modeling, Division of Hepatology, Department of Medicine, Stritch School of Medicine, Loyola University Chicago, Maywood, Illinois, USA, (2)Department of Gastroenterology, Faculty of Medicine, Oita University, Yufu, Japan, (3)Research Center for Hepatology and Gastroenterology, Hiroshima University, Hiroshima, Japan, (4)Department of Gastroenterology, Graduate School of Biomedical & Health Sciences, Hiroshima University, Hiroshima, Japan, (5)Soroka University Medical Center, Beer-Sheba, Israel, (6)Division of Gastroenterology and Hepatology, Departments of Medicine, Microbiology & Immunology, Stanford School of Medicine, Stanford, California, USA, (7)Liver Diseases Branch, Niddk, Nih, USA, (8)Collaborative Research Laboratory of Medical Innovation, Hiroshima University, (9)Riken Center for Integrative Medical Sciences, (10)Hiroshima Institute of Life Sciences

Background: We recently reported that the early kinetics of HDV decline with pegylated IFN-λ (Lambda) therapy in chronic HDV-infected patients [Hepatology.2023;77(6):2093-2103] was dramatically greater than with pegylated IFN-α (Alfa) therapy [Hepatology.2014;60(6):1902-10]. We investigated HDV RNA, HBV DNA, HBsAg and human albumin (hAlb) kinetics during Lambda and Alfa treatment in chimeric urokinase type plasminogen activator (uPA)/severe combined immunodeficiency mice reconstituted with humanized livers. The aim was to compare the antiviral efficacy of Lambda and Alfa in humanized mice that lack an adaptive immune response. **Methods:** Thirteen mice from 3 separate studies were treated twice weekly with 30 μg/kg of either Alfa (n = 7) or Lambda (n = 6) for either 12 weeks (n = 10) or 13 weeks (n = 3). Ten mice were coinfected with HBV and HDV, and 3 were superinfected (HBV infection followed by HDV after 10 weeks). HBV DNA, HDV RNA, and hAlb levels were measured weekly, and HBsAg levels were measured biweekly. **Results:** Baseline median levels of HBV DNA, HDV RNA, hAlb, and HBsAg were 8.8 log IU/mL (interquartile range, IQR 0.2), 9.8 IU/mL (IQR 0.5), 6.9 log ng/mL (IQR 0.12) and 4.0 IU/mL (IQR 0.35), respectively. Baseline values were similar between mice treated with Alfa vs. Lambda, or superinfection vs. coinfection. One mouse treated with Alfa died after 1 week and was excluded from analysis. The remaining 12 mice (Alfa n = 6; Lambda n = 6) had analysis of on treatment kinetics. Regardless of type of IFN, HDV RNA had a longer delay in decline than HBV DNA, with medians of 3 (n = 6, IQR 1.18) weeks and 1 (n = 5, IQR 0.02) day, respectively (Fig. 1A and B). Thereafter, mice treated with Alfa experienced a significantly greater decline in HBV DNA ($p < 0.049$, Fig.1A), HDV RNA ($p < 0.041$, Fig.1B), and HBsAg ($p < 0.017$, Fig.1C), starting at weeks 9, 6, and 5 after initiation of treatment, respectively, until end of treatment (EOT). Overall, the magnitude of decline from baseline to EOT for HBV DNA was significantly greater than that of HDV RNA, with medians of 1.55 (IQR 1.18) and 0.79 (IQR 0.98) log IU/mL, respectively ($p = 0.013$), with no association with hAlb levels which remained approximately at baseline values (Fig.1D). **Conclusion:** In contrast to our findings in immune competent patients (ibid), Alfa was more effective than Lambda in decreasing HBV DNA, HDV RNA, and HBsAg during treatment in humanized mice that lack of an adaptive immune response, suggesting that Alfa induces stronger innate immune responses than Lambda. The respective roles of the combined innate and adaptive immune systems in the antiviral efficacy of Alfa and Lambda against HBV and HDV requires further study.

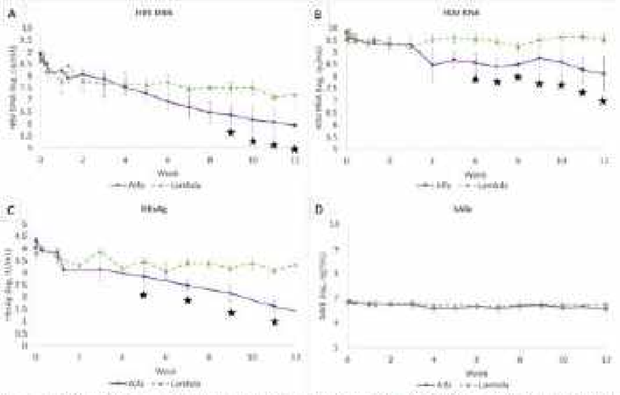

Figure 1. Median levels throughout Alfa or Lambda treatment in cDNA-uPA/SCID humanized mice. Solid line= Alfa treatment; Dashed line= Lambda treatment; Error bars=interquartile range; Black stars= timepoint where Alfa median viral level is significantly ($p<0.05$) different from Lambda. There were no differences between Alfa and Lambda or co-infection and superinfection for hAlb throughout treatment. The kinetic picture includes one super-infected mouse that died after 7 weeks of Lambda treatment.

Disclosures: The following people have nothing to disclose: Masataka Tsuge, Ohad Etzion, Christopher Koh, Theo Heller, Scott J. Cotler, Kazuaki Chayama, Harel Dahari

Disclosure information not available at the time of publication: Sarah Duehren, Takuro Uchida, Nobuhiko Hiraga, Abu Fahad Abbasi, Jeffrey Glenn

1470-C | GENOME-WIDE LOSS-OF-FUNCTION GENETIC SCREEN IDENTIFIES THE VULNERABILITY OF HBV-INTEGRATED HEPATOMA CELLS

Makoto Fukuoka[1], Takahiro Kodama[2], Hayato Hikita[1], Jihyun Sung[1], Akiyoshi Shimoda[1], Satoshi Shigeno[1], Kazuhiro Murai[1], Akira Nishio[1], Kunimaro Furuta[1], Tomohide Tatsumi[1] and Tetsuo Takehara[2], (1)Osaka University, Graduate School of Medicine, (2)Osaka University Graduate School of Medicine

Background: There are about 250 million people chronically infected with hepatitis B virus (HBV) worldwide. HBV is often integrated into the host genome and promotes hepatocarcinogenesis. In this study, we searched for the therapeutic vulnerability of HBV-integrated liver cancer cells using forward genetic screen. **Methods:** Loss-of function screen was performed in HepG2 and HBV-integrated HepG2.2.15 cells expressing SpCas9 cDNA using a pooled genome-wide clustered regularly interspaced short palindromic repeats (CRISPR) library. Genomic DNAs were extracted from these cells at immediately after the library infection (D2) and after 2-week culture (D14). They were sequenced to determine the abundance of each gRNA by a next-generation sequencer. Genes whose gRNA abundance significantly decreased in HepG2.2.15 cells but not in HepG2 cells were extracted using the MAGeCK algorithm. **Results:** We identified 38 genes potentially involved in the vulnerability of HBV-integrated cancer cells. We focused on 4 genes (BCL2L1, VPS37A, INSIG2, and CFLAR) that showed significant reductions of gRNA abundance. siRNA-mediated mRNA inhibition or CRISPR-mediated genetic deletion of INSIG2 significantly impaired cell proliferation in HepG2.2.15 cells but not in HepG2 cells. Its inhibitory effect was alleviated by co-transfection of siRNAs targeting HBV in HepG2.2.15 cells. INSIG2 inhibition suppressed the pathways related to cell cycle and DNA replication in HepG2.2.15 cells. INSIG2 inhibition downregulated CDK2 levels and delayed the G1-to-S transition in these cells. CDK2 inhibitor suppressed cell cycle progression in HepG2.2.15 cells and INSIG2 inhibition did not suppress cell proliferation in the presence of CDK2 inhibitor. **Conclusion:** INSIG2 inhibition induced cell cycle arrest in HBV-integrated hepatoma cells in CDK2-dependent manner, and thus might be a potential therapeutic for HBV-associated liver cancer.

Disclosures: The following people have nothing to disclose: Makoto Fukuoka, Takahiro Kodama, Hayato Hikita, Jihyun Sung, Akiyoshi Shimoda, Satoshi Shigeno, Kazuhiro Murai, Akira Nishio, Kunimaro Furuta, Tomohide Tatsumi, Tetsuo Takehara

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1471-C | HBV IMMUNE CHECKPOINT RECEPTOR CD33 (SIGLEC-3) IS A PROMISING THERAPEUTIC TARGET FOR CHRONIC HEPATITIS B INFECTION

Pei-Shan Sung[1,2], Chieh-Ju Lee[3], Yi-Hsiang Huang[3], Chang-Ru Wu[4] and Shie-Liang Hsieh[1], (1)Academia Sinica, (2)Academia Sinica, Taoyuan City, Taiwan, (3) Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, (4)Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University

Background: Currently, approximately 300 million people worldwide suffer from chronic hepatitis B (CHB), and the primary treatment option is antiviral nucleos(t)ide analogues. However, these treatments are seldom successful in stimulating the generation of anti-HBsAg antibody (HBsAb) that can effectively cure patients. In our previous study, we reported that CD33 (Siglec-3) serves as an immune checkpoint that triggers immunotolerance by binding to the sialic acid of HBsAg (hepatitis surface antigen). In CHB patients, a distinct group of B cells expressing CD33 was observed. Given the immune suppressive role of CD33, the hypothesis was that CD33 could be suppressing the production of HBsAb in B cells. **Methods:** We created a high-affinity antagonistic monoclonal antibody against CD33 (clone 4H33A) using a phage display platform. We evaluated its effectiveness in inducing HBsAb production by incubating it with PBMC and B cells from CHB patients. Subsequently, we analyzed the B cell subsets in PBMCs through flow cytometry after exposing them to 4H33A. We examined if there is a positive correlation between the level of HBsAg and HBV DNA in the blood and the production of HBsAb induced by 4H33A. Additionally, we calculated the correlation between HBV DNA, HBsAg, $CD33^+$ B cells percentage, and the response to anti-CD33 mAb that triggers HBsAb production. Furthermore, we established a hydrodynamic injection mouse model in which we administered AAV/HBV1.2 and AAV/HBV1.2-Y132A (HBcAg mutant strain) in wild-type (WT) and human CD33 transgenic mice (hCD33 Tg). We aimed to investigate whether the presence or absence of human CD33 affects the clearance of HBsAg and the efficacy of 4H33A in vivo. **Results:** Our results showed that the anti-CD33 monoclonal antibody 4H33A effectively induced the production of HBsAb in ex vivo assays, as demonstrated by PBMC/B cell ELISPOT and ELISA analyses. Additionally, after incubation for 5 days, 4H33A reduced the percentage of $CD33^+S100A9^+$ B cells, activated memory B cells, and atypical memory B cells. Furthermore, a positive correlation was observed between higher levels of HBV DNA and $CD33^+$ B cells

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

and a better response to the anti-CD33 monoclonal antibody 4H33A in promoting HBsAb production in ex vivo assays. In human CD33 transgenic mice, the presence of human CD33 extended the persistence of HBsAg, whereas treatment with the anti-CD33 monoclonal antibody 4H33A led to the clearance of HBsAg. **Conclusion:** Targeting CD33, which acts as an immune checkpoint receptor for HBV-induced immune tolerance, shows great potential as a strategy for reactivating the host's immune system to eliminate HBV in patients with CHB.

Disclosures: The following people have nothing to disclose: Pei-Shan Sung, Chieh-Ju Lee, Yi-Hsiang Huang, Chang-Ru Wu, Shie-Liang Hsieh

1472-C | IMPACT OF HBCAG SPECIFIC CTL ON HBsAg REDUCTION AFTER NASAL ADMINISTRATIVE THERAPEUTIC VACCINE TREATMENT IN CHRONIC HEPATITIS B PATIENTS

Kana Shiraishi, Ehime University Graduate School of Medicine

Background: The treatment goal of chronic hepatitis B (CHB) is HBs antigen (HBsAg) elimination, however it is difficult to achieve the goal with interferon and nucleos(t)ide analogues (NAs). We have developed a nasal administrative therapeutic vaccine containing HBs/HBcAg mixed viscosity enhancer (CVP-NASVAC). We conducted clinical trials of CVP-NASVAC against CHB and reported its capacities of HBsAg reduction and anti-HBs induction. In this study, we explored the immunological mechanism of CVP-NASVAC on HBsAg reduction. **Methods:** Fifty CHB patients (21 with NAs and 29 without NAs) participated in our clinical trial. Participants received total 10 doses of CVP-NASVAC via nose. We investigated the rate of HBsAg reduction/loss, anti-HBs induction including IgA-type by ELISA, and HBcAg-specific CTL by ELISPOT. The data or samples were obtained up to 54 months after the end of treatment. **Results:** At the 18 months after CVP-NASVAC administration, HBsAg was reduced in 64.7% (11/17) patients with NAs and 75.0% (15/20) without NAs, and HBsAg loss was observed in 1/21 with NAs and 3/29 without NAs. Anti-HBs was induced in 14.3% (3/21) with NAs and 42.9% (12/28) without NAs. IgA type anti-HBs titer and the number of HBc-specific interferon γ producing CTL were significantly elevated after CVP-NASVAC treatment in both with and without NAs. Interestingly, significant correlation was observed between the CTL increase and HBsAg reduction in CHB patients with NAs ($p < 0.005$). **Conclusion:** HBcAg-specific CTL induction might be an important immunological mechanism for reducing HBsAg in CHB patients under NAs treatment.

Disclosures: The following people have nothing to disclose: Kana Shiraishi

1473-C | IMPROVEMENT IN NONINVASIVE TESTS (LSM, FIB-4, AND APRI) IS SEEN THROUGH 96 WEEKS OF BULEVIRTIDE MONOTHERAPY IN CHD REGARDLESS OF VIROLOGIC RESPONSE

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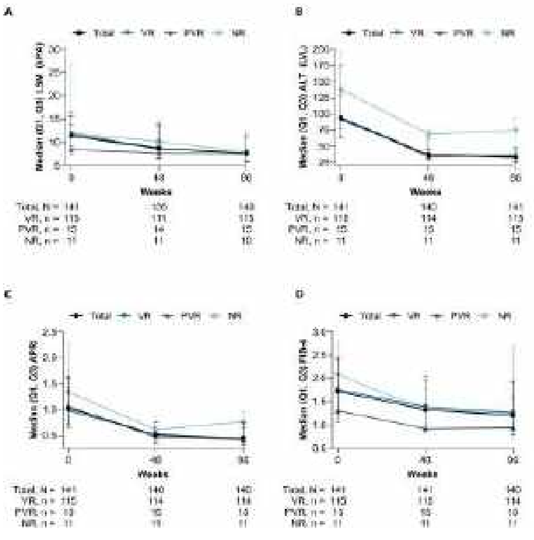
Background: Bulevirtide (BLV) is a novel entry inhibitor that is approved in Europe as therapy for patients with chronic hepatitis D (CHD). The impact of BLV on noninvasive tests (NITs) has not been fully explored. **Methods:** A longitudinal analysis was conducted using pooled data from Phase 2 MYR204 (NCT03852433) and Phase 3 MYR301 (NCT03852719) studies. The change in ALT, FIB-4, APRI, and liver stiffness measurements (LSM) was assessed in CHD patients treated with BLV monotherapy (2 and 10 mg) for 96 weeks (W). The change of NITs across HDV RNA virologic response groups at 96W were also compared:

viral responders (VR, defined as undetectable HDV RNA or **e** 2-$\log_{10}$ IU/mL decline from baseline [BL]), partial VR (PVR, defined as **e** 1-$\log_{10}$ IU/mL but $<$ 2-$\log_{10}$ IU/mL decline from BL), and nonresponders (NR, defined as $<$ 1-$\log_{10}$ IU/mL decline from BL). Results are reported as median (Q1, Q3) unless otherwise stated. **Results:** In total, 149 CHD patients treated with BLV monotherapy (49 BLV 2 mg, 100 BLV 10 mg) were included in this analysis. At BL across the total cohort, the ALT was 93 (64, 136) U/L, gamma-glutamyl transferase was 51 (28, 73) U/L, FIB-4 was 1.7 (1.3, 2.5), APRI score was 1.0 (0.7, 1.6), and LSM was 11.4 (8.8, 15.5) kPa. The mean (SD) HDV RNA and platelet count were 5.2 (1.3) $\log_{10}$ IU/mL and 164 (51.0) 10^9/L. In the total cohort, improvements were seen in ALT and NITs at W96: ALT change from BL, −55 (−97, −25) U/L; W96 ALT, 34 (26, 44) U/L; FIB-4 change from BL, −0.4 (−0.9, −0.1); W96 FIB-4, 1.2 (0.9, 1.9); APRI change from BL, −0.5 (−1.0, −0.2); W96 APRI, 0.5 (0.3, 0.8); LSM change from BL, −3.3 (−6.1, −1.3) kPa; and W96 LSM, 7.7 (5.8, 11.1) kPa. Improvements in ALT and NITs were seen across all viral-response groups including PVR (n = 15) and NR (n = 11) at 96W, with continued declines between 48 and 96W in most cases (Figure 1). Among PVR, changes from BL were: ALT, −57 (−148, −29) U/L; FIB-4, −0.3 (−0.6, 0.2); APRI, −0.6 (−0.9, 0.0); and LSM, −2.5 (−4.3, −1.1) kPa. Among NR, changes from BL were: ALT, −63 (−102, −14) U/L; FIB-4, −0.4 (−1.4, 0.0); APRI, −0.6 (−1.5, 0.0); and LSM, −2.5 (−6.3, −1.7) kPa. **Conclusion:** Treatment of CHD patients with either dosage of BLV monotherapy through 96W resulted in longitudinal improvements in NITs, with greater improvement in the first 48W. These improvements were seen even among those without viral response.

Figure 1. Improvements in ALT, FIB-4, APRI, and LSM Through Week 96 by Viral Response Category
(A) LSM, (B) ALT, (C) APRI, (D) FIB-4
Values expressed in median (Q1, Q3)
ALT, alanine aminotransferase; LSM, liver stiffness measurements; PVR, partial viral responders (defined as ≥1-$\log_{10}$ IU/mL but <2-$\log_{10}$ IU/mL decline from baseline but not undetectable); NR, non-viral responders (NR, defined as <1-$\log_{10}$ IU/mL decline from baseline), VR, viral responders (undetectable HDV RNA and/or ≥2-$\log_{10}$ IU/mL decline from baseline)



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The following people have nothing to disclose: Pavel Bogomolov

1474-C | IN VITRO AND IN VIVO PROFILING OF AN ORALLY BIOAVAILABLE SMALL MOLECULE INHIBITING HEPATITIS B VIRUS BY MIMICKING INTERFERON ALPHA

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Perron, Michael A. Walker, William Delaney, Min Zhong and Ken Zhang, Assembly Biosciences, Inc., South San Francisco, CA

Background: Interferon alpha (IFNα) has immunomodulatory and broad antiviral activities and has been shown to lead to HBV surface antigen (HBsAg) clearance (functional cure) in a subset of patients. However, the poor tolerability of injectable, systemically administered IFNα limits its clinical use. To overcome these limitations, we are optimizing a class of small molecule IFNα receptor (IFNAR) 2 agonists. Here we report the preclinical profiling of selected orally bioavailable small molecules that mimic an IFNα response *in vitro* and *in vivo*. **Methods:** The half-maximal effective concentrations (EC_{50}s) for HBV and HCV inhibition were measured in infected primary human hepatocytes (PHHs) and Huh-7 replicon cells by HBeAg enzyme-linked immunosorbent assay (ELISA) and reporter activity, respectively. Time- and dose-dependent interferon-stimulated gene (ISG) induction in PHHs was assessed by gene expression analysis. *In vitro* cytokine secretion from human peripheral blood mononuclear cells (PBMCs) was assessed by ELISA. The phosphorylation pattern of STATs was evaluated in hepatoma cells by ELISA and Western blot. Compound concentrations and ISG induction in the liver and serum/PBMCs were determined in mouse pharmacokinetic and pharmacodynamic (PK/PD) studies, respectively. **Results:** Novel small molecules were identified with distinct structural elements that inhibited HBV ($EC_{50}=0.8$–11.7 mM) and HCV ($EC_{50}=0.008$–0.2 mM) in a dose-dependent manner. A representative compound induced ISGs in PHHs at 0.1, 1, and 10 mM dose-dependently. Furthermore, at 10 μM compound, the ISG induction strongly correlated with 1000 IU/mL IFNα at 6 h and 24 h post-treatment ($R^{2=}$0.91 and 0.83, respectively). Cytokine secretion and STAT phosphorylation patterns induced by the small molecules also mimicked IFNα treatment in PBMCs and human hepatoma cells. PK/PD studies demonstrated that a representative compound has a liver-to-plasma ratio of approximately 5- to 7-fold at 6 h and 24 h post-dosing in mice treated with 100 mg/kg and efficiently induced ISGs, mimicking the ISG profile induced by 60,000 IU murine IFNα in a dose- and time-dependent manner ($R^{2=}$0.60–0.77 between 0.1–100 mg/kg). **Conclusion:** Novel, orally bioavailable small molecules are able to activate IFN signaling *in vitro* and *in vivo* and inhibit HBV replication in PHHs. Lead optimization is ongoing with the objective of nominating a development candidate for treatment of chronic HBV.

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1475-C | INITIAL EXPLORATION OF HEPATITIS B SURFACE ANTIGEN (HBsAg) BLIPS FOLLOWING BEPIROVIRSEN TREATMENT: A POST HOC ANALYSIS OF THE B-CLEAR STUDY

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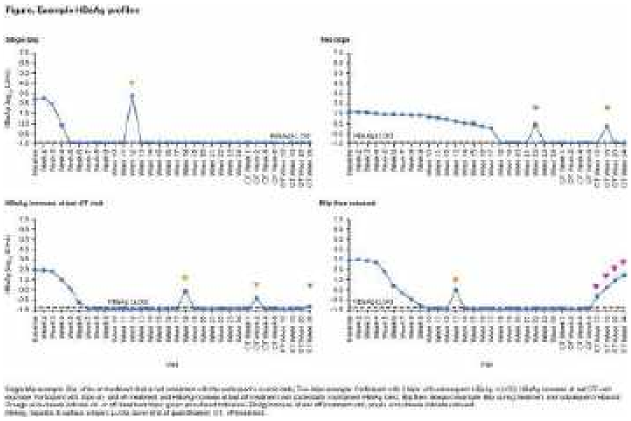
Background: Hepatitis B surface antigen (HBsAg) loss is key to achieving functional cure of chronic hepatitis B virus (HBV) infection. In the B-Clear study, 24-week treatment with 300 mg bepirovirsen (BPV), an antisense oligonucleotide, induced sustained HBsAg and HBV DNA loss in 9–10% of participants (pts) with chronic

HBV infection, with higher response rates in pts with lower HBsAg levels. This analysis examined characteristics of those with HBsAg decline to below the lower limit of quantification (LLOQ; 0.05 IU/mL). **Methods:** B-Clear was a Phase 2b, randomized study in pts with chronic HBV infection on stable nucleos(t)ide analog (NA) therapy (On-NA; N = 227) or not on NA therapy (Not-on-NA; N = 230). Pts received up to 300 mg BPV once weekly for 12 or 24 weeks with/without loading dose. Primary endpoint was the proportion of pts who achieved HBsAg and HBV DNA < LLOQ, sustained for 24 weeks after BPV treatment end in the absence of newly initiated antiviral treatment. A pre-specified modified primary endpoint permitted 'blips', i.e., single-timepoint increases in HBsAg or HBV DNA e LLOQ in the off-treatment period after becoming unquantifiable. This post hoc analysis explored pts who had a blip at any timepoint (on- or off-treatment), categorized as: 1) no blip (no HBsAg increase following HBsAg < LLOQ); 2) reached HBsAg < LLOQ then had e 1 blip but maintained HBsAg < LLOQ at all subsequent timepoints; 3) HBsAg increase at last off-treatment visit (potentially maintained HBsAg loss); 4) blip then sustained HBsAg increase (rebound). Treatment groups were pooled. **Results:** There were 22 pts with no blips (group 1: 12 On-NA, 10 Not-on-NA), 9 pts (group 2: 3 On-NA, 6 Not-on-NA) with e 1 blips and subsequently maintained HBsAg loss, 4 pts (group 3: 2 On-NA, 2 Not-on-NA) with HBsAg increase at the last visit, and 12 pts (group 4: 8 On-NA, 4 Not-on-NA) with blips then a rebound. Example pt profiles are shown in Figure. Numerical differences in pt characteristics between groups were observed but pt numbers were small. **Conclusion:** In this initial exploration, there were comparable number of pts with sustained HBsAg loss versus those with blips; however, low pt numbers limit interpretation of pt characteristics. Pts who had a blip were comparably split between those who rebounded, and those who maintained or potentially maintained HBsAg loss. Further investigation into the durability of effect with respect to blips is needed. Funding: GSK (study 209668)



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No, No; Merck Sharp and Dohme: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Springbank Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AbbVie: Speaking and Teaching, No, No; Dicerna Pharmaceuticals: Speaking and Teaching, No, No; Fujirebio Incorporation: Speaking and Teaching, No, No; Gilead Sciences: Speaking and Teaching, No, No; Roche: Speaking and Teaching, No, No; Sysmex Corporation: Speaking and Teaching, No, No;
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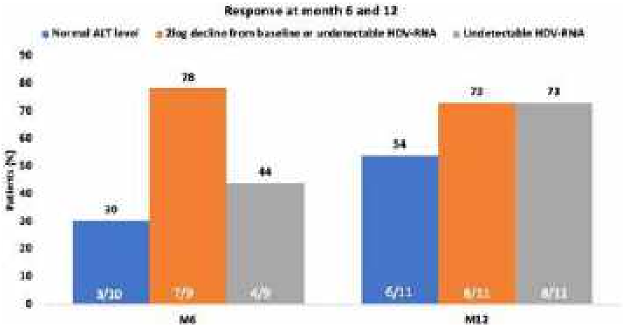
The following people have nothing to disclose: Gheorghe Iulian Diaconescu, Shigetoshi Fujiyama, Ju Hyun Kim, Young Oh Kweon, Nevin Idriz, Rosmawati Mohamed

1476-C | IS IT USEFUL TO ADD PEG-IFN IN POOR RESPONDER PATIENTS TO BULEVIRTIDE 2 MG? RESULTS FROM THE FRENCH MULTICENTER EARLY ACCESS PROGRAM

Victor De Ledinghen[1], Marie-Noelle Hilleret[2], Sophie Métivier[3], Louis D'Alteroche[4], Christiane Stern[5], Xavier Causse[6], Si Nafa Si Ahmed[7], Eric Billaud[8] and Juliette Foucher[1], (1)CHU Bordeaux, Bordeaux, France, (2) CHU Grenoble, (3)Service d'Hepatologie, CHU Rangueil, Université Toulouse 3, (4)CHU Tours, (5) Service d'Hépatologie, Hôpital Beaujon, (6)CHU Orléans, (7)Hopital Saint Joseph, (8)CHU Nantes

Background: Significant HDV RNA decline was observed in HBV/HDV patients who received 48 weeks of Bulevirtide (BLV) in monotherapy or in combination with PEG-interferon α 2a (PEG-IFNα) in the French early access program. However, some patients are poor virological responder. No data are available of adding PEG-IFN in poor responders to 2 mg BLV. The aim of this analysis was to evaluate the efficacy and safety of the adjunction of PEG-IFN in poor responder patients to BLV 2 mg. **Methods:** 11 patients (male 63.7%, mean age 37 y, cirrhosis 27.3%, median HDV-RNA at inclusion (day 0 BLV) 6.81 $\log_{10}$ IU/mL, after a median time of treatment with BLV 2 mg of 6 (extremes:3-12) months, with chronic HBV/HDV infection, with compensated cirrhosis/severe fibrosis or moderate fibrosis with elevated ALT levels, were included in this study. Patients received BLV 2mg qd sc in combination with PEG-IFNα once weekly sc (90 to 180 mg). **Results:** No specific side-effects were reported. At Day 0 of adjunction of PEG-IFN, median HDV RNA was 5.21 $\log_{10}$IU/ml and median ALT level 46 IU/L (4/10 patients had ALT level < 40 IU/L). Median decline of HDV RNA between day 0 BLV and day 0 PEG-IFN was -1.57 $\log_{10}$ IU/ml (extremes: -2.49 - +1.2), 8/11 patients (72.7%) with < 2 $\log_{10}$ decline. Main results (per protocol analysis) are indicated in Table. At M6 and M12, median HDV-RNA was 1.98, and 0 $\log_{10}$ IU/ml. All cirrhotic patients had undetectable HDV-RNA. Only three patients (without cirrhosis) did not have undetectable HDV-RNA after 12 months of BLV + PEG-IFN. Among them, one patient received only 3 months of PEG-IFN. The two other patients had less than 1 $\log_{10}$decline between day 0 BLV and day 0 PEG-IFN. **Conclusion:** In this first real-world cohort of HDV patients, weekly administration of PEG-IFN in poor responder patients to BLV 2 mg was safe and well tolerated. More than 2 out of 3 patients had undetectable HDV-RNA after 12 months of combined therapy. These preliminary results should be confirmed but are an encouraging option for poor responder patients to BLV 2 mg.



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

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The following people have nothing to disclose: Sophie Métivier, Louis D'Alteroche, Christiane Stern, Juliette Foucher

Disclosure information not available at the time of publication: Marie-Noelle Hilleret, Xavier Causse, Si Nafa Si Ahmed, Eric Billaud

1477-C | MATHEMATICAL MODELING OF HDV RNA, ALT AND HBsAg KINETICS SUGGESTS A DUAL MODE OF ACTION OF PEGINTERFERON LAMBDA: THE LIMT-1 STUDY

E. Fabian Cardozo-Ojeda[1,2], Sarah Duehren[1], Scott J. Cotler[1], Saeed S. Hamid[3], Yoav Lurie[4], Edward J. Gane[5], Anat Nevo-Shor[6], David Yardeni[6], Ingrid Choong[7], Jeffrey Glenn[8], Harel Dahari[1] and Ohad Etzion[6], (1)The Program for Experimental and Theoretical Modeling, Division of Hepatology, Department of Medicine, Stritch School of Medicine, Loyola University Chicago, Maywood, Illinois, USA, (2) Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, USA, (3) Aga Khan University Hospital, Karachi, Pakistan, (4) Shaare Zedek, Jerusalem, Israel, (5)Auckland Clinical Studies, (6)Soroka University Medical Center, Beer-Sheba, Israel, (7)Eiger BioPharmaceuticals, Inc., (8) Division of Gastroenterology and Hepatology, Departments of Medicine, Microbiology & Immunology, Stanford School of Medicine, Stanford, California, USA

Background: The recent LIMT-1 study demonstrated the safety and efficacy of Peginterferon Lambda (Lambda) monotherapy for chronic HDV (Hepatology.2023;77(6):2093-2103). Here we sought to predict Lambda mechanisms of action and efficacy using mathematical modeling of measured HDV RNA, ALT and HBsAg kinetics. **Methods:** 33 chronic HDV infected patients participated in the LIMT-1 study of Lambda 120 µg (n = 19) or 180 µg (n = 14), administered once weekly by subcutaneous injection for 48 weeks, with 24 weeks of follow-up. All were on entecavir or tenofovir treatment throughout the study. Samples were measured at baseline at weeks 1, 2 and 4 and every four weeks during and post Lambda therapy. 11 participants were excluded from analysis due to treatment null response (n = 3), HDV below detection at baseline (n = 3), or Lambda discontinuation. We evaluated models with or without proliferation of hepatocytes and Lambda blocks virus production and/or mediates death of HDV-infected cells. **Results:** We identified a mathematical model with hepatocyte proliferation that best describes HDV, ALT and HBsAg kinetics. The model recapitulates the three main HDV kinetic patterns under Lambda: (i) viral suppression, i.e., viral decline below limit of quantification, LOQ (n = 12, Fig. 1a), (ii) viral decline followed by a plateau above LOQ, termed flat-partial response (n = 3, Fig. 1b), and (iii) viral decline followed by a rebound not related to Lambda-dose reduction (n = 7, Fig. 1c). Modeling predicted that in participants with viral suppression Lambda blocks viral production with a median e = 98.6% efficacy (IQR: 81.6%-99.3%). The model reproduced the flat-partial response (Fig. 1b) and rebound (Fig. 1c) kinetic patterns, with a median suboptimal efficacy of e = 68.0% (IQR: 46.8%-92.0%), which was below each patient's critical drug efficacy (e_c) needed to reach viral suppression. Modeling predicted that viral rebound can occur during suboptimal therapy, if the number of hepatocytes susceptible to HDV infection (target cells) increases during therapy. To reproduce the ALT flares (Fig. 1a) the model estimated that Lambda increases the death rate of HDV-infected cells by a median of 1.7-fold (ranging from 1- to 6.7-fold, Fig. 1). Assuming that HBsAg levels were proportional to the sum of the infected target cells, the observed stability of HBsAg was explained by no significant change in the sum of HDV-infected and target cell number that produce HBsAg under Lambda therapy due to hepatocyte homeostasis. **Conclusion:** This study provides, for the first time, a dynamic description of HDV RNA, ALT and HBsAg response under Lambda monotherapy. Modeling suggests that Lambda blocks HDV viral production and mediates an increase in the death of HDV-infected cells that requires further study.

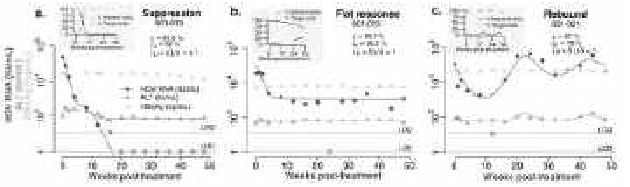

Figure 1. Illustrative examples of best model fits during Lambda therapy. (a) HDV suppressed below the limit of detection, (b) flat-partial response of HDV, and (c) HDV RNA decline followed by a rebound to pre-treatment levels. The gray inset figure on the top-left of each panel describes the model prediction of the percentage of infected and target hepatocytes (solid and dashed lines, respectively). Model predictions are represented by the dark, medium and light gray solid lines. ε describes the Lambda effectiveness in reducing virus production. ε_c, denotes the critical drug efficacy; $\varepsilon > \varepsilon_c$ leads to virus suppression and $\varepsilon < \varepsilon_c$ leads to flat-partial response or rebound. $(j+\delta)/\delta$, represents the fold increase in the death rate of infected cells mediated by Lambda. HDV clearance from blood and HDV-infected hepatocytes basal death rates were fixed to 0.43 day^{-1} and 0.05 day^{-1}, respectively. LOQ: limit of quantification (14 IU/mL) and LOD: limit of detection (1 IU/mL). The model was simultaneously fit with measured HDV, ALT, and HBsAg kinetic data using a nonlinear mixed-effects approach.

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

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The following people have nothing to disclose: Scott J. Cotler, Saeed S. Hamid, Harel Dahari, Ohad Etzion
Disclosure information not available at the time of publication: E. Fabian Cardozo-Ojeda, Sarah Duehren, Yoav Lurie, Anat Nevo-Shor, David Yardeni, Ingrid Choong, Jeffrey Glenn

1478-C | MECHANISTIC PK/PD MODELING AND SIMULATION OF BEPIROVIRSEN, HBsAg, AND ALT AFTER SEQUENTIAL BEPIROVIRSEN-PEGYLATED INTERFERON Α-2a THERAPY TO INFORM PHASE 3 STUDY DESIGN: B-TOGETHER STUDY

Amir Youssef[1], Mohamed Ismail[2], Donald E Mager[2,3], Mindy Magee[1], Susan Dixon[4], Dickens Theodore[5], Melanie Paff[6] and Ahmed Nader[1], (1)Clinical Pharmacology Modeling and Simulation, GSK, Collegeville, PA, USA, (2)Enhanced Pharmacodynamics LLC, Buffalo, NY, USA, (3) Department of Pharmaceutical Sciences, University at Buffalo, SUNY, Buffalo, NY, USA, (4)Development Clinical Sciences Hepatology/GI, GSK, Stevenage, Hertfordshire, UK, (5)GSK, Durham, NC, USA, (6)GSK, Collegeville, PA, USA

Background: Bepirovirsen (BPV; GSK3228836), an antisense oligonucleotide, inhibits all HBV RNAs resulting in reduction of hepatitis B surface antigen (HBsAg) levels. BPV monotherapy (300 mg for 24 weeks [wks]) met its primary endpoint (PE) (HBsAg < LLOQ and HBV DNA < LLOQ) in 9% of participants (pts) in B-Clear who remained on stable nucleos[t]ide (NA) analogs. A pharmacokinetic (PK)/pharmacodynamic (PD) model, previously developed for BPV monotherapy, was adapted to describe the changes in HBsAg after BPV-Pegylated Interferon α-2a (PegIFN) sequential therapy in B-Together. The model simulated HBsAg responses under different study designs, populations, and dose regimens. **Methods:** In B-Together, BPV (300 mg) was administrated weekly for 12 or 24 wks (with loading doses on Days 4 and 11), followed by 24 wks of PegIFN 180 mcg weekly for 24 wks to pts on stable NA therapy. The PE was assessed 24 wks after the end of PegIFN treatment. The effect of PegIFN in preventing relapse in pts who achieved virologic response (VR; HBsAg < LLOQ) at BPV treatment end was added to the model. The probability of a PegIFN effect (being sensitive to PegIFN) was estimated based on observed differences in achieving PE between Phase 2b study 209668 (B-Clear) and sequential BPV-PegIFN Phase 2b study 209348 (B-Together). ALT changes after both BPV and PegIFN were captured in the model. Simulations were conducted to describe response in all pts receiving sequential BPV-PegIFN treatment. **Results:** The model accurately captured the time-course of HBsAg and ALT after sequential BPV-PegIFN treatment; incorporation of B-Together data confirmed previous findings on predictors of response. Only baseline HBsAg was a statistically significant and clinically relevant predictor of response for BPV. Increase of ALT after BPV was described through an indirect mechanism (through reduction in HBsAg) whereas increase in ALT after PegIFN was captured in the model by a direct drug effect. Simulation results for 24- and 12-week arms are presented in the Table. **Conclusion**: The PK/PD model described HBsAg and ALT changes after sequential BPV-PegIFN treatment. Simulation results were generated to predict response rates for different study designs, populations, and dosing regimens. Funding: GSK (study 209348)

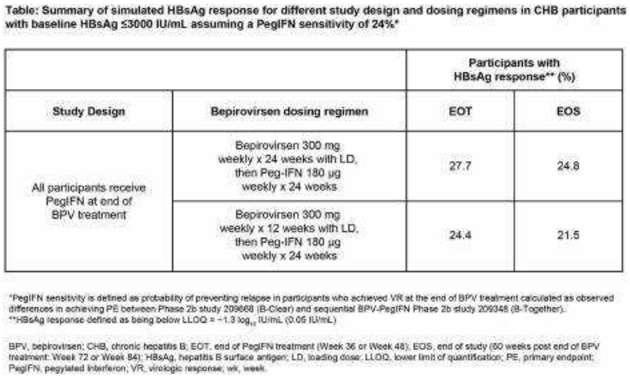
Table: Summary of simulated HBsAg response for different study design and dosing regimens in CHB participants with baseline HBsAg ≤3000 IU/mL assuming a PegIFN sensitivity of 24%*

		Participants with HBsAg response** (%)	
Study Design	**Bepirovirsen dosing regimen**	**EOT**	**EOS**
All participants receive PegIFN at end of BPV treatment	Bepirovirsen 300 mg weekly x 24 weeks with LD, then Peg-IFN 180 µg weekly x 24 weeks	27.7	24.8
	Bepirovirsen 300 mg weekly x 12 weeks with LD, then Peg-IFN 180 µg weekly x 24 weeks	24.4	21.5

*PegIFN sensitivity is defined as probability of preventing relapse in participants who achieved VR at the end of BPV treatment calculated as observed differences in achieving PE between Phase 2b study 209668 (B-Clear) and sequential BPV-PegIFN Phase 2b study 209348 (B-Together).
**HBsAg response defined as being below LLOQ = −1.3 $\log_{10}$ IU/mL (0.05 IU/mL)

BPV, bepirovirsen; CHB, chronic hepatitis B; EOT, end of PegIFN treatment (Week 36 or Week 48); EOS, end of study (60 weeks post end of BPV treatment: Week 72 or Week 84); HBsAg, hepatitis B surface antigen; LD, loading dose; LLOQ, lower limit of quantification; PE, primary endpoint; PegIFN, pegylated interferon; VR, virologic response; wk, week.

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Donald E Mager – Enhanced Pharmacodynamics LLC: Employee, Yes, No; GSK: Consultant, Yes, No;
Mindy Magee – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;
Susan Dixon – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;
Dickens Theodore – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;
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Ahmed Nader – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

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1479-C | PANGENOMIC ANTIVIRAL EFFECT OF REP 2139 IN CRISPR/Cas9 ENGINEERED CELL LINES EXPRESSING HEPATITIS B VIRUS HBsAg

Lena Angelo[1], Matthieu Blanchet[1,2], Andrew Vaillant[2] and Patrick Labonte[1], (1)Inrs-Centre Armand-Frappier Santé Biotechnologie, (2)Replicor Inc.

Background: Hepatitis B virus remains a global health problem with 296 million people living with chronic infection who are at increased risk of developing liver inflammation, cirrhosis and hepatocellular carcinoma. Subviral particles (SVP) are produced in large excess over Dane particles in patients and are the major source of HBsAg. SVPs inhibit /exhaust the immune response to HBV infection. Re-establishment of immune control of HBV (functional cure) requires the clearance of HBsAg from blood of patient. Nucleic acid polymers (NAPs) inhibit the assembly/release of SVP, resulting in rapid clearance of HBsAg from circulation *in vivo* and *in vitro* and in human studies. However, their efficacy has only been demonstrated in limited genotypes in phase IIA clinical trials. HBV exists as nine main genotypes (A to I), and our study assesses the activity of the lead NAP, REP 2139, in the most prevalent genotypes (A, B, C, D, E, G), which account for over 96% of chronic HBV infection. **Methods:** HBsAg ORFs from the previously mentioned genotypes were inserted into the AAVS1 safe-harbor of HepG2 cells using CRISPR/Cas9 knock-in. A cell line producing the D144A vaccine escape mutant was also engineered. The secretion of HBsAg into these new genotype cell lines (GCLs) was confirmed by immunofluorescence and ELISA. The antiviral activity of REP 2139 was then assessed in these GCLs by evaluating HBsAg secretion in the supernatant by ELISA. **Results:** The results show an efficient inhibition of HBsAg secretion in all GCLs. We demonstrate that REP 2139 exerts an antiviral effect in all genotypes and serotypes tested in this study, including in the vaccine escape mutant D144A. EC_{50} for REP 2139 against every genotype assessed in this study was in the nanomolar range, which is in line with previous *in vitro* and clinical studies. **Conclusion:** CRISPR/Cas9 was used to create in vitro HepG2-derivative cell lines expressing HBsAg from various genotypes and serotypes. Our results suggest that REP 2139 has a pangenomic antiviral effect, as well as an antiviral effect for vaccine escape mutants.

Disclosures: Matthieu Blanchet – Replicor Inc.: Employee, Yes, No; Replicor Inc.: Stock – privately held company (individual stocks and stock options), Yes, No;

Andrew Vaillant – Repicor Inc.: Employee, Yes, No; Replicor Inc.: Stock – privately held company (individual stocks and stock options), Yes, No;

The following people have nothing to disclose: Lena Angelo, Patrick Labonte

1480-C | PHARMACOKINETICS AND SAFETY OF VIR-2218 MONOTHERAPY IN ADULT CIRRHOTIC PARTICIPANTS WITH MODERATE HEPATIC IMPAIRMENT

Li Wang, Michael A. Chattergoon, Sophia Elie, Pan Wu, George Hristopoulos, Sneha Gupta and Maribel Reyes, Vir Biotechnology, Inc

Background: VIR-2218 is an investigational, N-acetyl-galactosamine (GalNAc)–conjugated, double-stranded RNA interference (RNAi) therapeutic that targets a region of the hepatitis B virus (HBV) genome that is common to all HBV viral RNA transcripts. VIR-2218 is in clinical development for the treatment of chronic HBV and HDV infection. We have previously demonstrated that VIR-2218 administered every 4 weeks at 200 mg subcutaneously (SC) results in sustained reductions in HBsAg. Here, we report the pharmacokinetics (PK) and safety of VIR-2218 in cirrhotic participants who have hepatic impairment (HI) with Childs-Pugh-Turcotte Class-B (CPT-B) score. **Methods:** VIR-2218-V107 (NCT05484206) is a Phase 1, open-label, single-dose parallel-group study. Adult participants with CPT-B HI and healthy participants (HV) were demographically matched. Participants received a single SC dose of VIR-2218 at 200 mg. Blood samples were collected up to 8 weeks and pooled urine samples were collected over 72 hours post-dose to measure the concentrations of VIR-2218 and its major metabolite, AS(N-1)3'VIR-2218. PK parameters were estimated using non-compartmental analysis in WinNonlin®. Safety and tolerability were monitored throughout the study. **Results:** Eight (8) cirrhotic participants with CPT-B HI and 8 HV were enrolled. The geometric mean ratios (GMR) of C_{max}, AUC_{last} and AUC_{inf} of VIR-2218 in CPT-B participants (test) vs. HV (reference) were 1.7, 2.1 and 1.9, respectively. Similarly, the GMR of C_{max} and AUC_{last} of VIR-2218 major metabolite AS(N-1)3'VIR-2218 in CPT-B participants vs. HV were 2.1 and 2.4, respectively. Accordingly, fraction of VIR-2218 and metabolite excreted in urine were higher in CPT-B participants vs. HV. Two SAEs of thrombocytopenia (Grade 4) in 1 participant were reported and resolved within 7 days with platelet transfusion. They were consistent with underlying cirrhosis and were considered unrelated to VIR-2218. There were no clinical cardiovascular events. **Conclusion:** A single dose of VIR-2218 at 200 mg was generally well tolerated in participants with moderate CPT-B HI. VIR-2218 exposures were higher in CPT-B participants vs HV. However, based on collective PK and safety data, no dose adjustment is warranted for VIR-2218 in CPT-A and CPT-B participants. PK and safety from a single dose of VIR-2218 support continued evaluation of 200 mg VIR-2218 in participants with HBV and HDV infection with up to moderate CPT-B HI.

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Maribel Reyes – Vir Biotechnology, Inc.: Employee, Yes, No; Vir Biotechnology, Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

1481-C | PRECLINICAL CHARACTERIZATION OF THE NOVEL, ORALLY BIOAVAILABLE NTCP INHIBITOR A7387

Ellen Strängberg[1], Britta Bonn[1], Phuong Phan[1], Ivana Uzelac[1], Ingemar Starke[1], Runa Pal[2], Ashwani Gaur[2], Ramesh Kangarajan[2], Shivendra Singh[2], Santosh Kulkarni[2], Paul A. Dawson[3] and Erik Lindström[1], (1) Albireo Pharma, Inc., (2)Syngene International Ltd., (3) Emory University

Background: Na^+-taurocholate co-transporting polypeptide (NTCP) is a hepatocyte sinusoidal membrane bile acid (BA) transporter. In addition to its major role in hepatocellular clearance of BAs, NTCP is used by hepatitis B and D viruses (HBV, HDV) to enter and infect human hepatocytes. We evaluated the effects of A7387 on the inhibition of BA uptake and HBV entry. **Methods:** NTCP and the related BA transporter apical sodium-dependent BA transporter (ASBT) from human were expressed in cell lines. Inhibition by A7387 was studied using [^{3}H]taurocholate as substrate. Cryopreserved human hepatocytes infected with a clinical isolate of HBV were used for infection experiments. Two female non-human primates (NHPs) were dosed with A7387 via oral gavage at dose levels of A7387 ranging between 3−30 mg/kg once daily for 5 days. Total serum, urine, and fecal BAs were analyzed enzymatically and A7387 plasma concentrations were assessed via liquid chromatography−tandem mass spectrometry. The oral pharmacokinetics of A7387 was also studied in mice, rats, and dogs. **Results:** A7387 had half-maximal inhibitory concentration (IC_{50}) values of 3.4 and 193 nmol/L vs human NTCP and ASBT, respectively. A7387 prevented HBV infection of human hepatocytes with an IC_{50} of 13.5 nmol/L without affecting cell viability. In NHPs, plasma exposure of A7387 increased with dose, and serum BAs increased in a dose-dependent manner in response to oral dosing of A7387 on both Day 1 and Day 5. Doses of 10 and 30 mg/kg A7387 evoked increases in serum BAs lasting for at least 8 hours on both Day 1 and Day 5. Serum BAs returned to baseline at 24 hours post-dose in response to 10 mg/kg A7387 while still being elevated in response to 30 mg/kg A7387. Urine excretion of BAs tended to increase in response to A7387 compared with vehicle, while the levels of fecal BAs did not change. Levels of the BA synthesis biomarker 7-alpha-hydroxy-4-cholesten-3-one (C4) did not change in response to A7387 after 5 days of repeated dosing. Good oral bioavailability was demonstrated in the pharmacokinetic studies across all species. **Conclusion:** A7387 is a highly potent, selective, orally available NTCP inhibitor with potential in HBV/HDV infection and cholestatic diseases.

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1482-C | PRECLINICAL RESISTANCE PROFILE AND ANTIVIRAL ACTIVITY OF THE BEST-IN-CLASS CAM-E ALG-001075, THE PARENT COMPOUND OF ALG-000184

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Background: The hepatitis B virus (HBV) capsid assembly process has emerged as a key target for the treatment of chronic hepatitis B (CHB). ALG-000184 is a prodrug of ALG-001075, a novel capsid assembly modulator leading to the formation of empty capsids (CAM-E). ALG-000184 has demonstrated best-in-class reduction of HBV-DNA, HBV-RNA and HBsAg in CHB patients. Here, we provide an update on the preclinical antiviral activity and viral resistance profile of ALG-001075. **Methods:** Antiviral activity on HBV DNA was determined in HepG2.2.15 and HepG2.117 cells using quantitative PCR, with and without 40% human serum. HepG2 cells were transfected with plasmids encoding an overlength HBV genome with amino acid mutations known to confer viral resistance to CAMs and nucleos(t)ide analogs. **Results:** ALG-001075 is a potent inhibiter of HBV DNA production in HepG2.2.15 and HepG2.117 cells with EC_{50}/EC_{90} values of 0.53/1.84 nM and 0.63/3.17 nM respectively. Inclusion of 40% human serum resulted in an average 5-fold shift in antiviral activity. ALG-001075 retains potent antiviral activity against isolates from HBV genotypes A-J. To date, T33N is the only mutation identified that mediates a major loss of activity of ALG-001075 (28-fold compared to wild-type), while T33P and V124G exhibit minor resistance in vitro (6- to 8-fold). F23Y, P25A, L37F, Y38F, I105L, I105T, T109I, F110I, Y118F and T128I did not substantially alter the antiviral activity of ALG-001075 (**d** 3-fold shift). ALG-001075 retained activity against mutations conferring resistance to the nucleos(t)ide analogs tenofovir, entecavir and lamivudine. **Conclusion:** With sub-nanomolar activity in cell-based assays, ALG-001075 is among the most potent CAM-E compounds reported to date and displays a favorable preclinical resistance profile thereby warranting further development as a potential best-in-class CAM-E.

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The following people have nothing to disclose: Tse-I Lin, Julian Symons, Lawrence M. Blatt, Leonid N. Beigelman

Disclosure information not available at the time of publication: Abel Acosta Sanchez, Lars Degrauwe

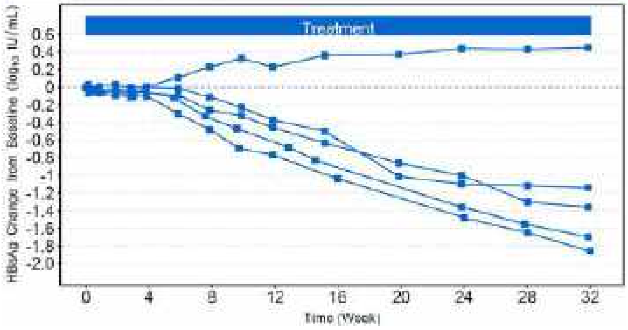
1483-C | PROLONGED (> 24 WEEK) DOSING WITH THE ORAL CAM-E COMPOUND ALG-000184 RESULTS IN MULTI-LOG REDUCTIONS IN HEPATITIS B SURFACE ANTIGEN, HBV DNA, AND HBV RNA LEVELS IN UNTREATED E ANTIGEN POSITIVE SUBJECTS WITH CHRONIC HEPATITIS B

Jinlin Hou[1], Yanhua Ding[2], Xieer Liang[1], Jia Xu[2], Man-Fung Yuen[3], Edward J. Gane[4], Kosh Agarwal[5], Junqi Niu[2], Min Wu[6], Kha Le[6], Christopher Westland[6], Maida Maderazo[6], Genevieve Harrington[6], Lawrence M. Blatt[6], Leonid N. Beigelman[6], Sushmita Chanda[6], Tse-I Lin[6] and Matthew McClure[6], (1)Nanfang Hospital of Southern Medical University, (2)The First Hospital of Jilin University, (3)State Key Laboratory of Liver Research, the University of Hong Kong, Hong Kong SAR, (4)Faculty of Medicine, University of Auckland, (5) Institute of Liver Studies, King's College Hospital, (6) Aligos Therapeutics, Inc.

Background: ALG-000184 is a prodrug of ALG-001075, a novel, pan-genotypic CAM-E (empty capsids) with picomolar potency in vitro. **Methods:** ALG-000184-201 is a multi-part, multi-center, double-blind, randomized, placebo-controlled Phase 1b study (NCT04536337) evaluating the safety, pharmacokinetic, and antiviral activity profiles of oral daily dosing with ALG-000184 in heathy volunteers (**d** 7 d) and subjects with chronic hepatitis B (**d** 48 weeks). These profiles have previously been reported to be favorable for dosing x **d** 24 weeks. Here we report emerging safety and antiviral activity data after dosing > 24 weeks in ongoing Part 4 cohorts, which are evaluating the antiviral activity of 300 mg ALG-000184 in untreated HBeAg+ CHB subjects. Available additional data will be presented at the conference. **Results:** To date, 5 untreated HBeAg+ subjects have been dosed with 300 mg ALG-000184 + Entecavir (ETV) for > 24 weeks, with all 5 subjects dosing for 32 weeks. All subjects are Asian, genotype B/C, and receiving background ETV; they have the following mean baseline levels: ALT 29.2 U/L, HBV DNA 8.1 $\log_{10}$ IU/mL, HBV RNA 6.9 $\log_{10}$ copies/mL, and HBsAg 4.3 $\log_{10}$ IU/mL. Long term

ALG-000184 dosing has been well tolerated with no serious adverse events (AEs) reported and no subjects requiring discontinuation of study drug. All treatment emergent AEs (TEAEs) in these subjects were Grade 1 or 2 in severity except in one subject who experienced a Grade 4 TEAE of ALT elevation, which peaked at 416 U/L (10.1xULN) on Day 171. This event is currently improving despite continued dosing with ALG-000184 and the study's safety oversight committee assessed it as not being related to drug toxicity. No concerning laboratory, ECG, vital sign, or physical examination findings or trends have been identified. Among these 5 subjects, 4 subjects have demonstrated a >1.1 $\log_{10}$ IU/mL decline in HBsAg levels with a maximum HBsAg decline of 1.9 $\log_{10}$ IU/mL (figure 1). All patients had HBV DNA level declines of **e** 5 $\log_{10}$ IU/mL, with 1 suppressed below the limit of detection. All patients had HBV RNA levels declines **e** 2 $\log_{10}$ IU/mL and all were below the limit of detection. **Conclusion:** Dosing of untreated HBeAg+ CHB subjects for >24 weeks with 300 mg ALG-000184 on an ETV background therapy has been well tolerated and resulted in multi-$\log_{10}$ reductions in HBsAg, DNA, and RNA. The associated declines in HBsAg levels suggest a potential secondary mechanism of action of CAM-Es. Dosing of more subjects and for longer durations to better understand the risk-benefit profile of ALG-000184 is currently ongoing.

Figure 1: Individual HBsAg Change from Baseline in 5 Subjects receiving 300 mg ALG-000184 in combination with ETV for 32 weeks



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Man-Fung Yuen – Abbvie: Consultant, No, No; Aligos Therapeutics: Consultant, No, No; Antios Therapeutics: Consultant, No, No; Arbutus Biopharma: Consultant, No, No; Arrowhead Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Arrowhead Pharmaceuticals: Consultant, No, No; Assembly Biosciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Assembly Biosciences: Consultant, No, No; Clear B Therapeutics: Consultant, No, No; Dicerna Pharmaceuticals: Consultant, No, No; Finch Therapeutics: Consultant, No, No; Fujirebio Incorporation: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Fujirebio Incorporation: Consultant, No, No; GSK: Consultant, Yes, No; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences: Consultant, No, No; Immunocore: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Immunocore: Consultant, No, No; Janssen: Consultant, No, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Consultant, No, No; Roche: Speaking and Teaching, No, No; Sysmex Corporation: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck Sharp and Dohme: Consultant, No, No; Merck Sharp and Dohme: Speaking and Teaching, No, No; Vir Biotechnology: Consultant, Yes, No; Bristol Myers Squibb: Consultant, No, No; Springbank Pharmaceuticals: Consultant, No, No; Silverback Therapeutics: Consultant, No, No; Sysmex Corporation: Consultant, No, No; Bristol Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck Sharp and Dohme: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Springbank Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AbbVie: Speaking and Teaching, No, No; Dicerna Pharmaceuticals: Speaking and Teaching, No, No; Fujirebio Incorporation: Speaking and Teaching, No, No; Gilead Sciences: Speaking and Teaching, No, No; Roche: Speaking and Teaching, No, No; Sysmex Corporation: Speaking and Teaching, No, No;

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1484-C | PROTEIN EXPRESSION ASSOCIATED WITH ALANINE AMINOTRANSFERASE INCREASE DURING BEPIROVIRSEN TREATMENT: ANALYSIS OF THE B-CLEAR STUDY

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Background: In the Phase 2b B-Clear study, 300 mg bepirovirsen (BPV; an antisense oligonucleotide) for 24 weeks induced sustained hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA loss in 9–10% of participants (pts) with chronic HBV infection. Transient alanine aminotransferase (ALT) increases occurred in association with HBsAg reduction. This post hoc analysis evaluated protein expression according to HBsAg response and presence of ALT increase in the first 12 weeks of treatment. **Methods:** Pts were categorized based on HBsAg response. For pts achieving HBsAg < lower limit of quantification (LLOQ), number of days to first reach LLOQ was quantized into three categories: early (< 47.3 d), intermediate (47.3–63.5 d), and late (> 63.5 d) responders. Pts not reaching LLOQ were classed as null (< 0.5 log HBsAg reduction) or partial (> 0.5 log reduction but not reaching LLOQ) responders. Presence or absence of ALT increase (ALT > 3 times upper limit of normal [women: > 99 IU/L; men: > 120 IU/L] at any timepoint) among these response categories was examined. Differential protein expression analysis comparing pts with ALT increase vs no increase was performed within each HBsAg response group. Expression of the proteins identified from each grouped comparison was evaluated over time and pathway analysis of differentially expressed proteins was performed. **Results:** Occurrence of an ALT increase was associated with overall response and rate of HBsAg decline, with a significant difference in the frequency of ALT increases in BPV responders vs null responders (~40% vs ~2%). Within BPV responders reaching LLOQ, ALT increases were significantly more likely in early vs late responders. Multiple proteins were consistently upregulated in pts with ALT increase, differentiating them from those with no increase across HBsAg response categories (false discovery rate d 0.1). Pathway analysis of post-baseline upregulated proteins found associations with pathways involved in interferon gamma signaling and drug metabolism, highlighting potential association of immune activation with ALT increase. Some proteins upregulated in pts with ALT increases (e.g., CXCL10, CXCL9, IL10) were also found to be associated with timing of ALT increase in the previous Phase 2a study (NCT02981602). **Conclusion:** This analysis identified a subset of proteins that were correlated with ALT increase during BPV treatment. Funding: GSK (study 209668; NCT04449029)

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Jennifer Singh – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

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Robert Elston – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Jared Delahaye – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

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1485-C | RECOMBINANT MOSAIC HBV CAPSID PARTICLES FOSTER ADAPTIVE IMMUNITY AGAINST THE MOST PREVALENT HBV GENOTYPES BY THERAPEUTIC VACCINATION

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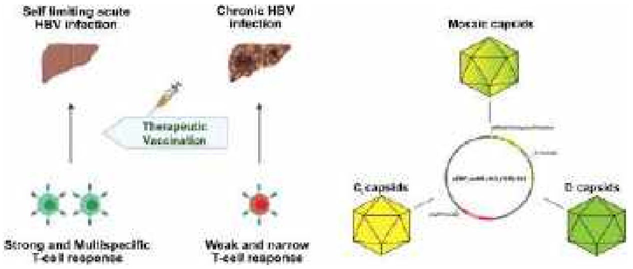
Background: Hepatitis B virus (HBV)-specific B- and T-cell responses are key to cure HBV. TherVacB, a heterologous protein-prime/modified vaccinia virus Ankara (MVA) vector-boost therapeutic vaccine was developed to activate both HBV-specific B- and T-cell responses. For a worldwide use, vaccine components should cover all major circulating HBV genotypes A-E. We have therefore previously developed MVA-HBVac, a boost vector covering B- and T-cell epitopes of all major HBV genotypes. To prime HBV core-specific CD4+ and CD8+ T cells, we designed a novel, recombinant, mosaic HBV capsid particle consisting of genotype C (gtC) and D (gtD) core proteins to activate CD4+ and CD8+ T-cell responses against the different HBV genotypes. **Methods:** Under individual promoters, open reading frames encoding a full-length gtD and a C-terminally truncated gtC HBV core protein were cloned into a single inducible bacterial expression vector. Using Western blotting, the expression of both core proteins in *E. coli* was confirmed. Self-assembling capsid particles were purified using ion-exchange chromatography. Structural characterization of purified mosaic capsid particles was performed with ELISA, native agarose gel electrophoresis, pull-down assay, electron microscopy and NMR spectroscopy. **Results:** Structural analysis confirmed the occurrence of fully functional HBV mosaic capsid particles comprising of core proteins from both the genotypes. Antigen-presenting cells primed with the mosaic capsid particles could *in vitro* activate HBV core-specific TCR-grafted T cells differentially recognizing genotype A, C and/or D epitopes. Immunization of mice with the mosaic capsid particles in a heterologous protein-prime/MVA-boost scheme resulted in strong core-specific antibody and T-cell responses. The assessment of stability of mosaic capsid in various conditions, exhibited their suitability for long-term storage and clinical application. **Conclusion:** We successfully designed and expressed highly functional and immunogenic mosaic capsid particles from a single vector that can now be used in *TherVacB* clinical trials. Our approach provides a promising treatment strategy to cure chronic hepatitis B targeting all major circulating HBV genotypes worldwide.


Self limiting acute HBV infection
Chronic HBV infection
Mosaic capsids
Therapeutic Vaccination
C capsids
D capsids
Strong and Multispecific T-cell response
Weak and narrow T-cell response

Disclosures: The following people have nothing to disclose: Shubhankar Ambike, Julia Sacherl, Alexander Seidler, Arie Geerlof, Anna Kosinska, Sophia Schreiber, Frank Thiele, Tanja Bauer, Michael Nassal, Anne Schütz, Ulrike Protzer

1486-C | RELATIONSHIP BETWEEN ALT NORMALIZATION RATES AND DIFFERENT VIROLOGIC RESPONSE CRITERIA IN CHRONIC HDV PATIENTS TREATED WITH BULEVIRTIDE MONOTHERAPY

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

Research, (9)Institute for Medical Virology, (10)Gilead Sciences, Inc., (11)Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, Reference Center of the Tuscany Region for Chronic Liver Disease and Cancer, University Hospital of Pisa, (12)University Hospital Frankfurt, Department of Medicine

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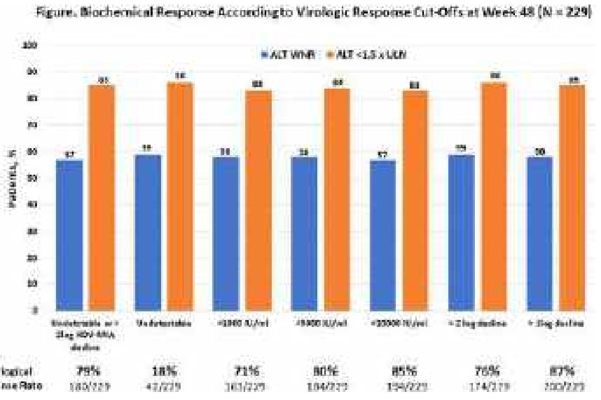
Background: Patients with chronic HDV (CHD) treated with 2 or 10 mg bulevirtide (BLV) showed superior responses at week (W)48 vs controls based on the combined response (CR) endpoint of virologic response (VR; a **e** 2-$\log_{10}$ decline from baseline [BL]) or undetectable HDV RNA and biochemical response (BR; ALT normalization). BR is a widely accepted endpoint for HDV antiviral effect, but optimal VR criteria are unclear. We explored the relationship between BR and VR criteria with BLV treatment. **Methods:** A pooled analysis of W48 BLV (2 and 10 mg) data from 2 Phase 2 and 1 Phase 3 study was performed. Rates of VR, VR +BR (ALT **d** upper limit of normal [ULN]), and VR+partial BR (ALT **d** 1.5×ULN) were determined using HDV RNA cutoffs for VR and the recommended VR definition. Subanalyses were performed to identify predictors of no BR in those with viral control at W48. **Results:** Included were 229 CHD patients: 64 on BLV 2 mg, 165 on 10 mg; 64% were male, 86% White, and 40% had cirrhosis. At BL, mean (SD) age and HDV RNA were 41 (8) y and 5.2 (1.4) $\log_{10}$ IU/mL. Median (Q1, Q3) ALT and liver stiffness were 84 (61, 127) U/L and 11.8 (8.7, 16.2) kPa; 25% had ALT **d** 1.5×ULN. At W48, VR ranged from 18% to 87% (Figure); 54% (123) achieved BR; 79% (180) met the standard VR definition, representing 85% (105/123) of BRs. Achieving **e** 1-$\log_{10}$ decline in HDV RNA was the most sensitive predictor of BR, representing 94% (116/123) of BRs. CR:VR ratios were consistent across VR cutoffs. Subgroup analysis showed 95/163 (58%) achieved HDV RNA < 1000 IU/mL at W48 and achieved BR. BRs were less likely to have cirrhosis but were otherwise comparable to non-BRs at BL. A similar mean change in HDV RNA level was seen in BRs and non-BRs at W48. Using HDV RNA < 1000 IU/mL at W48 (with exclusion of HBV DNA **e** LLOQ, normal ALT, or HDV RNA < 1000 IU/mL at BL), 30 patients had BR, and 19 did not. Assessment of non-BRs showed ALT improvements following control of HDV viremia in all but 3 patients; 16 non-BRs had partial BR at W48. Likely etiology for the lack of BR: cirrhosis (n = 7), nonalcoholic fatty liver disease (n = 8), and HBV reactivation (n = 1). **Conclusion:** Using a less stringent cutoff than the standard definition captures additional cases of BR/partial BR. **e** 1-$\log_{10}$ decline in HDV RNA was sufficient to predict BR in 94% of patients. Conversely, for those achieving HDV RNA < 1000 IU/mL, most had ALT normalization; in those without BR, other etiologies could usually be identified, although histologic evaluation should be considered.



Disclosures: Pietro Lampertico – MYR GmbH: Speaking and Teaching, No, No; Spring Bank Pharmaceuticals: Speaking and Teaching, No, No; Janssen: Speaking and Teaching, No, No; Alnylam: Speaking and Teaching, No, No; Arrowhead: Speaking and Teaching, No, No; MSD: Speaking and Teaching, No, No; AbbVie: Speaking and Teaching, No, No; GSK: Speaking and Teaching, No, No; Gilead Sciences, Inc.: Speaking and Teaching, No, No; Roche: Speaking and Teaching, No, No; BMS: Speaking and Teaching, No, No; Eiger: Speaking and Teaching, No, No; Antios: Speaking and Teaching, No, No; Aligos: Speaking and Teaching, No, No;

Soo Aleman – Gilead Sciences, Inc.: Speaking and Teaching, Yes, No; Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; AbbVie: Speaking and Teaching, No, No; AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; MSD and Biogen: Speaking and Teaching, No, No;

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Heiner Wedemeyer – Gilead Sciences, Inc.: Consultant, Yes, No; Gilead Sciences, Inc.: Speaking and Teaching, Yes, No; Roche: Consultant, No, No; Abbott: Consultant, No, No; Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; BMS: Consultant, No, No; AbbVie: Consultant, No, No; Boehringer Ingelheim: Consultant, No, No; Eiger: Consultant, No, No; Janssen: Consultant, No, No; MSD: Consultant, No, No; MYR GmbH: Consultant, No, No; Novartis: Consultant, No, No; Novira: Consultant, No, No; Siemens: Consultant, No, No; Transgene: Consultant, No, No; Abbott: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol-Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Novartis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Transgene: Consultant, No, No;
The following people have nothing to disclose: Pavel Bogomolov, Sandra Ciesek, Annemarie Berger, Yang Liu

1487-C | SAG-COMP, A NOVEL RNA DESTABILIZER, SPECIFICALLY DESTABILIZES HBV-RNA AND EXHIBITS POTENT ANTI-HBV ACTIVITY AND SAFETY.

Takehisa Watanabe[1], Sanae Hayashi[1], Yan Zhaoyu[1], Katsuya Nagaoka[2] and Yasuhito Tanaka[3], (1) Kumamoto University, (2)Faculty of Life Sciences, Kumamoto University, (3)Kumamoto University Hospital, Kumamoto, Japan

Background: Nucleic acid analogues (NAs), currently used as approved drugs for HBV treatment, are excellent agents with potent activity against HBV-DNA but poor efficacy against HBs antigen (HBsAg). In addition, the therapeutic efficacy and tolerability of peginterferon are unsatisfactory. Therefore, this study aims to develop a novel drug with a novel mode of action (MoA) against HBV and good tolerability. **Methods:** Drug screening from 30,000 library compounds using HepG2.2.15 cells and HBV-infected PXB cells was performed to optimize the hits that reduced the amount of HBsAg in the culture supernatant, especially those with potent anti-HBV activity, to obtain SAG compounds (SAG-comp; IC50 = 1.4 nM). The MoA of SAG was evaluated by Northern blotting, BRIC assay, NRO assay, and poly(A) assay. *In vivo* efficacy and safety were evaluated in animal models. **Results:** SAG-comp treatment shortened polyA and significantly destabilized pgRNA and PreS/S mRNA in HepG2.2.15 cells, but did not affect GAPDH mRNA, suggesting that destabilization may have occurred specifically for HBV-RNA. SAG-comp did not suppress transcription. Knockdown of PAPD5 with siRNA attenuated the effect of SAG-comp, suggesting that PAPD5 may be involved in MoA of SAG-comp. Knockdown of ELAVL1, an RNA-binding protein, decreased HBV-RNA, however, double knockdown of PAPD5 and ELAVL1 attenuated the siELAVL1-induced decrease in HBsAg, suggesting that PAPD5 may be directly and/or indirectly involved in the effect of ELAVL1. The efficacy of SAG-comp alone or in combination with NAs when administered orally was evaluated in human liver chimeric mice. The results showed that SAG-comp alone reduced HBsAg (minimum effective dose; 6 mg/kg/day) and in combination

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

with NAs markedly reduced both serum HBsAg and HBV-DNA. Furthermore, the safety examination in mice and monkeys showed that the SAG compound had no apparent toxicity. **Conclusion:** The SAG-comp, a novel anti-HBV therapeutic agent, is an orally available and well-tolerated drug that potently suppresses HBsAg. It can destabilize HBV-RNA and may induce functional cure in combination therapy with NA.

Disclosures: Yasuhito Tanaka – AbbVie: Speaking and Teaching, No, No; Gilead: Speaking and Teaching, No, No; AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Sysmex: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Fujirebio: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Takehisa Watanabe, Sanae Hayashi, Yan Zhaoyu, Katsuya Nagaoka

1488-C | SCREENING OF LOW-MOLECULAR COMPOUNDS THAT INHIBIT BINDING OF ENVELOPE AND CAPSID OF HEPATITIS B VIRUS

Kosuke Sato[1], Jun Inoue[1], Masashi Ninomiya[2], Akitoshi Sano[1], Mio Tsuruoka[2], Satoko Sawahashi[1] and Atsushi Masamune[2], (1)Tohoku University Hospital, (2)Tohoku University Graduate School of Medicine

Background: An unmet need in patients with chronic hepatitis B virus (HBV) infection is for treatment that enables efficient viral elimination, which requires the development of therapies with novel mechanisms of action. HBV replicates in infected hepatocytes, and binding of PreS1/S2 on the N-terminus of large HBs (LHBs) to the HBc protein-forming nucleocapsid is thought to be necessary for the HBV envelope formation, and an inhibition of this binding may be a target for anti-HBV drugs. In this study, we aimed to identify compounds with the above binding inhibition effects that could be used as therapeutic agents. **Methods:** A high-throughput screening method that measures the binding of LHBs and HBc was established using the NanoBRET system (Promega), which measures the fluorescent signal generated when the two proteins are in close proximity. Using HepG2 cells, we examined where specific proteins are tagged to optimize the NanoBRET assay. Next, we screened low-molecular compounds from our library that inhibit the binding of LHBs to HBc using the high throughput screening method as the 1st screening. The hit compounds were added to HepG2.2.15.7 cells, which are HBV-expressing cells, and HBV DNA levels in the culture supernatant after immunoprecipitation with anti-HBs antibody were measured by RT-PCR and HBsAg by CLIA as the 2nd screening. In addition, we tested the dose-dependent anti-HBV effects of compounds (1, 3, 10, 30 and 100 μM) that reduced HBV DNA levels in the above experiments. **Results:** The combination that resulted in the highest fluorescence signal intensity in BRET was when the NanoLuc was tagged to the N-terminus of the LHBs protein and the HaloTag was tagged to the N-terminus of the HBc protein. After the 1st screening, 33 of the 3200 compounds (10 μM) reduced the BRET signal to less than 60% of the positive control. All of them maintained cell viability of more than 80% and were considered to have low cytotoxicity. In the 2nd screening, 5 of these hit compounds (compound A-E) reduced HBV DNA compared to the positive control. When we tested the hit compounds at different concentrations that maintained cell viability, 30 μM compound A inhibited HBV DNA to 40.4% of control, 100 μM compound B inhibited to 29.6%, 10 μM compound C inhibited to 32.5% and 3 μM compound D inhibited to 72.5%. **Conclusion:** We have identified lead compounds that might inhibit the binding of LHBs and HBc. Further studies are required for clinical application.

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The following people have nothing to disclose: Kosuke Sato, Masashi Ninomiya, Akitoshi Sano, Mio Tsuruoka, Satoko Sawahashi, Atsushi Masamune

1489-C | THE ROLE OF NUCLEOPORIN 50 IN HEPATITIS B VIRUS REPLICATION

Wei-LUN Tsai[1], Wei-Chih Sun[1], Tsung Hsien Chang[2] and Chia-Ming Lu[1], (1)Kaohsiung Veterans General Hospital, (2)National Defense Medical Center, Taipei, Taiwan

Background: There remained no effective therapy to cure HBV. Nuclear transport is essential for the replication of many viruses in their life cycles. But the role of nuclear transport in HBV replication remained unclear. The aim of the study is to investigate the influence of Nucleoporin (Nup) 50 on HBV replication. **Methods:** The HBV infected HepG2-hNTCP-C4 cells will be used in the experiments. Short hairpin RNA (shRNA) or siRNA mediated knock-down of Nup50 will be done. Quantification of supernatant HBsAg and HBV DNA and intracellular cccDNA, pgRNA will be performed. Immunofluorescence assay (IFA) will be conducted. **Results:** We screened many molecules associated with nuclear transport in hepatocytes and investigated their impacts on HBV replication. We found that shRNA against Nup50 reduced supernatant HBsAg and HBV DNA and cellular cccDNA and pgRNA with good knockdown efficiency and similar cell viability compared with negative control in HBV infected HepG2-hNTCP-C4 cells. siRNA mediated knock-down against Nup50 also decreased supernatant HBsAg and HBV DNA secretion and cellular cccDNA in HBV infected HepG2-hNTCP-C4 cells with good knock-down efficiency of Nup50 and similar cell viability compared with negative control. IFA also found that HBV core Ag was decreased in the nucleus in HBV infected HepG2-hNTCP-C4 cells after treatment with siRNA against Nup50. **Conclusion:** Inhibition of Nup50 significantly reduced HBV replication in HBV infected HepG2-hNTCP-C4 cells. We plan to further investigate the molecular mechanism of Nup50 and HBV replication. Our data is promising and Nup50 may be a new therapeutic target for future anti-HBV treatment.

Disclosures: The following people have nothing to disclose: Wei-LUN Tsai, Wei-Chih Sun, Tsung Hsien Chang, Chia-Ming Lu

1490-C | TREATMENT EMERGENT BEPIROVIRSEN BINDING SITE NUCLEOTIDE POLYMORPHISMS IN PHASE 2b B-CLEAR STUDY

Jerome Bouquet[1], Robert Elston[2], Phil Yates[2], Shihyun You[3], Ji Won Cremer[4], Geoff Quinn[2], Fiona Campbell[2], Melanie Paff[3] and Dickens Theodore[4], (1)GSK, South San Francisco, CA, USA, (2)GSK, Stevenage, Hertfordshire, UK, (3)GSK, Collegeville, PA, USA, (4) GSK, Durham, NC, USA

Background: Bepirovirsen (BPV; GSK3228836) is an antisense oligonucleotide that targets a conserved 20-nucleotide sequence within HBV pregenomic RNA and mRNAs. B-Clear is a Phase 2b study (NCT04449029) assessing the efficacy and safety of 12 or 24 weeks (wks) of BPV treatment (tmt) in participants (pts) with chronic hepatitis B (CHB). This analysis assessed the association of BPV binding site single nucleotide polymorphism (SNP) detected in post-baseline samples and the impact on end of tmt (EOT) and end of study (EOS) hepatitis B surface antigen (HBsAg) serum level reduction. **Methods:** Multicenter, randomized, partial-blind study in pts with CHB who were either receiving concomitant stable nucleos(t)ide analogue therapy (On-NA) or were not receiving NA (Not-on-NA). Pts were randomized (3:3:3:1) to receive BPV 300 mg weekly either for 24 weeks (Arm 1); for 12 wks then 150 mg for 12 wks (Arm 2); for 12 wks then placebo (PBO) for 12 wks (Arm 3); or PBO for 12 wks then BPV 300 mg for 12 wks (Arm 4). Next-generation sequencing of HBV DNA or RNA was used. A SNP was reported if the frequency was **e** 5% compared to wild type. A SNP was considered tmt-emergent if it was reported at any post-baseline visit but not at baseline. This post-hoc analysis explored the relationship between resistance mutation and response in pts with non-response (NR; < 1 log decline), partial response (PR ; > 1 log decline, did not reach LLOQ) or breakthrough/relapse (detected after reaching LLOQ on-/off-tmt) for HBsAg or HBV DNA. **Results:** Post-baseline sequence information was available for 49/226 (22%) On-NA pts and 137/229 (60%) Not-on-NA pts. BPV binding site SNPs were detected in 16/186 (8.6%) pts. Three tmt-emergent SNPs were in On-NA pts and 5 were detected in Not-on-NA pts, across all tmt arms. The most common tmt-emergent SNP was C9A (n = 4/8, 50%). Tmt-emergent SNPs occurred in 4 NR and 4 PR, but were not detected in pts with breakthrough/relapse. **Conclusion:** Tmt-emergent SNPs within the BPV binding site were detected at similar frequency in Not-on-NA vs On-NA, were infrequent across tmt arms, and observed in NR and PR only. The % SNP were low and did not exceed 34%. In vitro fitness and drug susceptibility evaluation of tmt-emergent SNPs are needed to better understand potential resistance. Larger studies are also needed to confirm these findings. Funding: GSK (study 209668)

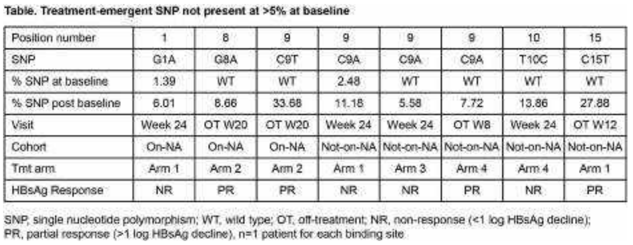

Table. Treatment-emergent SNP not present at >5% at baseline

Position number	1	8	9	9	9	9	10	15
SNP	G1A	G8A	C9T	C9A	C9A	C9A	T10C	C15T
% SNP at baseline	1.39	WT	WT	2.48	WT	WT	WT	WT
% SNP post baseline	6.01	8.66	33.68	11.18	5.58	7.72	13.86	27.88
Visit	Week 24	OT W20	OT W20	Week 24	Week 24	OT W8	Week 24	OT W12
Cohort	On-NA	On-NA	On-NA	Not-on-NA	Not-on-NA	Not-on-NA	Not-on-NA	Not-on-NA
Tmt arm	Arm 1	Arm 2	Arm 2	Arm 1	Arm 3	Arm 4	Arm 4	Arm 1
HBsAg Response	NR	PR	PR	NR	NR	PR	NR	PR

SNP, single nucleotide polymorphism; WT, wild type; OT, off-treatment; NR, non-response (<1 log HBsAg decline); PR, partial response (>1 log HBsAg decline), n=1 patient for each binding site

Disclosures: Jerome Bouquet – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Robert Elston – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

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Dickens Theodore – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/ index funds or pension plans), Yes, No;

1491-C | UNDERSTANDING THE INTERPLAY BETWEEN HDV RNA, HBV DNA AND HBsAg DURING LONAFARNIB-BASED THERAPY VIA MATHEMATICAL MODELING: THE LOWR HDV-1 STUDY

Adquate Mhlanga[1], Rami Zakh[2,3], Sarah Duehren[1], Alexander Churkin[3], Vladimir Reinharz[4], Danny Barash[2], Jeffrey Glenn[5], Ohad Etzion[6], Scott J. Cotler[7], Cihan Yurdaydin[8] and Harel Dahari[1], (1)The Program for Experimental and Theoretical Modeling, Division of Hepatology, Department of Medicine, Stritch School of Medicine, Loyola University Chicago, Maywood, Illinois, USA, (2)Department of Computer Science, Ben-Gurion University, Beer-Sheva, Israel, (3)Department of Software Engineering, Sami Shamoon College of Engineering, Beer-Sheva, Israel, (4)Department of Computer Science, Universit´e Du Qu´Ebec ´a Montr ´Eal, Montr´Eal, Canada, (5)Division of Gastroenterology and Hepatology, Departments of Medicine, Microbiology & Immunology, Stanford School of Medicine, Stanford, California, USA, (6)Translational Hepatology Section, Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, (7)Loyola University Chicago, (8)Department of Gastroenterology and Hepatology, Koç University Medical School,

Background: The frequent samples obtained in the LOWR HDV-1 study (Hepatology.2018;67(4):1224-1236) provide a unique opportunity to analyze and mathematically model the interplay among HDV RNA, HBV DNA, and HBsAg during lonafarnib (LNF)-based therapy. **Methods:** Fifteen patients (n = 3 per group) received LNF-based therapy (i) LNF 200mg twice daily (BID) for 12 weeks, (ii) LNF 300mg BID for 12 weeks; (iii) LNF 100mg thrice daily for 5 weeks; (iv) LNF 100mg BID + ritonavir (RTV) 100mg once daily for 8 weeks; or (v) LNF 100mg BID + pegIFNα 180g once weekly for 8 weeks. Kinetic data were measured on days 0, 1, 2, 3, 7, 14 and 28 and then every 4 weeks during treatment. Modeling was performed using a recently developed HDV/HBV mathematical model (Mathematics. 2022;10(20):3917) that was extended herein to include HBsAg kinetics. **Results:** Median baseline HDV RNA, HBV DNA, and HBsAg were 6.53 log IU/mL [interquartile, IQR:1.96], 2.67 log IU/mL [IQR:1.69] and 3.90 log IU/mL [IQR:0.42], respectively. After a delay of 0 to 2 days, all patients experienced a rapid 1st HDV decline phase (median slope of 0.14 log/day [IQR:0.06]), followed by a viral plateau (flat-partial response, FPR, n = 8; Fig.1A), a 2nd slower decline (0.04 log/day [IQR:0.02]) phase (biphasic, BP; n = 6;Fig.1B and C), or viral rebound (n = 1, not shown). LNF combination therapy with RTV or pegIFNα was associated with a BP HDV decline. LNF monotherapy was associated with FPR (n = 7) that was followed by a rebound in 4/7. In contrast, none of the patients who received combination therapy experienced HDV rebound. In all dosing groups except the pegIFNα group, at least one patient experienced an HBV DNA increase (Fig.1A and B). HBsAg levels did not change throughout treatment (Fig.1). The extended HBV/HDV model reproduced the observed kinetics in all patients (Fig.1). Modeling indicated that the 1st HDV decline phase represents the HDV half-life (median 1.3 d [IQR:0.42]) and the efficacy of treatment in blocking HDV production (median 97% [range: 67% - 99%]), which was similar under all treatments. The 2nd phase of HDV decline in BP patients was represented in the model by an additional (time-dependent) efficacy increase in blocking HDV production with rate reaching a maximal efficacy of 99.98% (range:97.44%-99.995%). The increase in HBV DNA was explained by ~2-fold increase in HBV production rate corresponding to the HDV decline. The stability of HBsAg suggests no change in HBsAg-producing cell number under all treatments. **Conclusion:** The similar antiviral response observed with LNF monotherapy and LNF with RTV or pegIFNα indicates that combination therapies do not increase treatment efficacy in blocking HDV production during the initial 1st phase decline. However, LNF with RTV or pegIFNα was associated with a BP response and lack of HDV rebound, which can be explained by LNF combination therapy augmenting HDV blocking production efficacy in a time dependent manner.

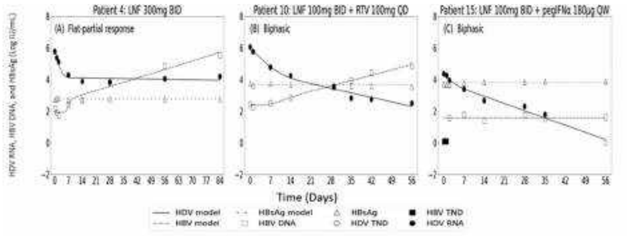

Figure 1: Representative kinetic patterns and mathematical modeling curves. (A) HDV flat-partial response, **(B)** biphasic HDV decline with HBV DNA increase, **(C)** biphasic HDV decline with no change in HBV DNA. TND, target not detected.

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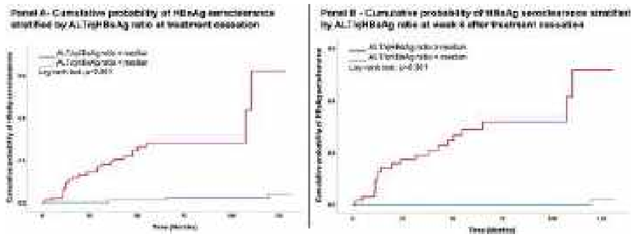
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Duehren, Alexander Churkin, Vladimir Reinharz, Danny Barash, Jeffrey Glenn, Cihan Yurdaydin

1492-C | ALANINE AMINOTRANSFERASE TO QUANTITATIVE HBsAg RATIO INDEPENDENTLY PREDICTS LONG-TERM HBsAg SEROCLEARANCE AFTER ENTECAVIR CESSATION IN CHINESE HEPATITIS B PATIENTS

Ryan Hin-Man Leung[1], Rex Wan-Hin Hui[1], Lung Yi Mak[1,2], Kevin Sze Hang Liu[1], Danny Ka-Ho Wong[1,2], James Fung[1,2], Wai-Kay Seto[2,3,4] and Man-Fung Yuen[2,5], (1)Department of Medicine, School of Clinical Medicine, the University of Hong Kong, Hong Kong SAR, (2)State Key Laboratory of Liver Research, the University of Hong Kong, Hong Kong SAR, (3) Department of Medicine, School of Clinical Medicine, the University of Hong Kong, (4)Department of Medicine, the University of Hong Kong-Shenzhen Hospital, Shenzhen, China, (5)Department of Medicine, Queen Mary Hospital, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, Hong Kong, China

Background: Nucleos(t)ide analogue cessation in chronic hepatitis B (CHB) may induce hepatitis B surface antigen (HBsAg) seroclearance. Good predictors at end-of-treatment (EOT) to predict long-term HBsAg seroclearance are needed. **Methods:** This study followed up Chinese CHB patients from two studies of entecavir cessation from Queen Mary Hospital, Hong Kong. The first study ($n = 80$) did not have inclusion criteria for quantitative HBsAg (qHBsAg), and the second ($n = 114$) recruited patients with qHBsAg < 200 IU/ml. All patients were non-cirrhotic, hepatitis B e-antigen negative, with undetectable HBV DNA (< 20 IU/ml) at EOT. They had close monitoring for 48 weeks with regular HBV DNA, qHBsAg and alanine aminotransferase (ALT) measurements, and were resumed on entecavir if HBV DNA > 2000 IU/ml. After 48 weeks, the patients were reviewed every 6 months, regardless of whether entecavir was resumed. **Results:** 194 patients (63.4% male, median age 55.6, on entecavir for a median of 47.2 mo) were recruited. The median (interquartile range) ALT and qHBsAg at EOT were 23.0 (18.0-31.0) U/L and 104.5 (30.8-616.0) IU/ml respectively. 139 (71.6%) patients had EOT qHBsAg < 500 IU/ml. 151 (77.8%) patients developed HBV DNA > 2000 IU/ml and were resumed on entecavir by week 48. After follow up for 70.7 (51.0-118.2) months, 28 (14.4%) patients had HBsAg seroclearance at 29.3 (12.3-47.7) months after EOT. EOT qHBsAg predicted HBsAg seroclearance in univariate analysis (HR 0.993 [95%CI 0.989-0.998], $p = 0.007$), and this association trended towards significance in multivariate analysis (HR 0.997 [95%CI 0.993-1.000], $p = 0.075$), possibly due to the low and narrow EOT qHBsAg range limiting statistical power. EOT ALT (HR 1.029 [95% CI 1.000-1.059], $p = 0.049$) and not resuming entecavir (HR 5.525 [95% CI 2.283-13.333], $p < 0.001$) were predictors of HBsAg seroclearance in multivariate analysis. The ratio of ALT/qHBsAg (conceptually viewed as the intensity of immune-mediated response per IU/mL of HBsAg) at EOT and week 6 after EOT independently predicted HBsAg seroclearance (Figure 1A-1B; EOT: HR 1.007 [95%CI 1.001-1.012], $p = 0.018$; Week 6: HR 1.033 [95%CI 1.015-1.052], $p < 0.001$), regardless of whether entecavir was later resumed. The ALT/qHBsAg ratio at EOT and week 6 achieved area-under-curve of 0.800 (95%CI 0.736-0.854) and 0.879 (95%CI 0.812-0.928) in predicting HBsAg seroclearance respectively. **Conclusion:** While the utility of ALT/qHBsAg ratio in predicting long-term HBsAg seroclearance needs further validation, it may be particularly useful in patients who are more likely to require early resumption of antivirals after treatment cessation.



Disclosures: Wai-Kay Seto – Mylan: Speaking and Teaching, No, No; AstraZeneca: Speaking and Teaching, No, No; Abbott: Advisor, No, No; Gilead Sciences, Inc.: Advisor, No, No; Gilead Sciences, Inc.: Speaking and Teaching, No, No; Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; AbbVie: Speaking and Teaching, No, No; AbbVie: Advisor, No, No;

Man-Fung Yuen – Abbvie: Consultant, No, No; Aligos Therapeutics: Consultant, No, No; Antios Therapeutics: Consultant, No, No; Arbutus Biopharma: Consultant, No, No; Arrowhead Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Arrowhead Pharmaceuticals: Consultant, No, No; Assembly Biosciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Assembly

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The following people have nothing to disclose: Rex Wan-Hin Hui, Lung Yi Mak

Disclosure information not available at the time of publication: Ryan Hin-Man Leung, Kevin Sze Hang Liu, Danny Ka-Ho Wong, James Fung

1493-C | ANTIVIRAL THERAPY REDUCES HEPATOCELLULAR CARCINOMA BY AMELIORATING ER STRESS, IMPROVING MITOCHONDRIAL DYSFUNCTION AND RESTORING AUTOPHAGY ACTIVITY IN A HYBRID HBV-ASSOCIATED HCC MOUSE MODEL

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Background: The role of hepatis B virus (HBV) in metabolic dysfunction and their interaction on hepatocellular carcinoma (HCC) development are unclear. Nucleos(t)ide analogues (NUCs) treatment reduces HCC incidence. The indication of antiviral treatment in HBV carriers with normal or minimally elevated ALT levels remains debated. MicroRNA-122 (miR-122) regulating fatty acid and cholesterol metabolism, is shown downregulated as hepatitis and HCC progressed. miR-122 as a tumor suppressor and its reciprocal inhibition with HBV highlight its role in HCC development. **Methods:** We generated a mouse model with a single copy of *Mir-122* by hybridizing an HBV transgenic mouse with a homozygous *Mir-122* knockout mouse. The hybrid mouse strain had 89% HCC incidence. The hybrid mice had been characterized by various experiments before and after antiviral therapy. Short-term NUCs treatments were to compare the withdrawal virological relapses between tenofovir disoproxil fumarate (TDF) and entecavir (ETV). And long-term therapies were to compare the reduction of HCC incidence. **Results:** The model exhibited early-onset hepatic steatosis, progressive liver fibrosis, and impaired late-phase autophagy without ALT elevation until HCC development. Metabolomics and microarray analysis identified impaired lipid metabolism, inflammation, and genomic instability, as early as 4-8 months. A combination of the Warburg effect, reduced TCA cycle flux, energy deficiency, and impaired free radical scavenging resulted in liver injury and HCC development. Hybrid mice demonstrated faster virological relapse (VR) one month after cessation of TDF

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

compared to that in ETV. Trace amount of residual HBV replication intermediates in the liver tissues of the TDF group, but not in the ETV groups. Longterm antiviral therapy reduced HCC incidence by 30-35% by improving endoplasmic reticulum stress, enhancing lysosomal degradation of P62 of autophagy, and inhibiting CHOP-mediated apoptosis. There was no significant difference in the reduction of HCC between the two treatment groups, but both groups had significantly lower HCC incidences than that that in the control group. **Conclusion:** This study highlights a novel mechanism of liver injury caused by HBV-induced mitochondrial dysfunction and autophagy hijacking, leading to metabolic dysregulation, prolonged ER stress, and cell death. It provides mechanistic explanation and therapeutic rationale for HBV carriers with normal or minimally elevated ALT levels.

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Disclosure information not available at the time of publication: Yu-Wei Chiou, Chin-Wei Lin

1494-C | CHARACTERISTICS OF GUT MICROBIOTA ASSOCIATED WITH FUNCTIONAL CURE IN CHRONIC HEPATITIS B PATIENTS WITH HBEAG-NEGATIVE; POSSIBLE INHIBITION OF HEPATITIS B VIRUS BY BUTYRATE-PRODUCING BACTERIA

Takashi Honda[1], Asako Murayama[2], Yosuke Inukai[1], Hisanori Muto[1], Shinya Yokoyama[1], Kenta Yamamoto[1], Takanori Ito[1], Norihiro Imai[1], Yoji Ishizu[1], Masatoshi Ishigami[1], Sachiyo Yoshio[3], Tetsuya Ishikawa[1], Hiroki Kawashima[1] and Takanobu Kato[2], (1)Nagoya University Graduate School of Medicine, (2)National Institute of Infectious Diseases, (3)The Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine

Background: Hepatitis B virus (HBV) infects approximately 320 million people worldwide and is difficult to eradicate. Achieving functional cure (FC) is the ultimate goal, however, factors contributing to FC are poorly understood. We investigate the impact of gut microbiota in chronic hepatitis B patients who achieved FC. **Methods:** Of 105 HBeAg-negative patients with chronic hepatitis B, 70 patients were enrolled excluding cirrhosis, hepatocellular carcinoma, and those receiving nucleoside analogue. The gut microbiome was evaluated in patients who achieved FC and compared with patients with a high titer HBV DNA (**e** 3.3 log IU/mL) [High Titer (HT) group] or patients with a low titer of HBV DNA (< 3.3 logs IU/mL) [Low Titer (LT) group]. The HBV infection system of the cell culture-generated HBV (HBVcc) was used to assess the effects of short-chain fatty acids (SCFAs) including butyric acid produced from identified gut microbiota. **Results:** There was no difference in α and β diversity of gut microbiota in the FC group compared to patients in other groups, but there was a significantly higher relative abundance of bacteria that produce SCFAs, including butyric acids, such as *Bifidobacterium breve* and *Coprococcus catus (Lachnospiraceae)* in patients of the FC group. Furthermore, the relative abundance of both *C. catus* and *B. breve* was gradually higher in sequence from the HT group to the LT group and FC group. In vitro study indicated that butyric acid treatment reduced the production of HBsAg in HBVcc infected cells at a concentration of 1.0mM. The most effective phase of the treatment with butyric acid was identified to be during the culture of infected cells. **Conclusion:** Our study suggested that bacteria that produce SCFAs, including butyrate, are associated with FC in HBeAg-negative patients with hepatitis B through the direct inhibition of HBV replication by butyric acid.

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1495-C | COMBINATION OF SINGLE-CELL AND BULK RNA-SEQ REVEALS IMMUNE CHARACTERISTICS OF NK CELLS IN DIFFERENT STAGES OF CHRONIC HBV INFECTION

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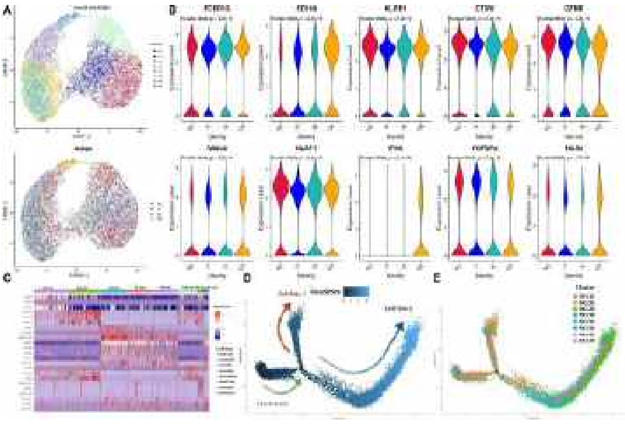
Background: Natural killer (NK) cells are important effector cells of the antiviral immune response. In hepatitis B virus (HBV) infection, NK cells display altered changes in phenotypes and functions. This study was designed to explore the immune characteristic alternation of NK cells in different stages of chronic HBV(CHB) infection. **Methods:** NK cell single-cell RNA sequencing (ScRNA-seq) data (GSE182159) from patients with CHB infection were analyzed, including 6 immune tolerant (IT), 5 immune active (IA), 3 chronic resolved (CR), and 6 healthy controls. NK cell clusters and subtypes were identified by Seurat pipeline and pseudotime analysis. The functions of different hepatic NK cell subtypes were investigated by enrichment analyses. The bulk RNA-seq data (GSE125686) from CD56+NK cells combined with the scRNA-seq data were analyzed to explore transcriptome profile changes and potential regulatory transcription factors (TFs) of NK cells in the distinct stage of CHB infection by hdWGCNA and WGCNA analysis. **Results:** Compared to healthy controls, CHB patients showed a significant decrease in hepatic NK cells, especially in the IA phases, as well as peripheral blood NK cells, especially in the CR phases. In addition, impaired expression of cytotoxic genes in hepatic NK cells was observed in the IT patients. Subclustering and pseudotime analysis revealed two subtypes of hepatic NK cells, conventional NK (cNK) cells and liver resident NK (LrNK) cells with different phenotypes and functions. The proportion of cNK cells was significantly decreased whereas LrNK cells were increased in all phases of CHB infection. Finally, Four TFs related to IT phases (YBX1, ID2, CNBP, and HOPX) and six TFs (BACH2, MYC, NFKB2, SMAD3, IRF8, and RERE) related to the IA phases were identified in the hepatic NK cells. **Conclusion:** Our research dissected the immune characteristic of NK cells and identified TFs involved in the transcriptional regulation of NK cells in different CHB infection stages, which provided novel insight into the mechanisms of antiviral immunity in CHB infection.



Disclosures: The following people have nothing to disclose: Yuwei Liu, Junqi Niu

1496-C | DEFICIENCY OF SCAP INHIBITS HBV PATHOGENESIS VIA ACTIVATION OF THE INTERFERON SIGNALING PATHWAY

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Background: Hepatitis B virus (HBV) infects the liver and is a major risk factor for liver cirrhosis and hepatocellular carcinoma. Currently, interferons and reverse transcriptase inhibitors are useful for treatment of HBV but they have substantial side effects and drug resistance, respectively. Approaches for an effective cure for the virus are thwarted by the limited knowledge on virus-host interactions. The purpose of this study is to identify novel host factors that may support the lifecycle of the HBV virus. **Methods:** Host molecules involved in HBV lifecycle were identified by a genome-wide siRNA based screening in primary human hepatocytes. Overexpression and knockdown were performed to investigate the role of the proteins. Gene expression was measured by PCR whereas protein was determined by immunoblotting. HBV infection was performed by inoculum derived from the serum of an HBV-infected patient. HBV DNA was quantified by immunoprecipitation. HBs and HBe antigens were measured by ELISA. Interferon activity was blocked by an interferon receptor blocking antibody. **Results:** We identified SCAP as a novel host factor that regulates HBV replication. SCAP which stands for **s**terol regulatory element-binding protein (SREBP) **c**leavage-**a**ctivating **p**rotein is an integral membrane protein located in the endoplasmic reticulum. The protein plays a central role in controlling lipid synthesis and uptake by cells. We found that gene silencing of SCAP significantly inhibited HBV production through activation of interferons (IFNs) and interferon stimulated genes (ISGs). Consequently, ectopic expression of SREBP-2, a downstream effector of SCAP in SCAP deficient cells inhibited the IFNs/ISGs expression thereby restoring HBV production. Importantly, treatment of SCAP deficient cells with an interferon blocking antibody also rescued HBV infection. Our results suggest that SCAP via its downstream effector SREBP2 participates in HBV replication through an effect on the interferon production. This observation was further characterized by an increase in HBV production through ectopic expression of SREBP2 compared to control in the parental HepG2-NTCP cells. **Conclusion:** We highlight a previously undocumented role of the cellular sterol pathway controlled by SCAP via the SREBPs in regulating IFN hemostasis to limit HBV infection of hepatocytes. These results may shed light on development of new antiviral strategies against HBV.

Disclosures: The following people have nothing to disclose: Grace Naswa Makokha, Hiromi Abe-Chayama, Clair Nelson Hayes, Kazuaki Chayama

1497-C | DEVELOPMENT OF A NOVEL HUMAN HEPATOMA CELL LINE SUPPORTING REPLICATION OF RECOMBINANT HBV GENOME WITH A REPORTER GENE AND PRODUCING INFECTIOUS RECOMBINANT HBV

Shotaro Kawase, Masaya Funaki, Tetsuro Shimakami, Kazuyuki Kuroki, Masaki Kakuya, Reona Suzuki, Koji Matsumori, Taro Kawane, Mika Yoshita, Ariunaa Sumiyadorj, Kazuhisa Murai, Kouki Nio, Masao Honda and Taro Yamashita, Kanazawa University

Background: For the development of antiviral agents to eliminate hepatitis B virus (HBV), an HBV cell culture system that can easily monitor HBV infection is needed. We reported an HBV infection monitoring system using a luminescent 11-amino-acid reporter (HiBiT) by inserting the HiBiT-coding sequence at the N-terminus of PreS1 in a 1.2-fold plasmid encoding a genotype C HBV genome. A recombinant cell culture-derived virus (HiBiT-HBVcc) prepared by transient transfection of this plasmid into HepG2 cells was infectious only to primary human hepatocytes, not to HepG2-NTCP cells. To update the previous system, we established a new HepG2 cell line supporting stable replication of the HiBiT-containing HBV genome and characterized this cell line. **Methods:** We inserted the HiBiT-coding sequence at the C terminus of HBV PreS1 into the plasmid encoding a genome length of genotype D HBV. Following transfection of this plasmid into HepG2 cells, several HepG2 cell clones which integrated the HBV genome into its genome were selected using the appropriate antibiotics. The cell line showing the highest extracellular HiBiT activity, designated as HepG2-B4 cells, was used for further characterization. **Results:** HepG2-B4 cells could be maintained in the presence of 2% DMSO without cell splitting by day 42 after seeding. Extracellular HiBiT activity, as well as the amounts of HBV markers in the supernatants such as HBV-DNA, HBsAg and HBcrAg, kept increasing until day 42. Entecavir or tenofovir treatment reduced extracellular HiBiT activity and HBV-DNA amount in a dose dependent manner. Covalently closed circular HBV-DNA was detected by Southern blot analysis. Furthermore, the supernatants of HepG2-B4 cells were concentrated, then tested for the ability to infect naïve HepG2-NTCP cells and primary human hepatocytes. HiBiT-HBVcc from HepG2-B4 cells could infect both naïve HepG2-NTCP cells and primary human hepatocytes as extracellular HiBiT activity showed continuously increasing and treatment upon infection by an HBV entry inhibitor, bulevirtide, inhibited the increase of HiBiT activity. **Conclusion:** The HepG2-B4 cells stably supported replication of the recombinant HBV genome containing a HiBiT genome and produced an infectious recombinant virus. HBV replication and infection can be easily assessed by measuring extracellular HiBiT activity. Thus, this cell line itself and HiBiT-HBVcc from HepG2-B4 cells can be a powerful tool to develop wide ranges of direct-acting antivirals.

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1498-C | GENOMIC LANDSCAPE OF NON-HODGKIN LYMPHOMA PATIENTS WITH CURRENT OR PAST HEPATITIS B VIRUS INFECTIONS

Moon Haeng Hur[1], Jeayeon Park[1], Youngsu Park[1], Yunmi Ko[1], Hyunjae Shin[1], Min Kyung Park[1], Yun Bin Lee[1], Eun Ju Cho[1], Jeong-Hoon Lee[2], Yoon Jun Kim[3], Jung-Hwan Yoon[1] and Su Jong Yu[1], (1)Seoul National University College of Medicine, (2)Seoul National University College of Medicine, Seoul, South Korea, (3) Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, South Korea

Background: Hepatitis B virus (HBV) infection is a risk factor for non-Hodgkin lymphoma (NHL). By evaluating the genomic landscape of patients with NHL, we aimed to assess the effect of current or past HBV infections on the development of NHL. **Methods:** Patients who were diagnosed with NHL and underwent targeted next-generation sequencing (NGS) for NHL tissue at Seoul National University Hospital between 2019 and 2022 were consecutively enrolled. Patients confirmed with Hodgkin lymphoma or those without clinical information were excluded. Targeted NGS was performed for 166 NHL-related genes, including *MYD88*, *MYC*, and *ATM*, to detect single nucleotide variant (SNV). Current and past HBV infections were defined by a positive HBV surface antigen (HBsAg) and a positive HBV core antibody (HBcAb) with a negative HBsAg, respectively. The incidence of SNV was compared among three groups (i.e., control group vs. current HBV infection group vs. past HBV infection group). **Results:** A total of 252 patients were included for analysis and 87 (34.5%) were diagnosed with diffuse large B-cell lymphoma. According to the HBsAg and HBcAb positivity, patients were classified into three groups: control ($n = 129$), current HBV infection group ($n = 23$), and past HBV infection group ($n = 100$). The incidence of *MYD88* (control vs. current HBV infection vs. past HBV infection: 14.0% vs. 34.8% vs. 30.0%; $p = 0.005$), *PIM1* (16.3% vs. 34.8% vs. 29.0%; $p = 0.03$), and *MYC* (3.1% vs. 8.7% vs. 12.0%; $p = 0.03$) gene mutation was significantly higher in the current or past HBV infection group compared to the control group. On the other hand, the current HBV infection group showed significantly higher incidence of *ATM* (4.7% vs. 13.0% vs. 0%; $p=0.004$), *BCL10* (3.9% vs. 17.4% vs. 6.0%; $p=0.046$), and *BIRC3* (0.8% vs. 13.0% vs. 0%; $p=0.003$) gene mutation than the other two groups. **Conclusion:** Although current or past HBV infections share some of the gene mutations associated with the development of NHL, current HBV infection exhibited other distinct gene mutations. These findings are expected to reveal the genomic pathways of NHL associated with HBV infection.

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1499-C | HBsAg EXPRESSION DOES NOT AFFECT THE HEPATOCYTE RESPONSE TO PEGYLATED INTERFERON AS ANALYZED BY SPATIAL TRANSCRIPTOMICS OF LIVER TISSUE

Nehna Abdul Majeed[1], Regina Umarova[2], Ahmad Alawad[2], David E Kleiner[3], Barbara Rehermann[4] and Marc G. Ghany[5], (1)Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, (2)National Institute of Diabetes and Digestive and Kidney Diseases, (3)Laboratory of Pathology, National Cancer Institute, Bethesda, MD, (4)Niddk, National Institutes of Health, (5)National Institute of Diabetes and Digestive and Kidney Diseases, Nih

Background: Treatment with pegylated interferon (Peg-IFN) results in hepatitis B surface antigen (HBsAg) loss in only 1-3% of patients with chronic hepatitis B. **Aim:** To evaluate whether HBsAg expression affects the hepatocyte response to Peg-IFN, we performed spatial transcriptomics on paired liver biopsies pre- and 6 hours post-Peg-IFN treatment of patients with chronic hepatitis B. **Methods:** Peg-IFN was added for 24 weeks to ongoing nucleotide analogue treatment in 13 patients with suppressed HBV DNA. A clinical response was defined as **e** 2 $\log_{10}$ IU/mL decline in HBsAg level at end of treatment. Paired liver biopsies pre- and 6 hours post-initial dose of Peg-IFN were stained with anti-HBs to distinguish HBsAg positive (+) from HBsAg negative (-) hepatocytes. Digital spatial profiling was used to select HBsAg (+) and (-) regions of interest (ROI) followed by transcriptomic analysis. Analysis of differentially expressed genes (DEG) and gene set enrichment were performed utilizing Hallmark gene sets. **Results:** One Peg-IFN responder with 2.6 $\log_{10}$ and 2 non-responders with 0.3 and 0 $\log_{10}$ IU/mL decline in HBsAg levels, respectively, were studied. In total, 17 HBsAg (+) and 19 HBsAg (-) ROIs were analyzed. Minimal change in gene expression post-Peg-IFN was observed in one non-responder. Using an absolute DEG-fold change of >2, comparing post- to pre-PEG-IFN injection analyzing all ROIs, independent of HBsAg staining, there were 52 DEGs, the majority of which were upregulated interferon stimulated genes (ISGs). Comparing HBsAg (+) to HBsAg (–) hepatocytes post- to pre-PEG-IFN, there were 42 upregulated genes common to both (majority of DEGs were ISGs), 32 genes unique to HBsAg (+) hepatocytes and 17 to HBsAg (-) hepatocytes. Finally, comparing HBsAg (+) and HBsAg (–) hepatocytes post- to pre-pIFN in the responder to the non-responder with no change in HBsAg level, there were 14 common DEGs (majority ISGs) and 59 genes unique to the responder (majority were upregulated ISGs) and 12 unique to the non-responder (majority non-ISGs). **Conclusion:** The presence of HBsAg does not substantially influence intrahepatic response to PEG-IFN. Rather, the intrahepatic response to Peg-IFN is highly variable among patients with responders displaying a greater breadth of DEGs (primarily ISGs) compared to non-responders.

Disclosures: The following people have nothing to disclose: Nehna Abdul Majeed, Regina Umarova, Ahmad Alawad, David E Kleiner, Barbara Rehermann, Marc G. Ghany

1500-C | HBsAg LOSS DURABILITY AND RATES OF HBsAg SEROREVERSION IN PATIENTS WITH CHRONIC HBV INFECTION, A SYSTEMATIC LITERATURE REVIEW

Vera Gielen[1], Supriya Desai[2], Mounika Adepu[2], Shayon Salehi[1] and Anadi Mahajan[2], (1)GSK, Brentford, UK, (2) Bridge Medical Consulting, London, UK

Background: Functional cure, defined as hepatitis B surface antigen (HBsAg) and HBV DNA undetectable after completion of all treatment, is regarded as the elevated treatment endpoint for patients with chronic HBV (CHB) infection, but is rarely achieved. HBsAg seroclearance is associated with greater reduction in risk of hepatocellular carcinoma than HBV DNA suppression alone. Limited data is available on durability of functional cure and/or HBsAg loss. The objective of this study is to identify data on durability of HBsAg loss, rates of HBsAg seroreversion and factors associated with these. **Methods:** A systematic review of studies in people with CHB infection was conducted. Searches were performed in MEDLINE® and Embase® (January 2000 to October 2022), with hand searches of relevant congress abstracts (2020–2022) and

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

bibliographic and grey literature searches. Outcomes included durability of HBsAg loss, rate of HBsAg seroreversion and predictors of HBsAg seroreversion. Clinical trials and observational studies were included. **Results:** In total, 36 studies (26 observational, 10 clinical trials) were identified. There was considerable heterogeneity among the studies by study design, geography, follow-up, sample size, study population, treatment and treatment cessation before or after HBsAg loss. Durability of HBsAg loss at predefined timepoints was only reported in observational studies. This varied by type of therapy and was mostly observed by 48 weeks; nucleos(t)ide analogues (NA, 88%-96%), interferon (IFN)-containing regimens (69%-80%) and untreated patients (~98%) with similar trends over extended follow-up. These data are consistent with the data on HBsAg seroreversion rates. Although data were limited to 5 studies, significant predictors of HBsAg seroreversion included type of therapy (IFN, 2 studies), duration of consolidation < 12 weeks (NA 1 study; IFN 2 studies), HBeAg-positive (vs. HBeAg-negative) at baseline (IFN 1 study). Anti-HBs seroconversion and levels were associated with durability of HBsAg loss in 2 studies; this was inconclusive in another. Age, alanine transaminase (ALT), duration of NA or IFN and NA cessation (vs NA continued) did not predict HBsAg seroreversion. **Conclusion:** HBsAg loss is durable with most HBsAg seroreversion occuring within 48 weeks after HBsAg loss. More research is needed to determine the role of consolidation therapy, other biomarkers and factors that might predict HBsAg seroreversion, as limited data is available. Funding: GSK (study 219256)

Disclosures: Vera Gielen – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

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Shayon Salehi – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Anadi Mahajan – Bridge Medical Consulting: Employee, No, No;

1501-C | HBV INDUCES LIVER FIBROSIS THROUGH A PYRUVATE-PPARA-ROS-DEPENDENT PATHWAY

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Background: Chronic hepatitis B (CHB) is a major cause of liver fibrosis and hepatocellular carcinoma (HCC). We previously found that pyruvate, a key intermediate in metabolic pathways, increases HBV replication. Pyruvate supplementation suppressed peroxisome proliferator-activated receptor α (PPARα) expression and increases reactive oxygen species (ROS) production as well as expression of profibrotic related genes. However, the mechanism by which pyruvate mediates HBV-induced liver fibrosis is still not well characterized. **Methods:** We studied HBV-induced fibrogenesis through pyruvate in HBV HepAD38, HBV infected NTCP-HepG2 cells, an hepatic stellate cell line (HSC, LX2), primary human hepatocytes (PHHs), HBV carrier mouse model and CHB patients. Cells were cultured in medium without pyruvate. Infectious HBV viral particles (HBVvp) were purified from HepAD38 supernatant (HBVsup). HBV carrier mouse was generated by hydrodynamic injection of pAAV/HBV1.2 plasmid though the tail vein into wild-type C57BL/6. We evaluated the effects of the PPARα agonist fenofibrate and of the PPARα antagonist GW6471 RNAi knockdown, as well as the ROS inhibitor diphenyliodonium chloride (DPI) on HBV induced liver fibrosis. HBV replication and expression of pyruvate, PPARα, TGF-β1, and liver fibrosis related genes were monitored by qRT-PCR, Western blot, or ELISA. **Results:** Pyruvate levels were significantly increased in HBV-infected NTCP-HepG2 cells, HepAD38 cells, HBV carrier mouse model, and CHB patients. Pyruvate supplementation further increased HBV-induced liver fibrosis through suppressed PPARα and subsequently activated ROS in NTCP-HepG2 and LX2 cells. PPARα antagonist or siRNA increased HBV-induced ROS production and profibrotic gene expression in NTCP-HepG2 and LX2 cells. In contrast, PPARα agonist or ROS inhibitor DPI abrogated HBV and pyruvate induced fibrogenesis and PPARα inhibition. We found that DPI did not affect PPARα expression, indicating that PPARα lies upstream of ROS regulation. **Conclusion:** We conclude that HBV promotes liver fibrogenesis through a pyruvate-PPARα-ROS-dependent pathway. These findings clarify the mechanisms underlying HBV-induced liver fibrosis and provide alternate strategies to monitor, prevent and treat HBV-related liver disease. Pyruvate and PPARα may be novel targets for antifibrotic therapeutic development in CHBV.

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The following people have nothing to disclose: Xiaoqiong Duan, Shasha Li, Min Xu, Shilin Li, Andre Jeyarajan, Charlotte Warner, Yujia Li, Min Xu, Chunhui Yang, Wenting Li, Tuo Shao, Pei-Jer Chen, Limin Chen, Wenyu Lin

1502-C | HEPATITIS B VIRUS HIJACK HOST TRIM26 TO AVOID PROTEASOME-DEPENDENT DEGRADATION OF VIRAL CORE PROTEIN

Kazumoto Murata[1], Yuki Nakaya[1], Tsutomu Nishizawa[1], Daichi Onomura[1], Tomoko Yamagata[1], Hiromi Morita[1] and Hironori Nishitsuji[2], (1)Jichi Medical University, (2)Ujita Health University School of Medicine

Background: Hepatitis B virus (HBV) is a life-threatening infectious virus involving a risk of cirrhosis and hepatocellular carcinoma. Current treatments such as nucleos(t)ide analogs or interferon (IFN) for chronic HBV infection safely control its replication and reduce the risk of disease progression; however, these treatments cannot eliminate HBV and novel treatment-strategies are required. We have previously done a small interfering RNA (siRNA) screening to identify most important host factors for HBV replication. Among these factors, we focused on the tripartite motif-containing protein 26 (TRIM26) because TRIM 26 is reported to down-regulate IFN regulatory factor 3 which is a key element for immunological responses against HBV. **Methods:** Human hepatoma cell lines with sodium taurocholate co-transporting polypeptide (HepG2/NTCP, Huh7/NTCP), PXB cells derived from chimeric mice with human primary hepatocytes and HEK293 cells were used. Protein expressions were examined by western blotting or co-immunoprecipitation (Co-IP). In cyto-ubiquitination assay was conducted by transfection of FLAG-tagged core, TRIM 26 or their mutants together with HA-tagged ubiquitin. Proximity ligation assay was used for intracellular interaction of each protein. **Results:** siRNA-mediated TRIM26 knockdown (KD) inhibited HBV DNA and RNA levels in HBV-infected human hepatoma cell lines as well as human hepatocytes (PXB cells). Therefore, we examined whether TRIM26 downregulated IFN responses during HBV infection, but no down-regulation of type I or type III IFN as well as some IFN-stimulated genes were observed by TRIM26 KD. To examine the other possibilities that TRIM26 modulates HBV protein function, we conducted Co-IP for TRIM26 and each HBV protein. Co-IP clearly demonstrated that both exogenous and endogenous TRIM26 physically interacted with HBV core protein (HBc), but not polymerase nor HBX, through the TRIM26 SPRY domain. Next, we analyzed whether TRIM26 affects HBc ubiquitination since TRIM26 is an E3 ubiquitin ligase. A proteasome inhibitor, MG132, significantly increased HBc protein levels in a dose-dependent manner in HEK293T cells transfected with HBc-FLAG expression plasmid. However, unexpectedly, TRIM26 KD promoted HBc ubiquitination and HBc degradation was inhibited by exogenous TRIM26 in a dose-dependent manner. Furthermore, RING domain deleted TRIM26 mutant (TRIM26ΔR), which interacted with HBc but did not have an ability to inhibit the ubiquitination of HBc, acted as dominant negative of TRIM26 and promoted HBc ubiquitination, suggesting that sequestration between TRIM26 and HBc induces HBc degradation by proteasome. **Conclusion:** We found that HBV hijacked TRIM26 to avoid the proteasome dependent HBc degradation for effective viral replication. The interaction between TRIM26 and HBc might be a novel therapeutic target against HBV infection.

Disclosures: The following people have nothing to disclose: Kazumoto Murata, Yuki Nakaya, Tsutomu Nishizawa, Daichi Onomura, Tomoko Yamagata, Hiromi Morita, Hironori Nishitsuji

1503-C | HEPATITIS B VIRUS-ENCODED MICRORNA (HBV-MIR-3) INHIBITS FIH-1 EXPRESSION TO PROMOTE TUMOR ANGIOGENESIS IN HBV-RELATED HEPATOCELLULAR CARCINOMA

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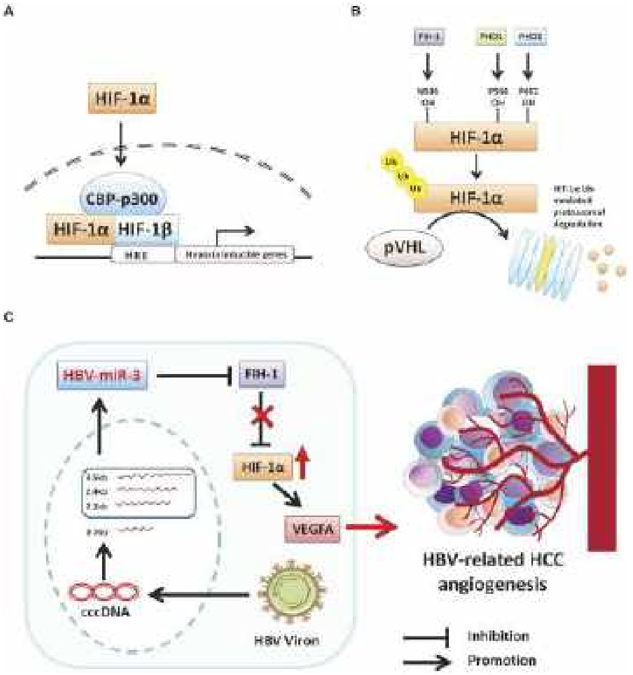
Background: HBV-cccDNA can produce microRNAs that bind target mRNAs to inhibit post-transcriptional gene expressions. Hepatitis B Virus-Encoded MicroRNA 3 (HBV-miR-3) has recently been reported to control the replication of HBV and regulate host gene expressions in HCC. Factor Inhibiting HIF-1 (FIH-1), also named Hypoxia Inducible Factor 1 Subunit Alpha Inhibitor (HIF1AN), Hydroxylates hypoxia-inducible factor 1-alpha (HIF-1α) to repress transcription of vascular endothelial growth factor A (VEGFA). It is interesting that in 3'-UTR of FIH-1, there is target sequence of HBV-miR-3.we aimed to elucidate the role of HBV-miR-3 in promoting HBV-related HCC angiogenesis. **Methods:** stem-loop qPCR was used to detect the expression of HBV-miR-3 in HBV-related HCC tissues and survival analysis was conducted. The expression of VEGFR2 in HCC tissues was detected by qPCR and its correlation with HBV-miR-3 was analyzed. HepG2 cells were transfected with HBV-miR-3 agomir, HepG2.2.15 cells were transfected with HBV-miR-3 antagomir, and the expression levels of FIH-1, HIF-1α and VEGFA were detected. A co-culture model of HepG2/HepG2.2.15 and human umbilical vein endothelial cells (HUVEC) was established to analyze the effect of HepG2 cells transfected with HBV-miR-3 agomir or HepG2.2.15 cells transfected with HBV-miR-3 antagomir on HUVEC tube formation. The binding site and nucleic acid sequence of HBV-miR-3 targeting FIH-1 mRNA 3'-UTR were verified by luciferase reporter assay. HepG2 and HepG2.2.15 cells were used to establish a mouse tumor-bearing model; HBV-miR-3 agomir and antagomir were injected into the tumors and the expression of FIH-1, HIF-1α, VEGFA and VEGFR2 were analyzed. **Results:** HBV-miR-3 expression was significantly correlated with angiogenesis related genes VEGFR2 and FIH-1. This suggests that HBV-miR-3 may participate in HBV-related HCC angiogenesis. In vitro, HBV-miR-3 agomir repressed HCC cell FIH-1 expression and promoted HIF-1α and VEGFA expression, resulting in increased human umbilical vein endothelial cell (HUVEC) lumen formation; HBV-miR-3 antagomir induced HCC cell FIH-1 expression and inhibited HIF-1α and VEGFA expression, resulting in decreased HUVEC lumen formation. There results suggest that HBV-miR-3 affect angiogenesis of HBV-related HCC by up-regulating HIF-1α/VEGFA expression. The binding site of HBV-miR-3 to 3'-UTR of FIH-1 mRNA was also confirmed by luciferase activity assay. The effect of HBV-miR-3 regulating tumor angiogenesis was also confirmed by mouse tumor bearing model. These data indicates that HBV-miR-3 regulates angiogenesis of HBV-related HCC by targeting 3'-UTR of FIH-1 mRNA to promote angiogenetic signaling. **Conclusion:** HBV-miR-3 promotes HBV-related HCC angiogenesis by repressing FIH-1 post-transcription and it may be a new mechanism by which HBV promotes angiogenesis in HBV-related Hepatocellular Carcinoma.



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1504-C | HYPEREXPRESSION OF INNATE-LIKE MARKERS ON ACTIVATED T CELLS, CONSISTENT WITH IMMUNOPATHOLOGY IN CHRONIC HEPATITIS B IS NOT FULLY REVERSED WITH ANTIVIRAL THERAPY

Lung Yi Mak[1,2], *Apostolos Koffas*[2], *Sabina Wellington*[2], *Sophie Stretch*[2], *Anna Riddell*[3], *Man-Fung Yuen*[1], *Patrick T. Kennedy*[2] *and Upkar Singh Gill*[2], *(1)State Key Laboratory of Liver Research, the University of Hong Kong, Hong Kong SAR, (2)Blizard Institute, Barts and the London SMD, Qmul, (3)Department of Virology, Barts Health NHS Trust, London*

Background: There is renewed focus on the importance of non-specific bystander T cells as contributors to hepatic immunopathology in chronic hepatitis B (CHB). It is key to ascertain further details on this understudied immune cell population to provide insights into the reasons for immunological failure of novel therapies for CHB cure. We studied the phenotypic innate-like properties of global CD4 and CD8 T cells in treatment naïve and experienced patients with CHB compared to healthy controls (HC) to determine any differences and correlated these with clinical parameters. **Methods:** Forty-six subjects (47.8% male, median age 39.5 y) were studied [CHB; 20, HC; 26]. The proportion of activated (HLA-DR+) T cells was determined along with the expression of NK cell receptors

(NKRs), markers of T cell differentiation and residency by multi-parameter flow cytometry. The impact of antiviral therapy in a cohort of CHB subjects was also analysed [median tenofovir treatment duration 7.6 years; median ALT: 43 (range: 31-72) U/L; median HBV DNA: 7.1 log IU/ml at treatment initiation]. **Results:** The overall proportion of HLA-DR+ T cells was higher in CHB patients compared to HCs, and significantly higher on CD4 T cells (3.1% vs 1.3%, $p = 0.041$). T cell expression of CXCR6 (0.7% vs 0.3%, $p = 0.010$) and the NKRs, NKG2A (4.4% vs 1.7%, $p = 0.015$) and NKp30 (2.0% vs 0.9%, $p = 0.023$) was increased in CHB, consistent with immunopathology. We noted augmented expression of NKG2A and CD56 (both $p < 0.0001$) on the activated (HLA-DR+) proportion of CD8 T cells compared to their HLA-DR- counterparts. On analysingCHB subjects undergoing antiviral therapy, the expression of NKRs [NKG2A: CD4; 35.4% vs 2.2% & CD8; 28.4% vs 3.6% (both $p < 0.001$); NKG2D: CD4; 79.6% vs. 2.4% & CD8; 20% vs 5.9% (both $p < 0.01$); NKp30: CD4; 2.9% vs 0.7% & CD8; 3.3% vs 0.5% (both $p < 0.01$)] and the residency marker CXCR6 (CD4; 10.6% vs 0.4%, $p < 0.0001$, CD8; 2.4% vs 0.3%, $p = 0.011$) remained significantly higher in those on antiviral therapy, despite undetectable HBV DNA and ALT normalisation, compared to those CHB treatment naïve patients with bona-fide immune control, indicating that the bystander innate like immune defects are not recovered by current antiviral therapy. **Conclusion:** CHB is associated with increased non-specific innate like activated T-cells, potentially causing immunopathology. Antiviral therapy is unable to reverse these immune cell defects suggesting the need for earlier treatment or add on therapies to achieve CHB cure. Further work is being undertaken to determine the functionality of these innate-like cells in this setting.

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1505-C | IDENTIFICATION OF NOVEL ANTIVIRAL HOST FACTORS BY FUNCTIONAL GENE EXPRESSION ANALYSIS USING IN VITRO HBV INFECTION ASSAY SYSTEMS

Takuto Nosaka, Tatsushi Naito, Yu Akazawa, Kazuto Takahashi, Hidetaka Matsuda, Masahiro Ohtani and Yasunari Nakamoto, University of Fukui

Background: Nucleos(t)ide analogs are effective antivirals that reduce hepatitis B virus (HBV) DNA but do not cure HBV infection due to the persistence of covalently closed circular DNA (cccDNA). We established a human hepatocyte HBV infection system and reported that IFN-γ regulates HBV cccDNA via STAT1-related pathway (Hepatol Res. 2020, 2022). In this study, using *in vitro* HBV infection systems, novel antiviral host factors that regulate the cccDNA and their molecular mechanisms were investigated by gene knockdown methods and functional gene expression analysis. **Methods:** The 1.3-mer HBV genome plasmid (genotype C2) with core promoter A1762T/G1764A and precore G1896A mutation was transfected into HepG2 cells and "HepG2.D11 clone" was established. The supernatant containing HBV was added to primary human hepatocytes (PXB cells). siRNA knockdown experiments and RNA microarray were performed. Gene expression was analyzed with GeneSpring GX software and Gene Set Enrichment Analysis. Single-cell RNA sequencing (scRNAseq) data from the Human Protein Atlas (HPA) for 30 major tissues/organs was analyzed. **Results:** In STAT1 knockdown experiment, HBsAg, intracellular HBV DNA, and cccDNA were decreased in PXB cells, whereas HBsAg and HBV DNA were increased in HepG2.D11 cells [HBV DNA (PXB-siSTAT1/HepG2.D11-siSTAT1), 0.51/1.91 folds; $p < 0.05$]. RNA microarray analysis showed that 65 genes expression was changed in PXB-siSTAT1 cells (>2.0 folds, 42 genes; <0.5 folds, 23 genes). The siRNA screening experiments of these 65 genes in PXB cells showed that knockdown of two anti-HBV candidate genes, fumarylacetoacetate hydrolase (FAH) and Nicotinamide N-methyltransferase (NNMT), increased HBsAg and cccDNA [HBsAg (PXB-siFAH/-siNNMT), 1.58/1.33 folds; $p < 0.05$]. In HepG2.D11 cells, knockdown of FAH and NNMT also increased HBsAg and HBV DNA ($p < 0.05$). To investigate the cells expressing FAH and NNMT, scRNAseq showed that both FAH and NNMT were highly expressed in the liver, particularly in hepatocytes. In these two candidate genes, FAH is the enzyme which catalyzes the hydrolysis into fumaric acid. In HepG2.D11 cells, dimethyl fumarate reduced HBsAg and HBV DNA (HBV DNA, 0.72 folds; $p < 0.05$). **Conclusion:** We identified novel antiviral host factors, FAH and NNMT, that reduce HBV cccDNA levels using *in vitro* HBV infection assay systems in primary human hepatocytes. A couple of undefined host factors were found to contribute to the control of viral infection independently of STAT1 by comprehensive functional screening.

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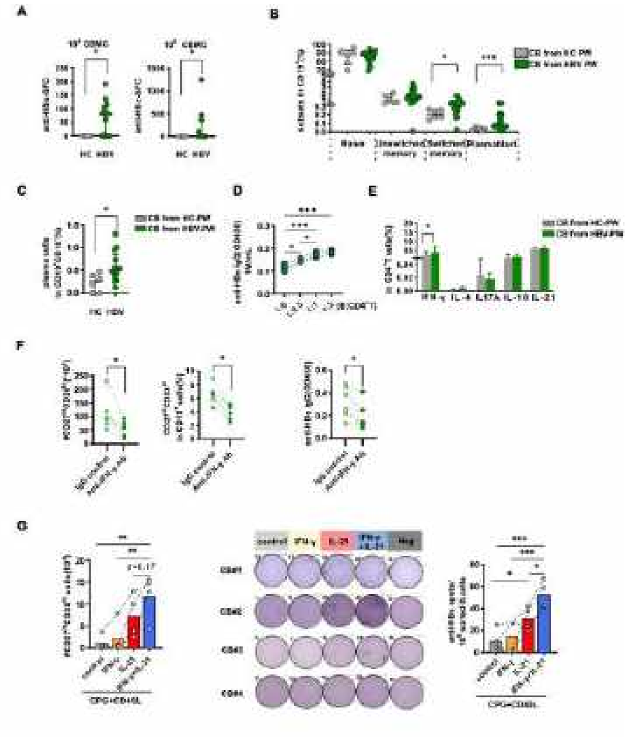
1506-C | IL-21 AND CD4+ T CELL-DERIVED IFN-GAMMA SYNERGISTICALLY ENHANCE HBSAB PRODUCTION IN INFANTS WITH INTRAUTERINE HBV ANTIGEN EXPOSURE

Yanchen Ma, Xiaoyi Liu, Haonan Lou, Weiying He, Qingqing Pan, Libo Tang and Yongyin Li, State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University

Background: The humoral immune response is widely acknowledged for its crucial role in protecting against pathogens. However, the specific characteristics of the humoral immune response to HBV-related antigens encountered during intrauterine exposure remain poorly understood. **Methods:** Twenty-seven cord blood from pregnant women with chronic hepatitis B virus (HBV-PW) and 9 cord blood from healthy pregnant women (HC-PW) as controls were enrolled. The frequency and phenotype of B cells and CD4^{+}T cells were assessed using flow cytometry. Functional responses of HBV-specific B cells were quantified through B cell ELISPOT assays and ELISA. In vitro co-culture experiments were conducted to investigate the role of CD4^{+} T cells in facilitating HBV-specific B cell responses. **Results:** Cord blood B cells from HBV-PW were capable of producing anti-HBs and anti-HBc, whereas cord blood B cells from HC-PW did not show detectable levels (Figure A). Additionally, a higher proportion of plasmablast and switched memory B cells in cord blood from HBV-PW was found (Figure B). Upon stimulation with HBsAg in vitro, cord blood B cells from HBV-PW demonstrated an increased expansion of plasmablast (Figure C). Cord blood CD4$^+$ T cells could also promote the production of HBsAb, and we found that cord blood CD4$^+$ T cells exhibited higher production of IFN-γ from HBV-PW (Figures D and E). Blockade of IFN-γ production from CD4$^+$ T cells markedly decreased the proportion and absolute count of plasmablast in cord blood and reduced supernatant levels of anti-HBs (Figure F). IFN-γ alone was insufficient to effectively promote the differentiation of B cells into plasmablast and induce anti-HBs production, but in the presence of IL-21, it effectively facilitated these processes (Figure G). **Conclusion:** B cells of infants can generate HBV-specific responses upon exposure to intrauterine HBsAg, and IFN-γ secreted by CD4$^+$ T cells enhances HBV-specific responses of cord blood B cells in the presence of IL-21. These findings contribute to our knowledge of fetal humoral immunity and provide evidence that fetal B cells can respond to HBV-related antigens encountered in utero.



*p < 0.05, **p < 0.01, ***p < 0.001

Anti-HBc: hepatitis B core antibody; Anti-HBs: hepatitis B surface antibody; CB: cord blood; CBMC: cord blood mononuclear cell; CD40L: CD40 ligand; CPG: unmethylated cytosine-guanine dinucleotides; HBV: hepatitis B virus; HBV-PW: pregnant women with chronic HBV infection; HC: healthy control; HC-PW: normal pregnant women as healthy control; IFN-γ: interferon-gamma; IL-21: interleukin-21; Neg: negative control; SFC: spot-forming cells

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1507-C | IMMUNE CORRELATES OF HDV CLEARANCE IN HDV/HBV COINFECTED INDIVIDUALS

Arshi Khanam[1], *Ameer Abutaleb*[2], *Alip Ghosh*[1], *Furkan Kaysin*[3], *Cihan Yurdaydin*[4] *and Shyam Kottilil*[1], *(1) Institute of Human Virology University of Maryland, (2) Department of Surgery, George Washington University Medical Faculty Associates, (3)Department of Gastroenterology and Hepatology, Koç University Medical School, (4)Koc University School of Medicine*

Background: Chronic hepatitis delta virus (CHD) infection causes the most severe form of viral hepatitis due to rapid progression towards end-stage liver disease leading to high mortality. In the presence or absence of antivirals, a very few patients resolve the infection in chronic hepatitis B/D coinfection (CHB/CHD-coinfection). An enhanced understanding of what derives the resolution of CHD infection is critical to project future therapeutic strategies. Here, we aimed to investigate hepatitis D virus (HDV)-specific T cell responses to determine the immune correlates of HDV clearance. **Methods:** We collected the peripheral blood from CHB/CHD-coinfected patients who did ($n = 11$, CHD-resolved) or did not ($n = 39$, CHD-viremic) clear CHD infection and compared them with patients who cleared both CHB/CHD infection (CHB/CHD-resolved $n = 3$). Circulating T cell phenotype and HBs/HDAg-specific responses were tested with overlapping peptides. Bulk RNAseq and scRNAseq were used to delineate transcriptional profiles of CD4/8 T cells associated with HDV clearance. **Results:** CHB/CHD-resolved patients constituted higher frequencies of effector memory cells with less expression of exhaustion markers including PD-1, CTLA4 and TIGIT in both CD4 and CD8 T cell compartment than those of CHD-resolved (CD4:$p = 0.04$, CD8:$p = 0.02$) and CHB/CHD-coinfection ($p = 0.003$, $p = 0.001$). Further, flow cytometry screening identified higher activation of these cells with improved HDV-specific CD4/CD8 T cells responses in terms of IFN-γ (CD4:$p = 0.001$, CD8: $p = 0.0003$), TNF-α (CD4:$p = 0.0001$, CD8:$p = 0.0008$) and IL-21 (CD4:$p = 0.02$, CD8: $p =$ ns) secretion and cytotoxic functions in CHB/CHD-resolved infection followed by CHD-resolved in comparison to CHB/CHD-coinfection, which display significantly limited functional activity. HBsAg-specific functional responses were also improved in patients who cleared CHD and CHB/CHD infection; however, the recovery was lower than HDV-specific responses and seemed inadequate to clear CHB infection, suggesting robust HDV-specific T cell responses may hold the capacity not only to clear CHD but CHB infection as well. Polyfunctional CD4 and CD8 T cells coproducing IFN-γ, TNF-α, IL-2 and IL-21, and exhibiting cytotoxic potential against HDV were mainly present in CHB/CHD-resolved infection while a very few patients with resolved CHD and CHB/CHD-coinfection established polyfunctional T cells and these patients were specifically those with significantly raised ALT levels. Transcriptional profiling demonstrated distinct adaptive immune responses that defined HDV clearance. **Conclusion:** HDV clearance is associated with higher frequencies of effector T cells producing robust HDV-specific cytokine secretory response while reflecting a transcriptional profile implying a broad anti-HDV peripheral immunity. Hence, these results may guide distinct correlates that define HDV functional cure with antiviral therapeutics.

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1508-C | IMMUNE PROFILING OF HBV-ASSOCIATED HEPATOCELLULAR CARCINOMA (HCC) IDENTIFIES TWO DISTINCT IMMUNE SUBTYPES

Davide De Battista[1], Rylee Yakymi[1], Evangeline Scheibe[1], Shinya Sato[1], Sandra Kendra Raini[1], Tovah Markowitz[2], Justin Lack[2], Roberto Mereu[3], Cristina Manieli[3], Fausto Zamboni[3] and Patrizia Farci[1], (1) Hepatic Pathogenesis Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, (2)NIAID Collaborative Bioinformatics Resource, National Institute of Allergy and Infectious Diseases, National Institutes of Health, (3)Liver Transplantation Center, Azienda Ospedaliera Brotzu

Background: Despite significant advances in immunotherapy, there is limited information on the HBV HCC tumor microenvironment (TME). Taking advantage of a unique series of liver specimens from patients with HBV HCC, we characterized the TME that may provide important clues to identify patients who could benefit from immunotherapy. **Methods:** We analyzed multiple paired liver samples from 10 well-characterized Caucasian patients with HBV HCC, comprising 20 liver specimens from the tumor and 20 from the nontumorous tissue, obtained at the time of liver transplantation or partial hepatectomy. We performed an extensive immunohistochemistry (IHC) analysis of immunologic markers, including CD3, CD4, CD8, CD20, CD56, CD163, PD-1, and a-SMA. Each marker was scored semi-quantitatively (score 0-4). IHC was combined with RNA-seq performed on paired tumor and nontumor tissue. **Results:** Analysis of immune cells identified two distinct tumor subtypes: immune-high and immune-low. Half of the tumors were immune-high. They were characterized by clusters of infiltrating B cells and T cells expressing PD1. Immune-high tumors also showed a significantly higher expression of a-SMA in stromal cells compared to the immune-low. The number of NK cells and macrophages were similar between the two subtypes. Outside the tumors, the distribution of the immune markers was similar in the 2 subtypes. Next, we compared tumor versus nontumor in both subtypes to identify differentially expressed genes. Immune-high tumors had a significantly higher proportion of upregulated genes (45%) compared to the immune-low tumors where only 19% of genes were upregulated. Most upregulated genes detected exclusively in immune-high tumors were related to cell cycle regulation (e.g., *CCNA2, CDK4, E2F7, E2F8, HDAC11, HDAC6, MKI67, TGFB3*). Direct comparison between immune-high and immune-low tumors showed that the immune-high was characterized by an enrichment of upregulated genes involved in anti-inflammatory pathways (e.g., WNT/Ca+ pathway, IL-10 signaling) and downregulated genes involved in pro-inflammatory pathways (e.g., Neuroinflammation Signaling Pathway, Th1 Pathway, TREM1 Signaling, Pathogen Induced Cytokine Storm Signaling Pathway). **Conclusion:** Immune profiling identified two subtypes in HBV-HCC with distinct molecular signatures. Immune-high tumors are characterized by abundant tumor-infiltrating immune cells, but upregulation of genes related to anti-inflammatory pathways.

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1509-C | IMPAIRED CROSSTALK BETWEEN HEPATOCYTES AND MACROPHAGES INCREASES HBV INFECTIVITY: THE EFFECTS OF ETHANOL METABOLISM

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Background: Hepatitis B virus (HBV) causes about 10% of chronic hepatitis (CHB), which is estimated as high as 250 million patients worldwide, with an annual death rate of 800,000. Alcohol abusers have a higher exposure rate to HBV and a subsequent acquisition of chronic infection. However, the complex interactions between alcohol and HBV infection remain unclear. HBV is not cytotoxic and infects only hepatocytes. Innate immunity, specifically, the activation of anti-viral interferon-stimulated genes (ISGs) prevents HBV spread and persistence. Here, we hypothesize that ethanol metabolism impairs extracellular vesicles

(EVs)-mediated crosstalk between hepatocytes and macrophages leading to impairment of anti-viral ISG response, thereby increasing HBV infectivity in hepatocytes. **Methods:** Tg05 HBV-replicating mice were fed control and ethanol liquid diets for 10+1 day (NIH model). Hepatocytes were isolated by collagenase perfusion, and the induction of ISGs (APOBEC3G, ISG15, and OAS1) has been ex vivo done by IFN type 1 on plated hepatocytes. We also used HBV +HepG2.2.15 and HBV- HepG2 cells exposed to the acetaldehyde-generating system (AGS) as well as human monocyte-derived macrophages (MDMs). **Results:** In ethanol-fed Tg05 mice, there was a decrease in anti-viral ISG activation due to suppression of IFNα-induced STAT1 phosphorylation (Western Blot), which increased HBV DNA (ddPCR), HBV RNA (RT-PCR), and HBcAg (IF staining) in hepatocytes Similar results were obtained in HBV+ HepG2.2.15 cells exposed to AGS. When MDMs were treated with supernatants (sups) from HepG2.2.15 cells exposed to AGS (but not with sups from control HBV+ or AGS-exposed HBV-hepatocytes), they showed reduced activation of ISGs by IFNα. These effects were absent when the EVs release from AGS-HepG2.2.15 cells was blocked by GW4869 inhibitor, suggesting that HBV is transferred to MDMs via sup-containing EVs with HBV DNAs and RNAs as part of their cargo. Importantly, sups from MDMs activated by EVs derived from control HepG2.2.15 cells reversed AGS-impaired ISG induction and an increase in HBV markers in AGS-exposed HBV+ cells, while sups from MDMs activated by EVs secreted by AGS-HepG2.2.15 cells were not protective **Conclusion:** Ethanol metabolism in HBV+ hepatocytes suppresses anti-viral ISG activation to enhance HBV infectivity which in the presence of acetaldehyde cannot be protected by EV-mediated crosstalk between these cells and hepatocyte EV-activated macrophages.

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1510-C | INHIBITION OF VIRAL REPLICATION CAN EFFECTIVELY REDUCE THE EXPRESSION OF HBV INTEGRATION BUT THE CLEARANCE OF FN1 EXON REGION INTEGRATION IS HARD BY LONG-TERM ETV TREATMENT

Xiajie Wen[1], Hong You[2], Ju-Tao Guo[3], Fengmin Lu[4] and Jidong Jia[1], (1)Liver Research Center, Beijing Friendship Hospital, Capital Medical University, National Clinical Research Center of Digestive Diseases, Beijing, China, (2)Liver Research Center, Beijing Friendship Hospital, Capital Medical University, (3)Baruch S. Blumberg Institute, (4)Peking University Health Science Center

Background: Integrated HBV DNA is the main source of serum HBsAg in HBeAg negative patients. Due to the inability of current antiviral therapy to directly clear the integrated HBV DNA, the clearance of serum HBsAg remains one of the clinical challenges. This study explored the profile of transcriptionally active HBV DNA integration during the long-term ETV or ETV combine IFN-α treatment and the characteristics of transcriptionally active HBV DNA was identified during the antivirus treatment. **Methods:** Liver biopsies and paired blood samples were obtained from CHB patients at baseline, 78 and 260 weeks after the treat. There are 16, 16 and 22 patients at each time points were finial included in the study, and among them 10 patients had series liver biopsy and blood test. Serum HBV markers, including HBV DNA, HBsAg and HBeAg were longitudinally assessed. No less than 40ng total RNA obtained from each sample, and RNA-seq was carried out. HIVID2 was used for the identification of HBV integration expression fragment. **Results:** After 78 weeks antivirus therapy, the replication of HBV was inhibited the mean level of serum HBV DNA decreased from to 6.91to 0.54(lg IU/mL), at the same time the HBV integration expression decreased 12.25 times compare with the baseline. However, no further significant decline of HBV integration expression was observed at week 260. The analysis of HBV breakpoints showed that more breakpoint or splicing set were detected in HBsAg expression region peeked at 458nt. The proportion of integrated expression occurring in FN1 greatly increases from 0.06% to 31.39% between baseline and week 260. **Conclusion:** Long term antivirus therapy can significantly benefit the patients by decrease the expression of integrated HBV DNA, however, the HBV breakpoint or splicing sit in s-HBsAg expression region near 458nt linking to FN1 gene might help the integrated hepatocytes gain survival and became one of the hard to clear integration express type.

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1511-C | INITIAL EVALUATION OF IMMUNE COMPLEX BINDING IN A PHASE 1 SAFETY AND TOLERABILITY STUDY OF CHRONIC HBV PARTICIPANTS GIVEN A SINGLE DOSE OF VIR-3434

Rachel Wong[1], Hasan Imam[1], Julia Di Iulio[1], Amin Momin[1], Yi-Pei Chen[1], Andrea L. Cathcart[1], Gregory Camus[1], Andre Arizpe[1], Sneha Gupta[2], David Sun[1], *Daniel Cloutier[1], Ann Arvin[1], Kosh Agarwal[3], Man-Fung Yuen[4], Heiner Wedemeyer[5] and Edward J. Gane[6], (1) Vir Biotechnology, Inc., (2)Vir Biotechnology, Inc, (3) Institute of Liver Studies, King's College Hospital, (4) State Key Laboratory of Liver Research, the University of Hong Kong, Hong Kong SAR, (5)Hannover Medical School, (6)Faculty of Medicine, University of Auckland*

Background: VIR-3434 is an investigational Fc-engineered human monoclonal antibody targeting the conserved antigenic loop of HBsAg in development for the treatment of chronic hepatitis B (CHB). Here, we report immune complex (IC) detection in participants with CHB given a single dose of VIR-3434. **Methods:** VIR-3434-1002 is a randomized, double-blind, placebo-controlled phase 1 single ascending dose study that evaluated the safety, tolerability, antiviral and immunologic activity of VIR-3434. In Parts B and C, participants received nucleos(t)ide reverse transcriptase inhibitors (NRTIs) for **e** 2 months prior to study entry and had baseline HBsAg levels < 3,000 and **e** 3,000 IU/mL, respectively. In Part D, participants were not on NRTIs and had baseline HBV DNA **e** 1000 IU/mL with any HBsAg level allowed. Participants in Parts B-D receiving 300 mg VIR-3434 subcutaneously were monitored for immunologic activity for 8 weeks after drug administration. Cell associated ICs were detected by flow cytometry using an anti-HBsAg antibody that can bind HBsAg complexed with VIR-3434. **Results:** 18 participants enrolled in Parts B-D received a single dose of 300 mg VIR-3434. Among these participants, 17 were analyzed for IC detection. 6/17 participants had detectable ICs on neutrophils and/or CD16+ monocytes in peripheral blood samples at one and/or two weeks after VIR-3434 administration. Preliminary analysis showed that participants with higher baseline HBsAg were more likely to have detectable ICs at any of the post-baseline visits. **Conclusion:** Initial evaluation of peripheral blood samples from participants in this study given 300 mg VIR-3434 validated the immune complex binding detection assay. These data provide proof of concept that VIR-3434 forms complexes with HBsAg and targets these immune complexes to immune cells in participants with CHB. Furthermore, a temporal relationship between IC detection and HBsAg reduction was observed. These findings support the continued development of VIR-3434 for functional cure of participants with CHB Infection.

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1512-C | LONGITUDINAL LIVER FINE NEEDLE ASPIRATION FOR SINGLE-CELL ANALYSIS OF HEPATITIS B IMMUNOLOGY IN A SUB-SAHARAN AFRICAN COHORT: FEASIBILITY, ACCEPTABILITY, AND SAFETY

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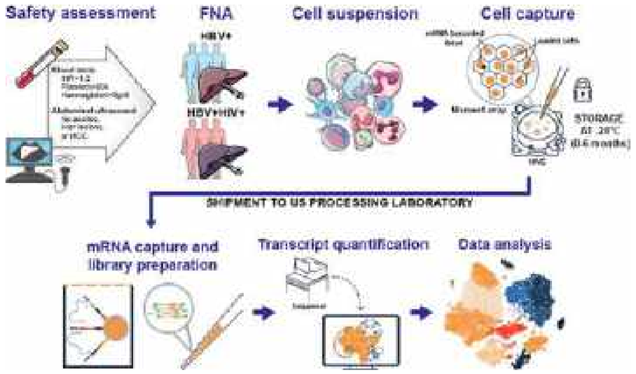
Background: Liver fine needle aspiration (FNA) has potential as a longitudinal research procedure for HBV immunology in the context of current and future therapies, but in low- and middle-income countries, its feasibility, patient acceptability, and safety are not established. We report on our initial use of longitudinal liver FNA in Zambia. **Methods:** Adults with treatment-naïve chronic HBV monoinfection or HBV/HIV coinfection enrolled. At enrollment and 1 year of antiviral therapy, following safety labs and ultrasound, Zambian hepatologists performed percutaneous liver FNAs (4 passes/visit) with ultrasound guidance using a 25g Quincke-type needle. After red blood cell (RBC) depletion, cells were loaded fresh in a Seq-well array. At a collaborating US laboratory, cDNA libraries were created, sequenced (NovaSeq 6000), and analyzed. FNA acceptability was based on completion of a second FNA and qualitative interviews. Safety was based on adverse events. **Results:** Of 113 participants (59-HBV/HIV and 54-HBV only), 103 completed pre-FNA safety tests, and of them, 10 (9.7%) had a contraindication to FNA (high INR, thrombocytopenia, or liver lesions). Of the remaining 93, 86 (92.5%) had an enrollment FNA. So far, 14 of the 29 (48.3%) who reached 1 year have completed a repeat FNA, 13 are waiting to schedule it, and only 2 declined. FNA sample quality was good as a median of 27,257 non-RBC immune cells per FNA pass were counted, and among 400 FNA passes, only 3.1% had few/no cells. Sequencing of an initial 12 cDNA libraries yielded 7,992 high-quality cells. We consistently captured major lymphoid and myeloid immune cell types in each patient, including neutrophils and small numbers of macrophages, hepatocytes, and hepatic stellate cells. In interviews, satisfaction with the clinical care provided in the cohort made the pain and anxiety of the liver FNA, which were typically short-lived, very acceptable. Post-FNA, the majority of participants reported pain that was treated with paracetamol, no patient developed vital sign changes during post-procedure monitoring, and 99% were allowed home after 1-2 hours. One participant was admitted for 24-hour observation due to severe pain but no major complications were found. **Conclusion:** In an HBV cohort in Zambia, longitudinal liver FNAs for HBV immunology research were feasible, acceptable, and safe. HBV clinical and translational research in Africa has potential to contribute to global scientific objectives within the cure agenda.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FNA
HBV+
HBV+HIV+
Cell suspension
Cell capture
STORAGE
SHIPMENT TO US PROCESSING LABORATORY
mRNA capture and library preparation
Transcript quantification
Data analysis

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1513-C | LOSS OF HEPATITIS B VIRUS HBEAG CONTRIBUTES TO IMMUNE ESCAPE FROM CD8+ T CELLS DIRECTED AGAINST THE CORE-PROTEIN

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Background: Epitopes in the hepatitis B virus core region are important targets of HBV-specific CD8$^+$ T-cell responses. Importantly, there are two different viral proteins in HBV-infected hepatocytes from which these epitopes can be processed and presented to T cells. One is the core protein itself, which is translated from the pregenomic mRNA and is required for nucleocapsid formation. The other is the N-terminally extended precore protein, which is translated from the precore mRNA and further processed and secreted as HBeAg. HBeAg status is an important marker of disease stage and prognosis in hepatitis B. While HBeAg-positive chronic infection is characterized by high viral loads and weak or undetectable CD8$^+$ T-cell responses, the transition to HBeAg-negative infection is associated with activation of HBV-specific CD8$^+$ T-cells. However, it is unclear whether epitopes processed by HBeAg contribute to the CD8$^+$ T cell response and whether the loss of HBeAg may be driven by CD8$^+$ T cell selection pressure. Here, we investigated whether mutations that reduce HBeAg production reduce epitope abundance and thereby contribute to CD8$^+$ T cell immune escape. **Methods:** Different variants of covalently closed circular HBV DNA (cccDNA), including HBV genotypes A and D with and without substitutions in the basal core promoter region, the precore start codon and at position G1896, were produced in vitro and transfected into HLA-A*02-positive HepG2-NTCP cells. Cells transfected with cccDNA were used as targets for CD8$^+$ Jurkat reporter cells carrying TCRs specific for HLA-A*02 restricted epitopes in core or HBsAg. **Results:** HepG2 cells transfected with different genotype A and D cccDNA showed reproducible secretion of HBeAg and HBsAg. These cells were effectively targeted by HBV-specific CD8$^+$ reporter cells, indicating processing and presentation of sufficient amounts of the core peptide for T-cell activation. As expected, the G1896A substitution, which changes the core position W28 to a stop codon, reduced supernatant HBeAg levels without affecting HBsAg levels or intracellular core protein levels. Importantly, the G1896A substitution resulted in an almost complete loss of activation of the HBV-specific CD8$^+$ reporter cells, suggesting that in the absence of HBeAg, the amount of the remaining core epitope was insufficient for CD8$^+$ T cell activation. In the control, the targeting of the epitope in HBsAg was not altered. **Conclusion:** Despite the contribution of HBeAg to an immunologically tolerant state of HBV infection, we find evidence that HBeAg-derived epitopes contribute to the presented peptide repertoire in a model system. Accordingly, when tolerance is broken and CD8$^+$ T cells are activated, mutations associated with loss of HBeAg production appear to contribute to immune escape.

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1514-C | MECHANISM OF A1762T/G1764A MUTATION IN PROMOTING HBV REPLICATION BY AFFECTING HBV TRANSCRIPTOME

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Background: Chronic hepatitis B virus (HBV) infection is still a major public health problem worldwide. The A1762T/G1764A mutation, one of the most common mutations in HBV basal core promoter, is associated with the progression of chronic HBV infection. However, the effect of this mutation on HBV replication remains controversial. Thus, we aimed to systematically address the effect of A1762T/G1764A mutation on HBV replication and explore the underlying mechanisms. **Methods:** To study the effect of the mutation on HBV viral replication, the prcccDNA-A1762T/G1764A mutant plasmid was constructed based on the prcccDNA/pCMV-Cre recombinant plasmid system and transfected into Huh-7 or HepG2 cells. Meanwhile, hydrodynamic injection was conducted. Chemiluminescence detection kit for the quantitative determination of HBsAg or HBeAg, qPCR, Western blot, Southern Blot and Northern blot were used to evaluate the impact of mutation on HBV replication. 5'-RACE assay and full-length transcriptome sequencing were performed to analyze the effect of the mutation on HBV transcripts. Dual luciferase reporter assay was conducted to detect the effect of the mutation on the transcriptional activity of P protein. Additionally, the transcription factors that mediated the A1762T/G1764A mutation to promote viral replication were explored through ChIP-qPCR assay. **Results:** Compared with the wild-type group, A1762T/G1764A mutation promotes HBV replication and suppresses HBeAg production in vitro and in vivo. Southern Blot and Northern Blot also indicated significantly higher intracellular levels of HBV rcDNA, replication intermediates, dslDNA, as well as intracellular HBV 3.5 kb RNA. RT-qPCR and 5'-RACE showed that A1762T/G1764A mutation relatively upregulated the transcription of pgRNA, while downregulated the transcription of preC RNA, which were further confirmed the full-length transcriptome sequencing results. More than that, a proportion of sub-pgRNAs with the potential to express HBV polymerase was also upregulated by A1762T/G1764A mutation. Further ChIP-qPCR assay showed that A1762T/G1764A mutation created a functional HNF1α binding site in BCP region, and overexpression of HNF1α enhanced the effect of A1762T/G1764A mutation on HBV. **Conclusion:** Our findings revealed A1762T/G1764A mutation selectively regulate preC RNA, pgRNA and sub-pgRNA transcription which hints it as an indicator for management of CHB patients, and provide HNF1α as a new target for curing HBV infected patients.

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1515-C | MOLECULAR EPIDEMIOLOGY OF HEPATITIS B VIRUS IN PEOPLE WITH AND WITHOUT HIV COINFECTION IN ZAMBIA, SOUTHERN AFRICA

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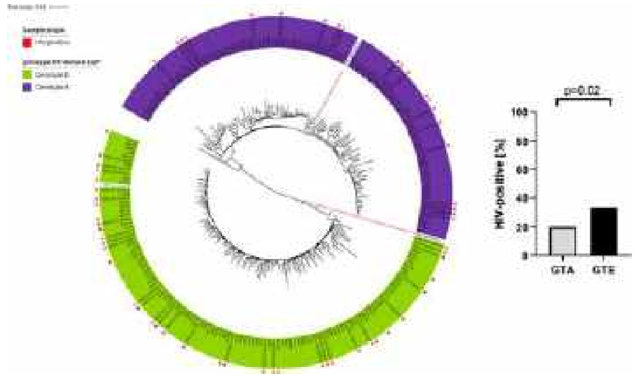
Background: Data are lacking on HBV's natural history in Africa, including host genetics, environmental exposures, and viral factors. The impact of different HBV genotypes found in Africa (A1, D, and E) is poorly understood, including in the context of HIV, a common coinfection in the region. We sequenced HBV in a unique clinical cohort in Zambia and analyzed viral differences by genotype and HIV coinfection status. **Methods:** We analyzed HBV viremic samples from a clinical cohort that recruited treatment-naïve adults (age 18+ years) with HBV/HIV coinfection and HBV monoinfection at 3 hospitals in Lusaka. Participants with coinfection were identified at enrollment into HIV care. Counterparts with HBV alone were identified due to both clinically-driven (i.e., signs/symptoms) or routine HBsAg testing. At enrollment, we measured liver transaminases, hepatitis B e antigen, and HBV DNA (plus CD4 count in HIV coinfection). When HBV DNA was >500 IU/ml, the complete HBV genome was amplified in two fragments and sequenced on the Nanopore platform. **Results:** Sequencing results from 220 adults with HBV DNA >500 IU/ml were analyzed. Their median age was 33.2 years, 65 (29.5%) were women, 60 (27.3%) had HIV coinfection, and in participants with coinfection, the median CD4 count was 137 cells/mm^3. HBV genotype A1 (gtA) and genotype E (gtE) were equally frequent (105 vs. 115); however, HIV coinfection was more common in participants with gtE than gtA (33.9% vs 20.0%; $p=0.02$). Interestingly, gtE isolates displayed less phylogenetic clustering and genetic distance than gtA (median patristic distance, 0.019 vs. 0.011; $p<0.0001$), consistent with more recent and local transmission of gtE in the population. The stop codon in the pre core region associated with HBeAg loss was detected in 42.6% of the gtE isolates, but was nearly absent in gtA. Notably, in gtE this HBeAg variant was less frequent in HBV/HIV coinfection compared to HBV alone (38.4% vs. 70.1%; $p=0.0014$), consistent with less immune pressure in the context of HIV. **Conclusion:** In Zambia, two HBV genotypes are circulating and may have unique transmission patterns. Whereas different gtA isolates were seemingly introduced on multiple occasions and continued to spread through the population, it appears that gtE is a more endemic form of HBV in this region and is still transmitted. Association of HIV with gtE may reflect shared transmission networks between HIV and gtE.



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1516-C | PATHOGENESIS OF FLARES IN LIVER INFLAMMATION IN HEPATITIS B VIRUS-INFECTED WOMEN DURING AND AFTER PREGNANCY

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Background: Pregnant women with chronic hepatitis B are at increased risk of liver inflammation. Here, we examined whether changes in the immune system and the gut microbiome during pregnancy play a role in the pathogenesis of these disease flares. **Methods:** Blood and stool samples from 18 women with chronic hepatitis B (12 without and 6 with NUC treatment) and 3 uninfected women were collected in each trimester of pregnancy and at two and six months postpartum. Increased ALT activity was defined as above the upper limit of normal and twice the baseline value in the respective patient. Plasma levels of cytokines, chemokines and soluble markers of immune cell activation, were assessed by Mesoscale assay. Gut microbial composition was determined by 16S ribosomal RNA amplicon sequencing. **Results:** Seven (58%) treatment-naïve and 2 (33%) NUC-treated patients developed perinatal hepatic flares. While plasma levels of soluble CD163, inflammatory cytokines, and chemokines increased during hepatic flares, IL-22 and IFN-γ levels increased prior to a postpartum hepatic flare in one case. Plasma levels of IL-27, a cytokine produced by the trophoblast, increased in the 3rd trimester even in women with normal ALT levels. The fecal microbiota of hepatitis B virus-infected patients with and without NUC therapy had a lower α-diversity (inverse Simpson index) than those of uninfected controls. 16S rRNA amplicon analysis and principal component analysis revealed patient-specific clustering of the microbiota. To identify predictive factors for postpartum hepatic flares, we compared 16S rRNA DNA data from patients with and without a postpartum hepatic flare (four patients per group). The gut microbiota of those with a hepatic flare was significantly different from those without a hepatic flare and the difference was maintained at all study time points. **Conclusion:** A postpartum ALT increase was preceded by an IL-27, and/or IL-22 and IFN-γ increase during pregnancy in some cases. The composition of the fecal microbiota was found to be patient- rather than time-point-dependent and differed between patients with and without postpartum liver disease flares.
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1517-C | PD-1 INHIBITOR-BASED THERAPIES COULD LEAD TO A DIVERSITY OF VIRAL KINETICS IN CANCER PATIENTS WITH CONCOMITANT HBV INFECTION

Yingfu Zeng, Xinhua Li and Yutian Chong, The Third Affiliated Hospital of Sun Yat-Sen University

Background: Previous studies have shown that blockade of programmed cell death-1 (PD-1) or programmed cell death- Ligand-1 (PD-L1) may improve anti-HBV responses in vitro and woodchuck models. However, due to the fact that PD-1/PD-L1 inhibitors are still under clinical trials, clinical data on their effects or side-effects in the treatment of chronic HBV infection is limited. Therefore, we aimed to observe the changes of serum HBsAg and HBV DNA levels in cancer patients concomitant with HBV infection ongoing PD-1 inhibitor-based therapies and identify the risk factors associated with HBsAg fluctuations and HBV reactivation (HBVr). **Methods:** A retrospective study including HBsAg-positive cancer patients (n = 677) who received PD-1 inhibitors between July 2019 and December 2022 was undertaken. The primary study endpoint was the significant changes of serum HBsAg during treatment, which was defined as serum HBsAg levels were more than 3 folds higher/lower than the baseline after receiving PD-1 inhibitors. The secondary study endpoint was

HBVr, which was defined by the American Association for the Study of Liver Diseases (AASLD) 2018 hepatitis B guidelines. The incidence of HBsAg loss and immune-related adverse events (irAEs) were also investigated. Univariable and multivariable analysis were performed to identify the risk factors for significant serum HBsAg fluctuations and HBVr. **Results:** Due to insufficient attention been paid to the detection of serum HBsAg levels in cancer patients by clinicians, only 121 patients were eligible according to the inclusion criteria of this study (as shown in Fig 1). With concurrent use of antiviral agents, we noticed that most patients with baseline serum HBsAg range between 50 and 500 IU/ml experienced a statistically significant decrease in serum HBsAg levels (Z = -3.2767, $p = 0.001$) after PD-1 inhibitor exposure (as shown in Fig 2), viral replication can be inhibited effectively in most patients undergoing anti-tumor therapies. HBsAg loss, HBVr and irAEs were developed in 6 patients (4.96%), 6 patients (4.96%) and 14 patients (11.57%), respectively. Multivariable analysis showed baseline serum HBsAg less than 100 IU/ml ($p = 0.01$) was the only significant risk factor for HBsAg decrease, irAEs occurrence was the only significant risk factor for HBVr ($p = 0.03$), while no risk factors were identified for HBsAg increase. **Conclusion:** PD-1 inhibitor combined with NAs may exert therapeutic potential for chronic HBV infection in cancer patients, attention also should be paid to the risk of HBVr and irAEs.

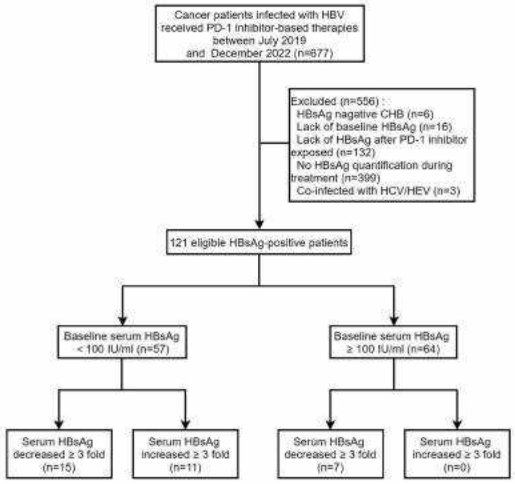

Cancer patients infected with HBV received PD-1 inhibitor-based therapies between July 2019 and December 2022 (n=677)
Excluded (n=556):
HBsAg nagative CHB (n=6)
Lack of baseline HBsAg (n=16)
Lack of HBsAg after PD-1 inhibitor exposed (n=132)
No HBsAg quantification during treatment (n=399)
Co-infected with HCV/HEV (n=3)
121 eligible HBsAg-positive patients
Baseline serum HBsAg < 100 IU/ml (n=57)
Baseline serum HBsAg ≥ 100 IU/ml (n=64)
Serum HBsAg decreased ≥ 3 fold (n=15)
Serum HBsAg increased ≥ 3 fold (n=11)
Serum HBsAg decreased ≥ 3 fold (n=7)
Serum HBsAg increased ≥ 3 fold (n=0)

Figure 1 Flow chart of the present study

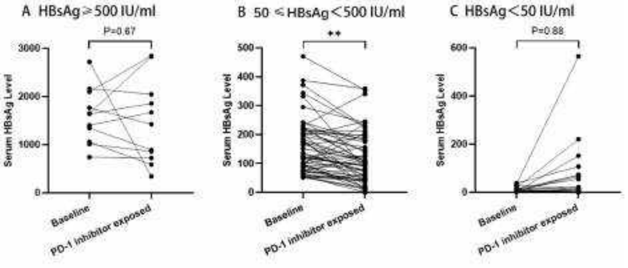


Figure 2 Comparison of serum HBsAg levels before and after PD-1 inhibitor exposure in cancer patients

Disclosures: The following people have nothing to disclose: Yingfu Zeng, Xinhua Li, Yutian Chong

1518-C | PRECORE MUTATION PROMOTES CHRONIC HEPATITIS B DISEASE PROGRESSION VIA ENHANCED VIRAL REPLICATION AND ABERRANT CORE PROTEIN EXPRESSION

Guixin Li[1], Danli Yang[2], Hongsong Chen[1], Xiangmei Chen[2] and Fengmin Lu[2,3], (1)Peking University People's Hospital, Peking University Hepatology Institute, Beijing Key Laboratory of Hepatitis C and Immunotherapy for Liver Disease, (2)Peking University, (3)Peking University People's Hospital

Background: Naturally occurred precore (PC, G1896A) and basal core promoter (BCP, A1762T/G1764A) mutations are prevalent in chronic hepatitis B (HBV)- infected patients. Numerous studies have focused on the role of these mutations in viral replication and disease progression but the conclusion remains ambiguous. This study aimed to explore the effects of PC mutation alone or BCP+PC combined mutations on virus replicative capacity, infectivity and pathogenicity. **Methods:** We searched Pubmed, Embase and Cochrane library to include studies about association of PC mutant with HBV DNA, liver cirrhosis or hepatocellular carcinoma up to June 18, 2022. Transfected or infected cell models and animal models were used. **Results:** Meta-analyses showed that serum HBV DNA load of patients without G1896A mutant was 0.37 $\log_{10}$copies/mL (2.34 foldchange) higher than those with PC mutant among HBeAg-positive patients, whereas it was 0.87 $\log_{10}$copies/mL (7.41 foldchange) lower than those with the mutant among the HBeAg-negative patients. Moreover, PC mutant was closely relevant with liver cirrhosis and hepatocellular carcinoma compared to well-stratified controls. Next, we found that PC mutation enabled preC RNA to serve pgRNA-like function, expressing Core and P protein, to promote HBV replication in transfected cell and mouse models. And compared to PC mutation alone, BCP+PC mutations could further elevated HBV DNA level. Consistently, PC and BCP+PC mutations decreased infectivity but increased replicative capacity in HepG2-NTCP cells and human liver chimeric mice. RNA sequencing of livers in chimeric mice implied BCP+PC mutants suppressed host IFN signaling pathways in human hepatocytes, which might account for elevated cccDNA level. Importantly, accumulation of core proteins likely led to severe human hepatocyte degeneration and cytoplasmic vacuolation via endoplasmic reticulum stress and TNF signaling pathway, which might in turn induce the compensatory proliferation

indicated by enhanced cell cycle and hippo pathways in mouse livers of BCP+PC group. **Conclusion:** PC and/or BCP mutations enhanced HBV replication *in vitro* and *in vivo*, but the association of PC mutant with higher HBV DNA level was observed solely in HBeAg-negative patients. PC mutant was closely associated with advanced liver diseases in chronic HBV-infected patients. BCP and PC combined mutations might induce severe hepatocyte damage via enhanced viral replication and aberrant core protein expression in human liver chimeric mice.

Disclosures: The following people have nothing to disclose: Guixin Li, Danli Yang, Hongsong Chen, Xiangmei Chen, Fengmin Lu

1519-C | SUPPRESSION OF HSPG2 EXPRESSION INHIBITS HBV ENTRY AND REPLICATION VIA INCREASED cMET EXPRESSION

Kazuhiro Murai[1], Hayato Hikita[1], Tasuku Nakabori[1], Shinji Kuriki[1], Emi Sometani[1], Jihyun Sung[1], Akiyoshi Shimoda[1], Makoto Fukuoka[1], Satoshi Shigeno[1], Akira Nishio[1], Takahiro Kodama[2], Tomohide Tatsumi[2], Hiroshi Suemizu[3] and Tetsuo Takehara[2], (1)Osaka University, Graduate School of Medicine, (2)Osaka University Graduate School of Medicine, (3)Central Institute for Experimental Animals

Background: Hepatitis B virus (HBV) entry into hepatocyte requires heparan sulfate proteoglycans (HSPGs) and NTCP, which is a bile acid transporter (BAT). Among HSPGs, we focused on HSPG2, which contributes to the binding of HGF fragments and cMET. We investigated the effect of HSPG2 suppression on HBV infection and its mechanism. **Methods:** Primary human hepatocytes isolated from humanized liver chimeric TK-NOG mice (HepaSH cells) were inoculated with HBV (500 genome equivalent (GEq)/cell) prepared by concentrating the culture supernatant of HBV genome-integrated cells (HepAD38.7). **Results:** The suppression of HSPG2 expression with siRNA 3 days before HBV inoculation significantly decreased the expression levels of covalently closed circular DNA (cccDNA). The suppression of HSPG2 expression significantly increased cMET expression and decreased NTCP expression. The suppression of NTCP expression by the suppression of HSPG2 expression was cancelled by the suppression of cMET. On the other hand, the suppression of NTCP expression did not alter the mRNA expression levels of HSPG2. The suppression of NTCP expression with siRNA 3 days before HBV inoculation significantly decreased the expression levels of cccDNA. The suppression of both HSPG2 and NTCP expression had no additional effect on cccDNA reduction compared to the suppression of NTCP alone. The suppression of HSPG2 may inhibit HBV entry by suppressing NTCP expression through upregulation of cMET expression. The suppression of NTCP expression 20 days after HBV inoculation did not reduce the expression levels of cccDNA, but the suppression of HSPG2 expression did. Considering the possibility that the suppression of HSPG2 expression may have other mechanisms to affect HBV replication than HBV entry inhibition, we focused on PPARγ, a host transcription factor that activates HBV transcription. The suppression of HSPG2 upregulated cMET and downregulated PPARγ. The Suppression of PPARγ downregulated NTCP, NR5A2, which regulates BAT expression, and CTNNB1, an activator of NR5A2. The Suppression of CTNNB1 downregulated NR5A2 and NTCP. The suppression of NR5A2 downregulated NTCP. It was suggested that cMET regulated NTCP expression via PPARγ, CTNNB1 and NR5A2. **Conclusion:** Suppression of HSPG2 expression was suggested to have an effect that suppress both HBV entry and replication via increased cMET expression.

Disclosures: The following people have nothing to disclose: Kazuhiro Murai, Hayato Hikita, Jihyun Sung, Akiyoshi Shimoda, Makoto Fukuoka, Akira Nishio, Takahiro Kodama, Tomohide Tatsumi, Tetsuo Takehara

Disclosure information not available at the time of publication: Tasuku Nakabori, Shinji Kuriki, Emi Sometani, Satoshi Shigeno, Hiroshi Suemizu

1520-C | SUPPRESSION OF MIR-451a TRIGGERS A MYC DEPENDENT OVERPRODUCTION OF ONCOMIR-126-5p LEADING TO ACTIVATION OF Β-CATENIN SIGNALING AXIS BY IMPEDING DKK1 THAT PROMOTES CHEMO-RESISTANCE TO HEPATOCELLULAR CARCINOMA CELLS.

Anannya Chakraborty[1], Sanjana Banerjee[1], Swagata Majumdar[1], Indrashish Dey[1], Amit Ghosh[1], Suchandrima Ghosh[1], Sayantani Bhowmik[1], Abhijit Chowdhury[2], Simanti Datta[1] and Soma Banerjee[1], (1) Institute of Post Graduate Medical Education and Research, (2)Institute of Post Graduate Medical Education & Research

Background: Despite availability of vaccine against Hepatitis B virus, chronic hepatitis B (CHB) is a global health threat and the major underlying risk factor for the development of Hepatocellular Carcinoma (HCC). Chemoresistance is the major obstacles in the current treatment modalities of HCC. This study explored the role of oncogenic transcription factor MYC on the deregulation of microRNA and its impact on chemo-resistance of HCC. **Methods:** Transcriptome-analysis/qRT-PCR/Bioinformatics/Luciferase assay/ELISA/Immuno-blotting/Chromatin-Immuno-precipitation/Transfection/Cell proliferation/ Apoptosis/ Migration/ Chemo-sensitivity assay, etc. were employed as required. **Results:** Transcriptome analysis of GSE 94660 that includes liver tissue of 21 HBV-HCC and 21 adjacent normal revealed that 52 oncogenic transcription factors (TF) were upregulated in HCC. Among which MYC was observed as one of the most overexpressed TFs. Subsequently, it was observed that MYC could activate the expression of endothelial growth factor 7 (EGFL7) intron derived miRNA, miR-126-5p, which was previously established as biomarker of HCC. ChIP-assay further confirmed the binding of MYC to the promoter of EGFL7/miR-126. HBX protein of HBV was the activator of MYC oncoprotein. Target prediction and pathway analysis with validated targets in transcriptome data revealed WNT signaling pathway was the most targeted pathway of this miRNA. Luciferase assay and western blot analysis showed that each protein of β-catenin destruction complex (GSK3β/ APC/AXIN) and DKK1, inhibitor of Wnt-β catenin pathway were impeded by miR-126-5p. Restoration of miR-126-5p in Huh7/Snu449 augmented the chemoresistance to 5FU/ sorafenib and triggered proliferation and stemness in HCC cells as MYC/OCT4/NANOG/CD44 was overproduced in the milieu and followed a feedback loop. The expression of MYC was observed to be maintained by a tumor suppressor miRNA, miR-451a in HCC. **Conclusion:** These results highlighted that targeting oncogenic transcription factor may be useful in the clinical management of HCC patients.

Disclosures: The following people have nothing to disclose: Anannya Chakraborty, Sanjana Banerjee, Swagata Majumdar, Indrashish Dey, Amit Ghosh, Suchandrima Ghosh, Sayantani Bhowmik, Abhijit Chowdhury, Simanti Datta, Soma Banerjee

1521-C | TARGETED VIRAL ADAPATION GENERATES A SIMIAN-TROPIC HEPATITIS B VIRUS THAT INFECTS MARMOSET CELLS

Yongzhen Liu[1], Thomas R. Cafiero[1], Debby Park[1], Abhishek Biswas[1], Benjamin Y. Winer[1], Cheul H. Cho[2], Yaron Bram[3], Vasuretha Chandar[3], Aoife K. O'Connell[4], Hans P. Gertje[4], Nicholas Crossland[4], Robert E. Schwartz[3] and Alexander Ploss[5], (1)Princeton University, (2)Visikol, Inc., (3)Weill Cornell Medicine, NY, (4)Boston University, (5)Princeton University, Princeton, NJ

Background: Hepatitis B virus (HBV) only infects humans and chimpanzees, posing major challenges for modeling HBV infection and chronic viral hepatitis. The major barrier in establishing HBV infection in non-human primates lies at incompatibilities between HBV and simian orthologues of the HBV receptor, sodium taurocholate co-transporting polypeptide (NTCP). **Methods:** Phylogenetic analysis among NTCP orthologues from Old World monkeys (OWM), New World monkeys (NWM) and prosimians were performed. Myristoylated preS1[2-48]-FITC peptides of HBV or woolly monkey HBV (WMHBV) were used for viral binding assays by fluorescence confocal microscopy and flow cytometry. HepG2 cells expressing different NTCP orthologues and mutagenesis analysis were used for HBV binding, entry, and infection assays. AlphaFold NTCP structure prediction was used for analyzing the structural basis. Sucrose density gradient centrifugation and transmission electron microscopy were employed for HBV/WMHBV preS1[1-48] chimeric virus characterization. Self-assembling co-cultures of primary marmoset hepatocytes (PMH) and murine non-parenchymal stromal cells were established to maintain the highly differentiated phenotype of primary hepatocytes for HBV, WMHBV and HBV/ WMHBV preS1[1-48] chimeric virus infection. Marmoset induced pluripotent stem cell (iPSC)-derived hepatocyte-like cells were developed for HBV and HBV/WMHBV preS1[1-48] infection. Southern blot, HBV cccDNA qPCR, multiplexed HBV RNA in situ hybridization (ISH), HBc and NTCP immunohistochemistry (IHC) were used to determine the infection. **Results:** Our results suggest R158G enables binding of preS1 to OWM-NTCP, whereas G158R abrogates preS1 binding to NWM-NTCP, underscoring that G158 is necessary for HBV binding while residues 84-87 are functional for HBV internalization. We also found L165 is another important residue to accelerate HBV infection by stabilize NTCP structure. More importantly, structure analysis among wild type NTCPs from OWM and NWM suggests marmoset has the lowest root mean squared deviation compared with hNTCP. We replaced residues 1-48 of HBV preS1, the key regions mediating HBV entry, with the equivalent WMHBV sequence that differs by 16 AAs, yielding a chimeric virus termed HBV/WMHBV preS1[1-48] which has similar biophysical properties with HBV. Functionally, HepG2 cells expressing marmoset-NTCP, primary marmoset hepatocytes and induced marmoset pluripotent stem cell-derived hepatocyte-like cells support HBV and more efficient woolly monkey HBV (WMHBV) infection. Adapted chimeric HBV genome harboring residues 1-48 of WMHBV preS1 led to a more efficient infection than wild-type HBV in primary and stem cell derived marmoset hepatocytes. **Conclusion:** Our data demonstrate that minimal targeted simianization of HBV can break the species barrier in small NHPs, paving the path for an HBV primate model.

Disclosures: Robert E. Schwartz – Miromatrix Inc: Advisor, No, No; Alnylam Pharmaceuticals: Speaking and Teaching, No, No; Lime Therapeutics: Advisor, No, No; Alnylam Pharmaceuticals: Consultant, No, No;

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

The following people have nothing to disclose: Yongzhen Liu
Disclosure information not available at the time of publication: Thomas R. Cafiero, Debby Park, Abhishek Biswas, Benjamin Y. Winer, Cheul H. Cho, Yaron Bram, Vasuretha Chandar, Aoife K. O'Connell, Hans P. Gertje, Nicholas Crossland, Alexander Ploss

1522-C | TENOFOVIR ALAFENAMIDE FUMARATE IN TREATMENT-NAÏVE CHRONIC HEPATITIS B PATIENTS WITH HISTOLOGICALLY CONFIRMED LIVER FIBROSIS: A 48-WEEK EFFICACY AND SAFETY RESULTS

Jialing Zhou[1], Xiaoning Wu[2], Chuanwu Zhu[3], Jiming Zhang[4], Ping Li[5], Tao Han[6,7], Huiguo Ding[8], Chenghai Liu[9,10], Wen Xie[11], Qing Xie[12], Yali Zong[13], Tongtong Meng[2], Xiaojuan Ou[2], Hong You[14] and Jidong Jia[2], (1) Beijing Friendship Hospital, Capital Medical University, National Clinical Research Center of Digestive Diseases, Beijing, China, (2)Liver Research Center, Beijing Friendship Hospital, Capital Medical University, National Clinical Research Center of Digestive Diseases, Beijing, China, (3)The Fifth People's Hospital of Suzhou, (4)Fudan University, (5)Department of Hepatology, Tianjin Second People's Hospital, Tianjin, China, (6)Tianjin Third Central Hospital, Tianjin, China, (7)Tianjin Medical University, Tianjin Union Medical Center Affiliated to Nankai University, (8)Department of Gastroenterology and Hepatology, Beijing You'an Hospital, Capital Medical University, Beijing, China, (9) Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, (10)Shanghai Key Laboratory of Traditional Chinese Clinical Medicine, (11) Center of Liver Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, China, (12)Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, (13) The Ninth Hospital of Nanchang, (14)Liver Research Center, Beijing Friendship Hospital, Capital Medical University

Background: The antiviral efficacy of tenofovir alafenamide (TAF) in both control trials and real-world studies are well documented in patients with chronic hepatitis B (CHB). However, its histological effect on liver fibrosis is still unknown. Therefore, we conducted a single arm study to investigate anti-fibrotic effect of 96 weeks of TAF. In this interim analysis, we present the effect of 48-week treatment with TAF on liver fibrosis evaluating by non-invasive methods. **Methods:** Treatment-naïve CHB patients with histologically confirmed liver fibrosis patients were prospectively recruited from 10 tertiary hospitals in China (NCT04939441). Virological responses (VR: HBVDNA < 20 IU/ml), alanine aminotransferase (ALT) normalization (< 40 IU/L) and noninvasive indicators including LSM, aspartate aminotransferase-to-platelet ratio index (APRI) and Fibrosis 4 Score (FIB-4) were used to assess liver fibrosis at every 24 weeks during treatment. Safety profiles covered estimated glomerular filtration rate (eGFR), bone density and lipid profiles at 48 weeks. **Results:** A total of 100 CHB patients were enrolled. At baseline, The mean age of the cohort was 42.2 ± 10.3 years and 59% of the subjects were male. There were 47, 30 and 23 patients staged at F2, F3 and F4 respectively according to Metavir score system before treatment. VRs at 12, 24 and 48 weeks were 34%, 49% and 74%, respectively. ALT normalization rates were 61% and 75% at 24 and 48 weeks, respectively. LSM, APRI and FIB-4 significantly declined ($p < 0.001$) at 48 weeks. LSM decreased from 9.6 to 6.8 kPa at 48 weeks with a steep decline in the first 24 weeks and then a gradual decline. There were 73.1% patients had LSM decrease, especially 44 patients (47.3%) decreased at least 30% of LSM at 48 weeks. Changes of APRI and FIB-4 were similar to LSM. From baseline to week 12, the median changes in eGFR, using the *CKD-EPI* equation, showed transient and mild reduction. There was no statistically significant in hip and spine BMD and lipid profiles (TG, TC, HDL and LDL) from baseline to week 48. During the 48-week treatment, five cases of serious adverse event occurred. **Conclusion:** TAF had good efficacy in virological response, biochemical response and safety profiles. More importantly, the study demonstrated that TAF could well reverse hepatitis B liver fibrosis by using non-invasive indicators.

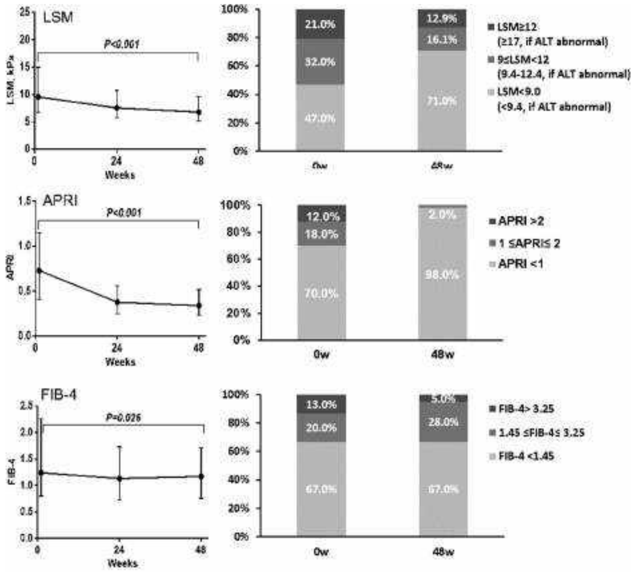


Figure 1. Liver fibrosis evaluation using noninvasive indicators for tenofovir alafenamide fumarate in treatment chronic hepatitis B patients

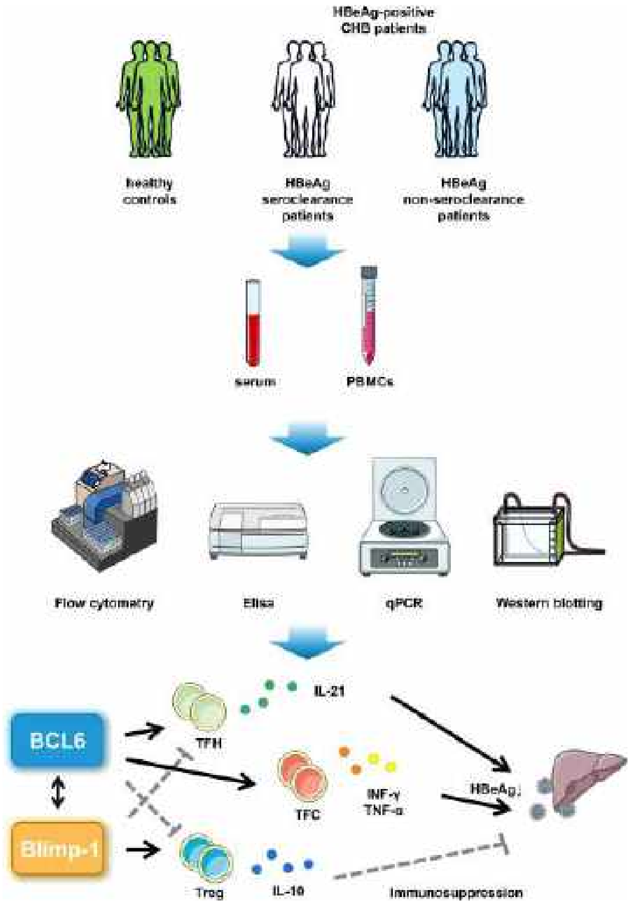
Disclosures: Jialing Zhou – Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's

institution receives the research grant and manages the funds), No, Yes;
The following people have nothing to disclose: Xiaoning Wu, Chuanwu Zhu, Jiming Zhang, Ping Li, Tao Han, Huiguo Ding, Chenghai Liu, Wen Xie, Qing Xie, Yali Zong, Tongtong Meng, Xiaojuan Ou, Hong You, Jidong Jia

1523-C | THE BCL6/Blimp1 AXIS REGULATES FOLLICULAR T CELLS TO PROMOTE HBEAG SEROCLEARANCE IN PATIENTS WITH HBEAG-POSITIVE CHRONIC HEPATITIS B

Shuo Li[1,2], Xiaoke Li[1,2], Xiaobin Zao[1,2], Hongbo Du[1,2], Da'Nan Gan[1,2] and Yong'An Ye[1,2], (1)Dongzhimen Hospital, Beijing University of Chinese Medicine, (2) Institute of Liver Diseases, Beijing University of Chinese Medicine

Background: T cells exert both protective and pathogenic effects in CHB. Follicular T cells, a particular subgroup of T cells that express the C-X-C pattern chemokine receptor 5 (CXCR5), have gained attention in recent years due to unique characteristics and potential impact on the immune response in chronic hepatitis B (CHB). This study aimed to investigate the role of the BCL6/Blimp1 axis in regulating follicular T cells and improving the seroclearance of hepatitis B e antigen (HBeAg) in CHB patients. **Methods:** Flow cytometry was conducted using circulating peripheral blood mononuclear cells (PBMCs) obtained from 15 healthy controls (HCs) and 40 patients with CHB. These patients exhibited different HBeAg responses (seroclearance response [SR] and non-seroclearance response [NR]) following a 96-week regimen of Entecavir (ETV). The potential correlations between the frequency of follicular T cells, clinical parameters, and relevant serum cytokines (IL-10, IL-21, IFN-γ, and TNF-α) expression were assessed. The mRNA and protein expression levels of BCL-6, Blimp-1, IL-21, and IFN-γ were evaluated by quantitation PCR and western blotting analyses, respectively. **Results:** The frequencies of $CD4^+CXCR5^+$ T follicular helper (TFH) cells and $CD8^+CXCR5^+$ T follicular cytotoxic cells (TFC) were significantly higher in HBeAg-positive CHB patients compared with HCs. Compared with the NR patients, there was an increase in the frequencies of TFH and TFC and a decrease in the frequency of $CD4^+CD25^+$ regulatory T cells (Tregs) in SR patients. The subgroups of TFH and TFC were analyzed. Compared with the NR patients, $ICOS^+CXCR5^+CD4^+$ TFH and $CD127^+CXCR5^+CD8^+$ TFC were significantly higher in SR patients. The SR patients showed higher levels of IL-21 and IFN-γ than the NR patients. Additionally, BCL-6, IL-21, and IFN-γ expression were significantly upregulated, while Blimp-1 expression was downregulated in SR patients. **Conclusion:** The BCL6/Blimp1 axis regulates follicular T cells to promote HBeAg seroclearance in patients with HBeAg-positive CHB. These findings may contribute to a better understanding of the function of follicular T cells and provide a potential immunotherapeutic target for chronic HBV infection.



Disclosures: The following people have nothing to disclose: Shuo Li, Xiaoke Li, Xiaobin Zao, Hongbo Du, Da'Nan Gan, Yong'An Ye

1524-C | THE HBV SMALL SURFACE ANTIGEN IS TRANSPORTED DIRECTLY FROM THE ENDOPLASMIC RETICULUM TO AN AUTOPHAGIC/LATE ENDOSOMAL PATHWAY

Mark A. McNiven[1], Hong Cao[2], Eugene Krueger[1], Jing Chen[1], Huiling Yang[3], JiaJun Chia[3], Jane Tam[3], Dimytro Kornyeyev[3] and Meghan Holdorf[3], (1)Mayo Clinic, (2)Mayo Clinic Rochester, Rochester, MN, (3) Gilead Sciences, Inc.

Background: Hepatitis B is a common infectious disease in humans and is associated with significant morbidity and mortality. The hepatitis B virus (HBV) encodes three transmembrane surface proteins of distinct sizes (HBsAg L,M,S) which contribute to the viral envelope and also assemble into capsid-free subviral particles/filaments (SVPs) that are secreted in massive amounts to potentiate infection. Currently the cellular mechanisms by which these SVPs are secreted from the host are unclear. Therefore, the **GOAL** of this study was to define the precise hepatocellular trafficking pathway utilized to support HBsAg (SVP) secretion. **Methods:** High resolution confocal microscopy and a novel mCherry-tagged HBsAg-probe were applied to a HepG2 cell line stably expressing the small surface antigen (SHBsAg), as well as HBV-infected primary human hepatocytes (PHH). The truncated SHBsAg-GFP/mCherry probe was constructed and characterized to observe SHBsAg trafficking in live cells, an approach that has been unsuccessful to date. Secretion of SHBsAg was also monitored by Western blot analysis and a chemiluminescence immunoassay. **Results:** Detailed imaging of both HepG2 and PHH cell models indicates that the SHBsAg transits directly from the ER to the late endosomal compartments including the multivesicular body (MVB) and lysosome while bypassing the Golgi apparatus. This unique SHBsAg secretory pathway was compared within the HepG2 and PHH models that were co-transfected with the vesicular stomatitis virus G (VSV-G) protein, well known to utilize a canonical ER to Golgi to surface pathway. Importantly, in both fixed and live cells the VSV-G protein was observed to transit from the ER-Golgi-surface while the SHBsAg trafficked directly from ER to MVBs, including autophagic LC3 positive structures. To further test for a direct ER to autophagosome SHBsAg pathway, we applied an siRNA knockdown approach to target autophagosome/ER-Phagy receptors/adaptors and found that disruption of this pathway resulted in reduced secretion and an intracellular accumulation of SHBsAg as a result of treatment with the lysosome inhibitor Baf-A1. **Conclusion:** this study indicates that in both HepG2 and PHH cell models the SHBsAg particles bypass the canonical ER-Golgi secretory pathway and instead are transited directly to the autophagic/MVB pathway via an ER-phagy process. These findings along with the development of a novel tagged bio-probe will facilitate the study and understanding of HBV infection.

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Disclosure information not available at the time of publication: Jing Chen, Huiling Yang, JiaJun Chia, Jane Tam, Dimytro Kornyeyev, Meghan Holdorf

1525-C | THE IMPACT OF SINGLE-NUCLEOTIDE VARIANTS AND SURFACE ANTIGEN MUTATION ON THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC HBV INFECTION

Yuh-Jin Liang, Taipei Veterans General Hospital; National Yang Ming Chiao Tung University

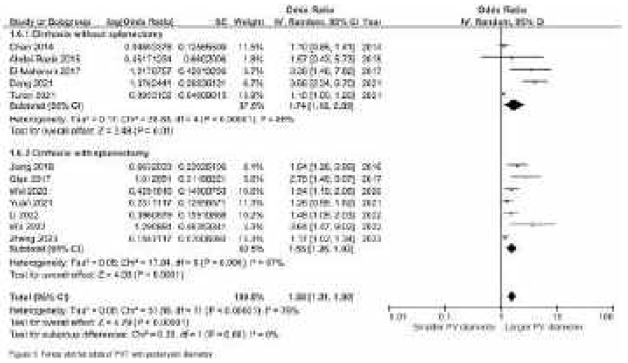
Background: Nucleos(t)ide analogues (NUC) therapy has shown efficacy in reducing hepatocellular carcinoma (HCC) incidence in HBV carriers with normal or mildly elevated ALT levels. Our previous study also identified mitochondrial dysfunction as a novel mechanism in HBV-related liver disease, particularly in carriers with secretion-defective Pre-S/S deletion mutants. Additionally, a genome-wide high-throughput analysis revealed HBV single-nucleotide variants (SNVs) associated with HCC development. **Methods:** In a separate report presented at this conference, our research team conducted a longitudinal case-control study to assess the predictive value of SNVs in the Pre-S/S region and the role of antiviral therapy in patients not meeting current treatment guidelines (ALT < 80 U/L or HBV DNA < 2000 IU/ml). This report investigates the impact of Pre-S/S region SNVs on mitochondrial function, calcium homeostasis, and HBV DNA retention/secretion in HCC cell lines. Methods included Seahorse XF real-time ATP rate assay, calcium imaging, quantitative PCR, and western blot. **Results:** HCC-associated SNVs generally led to ATP depletion, with genotype C SNVs, such as G530A and T724C, affecting mitochondrial ATP production and genotype B SNVs, such as A2889G and C3097A, impairing glycolysis-driven ATP production. Genotype C SNVs also correlated with higher ROS production and lower mitochondrial membrane potential. Calcium imaging revealed that T53C SNV and Pre-S/S region deletion-expressing cells exhibited elevated basal calcium levels and reduced calcium buffering capacity. Furthermore, T53C SNV and Pre-S/S deletion demonstrated higher intracellular retention of HBV DNA and HBsAg, accompanied by increased ER stress and unfolded protein response. **Conclusion:** Our findings suggest heterogeneity in the pathogenic role of HBV SNVs, with secretion-defective mutants, such as T53C and Pre-S/S deletion, inducing ER stress, impairing mitochondrial function, and reducing ATP production, while secretion-efficient SNVs, such as A293G and G633A, may enhance viral replication and infectivity. In a separate report presented at this conference, our research team also revealed that inhibition of late-phase autophagy by HBV contributes to liver injury and the development of HCC. Further investigations will assess the impact of these SNVs on autophagic and lysosomal activity.

Disclosures: The following people have nothing to disclose: Yuh-Jin Liang

1600-A | ASSESSMENT OF PORTAL SYSTEM HEMODYNAMICS FOR THE PREDICTION OF PORTAL VEIN THROMBOSIS IN CIRRHOSIS – A SYSTEMATIC REVIEW AND META-ANALYSIS

Marko Kozyk[1], Suprabhat Giri[2], Ankita Singh[3], Kailash Kolhe[4], Akash Roy[5] and Kateryna Strubchevska[1], (1) Corewell Health William Beaumont University Hospital, (2)Nizam's Institute of Medical Sciences, (3)Seth GS Medical College and Kem Hospital, (4)Narayana Hospital, (5)Apollo Hospitals, Kolkata

Background: The pathogenesis of portal vein thrombosis (PVT) in cirrhosis is multifactorial, with altered hemodynamics being proposed as a possible contributor. The present systematic review was conducted to study the role of assessment of portal hemodynamics for the prediction of PVT in patients with cirrhosis. **Methods:** Three databases (Medline, Embase, and Scopus) were searched from inception to February 2023 for studies comparing portal venous system parameters in patients with cirrhosis developing PVT with those not. Results were presented as mean difference (MD) or odds ratio (OR) with their 95% confidence intervals (CI). **Results:** A total of 31 studies (patients with cirrhosis: 19 studies, patients with cirrhosis undergoing splenectomy: 12 studies) were included. In patients with cirrhosis, portal vein diameter (PVD), splenic length, and splenic thickness were significantly shorter in those without PVT than those developing PVT with a MD of -1.62 (-2.51 to -0.73) cm, -1.17 (-1.59 to -0.75) cm, and -0.97 (-1.19 to -0.74) cm, respectively. On pooling the data from multivariable analyses of the included studies, a larger portal vein diameter was a significant predictor of PVT in patients with cirrhosis without or with splenectomy with OR 1.74 (1.12 – 2.69) and OR 1.55 (1.26 – 1.92), respectively (Figure 1). With each 1 cm increase in the PVD, there was 1.7 times higher odds of developing PVT in cirrhotics. On the other hand, portal vein velocity (PVV) was significantly higher in those not developing PVT than those developing PVT, with an MD of 5.23 (4.86 to 5.60) cm/s. A lower PVV was a significant predictor of PVT in cirrhotics without or with splenectomy with OR 0.93 (0.91 – 0.96) and OR 0.71 (0.61 – 0.83), respectively. With each 1 cm/s reduction in PVV, there was 1.1 times higher odds of developing PVT in cirrhotics. A PVV of < 15 cm/s was the most commonly used cut-off for the prediction of PVT. Patients developing PVT also had a significantly higher splenic length, thickness, and splenic vein velocity. **Conclusion:** The assessment of portal hemodynamic parameters at baseline evaluation in patients with cirrhosis may predict the development of PVT. Further studies are required to determine the optimal cut-offs for various parameters.



Disclosures: The following people have nothing to disclose: Marko Kozyk, Suprabhat Giri, Ankita Singh, Kailash Kolhe, Akash Roy, Kateryna Strubchevska

1601-A | EVALUATION OF RESPONSE TO HIGH-DOSE INTRAVENOUS VITAMIN K ADMINISTRATION

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Background: In addition to its use in the correction of clotting factor deficiencies and reversal of warfarin-induced bleeding, high-dose intravenous (IV) vitamin K (phytonadione) (IVK) is often used to lower INR in patients with cirrhosis to "challenge" INR elevation in the setting of nutritional deficiency. Limited data exists supporting repeat dosing. This study sought to characterize differences in responders and non-responders to high-dose IVK to guide dosing strategies. **Methods:** This was a subgroup analysis of patients with cirrhosis from a previously published case-control study of hospitalized adults (≥ 18 y) who received IVK 10 mg daily for 3 days for treatment of coagulopathy, defined as an international normalized ratio (INR) of > 1.5. Patients with an INR < 1.5 or ≥ 30% lower than baseline after the first dose of IVK were considered responders and compared to non-responders. The primary outcome was change in INR over time with subsequent doses. A linear mixed-effects model (LMM) compared reduction of INR at follow-up time points between groups. Secondary outcomes included factors associated with response to IVK and incidence of safety events. **Results:** 455 patients with were included; 151 were

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

IVK responders. Most patients were white (n = 335, 75%) males (n = 238, 52%) with a mean age of 53 ± 14 years. Most patients had alcohol-related cirrhosis (n = 249, 55%), with a mean MELD score of 25.3 (95% CI 18.9-31.2). INR decreased from 1.94 (adjusted least square mean from LMM, 95% CI 1.88-2.00) to 1.67 (1.63-1.71); a 16% reduction from baseline to day 3 (11.9-20.2%). In responders, the largest INR decrease occurred from 1.91 at baseline (95% CI 1.82-2.0) to 1.48 on day 1 (1.43-1.54) and to 1.39 on day 3 (1.34-1.44). In non-responders, INR changed from 1.96 at baseline (95% CI 1.89-2.03) to 1.84 on day 3 (1.79-1.89). Predictors of response included lower weight, compensated cirrhosis, cirrhosis etiologies other than alcohol, and lower bilirubin. There was a low incidence of anaphylactoid events. Risk of bleeding was not assessed. **Conclusion:** In this subgroup analysis of patients with cirrhosis, the overall adjusted change in INR over 3 days was 0.3 with minimal variation between responders and non-responders. In responders, the largest reduction in INR occurred after the first dose and minimal change occurred with subsequent doses. Future studies may serve to characterize patient populations who would benefit from sequential daily IVK versus single dosing.

Disclosures: Jason Yerke – DexCom, Inc.: Stock – privately held company (individual stocks and stock options), No, No; Semler Scientific, Inc.: Stock – privately held company (individual stocks and stock options), No, No; Intuitive Surgical, Inc.: Stock – privately held company (individual stocks and stock options), No, No; Repligen Corp: Stock – privately held company (individual stocks and stock options), No, No; Christina C. Lindenmeyer – Merck & Co. Author for Merck Manuals: Independent contractor (including contracted research), No, Yes;

The following people have nothing to disclose: April Chapman, Mollie Lumpkin, Michael Rudoni, Aanchal Kapoor, Lu Wang, Stephanie Bass

1602-A | MULTIDISCIPLINARY CARE IMPROVES SURVIVAL IN PATIENTS WITH SPLANCHNIC VEIN THROMBOSES

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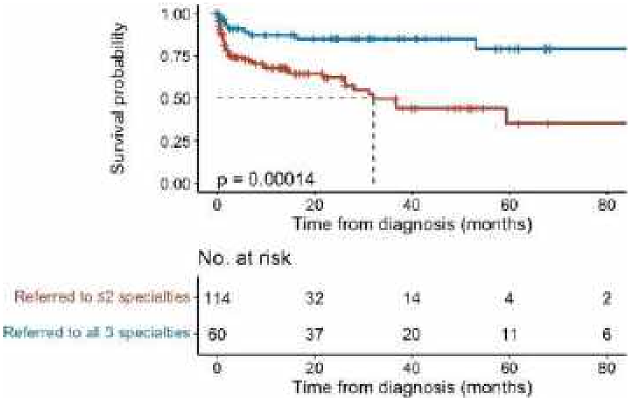
Background: Splanchnic vein thromboses (SVT) are complications of liver cirrhosis as well as underlying hypercoaguable states, notably myeloid proliferative neoplasms. When treatment is indicated, anti-coagulation is the mainstay of therapy. Procedural intervention, such as transjugular intrahepatic portosystemic shunt placement, is reserved for patients with ischemic or portal hypertensive complications. The management of SVTs is complex and requires weighing the risk and benefit of any intervention carefully. Multidisciplinary input from hematology, hepatology and interventional radiology (IR) is often solicited for this population. The aim of this study is to identify the rates of multidisciplinary care and its impact on patient survival. **Methods:** We queried our imaging database to identify patients with possible splanchnic vein thrombosis based on imaging report. We evaluated 307 consecutive patients with a multi-phasic cross-sectional imaging report from 2013 to present. 196 cases had a confirmed SVT. We recorded if the patients had been evaluated by hepatology, hematology, and/or IR after their SVT diagnosis. Overall survival (OS) was estimated via Kaplan Meier method. To account for immortal time bias, a landmark analysis was also performed. **Results:** Of the 196 patients with a confirmed SVT, 170 (87%) had portal vein thromboses. 22 (11%) had hepatic vein thromboses, 44 (22%) had splenic vein thromboses, and 77 (39%) had mesenteric vein thromboses. Of these, 84 patients (43%) had thrombosis at multiple sites. A majority of patients (73%) were seen by hepatology after their diagnosis, as well as by hematology (60%), and by IR (59%). A total of 149 patients (77%) were seen by a specialist within 1 month of their diagnosis. Only 61 patients (31%) saw all three specialists. After a median follow up of 22.7 months, 27 patients died. The median OS of patients seen by all three specialties was significantly longer (Not Reached [NR]) as compared to those seen by 2 or less specialties (32.0 mo, Figure). The landmark analysis demonstrated similar results. **Conclusion:** Most patients diagnosed with an SVT were seen by a specialist in hematology, hepatology, or IR. However, only a third of patients saw physicians from all three specialties. Increasing multidisciplinary care for patients with SVTs between hematology, hepatology, and IR may improve mortality. Multidisciplinary pathways to facilitate interdisciplinary communication may greatly impact outcomes among patients with SVTs.



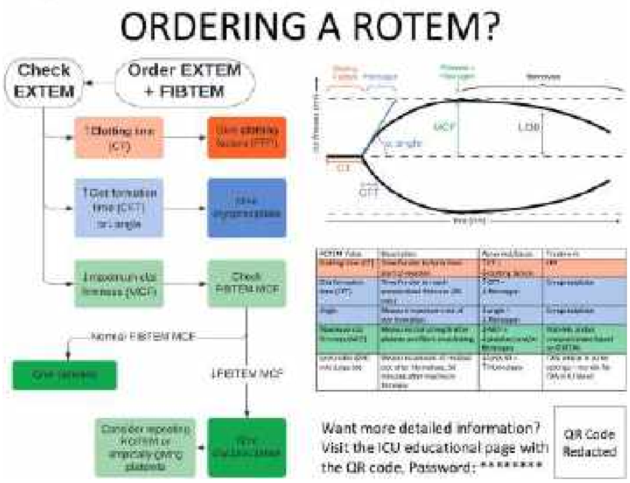
Disclosures: The following people have nothing to disclose: Dina Zaret, Thomas Schiano, Adam Winters
Disclosure information not available at the time of publication: Dahniel Sastow, Tyler Italiano, Rahul Patel, Douglas Tremblay

1603-A | QUALITY IMPROVEMENT AND EDUCATION PROJECT IMPROVES HOUSE STAFF CONFIDENCE AND PERFORMANCE IN ORDERING AND INTERPRETING ROTATIONAL THROMBOELASTOMETRY FOR PATIENTS WITH COAGULOPATHY OF END STAGE LIVER DISEASE

Alexander N. Scherer[1,2], Mary Clare McGregor[1], Jaquelyn F. Fleckenstein[1] and Daniel Reynolds[1], (1) Washington University School of Medicine in St. Louis, (2)Indiana University School of Medicine

Background: In patients with end stage liver disease (ESLD), INR values do not predict bleeding risk nor reflect dynamic changes in coagulopathy. Rotational thromboelastometry (ROTEM) is an alternative, real-time test of hemostasis performed on whole blood. ROTEM-based transfusion strategies have reduced transfusions, costs, and transfusion reactions in ESLD patients prior to procedures or during bleeding. One barrier to using such a strategy is provider familiarity with ordering and interpreting ROTEM tests. We implemented a quality improvement (QI) and education project to improve house staff knowledge of indications for and interpretation of ROTEM in ESLD patients. **Methods:** We implemented an education and QI project in an ICU setting at a single tertiary care center over six months. We provided educational resources in the form of a monthly lecture, infographics in work areas (Fig. 1), and an online literature review. House staff voluntarily responded to assessments before and after their ICU rotations. The primary outcome was confidence in ordering and interpreting ROTEM in ESLD patients. The secondary outcome was correctly ordering and interpreting test results in case-based questions. **Results:** Forty-one of 72 eligible participants (57%) completed at least one pre- or post-rotation assessment and 65 percent ordered at least one ROTEM test during their rotation. House staff confidence ordering (2.1/5 vs. 3.5/5, $p = 0.0001$) and interpreting (1.8/5 vs. 3.3/5, $p = 0.0001$) ROTEM tests increased significantly after their rotations. In case-based questions, correctly ordering ROTEM testing significantly improved after the rotation (80% vs. 100%, $p = 0.025$); however, there was no change in interpretation of the results (60% vs. 67%, $p = 0.78$). PGY-1 residents were less confident ordering ($p = 0.008$) and interpreting ($p = 0.02$) testing compared to senior residents before rotations, but afterward had no differences from their peers in confidence scores or case-based questions. **Conclusion:** This education and QI project significantly improved trainee confidence and performance in ordering ROTEM testing in ESLD patients, and also improved confidence in interpreting the results. ROTEM-based transfusion strategies for ESLD patients have shown promise, but more data with clinical endpoints are needed to apply this technology broadly. Collecting such data may be possible after first improving provider understanding of how to order and act on ROTEM results at the bedside.

Figure 1: ROTEM education and quality improvement infographic for house staff



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Disclosures: The following people have nothing to disclose: Alexander N. Scherer
Disclosure information not available at the time of publication: Mary Clare McGregor, Jaquelyn F. Fleckenstein, Daniel Reynolds

1604-A | REEVALUATING THE SIGNIFICANCE OF INR IN LIVER CIRRHOSIS: COLLABORATIVE DECISION-MAKING WITH INTERVENTIONAL RADIOLOGY FOR OPTIMAL PARACENTESIS

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Background: The liver plays a critical role in the production of nearly all clotting factors and their inhibitors. Despite having mean INR values above > 3, patients with acute liver failure or cirrhosis typically experience minimal changes in their in vivo coagulation profiles. In patients with liver disease, PT and INR calculations do not strongly correlate with more advanced and specific assessments of coagulation status, such as those obtained through the

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

use of thromboelastography (TEG). TEG serves as an alternative to measures like bleeding time, PT, and INR calculations in individual's with hepatic dysfunction whose healthcare provider wishes to evaluate a genuine coagulation profile that accurately reflects their in vivo clinical presentation. **Methods:** A collaborative effort between interventional radiology, internal medicine and gastroenterology with the introduction of thromboelastography (TEG) was proposed. **Results:** In our community practice, a significant number of patients (76%) hospitalized for acute decompensated cirrhosis or acute liver failure presented with an INR above 1.5, necessitating diagnostic or therapeutic paracentesis for abdominal ascites. However, due to concerns about elevated INR levels, only a fraction (23%) of these patients received timely paracentesis. It is worth noting that extensive research has consistently demonstrated minimal risk of bleeding associated with paracentesis, ranging from 0% to 0.99%. Nevertheless, the primary factor preventing patients from receiving timely paracentesis was the apprehension surrounding bleeding risks associated with elevated INR levels. To overcome these concerns, a multidisciplinary approach involving interventional radiology ,internal medicine and hepatology was implemented to perform thromboelastography in patients with INR levels above 1.5 and advanced liver disease. Out of the 72 patients included in the study, an overwhelming majority (approximately 98.3%) exhibited normal coagulation profiles as indicated by the thromboelastography results. Consequently, following the introduction of thromboelastography and a collaborative decision-making process involving interventional radiology, internal medicine, and gastroenterology teams, the rate of paracentesis within 12 hours saw a remarkable increase from 23% to 77%. **Conclusion:** Furthermore, this study reaffirms the inherent ability of individual's with liver cirrhosis to restore their hemostasis With the implementation of thromboelastography and the collaborative efforts of interventional radiology, internal medicine, and gastroenterology, the significant increase in the rate of paracentesis within 12 hours showcases the positive impact of evidence-based decision-making on patient care, ensuring timely and appropriate interventions.

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1605-A | ROTATIONAL THROMBOELASTOMETRY PREDICTS FUTURE BLEEDING EVENTS IN PATIENTS WITH CIRRHOSIS

Natasha Janko[1,2], Ammar Majeed[1,2], Isabella Commins[1], Paul J. Gow[3,4], William W. Kemp[1] and Stuart Keith Roberts[1], (1)Alfred Health, (2)Monash University, (3)Austin Health, (4)University of Melbourne

Background: Patients with cirrhosis of the liver are in a delicate state of rebalanced haemostasis and are at risk of developing both bleeding and thrombotic complications. Conventional haemostatic tests are unable to predict bleeding and thrombosis in these patients. We aimed to explore the role of Rotational Thromboelastometry (ROTEM) in predicting bleeding and thrombotic events in patients with cirrhosis. **Methods:** We conducted a prospective cohort study of patients with cirrhosis at two metropolitan hospitals. All patients underwent ROTEM analysis and were then followed to record any bleeding and thrombotic events. Univariate and multivariate logistic regression analyses were performed to explore associations with bleeding and thrombotic events. **Results:** Nineteen of the 162 patients recruited experienced a bleeding event within one year of ROTEM analysis. On univariate analysis, maximum clot firmness (MCF) using both EXTEM and INTEM tests was significantly reduced in patients who had a bleeding event, compared to those who did not (50mm vs 57mm, $p < 0.01$ and 48mm vs 54mm, $p < 0.01$, respectively). In addition, on univariate analysis, clotting time (CT) in the INTEM test was prolonged in the bleeding group (214 sec vs 198 sec, $p = 0.01$). After adjusting for age, gender, presence of clinically significant portal hypertension, use of beta-blockers, bilirubin, albumin, creatinine, INR and MCF_{EX}, only MCF_{EX} (HR 0.22, 95% CI; 0.05 – 0.90, $p = 0.04$) remained a significant predictor of a bleeding event within one year follow-up (see Table 1). In contrast, there was no association found between ROTEM parameters and development of thrombosis within a one-year period. **Conclusion:** ROTEM may provide a useful tool in predicting future bleeding events in patients with cirrhosis. Larger studies are required to further validate this finding and explore its application in clinical practice.

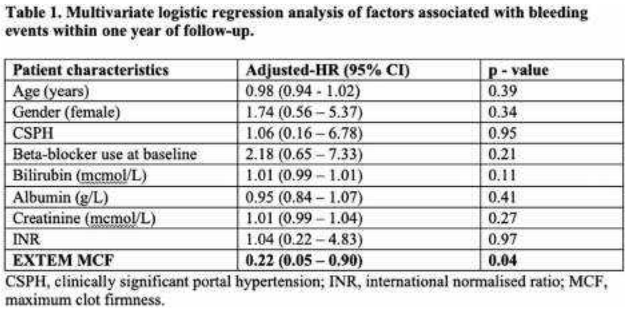


Table 1. Multivariate logistic regression analysis of factors associated with bleeding events within one year of follow-up.

Patient characteristics	**Adjusted-HR (95% CI)**	**p - value**
Age (years)	0.98 (0.94 - 1.02)	0.39
Gender (female)	1.74 (0.56 – 5.37)	0.34
CSPH	1.06 (0.16 – 6.78)	0.95
Beta-blocker use at baseline	2.18 (0.65 – 7.33)	0.21
Bilirubin (mcmol/L)	1.01 (0.99 – 1.01)	0.11
Albumin (g/L)	0.95 (0.84 – 1.07)	0.41
Creatinine (mcmol/L)	1.01 (0.99 – 1.04)	0.27
INR	1.04 (0.22 – 4.83)	0.97
EXTEM MCF	**0.22 (0.05 – 0.90)**	**0.04**

CSPH, clinically significant portal hypertension; INR, international normalised ratio; MCF, maximum clot firmness.

Disclosures: The following people have nothing to disclose: Natasha Janko

Disclosure information not available at the time of publication: Ammar Majeed, Isabella Commins, Paul J. Gow, William W. Kemp, Stuart Keith Roberts

1606-A | ROTATIONAL THROMBOELASTOMETRY PREDICTS TRANSPLANT-FREE SURVIVAL IN PATIENTS WITH LIVER CIRRHOSIS

Natasha Janko[1,2], Ammar Majeed[1,2], Isabella Commins[2], Paul J. Gow[3,4], William W. Kemp[2] and Stuart Keith Roberts[2], (1)Monash University, (2)Alfred Health, (3)University of Melbourne, (4)Austin Health

Background: There is emerging evidence that Rotational Thromboelastometry (ROTEM) is superior to conventional haemostatic tests, such as INR in the assessment and management of bleeding risk in patients with cirrhosis. Whether or not ROTEM may also be useful in assessing prognosis in patients with advanced liver disease is still unknown. We aimed to explore the role of ROTEM in predicting transplant-free survival in patients with cirrhosis. **Methods:** We conducted a prospective cohort study of patients with cirrhosis at two metropolitan hospitals. All patients underwent ROTEM analysis at baseline and were followed until death, liver transplant or the end of follow-up (28/2/2023). Univariate and multivariate Cox regression analyses were performed to explore associations with transplant-free survival and first episode of hepatic decompensation. **Results:** Between Apr 2018-Oct 2021, a total of 162 patients with cirrhosis were recruited and followed for a median of 42 months. During follow-up, 36 patients died and seven underwent liver transplant. On univariate analysis, maximum clot firmness (MCF) using both EXTEM and INTEM tests was significantly reduced in the death/liver transplant group, compared with the survivor group (52 vs 57, $p = 0.02$ and 51 vs 55, $p = 0.01$, respectively). After adjusting for age, gender, presence of clinically significant portal hypertension, hepatocellular carcinoma, care setting, bilirubin, sodium, creatinine, only albumin (HR; 0.92, 95% CI; 0.85 – 0.99, $p = 0.02$) and MCF_{EX} (HR 0.96, 95% CI; 0.92 – 0.99, $p = 0.03$) remained significant predictors of transplant free survival. The optimal cut-off of MCF_{EX} to predict transplant-free survival, as calculated with the Youden index, was 58mm with a sensitivity of 0.79 and specificity of 0.44. A Kaplan Meier curve (see Figure 1) shows that patients with a baseline MCF_{EX} of less than 58mm have a significantly lower transplant-free survival than those patients with an MCF_{EX} equal to or greater than 58mm (HR 0.40, 95% CI = 0.19 – 0.84, $p = 0.015$). Of the 101 patients who had not previously experienced hepatic decompensation, 20 developed a first hepatic decompensation event during follow-up after a median (IQR) of 19 months (4–31 mo). After adjusting for age, gender, presence of clinically significant portal hypertension, HCC, albumin, creatinine, INR, platelets and $MCF_{EX,}$ only albumin (HR 0.86, 95% CI 0.75 – 0.98, $p = 0.02$), platelet count (HR 1.01, 95% CI 1.00-1.02, $p = 0.02$) and MCF_{EX} (HR 0.82, 95% CI = 0.74 – 0.92, $p < 0.01$) remained significant predictors of first episode hepatic decompensation. **Conclusion:** ROTEM may be useful in assessing survival and first episode hepatic decompensation in patients with cirrhosis. Further research is needed to determine the clinical utility of ROTEM parameters as prognostic markers in patients with cirrhosis.

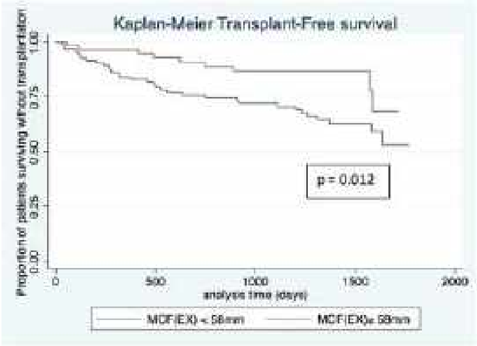


Figure 1. Kaplan Meier curve of transplant free survival according to MCF_{EX} cut-off of 58mm (Youden index-optimised cut-off). Proportion of patients surviving without liver transplantation during the follow-up period.

Disclosures: The following people have nothing to disclose: Natasha Janko

Disclosure information not available at the time of publication: Ammar Majeed, Isabella Commins, Paul J. Gow, William W. Kemp, Stuart Keith Roberts

1607-A | SAFETY OF DIRECT ORAL ANTICOAGULATION VERSUS WARFARIN IN CIRRHOTIC PATIENTS WITH PORTAL VEIN THROMBOSIS AND SIGNIFICANT THROMBOCYTOPENIA

Julton Tomanguillo Chumbe[1], Mark Ayoub[2], Lauren Searls[2], Frank Annie[2], Harleen Chela[2], Nadeem Anwar[1] and Ebubekir Daglilar[1], (1)West Virginia University - Charleston Area Medical Center, Charleston, WV, (2)Charleston Area Medical Center/ WVU Charleston Division

Background: In the treatment of portal vein thrombosis, direct oral anticoagulation (DOAC) such as Apixaban or Rivaroxaban have proven to be equally effective as warfarin. Nonetheless, patients with cirrhosis frequently exhibit significant thrombocytopenia ($< 50*10^3$/uL), a condition that poses management challenges due to safety concerns when administering anticoagulation. This study aims to compare the safe use of reduced dosage DOAC versus warfarin in treating PVT among patients with cirrhosis. **Methods:** Adult patients 18 years and older with the diagnosis of cirrhosis with and without the presence of significant thrombocytopenia, as defined by platelet count less than 50*10^3/uL, were identified using TriNetX between 2012 and 2023. TriNetx includes a total of 106 different healthcare organizations from 14 different countries. Patients with cirrhosis and thrombocytopenia on DOAC or warfarin within 1-month after the diagnosis of PVT were divided into two cohorts; the first cohort comprised patients receiving 50% reduced-dose DOAC (Apixaban or Rivaroxaban) and platelet between 30 and 49*10^3/uL, and a second cohort was patient on warfarin and platelet value were greater and equal than 50*10^3/uL. We compared the rate of mortality and significant bleeding such as intracranial bleeding and gastrointestinal bleeding between propensity-matched (PSM) pairs of patients. **Results:** 2,121 patients with cirrhosis and PVT were included in this analysis. Of these 16% (n = 338) had a platelet level between 30 and 49*10^3/uL and received a reduce-dose of DOAC, and 84% (n = 1,783) were on warfarin and had platelet level **e** 50*10^3/uL. The raw data showed that the patients on DOAC were significant younger (60.6 ± 12.3 vs 64.5 ± 12, $p < 0.0001$), and had a higher rate of diabetes (49.11% vs 40.58%, $p = 0.003$). Subsequently, two well-matched cohorts were created using a 1:1 propensity-scored matching model (337/337). No significant difference was noted between the two groups in the rate major bleedings at 6 or 12 months. At 6-months intracranial hemorrhage (2.96% vs 2.96%, $p = 1.00$), gastrointestinal bleeding (7.12% vs 8.60%, $p = 0.47$), and over-all mortality (19.28% vs 14.54%, $p = 0.10$). At 12-months intracranial hemorrhage (2.96% vs 2.96%, $p = 1.00$), gastrointestinal bleeding (9.19% vs 10.38%, $p = 0.60$), and over-all mortality (22.84% vs 17.50%, $p = 0.08$). **Conclusion:** The use of 50%-reduce dose of DOAC in patient with cirrhosis and platelets levels between 30-49*10^3/uL was not significantly associated with major bleedings such as intracranial hemorrhage, gastrointestinal bleeding, or mortality up to 12 months when compared with patient with platelets **e** 50*10^3/uL and on warfarin.

Disclosures: The following people have nothing to disclose: Julton Tomanguillo Chumbe, Mark Ayoub, Lauren Searls, Frank Annie, Harleen Chela, Nadeem Anwar, Ebubekir Daglilar

1608-A | THE ASSOCIATION BETWEEN HEPATIC DYSFUNCTION AND COAGULOPATHY IN PATIENTS PRESENTING WITH SHOCK LIVER: AN INSTITUTIONAL REVIEW

Simone A Jarrett[1], Jordan Carty[1], Sahana TIto[1], Brenda Chiang[1], Bruce Casipit[1], Alexander Prendergast[1], Jose Martinez Manzano[1], Isaac Ogunmola[1], Otoniel Ysea-Hill[1], Ahmer Khan[1], Kevin Robinson[1], Dominic E Jarrett[2], Sujani Yadlapati[3], Kevin B Lo[1], Zurab Azmaiparashvili[1] and Victor J. Navarro, Md[1], (1)Albert Einstein Medical Center, (2)University of the West Indies, Mona, (3)Cooper University Hospital

Background: Patients with shock liver, either ischemic or congestive, often have prolongation of the INR. The objective of this study is to examine whether the INR correlates with bleeding in patients with shock liver. **Methods:** This retrospective cohort study analyzed a sample of 232 patients by using ICD codes 9 and 10 to identify cases of ischemic hepatitis and congestive hepatopathy. Out of the initial sample,135 patients were excluded after review of the medical record due to factors such as hemorrhage as the cause of liver injury before diagnosis of ischemic hepatitis, missing INR values, and prior cirrhosis. Major bleeding was defined by the presence of a clinically identifiable bleeding source that was fatal or associated with a drop in hemoglobin levels by 2g/dl or transfusion of at least 2 units of packed red blood cells, or involvement of critical anatomical sites. These sites included gastrointestinal, intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, intramuscular with compartment syndrome. All other clinically apparent bleeding were considered minor bleeding. Admission and peak INR values were compared between patients with major bleeding, minor bleeding, both major & minor bleeding and those who did not experience bleeding events. Statistical analysis of the data was performed using chi-squared tests, Wilcoxon signed rank tests, and independent T-score tests. **Results:** Among the patients with shock liver, 84% had a clinical diagnosis of ischemic hepatitis, while 16% had congestive hepatopathy. Two-thirds of the patients (68%) already had liver injury upon admission, while 32% developed it during their hospital stay. Cardiac arrest was the leading cause of liver injury (40%), followed by cardiogenic shock (30%), sepsis (19%), and other causes (11%). With regards to bleeding events, 15% of the patients experienced major bleeding, and 22% had minor bleeding events. The combined rate of major and minor bleeding was 41%. The median INR upon admission was 1.5 (1.2-2.1) while the peak INR during hospitalization was 2.6 (1.7-4.2). There was no significant difference in INR values between patients with major bleeding and those without. (See table 1) **Conclusion:** The INR did not predict bleeding events in those with ischemic hepatitis or congestive hepatopathy. The degree of coagulopathy as reflected by INR values were not directly associated with bleeding events

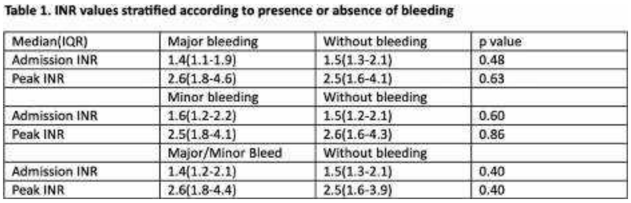


Table 1. INR values stratified according to presence or absence of bleeding

Median(IQR)	Major bleeding	Without bleeding	p value
Admission INR	1.4(1.1-1.9)	1.5(1.3-2.1)	0.48
Peak INR	2.6(1.8-4.6)	2.5(1.6-4.1)	0.63
	Minor bleeding	Without bleeding	
Admission INR	1.6(1.2-2.2)	1.5(1.2-2.1)	0.60
Peak INR	2.5(1.8-4.1)	2.6(1.6-4.3)	0.86
	Major/Minor Bleed	Without bleeding	
Admission INR	1.4(1.2-2.1)	1.5(1.3-2.1)	0.40
Peak INR	2.6(1.8-4.4)	2.5(1.6-3.9)	0.40

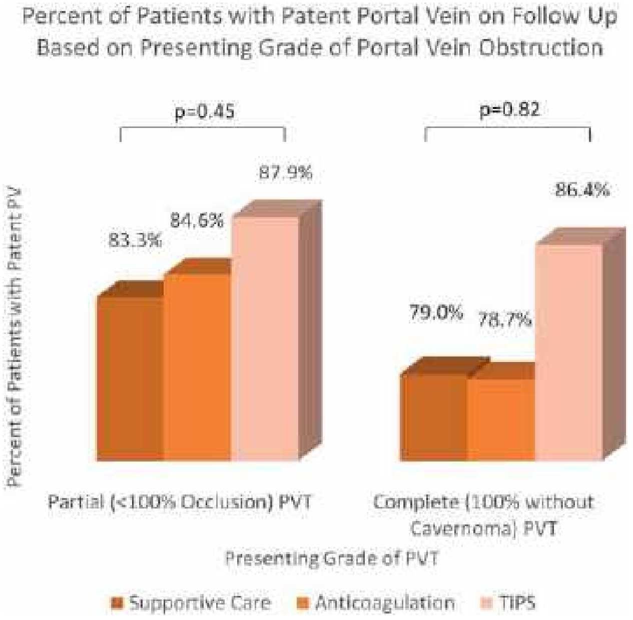
Disclosures: The following people have nothing to disclose: Simone A Jarrett, Jordan Carty, Alexander Prendergast, Isaac Ogunmola, Ahmer Khan, Kevin B Lo, Victor J. Navarro, Md

Disclosure information not available at the time of publication: Sahana TIto, Brenda Chiang, Bruce Casipit, Jose Martinez Manzano, Otoniel Ysea-Hill, Kevin Robinson, Dominic E Jarrett, Sujani Yadlapati, Zurab Azmaiparashvili

1609-A | TREATMENT OF PORTAL VEIN THROMBOSIS IN CIRRHOSIS IS ASSOCIATED WITH MINIMAL BENEFIT: A RETROSPECTIVE CONTROLLED STUDY

Abraham Z Cheloff[1], Joshua L Ross[2], Jenny L Engelman[2], Luke J Bonanni[2], Joshua D Kirschenbaum[2], Gabriel Fuligni[2], Naveena Luke[3], Yasmeen Mardi[2] and Patrick Grant Northup[4], (1)NYU Langone Health, New York, NY, (2)NYU Grossman School of Medicine, (3)NYU Langone Health, (4)NYU Langone Health, Saint Petersburg, FL

Background: The benefit of treating portal vein thrombosis (PVT) in patients with cirrhosis has not been proven. The aim of this study was to compare clinically meaningful endpoints in patients with cirrhosis and PVT who undergo different treatment strategies. **Methods:** Patients with established cirrhosis and PVT were retrospectively identified using electronic medical records from a single referral center and analyzed in three groups based on treatment course: 1) Anticoagulants, 2) TIPS or vascular interventional therapies, 3) Supportive care only. Groups were analyzed for clinically meaningful endpoints including death, transplantation, complete PVT resolution, and progression of PVT to complete obstruction of the portal vein. Analyses were adjusted for demographics, severity of liver disease, portal hypertension, and extent of initial PVT. **Results:** 222 patients were included. 112 were treated with anticoagulants, 80 with TIPS, and 30 with supportive care. 40 (18%) presented with cavernous transformation of the PV, 28 (13%) with complete obstruction of the PV, and the remainder with partial obstruction. Patients with a history of prior bleeding were offered anticoagulation less often than other groups ($p < 0.001$). Conversely, patients who presented with cavernous transformation ($p = 0.02$), older age (63 vs. 57, $p = 0.04$), and higher MELD score (13 vs. 10, $p = 0.02$) were offered supportive care more often. Of 154 (69% of total) patients presenting with partial or minimal obstruction of the PV, 132 (86%) remained patent regardless of whether targeted PVT therapy or supportive care was chosen (Figure 1). Initial PV patency (OR 11.9, 95%CI 5.7-24.9, $p < 0.0001$) was the only significant factor predicting PV patency at the end of follow up. MELD ($p = 0.24$), prior portal hypertensive bleeding ($p = 0.74$), patient age ($p = 0.35$), and treatment vs. supportive care ($p = 0.10$) were not predictive of PV patency at the end of follow-up. In 68 (30.6% of total) patients presenting with complete PV obstruction or cavernous transformation, 22 (34.4%) patients achieved some level of patency of the PV at the end of follow up but treatment arm had no impact on eventual patency ($p = 0.08$). In an adjusted competing risks analysis, lack of patency of the PV was directly correlated with death (HR 3.7, 1.3-10.4, $p = 0.01$) but treatment directed at the PV clot was not (HR 0.8 0.3-2.3, $p = 0.66$). **Conclusion:** In patients with cirrhosis and partial PVT, progression of clot to the point of complete occlusion is uncommon and treatment of the clot with TIPS or anticoagulation showed little benefit in the clinically meaningful outcomes including final PV patency and survival. Prospective, randomized studies investigating the benefit of thrombosis directed therapies in this population are needed.



Disclosures: The following people have nothing to disclose: Abraham Z Cheloff, Joshua L Ross, Jenny L Engelman, Luke J Bonanni, Joshua D Kirschenbaum, Gabriel Fuligni, Naveena Luke, Yasmeen Mardi, Patrick Grant Northup

f 1610-A | VARIATIONS IN PRACTICE IN PATIENTS WITH PORTAL VEIN THROMBOSIS AND ESOPHAGEAL VARICES: AN INTERNATIONAL SURVEY STUDY

Brandon G. Mui, Lauren T. Grinspan and James F. Crismale, Icahn School of Medicine at Mount Sinai

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

Background: Portal vein thrombosis (PVT) is common in cirrhosis. While current guidelines recommend anticoagulation for PVT in patients with cirrhosis, there exists no consensus regarding treatment protocols. The primary aim of this study is to better discern practice patterns surrounding anticoagulation and variceal hemorrhage prophylaxis in PVT patients and to assess guideline concordance. **Methods:** A questionnaire was created using RedCap and then distributed to practice sites across Canada and the USA. The survey included questions that assessed provider knowledge and attitudes regarding the management of PVT and prevention of portal hypertensive bleeding in such patients. **Results:** 136 of 237 (57%) providers responded to our survey. Most respondents identified as hepatologists (54%) and gastroenterologists (26%). Apixaban (47%) was the preferred anticoagulation agent. Providers were “more likely” to start anticoagulation if the patient was listed for liver transplantation (84%), symptomatic (91%), and in the setting of superior mesenteric vein thrombosis (92%) but were less likely to start anticoagulation among patients with a history of severe bleeding or thrombocytopenia. For the primary prophylaxis of variceal hemorrhage, practice was variable with 44% of responses discordant from Baveno VII guideline recommendations with an appreciable proportion of providers preferring combination therapy with endoscopic variceal ligation and beta-blockers over guideline-recommended monotherapy (see Table). There were significant differences in the timing of anticoagulant initiation among patients with symptomatic versus asymptomatic PVT. Most providers start anticoagulation prior to endoscopic investigation and eradication of varices among patients with symptomatic PVT versus asymptomatic PVT (65% vs. 23%, $p < 0.001$). Similarly, a greater proportion of providers immediately restart anticoagulation following band ligation among patients with symptomatic versus asymptomatic PVT (24% vs. 15%, $p = 0.01$). Practice patterns were similar between hepatologists and non-hepatologists. Notable differences included a greater tendency to initiate anticoagulation prior to endoscopic eradication of varices among patients with asymptomatic PVT (41% vs. 21%, $p = 0.04$), and a reduced tendency to start anticoagulation in the inpatient setting (10% vs. 52%, $p < 0.001$). **Conclusion:** There is consensus amongst providers on the factors that influence the decision to initiate/hold anticoagulation in PVT patients, often in alignment with guidelines. However, a wide variation in practice was observed regarding primary prevention of variceal hemorrhage in patients with cirrhosis and recent PVT and the use of endoscopic surveillance prior to anticoagulation. Several practice tendencies contrary to guidelines were identified in this study, highlighting the need for more efficacy-safety data on PVT treatment in cirrhosis.

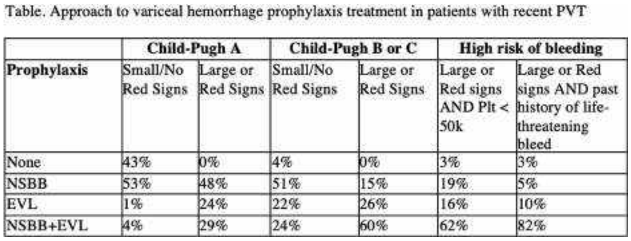


Table. Approach to variceal hemorrhage prophylaxis treatment in patients with recent PVT

	Child-Pugh A		Child-Pugh B or C		High risk of bleeding	
Prophylaxis	Small/No Red Signs	Large or Red Signs	Small/No Red Signs	Large or Red Signs	Large or Red signs AND Plt < 50k	Large or Red signs AND past history of life-threatening bleed
None	43%	0%	4%	0%	3%	3%
NSBB	53%	48%	51%	15%	19%	5%
EVL	1%	24%	22%	26%	16%	10%
NSBB+EVL	4%	29%	24%	60%	62%	82%

Disclosures: The following people have nothing to disclose: Brandon G. Mui, Lauren T. Grinspan, James F. Crismale

1611-A | LIVER ENDOTHELIAL Gimap5 IS REQUIRED TO MAINTAIN HEPATOCYTE ZONATION

Shanin Chowdhury, Chigoziri Konkwo, Kaitlyn Lee, Caroline Tippett, Joseph Brancale and Silvia M. Vilarinho, Yale School of Medicine, New Haven, CT

Background: Liver zonation is the spatial organization of metabolic and physiological functions across the liver lobule, which is critical to maintaining hepatic homeostasis and function. Emerging research suggests that signals originating from liver endothelial cells (LECs) play a critical role in maintaining hepatic parenchymal homeostasis and zonation. Our group discovered that rare bi-allelic loss-of-function mutations in *Gimap5* cause nodular regenerative hyperplasia and consequently non-cirrhotic portal hypertension. Moreover, we demonstrated that LECs express *Gimap5*, which is critical to maintain liver endothelial cell homeostasis. Hence, we postulated that endothelial Gimap5 is required to maintain hepatocyte zonation and function. **Methods:** We used loss-of-function (LOF) Gimap5 mice and Gimap5 sufficient littermate controls to conduct histological and protein studies to characterize hepatocyte zonation using zone 1 and zone 3 specific markers over the course of 3 to 8 weeks of age. These markers were established zonation markers such as E-Cadherin for zone 1, arginase-1 for zones 1/2, and glutamine synthetase and Cyp2e1 for zone 3. Single-cell RNA sequencing of enriched hepatocytes from 8-week-old LOF Gimap5 and WT littermate control mice was also performed. **Results:** Our data shows that zonation can be established and maintained up to 6 weeks-old but is disrupted by 8 weeks of age in LOF Gimap5 mice as compared to WT controls. In LOF Gimap5 mice, we observed an expansion of epithelial marker E-cadherin around the periportal region, and a reduction of zone 3 markers on pericentral region, such as glutamine synthetase and Cyp2e1. Furthermore, single-cell RNA sequencing data revealed that hepatocytes from

Gimap5 LOF livers exhibit distinct transcriptional profiles compared to wild-type hepatocytes, resembling immature hepatocytes. **Conclusion:** Our study uncovers a crucial role of liver endothelial Gimap5 to maintaining adult hepatocyte zonation, highlighting the importance of the endothelial cell compartment in liver homeostasis.

Disclosures: The following people have nothing to disclose: Shanin Chowdhury, Joseph Brancale

Disclosure information not available at the time of publication: Chigoziri Konkwo, Kaitlyn Lee, Caroline Tippett, Silvia M. Vilarinho

1612-A | CARDIOPULMONARY DYSFUNCTION AND ITS CORRELATION WITH DISEASE SEVERITY IN PORTO-SINUSOIDAL VASCULAR DISEASE

Harish Gopalakrishna[1], Maria Mironova[2], My-Le Nguyen[3], Gracia Viana[4], Gayatri Nair[5], David E Kleiner[6], Christopher Koh[7], Vandana Sachdev[3] and Theo Heller[1], (1)Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, (2)Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, (3)NHLBI, National Institutes of Health, (4)University of Maryland Medical Center, (5) Medstar Georgetown University Hospital, (6)Laboratory of Pathology, National Cancer Institute, National Institutes of Health, (7)National Institute of Diabetes and Digestive and Kidney Diseases, Nih

Background: Porto-sinusoidal vascular disease (PSVD) encompasses a group of hepatic vascular disorders affecting portal venules and sinusoids in the absence of cirrhosis. PSVD patients develop portal hypertension and associated complications including variceal bleeding, hepatic encephalopathy, and ascites. Cardiopulmonary complications of portal hypertension including hepatopulmonary syndrome and porto-pulmonary hypertension are well described in cirrhotic cohorts but not in PSVD patients. We aim to explore echocardiography findings of cardiopulmonary dysfunction in PSVD patients and its association with clinically significant portal hypertension (CSPH). **Methods:** We included a prospective cohort of 44 biopsy proven PSVD patients followed under the natural history protocol (NCT02417740) who underwent transthoracic echocardiogram with agitated saline study. Intrapulmonary shunting was defined as presence of microbubbles in the left atrium after at least four heartbeats. Porto-pulmonary hypertension (PoPH) was defined as elevated tricuspid regurgitation velocity (TRV) > 2.8 m/sec. All patients underwent liver stiffness measurement (LSM) using transient elastography, and investigations to evaluate for CSPH. CSPH was defined by presence of one specific feature as per BAVENO VII criteria. **Results:** Among the 44 subjects, 3 with intracardiac shunting were excluded; of the remaining 41 subjects, 17 (41%) had intrapulmonary shunting, 5 (12%) had PoPH and 3 (7%) had both features. AST/ALT ratio (1.28 vs 1.05, $p = 0.01$) and LSM (13.3 kPa vs 8.3 kPa, $p = 0.02$) were significantly higher in patients with shunting. A composite score combining LSM > 10 and AST/ALT ratio > 1 performed with specificity of 83%, negative predictive value (NPV) of 74% and positive predictive value (PPV) of 69% in predicting presence of shunting. Patients who met the composite score criteria had 6.4 (1.4-22.1) times higher odds of having shunting ($p < 0.001$). Patients with CSPH had higher left ventricular diastolic volume (124 ml vs 97 ml, $p = 0.04$), left atrial volume (64.5 ml vs 46 ml, $p = 0.01$), left atrial volume index (34.4 m^2 vs 23.1 m^2, $p < 0.01$), and left atrial dimension (40 mm vs 33 mm, $p < 0.001$) compared to patients without CSPH. **Conclusion:** Intra-pulmonary shunting, which is a feature of hepatopulmonary syndrome can be seen in PSVD patients especially in those with CSPH. A combination of AST/ALT ratio and LSM can be useful in risk stratification for HPS prior to developing hypoxia. Similar to decompensated cirrhotic patients, features suggestive of diastolic dysfunction can be seen in PSVD patients with CSPH. Collectively, these findings suggest screening patients with PSVD for cardiopulmonary dysfunction.

Disclosures: The following people have nothing to disclose: Harish Gopalakrishna, Maria Mironova, My-Le Nguyen, Gracia Viana, Gayatri Nair, David E Kleiner, Christopher Koh, Vandana Sachdev, Theo Heller

1613-A | FEATURES OF NON-CIRRHOTIC PORTAL HYPERTENSION IN A PROSPECTIVE EVALUATION OF MAGNETIC RESONANCE IMAGING.

Maria Mironova[1], Harish Gopalakrishna[2], Nehna Abdul Majeed[1], Asif Ali Hitawala[3], Shani Scott[4], David E Kleiner[5], Christopher Koh[3], Bernadette Redd[6] and Theo Heller[7], (1)National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, (2)Clinical Research Section, Gaithesberg, MD, (3)National Institute of Diabetes and Digestive and Kidney Diseases, Nih, (4)Clinical Research Section, National

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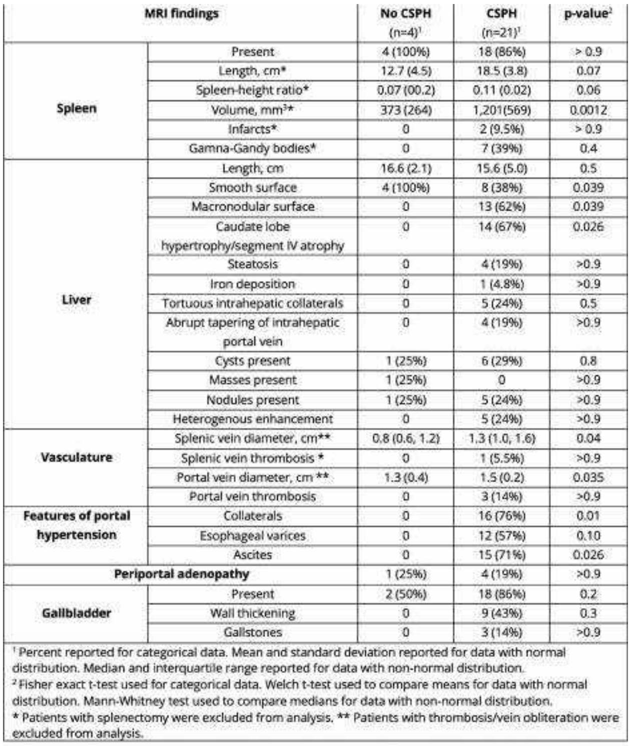
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, (5)Laboratory of Pathology, National Cancer Institute, Bethesda, MD, (6) National Institutes of Health, (7)Translational Hepatology Section, Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

Background: Non-cirrhotic portal hypertension (NCPH) is a spectrum of chronic liver diseases, characterized by increased portal pressures in absence of cirrhosis. The progression and pathophysiology of the disease is not fully explored. We aimed to explore magnetic resonance imaging (MRI) features of NCPH and correlate those with histologic findings. **Methods:** Patients with known NCPH or at risk for NCPH by the virtue of underlying disease were enrolled in a single center prospective study NCT02417740. Patients with cirrhosis and other liver diseases were excluded. Clinically significant portal hypertension (CSPH) was diagnosed by presence of portosystemic collaterals (PSS), varices, including esophageal varices (EV) and/or portal hypertensive gastropathy. All patients had an initial liver biopsy. Blood work and abdominal MRI were repeated every 6-12 months. MRI images were reviewed by an expert radiologist. **Results:** 25 patients were included in the analysis: 21 (84%) had CSPH, while 4 (16%) had no CSPH. Majority of patients with CSPH were males (62%), mean age was 51 ± 11 years. Patients without CSPH were mostly females (75%), median age 42 years. Most common underlying disease in both groups was common variable immunodeficiency (36%), followed by autoimmune and hematological disorders. 5 (24%) patients had no underlying disease identified. Most frequent findings on liver biopsy in both cohorts were perisinusoidal fibrosis (48% of all biopsies), nodular regenerative hyperplasia (48%), obliterative portal venopathy (36%), and sinusoidal dilation (20%). 71 MRIs were performed in this cohort, with a median follow-up time between MRIs of 12 months. Features of baseline MRIs are displayed in Table 1. Patients with CSPH had large splenic volumes, liver macronodularity, caudate lobe hypertrophy along with atrophy of segment IV, and significant dilation of portal and splenic veins when compared to patients without CSPH. Specific features of portal hypertension included ascites, mostly mild, esophageal varices and gastric varices, and PSS: portal (81%), splenic (76%), mesenteric (19%) and recanalization of umbilical or periumbilical vein (14%). Follow-up MRI was available for 3 patients without CSPH and 16 patients with CSPH. Patients without CSPH had no substantial changes. On the follow-up MRI more patients with CSPH developed splenic infarcts (21% vs 14%), liver macronodularity (81% vs 69%), abrupt tapering of portal vein branches (44% vs 25%), and PSS (81% vs 75%), none of which reached statistical significance. **Conclusion:** The presence of MRI findings that are common in patients with cirrhosis and NCPH may be misleading in the diagnosis of NCPH. It is important to augment the imaging diagnosis with liver histology and have a high suspicion of NCPH when a patient has a known NCPH-predisposing condition.



MRI findings		No CSPH (n=4)[1]	CSPH (n=21)[1]	p-value[2]
Spleen	Present	4 (100%)	18 (86%)	> 0.9
	Length, cm*	12.7 (4.5)	18.5 (3.8)	0.07
	Spleen-height ratio*	0.07 (00.2)	0.11 (0.02)	0.06
	Volume, mm³*	373 (264)	1,201(569)	0.0012
	Infarcts*	0	2 (9.5%)	> 0.9
	Gamna-Gandy bodies*	0	7 (39%)	0.4
Liver	Length, cm	16.6 (2.1)	15.6 (5.0)	0.5
	Smooth surface	4 (100%)	8 (38%)	0.039
	Macronodular surface	0	13 (62%)	0.039
	Caudate lobe hypertrophy/segment IV atrophy	0	14 (67%)	0.026
	Steatosis	0	4 (19%)	>0.9
	Iron deposition	0	1 (4.8%)	>0.9
	Tortuous intrahepatic collaterals	0	5 (24%)	0.5
	Abrupt tapering of intrahepatic portal vein	0	4 (19%)	>0.9
	Cysts present	1 (25%)	6 (29%)	0.8
	Masses present	1 (25%)	0	>0.9
	Nodules present	1 (25%)	5 (24%)	>0.9
	Heterogenous enhancement	0	5 (24%)	>0.9
Vasculature	Splenic vein diameter, cm**	0.8 (0.6, 1.2)	1.3 (1.0, 1.6)	0.04
	Splenic vein thrombosis *	0	1 (5.5%)	>0.9
	Portal vein diameter, cm **	1.3 (0.4)	1.5 (0.2)	0.035
	Portal vein thrombosis	0	3 (14%)	>0.9
Features of portal hypertension	Collaterals	0	16 (76%)	0.01
	Esophageal varices	0	12 (57%)	0.10
	Ascites	0	15 (71%)	0.026
Periportal adenopathy		1 (25%)	4 (19%)	>0.9
Gallbladder	Present	2 (50%)	18 (86%)	0.2
	Wall thickening	0	9 (43%)	0.3
	Gallstones	0	3 (14%)	>0.9

[1] Percent reported for categorical data. Mean and standard deviation reported for data with normal distribution. Median and interquartile range reported for data with non-normal distribution.

[2] Fisher exact t-test used for categorical data. Welch t-test used to compare means for data with normal distribution. Mann-Whitney test used to compare medians for data with non-normal distribution.

* Patients with splenectomy were excluded from analysis. ** Patients with thrombosis/vein obliteration were excluded from analysis.

Table 1. Baseline differences in the MRIs of patients without CSPH and with CSPH.

Disclosures: The following people have nothing to disclose: Maria Mironova, Harish Gopalakrishna, Asif Ali Hitawala, Shani Scott, David E Kleiner, Christopher Koh, Theo Heller

Disclosure information not available at the time of publication: Nehna Abdul Majeed, Bernadette Redd

1614-A | IMPACT OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT ON BUDD-CHIARI SYNDROME: ANALYSIS OF THE NIS DATABASE

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Background: Budd-Chiari syndrome (BCS) is a rare disorder characterized by hepatic venous flow obstruction or narrowing. If left untreated, BCS can lead to serious complications. Treatment options include anticoagulation, endovascular interventions, transjugular portosystemic shunt (TIPS) placement, and orthotopic liver transplantation. This study aims to examine the outcomes of TIPS in BCS using the National Inpatient Sample (NIS) database, contributing to our understanding of its effectiveness and safety as a therapeutic intervention. **Methods:** This study utilized a retrospective analysis of data from the NIS database, covering the period from 2016 to 2020, including patients diagnosed with BCS. Patient demographics, baseline comorbidities, liver-related complications, in-hospital mortality, LOS, total hospital cost, and other hospitalization outcomes were collected. Univariate analysis and multivariate analysis were performed to investigate factors associated with TIPS performance. **Results:** A total of 1,070 patients diagnosed with BCS were included. Among them, 105 patients underwent TIPS placement, while 965 patients did not receive TIPS. Comparison between the two groups revealed that patients who underwent TIPS placement were younger, with a mean age of 39.3 years compared to 48.6 years in the non-TIPS group ($p < 0.01$). Patients in the non-TIPS group had a higher prevalence of baseline comorbidities, including diabetes (17.1% vs 0; $p = 0.034$) and hypertension (42.5% vs 19.0%; $p = 0.036$). Regarding liver-related complications, the TIPS group had a higher incidence of portal pressure complications such as ascites (81.0% vs 53.4%; $p < 0.01$), hepatorenal syndrome (9.5% vs 2.6%; $p = 0.08$), and SBP (4.8% vs 2.1%; $p = 0.43$). Conversely, portal vein thrombosis (PVT) was more common in the non-TIPS group (26.9% vs 23.8%; $p = 0.75$). No significant differences were found between the groups in terms of in-hospital mortality, length of stay (LOS), and total hospital cost. However, patients in the TIPS group had a higher prevalence of acute liver failure (28.6% vs 13%; $p = 0.05$) and acute kidney failure (42.9% vs 23.3%; $p = 0.05$), which likely served as indications for TIPS placement (table 1). Multivariate logistic regression analysis revealed that ascites was independently associated with TIPS performance. **Conclusion:** Our findings indicate that TIPS was predominantly performed in younger patients with a higher incidence of ascites, acute liver and kidney failure, which likely influenced the decision for intervention. However, there were no significant differences in in-hospital mortality, length of stay, and total hospital cost between the TIPS and non-TIPS groups. The comparable outcomes achieved by the TIPS group, despite having a higher incidence of complications, provides evidence for the effectiveness of TIPS in improving clinical outcomes.

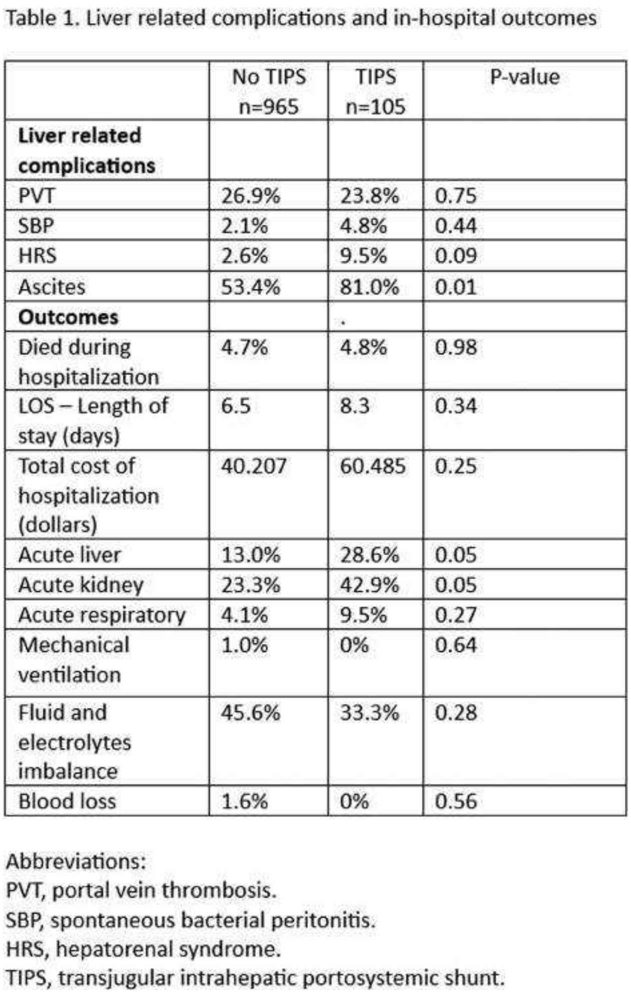


Table 1. Liver related complications and in-hospital outcomes

	No TIPS n=965	TIPS n=105	P-value
Liver related complications			
PVT	26.9%	23.8%	0.75
SBP	2.1%	4.8%	0.44
HRS	2.6%	9.5%	0.09
Ascites	53.4%	81.0%	0.01
Outcomes			
Died during hospitalization	4.7%	4.8%	0.98
LOS – Length of stay (days)	6.5	8.3	0.34
Total cost of hospitalization (dollars)	40.207	60.485	0.25
Acute liver	13.0%	28.6%	0.05
Acute kidney	23.3%	42.9%	0.05
Acute respiratory	4.1%	9.5%	0.27
Mechanical ventilation	1.0%	0%	0.64
Fluid and electrolytes imbalance	45.6%	33.3%	0.28
Blood loss	1.6%	0%	0.56

Abbreviations:
PVT, portal vein thrombosis.
SBP, spontaneous bacterial peritonitis.
HRS, hepatorenal syndrome.
TIPS, transjugular intrahepatic portosystemic shunt.

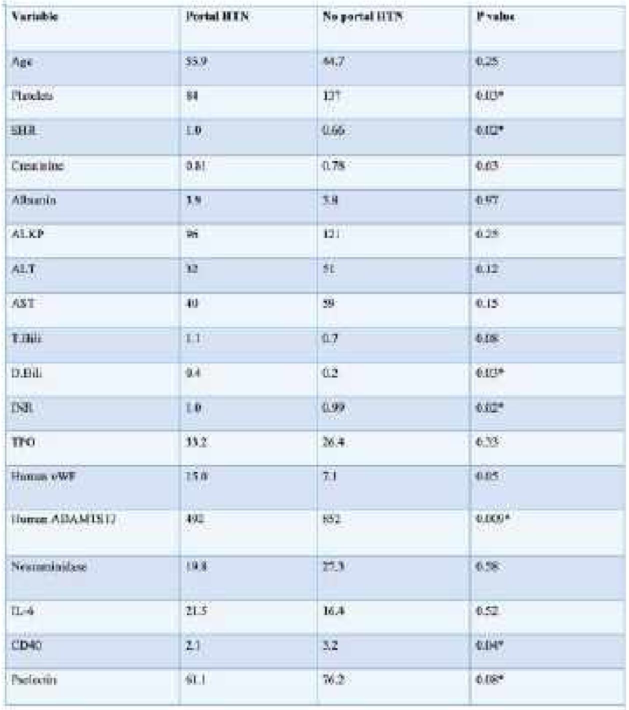
Disclosures: The following people have nothing to disclose: Xheni Deda, Khaled Elfert, Hazem Abosheaishaa, Ahmad Hassan Ali

1615-A | PORTO-SINUSOIDAL VASCULAR DISEASE: WHAT CAUSES THROMBOCYTOPENIA?

Nehna Abdul Majeed[1], Rownock Afruza[2], Moumita Chakraborty[3], Harish Gopalakrishna[4], Maria Mironova[5], Nicole San-Dee Minerva[2], Maleeha Ahmad[2], Adekanyinsola Onitiri[2], Asif Ali Hitawala[6], Shani Scott[1], David E Kleiner[7], Christopher Koh[6] and Theo Heller[2], (1)Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, (2)Translational Hepatology Section, Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, (3)Translational Hepatology

Section, National Institutes of Health, (4)National Institutes of Health, Rockville, MD, (5)Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, (6)National Institute of Diabetes and Digestive and Kidney Diseases, Nih, (7)Laboratory of Pathology, National Cancer Institute, National Institutes of Health

Background: Porto-sinusoidal vascular disease (PSVD) is caused by a myriad of diseases broadly classified into pre-sinusoidal, sinusoidal and post-sinusoidal. Liver synthetic function in PSVD is preserved, making identification of disease severity a challenge. Down trending platelet count and increasing spleen size are considered markers of disease progression. Though decreased thrombopoietin (TPO) production and splenic sequestration are observed to be the cause for thrombocytopenia in cirrhosis, the reason for the down trending platelet count in PSVD is unclear. **Aim:** The study sought to investigate the factors influencing the platelet count in PSVD. **Methods:** Patients enrolled in a natural history protocol for PSVD were screened (NCT02417740). Of the total 43 patients, 27 with portal hypertension (PHT) and 8 with a known disease predisposing to PSVD were included in the analysis. This also included 3 patients who had undergone splenectomy. Biochemical and imaging data were obtained from the most recent visit. Liver biopsies were obtained at study entry. ELISA assays were performed in stored sera to explore the influence of liver related (TPO, neuraminidase), portal vein related (vWF, ADAMTS13), inflammation related (IL-6, CD-40, Pselectin) and spleen related factors. Graph Pad software version 9.2.0 was utilized for data analysis. **Results:** The median age was 54.5 years (range, 21.26-75.3) with 31 White, 2 Multiracial and 2 African American. Hypogammaglobulinemia (CVID/XLA) was present in 21 patients (60%). All had liver biopsies and 15 patients were noted to have nodular regenerative hyperplasia. Median platelet count was 84k/ul and median spleen height ratio (SHR) was 1.0mm/cm. In the 27 patients with PHT, SHR, CD-40 and P selectin significantly correlated with platelet count on univariable analysis, and only CD-40 significantly correlated on multivariable analysis. Similar results were observed after exclusion of splenectomized patients. Patients with and without PHT were compared and the difference in platelet count, spleen height ratio (SHR), direct bilirubin, INR, vWF, ADAMTS13, CD40 and Pselectin were significantly correlated with PHT (Table 1). **Conclusion:** The declining platelet count in PSVD is considered a marker of disease progression. TPO level was expected to be elevated as liver synthetic function is preserved in PSVD. However, TPO levels were lower than previously published in chronic hepatitis C patients. Our findings do not suggest low thrombopoietin or splenic sequestration to be the leading causes of declining platelet count in PSVD. The finding of only CD-40 correlating significantly with platelet count in PHT on multivariable analysis suggests endothelial activation as a major cause of thrombocytopenia in PSVD. Future studies are needed to identify reliable factors to predict disease severity and progression of PSVD.



Variable	Portal HTN	No portal HTN	P value
Age	55.9	64.7	0.25
Platelets	84	127	0.03*
SHR	1.0	0.66	0.02*
Creatinine	0.81	0.78	0.63
Albumin	3.9	3.8	0.97
ALKP	96	121	0.25
ALT	32	51	0.12
AST	40	59	0.15
T.Bili	1.1	0.7	0.08
D.Bili	0.4	0.2	0.03*
INR	1.0	0.99	0.02*
TPO	33.2	26.4	0.33
Human vWF	15.0	7.1	0.05
Human ADAMTS13	492	852	0.009*
Neuraminidase	19.8	27.3	0.58
IL-6	21.5	16.4	0.52
CD40	2.1	3.2	0.04*
Pselectin	61.1	76.2	0.08*

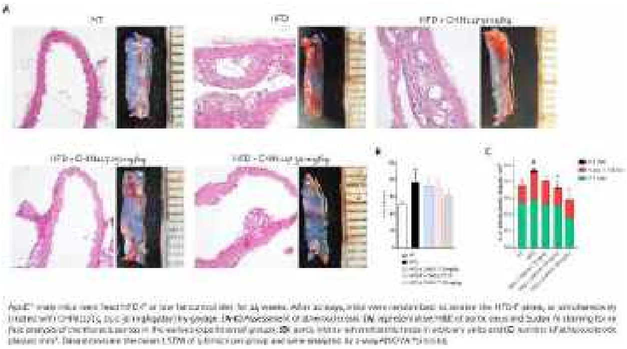
Table 1: Comparison of variables in patients with and without portal hypertension.

Disclosures: The following people have nothing to disclose: Nehna Abdul Majeed, Rownock Afruza, Moumita Chakraborty, Harish Gopalakrishna, Maria Mironova, Nicole San-Dee Minerva, Maleeha Ahmad, Adekanyinsola Onitiri, Asif Ali Hitawala, Shani Scott, David E Kleiner, Christopher Koh, Theo Heller

f 1616-A | POTENT AND ORALLY ACTIVE DUAL GPBAR1/CYSLT1R MODULATOR PROTECT FROM VASCULAR DYSFUNCTION IN A MOUSE MODEL OF NAFLD

Michele Biagioli[1], *Silvia Marchianò*[1], *Cristina Di Giorgio*[1], *Martina Bordoni*[1], *Rachele Bellini*[1], *Carmen Massa*[1], *Ginevra Urbani*[1], *Rosalinda Roselli*[2], *Eleonora Distrutti*[3], *Angela Zampella*[2] *and Stefano Fiorucci*[1], *(1)University of Perugia, (2)University of Naples, Federico II, (3)Azienda Ospedaliera Di Perugia*

Background: Several mediators are involved in the development of liver inflammation and fibrosis in NAFLD/NASH patients. Among these targets, the cysteinyl leukotriene receptor 1 (CysLT1R) and the bile acid receptor GPBAR1 have been shown to be involved in disease development in several animal models of NAFLD/NASH. CysLT1R and GPBAR1 are expressed by the liver resident macrophages, the Kupffer cells and the HSC. Thus, although CysLT1R promotes an inflammatory response, GPBAR1 agonists attenuate the production of inflammatory mediators, suggesting that CysLT1R antagonists might synergize with GPBAR1 agonists in reducing liver inflammation. Additionally, the two receptors are expressed by several metabolically active tissues, including the white adipose tissues (WAT) exerting antagonistic effects on adipocytes. Based on this background, we have developed a molecule, CHIN117, with dual activity: CysLT1R antagonist and GPBAR1 agonist. In a previous study we demonstrated that CHIN117 exerted beneficial effects on the liver when administered in a mouse model of NASH. However, it is increasingly recognized that CV-related events represent the main cause of death in patients with NAFLD, strongly suggesting that management of NAFLD/NASH should include the treatment of the CVD component of the disease. Whereas CysLT1R and GPBAR1 are also expressed on the vascular epithelium could represent an interesting therapeutic target for the management of NASH-related CVDs. To evaluate the effect of CHIN117 on the vascular component of NASH, we administered the new compound in a mouse model of atherosclerosis. **Methods:** Apolipoprotein E deficient mice (ApoE$^{-/-}$), a standard model of atherosclerosis, were fed with HFD-F alone or with BAR501 for 14 weeks and then sacrificed. The aortic rings, aorta and liver were isolated and analyzed. **Results**: Analysis of the aortas from ApoE$^{-/-}$ mice fed with HFD-F for 14 weeks showed severe wall thickening accompanied by the formation of atherosclerotic plaques of various sizes. Inhibition of CYSLT1R activity and simultaneous activation of GPBAR1 by CHIN117 alleviated the disease in a dose-dependent manner. CHIN117 reduced the thickness of the aorta and the number of atherosclerotic plaques. Furthermore, analysing the type of plaques, it was evident that the highest dose of CHIN117 (30 mg/kg/day) completely reversed the formation of plaques larger than 3 mm, which are the ones that are more likely to break. To further analyse the effects of the administration of the new compound, we performed an RNAseq analysis on the aorta of the mice of the various experimental groups. The data obtained showed that CHIN117 reduced the expression of many genes belonging to inflammatory pathways thus exerting an anti-inflammatory effect on the aortas. **Conclusion:** A novel dual CYSLT1R antagonist and GPBAR1 agonist CHIN117 exert beneficial effect dose-dependent versus NASH-associated vascular disease.



Disclosures: The following people have nothing to disclose: Michele Biagioli, Silvia Marchianò, Cristina Di Giorgio, Martina Bordoni, Rachele Bellini, Carmen Massa, Ginevra Urbani, Rosalinda Roselli
Disclosure information not available at the time of publication: Eleonora Distrutti, Angela Zampella, Stefano Fiorucci

1617-A | SURVIVAL OF NON-TRANSPLANTED PATIENTS WITH HEPATOPULMONARY SYNDROME (HPS)

Kathryn Teresa del Valle[1], *Hilary Megan DuBrock*[1] *and Michael J. Krowka*[2], *(1)Mayo Clinic, (2)Mayo Clinic Rochester, Rochester, MN*

Background: Hepatopulmonary syndrome (HPS) is the most common pulmonary vascular complication of liver disease, affecting 20-30% of patients with advanced liver disease. It is characterized by abnormal arterial oxygenation due to intrapulmonary vasodilatation. The majority of patients with HPS experience complete resolution following liver transplant (LT) and have a similarly favorable prognosis to non-HPS LT recipients. Therefore, HPS is considered an indication for LT, and patients with severe or very severe HPS (PaO2 < 60 mmHg) are eligible for Model for End Stage Liver Disease (MELD) exception points. On the contrary, patients with HPS who do not undergo LT have historically been shown to have poor outcomes. We sought to evaluate recent survival among patients with HPS who do not undergo LT in our center's large patient database. **Methods:** We performed a retrospective cohort study evaluating patients with moderate to very severe HPS in our single-site, academic center. We included patients diagnosed in 2005 and later with HPS and PaO2 **d** 70 mmHg. We excluded patients diagnosed with HPS before 2005. Survival in the non-transplanted cohort was analyzed using Kaplan Meier methods. **Results:** Since 2005, 151 patients in our database were diagnosed with HPS with initial PaO2 **d** 70 mmHg. 78/151 (52%) patients did not undergo LT, and the remaining 73/151 (48%) did. The 78 patients who did not undergo LT were included in our final analysis, with year of diagnosis ranging from 2005 through 2023. Five-year survival was 14% (11/78). Overall survival curve of the cohort is depicted in Figure 1. Mean PaO2 at time of HPS diagnosis was 56 mmHg ± 9mmHg. Of these, 47/78 (60%) have died. 19/78 (24%) patients remain living, and 12/78 (15%) have been lost to follow-up. **Conclusion:** Overall survival for patients with HPS who do not undergo LT remains poor since 2005, with five-year survival 14%. Additionally, mean PaO2 at time of diagnosis was 56 mmHg, consistent with severe HPS and potentially suggestive of delays in HPS diagnosis. Our findings underscore the importance of facilitating LT whenever feasible for patients with HPS and also the unmet need for targeted medical therapies for those who are not eligible for LT.

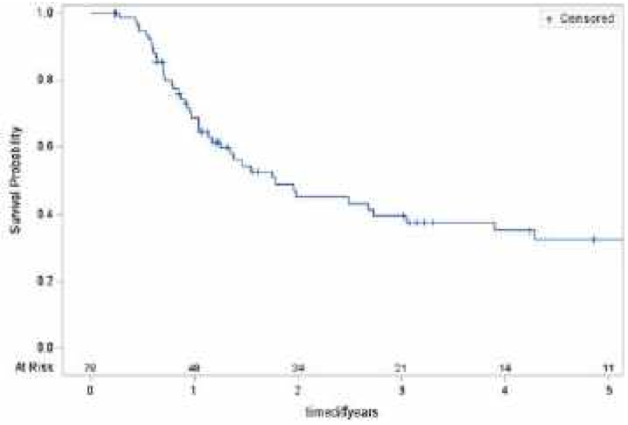


Figure 1: Survival in Patients with HPS who Do Not Undergo LT

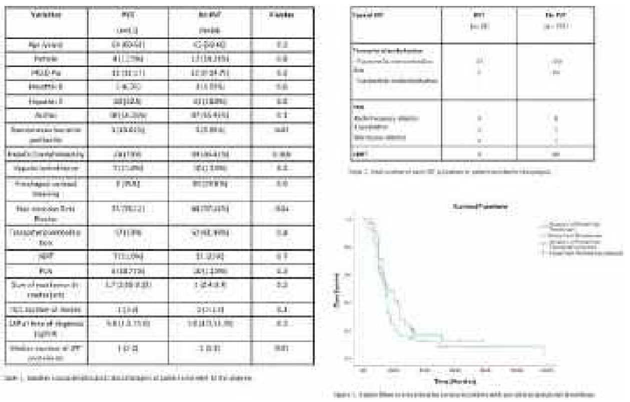
Disclosures: The following people have nothing to disclose: Kathryn Teresa del Valle

Disclosure information not available at the time of publication: Hilary Megan DuBrock, Michael J. Krowka

1618-A | THE OUTCOMES OF PORTAL VEIN THROMBOSIS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA WHO UNDERWENT LOCOREGIONAL THERAPY

Cristina Batarseh[1], Asahi Hoque[1], Karim Osman[1], Joseph Cappuccio[1], Judy Alrukby[1] and Amir Ahmed Qamar[2], (1)Lahey Hospital and Medical Center, (2) Lahey Clinic Medical Center

Background: Portal vein thrombosis (PVT) incidence is thought to be higher in hepatocellular carcinoma (HCC). Locoregional therapies (LRT) play a major role in managing the majority of HCC cases. They are used to prolong survival, bridge to transplant, or for downstaging when the tumor burden exceeds transplant criteria. In this study, we aim to develop further understanding of the outcomes of developing PVT in patients with HCC who underwent LRT. Specifically, we will examine rates of hepatic decompensation, mortality and access to LRT. **Methods:** Patients with HCC who underwent liver transplant evaluation at our institution from 2015 to 2022, were retrospectively reviewed. We included adult patients (age > 18 y) with a clear diagnosis of HCC made by multiphasic computed tomography, magnetic resonance imaging or liver biopsy. Portal vein thrombosis was defined by partial or complete occlusion of the portal venous flow due to luminal thrombus. Exclusion criteria included: unclear diagnosis of HCC, portal vein tumor thrombosis or portal vein compression by neoplasm. Baseline data was obtained at time of HCC diagnosis. Patients were followed from baseline until last follow up or death. Patients were divided into two cohort groups depending on the presence or absence of PVT. Censoring occurred at the time of last follow up. Cumulative incidence of outcomes was determined by the Kaplan-Meier method. Data was analyzed using SPSS software. The study was approved by the institutional IRB. **Results:** A total of 116 patients with HCC were included, among which 27.6 % had PVT. Age, gender, tumor burden, variceal bleeding, ascites, and MELD-Na were similar between the two groups. However, patients in PVT group had higher proportion of hepatic encephalopathy (HE) (*p*-value < 0.006), and use of non-selective beta-blockers (*p*-value 0.04) as shown in table (1). The median number of LRT performed in patients with and without PVT was 1 (1-2) and 2(1-2), respectively (*p*-value 0.02) table (1). Regardless of the presence or absence of PVT, the most performed LRT was transcatheter hepatic artery chemoembolization (TACE), followed by stereotactic body radiotherapy (SBRT), then percutaneous ablation therapy (PCA) as illustrated in table (2). Kaplan Meier survival analysis showed no difference in mortality between the groups. **Conclusion:** The presence of PVT in patients with HCC is associated with higher rates of HE and lower numbers of LRT. However, there was no significant difference in survival rates. Further studies with larger sample size are required to validate our results.



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

Disclosures: The following people have nothing to disclose: Cristina Batarseh, Asahi Hoque, Karim Osman, Joseph Cappuccio, Judy Alrukby, Amir Ahmed Qamar

1619-A | VASCULARIZED LIVER ORGAN-ON-A-CHIP: STEP FORWARD IN UNDERSTANDING LIVER PHYSIOLOGY

Subia Bano[1], Parinita Agrawal[1], Anupriya Mehra[1], Shanthini Kannan[1], Nisha Rajendran[1], Suvro Kanti Chowdhury[1], Joseph Christakiran Moses[1], Wenson David Rajan[1], Satish Nadig[1,2], Sonal Asthana[1,3], Ajith V Kamath[1], Arun Chandru[1] and Tuhin Bhowmick[1], (1) Pandorum Technologies, (2)Feinberg School of Medicine, (3)Aster CMI Hospital

Background: Human relevant 3D liver organoid models are instrumental in understanding healthy liver functions and pathophysiology, although inclusion of functional vasculature in such models remains a challenge. Micro-physiological systems (MPS) such as organ-on-chip (OOC) with functional vasculature offer real-time monitoring, high-throughput screening, and human-relevant pathophysiological responses. The proposed model exploits the potential of the OOC platform by encapsulating healthy liver organoids and advancing vasculature development in biomimetic matrix. **Methods:** Multicomponent liver organoids (400-450 µm diameter in size) comprised of primary hepatocytes, endothelial (HUVEC), and MSCs were encapsulated in photo-responsive biomimetic matrix in the central channel of a perfusion chip. HUVECs were seeded in side perfusion channels. Angiogenic cocktails (VEGF, FGF, PMA, S1P) was introduced on day 3 into the perfusion channels to create concentration gradient. Cellular viability (CTG and Live/Dead assay) and hepatocyte functionality (albumin ELISA) were assessed. Cell specific biomarkers expression were checked by immunofluorescence staining. The vascular network tube length and numbers were quantified using ImageJ software[1]. **Results:** Matrix embedded liver organoids were observed until 2 weeks in OOC platform (Aim biotech chip)[2]. Organoids showed good cellular viability and functionality of hepatocytes. Angiogenic cocktails triggered endothelial cells sprouting and formation of vascular network between the organoids as well as endothelial monolayer in the perfusion channel of the OOC. The embedded organoids retained the functionality of hepatocytes, indicated by albumin secretion (ELISA), CYP3A4 and albumin biomarker expression. Endothelial tube formation was confirmed with CD31 expression while MSCs were checked via CD90 biomarker expression. Quantitative analysis of vascular network indicated angiogenic cocktails promoted 3-fold increase in tube length and 2.5-fold increase in branch numbers compared to control. **Conclusion:** The current OOC platform with multi-component liver organoids successfully supported the formation of a functional vascular network. The preserved functionality of cells in organoids showcases the robustness of this OOC platform under angiogenic stimulation. Importantly, our work reveals the potential of such platform towards the advancement of disease modelling and drug screening. References: 1. Carpentier et al. *Sci Rep*10, 11568 (2020). 2.Anastasiia et al. *Front. Bioeng*. 10, 1-16 (2023).

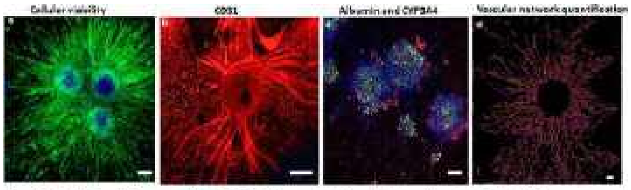


Figure1: Vascularized liver organoid on OOC platform: a. Live/dead staining (live cells: Calcein AM/green channel, dead cells: Ethidium homodimer/red channel, nucleus: DAPI/blue channel, scale bar 300µm. b. immunofluorescence images showing CD31 positive endothelial cells, scale bar 100µm. c. immunofluorescence images showing positive albumin (red channel) and CYP3A4 (green channel) hepatocyte marker expression, scale bar 200µm. d. Vascular network quantification for tube length and branch numbers using image J software (angiogenesis analyzer plugin)[1]. Scale bar 20µm.

Disclosures: The following people have nothing to disclose: Subia Bano, Tuhin Bhowmick

Disclosure information not available at the time of publication: Parinita Agrawal, Anupriya Mehra, Shanthini Kannan, Nisha Rajendran, Suvro Kanti Chowdhury, Joseph Christakiran Moses, Wenson David Rajan, Satish Nadig, Sonal Asthana, Ajith V Kamath, Arun Chandru

1700-A | A STUDY OF ACUTE LIVER INJURY ASSOCIATED WITH ORNIDAZOLE: ANALYSIS OF 82 CASES IN TÜRKIYE

Ilker Turan[1], Esra Nur Nur Durmazer[1], Sezgin Vatansever[2], Ali Rıza Calıskan[3], Murat Harputluoglu[4], Cumali Efe[5], Ramazan Idilman[6], Emin Bodakci[7], Zeki Karasu[1], Ulus S. Akarca[1] and Fulya Gunsar[1], (1)Ege University Faculty of Medicine, Izmir, Turkey, (2)Katip Celebi University ,Faculty of Medicine ,Izmir, (3) Adiyaman University Faculty of Medicine, Adiyaman, Turkey, (4)Inonu University Faculty of Medicine, Malatya, (5)Harran University Faculty of Medicine, Sanliurfa, (6)Ankara University, Ankara, Turkey, (7) Ankara University Faculty of Medicine, Ankara, Ankara, Turkey

Background: Ornidazole-induced acute liver injury has been described in a few case reports and series. The aim of this study was to examine the characteristics and outcomes of patients diagnosed with acute liver injury associated with ornidazole. **Methods:** Between December 2006 and March 2023, the clinical and laboratory data of patients diagnosed with acute liver injury associated with ornidazole were analyzed in six centers

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

in Türkiye. The endpoints were defined as death, liver transplantation, and post-transplantation mortality. **Results:** Out of the identified 82 patients, 62 (75.6%) were female, with a mean age of 46 years. Among them, 44 patients had used ornidazole alone, while 38 had used it in combination with other medications. The most common symptoms were jaundice (83%), darkening of urine (65%), nausea/vomiting (40%), and abdominal pain (22%). The mean peak levels of ALT, AST, ALP, GGT, total bilirubin, and INR were 1190 IU/L, 1124 IU/L, 234 IU/L, 236 IU/L, 17.6 mg/dL, and 1.75, respectively. Hepatocellular pattern of liver injury was observed in most patients (mean R [ALT/ULN ÷ ALP/ULN] 12 ± 0.7). Nine patients (10.9%) developed liver failure as a severe consequence of liver injury. Four patients died, and five patients underwent transplantation. Two transplant recipients died. One patient developed chronic hepatitis. Multivariate logistic regression analysis showed that INR level was a predictor of severe outcomes (OR: 337,059, $p = 0.0029$). **Conclusion:** This study demonstrates that ornidazole, either alone or in combination with other drugs, can cause severe drug-induced liver injury, and that INR level can predict poor outcomes.

Disclosures: The following people have nothing to disclose: Ilker Turan, Esra Nur Nur Durmazer, Sezgin Vatansever, Ali Rıza Calıskan, Murat Harputluoglu, Cumali Efe, Ramazan Idilman, Emin Bodakci, Zeki Karasu, Ulus S. Akarca, Fulya Gunsar

f 1701-A | AN OPTIMIZED STEROID STEPWISE DOSE REDUCTION THERAPY FOR CHRONIC DRUG-INDUCED LIVER INJURY WITH OR WITHOUT AIH-LIKE FEATURES: A RANDOMIZED PROSPECTIVE OPEN-LABEL TRIAL

Ang Huang[1,2], Yun Zhu[1], Shuhong Liu[1], Zherui Liu[1], Qingsheng Liang[1], Jun Zhao[1], Binxia Chang[1], Jing-Feng Bi[1], Xingran Zhai[1], Ning Li[1], Hui Tian[1], Lin Han[1], Yingjie Zhuang[1], Guang-Ju Teng[1], Wei Zhang[3], Ying Sun[1], Dong Ji[1], Jingmin Zhao[1] and Zhengsheng Zou[1], (1)Fifth Medical Center of PLA General Hospital, (2) First Medical Center of PLA General Hospital, (3)Peking University

Background: The use of corticosteroids to treat patients with chronic drug-induced liver injury (DILI) is an important challenge. Our previous study showed that patients with chronic DILI significantly benefit from the 48-week steroid stepwise reduction (SSR) therapy. However, it is unclear whether a shorter course steroid therapy is effective. The aim of this study was to assess if the short-term (36-week) SSR for patients with chronic DILI can achieve similar efficacy and safety to 48-week SSR. **Methods:** This was a randomized prospective open-label trial. Eligible patients were randomly assigned (1:1) either to 36-week SSR group or 48-week SSR group. Liver biopsies were performed at baseline and at the end of treatment period. The primary outcome was the proportion of patients with sustained biochemical response (SBR). The secondary outcomes were improvement in liver histology, time to biochemical normalization, and safety. **Results:** Of 90 participants, 84 (87.5%) completed the trial. The patients were predominantly female (68.9%), aged > 40 years (78.6%), and had a hepatocellular injury pattern of DILI (53.4%). After treatment, SBR was 92.9% in the 36-week SSR group compared with 95.2% in the 48-week SSR group by PPS analysis ($p = 1.000$). Significant histological improvements in both histological activity (93.1% vs. 92.9%, $p = 1.000$) and fibrosis (41.4% vs. 46.4%, $p = 0.701$) were observed in 36-week SSR and 48-week SSR group. There was also no difference in biochemical normalization time between the two groups. No severe adverse events were observed during the trial. **Conclusion:** Both 36-week SSR and 48-week SSR demonstrate similar efficacy in biochemical response and histological improvements with good safety, which support 36-week SSR as a preferable therapeutic choice. (ClinicalTrials.gov, NCT03266146)

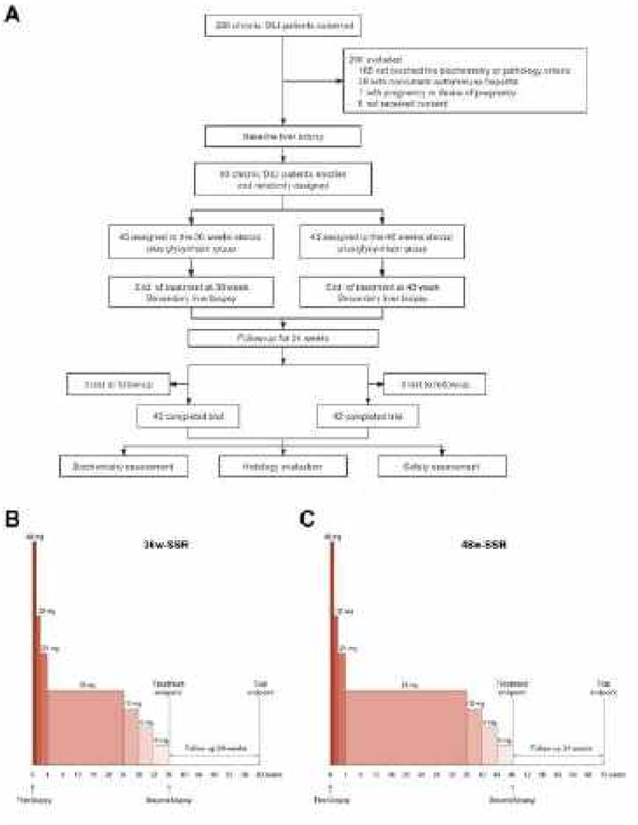


FIGURE 1. Flow diagram of the clinical trial and the steroid treatment protocol.
A. The study flow chart of the trial;
B. The protocol of the 36-week steroid stepwise reduction (36w-SSR) plus glycyrrhizin therapy;
C.The protocol of the 48-week steroid stepwise reduction (48w-SSR) plus glycyrrhizin therapy.

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

Disclosures: The following people have nothing to disclose: Ang Huang, Yun Zhu, Shuhong Liu, Zherui Liu, Qingsheng Liang, Jun Zhao, Binxia Chang, Jing-Feng Bi, Xingran Zhai, Ning Li, Hui Tian, Lin Han, Yingjie Zhuang, Guang-Ju Teng, Wei Zhang, Ying Sun, Dong Ji, Jingmin Zhao, Zhengsheng Zou

1702-A | CHARACTERIZATION OF A LIVER INJURY OUTBREAK IN 2022 AFTER INGESTION OF THE FROZEN FRENCH LENTIL AND LEEK CRUMBLE FOOD PRODUCT

Gina Choi[1], Jawad Ahmad[2], Victor J. Navarro, Md[3], Swan N. Thung[2], Ikhlas Khan[4], Bharathi Avula[4], Huiman Barnhart[5] and Andrew Stolz[6], (1)David Geffen School of Medicine at UCLA, (2)Icahn School of Medicine at Mount Sinai (ISMMS), (3)Albert Einstein Medical Center, Doylestown, PA, (4)University of Mississippi, (5)Duke University, Durham, NC, (6) University of Southern California, Los Angeles, CA

Background: In April 2022, French Lentil and Leek Crumble (FLLC), a new frozen food, was introduced online as part of a meal subscription plan. Soon thereafter, widespread anecdotal reports of acute gastrointestinal symptoms with liver injury were reported, leading to its voluntary withdrawal in June 2022, after shipment of 28,000 preparations. **Aim:** To report the clinical features, liver test abnormalities, liver histology, and initial chemical analysis of 17 patients with FLLC associated liver injury, enrolled in the Drug Induced Liver Injury Network (DILIN). **Methods**: Analysis of patients enrolled in the DILIN prospective study in 2022 with suspected FLLC associated liver injury. **Results:** The mean age was 41 years, 76% female, mean BMI of 24kg/m^2, and all were Caucasian without underlying liver disease. The median latency to onset was 5 days with 18 days to resolution. In some cases, abdominal pain proportional to the amount of FLLC consumed was observed. Regarding symptoms, 29% had jaundice, 35% nausea, 29% fever, 41% abdominal pain, 35% itching, and none had rash. The median initial serum ALT was 369 U/L, AST 117 U/L, alkaline phosphatase 176 U/L, and total bilirubin 2.7 mg/dL (see Table 1). The mean time to peak injury was 2 days. 53% had a hepatocellular pattern of liver injury at presentation, with the rest mixed or cholestatic. 24% of patients were hospitalized and there were no fatalities or transplants. Liver biopsy in one subject revealed mild ductular reaction, mild lymphocytic and eosinophilic portal inflammation with preserved bile ducts and no interface hepatitis. There was mild lobular necroinflammation without steatosis, granulomatous reaction or cholestasis, consistent with acute hepatitis of unknown etiology. Four FLLC samples underwent chemical analysis and no amatoxins, phallotoxins, aflatoxins, microcystins, or pyrrolizidine alkaloids were identified within limits of detection (10-25 ppb) and the heavy metals (As, Pb, Hg, Cr, Cd) were within acceptable limits. Phylogenetic analysis confirmed the presence of *Tara spinosa*, the source of Tara flour. Since removal of the product from the market, no further subjects have been enrolled into the DILIN. **Conclusion:** Ongoing studies will seek to identify the presumed hepatotoxin in addition to host factors, including genetic variants, which may predispose to liver injury.

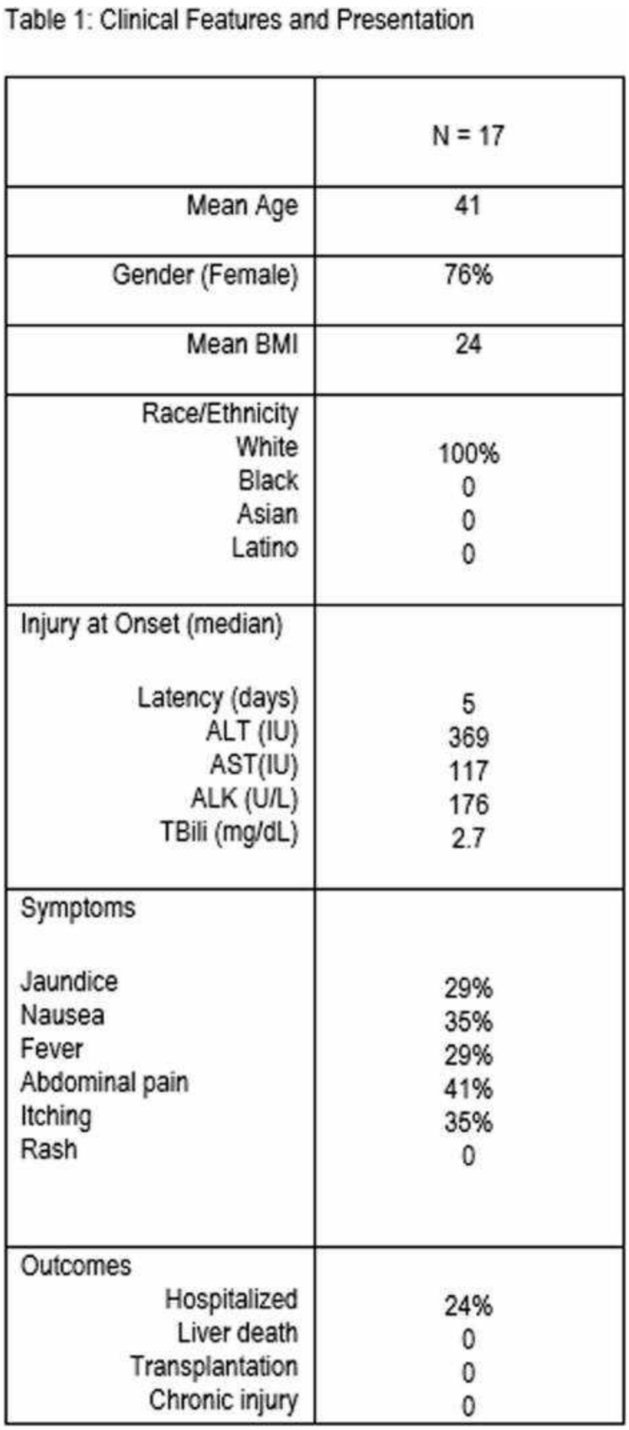


Table 1: Clinical Features and Presentation

	N = 17
Mean Age	41
Gender (Female)	76%
Mean BMI	24
Race/Ethnicity	
White	100%
Black	0
Asian	0
Latino	0
Injury at Onset (median)	
Latency (days)	5
ALT (IU)	369
AST(IU)	117
ALK (U/L)	176
TBili (mg/dL)	2.7
Symptoms	
Jaundice	29%
Nausea	35%
Fever	29%
Abdominal pain	41%
Itching	35%
Rash	0
Outcomes	
Hospitalized	24%
Liver death	0
Transplantation	0
Chronic injury	0

Disclosures: Gina Choi – Intercept: Speaking and Teaching, No, No; Gilead: Speaking and Teaching, No, No;
The following people have nothing to disclose: Victor J. Navarro, Md, Swan N. Thung, Andrew Stolz
Disclosure information not available at the time of publication: Jawad Ahmad, Ikhlas Khan, Bharathi Avula, Huiman Barnhart

1703-A | CLINICAL CHARACTERISTICS AND HLA ASSOCIATIONS OF AZITHROMYCIN INDUCED LIVER INJURY

Dina Halegoua-De Marzio[1], Caroline Conlon[2], Jawad Ahmad[3], Huiman Barnhart[4], Robert J. Fontana[5], Marwan S. Ghabril[6], Paul H. Hayashi[7], David E Kleiner[8], William M. Lee[9], Yi-Ju Li[4], Joseph Odin[10], Andrew Stolz[11], Raj Vuppalanchi[12], Victor J. Navarro, Md[13] and for the Drug Induced Liver Injury Network (DILIN), (1)Sidney Kimmel Medical College at Thomas Jefferson Unversity, (2)Thomas Jefferson University Hospital, (3)Icahn School of Medicine at Mount Sinai (ISMMS), (4)Duke University, Durham, NC, (5) University of Michigan Hospitals and Health Centers, (6) Indiana University, (7)FDA, (8)Laboratory of Pathology, National Cancer Institute, National Institutes of Health, (9)University of Texas Southwestern Medical Center, (10)Icahn School of Medicine at Mount Sinai, New York, NY, (11)University of Southern California, Los Angeles, CA, (12)Indiana University School of Medicine, (13) Einstein Medical Center

Background: Azithromycin (AZ) is a widely used macrolide antibiotic with a favorable safety profile, yet drug induced liver injury (DILI) has been reported. Our aim is to characterize the clinical features, outcomes, and human leukocyte antigen (HLA) associations in patients with AZ DILI. **Methods:** We evaluated individual's with definite, highly likely or probable AZ DILI enrolled by the US Drug Induced Liver Injury Network (DILIN). HLA typing was performed using an Illumina MiSeq platform. Analysis of HLA alleles was performed by Fisher's exact test to compare allele frequency (AF) in AZ DILI cases and population controls assembled from five dbGaP GWAS datasets. **Results:** Thirty cases (4 definite, 14 highly likely, 12 probable) of AZ DILI were included. These represent 2% of adult and 7% of pediatric high causality DILI cases enrolled in DILIN between 2004 and 2022 (n = 1635). Median age was 46 years (range 1-78). 83% were white. 60% were female. 17% had pre-existing liver disease. Median duration of use was 5 days (range 2-8 d) and latency was 18.5 days (range 2-65 d). 73% were jaundiced at presentation. The DILI pattern was hepatocellular in 60%, cholestatic in 27%, and mixed in 13%. Ten cases (33%) were considered severe or fatal, with 90% having hepatocellular injuries. Two patients (7%) required liver transplantation and one patient with chronic liver disease died of hepatic failure. Chronic liver injury developed in 17% of patients, of which 80% had hepatocellular injuries at onset. Of the 5 children included, 3 were hospitalized; 1 required transplantation; 1 suffered a severe cutaneous reaction; and 2 developed chronic liver injury. Of the 13 liver biopsies reviewed, 6 had acute or chronic hepatitis, 6 had cholestatic injuries, 4 had zone 3 to multiacinar necrosis, and 1 had severe ductopenia. HLA-DQA1*03:01 showed a significantly increased prevalence in AZ DILI versus population controls after correction for multiple testing (AF: 0.29 vs 0.11, p = 0.001, FDR = 0.03). The increased prevalence was non-significant when compared to other DILI cases (AF = 0.16, p = 0.053, FDR 0.50). **Conclusion:** AZ DILI can lead to significant morbidity and mortality in both adult and pediatric populations. Hepatocellular injury pattern and pediatric incidence were associated with worse outcomes. HLA-DQA1*03:01 was significantly more prevalent in AZ cases than in the population. However, this allele was not specific to AZ DILI compared with DILI caused by other drugs.

Disclosures: Dina Halegoua-De Marzio – Pfizer: Consultant, No, Yes; Glympse Bio: Consultant, No, Yes; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Viking: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Novo Nordisk: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; BMS: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Galectin: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
The following people have nothing to disclose: Caroline Conlon, Robert J. Fontana, Paul H. Hayashi, David E Kleiner, Andrew Stolz, Raj Vuppalanchi, Victor J. Navarro, Md
Disclosure information not available at the time of publication: Jawad Ahmad, Huiman Barnhart, Marwan S. Ghabril, William M. Lee, Yi-Ju Li, Joseph Odin

1704-A | CLINICAL FEATURES AND OUTCOME OF LIVER INJURY INDUCED BY IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH ADVANCED MALIGNANCIES

Takanori Ito[1], Takafumi Yamamoto[1], Kazuyuki Mizuno[1], Shinya Yokoyama[1], Norihiro Imai[1], Kenta Yamamoto[1], Yoji Ishizu[1], Takashi Honda[1], Satoshi Yasuda[2], Hidenori Toyoda[2], Masatoshi Ishigami[1] and Hiroki Kawashima[1], (1)Nagoya University Graduate School of Medicine, (2) Ogaki Municipal Hospital

Background: The clinical course of immune checkpoint inhibitor (ICI)-induced immune-mediated hepatotoxicity (IMH) differs significantly from that of classical drug-induced liver injury and varies widely among individual's. In this study, we aimed to clarify the clinical characteristics and outcomes in patients with IMH. **Methods:** We evaluated the characteristics and clinical course of IMH in 2071 patients treated with ICIs for advanced malignancies between September 2014 and March 2023. **Results:** During a median observation period of 298 days, 81 (3.9%) patients developed IMH (**e** Grade 3). Of these, 31 (38.3%) patients had a pathological diagnosis by liver biopsy. The number of ICI types were anti-PD-1 or PD-L1 antibody (Ab), anti-CTLA-4 Ab monotherapy/anti-PD-1, and anti-CTLA-4 Ab combination were 60, 7, and 14 patients, respectively. The median time from the first administration of ICI to the onset of IMH (**e** Grade 3) was 50 (range; 1-531) days. The liver-injury patterns were hepatocellular ($n = 38$), mixed ($n = 16$), or cholestatic ($n = 27$), respectively. The neutrophil-to-lymphocyte ratio (NLR), neutrophil count ($P < 0.01$), and CRP ($P < 0.05$) were significantly higher in IMH patients with cholestatic and mixed patterns than those with hepatocellular patterns ($P < 0.01$). Thirty-eight patients (37%) had immune-related adverse events (irAE) other than IMH during follow-up periods, the common type of were endocrine disorders ($n = 12$). Forty-six patients (56.8%) were treated with prednisolone (PSL), 7 patients with PSL/mycophenolate mofetil. The therapeutic response to PSL in the hepatocellular injury pattern was better than in mixed/cholestatic patterns. ICIs were re-administered in 21 patients (25.9%), and only one patient had a flare-up of liver injury, and seven patients developed irAEs in other organs. Immune-related sclerosing cholangitis (irSCs) was observed in 7 patients (8.7%), and as previously reported, the PSL response was poor. **Conclusion:** For the diagnosis of IMH, it is necessary to determine the treatment strategy according to the type of liver injury after excluding irSCs which is refractory to PSL treatment. Additionally, when ICI is re-administered after IMH occurrence, it is necessary to be aware not only of IMH recurrence but also of the occurrence of irAEs in other organs.

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1705-A | COMPARISON OF THE IMMUNE-MEDIATED LIVER INJURY INDUCED BY IMMUNE CHECKPOINT INHIBITORS IN CASES WITH HEPATOCELLULAR CARCINOMA AND OTHER MALIGNANT TUMOR

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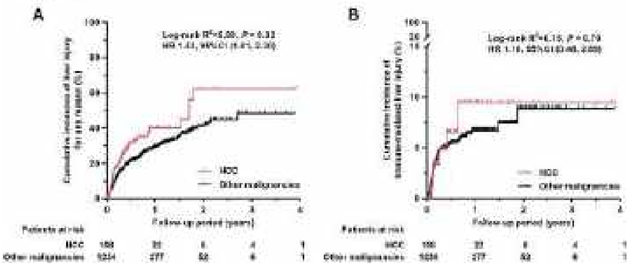
Background: Whether the incidence of immune-mediated liver injury induced by immune checkpoint inhibitors (ILICI) between liver carcinoma and other tumor are not well understood. We aim to compare the incidence of ILICI and clinical characteristics between the liver carcinoma and the other malignancies. **Methods:** Patients treated with immune checkpoint inhibitors at Beijing Friendship Hospital were retrospectively reviewed and categorized into liver carcinoma group and other malignant tumor group. The demographic and laboratory data, and mortality between the two groups were compared. Patients with liver carcinoma were further grouped into no liver injury, immune-mediated liver injury and other reasons caused liver injury groups. The demographic and laboratory data, and mortality among these three groups were compared. **Results:** A total of 109 liver carcinoma and 1247 other tumor cases were included, including 501 gastrointestinal malignancies, 348 pulmonary malignancies, 126 urological tumors and 272 other malignancies. All the cases were treated with anti-programmed death (PD)-1 or anti PD-L1. No difference of total ICIs cycles was found between the liver carcinoma and other malignancies group (2(1,6) vs. 3 (2,6) cycles, $p = 0.053$). Not surprisingly, the baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), total bilirubin (TB) of cases with liver carcinoma were significantly higher than those with other malignancies. More cases in the liver carcinoma group experienced acute liver injury of any reason (36 (33.0%) vs. 287 (23.0%), $p = 0.019$). However, the incidence of immune medicated liver injury of the two groups were similar (6 (5.5%) vs. 61 (4.9%), $p = 0.777$). No difference of mortality was found between the two groups. Furthermore, no difference of mortality was found between the cases with liver carcinoma who has no liver injury, immune mediated liver injury and any other causes induced liver injury (2 (2.7%) vs. 1 (16.7%) vs. 3 (10.0), $p = 0.159$). **Conclusion:** The incidence of immune medicated liver injury of the two groups were similar despite that more cases in the liver carcinoma group experienced acute liver injury of any reason. No difference of mortality was found between the liver carcinoma and other tumor groups.

Figure 3



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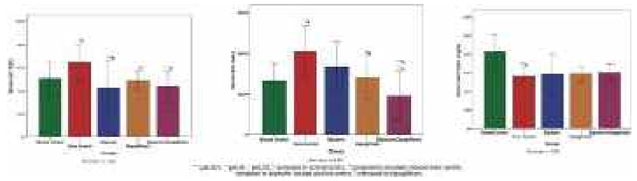
1706-A | DAPAGLIFLOZIN ALONE AND IN COMBINATION ATTENUATES CISPLATIN-INDUCED HEPATOTOXICITY BY MITIGATING OXIDATIVE STRESS : A PRE-CLINICAL STUDY.

Mohamed Farook[1], Mohammed Moin Khan[1], Anuradha Nair[1], Sofiya Khan[1], Nirmal Binu[1], Mohamed Yehya[1], Shakta Mani Satyam[2], Laxminarayana Kurady Bairy[2] and Abdul Rehman[2], (1)Ras Al Khaimah Medical and Health Sciences University, (2)Faculty Supervisors-Departments of Pharmacology and Pathology, Rakcoms, Rakmhsu

Background: The world wide prevalence of liver diseases is rising due to the lack of effective preventive or treatment measures. This study aimed to investigate the anticipated hepatoprotective potential of Dapagliflozin alone and in combination with Silymarin against Cisplatin-induced hepatotoxicity in Wistar rats. **Methods:** 30 adult Wistar rats were randomly divided into five groups ($n = 6$/group): Group I- Normal control, Group II- Negative control, Group- III- Positive control (Silymarin), Group IV- Dapagliflozin and Group V- Dapagliflozin + Silymarin. Hepatotoxicity was induced in Group II to Group V rats by administering Cisplatin per week for seven weeks. Serum ALT, AST, Total Protein,inflammatory cytokines, Heme oxygenase -1, Superoxide dismutase were estimated and H&E staining of the liver was performed. **Results:** Hepatotoxicity was significantly ($p < 0.05$) marked in negative control compared to normal control rats. Both silymarin and dapagliflozin alone and in combination significantly ($p < 0.05$) decreased serum ALT, AST, inflammatory cytokines and oxidative stress markers compared to negative control. **Conclusion:** The present study revealed that dapagliflozin alone and in combination with silymarin attenuates cisplatin-induced hepatotoxicity by mitigating oxidative stress.



Disclosures: The following people have nothing to disclose: Mohamed Farook, Mohammed Moin Khan, Anuradha Nair, Sofiya Khan, Nirmal Binu, Mohamed Yehya, Shakta Mani Satyam, Laxminarayana Kurady Bairy, Abdul Rehman

1707-A | DEUBIQUITINATING ENZYME JOSD1 MITIGATES PROTEOTOXIC HEPATOCELLULAR INJURY VIA THE SOCS1 PATHWAY

Saheli Chowdhury, Abhishek Sen and Partha Chakrabarti, Csir-Indian Institute of Chemical Biology

Background: Aberrant protein homeostasis and accumulation of intracellular hyperubiquitylated proteins are histopathological signatures in a multitude of chronic liver diseases. Aim of this study is to identify novel deubiquitinating enzymes (DUB) that could reverse pathological ubiquitylation and consequently mitigate the proteotoxic liver injury. **Methods:** Proteasomal inhibitor MG132 was used to induce proteotoxicity in HepG2 cells for assaying with 96 human DUB siRNA library to identify target DUBs modulating proteotoxic stress. DUB JOSD1 was identified and validated for protection against cell death by multiple *in vitro* assays. JOSD1 interacting proteins were analyzed by immunofluorescence microscopy and co-immunoprecipitation. JOSD1 mutant clones were generated by site directed mutagenesis. Knockdown and overexpression of Josephin domain-containing protein 1 (JOSD1) was done using adenovirus and adeno-associated virus (AAV) respectively in primary mouse hepatocytes and in mouse liver. **Results:** Screening of DUB unearthed

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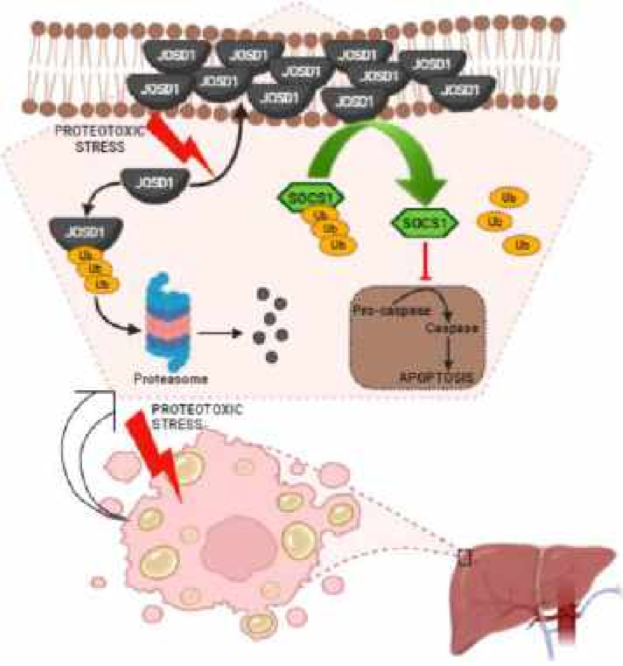
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

JOSD1 as one of the targets for reducing hepatocyte apoptosis under proteotoxicity. The hepato-protective role of JOSD1 was further validated by overexpression and knockdown of JOSD1 both *in vitro* and *in vivo*. Mechanistically, under proteotoxic stress JOSD1 accumulates and localizes to the plasma membrane where it binds, deubiquitinates and stabilizes suppressors of cytokine signaling 1 (SOCS1). Correspondingly, enzymatically inactive JOSD1^{C36A} mutant was neither able to mitigate cell death nor modulate the levels of its interacting partners. **Conclusion:** Our study thus unveils a candidate DUB, JOSD1, as a potent target of proteotoxicity induced hepatocellular apoptosis and proposes a mechanism for its protective action via the SOCS1 pathway.



Disclosures: The following people have nothing to disclose: Saheli Chowdhury, Abhishek Sen, Partha Chakrabarti

1708-A | EFFECTS OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR ON MARKERS OF LIVER FIBROSIS IN ADULTS WITH CYSTIC FIBROSIS

Olivia Portolese[1], Marc Bilodeau[2], Hélène Castel[1], Bernard E. Willems[1], Genevieve Huard[3], Catherine Vincent[2], Annick Lavoie[1] and Julian Hercun[1], (1)Centre Hospitalier De L'université De Montréal, Montréal, QC, Canada, (2)Centre De Recherche Du Centre Hospitalier De L'université De Montréal (CRCHUM), (3)Centre Hospitalier De l'Université De Montréal

Background: Cystic fibrosis (CF) is a genetic disease caused by a mutation in the CFTR gene, the most common being F508del. While lung involvement is predominant, it is estimated that 30% of adults will have cystic fibrosis liver disease (CFLD). Elexacaftor/tezacaftor/ivacaftor (ETI) modulates the F508del mutated protein and improves respiratory outcomes. Although ETI can cause increases in liver enzymes, it has the potential to improve long term liver outcomes as the CFTR protein is located on cholangiocytes. The aim of this study was to determine the short term and long-term effects of ETI on liver outcomes in adults with CF. **Methods:** This is a retrospective descriptive cohort including all adults with CF currently treated with ETI by the Respirology Division of the Centre hospitalier de l'Université de Montréal. Clinical data were collected prior to treatment initiation and on-therapy. Liver fibrosis was assessed by transient elastography (TE); a threshold of 6.8 kPa was used to define CFLD based on previous findings. For each patient, Fib4 and APRI scores were calculated using standard formulas; values of 1.3 and 0.7 were respectively used as thresholds for increased fibrosis. **Results:** The cohort included 154 patients, 51.3% male, with an average age at treatment initiation of 37. One patient had a prior liver transplant. Four (2.6%) patients had imaging findings compatible with cirrhosis. Only 3 (2%) patients had thrombopenia and 8 (5%) had splenomegaly. Baseline liver tests prior to initiating ETI were within normal limits in all but 6 patients presenting with an ALT > 1.5 times the upper limit of normal (ULN) and only case of elevated bilirubin. Thirty-one patients had a pre-treatment TE measurement: their average measure was 6.8 kPa (3.3-24.2 kPa). 29% were considered as having CFLD. Five patients had elevated Fib4 and only 1 elevated APRI scores. Over an average follow-up of 9 months (range 1 – 28), 26 patients (16.8%) had at least one episode of ALT > 1.5 x ULN and 4 presented with increased bilirubin (unconjugated in all cases). Three patients had treatment interruptions for liver related causes, with 1 patient successfully resuming therapy. There was one reported death (non-liver related). The average APRI increased from 0.20 to 0.32 (p = 0.0001) and Fib4 from 0.62 to 0.72 (p = 0.07): the former remained significant on paired analysis (Wilcoxon test < 0.0001). In 15 patients with paired measures, average TE decreased significantly from 6.8 to 6.1 kPa (p = 0.01). In patients with a baseline elevated TE score, measurement improved by 1.3 kPa on average. **Conclusion:** Severe drug-induced liver injury was infrequent in this cohort. Serum markers of fibrosis increased while remaining within normal range. However, TE values decreased, a potentially encouraging finding suggesting improvement in liver fibrosis. Additional long-term follow-up is required to determine trends in TE and explain the discrepancy with serological markers of fibrosis.

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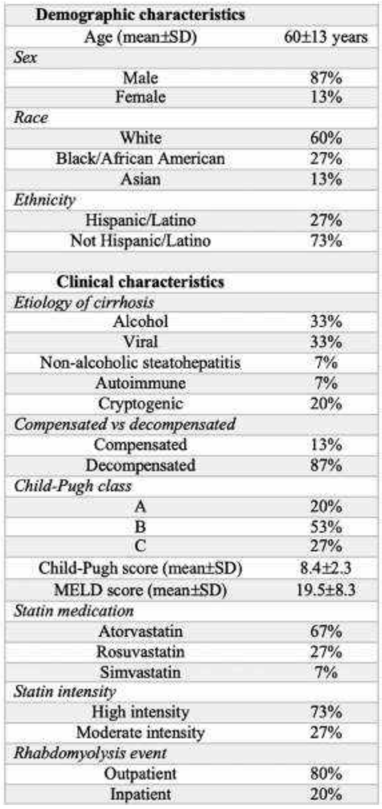
Disclosure information not available at the time of publication: Hélène Castel, Bernard E. Willems, Genevieve Huard, Catherine Vincent, Annick Lavoie, Julian Hercun

1709-A | HIGHER INCIDENCE OF STATIN-INDUCED RHABDOMYOLYSIS IN PATIENTS WITH CIRRHOSIS COMPARED WITH THE GENERAL POPULATION: A RETROSPECTIVE COHORT STUDY

George Chen[1], Meagan Alvarado[1], Elizabeth Cohen[1], Kara Ventura[1] and Uyen To[2], (1)Yale University, New Haven, CT, (2)Yale School of Medicine, New Haven, CT

Background: Statins have been shown to reduce portal hypertension and liver decompensation in patients with advanced chronic liver disease. However, the safety profile of statins in cirrhosis has not been investigated extensively. Although statin-induced rhabdomyolysis (SIR) events in cirrhosis have been reported by multiple case reports, their incidence and associated risk factors are unknown. To this end, we conducted a retrospective cohort study of SIR in patients with cirrhosis in a large United States healthcare system. **Methods:** We evaluated patients with cirrhosis in the Yale New Haven Health System (YNHHS) in Connecticut, USA from January 2012 to March 2023. The YNHHS electronic health record (EHR) was queried using Slicer Dicer, a data exploration tool in the Epic EHR system, to identify patients with cirrhosis who were prescribed statins and developed rhabdomyolysis following initiation of statin therapy. Patient charts were manually reviewed to confirm SIR diagnosis. Demographic and clinical data, including age, sex, race, ethnicity, etiology of cirrhosis, Child-Pugh score, Model for End-Stage Liver Disease (MELD) score, statin type and dose, and hospitalization status were extracted from patient charts. Categorial variables were compared using Chi-square tests at a significance level of < 0.05. **Results:** Among 20,251 patients diagnosed with cirrhosis, 8,239 (41%) were prescribed statins. A total of 15 patients developed SIR, with a cumulative incidence of 0.2%. Demographic and clinical characteristics are provided in Table 1. The majority of patients diagnosed with SIR (mean age of onset: 60 ± 13 y) were male (87%) and white (60%). A significantly higher proportion of SIR events occurred in patients with decompensated cirrhosis (0.87) compared to compensated cirrhosis ($p = 0.005$). Patients had a mean Child-Pugh score of 8.4 and MELD score of 19.5. Eleven patients (73%) were prescribed high-intensity statins, while the remaining four patients were on moderate-intensity statin therapy ($p = 0.002$). A significantly larger percentage of SIR events occurred in the outpatient setting (80%) compared to inpatient ($p = 0.02$). **Conclusion:** To our knowledge, this is the first cohort study to assess the risk of SIR in patients with cirrhosis. The cumulative incidence of SIR in cirrhosis was 0.2%, 20-fold higher than the estimated 0.01% risk of SIR in the general population. The safety profile of statins should be carefully weighed against their potential benefits on liver outcomes, particularly in patients with decompensated cirrhosis and those prescribed high-intensity statin therapy. Additional studies investigating risk factors associated with SIR in cirrhosis are warranted.

Table 1: Demographic and clinical characteristics of patients with cirrhosis diagnosed with statin-induced rhabdomyolysis



Demographic characteristics	
Age (mean±SD)	60±13 years
Sex	
Male	87%
Female	13%
Race	
White	60%
Black/African American	27%
Asian	13%
Ethnicity	
Hispanic/Latino	27%
Not Hispanic/Latino	73%
Clinical characteristics	
Etiology of cirrhosis	
Alcohol	33%
Viral	33%
Non-alcoholic steatohepatitis	7%
Autoimmune	7%
Cryptogenic	20%
Compensated vs decompensated	
Compensated	13%
Decompensated	87%
Child-Pugh class	
A	20%
B	53%
C	27%
Child-Pugh score (mean±SD)	8.4±2.3
MELD score (mean±SD)	19.5±8.3
Statin medication	
Atorvastatin	67%
Rosuvastatin	27%
Simvastatin	7%
Statin intensity	
High intensity	73%
Moderate intensity	27%
Rhabdomyolysis event	
Outpatient	80%
Inpatient	20%

Disclosures: The following people have nothing to disclose: George Chen, Meagan Alvarado, Elizabeth Cohen, Kara Ventura, Uyen To

1710-A | IMPACT OF CLINICAL TRIAL DATA QUALITY ON FDA DRUG-INDUCED LIVER INJURY RISK ASSESSMENT IN NEW DRUG AND BIOLOGIC APPLICATIONS

Ling Lan[1], Mark I. Avigan[2] and Paul H. Hayashi[1], (1) FDA, (2)Food and Drug Adminstration

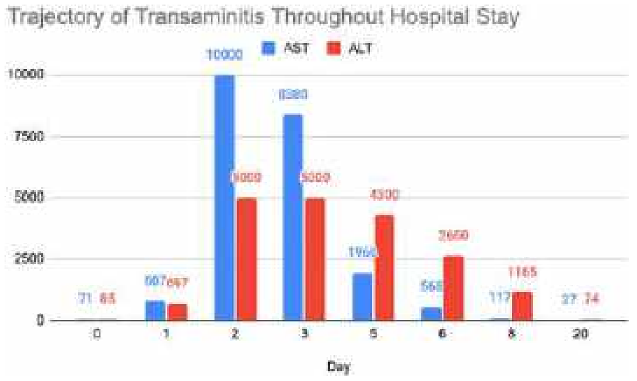
Background: One or two jaundiced hepatocellular DILI cases in clinical programs can significantly impact the benefit-risk assessment of a study drug; therefore, much depends on the completeness and accuracy of submitted data. Aim: To characterize the impact of liver injury data quality on new drug and biologics license application (NDA/BLA) reviews requiring FDA DILI Team assessment. **Methods:** We retrospectively assessed 22 applications for which the FDA DILI Team was consulted from 12/2021 to 3/2023. We assessed the quality of case level data by how many applications required information requests to obtain more data about individual subjects suspected of having DILI. For study level data, we identified applications having deficiencies in laboratory datasets used to generate eDISH (hepatocellular DILI screening) plots. **Results:** Seventy-seven percent (17/22) applications involved new molecular entities; and 86% (19/22) were approved. Labeling had DILI-related warnings and precautions in 84% (16/19) of the approved drugs. The DILI Team had to request more complete case level data in nearly all applications (95%, 21/22). The most common inadequacies were unclear evaluation testing for non-DILI causes, incomplete narratives, unclear concurrent medications, lack of chronologic lab results by table or graphics, and lack of follow-up. DILI Team analyses alleviated DILI concerns in three NDAs/BLAs once complete data were obtained. However, we found two applications with significant study level data limitations including missing local lab results, upper limit normal values, and units (i.e., U/L, mg/dL) that led to subjects meeting Hy's Law lab criteria being incorrectly plotted outside of Hy's Law quadrant in eDISH plots. These study level limitations were only discovered when manually cross-checking study reports and case level data with study level datasets. **Conclusion:** Case level data in applications are often inadequate to assess DILI attribution. Missing lab results from study level data can undermine eDISH as a sensitive screening tool. The extent of incorrect eDISH plotting across applications may be larger than captured in our analysis. Clearer communication between the FDA and drug sponsors throughout drug development is needed so that pre-specified means and expectations are set for collecting DILI-related data. Routine cross-checking of case and study level laboratory data by computer programming may be beneficial.

Disclosures: The following people have nothing to disclose: Ling Lan, Mark I. Avigan, Paul H. Hayashi

1711-A | IV AMIODARONE INFUSION INDUCED ACUTE HEPATOTOXICITY AND LIVER FAILURE

Tulsi Patel, Christianacare Hospital

Background: IV amiodarone is commonly indicated for rate control in hemodynamically stable arrhythmias, including atrial fibrillation. Existing literature reports the development of acute hepatotoxicity from IV amiodarone infusions in patients with reduced EF. We report a case of amiodarone induced acute hepatitis in the setting of cardiogenic shock where the patient also developed multi-organ failure, including acute liver failure. **Methods:** This is a 63 year old male with history of atrial fibrillation who presented with dyspnea and found to be in atrial fibrillation with rapid ventricular rate requiring admission for heart failure. Of note, initial transaminitis(AST 71, ALT 85) was thought to be due to some degree of congestive hepatopathy. Rate control with IV metoprolol was unsuccessful so he was loaded with 150mg IV amiodarone followed by continuous infusion. He received 1020 mg of amiodarone during the initial 22 hours of hospitalization. He eventually developed cardiogenic shock (lactic acid 10.6, CVP 22, SvO2 58%, Fick cardiac output 4.1) and acute renal failure requiring renal replacement therapy. Repeat labs revealed AST > 10000, ALT > 5000 and INR 5.7, peaking at 9.4. Ischemic hepatitis alone could not explain the trajectory of the transaminitis, especially with optimization of cardiogenic shock. Acute hepatitis and acute liver failure (evidenced by coagulopathy and hepatic encephalopathy) were suspected to be due to IV amiodarone. Transaminitis drastically improved within 24 hours of stopping amiodarone and near normalized within 1 week. N-acetylcysteine was initiated 48 hours after development of ALF for possible mortality benefit. **Results:** Hepatotoxicity due to oral amiodarone is a commonly known side effect. Less commonly encountered is the development of acute hepatitis or ALF from IV amiodarone. The mechanism by which this develops is not yet understood. Some literature (Rhodes et al., 1993) suggests that it is related to formulation of the IV infusion with Polysorbate 80. The pattern of injury described on liver pathology appears different in IV amiodarone hepatotoxicity compared to its oral counterpart; described as a pattern of injury similar to ischemic hepatitis. It is possible this could be in part due to the fact that these patients are receiving IV amiodarone for acute arrhythmias impending hemodynamic instability. One study (Nasser et al., 2013) suggests that reduced LV systolic function leads to prolongation of the half life of its metabolite. Further research needs to be conducted in order to assess if the level of injury is dose dependent. **Conclusion:** The mechanism for IV amiodarone induced hepatitis and ALF is not known yet. However, it seems to be a common theme that all of these patients have some degree of reduced left ventricular systolic function. Further research needs to be conducted to identify if there are prognostic factors that can predict this adverse event.



Disclosures: The following people have nothing to disclose: Tulsi Patel

1712-A | OPTIMIZING DILI DETECTION AND MANAGEMENT IN CLINICAL TRIALS FOR PATIENTS WITH ELEVATED AMINOTRANSFERASE LEVELS AT BASELINE

Michael Merz, Self-Employed, Don C. Rockey, Medical University of South Carolina, Hans L. Tillmann, East Carolina University; Greenville VA Health Care Center, Gerd A Kullak-Ublick, University Hospital Zurich, Zurich, Switzerland; Novartis, Anna Fettiplace, Astrazeneca and John F. Marcinak, Abbvie, Inc.

Optimizing DILI detection and management in clinical trials for patients with elevated aminotransferase levels at baseline **Background:** Drug-Induced Liver Injury (DILI) can be a serious problem during clinical development, especially in patients with abnormal baseline liver chemistry, such as in cancer or NASH patients. For patients with normal baseline ALT, there are established ALT thresholds triggering action ('action levels'), e.g. dose interruption or discontinuation; however, no consensus is yet available for thresholds in patients with abnormal baseline ALT. To address this, we developed a simple mathematical model using established ALT thresholds for patients with normal baseline ALT to calculate action levels in multiples of the upper limit of normal (ULN) for patients with abnormal baseline ALT. We then applied the model, as an example, to inclusion and action thresholds typically used in oncology studies, with 20 x ULN as maximum action level triggering permanent drug discontinuation. **Methods:** As per intercept theorem, on two parallel lines intersected by at least three lines, intersecting at a point outside the parallels, the ratio of two segments on one line equals the ratio of the corresponding segments on the parallel line. We used this theorem to translate ALT action levels in patients with normal baseline into action levels in patients with abnormal baselines (detailed derivation see Figure 1). **Results:** Calculation of action levels for patients entering clinical trials with abnormal ALT (i.e., 1 - 3 x ULN or 3 - 5 x ULN) at baseline, using intercept theorem, expressed in multiples of ULN and rounded up, results in the three projected action levels ($al_{1\text{-}3}$) presented below, along with action levels for patients with normal ALT at baseline: Normal ALT at baseline **d** ULN:

- al_1: 3
- al_2: 5
- al_3: 10

Abnormal ALT at baseline > 1 - 3 x ULN

- al_1: 5
- al_2: 7
- al_3: 11

Abnormal ALT at baseline > 3 - 5 x ULN

- al_1: 7
- al_2: 8
- al_3: 12

Thus, protocols placing action levels for ALT in patients with normal baseline at 3, 5 and 10 x ULN, respectively, for increased monitoring, dose interruption or drug discontinuation can use the above derived values to assign appropriate ALT action levels to patients with abnormal ALT at baseline. For example, a patient with a normal baseline may have drug interrupted at 5 x ULN, whereas a patient with a baseline ALT of 2 x ULN will reach interruption at 7 x ULN, resulting in the degree of permitted ALT elevation before interruption being proportional to the baseline ALT value. **Conclusion:** Here, we demonstrate an innovative method to create action levels for patients with abnormal baseline ALT levels. The resulting algorithm is simple, transparent, and provides grouped ALT threshold values without the need to calculate patient-specific multiples of baseline values. This logical, structured approach provides clear and practical guidance for hepatotoxicity management in clinical trials.

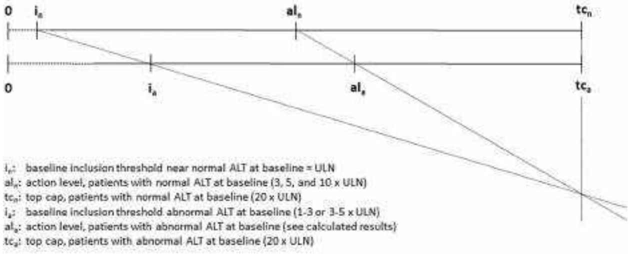


Figure 1: Derivation of action levels for patients with abnormal baseline ALT (lower parallel) from thresholds for patients with near normal baseline ALT (upper parallel).

i_n: baseline inclusion threshold near normal ALT at baseline = ULN
al_n: action level, patients with normal ALT at baseline (3, 5, and 10 x ULN)
tc_n: top cap, patients with normal ALT at baseline (20 x ULN)
i_a: baseline inclusion threshold abnormal ALT at baseline (1-3 or 3-5 x ULN)
al_a: action level, patients with abnormal ALT at baseline (see calculated results)
tc_a: top cap, patients with abnormal ALT at baseline (20 x ULN)

Calculation of action levels for patients with abnormal baselines then follows

$$\frac{tc_n - al_n}{tc_n - i_n} = \frac{tc_a - al_a}{tc_a - i_a}$$

i.e.

$$\frac{TopCap_{normal} - ActionLevel_{normal}}{TopCap - Baseline@Inclusion_{normal}} = \frac{TopCap_{abnormal} - ActionLevel_{abnormal}}{TopCap_a - Baseline@Inclusio_{abnormal}}$$

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

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1713-A | OUTCOMES IN WOMEN WITH CHRONIC LIVER DISEASE UNDERGOING INFERTILITY TREATMENT

Meera Garriga, Monika Sarkar and Marcelle Cedars, University of California, San Francisco

Background: Women with cirrhosis commonly have amenorrhea and subfertility, although data on the the safety and success of assisted reproductive technology (ART) across the spectrum of chronic liver diseases (CLDs) are limited, undermining appropriate pre-conception counseling in women with liver disease. Here, we report reproductive and liver-related outcomes following ART in women with CLD as compared to women without liver disease. **Methods:** We conducted a retrospective analysis of all adult women undergoing ART at our center from 2010-2022. CLD cases were matched to non-CLD controls by age at ART and ART protocol (to ensure consistency in hormonal exposure). Medical history and ART protocols were extracted from the electronic health record. Outcomes of interest included response to controlled ovarian stimulation, embryo fertilization rate, implantation rate, live birth rate, change in liver enzyme levels or hepatitis viral load. Chi-squared and t-tests were used to compare dichotomous and continuous

variables, respectively. **Results:** We identified 54 women with CLD who underwent 100 oocyte retrievals and 64 oocyte transfers between 2010-2022 at our center. Mean age at retrieval and transfer was 39.1 and 39.2 years, and were similar across CLD cases and controls (all $p > 0.05$). The most common causes of CLD were chronic hepatitis B (CHB) (46%), non-alcoholic fatty liver disease (NAFLD) (28%) and benign hepatic lesions (19%). Two patients had autoimmune hepatitis and one had alcoholic cirrhosis. There were no significant differences between CLD and non-CLD groups in number of oocytes retrieved (12.2 vs 13.0), or rates of embryo fertilization (0.69 vs 0.69), implantation (0.45 vs 0.47) or live birth (0.34 vs 0.33) (all $p > 0.05$). Notably, on subgroup analysis by type of CLD, the mean number of oocytes retrieved in patients with CHB was numerically lower compared to controls (12.8 vs 14.5, $p = 0.43$), though rates of embryo fertilization, implantation and live birth were similar. Among women with available liver tests, a rise in liver enzymes was observed during 4/73 (5.6%) cycles in patients with NAFLD, AIH, and CHB. The median (IQR) peak AST was 121.5 IU/L (86-157 IU/L) and median (IQR) peak ALT was 85 IU/L (59-185 IU/L). Among 20 women with CHB, one had rise in viral load from ~12,000 to 1 million IU/mL and concurrent rise in ALT from 18 to 53. OHSS occurred in no patients with CLD and in 1 non-CLD control. 5 patients with CLD (3 CHB, 1 NAFLD, 1 liver lesion) developed hypertension in pregnancy, compared to only one non-CLD control. There were no maternal deaths. **Conclusion:** women with CLD had similar ART outcomes to patients without CLD, and liver-related complications were uncommon. While reassuring, the absolute number of oocytes retrieved may be lower in some patients with CLD. Routine family planning discussions and consideration of early referral for ART planning may help to improve pregnancy potential in reproductive-aged women with CLD.

Disclosures: The following people have nothing to disclose: Meera Garriga

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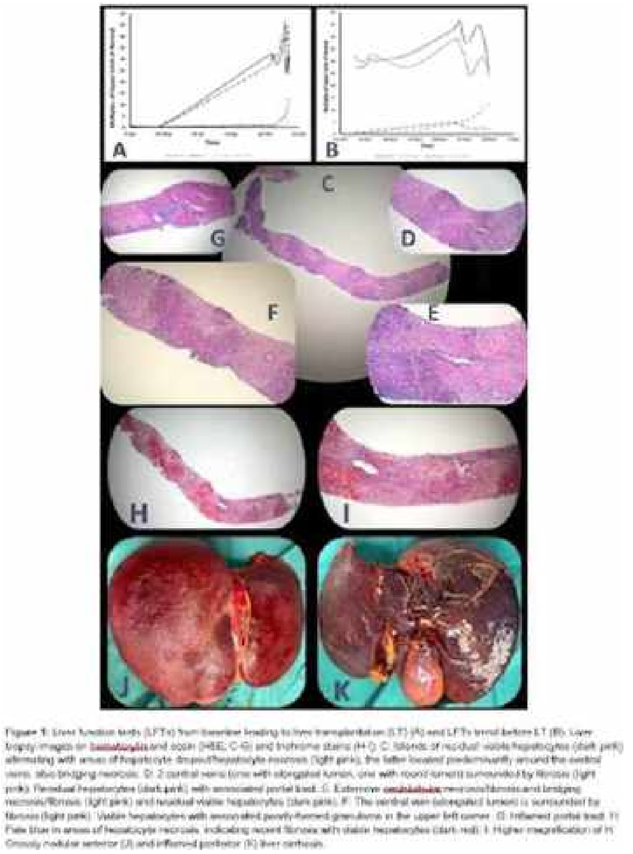
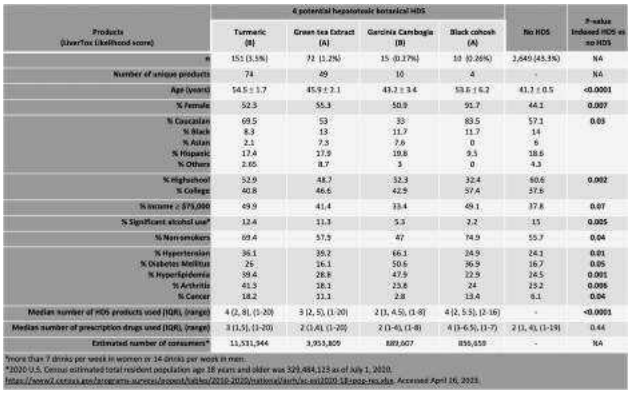
1714-A | OVERWHELMING CYTOCHROME P450 ISOENZYME ACTIVITY GENERATING DRUG-INDUCED LIVER INJURY RESULTING IN FULMINANT LIVER FAILURE

Jose R. Russe[1], Islam Abdelhamid[1], Raphael Meier[2], Georgeta Giblen[1] and Anurag Maheshwari[1], (1)Institute for Digestive Health and Liver Disease at Mercy Medical Center, (2)University of Maryland Medical Center

Background: Fulminant liver failure (FLF) is a severe and rapidly progressive form of liver injury with a high mortality rate without liver transplantation; drug-induced liver injury (DILI) is the leading cause in developed countries. The following case of FLF due to DILI is suspected to be caused by the synchronous use of multiple medications metabolized by the same liver enzyme cytochrome P450 (CYP450). **Methods:** In June, a 41-year-old Caucasian female started paroxetine for anxiety and depression and trazodone for insomnia. Although she improved in July, she noted poor focus and decreased concentration and started lisdexamfetamine. In August, after unrelenting abdominal symptoms, a colonoscopy found lymphocytic colitis, and she began budesonide. Finally, around September, she had COVID managed with molnupiravir. **Results:** A month later, she was severely ill, and biochemistry (BCH) showed elevated liver enzymes (LFTs)l; aspartate transferase (AST) 37 x upper limit of normal (ULN), alanine transaminase (ALT) 36 x ULN, elevated alkaline phosphatase (ALP), and normal bilirubin (TB) (Figure 1A). In November, imaging showed acute hepatitis, splenomegaly, and ascites; budesonide was stopped. A week later, she was hypotensive, dyspneic, and jaundiced; new BCH showed AST 50 x ULN, ALT 36 x ULN, ALP 6 x ULN, and TB of 5.3 with a model for end-stage liver disease score (MELDs) of 26 (Figure 1B). A liver biopsy (LBx) showed submassive necrosis, inflammation, interface hepatitis, and duct-sparing poorly-formed granulomas, suggesting drug-induced injury (Figure 1C-I). Therefore, all prior medications were stopped. Days later, she had MELDs of 29, TB of 13.6, and encephalopathy; her continued deterioration prompted a liver transplant. An explant LBx confirmed chronic hepatitis with massive eosinophils and grossly nodular inflamed liver consistent with drug-induced liver injury (Figure 1J-K). **Conclusion:** The pathophysiology of DILI begins when medications processed by CYP450 and its isoenzymes, including CYP1A2, CYP2D6, and CYP3A4, that metabolize the aforementioned drugs, produce metabolites that damage the liver. The resulting substrates inhibit, induce, or compete for the same enzymes resulting in an overwhelming accumulation of toxins directly injuring hepatocytes and ultimately leading to FLF. When co-medicating, if DILI is suspected, immediate cessation, close monitoring, and prompt action are crucial to prevent severe complications such as FLF.



exposure estimates were calculated based on 2020 U.S. Census data. **Results:** Among the 5,850 adults, 56.7% reported using ≥ 1 HDS products within the past 30 days, 11.3% used ≥ 1 botanical products, and 210 (4.78%) reported using at least one of the 4 botanicals of interest. Amongst the 210 adults, mean age was 52.5 ± 1.3 years, 54.7% female, and 64.7% White. A turmeric containing product was used in 151 patients, GTE products in 72 patients, Garcinia products in 15 and black cohosh products in 10. Compared to the 2,649 NHANES patients with no HDS use, patients taking these 4 products were significantly older, more likely female, had higher education, higher income, and non-smokers ($p < 0.01$ Table 1). They were also more likely to have underlying hypertension, diabetes, hyperlipidemia, arthritis, or cancer diagnosis. Multivariable analysis identified age 40-59 years (OR 3.6, $p < 0.001$), age 60 years or older (OR 5.2, $p < 0.0001$), some college (OR 9.5, $p = 0.009$), college graduates or above (OR 15, $p = 0.002$), hyperlipidemia (OR 2.8, $p = 0.005$), arthritis (OR 2, $p = 0.01$), and non-smokers (OR 1.9, $p = 0.026$) as associated with consumption of these 4 botanicals. Among turmeric and GTE users, 85% reported using on their own accord and 15% were recommended by a health provider. The most common reasons to use turmeric and GTE, respectively, were to improve/maintain health (62.3% & 68%), prevent health problems (26.5% & 26.4%), nutrition supplement (25.8% & 47.2%), and for metabolic or heart health (11.3% & 15.2). In addition, 36.4% used turmeric for muscle/joint or arthritis and 19.4% used GTE for weight loss. When extrapolating to the general US population, an estimated 15.7 million of US adults used at least of these 4 potentially hepatotoxic botanical products; 11.5 million used turmeric and 3.95 million used GTE. **Conclusion**: Over 15 million U.S. adults consumed potential hepatotoxic botanical products containing turmeric, GTE, Garcinia or black cohosh. Older age, higher education, present of arthritis or hyperlipidemia, and non-smokers were associated with potential hepatotoxic HDS products use.



Products (LiverTox Likelihood score)	4 potential hepatotoxic botanical HDS Turmeric (B)	Green tea Extract (A)	Garcinia Cambogia (B)	Black cohosh (A)	No HDS	P-value Induced HDS vs no HDS
n	151 (3.5%)	72 (1.2%)	15 (0.27%)	10 (0.26%)	2,649 (45.3%)	NA
Number of unique products	74	49	10	4	-	NA
Age (years)	54.5 ± 1.7	45.9 ± 2.1	43.2 ± 3.4	53.6 ± 6.2	41.1 ± 0.5	<0.0001
% Female	52.3	55.3	50.9	91.7	44.1	0.007
% Caucasian	69.5	53	33	83.5	57.1	0.03
% Black	8.3	13	11.7	11.7	14	
% Asian	2.1	7.3	7.6	0	6	
% Hispanic	17.4	17.9	19.8	9.5	18.6	
% Others	2.65	8.7	3	0	4.3	
% Highschool	52.9	48.7	32.3	32.4	60.6	0.002
% College	40.8	46.6	42.9	57.4	37.6	
% Income ≥ $75,000	49.9	41.4	33.4	49.1	37.8	0.07
% Significant alcohol use*	12.4	11.3	5.3	2.2	15	0.005
% Non-smokers	69.4	57.5	47	74.9	55.7	0.04
% Hypertension	36.1	39.2	66.1	24.9	24.1	0.01
% Diabetes Mellitus	26	16.1	50.6	36.9	16.7	0.05
% Hyperlipidemia	39.4	28.8	47.9	22.9	24.5	0.001
% Arthritis	41.5	18.1	23.8	24	25.2	0.006
% Cancer	18.2	11.1	2.8	13.4	6.1	0.04
Median number of HDS products used (IQR), (range)	4 (2, 8), (1-20)	3 (2, 5), (1-20)	2 (1, 4.5), (1-8)	4 (2, 5.5), (2-16)	-	<0.0001
Median number of prescription drugs used (IQR), (range)	3 (1,5), (1-20)	2 (1,4), (1-20)	2 (1-4), (1-8)	4 (3-6.5), (1-7)	2 (1, 4), (1-19)	0.44
Estimated number of consumers*	11,531,944	3,953,809	889,607	856,658	-	NA

*more than 7 drinks per week in women or 14 drinks per week in men.
*2020 U.S. Census estimated total resident population age 18 years and older was 329,484,123 as of July 1, 2020. https://www2.census.gov/programs-surveys/popest/tables/2010-2020/national/asrh/nc-est2020-18+pop-res.xlsx. Accessed April 16, 2023.

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1715-A | POPULATION LEVEL EXPOSURE ESTIMATES TO 4 POTENTIALLY HEPATOTOXIC HDS BOTANICAL PRODUCTS: RESULTS FROM THE NHANES 2017-2018 COHORT

Alisa Likhitsup, University of Michigan, Vincent Chen, University of Michigan Medical Center and Robert J. Fontana, University of Michigan Medical Center, Ann Arbor, MI

Background: Herbal and dietary supplements (HDS) such as green tea extract (GTE), turmeric, and Garcinia account for 20% of drug hepatotoxicity cases in the US. Our study was to determine the characteristics of individual's who consume 4 potentially hepatotoxic botanical products from the NHANES 2017-2018 cohort. **Methods:** The Dietary Supplement database of NHANES 2017-2018 was queried. Exposure to 4 potentially hepatotoxic botanical ingredients including turmeric, GTE, Garcinia cambogia, and black cohosh were identified by reviewing the constituent ingredients listed in the product names and labels. Total US

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should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AstraZeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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1716-A | RUCAM HAD BETTER AGREEMENT WITH DILIN EXPERT OPINION COMPARED TO RECAM FOR BONAFIDE DILI IN A RETROSPECTIVE COHORT

Adam Seth Myer, Jacob A Ciricillo, Askanda Osman, Farrah Rahim and Amoah Yeboah-Korang, University of Cincinnati

Background: RECAM, a revised, electronic version of RUCAM, was better than RUCAM at diagnostic extremes in two large prospective DILI registries. RECAM requires more extensive serologic evaluation to exclude alternative diagnoses, and has heavy penalties for missing serologic data. Limited data exists comparing RECAM versus RUCAM agreement with the gold standard DILIN expert opinion in retrospective databases. The primary aim of this study was to compare RECAM versus RUCAM agreement with DILIN expert opinion in a retrospective cohort. **Methods:** All EMR encounters were searched for potential DILI using ICD-10 codes for toxic liver injury between 10/1/2015 and 9/30/2019. Clinically significant liver injury was defined as: 1) AST **e** 5 x ULN, 2) ALT **e** 5 x ULN, 3) ALP **e** 2 x ULN, 4) total bilirubin **e** 2.5 mg/dL, or 5) INR **e** 1.5. Gold standard DILIN expert opinion scores were assigned to each case (1/2/3 = probable-DILI, 4/5 = non-DILI). RUCAM and RECAM scores were calculated for probable-DILI cases. Among probable-DILI, agreement between RECAM and DILIN expert opinion were compared to RUCAM and DILIN expert opinion. **Results:** Among 766,930 patients searched, 127 unique patients met inclusion criteria with 70 (55.1%) cases adjudicated as probable-DILI using DILIN expert opinion. The most frequent suspect drugs were antimicrobials (41.9%), herbal and dietary supplements (9.5%), and antineoplastic (8.1%). Mean age was 48.8 ± 16.9, 55.7% female, and 78.6% Caucasian. Pattern of liver injury was 48.6% hepatocellular, 30% cholestatic, and 21.4% mixed. Liver biopsy was completed in 25.4%. There were missing serological data for anti-HAV IgM (12.9%), anti-HBcore antibody (14.3%), anti-HCV (55.7%), anti-HEV IgM (71.4%), autoimmune markers (ANA, ASMA, IgG) - 32.9%, CMV IgM (84.3%), CMV PCR (65.7%), EBV IgM (71.4%), EBV PCR (68.6%), HSV IgM (85.7%), and HSV PCR (70%). RUCAM classified 65.7% of probable-DILI as probable or highly probable while RECAM classified 38.6% of probable-DILI as probable or highly probable ($p = 0.0023$). **Conclusion:** In a retrospective cohort of consecutive probable-DILI cases from a single center with incomplete viral and autoimmune serologies, RUCAM had better agreement with DILIN expert opinion compared to RECAM. Future efforts should focus on educating providers about the complete serologic evaluation needed for DILI diagnosis.

Disclosures: The following people have nothing to disclose: Adam Seth Myer, Jacob A Ciricillo, Askanda Osman, Farrah Rahim, Amoah Yeboah-Korang

1717-A | SIRT7 PROTECTS AGAINST OXALIPLATIN INDUCED LIVER INJURY VIA MAINTAINING NRF2 STABILIZATION AND ACTIVATION

Tingzi Yu, Cong Ding, Bohao Liu, Wenbin Tang, Wang Zhiqiang and Zhuan Li, Hunan Normal University

Background: Oxaliplatin (Oxa) is the core therapeutic agents which widely used for treatment of advanced stage of colorectal cancer patients, but it occasionally causes hepatotoxicity characterized by sinusoidal dilatation, hepatic plate atrophy and venular obstruction. Studies have suggested that oxidative stress and stellate cell activation are associated with Oxa induced liver injury. SIRT7 (sirtuin-7) is a NAD$^+$-dependent class III histone deacetylases (HDAC III), which mediates multiple biological processes such as lipid metabolism and cellular homeostasis. Whether SIRT7 plays role in Oxa induced liver injury remains unclear. **Methods:** Hepatocyte specific SIRT7 knockout mice (Alb-Cre SIRT7) were generated by crossing SIRT7$^{flox/flox}$ mice with Alb-Cre mice. Adeno-associated virus (AAV8)-TBG vectors were used for modulating hepatic gene expression *in vivo*. Mice were receiving Oxa (4mg/kg) interperitoneally daily for 12 days. Liver injury were accessed by ALT and histology, changes of proteins and mRNA were evaluated by WB and qRT-PCR. **Results:** Oxa administration caused elevation of ALT, hepatocyte parenchymal damage, sinusoidal dilation, and inflammation. Alb-Cre SIRT7 mice showed enhanced liver ALT elevation, inflammation and hepatocyte parenchymal damage after Oxa. We further demonstrated that SIRT7 regulates Nrf2 protein levels and activity. Knockdown SIRT7 led to decrease of Nrf2 protein expression, nuclear translocation and transcriptional activity, and increased intracellular ROS accumulation and apoptosis in response to various types of oxidative stress including acetaminophen (APAP) and hydrogen peroxide (H_2O_2). Mechanistically, SIRT7 interacts with Nrf2 and stabilizes Nrf2. In primary SIRT7 knockout hepatocyte, we observed decreased Keap1/Nrf2 binding when compare with WT. Most importantly, we found that both Nrf2 agonists (Oltipraz) and AAV8-TBG mediated overexpression of NRF2 in Alb-Cre SIRT7 mice alleviated Oxa induced elevation of ALT, hepatocyte parenchymal damage, sinusoidal dilation, and inflammation. **Conclusion:** We identify previously unidentified protective role of SIRT7 in chemotherapy drugs induced liver injury via acting as a positive regulator of Nrf2 protein level and activation.

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1718-A | THE IMPACT OF MEDIUM CHAIN TRIGLYCERIDE KETOGENIC DIET ON LIVER MITOCHONDRIA AND CYP2E1

Abigail S. Ryan[1], Kelly R. Misare[1], Joseph McQuail[2], Fiona Hollis[2] and Jessica H. Hartman[1], (1)Medical University of South Carolina, (2)University of South Carolina

Background: The ketogenic diet (KD) is a high fat, low carbohydrate diet that causes elevated levels of blood ketones due to increased fatty acid metabolism as a response to decreased glucose levels. Under these conditions, the liver produces ketone bodies that are metabolized for energy. A particularly effective variation of this diet is the medium chain triglyceride ketogenic diet (MCT-KD) which is comprised mainly of caprylic and capric acids (8 and 10 carbons). **Methods:** Rats (male and female, young and old rats) were fed a MCT-KD or a caloric-matched control diet for eight weeks, and reached maximal levels of plasma beta-hydroxybutyrate within one week. Liver mitochondrial fractions were tested for reaction rates of complexes I-IV of the mitochondrial electron transport chain. Western blot analyses were performed to quantify concentrations of CYP2E1, cytochrome c oxidase, and endoplasmic reticulum membrane oxidoreductase. HepG2 and CYP2E1-transduced HepG2 cell lines were cultured in low glucose media spiked with ketone bodies to determine the effect of CYP2E1 expression on cellular survival. **Results:** We found that MCT-KD caused a decrease in complex I and IV activity in young male and female rats but not old rats. No significant differences were observed between keto and control groups in complexes II and III. In western blot experiments, consistent and dramatic > 3-fold upregulation of CYP2E1 was observed in all rat livers from the MCT-KD group, regardless of sex or age. Similarly, we observed a ~2-fold increase in levels of the coenzyme P450 oxidoreductase. In *in vitro* experiments with HepG2 cells, cellular survival was decreased in low glucose media with and without the addition of ketone bodies, and was rescued by CYP2E1 expression, but there was no significant response to changes in the ketone concentration. **Conclusion:** The results of this study reveal a dramatic effect of the MCT-KD on liver mitochondria and the expression of CYP2E1. MCTs are likely substrates for CYP2E1, and metabolites formed in this pathway could contribute to the physiological effects of the diet. Ongoing and future studies are determining the importance of this pathway in MCT-KD safety and efficacy.

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1719-A | BH3-ONLY PROTEINS REGULATE HEPATOCYTE APOPTOSIS AND APOPTOSIS-RELATED LIVER INJURY

Shinnosuke Kudo[1], Hayato Hikita[1], Yoshinobu Saito[1], Takahiro Kodama[2], Tomohide Tatsumi[1] and Tetsuo Takehara[2], (1)Osaka University, Graduate School of Medicine, (2)Osaka University Graduate School of Medicine

Background: Continuous hepatocyte apoptosis with the activation of pro-apoptotic Bcl-2 family proteins, Bak/Bax, is observed in various chronic liver diseases like non-alcoholic steatohepatitis (NASH). BH3-only proteins, upstream of the core Bcl-2 family proteins, can activate Bak and Bax, and we previously reported that BH3-only proteins, Bid and Bim, were involved in regulating hepatocyte apoptosis. However, the whole participations of BH3-only proteins in regulation of hepatocyte integrity remain unclear, and we aimed to reveal their roles. **Methods:** As a model of chronic liver injury with Bak/Bax activation, we generated hepatocyte-specific Bcl-xL(-/-) Mcl-1(+/-) mice, which showed massive hepatocyte apoptosis and severe elevation of serum ALT levels at the age of 6 weeks. We crossed these mice with Bid, Bim, and Puma KO mice to examine the role of BH3-only protein, Puma. **Results:** Bid-/- Bim-/- Puma-/- Bcl-xL(-/-) Mcl-1(+/-) mice showed significantly lower levels of serum ALT and smaller number of TUNEL positive hepatocytes than Bid-/- Bim-/- Puma+/+ Bcl-xL(-/-) Mcl-1(+/-) mice. These findings showed that Puma had a role of inducing hepatocyte apoptosis. On the other hand, serum ALT levels of Bid-/- Bim-/- Puma-/- Bcl-xL(-/-) Mcl-1(+/-) mice were significantly higher than those of Bak-/- Bax(-/-) Bcl-xL(-/-) Mcl-1(+/-) mice, and this suggested there were other sensor proteins involved in hepatocyte apoptosis. In Vitro study, we immortalized Bim-/- Bid-/- Puma-/- Bcl-xL flox/flox Mcl-1flox/flox mouse primary hepatocyte and doxycycline-dependent Cre recombinase was expressed by pLenti-iCre-Neo. Among other BH-3 only proteins, Bad, Bmf and Noxa, only Noxa knockdown significantly suppress doxycycline-induced apoptosis and improved the cell viability. We next generated Bid-/- Bim-/- Puma-/- Noxa-/- Bcl-xL flox/flox Mcl-1flox/flox tamoxifen-inducible Albumin Cre mice by using CRISPR/Cas9 technology. Serum ALT levels and caspase3/7 activity, and the number of TUNEL positive hepatocytes in Bid-/- Bim-/- Puma-/- Noxa-/- mice significantly decreased compared with Bid-/- Bim-/- Puma-/- mice. These results showed that, in addition to Bid, Bim, and Puma, Noxa had an inducing role of Bak/Bax activation. We finally examined the role of Puma and Noxa in apoptosis related chronic liver disease, NASH. In NASH mice fed with Western diet, Noxa expression levels in their livers increased, while Puma expression levels did not change. In addition, Noxa expression levels strongly increased in liver specimens from NASH patients, and serum ALT levels of NASH patients were positively correlated with expression levels of Noxa in their livers. **Conclusion:** In addition to Bid and Bim, Puma and Noxa participate in Bak/Bax dependent hepatocyte apoptosis, and the activation of Noxa in hepatocyte may be associated with the pathophysiology of human NASH.

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1720-A | FATTY LIVER DISEASE AND ALTERED HEPATIC ENERGY METABOLISM CAUSED BY ENVIRONMENTAL TOXICANT MIXTURES ARE SEX-DEPENDENT

Yuan Hua, Oluwanifemi Esther Bolatimi, Jianzhu Luo, Ngozi Victoria Adiele, Tyler C Gripshover, Walter Watson and Banrida Wahlang, University of Louisville, Louisville, KY

Background: Epidemiologic studies have demonstrated that exposure to 'forever chemicals' such as organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs) were associated with elevated liver enzymes, indicative of liver injury. However, effects and mechanisms related to how 'mixtures' of such chemicals induce liver injury are still largely unknown. Thus, the study's objective is to investigate the sex-dependent effects of OCPs and PCBs, using chlordane and PCB126 as model compounds, in the context of fatty liver disease and metabolic disruption in a diet-induced obesity model. **Methods:** Male and female C57BL/6 mice were fed a high-fat diet (HFD) and administered either vehicle control or chlordane(20 mg/kg)+PCB126(20μg/kg) over a 12-week period. Tissues and plasma were collected at euthanasia for downstream analyses. **Results:** Female mice generally had lower fat content, but higher spleen and cecal weights *vs.* males. With regards to steatosis, females exhibited lower hepatic lipid accumulation (steatosis), confirmed by H&E staining and quantification of hepatic triglycerides, and could be attributed to estrogenic-protective effects with HFD feeding. However, compared to their sex-matched controls, mixture-exposed females showed elevated plasma alanine transaminase (ALT), increased liver weight and hepatic cholesterol levels, and trend for downregulated HDL, implicating liver injury and dyslipidemia . Moreover, exposure to the toxicant mixture decreased physical activity (assessed using metabolic chambers) in females. In contrast, mixture-exposed males had lower hepatic GSH/GSSG levels, suggesting oxidative stress. Chlordane+PCB126 exposure resulted in insulin resistance in both sexes. In terms of receptor activation, chlordane+PCB126 activated hepatic xenobiotic receptors, namely CAR (*Cyp1b10*) and AHR (*Cyp1a2*) but PXR (*Cyp3a11*) was activated only in males, implicating how sex+HFD interactions impact these receptors as potential drivers of toxicant-induced hepatic metabolic disruption and possibly injury. **Conclusion:** While females were more susceptible to steatosis, males were prone to oxidative stress, and glucose metabolism was impacted in both sexes with exposure. Toxicant-sex-HFD interactions also regulated receptor activation outcomes. Further assessment of off-liver targets including the gut microbiome and adipose tissue will help understand how these toxicant mixtures impact multi-organ toxicity in driving fatty liver disease.

Disclosures: The following people have nothing to disclose: Yuan Hua, Oluwanifemi Esther Bolatimi, Jianzhu Luo, Ngozi Victoria Adiele, Tyler C Gripshover, Walter Watson, Banrida Wahlang

1721-A | PRELIMBIC 5-HT6 RECEPTORS REGULATE ANXIETY IN CCL4 MODEL OF LIVER INJURY: EVIDENCE FROM BEHAVIOR, ELECTROPHYSIOLOGY, AND NEUROCHEMISTRY

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Background: Acute or chronic liver injury is associated with hyperammonemia which triggers several emotional disorders such as anxiety. Carbon tetrachloride (CCl4), is a potent hepatotoxic agent and extensively utilized to induce hepatotoxicity-related anxiety in rodent models. Unfortunately, an effective treatment for anxiety-like behaviors induced by CCl4 is yet to be found. Recent studies indicate that the prelimbic cortex (PrL) is involved in the pathophysiology of anxiety. PrL is innervated by 5-HT fibers, and the 5-HT system is regarded as a crucial role in anxiety. Our previous results demonstrated the PrL 5-HT$_6$ receptors regulated anxiety-like behaviors in Parkinson's rats. Thus, we speculate that the PrL 5-HT$_6$ receptors also may function in regulating anxiety-like behaviors induced by CCl4. **Methods:** CCl4 dissolved in olive oil was administered in the model rats by intraperitoneal (i.p) route before induction of anxiety. The sham-operated group received an equal volume of vehicle solution in the same schedule. Behavioral, electrophysiological, neurochemical and morphological methods were utilized to identify the role of PrL 5-HT$_6$ receptors in CCl4-induced anxiety. **Results:** Intra-PrL injection of 5-HT$_6$ receptor agonist WAY208466 induced anxiogenic responses in sham-operated rats, and injection of antagonist SB258585 showed anxiolytic effects. Interestingly, WAY208466 increased the expression of anxiolytic behaviors in model rats, and SB258585 produced anxiogenic responses. Neurochemical results showed that intra-PrL injection of WAY208466 and SB258585 decreased or increased DA, 5-HT and NA levels in the mPFC, amygdala, habenula and vHip in both rats, respectively. WAY208466 increased the firing rate of PrL GABA-ergic interneurons in both rats, while SB258585 decreased the firing rate of the interneurons. Compared to sham-operated rats, the duration of WAY208466 and SB258585 action on the firing rate of GABA-ergic interneurons was markedly prolonged in model rats. The CCl4 did not change the co-localization of PrL 5-HT$_6$ receptors and GABA-ergic interneurons. These findings indicate that PrL 5-HT$_6$ receptors are involved in the regulation of anxiety-like behaviors, which ascribe to changes in DA, 5-HT and NA levels in the limbic and limbic-related brain regions. Additionally, the findings suggest that the CCl4 leads to a hypersensitization of PrL 5-HT$_6$ receptors on GABA-ergic interneurons. **Conclusion:** Our study is the first to identify the role of PrL 5-HT$_6$ receptors in CCl4-induced anxiety. Present findings pave the way for more advanced and specific theories on the treatment of neuropsychiatric disorders in liver injury.

Disclosures: The following people have nothing to disclose: Yuming Zhang, Jiao Guo

1722-A | RECHALLENGE EPISODES IN DRUG-INDUCED LIVER INJURY: AN ANALYSIS OF CASES IN TWO PROSPECTIVES REGISTRIES ACCORDING TO EXISTING DEFINITIONS

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Background: Positive drug-induced liver injury (DILI) rechallenge has been traditionally related to higher severity. We analyse the clinical presentation, outcome and main drugs related with positive rechallenge in two prospective DILI registries. **Methods**: Cases from the Spanish and Latin American DILI registries were included. Demographics, clinical and biochemical parameters of cases with positive rechallenge were compared with those cases with single episode of DILI. **Results**: Of 1,410 patients with idiosyncratic DILI, 64 cases had positive rechallenge (4.5%). Patients with positive rechallenge had shorter duration of therapy and latency than cases with a first episode of DILI ($p < 0.001$). In addition, aspartate transaminase (AST) levels were significantly increased in patients with positive rechallenge when compared to those with a single episode (median 10 vs. 6.4 times the upper limit of normal, respectively; $p = 0.025$). Patients who rechallenged showed a longer time until normalization of liver parameters compared to cases with a first episode (median 138 vs. 93 d, respectively; $p = 0.022$) (Table). There were not significant differences in terms of fatal outcomes. The main drug implicated in positive rechallenge was amoxicillin-clavulanate ($n = 11$, 17.2%), followed by antituberculous drugs ($n = 4$, 6.2%), and by diclofenac and Herbalife® products ($n = 3$, 4.7%). Indeed, antiinfectives ($n = 20$, 31.2%), and herbal products and dietary supplements and NSAIDs (both $n = 7$, 11%) were the most common pharmacological groups. Most reexposure events were unintentional (72%) with lack of previous hepatotoxicity diagnosis being the main reason (70%), while self-medication (disregarding medical recommendations) constituted 9% of cases. **Conclusion**: Episodes of positive rechallenge were characterized by increased AST levels and shorter duration of therapy and latency. Furthermore, these cases had a prolonged recovery. Clinicians should be aware about the possibility of facing a DILI episode in patients with hypertransaminasemia with unknown etiology.

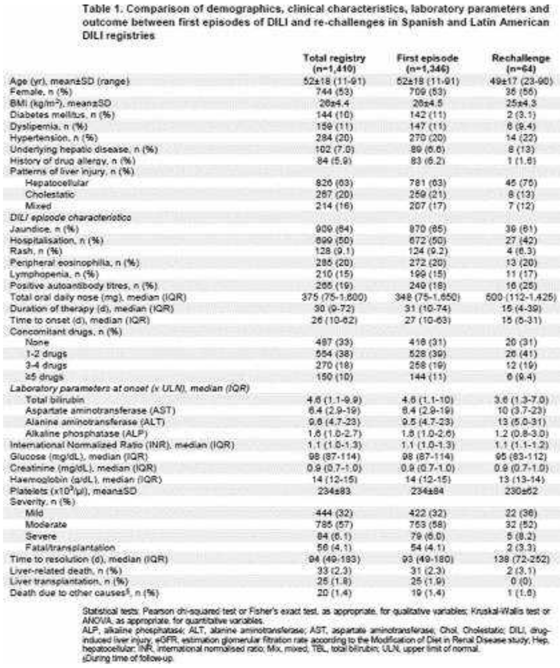


Table 1. Comparison of demographics, clinical characteristics, laboratory parameters and outcome between first episodes of DILI and re-challenges in Spanish and Latin American DILI registries

	Total registry (n=1,410)	First episode (n=1,346)	Rechallenge (n=64)	p value
Age (yr), mean±SD (range)	52±18 (11-91)	52±18 (11-91)	49±17 (23-90)	0.163
Female, n (%)	744 (53)	709 (53)	36 (56)	0.763
BMI (kg/m^2), mean±SD	26±4.4	26±4.5	25±4.3	0.190
Diabetes mellitus, n (%)	144 (10)	142 (11)	2 (3.1)	0.066
Dyslipemia, n (%)	159 (11)	147 (11)	6 (9.4)	0.698
Hypertension, n (%)	284 (20)	270 (20)	14 (22)	0.724
Underlying hepatic disease, n (%)	102 (7.0)	89 (6.6)	8 (13)	0.076
History of drug allergy, n (%)	84 (5.9)	83 (6.2)	1 (1.6)	0.175
Patterns of liver injury, n (%)				0.151
Hepatocellular	826 (63)	781 (63)	45 (76)	
Cholestatic	267 (20)	259 (21)	8 (13)	
Mixed	214 (16)	207 (17)	7 (12)	
DILI episode characteristics				
Jaundice, n (%)	909 (64)	870 (65)	39 (61)	0.546
Hospitalisation, n (%)	699 (50)	672 (50)	27 (42)	0.226
Rash, n (%)	128 (9.1)	124 (9.2)	4 (6.3)	0.654
Peripheral eosinophilia, n (%)	285 (20)	272 (20)	13 (20)	0.984
Lymphopenia, n (%)	210 (15)	199 (15)	11 (17)	0.598
Positive autoantibody titres, n (%)	265 (19)	249 (18)	16 (25)	0.193
Total oral daily nose (mg), median (IQR)	375 (75-1.600)	348 (75-1.650)	600 (112-1.425)	0.316
Duration of therapy (d), median (IQR)	30 (9-72)	31 (10-74)	15 (4-39)	**<0.001**
Time to onset (d), median (IQR)	26 (10-62)	27 (10-63)	15 (6-31)	**<0.001**
Concomitant drugs, n (%)				0.987
None	487 (33)	416 (31)	20 (31)	
1-2 drugs	554 (38)	528 (39)	26 (41)	
3-4 drugs	270 (18)	258 (19)	12 (19)	
≥5 drugs	150 (10)	144 (11)	6 (9.4)	
Laboratory parameters at onset (x ULN), median (IQR)				
Total bilirubin	4.6 (1.1-9.9)	4.6 (1.1-10)	3.6 (1.3-7.0)	0.276
Aspartate aminotransferase (AST)	6.4 (2.9-19)	6.4 (2.9-19)	10 (3.7-23)	**0.025**
Alanine aminotransferase (ALT)	9.6 (4.7-23)	9.5 (4.7-23)	13 (5.0-31)	0.127
Alkaline phosphatase (ALP)	1.6 (1.0-2.7)	1.6 (1.0-2.6)	1.2 (0.8-3.0)	0.112
International Normalized Ratio (INR), median (IQR)	1.1 (1.0-1.3)	1.1 (1.0-1.3)	1.1 (1.1-1.2)	0.703
Glucose (mg/dL), median (IQR)	98 (87-114)	98 (87-114)	95 (83-112)	0.519
Creatinine (mg/dL), median (IQR)	0.9 (0.7-1.0)	0.9 (0.7-1.0)	0.9 (0.7-1.0)	0.418
Haemoglobin (g/dL), median (IQR)	14 (12-15)	14 (12-15)	13 (13-14)	0.461
Platelets ($x10^3/\mu l$), mean±SD	234±83	234±84	230±62	0.776
Severity, n (%)				0.738
Mild	444 (32)	422 (32)	22 (36)	
Moderate	785 (57)	753 (58)	32 (52)	
Severe	84 (6.1)	79 (6.0)	5 (8.2)	
Fatal/transplantation	56 (4.1)	54 (4.1)	2 (3.3)	
Time to resolution (d), median (IQR)	94 (49-183)	93 (49-180)	138 (72-252)	**0.022**
Liver-related death, n (%)	33 (2.3)	31 (2.3)	2 (3.1)	0.659
Liver transplantation, n (%)	25 (1.8)	25 (1.9)	0 (0)	0.625
Death due to other causes[§], n (%)	20 (1.4)	19 (1.4)	1 (1.6)	0.608

Statistical tests: Pearson chi-squared test or Fisher's exact test, as appropriate, for qualitative variables; Kruskal-Wallis test or ANOVA, as appropriate, for quantitative variables.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Chol, Cholestatic; DILI, drug-induced liver injury; eGFR, estimation glomerular filtration rate according to the Modification of Diet in Renal Disease study; Hep, hepatocellular; INR, international normalised ratio; Mix, mixed; TBL, total bilirubin; ULN, upper limit of normal.

[§] During time of follow-up

Disclosures: The following people have nothing to disclose: José María Pinazo Bandera, Ismael Alvarez-Alvarez, Hao Niu, Inmaculada Medina-Cáliz, Enrique Del Campo-Herrera, Aida Ortega-Alonso, Mercedes Robles-Díaz, M I Lucena, Nelia Hernandez, Fernando Oscar Bessone, Miren Garcia Cortes, Raul J. Andrade

1723-A | REVEALING THE ROLE OF PHOSPHATIDYLETHANOLAMINE METHYLTRANSFERASE IN ALD AND NAFLD PATHOGENESIS USING MULTI-OMICS ANALYSES

Isin T Sakallioglu[1], Sathish Kumar Perumal[2,3], Madan Kumar Arumugam[2,3], Murali Ganesan[2,3], Natalia Osna[2,3], Karuna Rasineni[2,3], Robert Powers[1] and Kusum K. Kharbanda[2,3], (1)University of Nebraska-Lincoln, (2)University of Nebraska Medical Center, (3) Veterans Affairs Nebraska-Western Iowa Health Care System

Background: Our previous studies indicated that impaired phosphatidylcholine (PC) generation via the phosphatidylethanolamine methyltransferase (PEMT)-mediated methylation of phosphatidylethanolamine (PE) is a common feature in the development of alcohol- and non-alcohol-associated liver diseases (ALD and NAFLD, respectively). Indeed, spontaneous development of hepatic steatosis is observed in both male and female 3-month-old PEMT knockout (KO) mice, which progresses to inflammation and pericellular fibrosis by 6 months of age. No such pathology is seen in age-and gender-matched wildtype (WT) mice. **Methods:** To further gain mechanistic insights into the importance of PEMT, we conducted a multi-omics analyses on livers of 6-month-old PEMT KOs of both genders and their age-matched WTs using Waters Xevo G2-XS Quadrupole Time of Flight with optimized separation methods. **Results:** The metabolomic and lipidomic data yielded 8074 and 7983 spectral features respectively, proteomics data yielded 2634 proteins. The resulting unsupervised principal component analysis (PCA) model yielded a clear separation between the groups. The supervised orthogonal projection to latent structures discriminant analysis (OPLS-DA) model validated using a permutation test was determined to be of high quality given R^2 (0.92), Q^2 (0.89), and $p < 0.02$. These results indicated that the PEMT KOs exhibit a significant differences in the *~Ome* compared with their respective WTs. The tight clustering of the quality control samples in the center of the scores plot testified to the high quality of *~Ome* data set. In total, 60 metabolites, 40 lipids and 600 proteins were significantly different amongst the groups. Metabolomics enrichment analysis identified amino acids, peptides, purines, pyridines and sulfonic acid pathways as being the most altered upon PEMT loss. Lipidomics enrichment analysis identified increases in diacylglycerides (2.2-fold, $p < 0.001$), triacylglycerides (753-fold, $p < 0.001$) and PE (7.2-fold, $p < 0.001$) in livers of KO irrespective of gender compared with their respective WT counterparts. Further, while an overall ~3.5-fold increase in PC was evident, we observed a significant decrease in those species with a shorter chain length in the KOs. Proteomics pathways enrichment analysis identified alterations in glycolysis, gluconeogenesis, pyruvate and tryptophan metabolism in PEMT KOs. **Conclusion:** Taken together, our study further establishes the important role of PEMT in maintaining liver function homeostasis and in preventing development of liver disease even in the absence of second hits (alcohol/high-caloric intake). Since genetic loss-of-function PEMT polymorphism is common, such individual's should be cautioned about the potential for spontaneous development of liver disease and to abstain from alcohol and/or high-caloric intake.

Disclosures: The following people have nothing to disclose: Sathish Kumar Perumal, Madan Kumar Arumugam, Murali Ganesan, Natalia Osna, Karuna Rasineni, Kusum K. Kharbanda

Disclosure information not available at the time of publication: Isin T Sakallioglu, Robert Powers

1724-A | THE ENVIRONMENTAL TOXICANT VINYL CHLORIDE DYSREGULATES THE MITOCHONDRIAL RESPONSE TO STRESS IN MICE

Dexi Chen[1], Christine Dolin[2], Daniel Wilkey[2], Jiang Li[1], Michael Merchant[2], Gavin E. Arteel[3] and Juliane I

Beier[1], (1)University of Pittsburgh, (2)University of Louisville, Louisville, KY, (3)Pittsburgh Liver Research Center

Background: Vinyl chloride (VC), a common environmental pollutant, directly causes liver injury at high exposure levels, but lower concentrations (i.e., $<$ OSHA limits), which do not overtly damage the liver, can also enhance injury due to overnutrition. Previous work from this lab showed that VC induces endoplasmic reticulum (ER) stress, and impairs mitochondrial (mt) function. ER- and mt-stress are often linked events; for example, the unfolded protein response (UPR) releases factors that subsequently protect mitochondria from mt-stress and dysfunction. Here, a more detailed analysis of the underlying molecular underpinnings was performed and yielded insight the potential impact of VC exposure crosstalk between these ER- and mt-stress. **Methods:** C57Bl/6J mice were exposed to VC (sub-OSHA standard: <1 ppm), or air for 6 hrs/d, 5 d/wk for up to 12 wks. Mice were fed Western diet (WD) to induce experimental NAFLD, or control diets (CD). Plasma and liver samples were collected for determination of injury and mitochondria were isolated for respirometry, analysis of mt-(dys)function and mt-proteome via LC-MS/MS. **Results:** As previously observed, VC exposure enhanced experimental NAFLD caused by WD feeding. The major effect appeared to impact hepatic metabolic function versus other mechanisms (e.g., inflammation). Under these conditions VC exposure exacerbated ER stress, coupled with mitochondrial oxidative damage and dysfunction. Respirometry indicated that mitochondria from VC-exposed mice had impaired electron transport chain (ETC) function. Despite an observed decrease in mt respiration, proteomic analysis indicated that VC exposure actually increased expression of several proteins associated with Gene Ontology (GO) terms for ETC (e.g., GO:0005746 and GO:0022900). In contrast, the mitochondrial level of key UPR-mediated proteins that protect against mitochondrial damage was decreased. For example, VC strongly decreased mitochondrial levels of GRP78 (also known as BiP), which has been shown to protect mitochondrial function during ER stress. **Conclusion:** Taken together, these data suggest that VC causes mitochondrial dysfunction via mechanisms that are mediated, at least in part, by failed crosstalk between the ER and mitochondrial during nutrition overload. These results further shed light on the observation that mitochondria appear to be the key target of injury during low-level VC exposure.

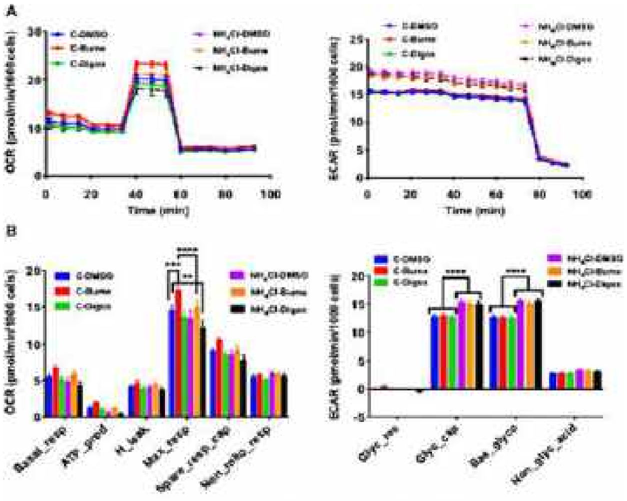
Disclosures: The following people have nothing to disclose: Daniel Wilkey, Jiang Li, Michael Merchant, Gavin E. Arteel, Juliane I Beier

Disclosure information not available at the time of publication: Dexi Chen, Christine Dolin

1725-A | THE NA�/K�-ATPASE AND THE NA+-K+-2CI- CO-TRANSPORTER AS POTENTIAL METABOLIC REGULATORS IN RESPONSE TO HYPERAMMONEMIA IN ASTROCYTES

Carlos Pérez-Monter, Lilia Noriega and Alma Estanes-Hernández, Incmnsz

Background: Hepatic encephalopathy (HE) is characterized by hyperammonemia derived from impairment of ammonia (NH_4^+) clearance capacity of the liver. Within central nervous system (CNS), astrocytes produce glutamine (Gln) by conjugating NH_4^+ and glutamate (Glu). Gln is exported to glutamatergic neurons in order to produce glutamate. During hyperammonemia, increased levels of Gln can enter mitochondria, where its converted into Glu by glutaminase-1, and then to alpha-ketoglutarate, fueling the Krebs cycle and releasing NH_4^+ in the process. Mitochondrial excess of NH_4^+ alters the internal pH and disable several protein complexes, including those related with electron transport; thus, altering the metabolic homeostasis. In addition, the $NH4^+$ ion strongly activates Na^+/K^+-ATPase and the Na^+-K^+-2Cl co-transporter in the cell membrane. Activation of both proteins consumes large quantities of intracellular ATP, leading the astrocyte to a condition of energy starving. Our main aim here was to determine whether astrocyte Na^+/K^+-ATPase and Na^+-K^+-2Cl co-transporter pharmacological inhibition, improves the metabolic status under hiperammonemia in astrocytes. Specifically, we focus on oxygen consumption rate (OCR) to evaluate mitochondrial function and extracellular acidification rate (ECAR) as an indirect measure of glycolytic activity. **Methods:** The astrocytoma C8-S cell-line was incubated in standard conditions (DMEM with 10% FBS and 1% penicillin/streptomycin/37°C/5% CO_2/95% O_2). Cells were seeded at $4x10^4$ cells/well in a 96 well plate. Twenty hours later, cells were exposed to Na^+-K^+-2Cl (50mM) or Na^+/K^+-ATPase (10mM), inhibitors (Bumetanide and Digoxyn, respectively) for 3hrs. Next, cells were exposed to NH_4Cl 10 mM for 24hrs. We then performed a XF Mito Stress test on a Seahorse Analyzer (Agilent). Na^+/K^+-ATPase and Na^+-K^+-2Cl proteins, were also evaluated by immunostaining after exposure to inhibitors. **Results:** NH_4Cl did not affect mitochondrial function, but increased basal glycolysis (12.7 ± 0.32 vs 15.63 ± 0.37, $p<0.001$) and glycolytic capacity (12.73 ± 0.39 *vs* 15.45 ± 0.41 $p<0.01$) of C8-S astrocytes, and this response is Gln-dependent. However, Bumetanide and Digoxyn treatment did not affect the glycolytic capacity nor basal glycolysis under hyperammonemia (ECAR of 15.45 ± 0.40 *vs* 15.14 ± 0.46 for Bumetanide and 15.45 ± 0.40 *vs* 14.95 ± 0.44 for Digoxyn). In addition, Bumetanide significantly increased maximal respiration (OCR of 14.62 ± 0.68 vs 17.33 ± 0.58, $p < 0.01$) only in basal conditions, suggesting an improvement of mitochondrial function. Corrected total cell fluorescence (CTCF) signal indicates that Bumetanide diminished the Na^+-K^+-2Cl co-transporter expression, while Digoxyn has the opposite effect on Na^+/K^+-ATPase protein expression. **Conclusion:** Altogether, our data indicates that maximal respiration is regulated by both inhibitors, Bumetanide and Digoxyn, under hyperammonemia



Oxygen consumption and extracellular acidification rates (OCR & ECAR) plots (A), and the corresponding quantitations (B), in C6-S exposed to hyperammonemia in control conditions (DMSO) or in presence of inhibitors (Bume or Digox). ** p<0.05; *** p<0.01; ****p<0.001.

Disclosures: The following people have nothing to disclose: Carlos Pérez-Monter, Lilia Noriega, Alma Estanes-Hernández

1726-A | THE STRUCTURAL BASIS OF IMMUNOLOGICALLY-MEDIATED GREEN TEA [GT] -INDUCED LIVER INJURY.

David A. Ostrov[1], James Line[2], Danmeng Li[1], Serat-E Ali[2], Sophie Grice[2], Dean J. Naisbitt[2] and Herbert L. Bonkovsky[3], (1)University of Florida, (2)University of Liverpool, (3)Atrium Health Wake Forest Baptist

Background: Green tea [GT] is used as a beverage and extracts of GT are used as popular dietary supplements. Epigallocatechin-3-O-gallate (EGCG) is an abundant polyphenol in GT and has been implicated in GT-induced liver injury. Recent studies have shown striking associations between GT-induced liver injury and presence and expression of the *HLA-B*35:01*[1]. This association suggests a model in which immunogenic structures are recognized by *HLA-B*35:01*-restricted T cells. The **aims** of this study were to 1) understand structural interactions between EGCG and *HLA-B*35:01*, and 2) determine if immunogenic structures are generated as a result of such putative interactions by measuring T cell responsiveness to EGCG in individual's that express *HLA-B*35:01*. **Methods:** We refolded *HLA-B*35:01* and β_2-microglobulin *in vitro* in the presence of high and low affinity peptides, in the presence or absence of EGCG. We characterized refolded complexes by gel filtration chromatography. The immunogenicity of EGCG was measured with peripheral blood mononuclear cells from *HLA-B*35:01* positive and negative healthy donors ($n = 3$). **Results:** Peptide binding was required for generation of complexes of *HLA* in the presence of EGCG. A peptide with low affinity for *HLA-B*35:01* (LRAREEAY, estimated affinity for *HLA-B*35:01* $K_d = 5.3$ μM) formed complexes with *HLA-B*35:01* and β_2-microglobulin in the presence of EGCG, but not in the absence of EGCG. EGCG stabilized the interaction between a low affinity peptide and *HLA-B*35:01*. EGCG stimulated T cells from *HLA-B*35:01* positive and negative healthy donors. **Conclusion:** These data suggest a model in which EGCG forms direct interactions with *HLA-B*35:01* to produce immunogenic structures on hepatocytes. Since thermostability profiles of *HLA-B*35:01* differ drastically depending on bound ligands,[2] these data suggest that EGCG has the potential to form stabilizing intermolecular contacts with loosely bound peptide and *HLA-B*35:01*. Because T cell responses to EGCG were also observed in individual's lacking HLA-B*35:01, our results are consistent with recent data that showed that GT-induced liver damage can occur in individual's lacking *HLA-B*35:01*,[1] suggesting that EGCG has the potential to bind additional *HLA* molecules. In this model, pathogenic T cells cause liver damage by specific recognition of *HLA*-bound EGCG. We speculate that such a model likely also plays a role in other immune-mediated responses to many compounds, including drugs and other components of herbal and dietary supplements.

1. Hoofnagle et al. Hepatology 2021; 73:2484-93. PMID: 32892374
2. Yanaka et al. J Biol Chem 2014; 289: 24680-90. PMID: 25028510

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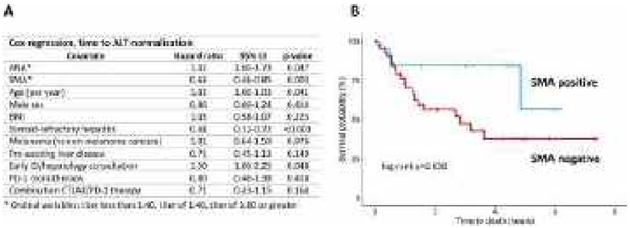
1727-A | A MULTICENTER STUDY OF THE DIAGNOSTIC AND PROGNOSTIC UTILITY OF AUTOANTIBODIES IN HIGH-GRADE IMMUNE CHECKPOINT INHIBITOR HEPATITIS

Michael Li[1], Alexander Vogel[2], Jordan S Sack[2], Lawrence Fong[1], Jennifer C. Lai[3], Shilpa Grover[2] and Stephen D. Zucker[2], (1)University of California, San Francisco, (2)The Brigham and Women's Hospital, (3) University of California-San Francisco

Background: Similarities exist between immune checkpoint inhibitor (ICI) hepatitis and autoimmune hepatitis (AIH), though the role of well-described serological markers of AIH like antinuclear antibodies (ANA), smooth muscle antibodies (SMA), total IgG level, and liver-kidney microsome type 1 antibodies (anti-LKM1) in the evaluation of ICI hepatitis is unclear. **Methods:** We conducted a multicenter retrospective cohort study of patients with grade **e** 3 (ALT > 200 U/L) ICI hepatitis. ANA/SMA/anti-LKM1 positivity was defined as **e** 1:40, and ANA/SMA **e** 1:80 were considered strongly positive. The primary outcome was time to ALT normalization (defined as **d** 40 U/L). The secondary outcome was time to all-cause death; this outcome was assessed in the subgroup of patients with melanoma to avoid confounding of long-term survival due to different cancer types. **Results:** Of 294 study patients who developed high-grade ICI hepatitis, 180 (61%) received testing for at least one autoantibody; 49% had melanoma, and anti-PD-1 monotherapy was the most common ICI regimen (45%). The sensitivities of ANA and SMA were 45% (75/165) and 21% (28/135), respectively. The median IgG level among 105 tested patients was 814 [IQR 669, 1045] mg/dL, and only two patients had an elevated IgG > 1600 mg/dL. Only one patient out of 77 tested positive for anti-LKM1. After multivariable adjustment using Cox regression, ANA-positivity was associated with faster ALT normalization (HR 1.32, 95% CI 1.00-1.73, p = 0.047) and SMA-positivity was associated with slower ALT normalization (HR 0.63, 95% CI 0.46-0.85, p = 0.003) (Figure A). When assessing survival, ANA-positivity had no effect on long-term all-cause mortality. However, SMA-positive patients experienced reduced all-cause mortality compared to SMA-negative patients (median not reached vs 2.9 years, log-rank p = 0.036; Figure B). After adjusting for age and combination CTLA4/PD-1 therapy, SMA-positivity remained significantly associated with reduced risk of death (HR 0.32, 95% CI 0.11-0.93, p = 0.037). **Conclusion:** ANA and SMA have moderate and low sensitivity for high-grade ICI hepatitis, though the prognostic implications of ANA- or SMA-positivity suggest that testing for these autoantibodies may be useful. IgG and anti-LKM1 do not appear to have any diagnostic utility in ICI hepatitis. SMA-positivity was associated with improved long-term cancer survival, though further studies are needed to investigate this effect.



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1728-A | CHARACTERISTICS AND OUTCOMES OF LIVER INJURY DUE TO HERBAL AND DIETARY SUPPLEMENTS IN THE U.S.

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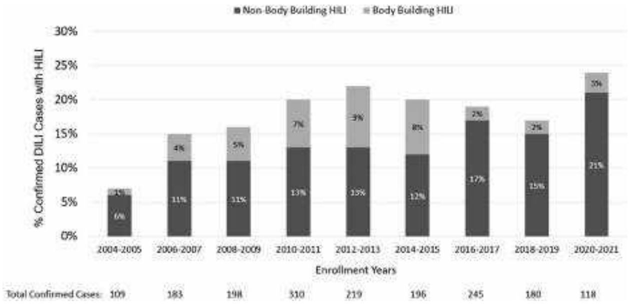
(ISMMS), Huiman Barnhart, Duke University, Durham, NC, Alfred Sidney Barritt IV, University of North Carolina, Herbert L. Bonkovsky, Atrium Health Wake Forest Baptist, Robert J. Fontana, University of Michigan Hospitals and Health Centers, Paul H. Hayashi, FDA, Christopher Koh, National Institute of Diabetes and Digestive and Kidney Diseases, Nih, Jose Serrano, National Institute of Diabetes, Bethesda, MD, United States, Averell H. Sherker, NIH/NIDDK and Raj Vuppalanchi, Indiana University School of Medicine

Background: The Drug Induced Liver Injury Network (DILIN) enrolls patients with injury from drugs, and herbal and dietary supplements (HDS). Aim: To define features of HDS induced liver injury (HILI) enrolled in DILIN **Methods:** Among a total of 1780 high-confidence cases (definite, highly likely, probable) enrolled between 2004 and 2021, 325 (18%) were due to HDS. HILI cases were grouped as due to bodybuilding (BB) or non-bodybuilding (non-BB) agents based on purpose for use. **Results:** Since 2004, the majority of HILI was due to non-BB agents (239: 73%) which were most frequently used for weight loss (23%). Since 2010, the number and proportion of BB-HILI cases fell ($p < 0.001$ for trend) while those of non-BB-HILI rose ($p = 0.03$ for trend) (figure). BB HILI cases were younger than non-BB HILI and drug injury cases; median ages 32 vs 46, and 54 years ($p < 0.001$). BB HILI occurred almost exclusively in men (97%), compared with non-BB HILI (60%) and drug injury (61%). Most HILI patients were white (75%). Non-BB HILI had a higher rate of Latinos (21%), compared to BB-HILI (12%) and drug injury (8%) ($p < 0.001$). BB and Non-BB HILI had longer median latencies (71 and 68 d) than drugs (41 d, $p < 0.001$), and BB HILI was more likely to present with jaundice ($p < 0.001$). Peak median ALT levels were highest in non-BB HILI (1252 U/L), compared with BB HILI (560 U/L) and drugs (964 U/L) ($p < 0.001$) while peak median bilirubin levels were highest in BB HILI (10 mg/dL vs 5.0 and 6.5 mg/dL, $p < 0.001$). Median time to return of peak bilirubin and ALT levels to normal was longest for BB HILI (median 70 and 106 d) vs non-BB HDS (35 and 71 d) and drugs (29 and 62 d; $p < 0.01$). None of the 86 BB-HILI cases died or required liver transplant (LT), compared to 27 (11%) of non-BB-HILI cases (10, 4% deaths; 17, 7% LTs) and 196 (13%) of drug cases (152, 10% deaths; 44, 3% LTs) $p = 0.001$. Persistent liver test abnormalities at 6 months were more frequent among drug compared to non-BB and BB cases (18% vs 12% and 9%: $p < 0.05$). **Conclusion:** HILI accounts for an increasing proportion of DILIN cases; BB HILI becoming less and non-BB HILI more frequent, the latter particularly among Latinos. Changes in HILI may reflect changes in US population characteristics and the increasing use of HDS for conditions such as obesity not responsive to or in lieu of other treatments.



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1729-A | CLINICAL AND HLA CORRELATES IN CEPHALOSPORIN INDUCED LIVER INJURY

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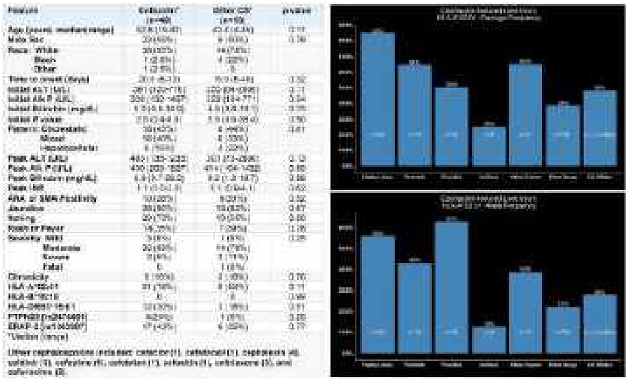
Background: Cephalosporins (CS) are among the most used antibiotics in clinical practice and are notable

for their efficacy and safety profile. Acute, idiosyncratic liver injury from CS occurs, but is rare and typically mild to moderate in severity and self-limited in course. **Methods:** We sought to characterize the clinical, biochemical features and HLA associations of liver injury attributed CS in the DILIN prospective study. **Results:** Between 2004 and Nov 2, 2022, a total of 2347 cases of drug-induced liver injury (DILI) were enrolled in the prospective DILIN study and had 6 months of follow up and formal adjudication. 1854 cases were scored as being probable, highly likely or definite DILI, 58 of which (3%) were attributed to different CS, including cefazolin (n = 40), cephalexin (n = 4), ceftriaxone (n = 3), cefdinir (n = 3), cefuroxime (n = 3) and 5 others with one each. Characteristic clinical features of CS DILI were a self-limited, mixed or cholestatic hepatitis arising 1 to 4 weeks after starting and often several weeks after stopping the antibiotic. Most striking was the phenotype of cefazolin and other parenteral cephalosporins given as a single dose with onset of jaundice, fatigue and itching 1 to 3 weeks later. HLA sequencing performed on 57 CS cases revealed a significant association with HLA-A*02:01, an allele also found to be linked to amoxicillin and amoxicillin/clavulanate [A/C] DILI (PMID: 36496055). The association was strongest with cefazolin with an allele frequency [AF] 51% and carriage frequency [CF] 78% compared to population-based AF of 23% and CF of 39% (Figure). Other A/C related HLA and genetic variants (HLA-B*15:18, DRB1*15:01, ERAP2 [rs1363907] and PTPN22 [rs2476601]) were not increased in frequency with CS liver injury. The HLA-A*02:01 association found with cefazolin was not found in the 17 other CS cases [AF 0.31]. The clinical features of cefazolin cases with and without HLA-A*02:01 were similar, although the cases with the allele tended to be more severe (81% vs. 44% with either moderate-hospitalized or severe by DILIN. **Conclusion:** The cephalosporins are rare causes of liver injury and have a self-limited, mixed/cholestatic hepatitis that arises after a short course of therapy. Most cases are due to cefazolin which has an HLA association similar but not identical to amoxicillin and A/C.



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Disclosure information not available at the time of publication: Yi-Ju Li, Victor J. Navarro, Md, Joseph Odin, Huiman Barnhart

1730-A | DEVELOPMENT OF ACUTE LIVER FAILURE AND MORTALITY IN PATIENTS WITH DRUG-INDUCED LIVER INJURY: A RISK FACTORS ANALYSIS.

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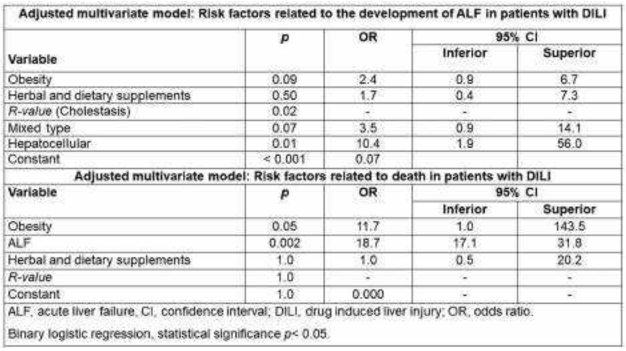
Background: Drug-induced liver injury (DILI) can cause acute liver failure (ALF) or death. DILI is an exclusion diagnosis. No specific therapy is available. Aim: To describe the main characteristics of patients with DILI, and to identify risk factors to develop ALF and death. **Methods:** An observational, retrospective cohort study including patients with DILI diagnosis, identified between January 2006 to January 2023 in two medical centers. Univariate and multivariate regression models were performed to identify risk factors associated with ALF and death. **Results:** 110 patients were included, 84(76.4%) women, 42.6 ± 14.1 year-old; according to *R-value* 43(39.1%) had cholestasis, 38(34.5%) hepatocellular injury, and 29 (26.4%) mixed; 42(38.2%) were obese; 35 (31.8%) developed ALF; 11 (10%) died. The most frequent DILI causal agents were: antibiotics 35.6%, herbal and dietary supplements (HDS) 29.1%, immunosuppressive agents 7.2%, statins 6.4%, oral antimycotics 5.5%, AINEs 4.5%, carbamazepine 3.6%, anti-tuberculous drugs 2.7%, contraceptives 1.8%, oral dermatological agents 1.8%, antineoplastic 0.9%, valproate 0.9%. Some patients received empirical therapy to treat DILI: 11 (10%) received ursodeoxycholic acid (UDCA), 26 (23.6%) S-adenosylmethionine (SAMe), 25 (22.7%) vitamin E, and 30 (27.3%) metadoxine (MTD). In the univariate analysis, the following were risk factors for ALF: hepatocellular injury (OR 16.7, 95%CI: 4.9-56.7, $p < 0.0001$), HDS (OR 8.7, 95%CI: 3.4-22.1, $p < 0.0001$), obesity (OR 3.2, 95%CI: 1.4-7.4, $p = 0.006$). Other factors like gender, and treatment with MTD, vitamin E, UDCA, or SAMe were not significant. In the adjusted multivariate analysis, just hepatocellular injury was a risk factor to develop ALF (see Table). In the univariate analysis, the following were risk factors for death: developing of ALF (OR 70.9, 95CI%: 4.0-1247.4, $p < 0.0001$), hepatocellular injury (OR 60.6, 95%CI: 3.5-1064.4, $p < 0.0001$), HDS (OR 35.0, 95%CI: 4.2-288.5, $p = 0.001$), obesity (OR 20.9, 95%CI: 2.6-170.7, $p < 0.004$). Gender, vitamin E, MTD, SAMe, and UDCA were not significant. In the adjusted multivariate analysis, the development of ALF was the most relevant risk factor associated with death, also there was a tendency to significance with the presence of obesity (see Table). **Conclusion:** Antibiotics and HDS were the most frequent agents related to DILI. The hepatocellular injury was related to the development of ALF, and ALF is related to death. No empirical therapy was useful to prevent ALF or death.



Adjusted multivariate model: Risk factors related to the development of ALF in patients with DILI

Variable	*p*	OR	95% CI	
			Inferior	Superior
Obesity	0.09	2.4	0.9	6.7
Herbal and dietary supplements	0.50	1.7	0.4	7.3
R-value (Cholestasis)	0.02	-	-	-
Mixed type	0.07	3.5	0.9	14.1
Hepatocellular	0.01	10.4	1.9	56.0
Constant	< 0.001	0.07		

Adjusted multivariate model: Risk factors related to death in patients with DILI

Variable	*p*	OR	95% CI	
			Inferior	Superior
Obesity	0.05	11.7	1.0	143.5
ALF	0.002	18.7	17.1	31.8
Herbal and dietary supplements	1.0	1.0	0.5	20.2
R-value	1.0	-	-	-
Constant	1.0	0.000	-	-

ALF, acute liver failure, CI, confidence interval; DILI, drug induced liver injury; OR, odds ratio.

Binary logistic regression, statistical significance $p < 0.05$.

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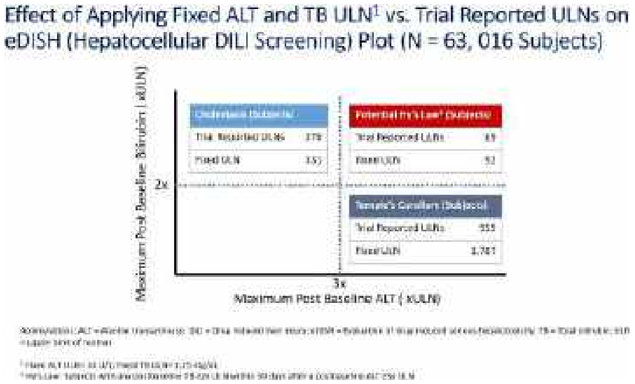
Disclosure information not available at the time of publication: José Antonio Velarde-Ruiz Velasco, José

Miguel Córdoba-Reyes, Juan Manuel Aldana-Ledesma, Alfredo Servin-Caamaño, José Luis Pérez-Hernández

1731-A | EFFECT OF VARIATION IN ALANINE AMINOTRANSFERASE (ALT) AND TOTAL BILIRUBIN (TB) UPPER LIMITS OF NORMAL (ULN) ON THE EVALUATION OF HEPATOCELLULAR DRUG-INDUCED LIVER INJURY (DILI) IN CLINICAL TRIALS

Chih-Hao Huang, Ling Lan, Paul H. Hayashi and Y. Veronica Pei, FDA

Background: Increased ALT and total bilirubin based on multiples of ULN identify potential DILI of concern in clinical trials (e.g., Hy's Law cases). However, ALT ULNs vary across laboratories and have increased over time. Variability in ALT and TB ULNs may hinder consistent identification of DILI cases. Using a fixed, acceptable, and lower ALT ULN may impact potential DILI case identification. **Methods:** We identified 121 clinical trials submitted to the FDA in 2022 that enrolled subjects > 18 years old with baseline ALT < 1.5 times trial reported ULN. We used descriptive statistics to summarize the distribution of trial reported ULNs for ALT and TB across all 121 trials. In addition to using trial reported ULNs of ALT and TB, we examined the number of subjects in each eDISH (Hepatocellular DILI screening) plot quadrants using a published reference for ALT (Kwo PY et al. Am J Gastro 2017) and fixed TB at 33 U/L and 1.25 mg/dL, respectively. **Results:** Maximum post-baseline and ULN ALT and TB values from 63,016 subjects across the 121 trials were analyzed. We excluded clinically unfeasible values for ALT (> 50,000 U/L) and TB (> 100 mg/dL). The maximum number of unique ALT and TB ULNs reported in a single trial were 54 and 41, respectively. Median value of trial reported ALT ULNs was 43 U/L (range = 0.6 to 306 U/L) with 85.9% of the reported ULN values > 33 U/L. Median value of trial reported TB ULNs was 1.23 mg/dL (range = 0.000076 to 16.6 mg/dL) with 23.9% of trial reported ULN values > 1.25 mg/dL. Using ALT ULN of 33 U/L and TB ULN of 1.25 mg/dL resulted in identification of 23 additional cases in Hy's Law quadrant (33.3% increase) and 828 additional cases (86.3% increase) in Temple's Corollary quadrant compared to using trial provided ULNs. (Figure) **Conclusion:** Current reported ALT and TB ULNs from clinical trials vary widely. Most trial reported ALT values were also coupled with ALT ULNs higher than 33 U/L, which led to a lower frequency in subject identification on eDISH plots of either Hy's Law or Temple's Corollary quadrants compared to using a fixed ALT ULN of 33 U/L and TB ULN of 1.25 mg/dL. Variability of ALT ULN can affect eDISH's function as a DILI screening tool and DILI assessment in clinical rials may benefit from standardized, uniform TB ULN and lower fixed ALT ULN. Assessment for potential DILI cases based on trial reported ULNs may result in missed cases of DILI. Gender-based ALT and TB ULN values should also be considered for DILI analysis.



Effect of Applying Fixed ALT and TB ULN[1] vs. Trial Reported ULNs on eDISH (Hepatocellular DILI Screening) Plot (N = 63, 016 Subjects)

Disclosures: The following people have nothing to disclose: Chih-Hao Huang, Ling Lan, Paul H. Hayashi, Y. Veronica Pei

1732-A | ESTIMATING THE INCIDENCE OF IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY

Jay H. Hoofnagle, Niddk, Rockville, MD, Einar Stefan Bjornsson, Landspitali University Hospital, Reykjavik, Iceland, Vincent Chen, University of Michigan Medical Center, Huiman Barnhart, Duke University, Durham, NC and Don C. Rockey, Medical University of South Carolina

Background: Idiosyncratic drug-induced liver injury (DILI) is rare, occurring at rates of 1:100 to 1:1,000,000 exposed-persons. However, the incidence of liver injury from individual agents is rarely known. Using the relative rates of the major causes of DILI in the DILIN Prospective Study (NCT NCT00345930) and the known rate for amoxicillin/clavulanate (43/100,000) from a population-based study from Iceland, we sought to estimate the incidence of the major causes of idiosyncratic DILI. **Methods**: DILIN has enrolled cases of suspected DILI in the United States (US) since 2004. Cases were carefully assessed, followed for at least 6 months, and then adjudicated for causality. The estimated incidence of DILI (*EID*) was calculated for all prescription medications with 5 or more cases adjudicated as definite, highly likely or probable. The average yearly usage of drugs was extracted from https://clincalc.com/. *EID* was calculated based upon relative number of cases in DILIN due to the agent (Drug X) to those of amoxicillin/clavulanate and adjusted for the yearly usage relative to A/C using the following formula: *EID* (Drug X) = *EID* (A/C) x [No cases of X ÷ No cases A/C] x [yearly usage of *A/C* ÷ yearly usage of *X*]. **Results:** As of 2021, 55 drugs were implicated in at least 5 cases of DILI in DILIN. Data on prescription usage was available for 33 of the drugs. The *EID*, as expressed as number of patients given a prescription for each case, ranged from 1:1,000 to 1:250,000 (Table). Drugs with the highest *EID* (1:1000-1:5000) included amoxicillin/clavulanate, trimethoprim/sulfamethoxazole (TMP/SMZ), nitrofurantoin, phenytoin, and carbamazepine. Drugs with moderately high *EID* (1:5000-1:10,000) included levofloxacin, moxifloxacin, lamotrigine, valproate, and diclofenac. Classic anticonvulsants such as pheytoin and carbamazepine had a relatively high *EID* (< 1:10,000). Importantly, among drugs with the lowest EID are included the statins (all 4 statins had an *EID* > 1:50,000). Some antibiotics had a high *EID* (sulfonamides, fluoroquinolones), while others had a low EID (amoxicillin, cephalexin, doxycycline). Because of lack of data on usage, *EID* could not be calculated for drugs not among the top 300 prescribed in the US or for those given parenterally. **Conclusion:** The calculated *EID* for DILI of commonly prescribed drugs clearly demonstrates substantial differences for DILI incidences with different drugs. Although these are rough estimates that rest upon assumptions about the relative rates and ability to detect DILI between different drugs (and between the US and Iceland), the *EID* provides informative rates for these rare events and likely explains why the risk of DILI may be missed in registration trials of new drugs which may enroll fewer than 1,000-3,000 patients.

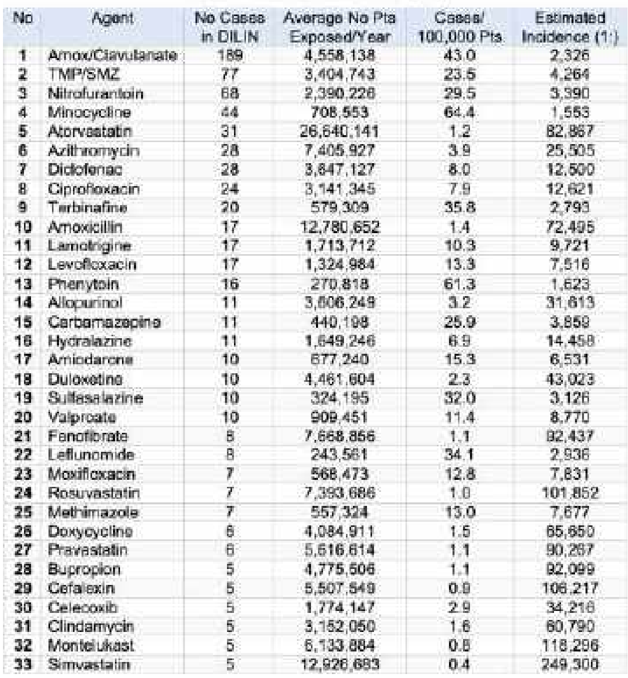


Table: Estimated Risk of Liver Injury

No	Agent	No Cases in DILIN	Average No Pts Exposed/Year	Cases/ 100,000 Pts	Estimated Incidence (1:)
1	Amox/Clavulanate	189	4,558,138	43.0	2,326
2	TMP/SMZ	77	3,404,743	23.5	4,264
3	Nitrofurantoin	68	2,390,228	29.5	3,390
4	Minocycline	44	708,553	64.4	1,553
5	Atorvastatin	31	26,640,141	1.2	82,867
6	Azithromycin	28	7,405,927	3.9	25,505
7	Diclofenac	28	3,847,127	8.0	12,500
8	Ciprofloxacin	24	3,141,345	7.9	12,621
9	Terbinafine	20	579,309	35.8	2,793
10	Amoxicillin	17	12,780,652	1.4	72,495
11	Lamotrigine	17	1,713,712	10.3	9,721
12	Levofloxacin	17	1,324,984	13.3	7,516
13	Phenytoin	16	270,818	61.3	1,623
14	Allopurinol	11	3,606,249	3.2	31,613
15	Carbamazepine	11	440,198	25.9	3,859
16	Hydralazine	11	1,649,246	6.9	14,458
17	Amiodarone	10	677,240	15.3	6,531
18	Duloxetine	10	4,461,604	2.3	43,023
19	Sulfasalazine	10	324,195	32.0	3,126
20	Valproate	10	909,451	11.4	8,770
21	Fenofibrate	8	7,668,856	1.1	92,437
22	Leflunomide	8	243,561	34.1	2,936
23	Moxifloxacin	7	568,473	12.8	7,831
24	Rosuvastatin	7	7,393,686	1.0	101,852
25	Methimazole	7	557,324	13.0	7,677
26	Doxycycline	6	4,084,911	1.5	65,650
27	Pravastatin	6	5,616,614	1.1	90,267
28	Bupropion	5	4,775,506	1.1	92,099
29	Cefalexin	5	5,507,549	0.9	106,217
30	Celecoxib	5	1,774,147	2.9	34,216
31	Clindamycin	5	3,152,050	1.6	60,790
32	Montelukast	5	6,133,884	0.8	118,296
33	Simvastatin	5	12,926,683	0.4	249,300

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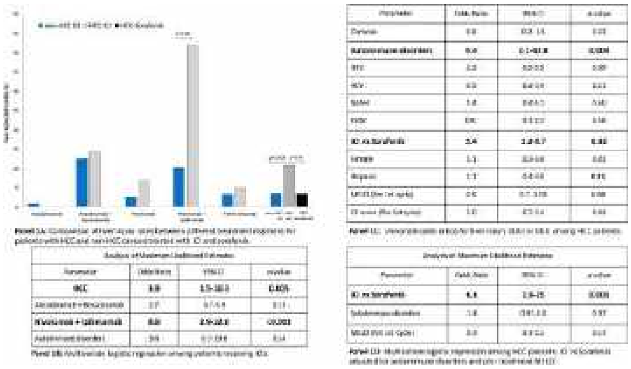
1733-A | IMMUNE CHECKPOINT INHIBITOR THERAPY FOR HCC IS ASSOCIATED WITH INCREASED INCIDENCE OF HEPATOTOXICITY, COMPARED TO SORAFENIB

Elsie Ennin[1], *Niharika Mallepally*[2], *Layla Shojaie*[1], *Myra Ali*[3], *Sean Dewberry*[3], *Melissa Trieu*[3], *Kali Zhou*[2], *Jeffrey A Kahn*[2], *Jennifer L. Dodge*[4] *and Lily Dara*[2], *(1) Department of Medicine, Keck School of Medicine, University of Southern California, (2)Division of Gastrointestinal and Liver Diseases, Keck School of Medicine, University of Southern California, (3)Keck School of Medicine, University of Southern California, (4)USC Research Center for Liver Disease, Keck School of Medicine, University of Southern California*

Background: Immune checkpoint inhibitors (ICIs) are approved systemic therapy for many malignancies including HCC. The impact of chronic liver disease and HCC on the incidence of immune-mediated liver injury from checkpoint inhibitors (ILICI) is unknown. Sorafenib drug induced liver injury (DILI) occurs in 1-3% of HCC patients. No direct comparison has been made of hepatotoxicity rates between ICI and sorafenib in HCC. **Methods:** We retrospectively identified patients with HCC who received 1 of 5 ICI regimens indicated for HCC, patients with various non-HCC cancers who received the same ICI drugs, and HCC patients who received sorafenib between 2010-2020. The primary outcome was grade **e** 3 liver injury (AST/ALT > 5X upper limit of normal) with ICI (ILICI) or sorafenib (DILI) with incidence (Clopper-Pearson 95% confidence intervals (CI)) compared using the Fisher's exact test. Logistic regression estimated odds ratios (OR) for hepatotoxicity. **Results:** We identified 530 patients, 129 (24%) HCC-ICI, 256 (48%) non-HCC ICI and 145 (27%) HCC-Sorafenib (mean age 65 (SD ± 12), autoimmune disorders 3%). Compared to non-HCC ICI, HCC-ICI and HCC-Sorafenib were more often male (57%, 82%, 77%), Hispanic (14%, 35%, 34%), and cirrhotic (1%, 85%, 88%). ILICI incidence was higher for HCC-ICI (11%, CI 6-18) vs non-HCC ICI (4%, CI 2-6, p = 0.006) and DILI in HCC-Sorafenib (3%, CI 1-8, p = 0.02) with incidence highest for nivolumab+ipilimumab (HCC-ICI 42%, CI 15-72 vs non-HCC 10%, CI 3-24; p = 0.02). On multivariate regression, ILICI was independently associated with HCC (OR 3.9, CI 1.5-10.3, p = 0.005) and nivolumab+ipilimumab (OR 8.0, CI 2.9-22.0, p < 0.001). ILICI was elevated in patients who received atezolizumab + bevacizumab (OR 2.7, CI 0.7-9.9, p = 0.13) and/or had autoimmune disorders (OR 3.6, CI 0.7-19.6, p = 0.14), though not statistically significant. In HCC cases, liver injury remained elevated for ICI vs. sorafenib (OR 6.6, CI 1.8-25.0, p = 0.005) and potentially for autoimmune disorders (OR 1.8, CI 0.97-3.3, p = 0.07). Among the 19 HCC cases with DILI, those with ICI vs. sorafenib had higher median peak serum AST (353 vs 172, p = 0.03) and ALT (250 vs 109, p = 0.04). **Conclusion:** We identified an elevated risk of liver injury in ICI treated patients with HCC that exceeded the risk in ICI treated non-HCC cancers and sorafenib treated HCC cancers. The use of nivolumab + ipilimumab was specifically associated with increased odds of ILICI. Notably, our data suggests autoimmune disorders may also increase risk of developing ILICI though more research is needed to confirm these findings in a larger population. HCC patients treated with ICIs should be monitored closely as they are at higher risk of decompensation than are their non-ICI counterparts.

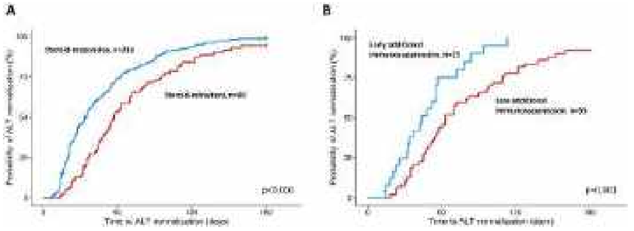


Disclosures: Kali Zhou – Gilead Inc: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
The following people have nothing to disclose: Elsie Ennin, Layla Shojaie, Jeffrey A Kahn
Disclosure information not available at the time of publication: Niharika Mallepally, Myra Ali, Sean Dewberry, Melissa Trieu, Jennifer L. Dodge, Lily Dara

1734-A | PREDICTING STEROID-REFRACTORY IMMUNE CHECKPOINT INHIBITOR HEPATITIS: DEVELOPMENT AND EXTERNAL VALIDATION OF THE NOVEL SUNLIT MODEL AND IDENTIFYING A CUTOFF FOR BIOCHEMICAL NONRESPONSE AFTER STEROID TREATMENT

Michael Li[1], Jordan S Sack[2], Alexander Vogel[2], Lawrence Fong[1], Stephen D. Zucker[2], Shilpa Grover[2] and Jennifer C. Lai[3], (1)University of California, San Francisco, (2)The Brigham and Women's Hospital, (3) University of California-San Francisco

Background: Immune checkpoint inhibitor (ICI) hepatitis is one of the most frequent severe immune-related adverse events (irAEs) caused by cancer immunotherapy. Many patients have inadequate response to corticosteroids, but there are limited data regarding predictors of steroid-refractory ICI hepatitis and when to initiate additional immunosuppression. **Methods:** We conducted a multicenter, retrospective cohort study of cancer patients who developed grade 3-4 ICI hepatitis. The SUNLIT (Steroid UNresponsive Liver Immune Toxicity) model was derived using LASSO regression in a training set of 222 patients (Boston cohort) and then externally validated in 72 patients (San Francisco cohort). **Results:** Out of 294 patients, 80 (27%) developed steroid-refractory hepatitis, and 91% of these patients received mycophenolate mofetil. Steroid-refractory patients had higher peak ALT (median 703 vs 368 U/L, p < 0.001) and longer time to ALT normalization (median 57 vs 35 d, log-rank p < 0.001; Figure A) compared to steroid-responsive patients. The SUNLIT model included five pre-steroid treatment variables: pre-existing liver disease, alcohol use, liver metastasis, combination anti-CTLA4/PD1 therapy, and prior irAE of any organ system. SUNLIT had good discrimination for development of steroid-refractory hepatitis, with c-statistics of 0.79 (95% CI 0.73-0.86) and 0.82 (95% CI 0.71-0.93) in the training and validation sets, respectively. The median percent change in ALT after 7 days of steroid treatment differed significantly between steroid-refractory and responsive patients (-12% [IQR -40%, +24%] vs -58% [-73%, -40%], p < 0.001). As a single predictor of steroid-refractory disease, the percent change in ALT after 7 days of steroids had a c-statistic of 0.83, and the optimal cutoff based on maximizing the J statistic was -30% (sensitivity 68%, specificity 85%). Early additional immunosuppression **d** 7 days of steroid initiation was associated with faster ALT normalization in steroid-refractory patients (median 44 vs 63 days, log-rank p < 0.001, Figure B; adjusted HR 2.46, 95% CI 1.41-4.27, p = 0.001). **Conclusion:** The SUNLIT model uses baseline variables to predict development of steroid-refractory ICI hepatitis and can identify high-risk patients who require frequent lab monitoring while receiving high-dose steroid treatment. We propose that patients who do not demonstrate at least a 30% improvement in ALT after 7 days of steroid treatment should initiate additional immunosuppression.



Disclosures: Jennifer C. Lai – Novo Nordisk: Advisor, No, No; Genfit: Consultant, No, No; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Vir: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gore: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Flagship Pioneering: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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Disclosure information not available at the time of publication: Jordan S Sack, Lawrence Fong, Stephen D. Zucker, Shilpa Grover

1735-A | PREDICTORS OF HEPATIC ENCEPHALOPATHY AMONG ADULTS ADMITTED WITH ACETAMINOPHEN POISONING.

Omar Almetwali, Marshall University School of Medicine, Renuka Verma, Guru Gobind Singh Medical School, Kamleshun Ramphul, Independent Researcher, Hemamalini Sakthivel, One Brooklyn Health System/ Interfaith Medical Center Program and Tejas Vijay Joshi, Marshall University

Background: Acetaminophen poisoning is a medical emergency that requires prompt and effective management to mitigate the risk of serious complications including hepatic encephalopathy (HE). The aim of this project is to construct a machine learning model to evaluate and predict the risk of impending HE by taking into account signs and sociodemographic determinants that predispose patients at risk to developing HE. **Methods:** Patients (aged e 18 y) admitted with acetaminophen poisoning (Without a pre-existing diagnosis of liver cirrhosis) were included in our patient sample. Patient population was derived from the 2016-2020 National inpatient census. Prognostic factors predisposing to HE were studied via logistic regression models. **Results:** We found 132040 hospitalizations involving acetaminophen poisoning amongst adults in the United States that matched our selection criteria, of which 11985 (9.1%) cases reported events of hepatic encephalopathy. Multiple patient attributes and comorbidities were considered. Factors such as Charlson Comorbidity index score e 4 (aOR 23.179, $p < 0.01$), Cardiogenic shock (aOR 1.574, $p < 0.01$), history of alcohol abuse (aOR 1.158, $p < 0.01$), history of drug use (aOR 1.06, $p = 0.045$), hypertension (aOR 1.081, $p < 0.01$), acute kidney injury (aOR 1.864, $p < 0.01$) and weekend admissions (aOR 1.18, $p < 0.01$) showed a higher predisposition of reporting hepatic encephalopathy. On the contrary, patients aged over 60 (vs. ages < 60, aOR 0.802, $p < 0.01$), diabetic (aOR 0.584, $p < 0.01$), peripheral vascular disease (aOR 0.46, $p < 0.01$), smoking history (aOR 0.822, $p < 0.01$), chronic kidney disease (aOR 0.477, $p < 0.010$), African American (vs. Caucasian, aOR 0.657, $p < 0.01$) and covered by Medicaid (vs. Medicare, aOR 0.876, $p < 0.01$) reported lower incidence of HE. **Conclusion:** Our study highlighted the role of various contributing factors attributed with inducing HE in the setting of acetaminophen poisoning. While the data did show a direct correlation between some of the aforementioned variables and the risk of developing HE, our study was unable to ascertain the exact dose and timeline between drug ingestion and onset of HE. Further studies can help evaluate the potential relationship between such variables and possible changes in outcomes.

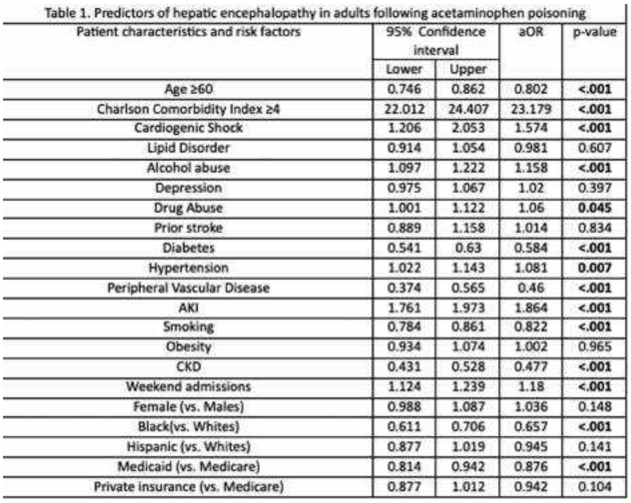

Table 1. Predictors of hepatic encephalopathy in adults following acetaminophen poisoning

Patient characteristics and risk factors	95% Confidence interval		aOR	p-value
	Lower	Upper		
Age ≥60	0.746	0.862	0.802	**<.001**
Charlson Comorbidity Index ≥4	22.012	24.407	23.179	**<.001**
Cardiogenic Shock	1.206	2.053	1.574	**<.001**
Lipid Disorder	0.914	1.054	0.981	0.607
Alcohol abuse	1.097	1.222	1.158	**<.001**
Depression	0.975	1.067	1.02	0.397
Drug Abuse	1.001	1.122	1.06	**0.045**
Prior stroke	0.889	1.158	1.014	0.834
Diabetes	0.541	0.63	0.584	**<.001**
Hypertension	1.022	1.143	1.081	**0.007**
Peripheral Vascular Disease	0.374	0.565	0.46	**<.001**
AKI	1.761	1.973	1.864	**<.001**
Smoking	0.784	0.861	0.822	**<.001**
Obesity	0.934	1.074	1.002	0.965
CKD	0.431	0.528	0.477	**<.001**
Weekend admissions	1.124	1.239	1.18	**<.001**
Female (vs. Males)	0.988	1.087	1.036	0.148
Black(vs. Whites)	0.611	0.706	0.657	**<.001**
Hispanic (vs. Whites)	0.877	1.019	0.945	0.141
Medicaid (vs. Medicare)	0.814	0.942	0.876	**<.001**
Private insurance (vs. Medicare)	0.877	1.012	0.942	0.104

Disclosures: Tejas Vijay Joshi – Fibroscan: Consultant, No, No; Novo Nordisk: Speaking and Teaching, No, No; The following people have nothing to disclose: Omar Almetwali, Renuka Verma, Kamleshun Ramphul, Hemamalini Sakthivel

1736-A | PREVALENCE AND RISK FACTORS ASSOCIATED WITH DRUG-INDUCED LIVER INJURY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A 28-YEAR SINGLE CENTER EXPERIENCE

Asif Ali Hitawala[1], Zerai Manna[2], Yenealem Temesgen-Oyelakin[2], Elaine Poncio[2], Christopher Koh[1], Sarfaraz Hasni[2] and Theo Heller[3], (1)National Institute of Diabetes and Digestive and Kidney Diseases, Nih, (2) National Institute of Arthritis and Musculoskeletal and Skin Diseases, (3)Translational Hepatology Section, Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

Background: Patients with systemic lupus erythematosus (SLE) may require multiple medications for disease control. Drug-induced liver injury (DILI) is an important cause of hepatic injury (HI) in these patients, sometimes requiring therapy modification. We assessed prevalence and risk factors of the same. **Methods:** A retrospective longitudinal single center study was conducted from 1994-2022. Inclusion: 1) Age e 18 years; 2) Diagnosis of SLE based on 1997 American College of Rheumatology revised criteria. Exclusion: Patients with either < 3 visits or < 6 months of follow-up. Demographic, laboratory, medication and liver histology data were obtained from the electronic medical records. Prescriber notes were queried to identify patients with DILI. The patients were initially divided into those with and without HI, followed by HI secondary to DILI or another cause. The groups were then compared to identify risk factors. Chi-square test was used for comparing categorical variables, while Kruskal-Wallis test was used for numerical variables. P-value < 0.05 was considered statistically significant. **Results:** Out of 1106 patients, 636 patients were included in the final cohort, with median duration of follow-up of 9.7 yrs (4.15-16.96). There were 82 deaths, but only six patients had documented cause of death (all non-liver related). Mean age was 53.85 yrs (± 15.31) and majority were females (555, 87.26%). About half the patients (303, 47.64%) developed HI during follow-up and majority (230, 75.91%) did not have an identifiable cause. Of the remaining 73 patients, 14 patients, all females, were suspected or diagnosed with DILI. The most common drug implicated was azathioprine (5 cases), followed by cyclophosphamide (2 cases), with 1 case each of a Janus-Kinase inhibitor (trial drug), methotrexate, meropenem, trimethoprim-sulphamethoxazole and enoxaparin. No drug could be identified in two patients. One patient had a liver biopsy suggestive of DILI, although no drug could be implicated. The rest were diagnosed clinically. There were no deaths recorded in the DILI group. Patients with DILI were younger but had similar body mass index (BMI). They had longer duration of follow-up than those without HI, but similar to those with other causes of HI. They had higher liver enzymes, direct bilirubin, prothrombin time, ferritin and C-reactive protein but lower albumin. Interestingly, these patients had higher anti-ribonucleoprotein antibody levels. In addition, they were more likely to be exposed to hydroxychloroquine, azathioprine, methotrexate and corticosteroids. **Conclusion:** HI is common in SLE, and the cause is often unknown. DILI remains an important cause of HI, and its risk increases in patients on multiple medications, emphasizing the importance of avoiding polypharmacy. Higher anti-ribonucleoprotein antibody levels may be helpful in identifying these patients, although further research is needed.

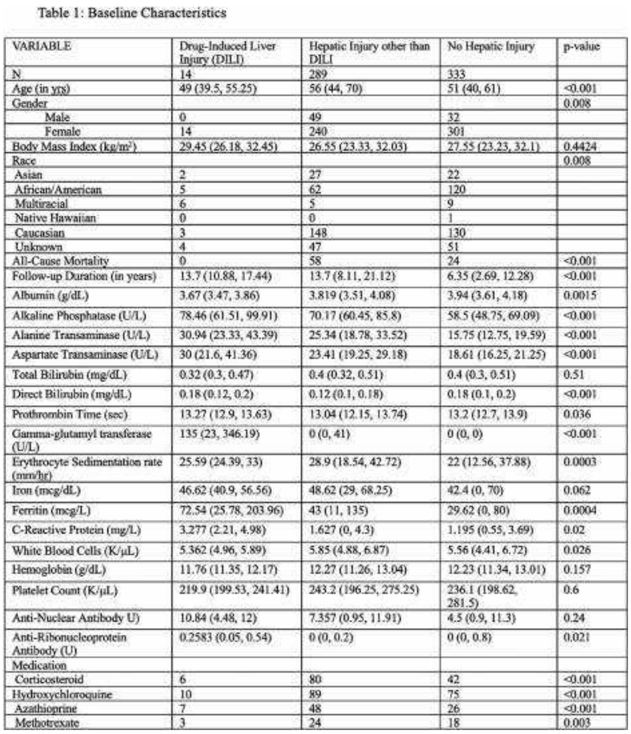

Table 1: Baseline Characteristics

VARIABLE	Drug-Induced Liver Injury (DILI)	Hepatic Injury other than DILI	No Hepatic Injury	p-value
N	14	289	333	
Age (in yrs)	49 (39.5, 55.25)	56 (44, 70)	51 (40, 61)	<0.001
Gender				0.008
Male	0	49	32	
Female	14	240	301	
Body Mass Index (kg/m^2)	29.45 (26.18, 32.45)	26.55 (23.33, 32.03)	27.55 (23.23, 32.1)	0.4424
Race				0.008
Asian	2	27	22	
African/American	5	62	120	
Multiracial	6	5	9	
Native Hawaiian	0	0	1	
Caucasian	3	148	130	
Unknown	4	47	51	
All-Cause Mortality	0	58	24	<0.001
Follow-up Duration (in years)	13.7 (10.88, 17.44)	13.7 (8.11, 21.12)	6.35 (2.69, 12.28)	<0.001
Albumin (g/dL)	3.67 (3.47, 3.86)	3.819 (3.51, 4.08)	3.94 (3.61, 4.18)	0.0015
Alkaline Phosphatase (U/L)	78.46 (61.51, 99.91)	70.17 (60.45, 85.8)	58.5 (48.75, 69.09)	<0.001
Alanine Transaminase (U/L)	30.94 (23.33, 43.39)	25.34 (18.78, 33.52)	15.75 (12.75, 19.59)	<0.001
Aspartate Transaminase (U/L)	30 (21.6, 41.36)	23.41 (19.25, 29.18)	18.61 (16.25, 21.25)	<0.001
Total Bilirubin (mg/dL)	0.32 (0.3, 0.47)	0.4 (0.32, 0.51)	0.4 (0.3, 0.51)	0.51
Direct Bilirubin (mg/dL)	0.18 (0.12, 0.2)	0.12 (0.1, 0.18)	0.18 (0.1, 0.2)	<0.001
Prothrombin Time (sec)	13.27 (12.9, 13.63)	13.04 (12.15, 13.74)	13.2 (12.7, 13.9)	0.036
Gamma-glutamyl transferase (U/L)	135 (23, 346.19)	0 (0, 41)	0 (0, 0)	<0.001
Erythrocyte Sedimentation rate (mm/hr)	25.59 (24.39, 33)	28.9 (18.54, 42.72)	22 (12.56, 37.88)	0.0003
Iron (mcg/dL)	46.62 (40.9, 56.56)	48.62 (29, 68.25)	42.4 (0, 70)	0.062
Ferritin (mcg/L)	72.54 (25.78, 203.96)	43 (11, 135)	29.62 (0, 80)	0.0004
C-Reactive Protein (mg/L)	3.277 (2.21, 4.98)	1.627 (0, 4.3)	1.195 (0.55, 3.69)	0.02
White Blood Cells (K/µL)	5.362 (4.96, 5.89)	5.85 (4.88, 6.87)	5.56 (4.41, 6.72)	0.026
Hemoglobin (g/dL)	11.76 (11.35, 12.17)	12.27 (11.26, 13.04)	12.23 (11.34, 13.01)	0.157
Platelet Count (K/µL)	219.9 (199.53, 241.41)	243.2 (196.25, 275.25)	236.1 (198.62, 281.5)	0.6
Anti-Nuclear Antibody U)	10.84 (4.48, 12)	7.357 (0.95, 11.91)	4.5 (0.9, 11.3)	0.24
Anti-Ribonucleoprotein Antibody (U)	0.2583 (0.05, 0.54)	0 (0, 0.2)	0 (0, 0.8)	0.021
Medication				
Corticosteroid	6	80	42	<0.001
Hydroxychloroquine	10	89	75	<0.001
Azathioprine	7	48	26	<0.001
Methotrexate	3	24	18	0.003

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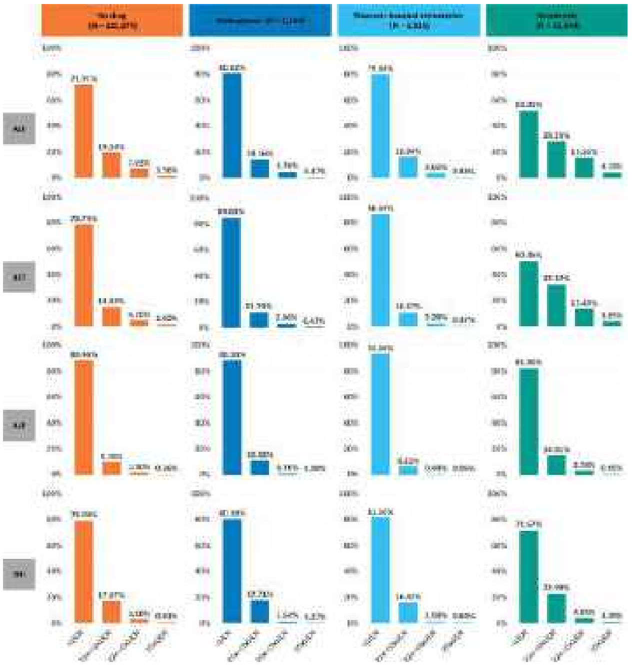
Disclosure information not available at the time of publication: Zerai Manna, Yenealem Temesgen-Oyelakin, Elaine Poncio, Sarfaraz Hasni

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

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

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



Disclosures: Binu V John – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Exact Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Glycotest, Inc: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GSK: Advisor, No, Yes; Astra Zeneca: Advisor, No, Yes; GSK: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;

K Rajender Rajender Reddy – BMS: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Mallinckrodt Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Sequana: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Grifols: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Exact Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; HCC-TARGET: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; NASH-TARGET: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Spark Therapeutics: Consultant, No, No; Novo Nordisk: Consultant, No, No; Genfit: Consultant, No, No; BioVie: Consultant, No, No; Novartis: Advisor, No, No; Astra Zeneca: Advisor, No, No; Associate Editor Gastroenterology: Executive role , No, No; UptoDate: Royalties or patent beneficiary, No, No;

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The following people have nothing to disclose: Dustin R Bastaich, Ashwani K. Singal

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

Masoud Moghtaderi[1]*, Mohammad Ali Nazarinia*[2]*, Saeedeh Shenavandeh*[2]*, Elham Aflaki*[2] *and Maryam Moini*[3]*, (1)Gastroenterohepatology Research Center, Shiraz University of Medical Sciences, (2)Shiraz University of Medical Sciences, (3)University of Ottawa*

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

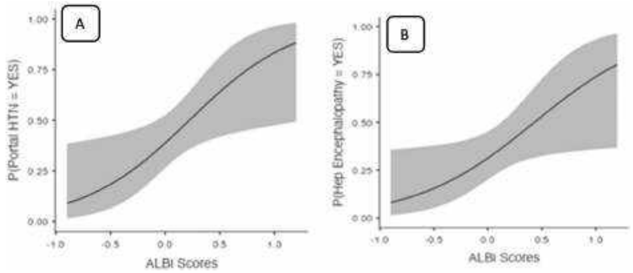
Disclosures: The following people have nothing to disclose: Maryam Moini

Disclosure information not available at the time of publication: Masoud Moghtaderi, Mohammad Ali Nazarinia, Saeedeh Shenavandeh, Elham Aflaki

1800-A | ALBI (ALBUMIN-BILIRUBIN) SCORE AS A USEFUL PREDICTOR OF PORTAL HYPERTENSION AND HEPATIC ENCEPHALOPATHY IN PATIENTS WITH HEPATITIS C CIRRHOSIS

Miriam Mercedes Sanchez[1], Gail Fernandes[2], Natalie Nguyen[2], Stephanie Paduano[2], Geovanny Manuel Gutierrez-Brito[2], Quynh-An Phan[2], Destny Agubuzo[2], Chukwuma Egwim[2] and Victor Ankoma-Sey[2], (1)Liver Associates of Texas, (2)Liver Associates of Texas, P.a.

Background: Hepatitis C Virus (HCV) infection remains a global health problem that can progress to liver cirrhosis. Patients with cirrhosis are subject to a variety of complications related to portal hypertension. The ALBI score has been mainly investigated as a non-invasive method to evaluate liver dysfunction and assess prognosis in patients with hepatocellular carcinoma (HCC). The aim of our study is to determine if there is a correlation between the ALBI score and portal hypertension and ALBI score and hepatic encephalopathy in patients with cirrhosis due to HCV. **Methods:** A retrospective study was conducted for all patients diagnosed with chronic hepatitis C from September 1, 2018, to May 1, 2021, at Liver Associates of Texas, P.A., clinics in Houston, TX. Individual's with chronic hepatitis C (CHC) were identified as patients with a positive anti-HCV antibody and detectable HCV RNA with or without elevated liver transaminases. Patients with chronic liver diseases secondary to causes other than HCV infection were not included. The ALBI score was calculated using the formula: ALBI score = (log10 bilirubin × 0.66) - (albumin × 0.085). A multivariate binomial logistic regression model was employed to demonstrate the correlation of the ALBI score with the presence of portal hypertension and hepatic encephalopathy. A p-value of less than 0.05 was considered significant. **Results:** The study comprised 61 patients diagnosed with cirrhosis due to CHC, of which 43.3% were identified with portal hypertension and 35.6% with a history of hepatic encephalopathy. The ages ranged from 37 to 80 years, with a mean of 61.5 years. ALBI scores were found to positively correlate with the presence of portal hypertension ($p = 0.023$) and hepatic encephalopathy ($p = 0.038$) in patients with cirrhosis secondary to HCV infection. Using a cut-off value of 25%, the ALBI score resulted with a sensitivity of 92.3% and specificity of 8.82% for portal hypertension in patients with HCV cirrhosis. **Conclusion:** This study shows a positive correlation between the ALBI score and both portal hypertension and hepatic encephalopathy in patients with cirrhosis due to chronic HCV infection. This correlation must be further studied in larger populations to determine its prognostic value. The ALBI score only uses two standard laboratory parameters, making it easier to calculate compared to other well-known scoring systems available to assess the severity of liver dysfunction. A high ALBI score may be used as a screening tool to exclude portal hypertension in patients with cirrhosis due to HCV infection. Further studies are needed for a larger cohort of patients to further study the sensitivity and specificity value of the ALBI score in this setting.



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1801-A | AN ARTIFICIAL INTELLIGENCE MODEL FOR PREDICTION OF HEPATOCELLULAR CARCINOMA DEVELOPMENT AFTER ORAL ANTIVIRAL THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C★

Yu Rim Lee[1], Hyun Young Woo[2], Jung Gil Park[3], Min Kyu Kang[3], Jeongeun Song[4], Jang Byoung Kuk[5], Young-Oh Kweon[6], Won Young Tak[7], Se Young Jang[1], Soo Young Park[1], Chang-Hyeong Lee[4], Byung Seok Kim[4], Jaeseok Hwang[8], Woo Jin Chung[5], Jeong Heo[9] and Keun Hur[6], (1)School of Medicine, Kyungpook National University, (2)Pusan National University, (3) Yeungnam University College of Medicine, (4)Daegu Catholic University School of Medicine, (5)Keimyung University School of Medicine, (6)Kyungpook National University, (7)College of Medicine, Kyungpook National University, (8)Keimyung university, (9)Department of Internal Medicine, College of Medicine, Pusan National University, Busan, South Korea

Background: Hepatocellular carcinoma (HCC) can still occur after achieving a sustained virologic response (SVR) to direct-acting antiviral (DAA) therapy in patients with hepatitis C. Several models have been developed to predict risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C. We aimed to develop an artificial intelligence-assisted prediction model of

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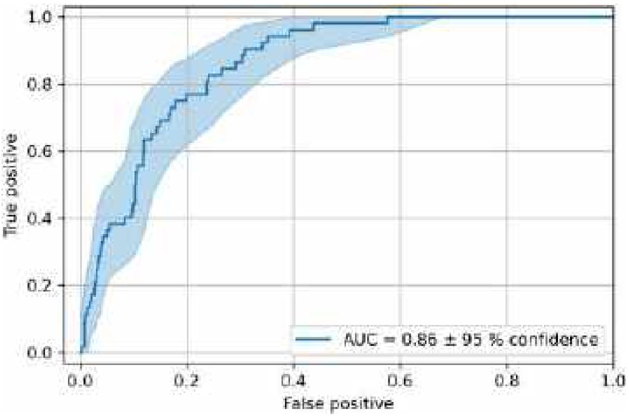
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

HCC risk. **Methods:** A total of 3,489 HCV patients who treated with DAAs and had achieved SVR from ten hospitals in South Korea were included in this study. HCC risk prediction models were developed using machine learning including Decision tree and Gradient Boosting. **Results:** Age, platelet, AST, ALT, bilirubin, and albumin at baseline and 1 year after treatment were determined to be important factors predicting HCC risk. Prediction models using these parameters at baseline and 1 year after treatment was showed good predictive abilities (AUROC values of 0.83 to 0.86). This model showed significantly better discrimination than previous models. **Conclusion:** HCC risk prediction models using machine learning including Decision tree and Gradient Boosting accurately predicted the risk of HCC in patients with chronic hepatitis C who have achieved SVR with DAAs.



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Disclosure information not available at the time of publication: Min Kyu Kang, Jang Byoung Kuk, Young-Oh Kweon, Se Young Jang, Jaeseok Hwang, Keun Hur

1802-A | APPLICATION OF LIVERFAST BIOMARKERS TO EVALUATE LONGITUDINAL HEPATIC FIBROSIS AND INFLAMMATION AFTER HCV CURE

Mati Ullah Dad Ullah[1], Arjun P. Kelaiya[1], Rohullah Rasikh[1], Mehdi Sakka[2], Rana Alkouri[2], Mukarram Jamat Ali[1], Hao Wei Chen[1], Iman Waheed Khan[1], Mina Choudhry[1], Muhammad Ashar Ali[1], Maxime Deregnaucourt[2], Dominique Bonnefont-Rousselot[2,3], Mona Munteanu[4], Ronald Quiambao[4] and Daryl T. Y. Lau[1], (1)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (2)Metabolic Biochemistry Department, Pitié-Salpêtrière Hospital, Public Assistance Paris Hospitals,Aphp Sorbonne University, France, (3)Pharmacy Training and Research Unit (UFR), Paris Cité University; Cnrs, Inserm, Utcbs, France, (4)Fibronostics US Inc, USA

Background: HCV infection is a leading cause of cirrhosis and hepatocellular carcinoma (HCC). Direct antiviral agents (DAA) therapy is associated with > 95% sustained virological response (SVR). It is important to identify patients who continue to be at risk for HCC and liver disease progression after HCV cure. In this study, we applied LIVERFASt to evaluate changes in hepatic fibrosis and inflammation post-DAA therapy and to identify risks for liver disease complications after achieving SVR. **Methods:** This is a retrospective cohort study in a single tertiary liver center. Patients who achieved DAA-induced HCV cure with > 1 year follow up and had serial stored sera from pretreatment were selected. LIVERFASt ™ (Fibronostics) fibrosis and inflammation activity scores were computed for each sample. APRI and FIB-4 scores were correlated with the LIVERFASt fibrosis scores at baseline. Medical chart review was performed to record demographics, HCC, hepatic decompensation, and comorbid liver conditions. **Results:** A total of 40 patients with a follow-up period of 37(17-62) months post-DAA were included. This male predominant (62.5%) cohort had 26 (65%) White, 9(22.5%) Black and 3(7.5%) Asian; 34 (85%) had HCV genotype 1. 28(70%) patients had advanced F3-4 fibrosis prior to treatment. The baseline LIVERFASt fibrosis scores correlated with APRI ($r = 0.56$, $p < 0.0001$) and FIB-4 ($r = 0.48$, $p = 0.001$). At follow up, 23(58%) had **e** 1 stage fibrosis regression, 3 (7.5%) had progressive fibrosis and 14(35%) had no change including 4 with F0-F1 at baseline [Figure 1a]. Prior to therapy, 16(70%) and 8(47%) patients with and without subsequent fibrosis regression had inflammation Activity (A) score **e** 1 grade respectively ($p = 0.15$). At last follow up, 22(96%) patients with fibrosis regression had no inflammation (A = grade 0). In contrast,10(59%) of those without fibrosis regression continued to have inflammation (A = grade 1)

[Figure 1b]. 9(23%) patients developed de-novo HCC between 2.1 and 5.8 years after HCV cure; 8 (F3 = 2, F4 = 6) had advanced fibrosis prior to DAA. At the time of HCC diagnosis, 5 had no fibrosis regression and 1 had progressed to cirrhosis; 4(67%) continued to have inflammation. 3 HCC patients who had fibrosis regression without inflammation had at least 1 episode of hepatic decompensation prior to DAA. Among the remaining 6 non-HCC patients with active inflammation at follow up, 4 had unchanged fibrosis and 2 had fibrosis progression. 3 had pre-existing cirrhosis with portal hypertension, 2 continued active alcohol use and 1 developed autoimmune hepatitis. **Conclusion:** LIVERFASt has prognostic values in monitoring inflammation and fibrosis after HCV cure. Patients who continue to have advanced fibrosis and persistent inflammation after HCV cure remain at risk for HCC and require regular HCC surveillance. Other liver conditions must be considered for those with active hepatic inflammation or progressive fibrosis after successful DAA therapy.

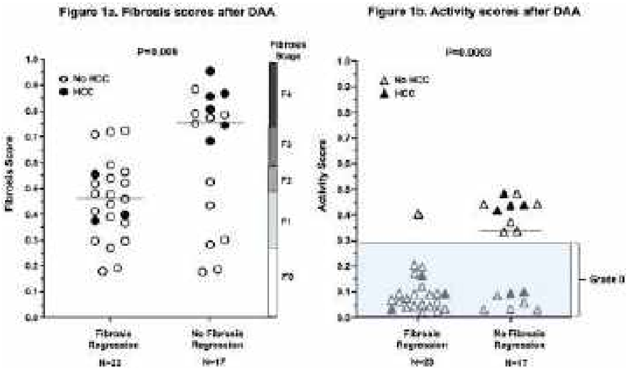

Figure 1a. Fibrosis scores after DAA

Figure 1b. Activity scores after DAA

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1803-A | EARLY READ-TIME PERFORMANCE OF THE ORAQUICK® HCV RAPID ANTIBODY ASSAY FOR THE EXCLUSION OF HCV VIREMIA

Jessie Torgersen[1], Rebecca Russell[2], Julia Gasior[1], Dena Carbonari[1], Nancy Aitcheson[1], David Smookler[3], Camelia Capraru[3], Bettina E. E. Hansen[4], Jordan J. Feld[5] and Vincent Lo Re III[1], (1)University of Pennsylvania Perelman School of Medicine, (2) University of Pennsylvania Health System, (3)Toronto Centre for Liver Disease/Viral Hepatitis Care Network (VIRCAN), University Health Network, Toronto, Canada, (4)Toronto General Hospital University Health Network, Rotterdam, Netherlands, (5)Toronto General Hospital Research Institute

Background: Rapid point-of-care tests for hepatitis C virus (HCV) allow for testing and linkage to care for difficult-to-reach populations. The OraQuick® rapid HCV antibody lateral flow immunoassay (OQ) detects anti-HCV antibodies in blood with results finalized after 20 minutes. Prior work has suggested OQ-positivity beyond 5 minutes could identify people who do not have current HCV viremia; however, these observations have not been externally validated. **Methods:** We conducted a single-center cohort study between June 2021-April 2023 to evaluate the performance of OQ early reading time for the exclusion of HCV viremia among patients with reactive HCV antibody. Consenting adult inpatients and outpatients were screened for HCV antibody using OQ, and those with positive results were tested for HCV RNA. Patients were excluded if there was clinical evidence to suggest likely acute HCV infection. The OQ was used according to the manufacturer's instructions. The presence of both control and test bands was evaluated and recorded at every minute between 5-10 minutes, then at 20- and 40-minutes following dipstick insertion. Performance of an early reading time of the OQ assay was evaluated against the standard-of-care HCV RNA completed as part of routine clinical care. The proportion of participants identified by positive OQ were compared by HCV viremic status. **Results:** The OQ was completed by 155 participants (69.6% male; 18.1% HIV+; median age, 54.3 y) with reactive HCV antibody, including 109 (70.3%) with HCV viremia. Among HCV viremic patients, 105/109 (96%) had a positive OQ by 5 minutes and 108 (99%) had a positive result by 7 minutes. In contrast, 18/46 (39%; $p < 0.0001$) and 22/46 (47.8%; $p < 0.0001$) of HCV nonviremic patients had a positive OQ by 5 and 7 minutes, respectively (Table 1). Among the 25 participants with a negative OQ at 7 minutes, 24 (96%) were HCV nonviremic. The one HCV viremic patient not identified by OQ by 7 minutes was profoundly immunosuppressed due to recent critical illness and HIV; after excluding this participant, both the sensitivity and negative predictive value of the OQ by 7 minutes improved to 100%. Among patients with a positive OQ, there was no time threshold that accurately identified only participants with HCV viremia. **Conclusion:** A negative OQ by 7 minutes reliably excludes HCV viremia, which may reduce the need for RNA testing and improve throughput. Early results (by 7 minutes) cannot be used to exclusively identify viremia and should be used with caution in those with severe immunosuppression or if acute HCV is suspected.

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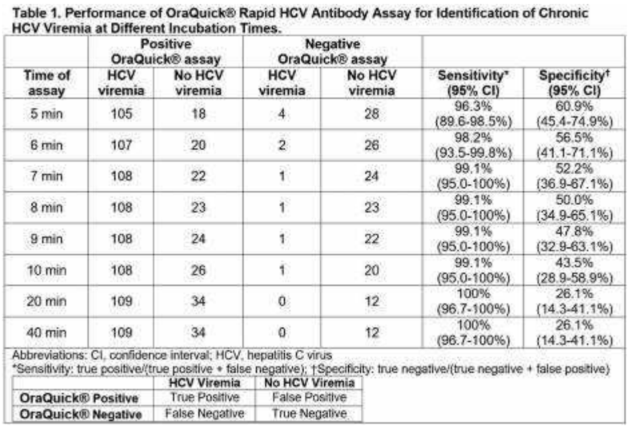

Table 1. Performance of OraQuick® Rapid HCV Antibody Assay for Identification of Chronic HCV Viremia at Different Incubation Times.

	Positive OraQuick® assay		Negative OraQuick® assay			
Time of assay	HCV viremia	No HCV viremia	HCV viremia	No HCV viremia	Sensitivity* (95% CI)	Specificity† (95% CI)
5 min	105	18	4	28	96.3% (89.6-98.5%)	60.9% (45.4-74.9%)
6 min	107	20	2	26	98.2% (93.5-99.8%)	56.5% (41.1-71.1%)
7 min	108	22	1	24	99.1% (95.0-100%)	52.2% (36.9-67.1%)
8 min	108	23	1	23	99.1% (95.0-100%)	50.0% (34.9-65.1%)
9 min	108	24	1	22	99.1% (95.0-100%)	47.8% (32.9-63.1%)
10 min	108	26	1	20	99.1% (95.0-100%)	43.5% (28.9-58.9%)
20 min	109	34	0	12	100% (96.7-100%)	26.1% (14.3-41.1%)
40 min	109	34	0	12	100% (96.7-100%)	26.1% (14.3-41.1%)

Abbreviations: CI, confidence interval; HCV, hepatitis C virus
*Sensitivity: true positive/(true positive + false negative); †Specificity: true negative/(true negative + false positive)

	HCV Viremia	No HCV Viremia
OraQuick® Positive	True Positive	False Positive
OraQuick® Negative	False Negative	True Negative

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Disclosure information not available at the time of publication: Rebecca Russell, Julia Gasior, Dena Carbonari, Nancy Aitcheson, David Smookler, Camelia Capraru, Vincent Lo Re

1804-A | HCC PREDICTION MODELS EFFECTIVELY ASSESS THE RISK OF HCC IN CHRONIC HEPATITIS C PATIENTS WITHOUT ADVANCED FIBROSIS AFTER ORAL ANTIVIRAL THERAPY: A MULTICENTER STUDY

Yu Rim Lee[1], Hyun Young Woo[2], Jung Gil Park[3], Min Kyu Kang[3], Jeongeun Song[4], Byoung-Kuk Jang[5], Young-Oh Kweon[6], Won Young Tak[7], Se Young Jang[1], Soo Young Park[1], Keun Hur[6], Chang-Hyeong Lee[4], Byung Seok Kim[4], Jaeseok Hwang[8], Woo Jin Chung[5], Jeong Heo[9], Nae-Yun Heo[10], Seung Ha Park[10], Junsik Yoon[11] and Yang Hyun Baek[12], (1)School of Medicine, Kyungpook National University, (2)Pusan National University, (3)Yeungnam University College of Medicine, (4)Daegu Catholic University School of Medicine, (5)Keimyung University School of Medicine, (6)Kyungpook National University, (7)College of Medicine, Kyungpook National University, (8)Keimyung university, (9)Department of Internal Medicine, College of Medicine, Pusan National University, Busan, South Korea, (10)Inje University Haeundae Paik Hospital, (11) Busan Paik Hospital, (12)Dong-a University College of Medicine

Background: The current guidelines recommend lifelong ultrasound surveillance for chronic hepatitis C patients with advanced fibrosis or cirrhosis after achieving SVR with DAA therapy. However, there are limited studies on the risk of HCC in patients without advanced fibrosis. Therefore, we aimed to identify high risk group for HCC development using HCC prediction models. **Methods:** This study included 1,839 chronic hepatitis C patients without advanced chronic liver disease from 10 tertiary hospitals who were treated with DAA. Advanced fibrosis was defined as LSM **e** 10 kPa, FIB-4 $>$ 3.25, or APRI **e** 1.5 at baseline. The predictors of HCC occurrence and predictive ability of HCC risk scores were assessed. **Results:** During a median follow-up of 2.8 years, 28 (1.5%) patients developed HCC at a median of 2.77 years. The mean age was 56 years, and 852 (46.3%) patients were male. When the patients were divided into HCC and non-HCC groups, patients who developed HCC during follow-up were significantly older, and had lower platelet count and albumin level before antiviral treatment. In addition, patients who developed HCC had a higher FIB-4 score ($P < 0.001$). Comorbidities, such as diabetes and hypertension, were more common among patients with HCC than those without HCC ($P < 0.05$). In multivariate analysis, old age, platelet count, albumin level, and

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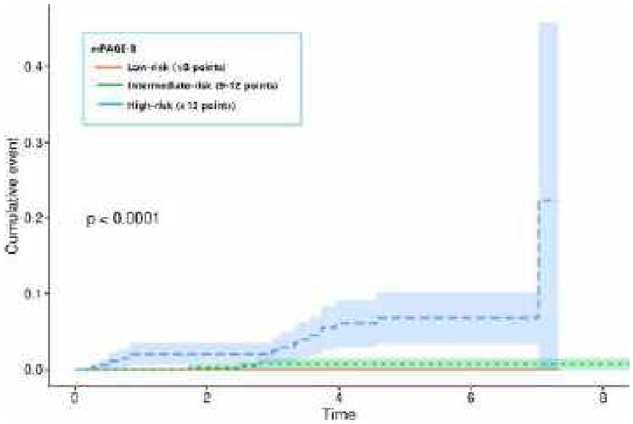
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

sodium level before treatment were significantly associated with the occurrence of HCC (all $P < 0.05$). The high-risk group defined by previously published HCC prediction models showed a significantly high HCC occurrence. This finding was observed in most validated HCC prediction models including aMAP and mPAGE-B, and the incidence of HCC ranged from 1.5% to 7.4% at 3-years and from 3.8% to 24.2% at 5-years at SVR in high-risk patients (Figure). HCC rarely occurred during the first 5-years of follow-up in low and intermediate-risk patients defined by HCC risk scores. **Conclusion:** HCC risk models effectively assess the risk of HCC in chronic hepatitis C patients without advanced fibrosis after achieving SVR. Therefore, even in patients without advanced liver fibrosis before treatment, surveillance should be considered if they are included in the high-risk group of the HCC prediction model.



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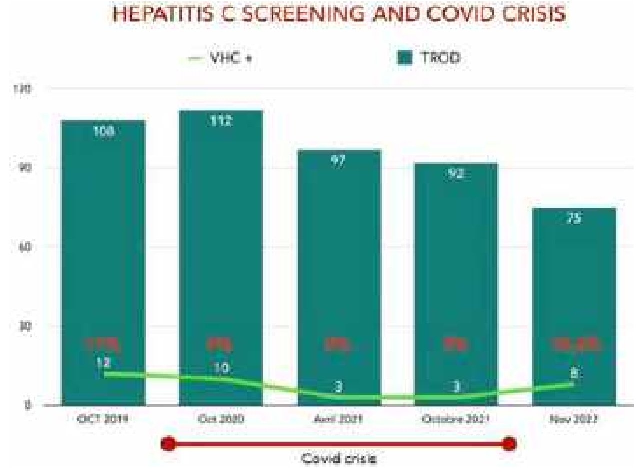
Disclosure information not available at the time of publication: Min Kyu Kang, Young-Oh Kweon, Se Young Jang, Keun Hur, Jaeseok Hwang, Nae-Yun Heo, Seung Ha Park

1805-A | IMPACT OF COVID ON PREVALENCE HEPATITIS C IN FRANCE : 5 SCREENING HCV ACTIONS, BEFORE, DURING AND AFTER COVID-19

Juliette Pont[1], Pascal Melin[2], Laurence Garbet[3], Veronique Monot[4], Jacky Sainty[3], Solange Bresson[5] and AASLD Authors group', (1)SOS Hepatites, (2) Hospital, (3)Sos Hepatites, (4)CHU Dijon, (5)CHU Besançon

Background: In France, it has been estimated that at least 90 000 people are unaware of their HCV infection. Many reports indicated declines in hepatitis C virus (HCV) testing during covid crisis. But, what are the consequences for new contaminations in France? The aim is to compile and analyze the results of 5 roadtrips between March 2020 until the end of 2021 to compare results before Covid, during crisis and one year after is a way to see if they're different. **Methods:** A team made up of caregivers and peers has been carrying out roadtrips for several years to screen people who use drugs (PWUDs) for hepatitis C. Around the same number of people seen, drug users, same addiction centers, the results are absolutely comparable. **Results:** First roadtrip : done during the pre-COVID-19 period (October 2019), 108 HCV antibodies done, 12 RNA + tests with POC, prevalence 11%. Second roadtrip: October 2020, after first confinement, 112 HCV antibodies, 10 RNA + tests, prevalence 9%. Third and forth roadtrip: April and October 2021, after a year and half crisis, results are : 97 and 92 HCV antibodies tests respectively and 3 RNA tests + for each, prevalence 3% and 3,26% respectively. Fifth roadtrip: after Covid, 75 antibodies VHC antibodies tests, 8 RNA+, prevalence 10,7%. Before Covid, during the preliminary interviews, very few drug users said they share injection equipment. They were much more at the last roadtrip, after crisis. Behaviors have changed? Harm reduction centers were more closed during Covid-19? Difficulties to move with the confinements? Hard to say, but results speak for themselves. **Conclusion:** Achieve elimination hepatitis C by 2030 is not certain when if an event like Covid-19 seems to reactivate the epidemic. the years to come will show if behaviors return to the way they were before covid



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The following people have nothing to disclose: Veronique Monot, Solange Bresson

1806-A | INVOLVEMENT OF CIRCULATORY CELL-FREE MITOCHONDRIAL DNA IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION: BEFORE AND AFTER CLEARANCE

Rownock Afruza[1], Adekanyinsola Onitiri[1], Moumita Chakraborty[1], Nicole San-Dee Minerva[1], Maleeha Ahmad[1], Rabab Ali[1], Kareen Hill[1], Grace Zhang[1], Elizabeth Townsend[1], Lisa Scheuing[1], Jenna Leigh Oringher[1], Elliot Levy[2], Ohad Etzion[1], David E Kleiner[3], Christopher Koh[4] and Theo Heller[1], (1)Translational Hepatology Section, Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, (2)Radiology & Imaging Sciences Department, Clinical Center, National Institutes of Health, (3)Laboratory of Pathology, National Cancer Institute, National Institutes of Health, (4) National Institute of Diabetes and Digestive and Kidney Diseases, Nih

Background: Disruption of mitochondrial functions, increased reactive oxygen species production and apoptosis, and decreased mitochondrial DNA content along with inflammation are often associated with HCV infection. We have previously shown the central role of mitochondria and peroxisomes in hepatic metabolic dysregulation during HCV infection and advanced fibrosis. The aim of this project is to investigate the role of circulatory cell free mtDNA (ccfmtDNA) during HCV infection and after clearance in both cirrhotic and non-cirrhotic groups. **Methods:** Peripheral blood was collected before (HCVi, $n = 29$) and after DAA therapy (SVR, $n = 23$), and from healthy controls ($n = 13$) (NCT02400216). Cell-free DNA was extracted from peripheral plasma and used for calculating mtDNA copy numbers via qPCR. Total mtDNA copy numbers were calculated using the average copy numbers for human mitochondrial genes: NADH dehydrogenase 1 (*ND1*), NADH dehydrogenase 6 (*ND6*), Cytochrome C Oxidase III (*COXIII*) and ATP synthase 5A1 (*ATP5A*1). For significance, all $p < 0.05$. **Results:** ccfmtDNA copies were significantly lower in both HCVi and SVR compared to healthy controls. Interestingly, a significant reduction of ccfmtDNA copy numbers in HCVi cirrhotic compared to HCVi non-cirrhotic indicates an effect of fibrosis on mitochondria. ccfmtDNA copy numbers correlated with serum inflammatory (CRP; spearman $r = 0.374$), angiogenesis (Tie-2; spearman $r = 0.374$), and complement (C5a; spearman $r = 0.5327$) markers during HCVi. A correlation was noted between ccfmtDNA copy numbers and c3a (spearman $r = 0.75$, $p = 0.06$) in HCVi cirrhotics, suggesting a relationship between C3a pathway and ccfmtDNA during advanced fibrosis. After SVR, there were correlations between ccfmtDNA copy numbers and serum growth factors (TGFb; $r = 0.4722$ and PDGF-AA; $r = 0.582$) as well as with serum vascular injury marker (sICAM-1; $r = 0.626$), all of which may play a role in tissue repair. There was a significant reduction of ccfmtDNA copy numbers in SVR compared to HCVi. mtDNA copy numbers were not different between SVR non-cirrhotic and cirrhotic, although they were lower in both compared to HCVi non-cirrhotic. **Conclusion:** HCV infection impairs mitochondrial function and lowers copy number of ccfmtDNA compared to healthy controls. A decrease in ccfmtDNA copy number in cirrhotic compared to non-cirrhotic during HCV infection links mitochondrial dysfunction with severe fibrosis. In SVR, there was no increase of ccfmtDNA copy numbers, suggesting regulatory mechanisms other than HCV infection. Elucidation of these mechanisms has potential therapeutic implications beyond chronic HCV infection.

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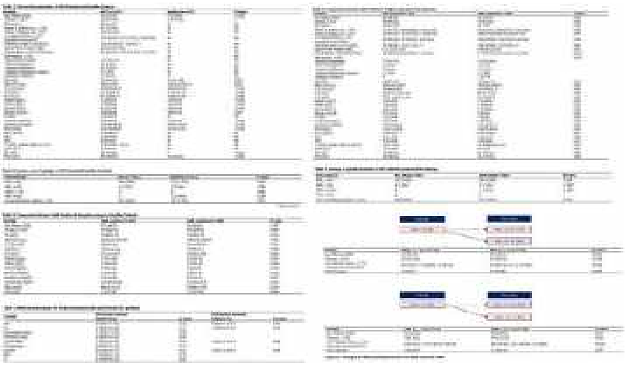
1807-A | POSITIVE RATES OF AUTOANTIBODIES IN CHRONIC HEPATITIS C PATIENTS BEFORE AND AFTER DAA THERAPY: A PROSPECTIVE, MULTICENTER STUDY IN SOUTH KOREA

Su Hyun Choi and Sook-Hyang Jeong, Seoul National University Bundang Hospital

Background: Hepatitis C Virus (HCV) infection causes extrahepatic diseases, involving B-cell dysregulations and autoantibody (autoAb) production. This study aimed to investigate the positive rates of 4 conventional autoAbs (anti-nuclear, anti-smooth muscle, anti-LKM type1, and anti-mitochondrial; ANA, ASM, Anti-LKM1, and AMA, respectively) in the patients with chronic HCV infection (CHC) at 2-time points of pretreatment (PreTx) and at 12 weeks after the end of treatment for evaluation of sustained virological response (SVR) of direct-acting antiviral (DAA) therapy, and compared to those in healthy controls. **Methods:** Using a prospectively collected plasma obtained from 201 CHC patients (median age 62, 49.8% of female, 7.5% of cirrhosis) enrolled in 8 hospitals before and after DAA therapy, ANA, ASM, Anti-LKM1, and AMA were detected by indirect immunofluorescence with cutoff level of 1:80, 1:10, 1:10 and 1:10, respectively, according to the manufacturer's protocols. As a control group, plasma samples from 127 healthy person representative of age and sex standardized Korean adult population (median age 55, 49.6% of female) were obtained from a biobank. The prevalence of these autoAbs was compared between CHC patients at PreTx. and healthy controls, and between at PreTx and at SVR in CHC patients. In addition, clinical variables associated with ANA positivity were analyzed using multivariate logistic analysis. **Results:** The positive rate of ANA in CHC patients was significantly higher than that in healthy controls (32.3% vs 21.3%, p = 0.032) however, ASM (2.0% vs 2.4%), LKM1 (0% vs 0%), and AMA (0% vs 0.79%) were not. In CHC patients, ANA positivity at PreTx tended to decrease at SVR (32.3% vs 23.9%, p = 0.059) In healthy controls, ANA positivity was higher in females than males regardless of age, while in CHC patients, ANA positivity was not associated with sex, but higher globulin level. HCV RNA titer was significantly lower in the any-autoAb positive group (5.69) than the negative group (median 5.69 vs 6.10 log10 IU/mL, p = 0.046), though not an independent factor in multivariate analysis.

The 37 (57%) patients among 65 ANA-positive CHC at PreTx maintained positive at SVR, and 11 (8%) patients among 136 ANA-negative CHC at PreTx converted positive at SVR. In CHC patients who maintained or converted ANA-positive at SVR, were older (67 vs 59, p = 0.013) with higher proportion of cirrhosis or HCC (27% vs 17.9%, p = 0.032). **Conclusion:** In this prospective study, Korean CHC patients showed higher ANA positivity than controls, and PreTx ANA positivity decreased after SVR. However, about half of the ANA-positive CHC patients remained in ANA-positive state and less than 10% of ANA-negative patents turned out to be positive after SVR, mostly older age with higher portion of cirrhosis or HCC.



Disclosures: The following people have nothing to disclose: Su Hyun Choi, Sook-Hyang Jeong

1808-A | VERY LOW DETECTION LIMIT FOR A NOVEL POINT OF CARE TEST OF HCV VIREMIA USING TEMPERATURE-SENSITIVE SMART POLYMER TECHNOLOGY★

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

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Background: We previously developed a novel technology for extraction and enrichment of HCV antigen using a thermo-sensitive smart polymer (NIPAAm-co-HIPAAm-co-SAKIPAAm (Patent: 2019/2002) as a point of care testing which has the same diagnostic accuracy as the gold standard PCR (1). The laboratory-based Roche COBAS®TaqMan® HCV test is able to detect and measure HCV RNA down to 15 international units per ml (IU/ml) with $> 99\%$ sensitivity. Our aim is to determine the target limit of detection (LOD) of this technology. **Methods:** We predefined 60 serum samples subdivided to three groups according to HCV viral load distribution in log 10 IU/ml by (Cobas ampliprep/TaqMan®, Roche); 20 samples with viral load from 500 up to 1000 IU/ml., 20 samples with viral load from 100 up to 500 IU/ml., 20 samples with viral load from < 100 IU/ml. **Results:** Extraction and enrichment of HCV antigen using a thermo-sensitive smart polymer (NIPAAm-co-HIPAAm-co-SAKIPAAm) in all 60 samples yields positive results. The lowest HCV viral load of the study samples is 36 IU/ml. **Conclusion:** The novel thermo-sensitive smart polymer technology was able to detect very low viremia which could be used as an accurate point of care test for diagnosis of HCV viremia when validated in multicentre studies of different ethnicities and genotypes. References: Shiha et al., A novel technology for diagnosis of HCV viremia using thermo sensitive smart polymer: pilot study of a point of care test of HCV compared to polymerase chain reaction test (PCR).Hepatol Int (2023) 17:S1–S267

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1809-A | ZONAL DISTRIBUTION OF MITOCHONDRIAL AND PEROXISOMAL DAMAGE IN CHRONIC HEPATITIS C VIRUS INFECTION AND CIRRHOSIS WITH MITOCHONDRIAL RECOVERY AFTER CLEARANCE

Moumita Chakraborty[1], Maleeha Ahmad[1], Adekanyinsola Onitiri[1], Rownock Afruza[1], Nicole San-Dee Minerva[1], Rabab Ali[1], Elliot Levy[2], Ohad Etzion[3], David E Kleiner[4], Christopher Koh[5] and Theo Heller[1], (1)Translational Hepatology Section, Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, (2) Radiology & Imaging Sciences Department, Clinical Center, National Institutes of Health, (3)Soroka University Medical Center, Beer-Sheba, Israel, (4) Laboratory of Pathology, National Cancer Institute, Bethesda, MD, (5)National Institute of Diabetes and Digestive and Kidney Diseases, Nih

Background: HCV-infected individual's have been shown to have metabolic alterations predominantly localized to mitochondria and peroxisomes. However, the changes in these organelles across different zones of the liver before and after HCV clearance is unclear. Aim: To understand the changes in mitochondria and peroxisomes across liver zones before and after HCV clearance in non-cirrhotic vs cirrhotic patients. **Methods:** HCV patients had a liver biopsy before Phase 1 ($n = 29$), and 1 year after DAA therapy Phase 2 ($n = 23$) (NCT02400216). Immunofluorescence staining was performed on the liver biopsies (Phase 1 Non-Cirrhotic/Cirrhotic and Phase 2 Non-Cirrhotic/Cirrhotic). ATP5A, a classical marker for mitochondria, and Catalase, for peroxisomes, were utilized. Image segmentation analyses were then performed on the confocal microscopy images using LABKIT, a FIJI plugin, to analyze the particle count in the hepatocytes for these two markers. All the images were normalized by the number of nuclei. Mann-Whitney U test ($p < 0.05$) was used for marker comparison between groups. **Results:** Phase 1 cirrhotic patients when compared with non-cirrhotic patients exhibited significantly reduced expression of both ATP5A ($p = 0.007$) and Catalase ($p = 0.03$) in zone 1 hepatocytes, but no significant difference in zone 2 hepatocytes. After clearance of HCV, Phase 2 non-cirrhotic patients showed a significant increase of ATP5A in both zone 1 ($p = 0.0003$) and zone 2 ($p = 0.002$) hepatocytes when compared with Phase 1 non-cirrhotic patients. The Catalase expression was still low in zone 1 ($p = 0.003$) hepatocytes and no significant difference was observed in Zone 2 hepatocytes. Interestingly, when ATP5A levels of Phase 2 cirrhotic patients were compared to Phase 1 cirrhotic patients, significantly elevated levels were observed in both zone 1 ($p = 0.02$) and zone 2 ($p = 0.01$) hepatocytes, while there were no significant changes in Catalase expression. **Conclusion:** ATP5A and Catalase expression in HCV-infected patients are affected in a zonal pattern suggesting the greatest perturbations in the most metabolically active zone, zone 1 and in the patients with the greatest disease progression, those with cirrhosis. Intriguingly, after DAA therapy, there was an increase in ATP5A but a decrease in Catalase expression in zone 1, suggesting improvement of mitochondrial but not peroxisomal function after SVR. These findings suggest that peroxisomes and mitochondria are differentially affected in different liver zones before and after HCV clearance. This has relevance and implications for metabolic function of the liver as disease progresses, suggesting mitochondrial rescue as a possible therapeutic target.

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1810-A | A GLOBAL SURVEY OF PHYSICIAN KNOWLEDGE ABOUT MANAGEMENT OF CHRONIC HEPATITIS C

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Background: Knowledge about disease management can affect patient outcomes. Recent advances in treatment of chronic hepatitis C virus (HCV) may have affected the physicians' awareness and knowledge of HCV guidelines. **Methods:** Providers who treat HCV patients were asked to complete a specifically designed 48-question survey about HCV practice, familiarity with guidelines, attitudes, perception, self-efficacy, and barriers of treatment. **Results:** 183 physicians completed the survey: 32% hepatologists, 39% gastroenterologists, 12% internal medicine, 16% infectious diseases specialists, mean 18 ± 11 years in practice, seeing median (IQR) 50 (20 - 250) patients with HCV annually. When asked to mention all the HCV treatment guidelines they know (95% at least one), guidelines by AASLD, EASL, APASL and WHO were mentioned by 72%, 84%, 11% and 28%. The most common source of guideline knowledge was Internet (48%) then conferences (23%). The most commonly followed guideline was EASL (46%) followed by AASLD (23%). Of the survey completers, 50% reported regularly attending workshops, conferences, or training courses about HCV treatment mostly organized by AASLD, EASL, and UCHID (10-12% each). 91% believed that guidelines for HCV treatment are based on sound evidence but 39% reported inconsistencies; while 90% reported feeling well-informed about guidelines for HCV treatment. There were 94% who believed that post-treatment follow-up is effective for early detection of HCC, cirrhosis, and other complications among treated HCV patients, and 93% recommend their patients to continue with post-treatment follow-up. Regarding specific knowledge, 61% were aware that in patients with advanced fibrosis and cirrhosis, HCV eradication reduces the rate of decompensation but does not abolish the risk of HCC. Before treatment, 79% reported assessing fibrosis stage using only non-invasive tests (NITs), and 12% reported using both NITs and a biopsy. After treatment, 65% of providers ask their non-cirrhotic patients with SVR-12 to repeat ALT and HCV RNA assessments later, 96% would explain the risk of reinfection to patients from high-risk populations, and 87% recommend annual HCV RNA testing to those populations. Overall, 86% believed that there is a need for following up patients who achieved SVR, with the most commonly recommended periods being 6 months for non-cirrhotic and 3 months for cirrhotic patients; however, hepatologists and gastroenterologists more commonly believed that there was no need to follow-up non-cirrhotic patients (49% vs. 28% others). Finally, < 5% reported not telling their HCV patients about post-treatment follow-up or not discussing its potential benefits. **Conclusion:** Participating physicians appear well aware of the current guidelines for treatment and post-treatment follow-up for HCV. Awareness could be lower among providers working in community clinics and/or in locations with limited resources.

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Zobair M. Younossi – Bristol Myers Squibb: Consultant, No, No; Gilead: Consultant, No, No; Intercept: Consultant, No, No; Novo Nordisk: Consultant, No, No; Terns: Consultant, No, No; Merck: Consultant, No, No; Quest: Consultant, No, No; Siemens: Consultant, No, No; Madrigal: Consultant, No, No;

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1811-A | A LOW RATE OF INDIVIDUALS ARE SCREENED FOR HEPATITIS C IN PRIMARY CARE CENTERS IN BARCELONA

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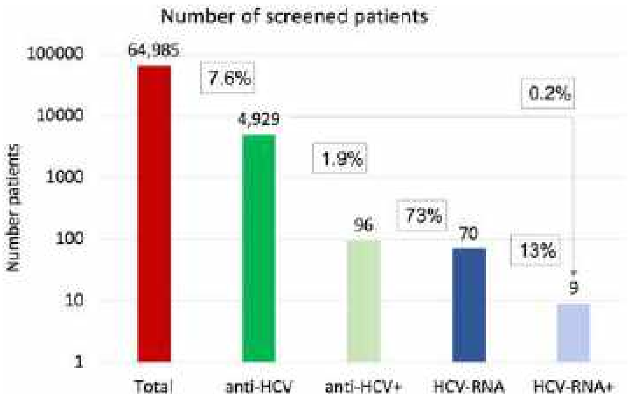
Background: The WHO proposed the elimination of viral hepatitis as a public health threat by 2030. In order to achieve this goal 90% of patients with hepatitis C need to be diagnosed and 80% of these individual's need to be treated. In Spain, it is described that the prevalence of anti-HCV+ and HCV-RNA+ is 0.85% and 0.22% respectively in the general population attending the primary care centers but little data are available on the HCV testing rates. The aim of this study was to assess the percentage of individual's screened for hepatitis C in the primary care centers of the Barcelona northern area and the rates of HCV detection. **Methods:** Retrospective search in the microbiology database of the Barcelona northern area primary care centers to assess the percentage of patients screened for hepatitis C and the percentage of patients anti-HCV+ and HCV-RNA +. Medical records of those HCV-RNA+ patients are being reviewed to identify lost to follow-up patients and link them to care. **Results:** HCV testing data from 2022 were analyzed from six primary care centers from the northern area of Barcelona. A total of 64,985 individual's attended these primary care centers and had a blood test. From these 64,985 patients, only 4,929 (7.6%) were screened for anti-HCV. Anti-HCV antibodies were detected in 96 (1.9%) and HCV-RNA was performed by reflex testing in 70 (73%) of these patients. Nine patients were HCV-RNA+, accounting for 9.37% of the anti-HCV+ patients and a 0.2% of the 4,929 screened patients. 61 patients had indetectable HCV-RNA but 32 (53%) of these 61 patients were previously treated for hepatitis C. Patients with antibodies anti-HCV were 57% male with a median age of 55 years, with basal median AST and ALT of 23 and 25 IU/L respectively and basal FIB-4 and APRI of 1,26 and 0,25, respectively. The 9 positive cases were 77% female, with a median age of 68 years, with basal median AST and ALT of 32,5 and 29 IU/L respectively and basal FIB-4 and APRI of 1,4 and 0,3, respectively. **Conclusion:** A low percentage of individual's are screened for hepatitis C in primary care centers. The majority of those tested positive for anti-HCV antibodies are not viremic.



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The following people have nothing to disclose: Elena Vargas-Accarino, Ariadna Rando, Ingrid Arcusa, Núria García, Elena Monserrat, Marta Selvi, Imma Valls, Carla Ventosa, Juan Carlos Ruiz Cobo

1812-A | CASCADE OF CARE FOR CHRONIC HEPATITIS C IN SOUTH KOREA: A STUDY ON TREATMENT UPTAKE AND BARRIERS

Sang Bong Ahn[1], Dae Won Jun[2], Joo Hyun Oh[3] and Eileen Yoon[2], (1)Nowon Eulji Medical Center, (2) Hanyang University College of Medicine, (3)Eulji Medical Center

Background: The World Health Organization has set ambitious targets for the elimination of hepatitis C virus (HCV) by 2030, aiming to diagnose 90% of people with HCV and treat 80% of those diagnosed. However, significant barriers hinder progress in accessing affordable HCV testing, direct-acting antiviral (DAA) treatment, and effective patient linkage to HCV care. The HCV care cascade plays a crucial role in improving treatment rates. This study aims to examine the cascade of care for chronic hepatitis C patients in South Korea and identify factors impeding treatment.

Methods: We conducted an analysis using data from the Korea Disease Control and Prevention Agency, which registered 8,810 patients with chronic hepatitis C in 2019. We collected and analyzed baseline characteristics, income levels, healthcare facility utilization, actual treatment status, comorbidities, and laboratory test results. **Results:** The proportions of patients diagnosed at primary, secondary, and tertiary healthcare facilities were 26%, 53%, and 21%, respectively. Among all diagnosed patients, 41% did not receive actual treatment. Treatment rates were 11.5% at primary healthcare facilities and 47.3% and 59.4% at secondary and tertiary healthcare facilities, respectively, for patients diagnosed at these respective levels. Among patients diagnosed at primary healthcare facilities, 60% were referred to higher-level facilities, and 80% of those referred received treatment. Treatment rates did not significantly differ by region, but the lowest income group (below 25%) exhibited lower treatment rates. However, income level did not show a proportional relationship with treatment rates. Treatment rates were also lower for elderly patients, those with underlying comorbidity, and patients with liver cirrhosis. **Conclusion:** Treatment uptake for chronic hepatitis C in South Korea falls below optimal levels, posing a challenge to achieving the goal of HCV elimination. Efforts are needed to address barriers that reduce treatment rates and improve the cascade of care for HCV patients.

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Disclosure information not available at the time of publication: Joo Hyun Oh, Eileen Yoon

1813-A | CHANGES OF ADIPONECTIN-LEPTIN RATIO IN CHRONIC HEPATITIS C PATIENTS BEFORE AND AFTER DAA THERAPY: A PROSPECTIVE, MULTICENTER STUDY IN KOREA

Jung Hoon Yoo, Seoul National University Bundang Hospital and Gwang Hyeon Choi, Seoul National University Bundang Hospital, Seoul National University College of Medicine

Background: Some studies suggested an increase of hepatic steatosis after achieving sustained virological response (SVR) in patients with chronic hepatitis C. Recently, adiponectin-leptin (A-L) ratio is proposed as a predictor of CVD risk. Therefore, we investigated the plasma levels of A-L ratio in the Korean chronic hepatitis C patients treated with DAA at 3 time points of pretreatment (PreTx), end-of treatment (EOT) and SVR12. **Methods:** Using a prospectively collected 179 plasma samples at the 3 time points from 179 patients with chronic hepatitis C virus (HCV) infection who were treated with direct acting antivirals (DAAs) (mean age 59.9, 50.3% of female, 29.7% of cirrhosis) enrolled in 8 hospitals from Mar 2020 to Jan 2022, adiponectin and leptin levels were measured and compared. In addition, factors related to low A-L ratio < 0.5, which can be considered high cardiometabolic risk, were analysed. **Results:** All 179 patients achieved SVR12. The A-L ratio showed negative association with pretreatment HCV RNA (R = -0.28, p = 0.017) and body mass index (BMI, R = -0.5, p < 0.001). The median plasma leptin level showed a transient increase of leptin level at EOT compared to PreTx (6.0, 6.6, and 6.0 ng/mL, respectively). The median plasma adiponectin level showed a significant decrease at SVR12 than PreTx level (4.0, 4.1, and 3.5 ug/mL, respectively). The median A-L ratio showed a significant decrease at EOT and SVR12 than preTx level (0.63, 0.63, and 0.56, respectively) The proportion of high CV risk groups with an A-L ratio < 0.5 significantly increased to 39.1%, 44.1%, and 47.2% at PreTx, EOT and SVR12, respectively (p = 0.006). Among normal A-L group (n = 109), pretreatment A-L ratio (OR 0.33, p = 0.024) and BMI is independently associated with transition to low A-L ratio group at SVR12 (OR 1.23, p = 0.048). **Conclusion:** During DAA therapy and achieving SVR, plasma A/L ratio tended to decrease, suggesting potential CV risk after DAA treatment.

Disclosures: The following people have nothing to disclose: Jung Hoon Yoo, Gwang Hyeon Choi

1814-A | CHEMOPREVENTIVE EFFECT OF METFORMIN AND STATIN ON RISK OF HEPATOCELLULAR CARCINOMA AMONG CHRONIC HEPATITIS C PATIENTS WHO FAILED TO ANTIVIRAL THERAPY

Pei-Chien Tsai[1], Chung-Feng Huang[1], Ming-Lung Yu[1,2] and T-COACH Study Group, (1)Hepatobiliary Section, Department of Internal Medicine, and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, (2)School of Medicine and Doctoral Program of Clinical and Experimental Medicine, College of Medicine and Center of Excellence for Metabolic Associated Fatty Liver Disease, National Sun Yat-Sen University, Kaohsiung, Taiwan

Background: Chronic hepatitis C (CHC) patients who failed antiviral therapy are at high risk of hepatocellular carcinoma (HCC), especially among patients with diabetes mellitus (DM). We aimed to investigate if metformin or/and statin can reduce HCC risk among CHC patients with DM and/or hyperlipidemia (HLP) who failed antiviral therapy. **Methods:** CHC patients who failed interferon-based therapy were enrolled in a large-scale, multicenter cohort in Taiwan (T-COACH). HCC 1.5-year after interferon-based therapy was identified by linking to the cancer registry databases from 2003 to

2019. After considering death and liver transplant as competing risks, Gray's cumulative incidence method and Cox subdistribution hazards for HCC development were used. **Results:** Of 2,779 CHC interferon-failed patients, 480 (17.3%) developed new-onset HCC after antiviral therapy. Patients with DM who did not use metformin had a 1.5-fold higher risk of HCC, while those with HLP who used statins had a 47% lower risk of HCC. We redefined HCC risk levels as high-, intermediate-, and low-risk based on the risk number of DM risk [DM non-metformin] and lipid risk [HLP non-statin or non-HLP]. Annual incidence rates of HCC were 519.7 per 10,000 person-years for patients with both risks, 275.2 for patients with only lipid risk, and 117.7 for patients with only sugar risk or no risk. After adjusting for confounding factors, patients with both risks had a 3-fold higher risk of developing HCC, while patients with only lipid risk had a 2-fold higher risk compared to patients with only sugar risk or no risk. **Conclusion:** Among non-SVR CHC patients, metformin use in DM patients or statin use in HLP patients significantly reduced HCC risk after antiviral therapy. A simple risk score based on DM non-metformin use at high risk and HLP statin use at low risk could predict the new-onset HCC among those patients.

Disclosures: The following people have nothing to disclose: Pei-Chien Tsai, Chung-Feng Huang, Ming-Lung Yu

1815-A | COLLABORATIVE IN-HOSPITAL HCV MICRO-ELIMINATION MODEL AND CALL BACK STRATEGY FOR DIAGNOSED BUT UNTREATED PATIENTS IN CHINA

Chunfang You, Yangyang Pu, Wei Deng, Jing Tang, Chunqi Zheng, Xuerong Wang, Yibei Li, Dan Song, Jie Wang and Juan Tang, The First People's Hospital of Zigong, Sichuan, China

Background: We explored an in-hospital and outside hospital model targeting HCV elimination in a tier 3 city in China. The study aimed to evaluate the HCV screening, linkage to care and treatment outcomes with Sofosbuvir/Velpatasvir(SOF/VEL) treatment. **Methods:** The First People's Hospital of Zigong City initiated the collaborative HCV micro-elimination model (in-hospital action plan and call-back program). For the in-hospital patients, all the inpatients and outpatients received HCV screening. Those with anti-HCV positive results would come out pop-up window by operation systems to remind patients to infectious disease (ID) department to receive HCV RNA testing and receive 12-week SOF/VEL treatment if HCV viremic (Figure 1). On the other side, for all the individual's with anti-HCV positive result but untreated, the local primary community hospital called them back. Free HCV RNA testing and HCV education was provided. HCV viremic patients could be linked to the ID specialists once confirmed. With pre-treatment assessment, patients could receive reimbursed SOF/VEL within 1 day. Rate of screening, diagnosis and linkage to treatment would be report back to CDC (Figure 2). **Results:** For in-hospital action plan, a total of 26,235 patients received HCV screening from January to April 2023 and 492 anti-HCV positive individual's were identified. 92%(453/492) patients received HCV RNA testing. 165 patients were HCV viremic and 82.4%(136/165) initiated SOF/VEL treatment. All the patients were under treatment period and follow-up. Before in-hospital model established, only 49.8%(147/295) patients received HCV RNA testing and 74 were HCV RNA positive. The rate of link-to-treatment was only 55.4%(41/74), and 97.6%(40/41) achieved SVR12 after SOF/VEL treatment. For the call-back program, during January to April 2023, a total of 23%(500/2200) patients with anti-HCV(+) were re-linked to care and received HCV RNA testing. 38% (189/500) were HCV RNA positive. 21%(40/189) patients initiated SOF/VEL treatment. **Conclusion:** Screening number and rate of link-to-treatment were significantly improved after cooperation model established. This model could help targeting HCV elimination in low-level cities.

Figure 1. Action Plan for HCV Elimination for outside patients

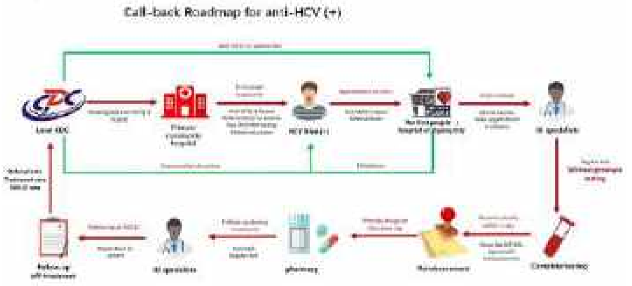

Call-back Roadmap for anti-HCV (+)
Local CDC
Primary community hospital
HCV RNA (+)
ID specialists
pharmacy
ID specialists

Figure 2. Action Plan for HCV Elimination for outside patients

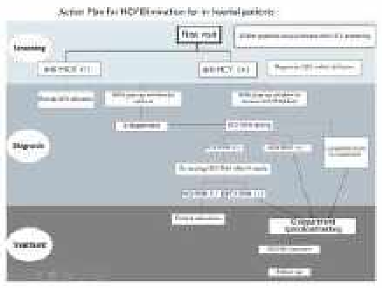
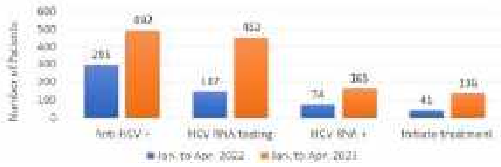


Figure 3. HCV care cascade before and after in-hospital cooperation model

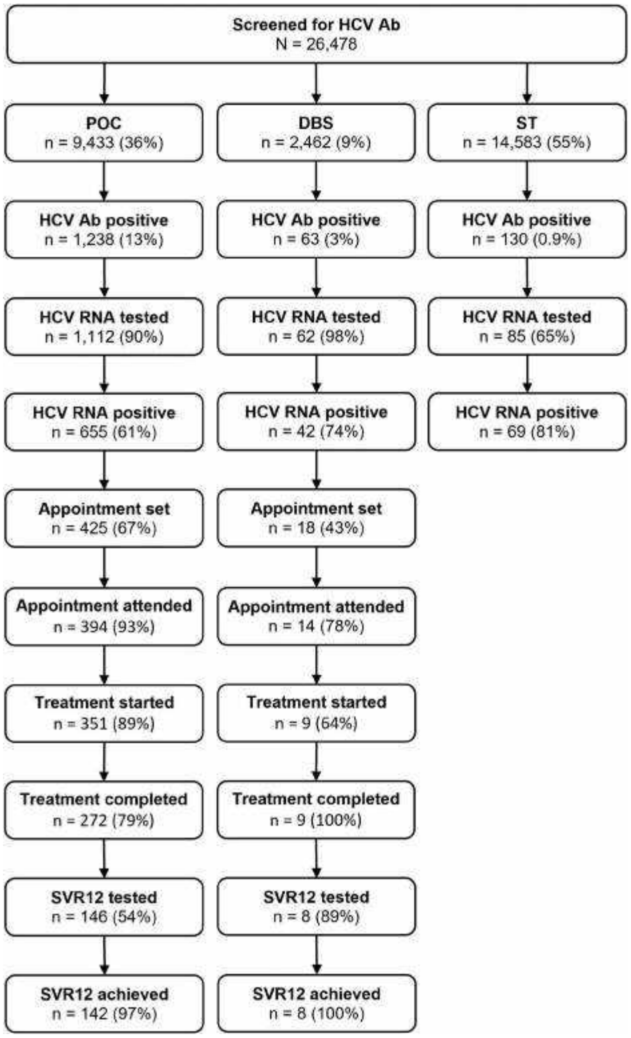


Disclosures: The following people have nothing to disclose: Chunfang You, Yangyang Pu, Wei Deng, Jing Tang, Chunqi Zheng, Xuerong Wang, Yibei Li, Dan Song, Jie Wang, Juan Tang

1816-A | COMPARISON OF HEPATITIS C VIRUS ANTIBODY SCREENING STRATEGIES IN VARIOUS COMMUNITY AND CLINICAL SETTINGS IN ONTARIO, CANADA

Grishma Hirode[1], Brett Wolfson-Stofko[1], Aaron Vanderhoff[1], Camelia Capraru[1], Joel Karkada[1], David Smookler[1], Steven M Friedman[2], Kathy Bates[3], Tony Mazzulli[4,5], Joshua V. Juan[6], Hemant A. Shah[1], Bettina E. Hansen[7], Harry L. A. Janssen[7], Mia Biondi[1,8] and Jordan J. Feld[1], (1)Toronto Centre for Liver Disease/ Viral Hepatitis Care Network (VIRCAN), University Health Network, Toronto, Canada, (2)Department of Emergency Medicine, University Health Network, Toronto, Canada, (3)Emergency Department, Toronto Western Hospital, University Health Network, Toronto, Canada, (4)Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada, (5)Department of Microbiology, University Health Network/Mount Sinai Health System, Toronto, Canada, (6)Albany Medical Clinic, Albany, NY, (7)Erasmus MC, University Medical Center Rotterdam, (8)School of Nursing, York University, Toronto, Canada

Background: Extensive hepatitis C virus (HCV) screening and linkage to care with ongoing patient engagement is vital to prevent transmission and progression to advanced liver disease. Current strategies largely focus on risk-based and population-based screening rather than testing modality. We aimed to analyze the effectiveness of different types of HCV antibody (Ab) testing including point-of-care tests (POC), dried blood spot collection cards (DBS), and phlebotomy-based serologic tests (ST) conducted in a large, real-world cohort across diverse clinical and community settings in Ontario, Canada. **Methods:** Cross-sectional study of individual's who completed HCV Ab testing at various centers in partnership with the Viral Hepatitis Care Network (VIRCAN). HCV RNA testing used DBS for POC and DBS Ab, and phlebotomy-based tests for ST (no reflex testing). Similar to ST, turnaround time for DBS was ~2 weeks for Ab and RNA. Test settings included primary care or HIV pre-exposure prophylaxis clinics (PC/PrEP), emergency department or walk-in clinics (ED/walk-in), one-time screening events (SE), community outreach programs (CO), and drug treatment centres (DC). **Results:** Among 26,478 individual's HCV Ab tested, 36% were POC, 9% were DBS, and 55% were ST (figure). By setting, SE, CO, and AC largely used POC (e 95%), PC/PrEP used ST (92%), and ED/walk-in used a combination of POC (38%) and DBS (62%). Overall HCV Ab prevalence was 5.4% (n = 1,431); 13% among POC, 3% among DBS, and 0.9% among ST. Among HCV Ab positives, 62% were newly identified infections of which 79% were POC (n = 708), 7% were DBS (n = 58), and 14% were ST (n = 122). After an HCV Ab positive test, POC and DBS had higher proportions of RNA tests completed compared to ST. After an HCV RNA positive test result, POC had better engagement in the cascade of care compared to DBS, particularly in setting the first appointment across settings. No linkage to care data was available for ST. **Conclusion:** POC and DBS are feasible and effective alternatives to conventional screening methods and improve linkage to care. POC Ab testing was most effective for identifying new HCV Ab infections but POC and DBS both improved HCV RNA testing compared to ST. Quicker turnaround using POC likely increased patient engagement by efficiently setting up the first appointment after an RNA positive result. Given that the type of Ab test was closely related to setting and available resources, matching the optimal Ab screening modality to the test setting will be critical to reach elimination targets.


Screened for HCV Ab
N = 26,478
POC
n = 9,433 (36%)
DBS
n = 2,462 (9%)
ST
n = 14,583 (55%)
HCV Ab positive
n = 1,238 (13%)
HCV Ab positive
n = 63 (3%)
HCV Ab positive
n = 130 (0.9%)
HCV RNA tested
n = 1,112 (90%)
HCV RNA tested
n = 62 (98%)
HCV RNA tested
n = 85 (65%)
HCV RNA positive
n = 655 (61%)
HCV RNA positive
n = 42 (74%)
HCV RNA positive
n = 69 (81%)
Appointment set
n = 425 (67%)
Appointment set
n = 18 (43%)
Appointment attended
n = 394 (93%)
Appointment attended
n = 14 (78%)
Treatment started
n = 351 (89%)
Treatment started
n = 9 (64%)
Treatment completed
n = 272 (79%)
Treatment completed
n = 9 (100%)
SVR12 tested
n = 146 (54%)
SVR12 tested
n = 8 (89%)
SVR12 achieved
n = 142 (97%)
SVR12 achieved
n = 8 (100%)

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

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Jordan J. Feld – AbbVie: Consultant, No, No; AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Eiger: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Consultant, No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GSK: Consultant, No, No; Janssen: Consultant, No, No; Janssen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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Disclosure information not available at the time of publication: Brett Wolfson-Stofko, Aaron Vanderhoff, Camelia Capraru, Joel Karkada, David Smookler, Steven M Friedman, Kathy Bates, Tony Mazzulli, Joshua V. Juan, Hemant A. Shah, Mia Biondi

1817-A | COMPLEXITY OF HCV PATIENTS ATTENDED AT ADDICTION SETTING IN REAL-WORLD PRACTICE. RESULTS FROM COMPLEXADIC STUDY

Francisco Pascual Pastor[1], *Rosario Ballesta Gómez*[2], *Juan Jesus Ruiz*[3], *Joan Colom*[4], *María Yébenes*[5] *and Miguel Angel Casado*[5], *(1)Socidrogalcohol, (2)Jefatura De Inclusión Social y Gestión Del Conocimiento De La Agencia De Servicios Sociales y Dependencia De Andalucía, (3)Centro Provincial De Drogodependencias (CPD) De Málaga, Diputación De Málaga, (4) Subdirector General De Adicciones, VIH, Its y Hepatitis Víricas. Agència De Salut Pública De Catalunya. Generalitat De Catalunya, (5)Pharmacoeconomics & Outcomes Research Iberia (PORIB)*

Background: To achieve WHO HCV elimination is necessary to target people who use drugs. Complexadic study aimed to describe the profile of user with HCV at addiction center (AC) to understand their special needs and to guide it toward HCV elimination. **Methods:** Anonymous, online, cross-sectional survey aimed at healthcare professionals (HP) from AC with experience in addictive disorders patients in Spain. All addiction specialists belonging to AC that attended at least 50 drug users/year were considered. The survey collected characteristics of HCV patients attended at AC and their patient´s journey. The survey questions were answered by HP based on their last 3 years of experience, without reviewing the patient's medical record. **Results:** Eighty questionnaires were included in the analysis. More than half (58%) of users with HCV were on opioid substitution treatment and 28% were injecting drug users. The main illegal substances consumed were cannabis (53%) and heroin (45%). The mean age of the patients was 45 years; 85% were men. 51% presented psychiatric comorbidities: major depressive disorder (36% of patients), anxiety (35%) and personality disorders (31%). The most frequent organic pathologies were pulmonary disease and HIV (both 23%) and heart disease (10%). Polypharmacy was common, with 67% of patients receiving 3 or more medications. 49% take more substances or medications than they say at the first visit. According to the most important characteristics of HCV medication that could have an impact on adherence and persistence of addiction patients, HP highlighted efficacy even if the

patient forget any dose, number of tablets per day and treatment duration (50.8%, 35.8% and 26.2% of professionals rated each characteristic individually, respectively). When HP were asked about the combined characteristics of HCV medication that best suited the addiction patient profile, 77.5% selected the therapeutic option of one tablet/day, with or without meal co-administration for 12 weeks, while the remining 22.5% selected the option of 3 tablets/day (single dose), with meal co-administration, for 8 weeks ($p < 0.001$). **Conclusion:** HCV drug users present a complex profile, including organic, addictive, and psychosocial problems that require an interdisciplinary approach. HCV treatment simplifications would be key to favour treatment adherence and persistence. Integrating AC into the health circuit is key to achieve the elimination of HCV in these patients

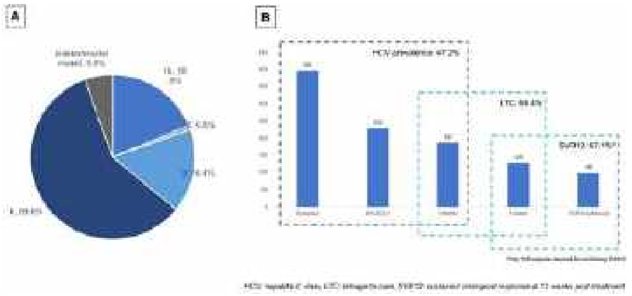
Disclosures: Francisco Pascual Pastor – Gielad: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;

The following people have nothing to disclose: Rosario Ballesta Gómez, Juan Jesus Ruiz, Joan Colom, María Yébenes, Miguel Angel Casado

1818-A | CONQUERING HEPATITIS VIA MICRO-ELIMINATION (CHIME) PROGRAM FOR CHRONIC HEPATITIS C INFECTION IN HIGH-RISK POPULATIONS IN HONG KONG: FINAL RESULTS

Lung Yi Mak[1], Wai Pan To[2], Vivien Tsui[2], Ka-Yin Hui[2], Trevor Kwan-Hung Wu[2], Anthony Kwok[2], Kwan-Lung Ko[2], Danny Ka-Ho Wong[1], Siu-Yin Wong[2], Kevin Sze Hang Liu[1], Wai-Kay Seto[3] and Man-Fung Yuen[4], (1) Department of Medicine, School of Clinical Medicine, the University of Hong Kong, Hong Kong SAR, (2)The University of Hong Kong, (3)Department of Medicine, School of Clinical Medicine, the University of Hong Kong, (4)State Key Laboratory of Liver Research, the University of Hong Kong, Hong Kong SAR

Background: To achieve elimination of hepatitis C virus (HCV) infection, targeted screening of HCV among high-risk groups is a reasonable approach. We aimed to screen for HCV and provide linkage to care (LTC) for high-risk populations in Hong Kong. **Methods:** Between 2019 and 2021, we initiated the Conquering Hepatitis vIa Micro-Elimination (CHIME) program involving outreach visits to halfway house or drug rehabilitation centers run by non-governmental organizations in Hong Kong. Subjects with history of illicit drug use, needle sharing, or prior imprisonment were included. We performed point-of-care (POC) test for antibody to HCV (anti-HCV), and reflex HCV RNA testing by formal venipuncture. Viraemic subjects were invited to attend the LTC clinic for counselling and treatment with direct acting antiviral (DAA). **Results:** 22 site visits were conducted and 396 subjects were screened. A total of 229 subjects had positive POC (57.8% anti-HCV+), while 187 subjects were found to have HCV infection (47.2% RNA+). Among 187 viraemic subjects, 128 (68.4%) attended LTC (median waiting time: 23.9 weeks) and 59 (31.6%) defaulted the clinic visits. The median age was 50 (interquartile range, 43-57), with 93% male; 79.7% reported needle sharing. All of them were smokers and heterosexual, with the majority of them having multiple sexual partners (74.3%), being unmarried (69.5%), heavy drinkers (53.1%), and with history of tattoos (54.7%). All of them were willing to receive DAA treatment, although only 44.5% was aware of HCV infection prior to the program. The most predominant genotype was 6 (58.6%) (Figure 1A). Two-thirds (70.3%) had abnormal alanine aminotransferase (ALT) and 16.4% subjects were cirrhotic (defined by liver stiffness e 12.5 kPa at transient elastography, with only 1 being Child Pugh class B/C). Co-infection with hepatitis B virus was found in 4.7%. Post-treatment blood was checked in 102 subjects (default rate 20.3%), with sustained virological response (SVR) achieved in 97.1% (99/102); Figure 1B. No serious side effects were reported, and 90% achieved normalization of ALT after DAA. **Conclusion:** The CHIME program successfully identified high risk populations with HCV in Hong Kong. The prevalence of chronic HCV is > 45% with distinct socio-demographic features. Although these subjects are prone to non-engagement, for those who were successfully linked to the care system, all had high intention to receive treatment which resulted in a high rate of SVR. Figure legend: 1A: Genotype distribution among HCV+ subjects attending the LTC clinic 1B: Proportion of subjects with active HCV infection, being linked to care, and achieved SVR12



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Man-Fung Yuen – Abbvie: Consultant, No, No; Aligos Therapeutics: Consultant, No, No; Antios Therapeutics: Consultant, No, No; Arbutus Biopharma: Consultant, No, No; Arrowhead Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Arrowhead Pharmaceuticals: Consultant, No, No; Assembly Biosciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Assembly Biosciences: Consultant, No, No; Clear B Therapeutics: Consultant, No, No; Dicerna Pharmaceuticals: Consultant, No, No; Finch Therapeutics: Consultant, No, No; Fujirebio Incorporation: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Fujirebio Incorporation: Consultant, No, No; GSK: Consultant, Yes, No; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences: Consultant, No, No; Immunocore: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Immunocore: Consultant, No, No; Janssen: Consultant, No, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Consultant, No, No; Roche: Speaking and Teaching, No, No; Sysmex Corporation: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck Sharp and Dohme: Consultant, No, No; Merck Sharp and Dohme: Speaking and Teaching, No, No; Vir Biotechnology: Consultant, Yes, No; Bristol Myers Squibb: Consultant, No, No; Springbank Pharmaceuticals: Consultant, No, No; Silverback Therapeutics: Consultant, No, No; Sysmex Corporation: Consultant, No, No; Bristol Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck Sharp and Dohme: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Springbank Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AbbVie: Speaking and Teaching, No, No; Dicerna Pharmaceuticals: Speaking and Teaching, No, No; Fujirebio Incorporation: Speaking and Teaching, No, No; Gilead Sciences: Speaking and Teaching, No, No; Roche: Speaking and Teaching, No, No; Sysmex Corporation: Speaking and Teaching, No, No;

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1819-A | COST-EFFECTIVENESS AND HEALTH-RELATED OUTCOMES OF ONE-TIME SCREENING AND TREATMENT FOR HEPATITIS C IN KOREAN POPULATION: A PILOT PROJECT FOR HEPATITIS C SCREENING

Young Chang, Soonchunhyang University

Background: As a part of a pilot project for early detection of hepatitis C patients in Korea, hepatitis C screening was temporarily performed in 56-year-old general population in Korea. This study investigated the cost-effectiveness of one-time screening and treatment strategy for hepatitis C patients as compared to no screening or risk-based screening strategies. **Methods:** From September 1, 2020 to October 31, 2020, 56-year-old general Korean population received hepatitis C virus (HCV) antibody (Ab) tests at the national general health checkup, followed by HCV RNA tests for HCV Ab-positive subjects as a confirmatory test. To model different screening and treatment strategies for hepatitis C patients, a Markov disease progression model with screening and treatment decision tree was used. The screening strategies included "Scree-all", "Risk-based screening", and "No screening" strategies followed by treatment. Treatment strategies included 8 or 12 weeks of ledipasvir/sofosbuvir and 8 weeks of glecaprevir/

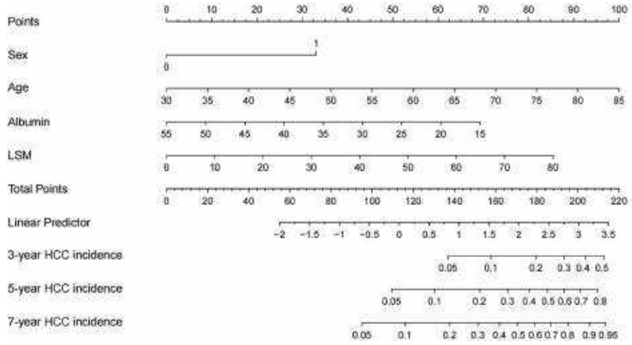
pibrentasvir. Model inputs were primarily sourced from the results of the hepatitis C screening pilot project, and from published literature. **Results:** A total of 133,705 subject, 104,918 subjects received hepatitis C screening test with acceptability of screening rate of 78.47%. Of the 104,918 examinees, 792 cases (0.75%) were positive for HCV Ab and 189 cases (0.18%) were positive for HCV RNA. The acceptability of treatment is estimated to be 70.34% based on the results of the survey. In cost-effective analyses, the screen-all strategy led to the lowest rates of advanced liver disease events. When screening with the screen-all strategy, compared to the no-screening strategy, compensated cirrhosis was expected to decrease by 50%, decompensated cirrhosis by 48%, hepatocellular carcinoma by 49%, liver transplantation by 43%, and death by 49%. The incremental cost-effectiveness ratio (ICER) of the screen-all strategy compared to the no screening strategy was $7,258/quality-adjusted life-year (QALY), which was much lower than the cost-effectiveness threshold of gross domestic product per capita, $31,846. When compared with the risk-based strategy, the screen-all strategy was consistently cost-effective with ICER of $7,080/QALY. In both deterministic and probabilistic sensitivity analyses, the cost-effectiveness of the screen-all strategy over the no screening or risk-based screening strategies was robust in all situations. **Conclusion:** Screening all 56-aged Korean population once followed by effective treatment is expected to reduce the incidence of adverse liver disease and is cost-effective when compared with risk-based screening or no screening.

Disclosures: The following people have nothing to disclose: Young Chang

1820-A | DEVELOPMENT AND VALIDATION A RISK MODEL OF HEPATOCELLULAR CARCINOMA FOR PATIENTS WITH ADVANCED FIBROSIS AND CIRRHOSIS WHO ACHIEVED SUSTAINED HCV CLEARANCE

Shanshan Xu[1], Lixia Qiu[1] and Jing Zhang[2], (1)Beijing Youan Hospital Capital Medical University, Beijing, China, (2)Beijing Youan Hospital, Capital Medical University

Background: Hepatitis C patients with advanced fibrosis or cirrhosis are at high risk of developing hepatocellular carcinoma (HCC) even after sustained virological response (SVR). Clinical guidelines recommend lifelong screening for HCC every six months, which places a heavy burden on them. We aimed to stratify the risk of HCC accurately and refine the current screening strategy. **Methods:** A total of 551 adult hepatitis C patients with baseline advanced fibrosis or cirrhosis after SVR were included and followed-up every six months. The patients were randomized into a derivation cohort (70%, n = 385) and an internal validation cohort (30%, n = 166). A total of 221 similar patients from another hospital served as the external validation cohort. Demographic data, medical history, and laboratory results were recorded. HCC was diagnosed using radiography, alpha-fetoprotein (AFP), or liver histology. Advanced fibrosis and cirrhosis were diagnosed by liver stiffness measurement (LSM) or clinical manifestations. **Results:** The derivation cohort's median follow-up period was 66.60 ± 12.28 months, during which 37 (9.61%) patients developed HCC. Older age (HR: 1.08, 95% CI 1.01-1.15, $p = 0.029$), male gender (HR: 2.41, 95% CI 1.15-5.03, $p = 0.020$), baseline serum albumin levels (HR: 0.88, 95% CI 0.82-0.94, $p = 0.000$), and LSM (HR: 1.02, 95% CI 1.00-1.05, $p = 0.032$) were all independent predictors of HCC development. The derivation cohort's Harrell's C-index was 0.81. The time-dependent AUROC of the model at 3-, 5- and 7-year were 0.84 (95% CI 0.80-0.88), 0.83 (95% CI 0.79-0.87) and 0.81 (95% CI 0.77-0.85), respectively ($p > 0.05$). Patients could be classified as low, intermediate, or high risk based on the prediction model. The three groups had annual HCC incidence rates of 0.18%, 1.29%, and 4.45%, respectively ($p < 0.05$). **Conclusion:** We developed and validated a model for predicting HCC risk in patients with advanced fibrosis or cirrhosis at baseline and after SVR. The model can stratify patients based on their HCC risk and, as a result, determine an appropriate screening strategy based on their HCC risk.



Disclosures: The following people have nothing to disclose: Shanshan Xu, Lixia Qiu, Jing Zhang

1821-A | DIFFERENCES IN BASELINE CHARACTERISTICS OF DIRECT ACTING ANTIVIRAL (DAA)-TREATED GREEK HCV PATIENTS ACCORDING TO SOURCE OF INFECTION

Spyros Siakavellas[1], Charikleia Kranidioti[1], Anastasia Kourikou[1], Charalampos Karageorgos[1], Anestis

Goulas[1], Sofia Vasileiadi[1], Georgios Kontos[1], Nikolaos Papadopoulos[1], Maria Melanie Deutsch[1], Spilios Manolakopoulos[1] and Heraclis Authors Group, (1) Geniko Nosokomeio Athinon "Hippokratio" Athens, Greece

Background: With the introduction of direct-antiviral medication (DAAs), eradication of HCV infection is considered now an achievable goal. While people with history of drug use (PWHD) form the most common population at risk for the infection, in Greece historically there has been a significant proportion of patients arising from the general population with no prior drug use. These two different subgroups exhibit different characteristics, that may be pertinent in the management of HCV infection and long-term follow up. The aim of this study was to identify potential differences in the makeup of these two HCV patient subgroups. **Methods:** The HERACLIS cohort, is the largest national HCV registry of patients treated with DAAs in tertiary liver centers from 2015 until 2022. Clinical data and characteristics were obtained from medical records, while transient elastography (TE) measurements and APRI and FIB-4 score calculations were conducted at baseline. Patients were followed up initially for the duration of their treatment. **Results:** 680 patients were included in the study, 70.9% ($n = 482$) of them were men with median age 50.8 years old and 13.6% of these had decompensated liver disease at DAA initiation. 62% ($n = 422$) of this cohort were PWHD, while the rest had been infected in another manner (nonPWHD). When comparing these two populations, PWHD were younger in age (47.3 ± 9.8 vs 56.3 ± 12.8 years, $p < 0.001$) and with lower BMI (24.3 ± 4.2 vs 26.1 ± 4.6 kg/m2, $p < 0.001$). NonPWHD cases had more often diabetes (4.9% vs 1.3%, $p < 0.001$), hypertension (10.7% vs 8.8%, $p < 0.001$) as well as decompensated liver disease (8.0% vs 5.6%, $p < 0.001$). This was also reflected by TE measurements (14.6 ± 11.1 vs 11.3 ± 7.9 kPa, $p = 0.001$) and FIB-4 score calculations (2.8 ± 2.6 vs 2.2 ± 4.0 vs, $p < 0.001$) but not by the APRI score. Moreover, PWHD patients tended to have been more often infected with genotype 3 (36.8% vs 8.8%, $p < 0.001$) while for other genotypes no such stark differences were observed. There was no significant variance observed regarding DAA regimen use but non-PWHD patients tended to suffer more often from adverse events secondary to DAA treatment (1.6% vs 0.3%, $p = 0.001$). **Conclusion:** The Greek PWHD and non-PWHD populations of HCV patients seem to exhibit different baseline characteristics which may be relevant to treatment selection and long-term follow up regimens. The main differences observed imply the concomitant presence of an element of metabolic syndrome in the non-PWHD cohort with a subsequent potential effect on the degree of underlying liver fibrosis.

Disclosures: The following people have nothing to disclose: Spyros Siakavellas, Charikleia Kranidioti, Anastasia Kourikou, Charalampos Karageorgos, Anestis Goulas, Sofia Vasileiadi, Georgios Kontos, Nikolaos Papadopoulos, Maria Melanie Deutsch, Spilios Manolakopoulos

1822-A | ETHNIC DISPARITIES IN HCV-RELATED EXTRAHEPATIC MANIFESTATIONS: A POPULATION-BASED STUDY IN BRITISH COLUMBIA, CANADA

Dahn Jeong[1], Stanley Wong[2], Héctor Alexander Velásquez García[1,3], Prince Asumadu Adu[3], Jean Damascene Makuza[1], Sofia R. Bartlett[1,3], Eric M. Yoshida[1], Alnoor Ramji[4], Mawuena Binka[3], Amee R. Manges[1,3], Mohammad Ehsanul Karim[1,5], Amanda Yu[2], Maria Jose Alvarez[2], Mel Krajden[1,2] and Naveed Zafar Janjua[1,2], (1)University of British Columbia, (2)BC Centre for Disease Control, (3)British Columbia Centre for Disease Control, (4)Division of Gastroenterology, University of British Columbia, BC, Canada, (5)St. Paul's Hospital

Background: Chronic hepatitis C virus (HCV) infection often leads to extrahepatic manifestations (EHMs). The risk of EHMs may vary among different ethnic groups due to biological differences and socioeconomic disparities. We examined the differing risk of EHMs in people with chronic HCV, focusing on people of East Asian and South Asian backgrounds in British Columbia (BC), Canada. **Methods:** Using the BC Hepatitis Testers Cohort (BC-HTC) comprising ~1.3 million people tested for HCV from 1990-2015 with linked health administrative data, we identified those diagnosed with chronic HCV infection by March 31, 2020. Participants were followed from their first HCV diagnosis date until incident EHM, death, or study end date (March 31, 2021). We assessed incident chronic kidney disease (CKD), type 2 diabetes (DM), major adverse cardiac events (MACE) and neurocognitive disorders (NCD; dementia, delirium and Alzheimer's disease) using ICD-9/10 diagnostic and procedure codes and treatment dispensation data. Ethnicity was determined based on first and last name using a name recognition software (> 98% specificity for East and South Asian). Persons with prevalent conditions were excluded from analysis for the specific EHM. Cumulative incidence rates were calculated for each ethnic group (East Asian, South Asian, and Other) by HCV treatment status. Multivariable cause-specific competing risk models were used to estimate EHM risks, adjusting for time-varying HCV treatment status, competing mortality risk, and baseline sociodemographic and clinical characteristics. **Results:** The study included 1,372 East Asians, 1,390

South Asians and 37,680 persons of other backgrounds diagnosed with chronic HCV in the BC-HTC. Incident EHMs were more frequent among untreated individual's overall, except for type 2 diabetes. Untreated South Asians had the highest EHM rates per 1000 person-years: CKD (Other 9.1, East Asian 12.5, South Asian 17.3); DM (Other 5.0, East Asian 8.4, South Asian 11.4); MACE (Other 11.6, East Asian 15.0, South Asian 16.2); NCD (Other 9.2, East Asian 9.1, South Asian 10.8). In the multivariable models, compared to untreated Others, untreated South Asians had a higher risk of CKD (adjusted cause-specific hazard ratio [aCSHR] 1.26, 95%CI 1.01-1.57), while treatment reduced the risk for all groups. South Asians had the highest risk of DM (untreated aCSHR 2.03, 95%CI 1.50-2.74; treated aCSHR 1.87, 95%CI 1.50-2.34), compared to untreated Others. East Asians had a lower risk of MACE and NCD compared to Others. **Conclusion:** In British Columbia, East and South Asians with chronic HCV had a differing risk of developing EHMs, particularly elevated for chronic kidney diseases and type 2 diabetes. HCV treatment was able to reduce the risk for incident CKD and MACE but not for type 2 diabetes among South Asians. Tailored interventions and screening programs may benefit East and South Asians living with HCV infection.

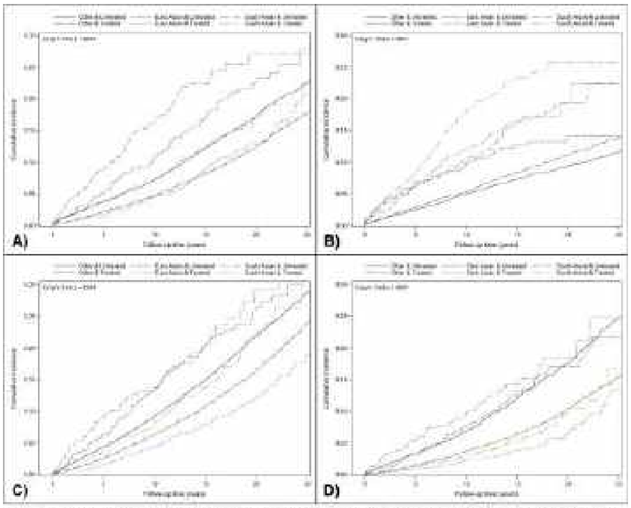


Figure 1. Cumulative incidence curves by ethnicity and treatment status for A) chronic kidney diseases, B) type 2 diabetes, C) major adverse cardiac events, D) neurocognitive disorders, among people diagnosed with chronic HCV infection in British Columbia, Canada

Disclosures: Sofia R. Bartlett – Cepheid: Consultant, No, No; Gilead: Consultant, No, No; Abbvie: Consultant, No, No;

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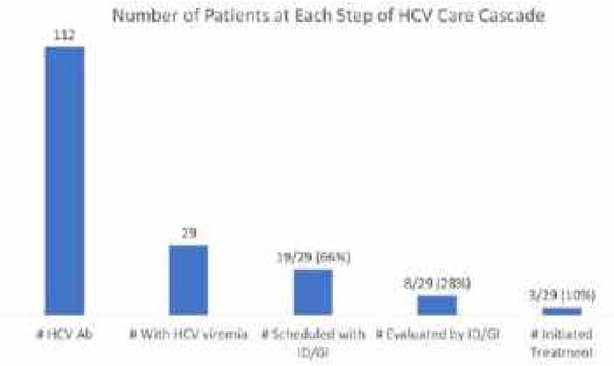
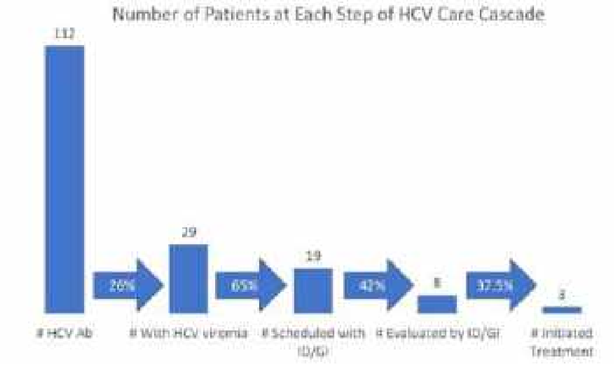
The following people have nothing to disclose: Dahn Jeong, Stanley Wong, Héctor Alexander Velásquez García, Prince Asumadu Adu, Jean Damascene Makuza, Eric M. Yoshida, Alnoor Ramji, Mawuena Binka, Amee R. Manges, Mohammad Ehsanul Karim, Amanda Yu, Maria Jose Alvarez, Naveed Zafar Janjua

1823-A | EVALUATION OF AN OPT-OUT UNIVERSAL HEPATITIS C SCREENING PROGRAM IN THE EMERGENCY DEPARTMENT AND URGENT CARE AT A SINGLE VA HEALTHCARE SYSTEM

Huy Ha[1], Yash Motwani[1,2], Jenna H Kawamoto[1], Neaka Mohtashemi[1,2], Cassandra Coleman Lautredou[1,2], Arpan Arun Patel[1,2], Manuel Celedon[1,2] and Debika Bhattacharya[1,2], (1)Greater Los Angeles VA Healthcare System, (2)University of California, Los Angeles

Background: Universal Hepatitis C Virus (HCV) Screening in the US was recommended in 2020. The objectives of this study were to characterize the HCV care cascade in the Emergency Department following implementation of an opt-out universal HCV screening program in the Emergency Department and Urgent Care Center (ED/UCC) at the Veteran's Affairs Greater Los Angeles Healthcare System (VAGLAHCS), identify barriers to linkage to care, and determine associations of HCV viremia. **Methods:** The assessment period was from September 2021 to September 2022. Baseline characteristics of those who were HCV antibody (Ab) positive were collected, and we identified barriers to linkage to care in those with HCV viremia. We performed Fisher's exact and Chi-square tests to determine associations for HCV viremia. **Results:** 850 Veterans accepted HCV screening. Of the Veterans, 13% (112/850) were HCV Ab positive, and 26% (29/112) had HCV viremia. Of those who were Ab positive, 96% (108/112) were male, 45% (50/112) were White, 42% (47/112) were African American and only 44% (49/112) had stable housing. Regarding comorbid substance use disorder diagnoses, 19% (21/112) had previous or current opioid use disorder, 43% (48/112) had previous or current stimulant use disorder (stimulant UD), and 32% (36/112) had previous or current alcohol use disorder. Ever having a stimulant UD (p = 0.015) was associated with HCV viremia. Of those who had HCV viremia, 65% (19/29) were scheduled with the Infectious Disease (ID) and/or Gastroenterology (GI) clinics, 28% (8/29) were evaluated by ID/GI and 10.3% (3/29) were initiated on HCV therapy. The most common reason for non-linkage to care was the inability to reach the Veteran after discharge in 62% (18/29). **Conclusion:** During a 12-month pilot of opt-out universal ED/UCC HCV screening in a Los Angeles VAMC ED, the HCV Ab prevalence was 13% (112/850), higher than in other similar cohorts. A quarter of those Veterans had active HCV infection. In univariate analysis, ever having a stimulant use diagnosis was associated with HCV viremia. Inability to reach Veterans after discharge was common and led to non-linkage to care. This study highlights the importance of point of care HCV screening and subsequent rapid linkage to care, given the high loss to follow up rates. Future research should focus on novel HCV linkage to care interventions for ED patients that minimize immediate loss to follow up.





Disclosures: Debika Bhattacharya – Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;

The following people have nothing to disclose: Huy Ha, Yash Motwani, Jenna H Kawamoto, Neaka Mohtashemi, Cassandra Coleman Lautredou, Arpan Arun Patel, Manuel Celedon

1824-A | EXPLORING HEPATITIS C VIRUS TRANSMISSION AMONG PEOPLE WHO INJECT DRUGS AND MEN WHO HAVE SEX WITH MEN: RARE AND LIMITED RISK GROUPS IN JAPAN

Zayar Phyo[1], Ko Ko[1], Aya Sugiyama[1], Tomoyuki Akita[1], Kazuaki Takahashi[1], Satoshi Tanaka[2], Ryotaro Sakamori[2] and Junko Tanaka[1], (1)Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima University, Japan, (2)National Hospital Organization, Osaka National Hospital, Osaka, Japan

Background: In Japan, people who injects drugs (PWID) and men who have sex with men (MSM) represent small and rare. Although Japan is on track for elimination of hepatitis C virus (HCV) by the World Health Organization's (WHO) 2030 goal, the epidemiology of HCV among PWID and MSM is very limited and poses a remaining challenge. Therefore, this study aimed to examine the potential existence of cross-transmission of HCV infection among PWID and MSM in Japan. **Methods:** This retrospective cohort study was jointly conducted by Hiroshima University and Gastroenterology Department of National Hospital Organization, Osaka, Japan. We recruited HCV infected patients treated at the hospital between January 2009, and February 2023. Patients who visited the hospital from June 2022 to February 2023 were recruited prospectively with informed consent, while patients who had not visited the hospital until June 2022 were recruited retrospectively through opt-out system. We recruited all patients with either PWID or MSM, or both whereas patients with neither PWID nor MSM were randomly recruited. Stored serum samples collected before anti-HCV treatment was analyzed at Hiroshima University. HCV RNA was extracted, full core region (576 base-pairs) was sequenced by Sanger method and genotype distribution was determined by phylogenetic analysis. The study was approved by the Ethics Review Committee of Hiroshima University and Osaka National Hospital. **Results:** The subjects were divided into four groups: 26 Non-MSM PWID, 14 MSM PWID, 22 MSM Non-PWID, and 42 Non-MSM Non-PWID. Out of 104 samples, 94 could be amplified and sequenced. The most common genotype in Non-MSM PWID was 2a (58%), while in MSM PWID, MSM Non-PWID, and Non-MSM Non-PWID groups, it was 1b (82%, 53%, and 73%, respectively). By phylogenetic analysis, cluster cases were found in MSM group regardless of drug abuse (MSM PWID and MSM Non-PWID) but no cluster case was found in PWID group regardless of homosexuality (MSM PWID and Non-MSM PWID). **Conclusion:** This study explored that MSM group had same HCV transmission route regardless of PWID status, but transmission route was differed in PWID group regardless of MSM status. MSM status determined the transmission route among PWID. Our study suggests that prioritizing control measures on MSM is more crucial than on the PWID for achieving HCV elimination in Japan.

Disclosures: The following people have nothing to disclose: Zayar Phyo, Ko Ko, Aya Sugiyama, Tomoyuki Akita, Kazuaki Takahashi, Satoshi Tanaka, Ryotaro Sakamori, Junko Tanaka

1825-A | HEALTH OUTCOMES OF HEPATITIS C DIRECT-ACTING ANTIVIRALS: BEYOND REAL LIFE SUSTAINED VIRAL RESPONSE DATA

Gloria Sanchez Antolín, Carmen Alonso Martín, Carolina Almohalla Álvarez, Irene Peñas Herrero and Felix Garcia Pajares, Hospital Universitario Rio Hortega

Background: Hepatitis C (HCV) infection was the leading cause of liver transplantation worldwide, causing significant mortality associated with end-stage liver disease. The appearance in 2015 of HCV direct-acting antivirals (DAAs) for the treatment of Hepatitis C with an efficacy close to 100% has changed the natural history of hepatitis C. Its economic impact conditioned the prioritization of its use, initially in more severe patients. Health results of DAA treatment have been described, such as reducing the liver transplant waiting list, but there are no studies on the impact of DAAs on the activity of health systems. The aim of our study is to find out if new DAA-based treatments for hepatitis C have had an impact on the outcomes of a healthcare system. We analyzed the evolution of hospital discharges of patients with a primary diagnosis of hepatitis C, hospital discharges for hepatocellular carcinoma, and hospital discharges for other causes with an additional diagnosis of hepatitis C. **Methods:** The number of hospital discharges from 2012 to 2022 was analyzed, selecting patients with hepatitis C as primary or secondary diagnosis. The information of the admitted patients was obtained from the minimum basic set of hospital discharge data. We also analyzed the average number of discharges due to hepatocellular carcinoma or bile duct neoplasm in the same period and compared the average number of discharges for the period 2012-2015 with the average for 2016-2020. **Results:** Hospital discharges associated with HCV infection decreased progressively from 2015 to 2022. The average number of discharges in the period 2012-2015 was significantly higher than that of 2016-2020 for patients admitted for any reason with a diagnosis of hepatitis C associated (2327.5 vs. 1505.2, $p < 0.005$). The mean number of discharges due to hepatocarcinoma and cholangiocarcinoma was also significantly higher in the first period (95.5 vs. 72.8, $p < 0.05$). The % variation of hospital discharges compared to 2012 was -32.74% in 2015, -40.93% in 2016, -44.84 in 2017, -55.52% in 2018, -53.38 in 2019 and -61 .57% in 2020. The average age ranged from 54 years old in the 2012-2015 period to 57 in the 2016-2020 period. **Conclusion:** The introduction of direct-acting antivirals (DAAs) for the treatment of chronic hepatitis C infection (HCC) has led to a significant decrease in the number of hospital discharges for hepatitis C-related diseases. The variation in hospital discharges since 2012 represents a drop of up to 60% in 2022. A progressive decrease in the number of discharges due to hepatocellular carcinoma and other causes with an additional diagnosis of HCV was also demonstrated. Most of the hospital discharges of patients with HCV due to other causes were classified in ICD10 group 9: diseases of the digestive system, followed by group 1: infectious and parasitic diseases, and group 2: neoplasms. Our study demonstrates the efficacy of DAAs on health outcomes.

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Disclosure information not available at the time of publication: Carmen Alonso Martín, Irene Peñas Herrero, Felix Garcia Pajares

1826-A | HEPATITIS C CIRRHOSIS IS ASSOCIATED WITH AN INCREASED RISK OF DEVELOPING GASTROESOPHAGEAL REFLUX DISEASE AND ITS COMPLICATIONS: RESULTS FROM A NATIONAL HEALTHCARE DATABASE

Samantha Mathialagan[1], Benjamin Liu[2] and Gengqing Song[2], (1)Metrohealth/Case Western Reserve University, (2)Case Western Reserve University/ Metrohealth

HEPATITIS C CIRRHOSIS IS ASSOCIATED WITH INCREASED RISK OF DEVELOPING GASTROESOPHAGEAL REFLUX DISEASE AND ITS COMPLICATIONS: RESULTS FROM A NATIONAL HEALTHCARE DATABASE Samantha, Mathialagan[1] MD, Benjamin Liu[1] MD, Gengqing Song[1] MD [1]Department of Medicine, Case Western Reserve University/MetroHealth **Background:** Gastroesophageal reflux disease (GERD) related symptoms frequently occur in patients with liver disease, yet limited data is available on the impact of liver cirrhosis on the development of GERD and its complications in patients with chronic hepatitis C viral infection. Our study aimed to evaluate whether patients with cirrhosis secondary to hepatitis C virus were at increased risk of developing GERD, esophagitis, Barrett's esophagus and esophageal strictures, compared to

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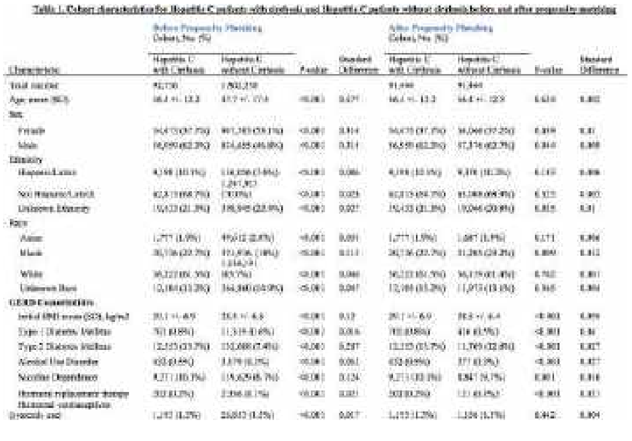
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

patients with hepatitis C who had not developed cirrhosis. **Methods:** To study this, we utilized TriNetX, a global health research platform, to develop a retrospective query across 55 healthcare organizations in the United States. The control group and treatment group consist of patients at index event who meet the criteria of chronic viral hepatitis C, or hepatitis C virus RNA in serum or plasma. Patients in the treatment group were eligible for inclusion if they met the criteria for cirrhosis and one of the criteria for chronic hepatitis C and were excluded if they had a diagnosis of hepatic failure or ascites. Patients in the control group were excluded if they had liver cirrhosis. Propensity score matching performed between cohorts controlled for GERD risk factors, including alcohol use, nicotine dependence, T1DM, T2DM, hormone replacement therapy, and hormonal contraceptive for systemic use. We assessed primary outcomes: esophagitis, GERD, esophageal stricture, Barrett's esophagus with and without dysplasia. Odds ratios were calculated within the TriNetX Analytics Platform with significance set at a 2-sided P value < 0.05. **Results:** After propensity matching, there were a total of 91,444 patients in both the treatment and control cohorts. Patients with hepatitis C cirrhosis were more likely to experience GERD (OR 1.088; 95% CI 1.064 - 1,114), erosive esophagitis (OR 1.365; 95% CI 1.273 - 1.444), esophageal stricture (OR 1.336; 95% CI 1.206 - 1.479), and Barrett's esophagus without dysplasia (OR 1.440; 95% CI 1.319 - 1.573), and Barrett's esophagus with dysplasia (OR 1.510; 95% CI 1.191 - 1.913) compared to the control group chronic hepatitis C patients without cirrhosis, ($p < 0.0001$). **Conclusion:** Our findings suggest that cirrhosis resulting from chronic hepatitis C infection is associated with an increased odds of developing GERD and its complications, including esophageal strictures and Barrett's esophagus. Additional research studies are required to elucidate the relationship between cirrhosis in patients with chronic hepatitis C virus and the development of esophagitis.



Disclosures: The following people have nothing to disclose: Samantha Mathialagan, Benjamin Liu, Gengqing Song

1827-A | HEPATITIS C ELIMINATION IN NANFANG HOSPITAL - PROACTIVE MANAGEMENT TO PREVENT LOSS OF EVERY HEPATITIS C PATIENT

Yuyuan Xu, Suling Chen, Chunxiu Zhong, Junhua Yin and Jie Peng, Nanfang Hospital, Southern Medical University

Background: The World Health Organization has set a goal of eliminating the threat of hepatitis C by 2030. The challenge lies in identifying patients and connecting them to treatment. Hospitals play a crucial role in it. Previous data showed that anti-HCV antibody positive rate of inpatient was 0.88%, higher than general population. Our hospital has established a dedicated team to realize hepatitis C elimination in hospital. **Methods:** Led by the Department of Infectious Diseases, Liver Disease Center at Nanfang Hospital, various departments collaborated on the project. The Liver Disease Center took the lead in developing the core program for proactive management of hepatitis C within the hospital. The key components included daily follow-up by the dedicated hepatitis C team at the Liver Disease Center, expanded screening within the hospital, recalled of previously patients, enhanced disease awareness among non-specialists and patients, established hepatitis C clinics, and more (Figure 1). Multiple departments, channels, and approaches were employed to facilitate comprehensive management of hepatitis C patients starting from the screening stage. **Results:** From March 2021 to March 2023, a total of 5,588,406 outpatient visits and 300,203 discharges were recorded. Anti-HCV antibody was performed on 154,404 individual's, HCV screening rate was 2.62% (154,404/5,888,609). Among them, 1,683 individual's tested positive for Anti-HCV antibody, with a positivity rate of 1.09% (1,683/154,404). It is worth noting that the anti-HCV antibody positivity rate in our hospital (screening data) is higher than 0.43%, the anti-HCV antibody (+) rate in China. The top 10 departments where anti-HCV antibody (+) were identified were as follows: Liver Disease Center (18%), Cardiology (11%), Orthopedics (11%), Gastroenterology (7%), Hepatobiliary Surgery (7%), Interventional Radiology (7%), Neurology (7%), Geriatrics (7%), General Surgery (5%), and Hematology (4%). The HCV RNA detection rate was 80.69% (1,358/1,683), slightly below the year 2025 target of 90% set in our country. 497 individual's tested positive for HCV RNA; the HCV RNA (+) rate was 36.60% (497/1,358). Treatment was initiated in 465 individual's, the treatment rate was 93.56% (465/497), surpassing the target of **e** 80% set in the national action plan. 462 individual's achieved virological cure, with a sustained virologic response rate of 99.35% (462/465). During the implementation process, 99 individual's were lost to follow-up, with the outpatient loss-to-follow-up rate of 16%, higher than the inpatient (2%). **Conclusion:** Currently, hepatitis C treatment rate and the cure rate in our hospital have met the target, but the antibody screening rate and the RNA testing rate still need to be further improved. It is crucial for us to address the issue of loss to follow-up among hepatitis C patients in the outpatient clinic.

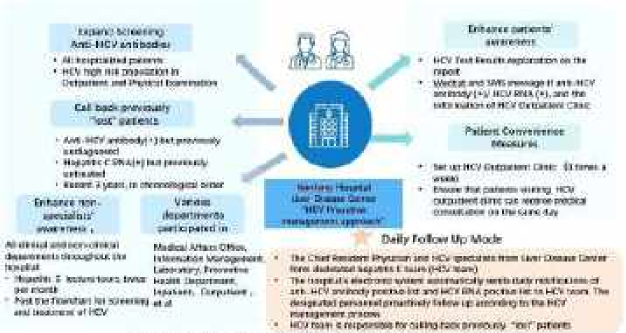

Expand Screening Anti-HCV antibodies
Call back previously "lost" patients
Enhance non-specialists' awareness
Various departments participated in
Enhance patients' awareness
Patient Convenience Measures
Daily Follow Up Mode

Figure 1: Proactive management of hepatitis C within Nanfang Hospital

Disclosures: The following people have nothing to disclose: Yuyuan Xu, Suling Chen, Chunxiu Zhong, Junhua Yin, Jie Peng

1828-A | HEPATITIS C VIRUS INFECTION AND COVID-19 INPATIENT MORTALITY

Spencer Goble, Hennepin Healthcare and Jose D. Debes, University of Minnesota

Background: The impact of chronic hepatitis C virus (HCV) infection on outcomes in patients with COVID-19 remains unclear as studies have showed mixed results. We performed a United States nationwide study to determine if a history of HCV infection impacted outcomes in those hospitalized with COVID-19. **Methods:** We retrospectively assessed hospitalizations for COVID-19 in the year 2020 using the National Inpatient Sample database. ICD-10 codes were used to establish a primary diagnosis of COVID-19 and to determine patients with a history of HCV infection including those with documented chronic infection, acute infection, and HCV carriers. Our study did not include HCV treatment data. Outcomes were compared between those with and without a history of HCV using logistical regression analysis, controlled for age, sex and Charlson Comorbidity Index. **Results:** A total of 1,050,720 hospitalizations for COVID-19 were identified, 8,040 (0.8%) of which occurred in individual's with history of HCV. Those with a history of HCV were younger (mean age 62.1 y vs 64.8 y, $p < 0.001$) more likely to be men (68.2% vs 52.9%, $p < 0.001$), Black (35.2% vs 18.3%, $p < 0.001$) and had a higher burden of comorbid diseases. Mortality (OR = 1.04, 95% CI: 0.90-1.22, $p = 0.549$) and intubation (OR = 1.14, 95% CI: 0.98-1.33, $p = 0.092$) showed an increased trend in those with a positive history for HCV after adjusting for confounders, but the differences were not statistically significant. Mortality was increased in the HCV cohort when it was restricted to those with cirrhosis (adjusted OR = 1.42, 95% CI: 1.05-1.91, $p = 0.023$). **Conclusion:** While cirrhosis increases mortality in those hospitalized with COVID-19, HCV in the absence of cirrhosis does not appear to be a risk factor for COVID-19 related mortality.

Disclosures: The following people have nothing to disclose: Spencer Goble, Jose D. Debes

1829-A | HEPATOCELLULAR CARCINOMA RISK IN SPONTANEOUSLY CLEARED HEPATITIS C PATIENTS

Asif Ali Hitawala[1], Elizabeth C. Wright[1], Tomilowo Abijo[1], Kyong-Mi Chang[2], David E. Kaplan[2] and Christine C Hsu[3], (1)National Institute of Diabetes and Digestive and Kidney Diseases, Nih, (2)Division of Gastroenterology and Hepatology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA, (3)National Institute of Health

Background: A quarter to a third of patients who acquire hepatitis C infection spontaneously clear. Despite rapid clearance, epigenetic changes of hepatocytes occur and persist. The impact of short-term HCV infection on long-term hepatic outcomes such as hepatocellular carcinoma (HCC) is unknown. We therefore evaluated the long-term HCC risk and associated risk factors in a spontaneously cleared HCV cohort. **Methods:** This is a retrospective study of patients from US Veterans Administration (VA) from 1999-2022 who achieved spontaneous SVR, defined as presence of positive anti-HCV antibody but negative HCV RNA without treatment at the time of initial diagnosis. We excluded patients with baseline diagnosis of cirrhosis, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis, alpha-1 antitrypsin, and autoimmune hepatitis, HIV, chronic Hepatitis B, < 1 year of follow-up, HCC within 1 year after diagnosis and missing baseline FIB-4 values. The final cohort was created after further excluding patients with concomitant NAFLD (defined as 2 sets of elevated liver enzymes 6 mo apart with metabolic risk factors) or alcohol use disorder (AUD, based on AUDIT-C **e** 4), and the these were analyzed separately. Univariable and multivariable analyses were performed using Cox proportional hazards model, with FIB-4 as a time-varying variable. All analyses were done using SAS (SAS Institute), and p-value < 0.05 was considered statistically significant. **Results:** Out of 21,154 patients, 421 developed HCC (1.99%) with mean follow-up of 10 ± 5.3 yrs. After excluding patients with NAFLD and AUD, 93 out of 5,882 patients developed HCC at a rate

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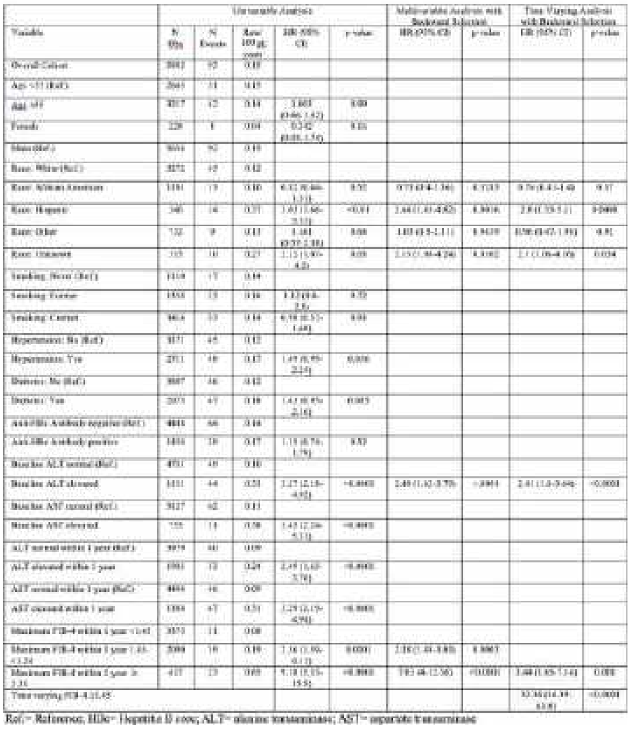
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

of 0.15 per 100 patient-years, with mean follow-up of 10.9 ± 5.4 yrs. On univariable analysis, Hispanic race, elevated baseline ALT and AST, and max FIB-4 within 1 year of initial diagnosis > 1.45 were associated with increased risk of developing HCC. On multivariable analysis, Hispanic race, elevated ALT, max FIB-4 within 1 year of 1.45-3.24 and > 3.25 were associated with increased risk of HCC, even on a time varying scale. In comparison, the rate of HCC of spontaneously cleared HCV patients with NAFLD or AUD was 0.15 and 0.33 per 100 patient-years, respectively, with age **e** 55 years, elevated baseline ALT and AST and FIB-4 **e** 1.45 as significant risk factors in univariable and multivariable analyses for both the latter cohorts. Interestingly, anti-Hepatitis B core antibody positivity was not a significant risk factor for HCC in any cohort. **Conclusion:** There continues to be an increased HCC risk in patients of Hispanic race and those with baseline elevated ALT and FIB-4 levels in patients who have spontaneously cleared HCV. Hence, in patients with baseline elevated FIB-4 > 1.45, Hispanic race, elevated liver enzymes, additional risk-stratification for chronic liver disease and HCC risk is recommended.

Table 1: Univariable and Multivariable Analyses of the Final Cohort



Ref.= Reference; HBc= Hepatitis B core; ALT= alanine transaminase; AST= aspartate transaminase

Disclosures: David E. Kaplan – Exact Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Glycotest: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AstraZeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genentech: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; BauschHealth: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Asif Ali Hitawala, Christine C Hsu

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1830-A | HEPCITYFREE/SPANISH ALLIANCE FOR VIRAL HEPATITIS ELIMINATION: THE COMMITMENT OF SPANISH CITIES FOR HEPATITIS C ELIMINATION

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Hospital, Instituto De Biomedicina De Sevilla, Ciberehd, University of Seville, Sevilla, Spain

Background: #HepCityFree is an action launched by the Spanish Alliance for Viral Hepatitis Elimination (AEHVE) to promote the commitment of cities on the elimination of hepatitis C. The goal of the study is to evaluate the response of the Spanish cities to #HepCityFree since its launch in 2020. **Methods:** Compilation of the processes of adherence to #HepCityFree initiated or completed by Spanish cities and the population they cover. Both the constitution and activities developed by the local committees (LC), as well as other awareness results obtained through #HepCityFree were analysed. **Results:** Until November 28, 2022, there are 17 cities adhered to #HepCityFree by agreement of the Government bodies of their Town Halls (Plenary or Governing Boards), which add up to a population of about 7.5 million people. The cities are: Sevilla, Valencia, Santander, Gijón, Granada, Alcoy, Vigo, Madrid, Santiago de Compostela, Ferrol, Pontevedra, León, Córdoba, Salamanca, Écija, Málaga and A Coruña. Moreover, there are another 10 cities completing the process of accession, that add up to another 1.7 million people and 21 LC coordinators (hepatologists and microbiologists) who participate in meetings with council governments for accession and/or starting actions. #HepCityFree has got the support of the Public Health Commission of the Spanish Federation of Municipalities and Provinces (FEMP), which will promote it among their cities from 2023. AEHVE is also involved in the elimination plans of two regional Spanish governments, published in 2022, and incorporated their strategic lines for local entities in accordance with the objectives of #HepCityFree, which has also received the recognition from the Health Commission of the Spanish Parlament. Seven cities (Sevilla, Madrid, Écija, Santander, Ferrol, Vigo and Alcoy) have already designed and/or started their respective roadmaps that include, among others, micro-elimination actions in centers attending vulnerable persons under local jurisdiction (immigrants, homeless, IDUs), review of medical records, telemedicine, training and awareness. All of these have allowed the screening of more than 3,800 patients. **Conclusion:** The commitment of cities with the elimination of hepatitis C is feasible and viable despite the fact that health service responsabilities depend on the Regional Governments rather than councils. In addition, there is a high predisposition of the councils with this AEHVE action, as demonstrated by the high number of cities involved to #HepCityFree. Specific roadmaps are currently being defined for each council, through direct actions in local centers that attend vulnerable groups.

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Joaquin Cabezas – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Abbvie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Consultant, No, No; Gilead: Speaking and Teaching, No, No; Abbvie: Speaking and Teaching, No, No;

Esther Molina – Intercept Pharmaceuticals: Consultant, Yes, Yes;

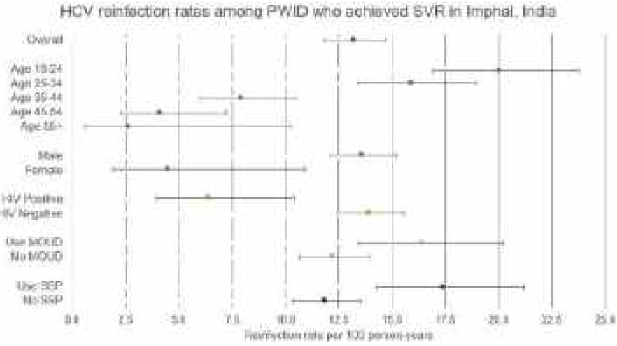
Manuel Romero-Gómez – Gilead, Intercept, Siemens; co-inventor of Hepamet Fibrosis Score, DeMILI, and DeMILI 3.0: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; AbbVie, Alpha-sigma, Allergan, Astra-Zeneca, Axcella, BMS, Boehringer-Ingelheim, Gilead, Intercept, Inventia, Kaleido, MSD, Novo-Nordisk, Pfizer, Prosciento, RubiÃ³, Siemens, Shionogi, Sobi, and Zydus: Advisor, Yes, No;

The following people have nothing to disclose: Federico Garcia, Juan Turnes, Violeta Mauriz, Javier Crespo Garcia, Pablo Ryan, Antonio Madejon, Francisco Jorquera, Raul J. Andrade, Moises Diago, Jose-Luis Montero

1831-A | HIGH HCV REINFECTION RATE IN A COMMUNITY-BASED COHORT OF PEOPLE WHO INJECT DRUGS (PWID) IN IMPHAL, INDIA

Ashwini Kedar[1], Mihili P. Gunaratne[2], Aylur K. Srikrishnan[1], Allison M. McFall[2], Shanta Chingtham[1], Pradeep Amrose[1], Jiban J. Baishya[3], Archit K. Sinha[1], Shruti H. Mehta[2] and Sunil S. Solomon[3], (1)Y.R. Gaitonde Centre for AIDS Research and Education, (2) The Johns Hopkins Bloomberg School of Public Health, (3)The Johns Hopkins University School of Medicine

Background: In order to achieve WHO elimination targets, PWID, who bear a disproportionate burden of hepatitis C virus (HCV) need to be treated, cured and subsequently supported with harm reduction services to prevent reinfection. To date, most data on HCV reinfection derive from clinical trial samples or PWID on medication for opioid use disorder (MOUD) and may underestimate reinfection rates in the community. We characterize HCV reinfection among PWID who were cured through a community-based treatment program in the northeastern Indian city of Imphal, which has the most comprehensive harm reduction program in India. **Methods:** 1,370 PWID with documented evidence of sustained virologic response (SVR) following direct acting antiviral (DAA) therapy were screened for a longitudinal cohort between April 2021 – November 2022. HCV RNA was quantified at baseline and semi-annual follow-up visits. We present reinfection incidence rates with the period at risk calculated from the date the participants achieved SVR to the baseline visit date. Reinfection date was the mid-point period for those reinfected. Correlates of HCV reinfection were estimated using Poisson regression. **Results:** Median age of the 1,267 with available HCV RNA data was 30 years, 4% were women, and 12% were HIV co-infected. At baseline, 51% reported injecting, 24% reported MOUD use and 25% syringe service programs (SSP) use. Overall, 315 cases of reinfection were documented over 2,395 person-years of follow-up (incidence rate: 13.2 per 100 person years [PY] [95% CI: 11.8, 14.7]). Reinfection was significantly higher among men vs. women (13.6 vs. 4.5 per 100 PY; $p < 0.05$) and among HIV-negative vs. people living with HIV (13.9 vs. 6.4 per 100 PY; $p < 0.01$); incidence of reinfection was highest among those 18-24 years old (20.0 per 100 PY; Figure). In multivariable regression, age was independently associated with reinfection risk (incidence rate ratio for 18–24 vs. 45–54 years = 5.2 [95% CI: 2.7, 9.8]). Neither MOUD nor SSP use was associated with reduced reinfection risk in multivariable analysis. **Conclusion:** We observed a high reinfection rate among PWID in this Indian city, highlighting gaps in engagement in harm reduction and other preventive services. The particularly high incidence among younger PWID reinforces that programs must be tailored to individual needs to reach all those at risk and maintain the gains towards HCV elimination that have been achieved by expanded DAA-based treatment.



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Disclosure information not available at the time of publication: Ashwini Kedar, Aylur K. Srikrishnan, Allison M. McFall, Shanta Chingtham, Pradeep Amrose, Jiban J. Baishya, Archit K. Sinha, Shruti H. Mehta, Sunil S. Solomon

1832-A | HYBRID AGENT-BASED AND VIRAL KINETICS MODELING OF HEPATITIS C MICRO-ELIMINATION AMONG PEOPLE WHO INJECT DRUGS WITH DIRECT-ACTING ANTIVIRALS IN METROPOLITAN CHICAGO

Eric Tatara[1], Louis Shekhtman[2,3], Nicholson T Collier[1], Basmattee Boodram[4], Jonathan Ozik[1] and Harel Dahari[3], (1)Consortium for Advanced Science and Engineering, University of Chicago, Chicago, Il; Decision and Infrastructure Sciences, Argonne National Laboratory, Argonne, IL, USA, (2)Network Science Institute, Northeastern University, Boston, MA, USA, (3) The Program for Experimental and Theoretical Modeling, Division of Hepatology, Department of Medicine, Stritch School of Medicine, Loyola University Chicago, Maywood, Illinois, USA, (4)Division of Community Health Sciences, School of Public Health, University of Illinois at Chicago

Background: Persons who inject drugs (PWID) are at high risk for acquiring and transmitting hepatitis C virus (HCV) infection. Direct-acting antiviral (DAA) therapy leads to high cure rates among PWID, however high rates of reinfection after cure and may require multiple DAA treatments to reach the World Health Organization's (WHO) goal of HCV elimination by 2030. In this modeling study we use an agent-based model (ABM) with a kinetic model of HCV transmission via syringe sharing to show that continued courses of DAA treatment among networks of HCV infected PWID is required to achieve elimination in a large population of PWID from Chicago, IL, and surrounding suburbs. **Methods:** We extended our previously developed agent-based Hepatitis C Elimination in PWID (HepCEP) model [PLoS One. 2022 Mar 10;17(3):e0264983] to identify and optimize DAA therapy scale-up and treatment strategies. We previously used a fixed probability (1%) of HCV transmission through syringe sharing among infected PWID [ibid]. The updated HepCEP model uses a mathematical model to determine transmission probabilities relative to the HCV RNA titers of needle/syringe-sharing donors. Individual temporal viral load profiles are sampled from unique distributions for acute and chronic naïve and reinfected individual's, and for individual's undergoing DAA treatment. We compared the rates of new chronic infections using the fixed and variable HCV transmission models for different combination(s) of DAA enrollment and frequency of DAA treatment courses. **Results:** When DAA retreatment limitations are not imposed, annual

DAA enrollment rates of > = 5% of the PWID population are able to achieve elimination using a fixed HCV transmission probability of 1% (Figure 1A). The updated model, that accounts for in host viral kinetics, shows that elimination is possible only for DAA enrollment rates > = 7.5% and that the elimination goal is shifted later by several years (Figure 1B). The large increase in new chronic infections apparent (Figure 1A and B) is due to reinfections among recently cured PWID. When a retreatment limitation is imposed such that PWID are only eligible for four total DAA treatments (after cure and reinfection), the fixed HCV transmission model again shows that elimination is feasible for DAA enrollment rates of > = 5% (Figure 1C), while the updated model shows that elimination is not possible for DAA enrollment rates up to 10% of the PWID population (Figure 1D). **Conclusion:** The updated HepCEP model simulations underscore the importance of DAA scale-up without any re-treatment prohibition to achieve significant reductions in HCV incidence when the rates of reinfection among PWID networks are high. An unbiased DAA scale-up of > 7.5% (or 75 per 1000 PWID) is projected to achieve the WHO target of 90% HCV incidence reduction by 2030 using the updated kinetic model of HCV transmission probability.

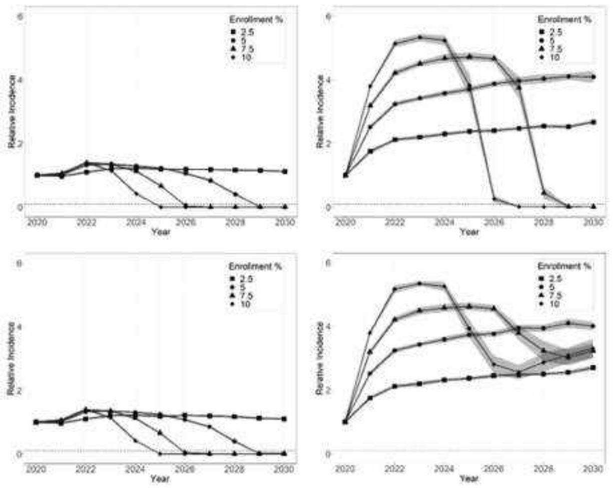

Figure 1. Projected HCV mean incidence of new chronic infections among PWID relative to the predicted 2020 incidence during with no restriction on DAA treatment frequency for the (**A**) HepCEP model with fixed 1% HCV transmission probability, and for the (**B**) Updated HepCEP model that accounts for in host viral kinetics and transmission probabilities. Mean incidence of new chronic infections when DAA treatment is limited to four times per individual for the (**C**) fixed 1% HCV transmission probability, and for the (**D**) Updated HepCEP model transmission probabilities. Enrollment percent is DAA rate (e.g., enrollment of 10% is treatment of 100 per 1000 PWID per year). The ribbons represent the 95% confidence interval around the mean of 20 simulation runs. The horizontal dashed line represents the WHO 2030 goal of 90% reduction in the incidence rate.

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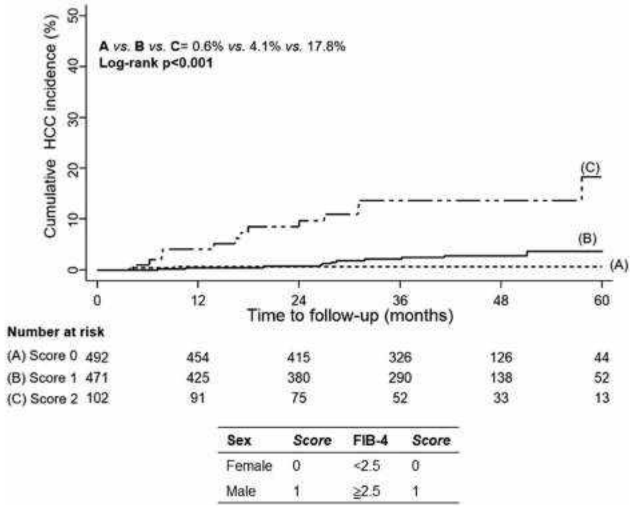
Disclosure information not available at the time of publication: Eric Tatara, Louis Shekhtman, Nicholson T Collier, Basmattee Boodram, Jonathan Ozik

1833-A | IDENTIFYING THE POPULATION AT RISK OF HCC IN NON-ACLD CHRONIC HEPATITIS C PATIENTS CURED BY DIRECT-ACTING AGENTS: A STRATEGIC APPROACH

Yen-Chun Liu[1,2], Ya-Ting Cheng[1,2], Yi-Cheng Chen[1,2], Rachel Wen-Juei Jeng[1,2], Chun-Yen Lin[1,2], Rong-Nan Chien[1,2], Dar-In Tai[1,2], I-Shyan Sheen[1,2] and Yi-Chung Hsieh[1,2], (1)Chang Gung Memorial Hospital, Linkou Branch, Taiwan, (2)College of Medicine, Chang Gung University, Taiwan

Background: HCC surveillance is recommended for chronic hepatitis C (CHC) patients with advanced fibrosis (F3) or cirrhosis (F4) after successful viral eradication, according to clinical guidelines. However, the risk of hepatocellular carcinoma (HCC) persists in CHC patients without advanced fibrosis or cirrhosis. The objective of this study is to identify the risk factors for HCC in patients with pre-treatment FIB-4 scores below 3.25 and develop a scoring system to stratify the population that would benefit from HCC surveillance after achieving sustained virological response (SVR). **Methods:** We enrolled chronic hepatitis C patients from Chang Gung Memorial Hospital who achieved HCV eradication using direct-acting antiviral agents (DAA) during 2015 to 2020 and had pretherapy FIB-4 scores available. Patients with a history of prior HCC before DAA therapy were excluded. Cox regression analysis was performed to assess the occurrence of HCC, and predictive scores were derived based on adjusted hazard ratios. The cumulative incidences of de novo HCC were calculated using the Kaplan-Meier method. **Results:** Out of the 1597 patients enrolled, 1065 (67%) had pre-DAA FIB-4 < 3.25, with a mean age of 59 years and 43% being male. Over a median follow-up period of 43 (IQR:31-52) months, 27 of the 1065 non-ACLD patients developed de-novo HCC, resulting in an annual incidence of 0.76% person-year. By multivariate Cox regression analysis, it was revealed that male [adjusted hazard ratio (aHR): 4.262 (95% CI: 1.781-10.198), p = 0.001] and FIB-4 **e** 2.5 [aHR: 4.125 (1.864-9.126), p < 0.001] were two independent factors associated with HCC in patients with FIB-4 < 3.25. We derived a non-ACLD-HCC score = 1 x (Male: 1, Female: 0) + 1 x (FIB-4 **e** 2.5: 1, < 2.5: 0), which ranged from 0-2.The 5-year cumulative HCC incidences for scores 0, 1 and 2 were 0.6%, 4.1% and 17.8%, respectively (annual incidences: 0.18%, 0.71%, 3.76% person-year; log-rank p < 0.001) (Figure). Applying the same annual incidence threshold for HCC surveillance in CHB (0.2%/year), patients with a predictive score **e** 1 should undergo

HCC surveillance even after SVR. Notably, 10% of non-ACLD patients with a predictive score of 2 (FIB-4 e 2.5 plus male) had significantly higher HCC risks compared to those with predictive scores < 2 (annual incidence: score = 2 vs. < 2: 3.76% vs. 0.43% person-year, p < 0.01). **Conclusion:** A simple scoring system utilizing the FIB-4 cut-off of 2.5 and gender can identify 10% of non-ACLD CHC-SVR patients with a predictive score of 2 who are at higher risk of HCC. These patients should be considered for inclusion in an HCC surveillance program.



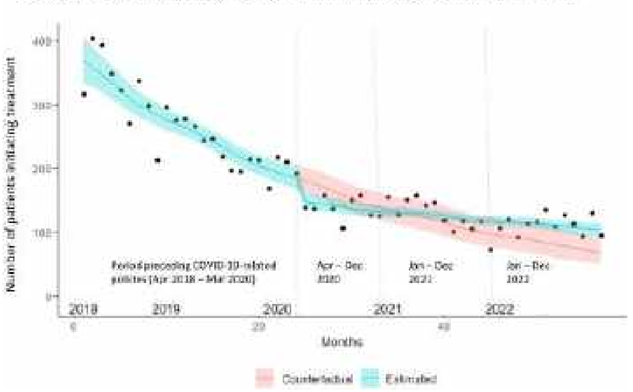
Disclosures: The following people have nothing to disclose: Yen-Chun Liu, Ya-Ting Cheng, Yi-Cheng Chen, Rachel Wen-Juei Jeng, Chun-Yen Lin, Rong-Nan Chien, Dar-In Tai, I-Shyan Sheen, Yi-Chung Hsieh

1834-A | IMPACT OF COVID-19-RELATED PUBLIC HEALTH MEASURES ON HEPATITIS C TREATMENT INITIATION IN BRITISH COLUMBIA, CANADA: AN INTERRUPTED TIME SERIES ANALYSIS

Richard L Morrow[1], Mawuena Binka[2], Julia Li[3], Mike Irvine[3], Sofia R. Bartlett[1], Stanley Wong[3], Dahn Jeong[1], Jean Damascene Makuza[3], Jason Wong[3], Amanda Yu[3], Maria Jose Alvarez[3], Mel Krajden[3] and Naveed Zafar Janjua[1,3], (1)University of British Columbia, (2) British Columbia Centre for Disease Control, (3)BC Centre for Disease Control

Background: Previous research highlighted that testing for hepatitis C (HCV) in the Canadian province of British Columbia (BC) decreased immediately following the introduction of public health measures to address the coronavirus disease 2019 (COVID-19) pandemic in March 2020, but recovered to near prior levels later in 2020. In this analysis, we aimed to assess the impact of COVID-19-related public health measures on HCV treatment initiation in BC. **Methods:** We conducted an interrupted time series analysis using administrative health data from the province's COVID-19 Cohort to estimate changes in HCV treatment initiation following the introduction of COVID-19-related public health measures in March 2020. The study period included a 24-month pre-policy period (April 2018 to March 2020) and 3 follow-up periods (April to December 2020, January to December 2021, and January to December 2022). As the pre-policy trend in HCV treatment initiation was non-linear, we used a generalized additive model with a smoothing function for the pre-policy trend, a binary variable for a post-policy level change, a smoothing function for a post-policy trend change, and a smoothing function to adjust for seasonality. The model also adjusted for autocorrelation. We calculated the absolute difference in the number of individual's initiating HCV treatment estimated by the model compared to predicted (or counterfactual) levels based on the pre-policy trend. **Results:** HCV treatment initiation was characterized by a declining trend during the pre-policy period and decreased to a level of approximately 200 patients initiating treatment per month by early 2020. After March 2020, HCV treatment initiation fell abruptly and then resumed a decreasing trend that gradually rose above the predicted (i.e., counterfactual) trend. Due to this pattern, an estimated 176 fewer patients than predicted initiated HCV treatment during April to December 2020 and 104 fewer patients than predicted initiated treatment in 2021, while the number of patients initiating treatment showed an increase of 351 patients compared to the predicted level in 2022. **Conclusion:** Following the introduction of COVID-19-related public health measures in March 2020, HCV treatment initiation initially fell but gradually rose above levels predicted by the pre-policy trend in BC. Further investigation is needed to assess the distributional impacts of these trends.

Figure 1. Number of individuals initiating HCV treatment in BC following the start of COVID-19-related policies (estimated vs counterfactual based on pre-policy trend)



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Mel Krajden – Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Siemens: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boeringer Ingelheim and Hologic: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
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Disclosure information not available at the time of publication: Julia Li, Mike Irvine, Jean Damascene Makuza, Jason Wong

1835-A | IMPLEMENTATION OF UNIVERSAL HEPATITIS C VIRUS SCREENING IN A TERTIARY CARE CANCER CENTER

Harrys A. Torres, Khalis Mustafayev, Ruston Juneau, Jessica P. Hwang, Lan Sun Wang, Georgios Angelidakis, Bruno P. Granwehr, Eduardo Yepez Guevara and Anita K. Ying, The University of Texas MD Anderson Cancer Center

Background: The prevalence of chronic hepatitis C virus (HCV) infection in the general United States (US) population is **d** 1%. Oncologic professional societies recommend universal HCV screening for cancer patients. Here we describe our experience implementing universal HCV screening at MD Anderson Cancer Center (MDACC), one of the largest cancer centers in the US. **Methods:** In October 2016, universal HCV screening with HCV antibody (anti–HCV) was initiated at MDACC for all new outpatients by implementing widespread provider education and the use of newly created electronic health records (EHR) orders (SmartSets) and automated reminders (best practice alerts or BPA). Only solid tumor patients were targeted, as hematologic cancer patients were already being screened for HCV before the study period. The primary outcomes of the study were the proportion of patients who were screened for HCV and then linked to HCV care. Epic's Reporting Workbench business intelligence tools were used. Statistical significance was defined as $p < 0.05$ on Chi-square analysis. **Results:** Between April 2016 and April 2023, 85,836 cancer patients were screened for HCV. Among them, 56,075 (65.3%) patients had solid tumors and were further analyzed. The prevalence of reactive anti-HCV was 2.3% (1,300/56,075 patients). The highest HCV prevalence rates were seen in patients with gastrointestinal (5.6%), head and neck (3.97%), and thoracic cancers (3.97%). The screening was performed by using SmartSets (39,332 patients or 45.8%) followed by BPAs (10,972 patients or 12.8%). Universal screening led to the identification of 1,300 new outpatients. Most of them were linked to HCV care (765/1,300 or 59%) and treated (425/562 or 76%) (Figure 1). The majority of patients achieved a sustained virologic response (414/425 or 97%). There was a continuous increase in screening over time, except during the peak of the COVID-19 pandemic. The proportion of new patients screened increased between the first 6 months before the study implementation and the last 6 months of the study period (10.1% vs 34.4%, $p < 0.001$). **Conclusion:** The prevalence of HCV remains higher in cancer patients compared to the general population. Universal HCV screening can be successfully implemented in cancer hospitals using an EHR-based multi-pronged approach. This strategy can be implemented in cancer centers nationwide to contribute to HCV elimination targets.

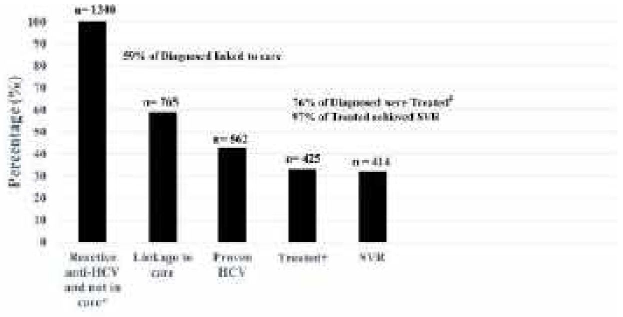

Figure 1. Cascade of care for solid tumor patients with chronic HCV infection during the post-implementation phase of universal HCV screening
Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response
* 370 (28%) were lost to follow-up, 72 (6%) not chronically infected, and 93 (7%) died
† 322 patients (25%) were treated before arriving at MDACC, and 103 patients (8%) were treated at MDACC
‡ 137 HCV-infected patients (24%) were not treated, 103 of them because of progressive cancer, 28 patients were lost to follow-up, and 6 patients were not treated to avoid drug-drug interactions

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

that individual's institution receives the research grant and manages the funds), No, Yes;
The following people have nothing to disclose: Khalis Mustafayev, Ruston Juneau, Jessica P. Hwang, Lan Sun Wang, Georgios Angelidakis, Bruno P. Granwehr, Eduardo Yepez Guevara, Anita K. Ying

1836-A | IMPROVING THE HCV CARE CASCADE AMONG IMMIGRANTS IN CANADA THROUGH LINKAGE TO CARE AND TREATMENT SUPPORTS: A COST-EFFECTIVENESS ANALYSIS

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Background: High uptake in the care cascade for all groups will be necessary to achieve hepatitis C virus (HCV) elimination. We used decision analysis modelling to assess the cost-effectiveness of systematic HCV screening interventions among new immigrants to Canada, with or without linkage to care and treatment supports, compared to the status quo of limited screening. **Methods:** We modelled a hypothetical cohort to reflect the 341,180 immigrants admitted as permanent residents in Canada in 2019 as of country of origin, age, and sex distribution. Adult immigrants from e 2% HCV-prevalence countries were included in the main cost-utility analysis (N = 30,270). A Markov model was used to estimate costs, quality-adjusted life years (QALYs), decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC) cases, and liver-related deaths (LRD) over a lifetime horizon. Linkage to care and treatment supports included interpreters, peer navigators, written educational material, and text-message reminders. Input parameters and costs were obtained from the literature, including Canadian costs. We used the healthcare payer perspective, with costs expressed in 2020 Canadian dollars, and future costs and outcomes discounted at an annual rate of 1.5%, according to Canadian guidelines. We performed one-way and probabilistic sensitivity analysis (PSA), and tested alternative scenarios of 1% (N = 107,414) and 0% (N = 279,465) HCV prevalence threshold. **Results:** Compared to the status quo, screening with linkage to care and treatment supports averted 13.8 [95% uncertainty range (UR) 9.2-17.5] DC, 11.0 (6.9-14.0) HCC cases, and 20.2 (13.1-23.4) LRD per 1000 persons screened (Table). It was estimated to cost an additional $1,027,042 ($355,830-$1,201,290) and result in 259 (214-280) additional QALYs; translating to an incremental cost-effectiveness ratio (ICER) of $3957 per QALY. While screening without supports also improved outcomes, it was more costly and less effective than with care supports (extended dominance; ICER $4837 vs. no screening). Screening with care supports was cost-effective (< $50,000 per QALY gained) in 100% of PSA simulations (n = 100), compared to no screening. It was also cost-effective in alternative prevalence threshold scenarios of 1% (ICER $4003) and 0% (ICER $4230) compared to no screening. As health events among immigrants from e 2% prevalence countries accounted for only 37.9% of outcomes in the entire simulated cohort, screening with care support for all adult immigrants averted an additional 613 DC, 586 HCC cases, and 998 LRD, overall, compared to the e 2% threshold. Screening with care support for all vs. e 2% prevalence averted 3.7 vs. 1.5 DC, 3.3 vs. 1.2 HCC cases, and 5.8 vs. 2.2 LRD per 1000 newly arrived adult immigrants. **Conclusion:** Systematic mass HCV immigrant screening with linkage to care and treatment supports can greatly reduce DC and HCC cases, and LRD, and improve quality of life while being cost-effective.

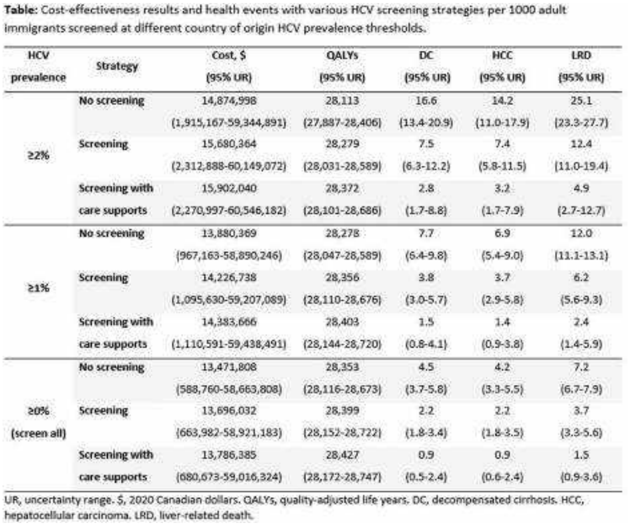

Table: Cost-effectiveness results and health events with various HCV screening strategies per 1000 adult immigrants screened at different country of origin HCV prevalence thresholds.

HCV prevalence	Strategy	Cost, $ (95% UR)	QALYs (95% UR)	DC (95% UR)	HCC (95% UR)	LRD (95% UR)
≥2%	No screening	14,874,998 (1,915,167-59,344,891)	28,113 (27,887-28,406)	16.6 (13.4-20.9)	14.2 (11.0-17.9)	25.1 (23.3-27.7)
	Screening	15,680,364 (2,312,888-60,149,072)	28,279 (28,031-28,589)	7.5 (6.3-12.2)	7.4 (5.8-11.5)	12.4 (11.0-19.4)
	Screening with care supports	15,902,040 (2,270,997-60,546,182)	28,372 (28,101-28,686)	2.8 (1.7-8.8)	3.2 (1.7-7.9)	4.9 (2.7-12.7)
≥1%	No screening	13,880,369 (967,163-58,890,246)	28,278 (28,047-28,589)	7.7 (6.4-9.8)	6.9 (5.4-9.0)	12.0 (11.1-13.1)
	Screening	14,226,738 (1,095,630-59,207,089)	28,356 (28,110-28,676)	3.8 (3.0-5.7)	3.7 (2.9-5.8)	6.2 (5.6-9.3)
	Screening with care supports	14,383,666 (1,110,591-59,438,491)	28,403 (28,144-28,720)	1.5 (0.8-4.1)	1.4 (0.9-3.8)	2.4 (1.4-5.9)
≥0% (screen all)	No screening	13,471,808 (588,760-58,663,808)	28,353 (28,116-28,673)	4.5 (3.7-5.8)	4.2 (3.3-5.5)	7.2 (6.7-7.9)
	Screening	13,696,032 (663,982-58,921,183)	28,399 (28,152-28,722)	2.2 (1.8-3.4)	2.2 (1.8-3.5)	3.7 (3.3-5.6)
	Screening with care supports	13,786,385 (680,673-59,016,324)	28,427 (28,172-28,747)	0.9 (0.5-2.4)	0.9 (0.6-2.4)	1.5 (0.9-3.6)

UR, uncertainty range. $, 2020 Canadian dollars. QALYs, quality-adjusted life years. DC, decompensated cirrhosis. HCC, hepatocellular carcinoma. LRD, liver-related death.

Disclosures: Jordan J. Feld – AbbVie: Consultant, No, No; AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Eiger: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Consultant, No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GSK: Consultant, No, No; Janssen: Consultant, No, No; Janssen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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1837-A | INCIDENCE AND ASSOCIATIONS OF HCV REINFECTION IN THE ERA OF DIRECT ACTING ANTIVIRALS. THE RECARE STUDY

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Background: The introduction of highly effective direct acting antivirals (DAAs) has dramatically changed practice against HCV infection with high therapy uptake and high response rates; one may argue for higher reinfection rates. Reinfection rates especially in high risk populations could become a significant barrier in the strategy of HCV elimination. Our aim is to explore the HCV reinfection rate after successful HCV therapy with DAAs in a cohort of people who use drugs (PWUD) and define factors associated with reinfection. **Methods:** We included patients with chronic compensated hepatitis C who had history of past or current illicit drug use. All had been treated successfully with DAAs in our tertiary center between 2014-2021. SVR was defined with serum HCV RNA no detectability 3-12 months after the end of treatment. All patients were contacted at least one year after end of treatment via phone call and were invited for follow up visit where serum HCV RNA levels, liver function tests and transient elastography were performed. Parameters regarding socioeconomic status and drug use habits, were also recorded. Detectable serum HCV RNA after achieving SVR was defined as reinfection. 223 patients were called twice; 94 of them did respond. **Results:** 129 patients (78.3% men) were included in this preliminary analysis. Median age was 52 (range 34-73) years and 18.6%(n = 24) had evidence of cirrhosis. 58.1%(n = 75) were unemployed, 58.9%(n = 76) were single and 25.6%(n = 33) had been incarcerated at some point in the past. 65%(n = 84) attended a substitution or therapeutic community program for drug use, with 30.2%(n = 39) reporting drug use in the last 12 months, of which 38.5%(n = 15) shared syringes/other paraphernalia, while 41%(n = 16) reported intravenous drug use. We identified 9 reinfections during 309.9 PY of follow-up, yielding a reinfection rate of 2.9/100 PY. HCV genotypes in reinfected patients were different compared to baseline pretherapy ones. We found that the reinfection group included younger (43 ± 5 vs 52 ± 8 y,p = 0.001) patients, the majority (n = 8, 88.9%) of them under the age of 50, and with a concomitant history of having been imprisoned (67% vs 23%,p = 0.003). Moreover, people in the reinfection group reported longer total history of intravenous drug use (24 ± 7 vs 14 ± 8 y,p = 0.002), more often active drug use in the past 12 months (89% vs 26%, p < 0.001), intravenous drug use (67% vs 9%,p < 0.001) and shared syringes/paraphernalia (89% vs 31%, p < 0.001). Reinfection was also significantly associated with HIV co-infection (44% vs 0%,p < 0.001) and cannabis consumption (78% vs 38%,p = 0.02). **Conclusion:** Our prospective study clearly showed that HCV reinfection rates after SVR with DAAs were higher among younger patients who continued high risk behaviors. These data highlight the importance of close follow-up for PWUD with widespread testing, harm reduction interventions and sustained linkage to health care services.

Disclosures: The following people have nothing to disclose: Sofia Vasileiadi, Olga Anagnostou, Kanellos Koustenis, Maria Manolakopoulou, Charalampos Karageorgos, Anestis Goulas, Charikleia Kranidioti, Spyros Siakavellas, Emilia Hadziyannis, Maria Melanie Deutsch, Spilios Manolakopoulos

1838-A | INCIDENCE AND PREDICTIVE FACTORS OF PORTAL VEIN THROMBOSIS IN PATIENTS WITH HCV-RELATED CIRRHOSIS AFTER SUSTAINED VIROLOGICAL RESPONSE: LONG TERM COMPETING RISK ANALYSIS IN THE PITER COHORT

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Madonia[11], Liliana Chemello[2], Luisa Cavalletto[2], Carmine Coppola[12], Filomena Morisco[13], Francesco Barbaro[14], Anna Licata[15], Alessandro Federico[16], Federica Cerini[17], Marcello Persico[18], Maurizio Pompili[19], Alessia Ciancio[20], Fabio Piscaglia[21], Luchino Chessa[22], Andrea Giacometti[23], Pietro Invernizzi[24], Giuseppina Brancaccio[2], Antonio Benedetti[25], Leonardo Baiocchi[26], Ivan Gentile[13], Nicola Coppola[27], Gerardo Nardone[13], Antonio Craxi[15], Francesco Paolo Paolo Russo[2] and PITER Collaborating Group, (1) Istituto Superiore Di Sanità, (2)University of Padova, (3) L'altrastatistica Srl, Consultancy & Training, Biostatistics Office, (4)Gastroenterology & Hepatology Unit, Department of Health Promotion, Mother & Child Care, Internal Medicine & Medical Specialties (PROMISE), University of Palermo, Palermo, Italy, (5)University of Florence, (6)Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, Reference Center of the Tuscany Region for Chronic Liver Disease and Cancer, University Hospital of Pisa, (7)University of Messina, (8)"Policlinico Umberto I" Hospital, Sapienza University of Rome, (9)University Hospital of Verona, (10)University of Bari, (11)Villa Sofia-Cervello Hospital, (12)Gragnano Hospital, (13)University of Naples "Federico II", (14)University Hospital of Padova, (15)University of Palermo, (16)Division of Hepatogastroenterology, Department of Precision Medicine, Università Della Campania "Luigi Vanvitelli", Naples, Italy, (17)San Giuseppe Hospital, (18)University of Salerno, Baronissi, (19)Fondazione Policlinico Universitario Agostino Gemelli Irccs, (20)Gastrohepatology Unit, Aou Città Della Salute e Della Scienza Di Torino, (21)University of Bologna, (22)University Hospital, Monserrato, Cagliari, (23)Polytechnic University of Marche, (24)University of Milano-Bicocca, (25)University of Ancona, (26)University of Tor Vergata, (27)University of Campania "Luigi Vanvitelli"

Background: Sustained virological response (SVR) by direct-acting antivirals (DAA) may reverse the hypercoagulable state associated with HCV cirrhosis. However, whether DAA-driven SVR reduces the risk of portal vein thrombosis (PVT) is unclear. We evaluated the incidence and predictive factors of *de-novo*, non-tumoral PVT in HCV cirrhosis after SVR. **Methods:** DAA-treated cirrhosis patients consecutively enrolled in the multicentric PITER cohort since 2014 were prospectively evaluated. A group of untreated patients ($n = 448$) were included as propensity-matched (inverse probability weighting) controls for PVT development. Kaplan-Meier analysis and competing risk regression analysis were performed to evaluate the PVT incidence and predictive factors. **Results:** The 3-year PVT weighted cumulative incidence rate was significantly lower in SVR+ patients than in untreated controls (1.3% vs. 2.4%, $p < 0.0001$). During a median follow-up of 38.3 (IQR 25.1-48.7) months, of 1609 consecutive DAA-treated patients with cirrhosis who achieved the SVR, 32 (2.2%) developed PVT. Patients who developed PVT had more severe liver disease as reflected by a lower platelet (PLT) count, higher bilirubin and a more frequent history of decompensation. In a multivariable model, considering death and liver transplantation as competing risk events, adjusting for the use of non-selective beta-blockers (NSBBs) and PLT count $<$ 120.000/µl, pre-treatment ALBI grade > 2 (subHR: 4.02; CI95% 1.24-13.04) and presence of esophageal varices (subHR: 8.58; CI95% 3.37-21.82) were independent PVT predictors. Notably, patients who developed PVT have no significant improvement in portal hypertension severity and liver function tests after the SVR. There was a significant variation ($p < 0.001$) in the post-SVR *vs* baseline PLT, albumin, and bilirubin levels in patients who did not develop PVT, whereas in those who developed PVT no significant improvements were observed for all variables evaluated ($p > 0.05$). ALBI grade > 2, evaluated within the first year after the end of treatment and the presence of esophageal varices, adjusted for NSBBs and post SVR PLT count $<$ 120.000/µl, remained associated with *de-novo* PVT (subHR: 5.5; CI95% 1,67-18.13 and subHR: 9.32; CI95% 3.16-27.53, respectively). **Conclusion:** SVR is associated with a significant reduction in the risk of PVT. Patients with more advanced liver disease prior and after viral eradication by DAA treatment remained at risk of PVT.

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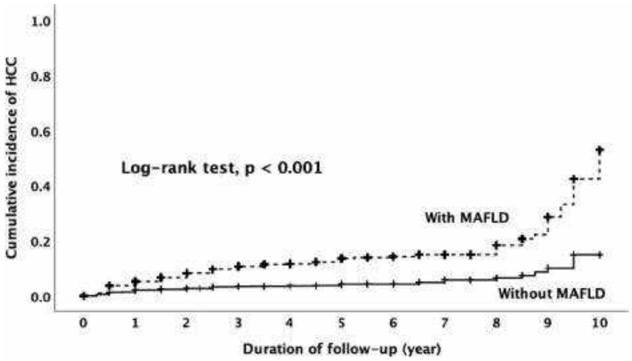
1839-A | INCREASED RISK OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CONCURRENT HEPATITIS C VIRUS INFECTION AND METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE AFTER ACHIEVING SUSTAINED VIROLOGIC RESPONSE WITH DIRECT-ACTING ANTIVIRALS

Chen-Hua Liu[1], Yu-Jen Fang[2], Chi-Yi Chen[3], Wei-Yu Kao[4], Chih-Lin Lin[5], Pin-Nan Cheng[6], Sheng-Shun Yang[7], Yu-Lueng Shih[8], Shang-Chin Huang[9], Tung-Hung Su[1], Tai-Chung Tseng[10], Chun-Jen Liu[1], Pei-Jer Chen[1] and Jia-Horng Kao[1], (1)National Taiwan University Hospital, (2)National Taiwan University Hospital, Yun-Lin Branch, (3)Ditmanson Medical Foundation Chiayi Christian Hospital, Chia Yi, Taiwan, (4)Taipei Medical University Hospital, (5)Renai Branch, Taipei City Hospital, Taipei, Taiwan, (6)National Cheng Kung University Hospital, Taiwan, (7)Taichung Veterans General Hospital, (8)Tri-Service General Hospital, (9)National Taiwan University Hospital Bei-Hu Branch, Taipei City, Taiwan, (10)National Taiwan University Hospital, Taiwan

Background: Data are limited regarding the risk of hepatocellular carcinoma (HCC) in patients with concurrent hepatitis C virus (HCV) infection and metabolic dysfunction-associated fatty liver disease (MAFLD) who achieve sustained virologic response (SVR) with direct-acting antivirals (DAAs). **Methods:** We retrospectively analyzed a prospective cohort assessing the risk of HCC in patients with HCV after achieving SVR_{12} with DAAs at eight academic centers in Taiwan. MAFLD was defined as the presence of hepatic steatosis with a controlled attenuation parameter (CAP) of 248 dB/m or more, in combination with type 2 diabetes mellitus (DM), overweight or obesity, or lean/normal weight. Baseline characteristics, including age, sex, stage of hepatic fibrosis, fibrosis index based on four parameters (FIB-4), albumin-bilirubin (ALBI) grade, were also assessed at the time point of SVR_{12}. The cumulative incidence rates between patients with or without concurrent MAFLD were calculated using Kaplan-Meier methods and were compared by log-rank tests. Multivariate Cox regression model, which was shown as hazard ratio (HR) with 95% CI, to assess the association between the risk of HCC and factors of interest. **Results:** A total of 2018 patients were included in the study. After a median of post-SVR_{12} follow-up of 4.5 years, 164 (8.1%) of them developed HCC. Patients with concurrent MAFLD had a significantly higher cumulative incidence rate of HCC than those without MAFLD (Log-rank test, $p < 0.001$)(Figure 1). Among patients with concurrent MAFLD, those with type 2 DM had a significantly higher cumulative incidence rate of HCC than those with overweight or obesity, or lean/normal weight (Log-rank test, $p = 0.005$). Multivariate Cox regression analysis revealed that age > 50 years (HR: 5.26 [95% CI: 2.80-9.88], $p < 0.001$), male (HR: 2.38 [95% CI: 1.71-3.32], $p < 0.001$), cirrhosis (HR: 4.98 (95% CI: 3.33-7.45, $p < 0.001$), ALBI grade (HR: 1.89 [95% CI: 1.23-2.92], $p < 0.001$), and MAFLD (HR: 1.96 (95% CI: 1.39-2.76, $p < 0.001$) were associated with HCC in patients achieving SVR_{12} with DAAs. **Conclusion:** In addition to age, sex, cirrhosis, and ALBI grade, patients who achieved SVR_{12} with DAAs had an independently higher risk of HCC during post-SVR_{12} follow-up if they had concurrent MAFLD, particularly for type 2 DM.



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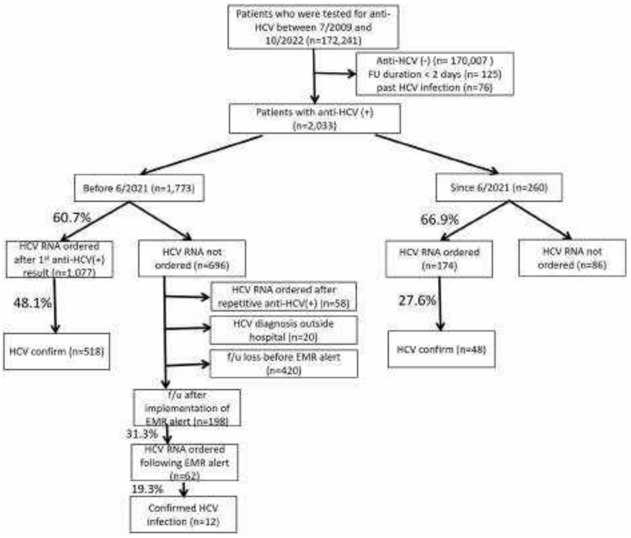
1840-A | INTERIM RESULTS OF AN AUTOMATED ELECTRONIC MEDICAL RECORD-BASED ALERT SYSTEM FOR THE MICRO-ELIMINATION OF HEPATITIS C – A SINGLE CENTER-BASED EXPERIENCE

Hee Yeon Kim[1], Sung Won Lee[1], Jung Hyun Kwon[1], Chang Wook Kim[1], Se Hyun Cho[1], Heechul Nam[1], Hyun Yang[1], Keungmo Yang[1], Do Seon Song[1], U Im Chang[1], Jin Mo Yang[1], Hae Lim Lee[1], Soon Woo Nam[1], Soon Kyu Lee[1], Seok-Hwan Kim[1], Myeong Jun Song[1], Pil Soo Sung[2], Ji Won Han[1], Jeong Won Jang[1], Si Hyun Bae[1], Jong Choi[3] and Seung Kew Yoon[1], (1)The Catholic University of Korea, (2)The Catholic University Liver Research Center, Department of Biomedicine & Health Sciences, College of Medicine, the Catholic University of Korea, (3)College of Medicine, the Catholic University of Korea

Background: The diagnostic process and linkage to care continue to represent the primary obstacles impeding the micro-elimination of the hepatitis C virus (HCV). This study aimed to evaluate the effectiveness of integrating an automated electronic medical record (EMR)-based alert system in a tertiary referral center. **Methods:** The analysis included 2,234 patients who tested positive for HCV

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

antibodies between July 2009 and October 2022. Starting from June 2021, an EMR-based alert system was implemented to remind physicians to conduct HCV RNA testing for patients with a history of positive HCV tests but no confirmatory HCV RNA test or recent positive HCV test result. **Results:** Out of the 172,241 patients who underwent anti-HCV testing during the study period, 2,234 patients (1.3%) tested positive for anti-HCV. After excluding patients previously diagnosed with HCV and those with a follow-up duration of less than 2 days, 2,033 patients were included in the analysis. Before the introduction of the automated EMR-based alert system, 60.7%(1077/1773) of the patients underwent HCV RNA testing following the initial positive anti-HCV result. Among them, 48.1% (518/1077) were confirmed to have HCV infection. Among the patients who did not undergo the HCV RNA confirmatory test following the initial positive anti-HCV result, 58 patients received the HCV RNA test after repetitive positive anti-HCV results. Notably, 3.1%(20/638) of patients who did not undergo the HCV RNA confirmatory test within our hospital were diagnosed with HCV elsewhere. Among 198 patients who had not undergone HCV RNA test before EMR-based alert system and had been followed up after alert system, 31.3% (62/198) were tested following the alert notification, resulting in confirmation of 12 new HCV infections. After incorporating an EMR-based alert system, 66.9%(174/260) of anti-HCV-positive patients were ordered an HCV RNA test, with 27.6%(48/174) confirmed cases. **Conclusion:** The integration of an EMR-based alert system for HCV microelimination improved RNA testing rates in new anti-HCV positive patients and diagnosis of previously missed HCV infection in a hospital-based setting. However, further modification and promotion of EMR-based alert system is needed to enhance HCV confirmation rates.


Patients who were tested for anti-HCV between 7/2009 and 10/2022 (n=172,241)
Anti-HCV (-) (n= 170,007)
FU duration < 2 days (n= 125)
past HCV infection (n=76)
Patients with anti-HCV (+) (n=2,033)
Before 6/2021 (n=1,773)
Since 6/2021 (n=260)
60.7%
HCV RNA ordered after 1st anti-HCV(+) result (n=1,077)
HCV RNA not ordered (n=696)
66.9%
HCV RNA ordered (n=174)
HCV RNA not ordered (n=86)
48.1%
HCV confirm (n=518)
HCV RNA ordered after repetitive anti-HCV(+) (n=58)
HCV diagnosis outside hospital (n=20)
f/u loss before EMR alert (n=420)
27.6%
HCV confirm (n=48)
f/u after implementation of EMR alert (n=198)
31.3%
HCV RNA ordered following EMR alert (n=62)
19.3%
Confirmed HCV infection (n=12)

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1841-A | LONG TERM OUTCOMES OF CIRRHOTIC PATIENTS WITH CHRONIC HEPATITIS C VIRUS AFTER ACHIEVING SUSTAINED VIROLOGIC RESPONSE

Justin Canakis[1], Reid Schalet[1] and Marc Siegel[2], (1) The George Washington University School of Medicine and Health Sciences, (2)George Washington University School of Medicine and Health Sciences

Background: Achieving sustained virologic response (SVR) with direct acting antivirals can lead to improvement in liver-related events (LREs) and non-liver-related events (NLREs). Most studies have explored the long-term outcomes of patients treated with interferon-based therapy and do not describe the outcomes in patient with hepatitis C virus (HCV)-related cirrhosis. There this is little data describing the long-term outcomes of patients with advanced fibrosis and cirrhosis after being treated with HCV directly acting agents (DAAs). Our aim was to assess to long term outcomes of liver related disease and non-liver related disease in patients with HCV-related cirrhosis following SVR after therapy with DAAs. **Methods:** We conducted a retrospective, observational cohort study of 248 patients who had received treated for Hepatitis C from 2008-2021. All patients had confirmed HCV by PCR and were treated with DAAs for 8, 12, or 24 weeks or as clinically indicated. Inclusion criteria included either confirmed cirrhosis on liver biopsy or stage F4 on transient elastography and platelet count less than 150 in order to weed of Fibroscans that were artificially elevated. We then conducted retrospective chart reviews of all cirrhotic patients successfully treated with DAAs and explored if they were diagnosed with hepatocellular carcinoma (HCC), esophageal varices, non-Hodgkins lymphoma (NHL), diabetes mellitus (DM), myocardial infarction (MI), or thyroid disease after treatment. We also reviewed performance of esophagogastroduodenoscopies (EGDs) and radiographic screenings for HCC to determine the incidence of variceal monitoring and HCC screening. **Results:** 59 patients (24%) had cirrhosis diagnosed by liver biopsy or transient elastography. 36 patients (61%) were men. The average age was 59.5 years. The average duration of HCV infection was 30 years (range 6 to 50 y). 62.7% never had an EGD, 22% had one EGD, and 15% had two or more EGDs. Esophageal varices were detected in 7 patients (32%) of patients who were screened. Regarding HCC screening with abdominal ultrasounds, 37.3% had no ultrasound performed, 28.8% had one, and 34% had greater than two. (Table 2). 15.3% of patients had an MRI performed and 18.7% had a CT scan for HCC screening (Tables 3 and 4). Regarding long term health outcomes, 4 patients (6.8%) were diagnosed with HCC, no patients was diagnosed with NHL, 10 patients developed diabetes, 2 patients had a MI, and 2 developed thyroid disease. **Conclusion:** Patients with HCV-related cirrhosis remain at substantial risk for developing liver-related and non-liver-related events after achieving SVR with DAA therapy. However, our cohort revealed sub-optimal rates of surveillance for HCC and esophageal varices.

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1842-A | LONG-TERM PROGNOSIS AFTER DIRECT ACTING ANTIVIRALS TREATMENT WITH HEPATITIS C VIRUS ERADICATION

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Background: Almost all patients with chronic hepatitis C can achieve sustained virologic response (SVR) with direct-acting antiviral (DAA) treatment. However, the long-term prognosis after SVR remains unclear. The aim of this study was to evaluate the prognosis of patients who achieved SVR. **Methods:** In this nationwide prospective study involving 12 hospitals of the Japanese Red Cross Liver Study Group, a total of 5665 patients who achieved SVR with DAA treatment were enrolled. Liver-related and non-liver-related mortality were evaluated. The change in mortality was also evaluated. **Results:** The median (interquartile range) follow-up was 3.4 (2.2-5.0) years, and 293 patients (5.1%) died during follow-up. Among these patients, 108 patients died due to liver-related events and 185 patients died due to non-liver-related events. Among patients with non-liver-related death, 41, 47, 10, 8, 12, 32, and 35 patients died due to cardiovascular disease, gastrointestinal cancer, lung cancer, hematologic malignancy, other cancer, infectious disease, and other causes of death, respectively. The 1-, 3-, and 5-year all-cause mortality rates were 0.4%, 2.9%, and 6.2%, respectively. Similarly, the 1-, 3-, and 5-year liver-related mortality rates were 0.1%, 1.0%, and 2.1%, respectively. The proportion of liver-related deaths at 1, 3, and 5 years was 26%, 47%, and 38%, respectively. Liver-related mortality did not decrease over at least five years of follow-up. When patients were stratified by fibrosis stage, the 5-year mortality rates in patients with advanced fibrosis (defined by FIB-4) and those without advanced fibrosis were 10.3% and 3.5%, respectively. In patients with advanced fibrosis, the 5-year mortality rates for liver-related and non-liver-related events were 4.4% and 5.1%, respectively. Similarly, in patients without advanced fibrosis, the 5-year mortality rates for liver-related and non-liver-related events were 0.8% and 2.5%, respectively. The mortality rates for liver-related and non-liver-related events were equivalent in patients with advanced fibrosis, whereas in patients without advanced fibrosis, liver-related mortality is low and attention should be paid to non-liver-related mortality. **Conclusion:** In patients who achieved SVR, liver-related mortality did not decrease after at least five years of follow-up, and regular surveillance must be continued. In patients with advanced fibrosis, the risk of liver-related and non-liver-related mortality was high, and regular surveillance for liver-related and non-liver-related events is needed. In patients without advanced fibrosis, the risk of death was higher for non-liver-related events than for liver-related events.

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Namiki Izumi – Gilead: Speaking and Teaching, No, No;
The following people have nothing to disclose: Nobuharu Tamaki

1843-A | LOW PREVALENCE OF HEPATITIS C (HCV) VIREMIA WITH POPULATION-BASED SCREENING IN AN URBAN SAFETY-NET HOSPITAL

Melissa Osborn Jenkins[1,2], Peter Greco[1,2], David Kaelber[1,2], Nicholas Riley[1,2], James Misak[1,2], Michael Gierlach[1] and Ann Avery[1,2], (1)Metrohealth Medical Center, (2)Case Western Reserve University School of Medicine

Background: CDC recommends one-time HCV screening for all adults **e** 18 years old, due to a rise in HCV incidence in persons aged 20-39 fueled by the opioid epidemic. To facilitate this recommendation, we instituted bulk ordering of HCV testing in the electronic health record (EHR) for those meeting eligibility criteria. A pilot study of bulk HCV ordering at our hospital led to a 70% increase in completion of HCV screening compared to usual care (health maintenance reminder with provider-driven orders). **Methods:** Eligible patients were adults aged 18-79 who were enrolled in primary care with a visit in the last 12 months and had no prior HCV test or history of HCV. Patients were excluded if “deceased” in the EHR, had a positive HCV RNA in the EHR, had an appointment in Liver Clinic, or had a diagnosis of chronic HCV, cirrhosis secondary to HCV, or hepatitis C antibody (Ab) positive on their problem list. Bulk orders were placed over 1 year in batches ~ 1000 every other week by the study team. Patients received a single mailed letter or electronic message through the patient portal advising them of the recommendation and rationale for testing, as well as instructions for completion. Results were delivered to the study team for follow up of positive results, including informing patients of the diagnosis and linking them for HCV care. **Results:** Over the course of 1 year, a total of 28753 bulk orders for HCV Ab were placed, with invitations sent via patient portal (21419 (74.5%)) or mailed letter (7330 (25.5%)). Of those invited, 7795 (27.1%) completed testing within 1 year (Table). Out of the 41 patients with a reactive HCV Ab, 21/41 (51.2%) had a negative HCV RNA. 19/41 (46.3%) had a detectable HCV RNA. 1 person did not have HCV RNA testing due to inadequate sample. The overall prevalence of chronic HCV was 19/7795 (0.2%). Among 19 patients with +HCV RNA, 14 (74%) were successfully linked to HCV care and 10 (53%) have achieved cure (SVR12) to date. **Conclusion:** The overall prevalence of undiagnosed HCV in our primary care population was low (0.2%), compared to recent studies in our system (4%) or the US (0.8%). Our prior screening initiatives among high-risk patients (birth cohort, jail, emergency department) likely account for the low prevalence in patients targeted by the current intervention. The linkage-to-care rate among those identified was high, and over half have been successfully treated thus far. Although prevalence was low, bulk ordering was an easy intervention that identified patients who might not otherwise be tested, and whose treatment can help reach the 2030 goal of HCV elimination.

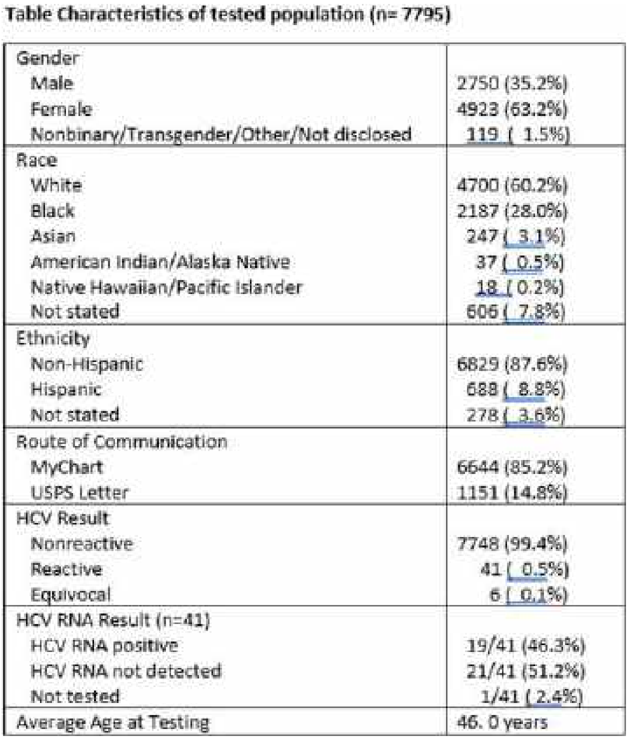

Table Characteristics of tested population (n= 7795)

Gender	
Male	2750 (35.2%)
Female	4923 (63.2%)
Nonbinary/Transgender/Other/Not disclosed	119 (1.5%)
Race	
White	4700 (60.2%)
Black	2187 (28.0%)
Asian	247 (3.1%)
American Indian/Alaska Native	37 (0.5%)
Native Hawaiian/Pacific Islander	18 (0.2%)
Not stated	606 (7.8%)
Ethnicity	
Non-Hispanic	6829 (87.6%)
Hispanic	688 (8.8%)
Not stated	278 (3.6%)
Route of Communication	
MyChart	6644 (85.2%)
USPS Letter	1151 (14.8%)
HCV Result	
Nonreactive	7748 (99.4%)
Reactive	41 (0.5%)
Equivocal	6 (0.1%)
HCV RNA Result (n=41)	
HCV RNA positive	19/41 (46.3%)
HCV RNA not detected	21/41 (51.2%)
Not tested	1/41 (2.4%)
Average Age at Testing	46. 0 years

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Disclosure information not available at the time of publication: Peter Greco, David Kaelber, Nicholas Riley, James Misak, Michael Gierlach, Ann Avery

1844-A | OPTIMIZING METHADONE PROVIDER LOCATIONS FOR REDUCING SYRINGE SHARING BEHAVIOR AND HCV TRANSMISSION RISK AMONG PERSONS WHO INJECT DRUGS IN METROPOLITAN CHICAGO

Eric Tatara[1], Qinyun Lin[2], Jonathan Ozik[1], Marynia Kolak[2], Nicholson T Collier[1], Dylan Halpern[2], Luc Anselin[2], Harel Dahari[3], Basmattee Boodram[4] and John Schneider[5], (1)Decision and Infrastructure Sciences Division, Argonne National Laboratory and Consortium for Advanced Science and Engineering, University of Chicago, (2)University of Chicago, Center for Spatial Data Science, Chicago, IL, (3)The Program for Experimental and Theoretical Modeling, Division of Hepatology, Department of Medicine, Stritch School of Medicine, Loyola University Chicago, Maywood, Illinois, USA, Highland Park, IL, (4)Division of Community Health Sciences, School of Public Health, University of Illinois at Chicago, (5)Department of Infectious Disease, Uchicago Medicine

Background: Ensuring that individual's have access to treatment and medication for opioid use disorder (MOUD), such as methadone, is crucial for enhancing health outcomes by mitigating the risks of infection and overdose associated with injecting drugs. However, the distribution of MOUD resources is influenced by intricate social and structural factors, leading to nuanced patterns that expose underlying disparities in social and spatial contexts Persons who inject drugs (PWID) face a heightened vulnerability to acquiring and transmitting hepatitis C virus (HCV) infection. PWID receiving MOUD treatment experience a decrease in the frequency of daily injection episodes where they share syringes with others. By reducing individual instances of syringe sharing, the cumulative probability of HCV transmission can be significantly diminished. **Methods:** The HepCEP agent-based model [PMID: 32624641], a validated tool for analyzing syringe sharing behaviors among PWID in metropolitan Chicago, Illinois, U.S.A., was used to assess actual (real-world) and hypothetical scenarios involving different levels of social and spatial inequity in methadone provider access. Synthetic spatial distributions, representative of varying geographic patterns of methadone provider locations and population characteristics, were used to demonstrate corresponding variations in population-level health outcomes (Figure 1). Through simulation studies, we examined the impact of adherent methadone treatment on reducing syringe sharing behaviors among PWID. **Results:** Irrespective of the assumptions regarding methadone access and the distribution of providers, the redistribution of methadone providers consistently leads to certain areas experiencing inadequate access to MOUDs. In all scenarios, there were regions with limited access, underscoring the significant challenge posed by the scarcity of providers in the area. Need-based distributions closely resemble the actual distribution of providers (Figure 1), suggesting that the current spatial arrangement of methadone providers already aligns with the local demand for MOUD resources. **Conclusion:** The influence of the spatial distribution of methadone providers on the frequency of syringe sharing is contingent upon access. In situations where substantial structural obstacles hinder access to methadone providers, it is most effective to distribute providers in close proximity to areas characterized by the highest need, as determined by the geographical density of PWID.

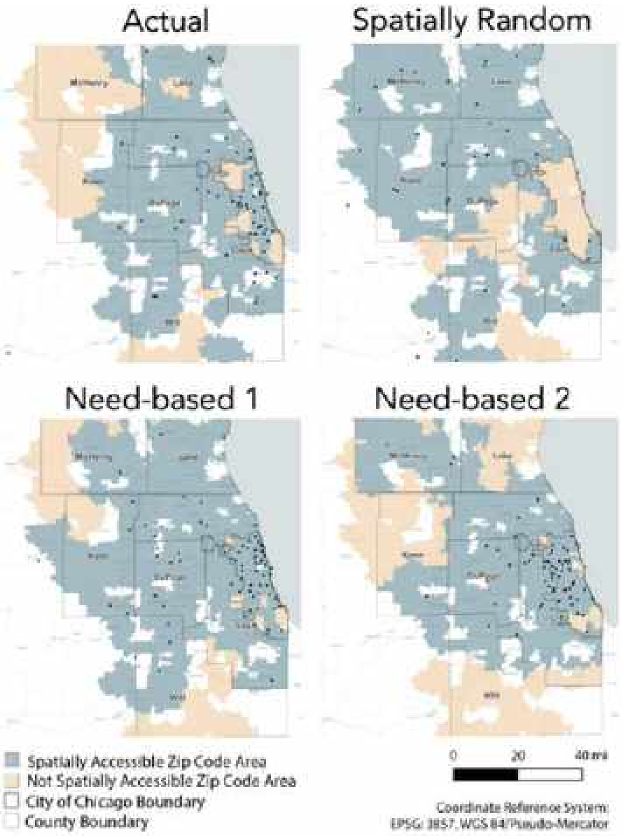
Actual
Spatially Random
Need-based 1
Need-based 2
Spatially Accessible Zip Code Area
Not Spatially Accessible Zip Code Area
City of Chicago Boundary
County Boundary
0
20
40 mi
Coordinate Reference System:
EPSG: 3857, WGS 84/Pseudo-Mercator

Figure 1. Spatial access to methadone providers for the actual scenario and three counterfactual distribution scenarios. Each dot represents the location of a single methadone provider. City of Chicago and collar county borders are indicated. Spatial access to methadone providers is calculated as distance to nearest provider to the center of each zip code area. Zip codes areas are not identified as accessible if there is no provider within a mile of its geographic center.

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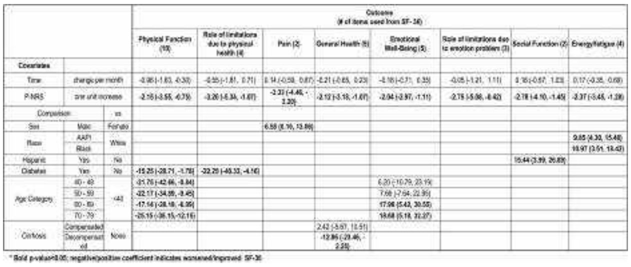
Disclosure information not available at the time of publication: Eric Tatara, Qinyun Lin, Jonathan Ozik, Marynia Kolak, Nicholson T Collier, Dylan Halpern, Luc Anselin, Basmattee Boodram, John Schneider

1845-A | PERSISTENT PRURITUS ASSOCIATED WITH WORSE QUALITY OF LIFE IN PATIENTS WITH CHRONIC HEPATITIS

Mei Lu[1], Lora Rupp[2], Christina Melkonian[2], Sheri Trudeau[2], Yihe G Daida[3], Mark A Schmidt[4] and Stuart C. Gordon[5], (1)156 Pocatello Rd, (2)Henry Ford Health, (3)Kaiser Permanente Hawai'I, (4)Kaiser Permanente Northwest, (5)William Beaumont Hospital

Background: Pruritus—itching—is common with liver disease, but its prevalence and severity among US patients with chronic hepatitis B and C (HBV, HCV) are not well-documented. A subset of patients from the Chronic Hepatitis Cohort Study (CHeCS) were surveyed to examine pruritus prevalence, persistence, and management, and the impact on patients' quality of life (QoL). **Methods:** The validated Pruritus Numeric Rating Scale (NRS) was used to assess pruritus intensity; patients who reported a score **e** 3 in the last 30 days were invited to participate in a 6-month study using the validated SF-36 questionnaire. A general regression model (univariate followed by multivariable modeling) was used to analyze associations between pruritus intensity and eight dimensions of QoL. **Results:** Among 1654 patients (HBV = 358, HCV = 1296, HBV/HCV = 6), pruritus prevalence was significantly higher among patients with HCV than those with HBV (44% vs 35%; $p < 0.05$ excluding HBV/HCV). A total of 123 patients (21 HBV and 102 HCV) with pruritus agreed to participate in a 6-month questionnaire-based study; 72% were **e** 60 years, 50% were men, 25% were Black, 22% had compensated cirrhosis, 15% had decompensated cirrhosis, and 66% had BMI > 25. Mean NRS was 4.9–5.3. QoL responses for social functioning and emotional well-being were relatively high (70–72 points), but responses for energy/fatigue were lower (50–51 points). Rates of antiviral treatment were higher in HCV patients (92%, SVR rate 99%) and 71% in patients with HBV patients (with 43% receiving ongoing treatment). Multivariable analyses showed no significant effect of either hepatitis type or antiviral treatments on itch. Antihistamine treatment was associated with severe itch. Higher NRS was associated with significantly reduced QoL across all eight dimensions analyzed (Table 1; negative coefficients indicate worse QoL, positive values indicate improvement). The strongest association was between increased itching and the impact of pain on QoL; for each additional point in the NRS, QoL changed by -3.33 units (95%CI -4.46, -2.20). There was a similar effect on the role of physical limitations on QoL (-3.20, 95%CI -5.34, -1.07). Each unit increase in NRS was also associated with a 2 to 3-unit decline in reported QoL for the remaining dimensions of emotional well-being, general health, physical function, energy/ fatigue, social functioning, and the impact of emotional health. **Conclusion:** Pruritus affects a large proportion of viral hepatitis patients, regardless of antiviral treatment status. Improved treatment options are needed to address the significant negative impact of itch on their



			Outcome (# of items used from SF-36)							
			Physical Function (10)	Role of limitations due to physical health (4)	Pain (2)	General Health (5)	Emotional Well-Being (5)	Role of limitations due to emotion problem (3)	Social Function (2)	Energy/fatigue (4)
Covariates										
Time	change per month		-0.98 (-1.63, -0.33)	-0.55 (-1.81, 0.71)	0.14 (-0.59, 0.87)	-0.21 (-0.65, 0.23)	-0.18 (-0.71, 0.35)	-0.05 (-1.21, 1.11)	0.18 (-0.87, 1.23)	0.17 (-0.35, 0.69)
P-NRS	one unit increase		-2.15 (-3.55, -0.75)	-3.20 (-5.34, -1.07)	-3.33 (-4.46, -2.20)	-2.12 (-3.18, -1.07)	-2.04 (-2.97, -1.11)	-2.75 (-5.08, -0.42)	-2.78 (-4.10, -1.45)	-2.37 (-3.45, -1.28)
Comparison		vs								
Sex	Male	Female			6.55 (0.10, 12.99)					
Race	AAPI	White								9.85 (4.30, 15.40)
	Black									10.97 (3.51, 18.43)
Hispanic	Yes	No							15.44 (3.99, 26.89)	
Diabetes	Yes	No	-15.25 (-28.71, -1.78)	-22.25 (-40.33, -4.16)						
Age Category	40 - 49	<40	-31.76 (-42.66, -8.84)				6.20 (-10.79, 23.19)			
	50 - 59		-22.17 (-34.89, -9.45)				7.66 (-7.64, 22.96)			
	60 - 69		-17.14 (-28.18, -6.09)				17.98 (5.42, 30.55)			
	70 - 79		-25.15 (-38.15, -12.15)				18.68 (5.18, 32.27)			
Cirrhosis	Compensated	None				2.42 (-5.67, 10.51)				
	Decompensated					-12.86 (-23.46, -2.25)				

* Bold p-value<0.05; negative/positive coefficient indicates worsened/improved SF-36

Disclosures: Stuart C. Gordon – AbbVie Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Arbutus: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; CymaBay: Grant/ Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; DURECT: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genfit: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GSK: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Hightide: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Mirum: Grant/ Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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1846-A | REDUCTION OF DISEASE BURDEN IN KOREAN PATIENTS WITH CHRONIC HEPATITIS C RECEIVING DIRECT-ACTING ANTIVIRALS: A NATIONWIDE, MULTICENTER, RETROSPECTIVE COHORT STUDY

Seung Up Kim[1], Won Sohn[2], Sang Hoon Ahn[1] and Young Seok Kim[3], (1)Yonsei University College of Medicine, Seoul, Republic of Korea, (2)Sungkyunkwan University School of Medicine, (3)Soon Chun Hyang University

Background: Direct-acting antivirals (DAAs) improve the prognosis of patients with chronic hepatitis C (CHC). This study investigated whether DAA treatment improves the disease burden by ameliorating the fibrotic burden in Korean patients with CHC. **Methods:** A nationwide, multicenter, retrospective cohort study was conducted that included patients with CHC recruited from 29 tertiary academic institutes in South Korea. The primary outcome was disease burden, assessed using the measure disability-adjusted life years (DALYs), with age weighting and discounting in untreated and DAA-treated groups. Improvement of fibrotic burden after DAA treatment was assessed using the APRI score and FIB-4 index. The clinical outcomes were hepatocellular carcinoma, liver transplantation, decompensation, or death. **Results:** Between January 2007 and December 2022, data from 11,726 patients with CHC, including

8,464 (72%) treated with DAAs, were analysed. During the follow-up period (median 27.5 mo), 469 patients died (353 [10.8%] in the untreated group, 116 [1.4%] in the DAA-treated group), 586 developed hepatocellular carcinoma (343 [10.5%] in the untreated group, 243 [2.9%] in the DAA-treated group), 580 developed decompensation (372 [11.4%] in the untreated group, 208 [2.5%] in the DAA-treated group), and 18 underwent liver transplantation (8 [0.2%] in the untreated group, 10 [0.1%] in the DAA-treated group). The multivariable analyses showed that DAA-treated group significantly reduced mortality, HCC risk, and decompensation development compared to the untreated group (hazard ratio [HR] = 0.22, 95% confidence interval [CI] 0.17-0.27; HR = 0.47, 95% CI 0.39-0.58; and HR = 0.31, 95% CI 0.26-0.37, respectively) (all $p < 0.001$). The APRI-based DALY estimate was significantly lower in the DAA-treated group than in the untreated group (mean 5.0 ± 2.9 vs. 5.9 ± 3.8 y, $p < 0.001$), as was the FIB-4-based DAL estimate (mean 5.7 ± 2.7 vs. 6.3 ± 3.5 y, $p < 0.001$). The difference between the two groups with respect to either the APRI- or FIB-4-based DALYs was highest in patients 40–60 years of age. **Conclusion:** DAA treatment significantly improved the clinical outcomes of CHC patients and reduced the disease burden, by improving the fibrotic burden after DAA treatment.

Disclosures: The following people have nothing to disclose: Seung Up Kim, Won Sohn, Sang Hoon Ahn, Young Seok Kim

1847-A | RISK FACTORS FOR LIVER-RELATED OUTCOMES AFTER SUSTAINED VIROLOGIC RESPONSE TO DIRECT ACTING ANTIVIRALS IN PATIENTS WITH CHRONIC HEPATITIS C

Seung Up Kim, Severance Hospital, Seoul, Republic of Korea, Won Sohn, Sungkyunkwan University School of Medicine, Sang Hoon Ahn, Yonsei University College of Medicine, Seoul, Republic of Korea and Young Seok Kim, Soon Chun Hyang University

Background: Direct acting antivirals (DAAs) is the mainstay of antiviral therapy for patients with chronic hepatitis C (CHC). We investigated risk factors for liver-related outcomes after sustained virologic response (SVR) to DAAs in patients with CHC. **Methods:** This multicenter, retrospective, nationwide cohort study consisted of 1,248 patients with CHC who were seen at 29 expert hepatology centres in Korea from January 2015 to December 2022 and who achieved SVR after DAA therapy. The primary outcome was the development of liver-related events (LREs) after SVR, including all-cause death, hepatocellular carcinoma (HCC), decompensation, or liver transplantation. The fibrotic burden at baseline and at SVR was assessed using transient elastography (TE) and the FIB-4 index. **Results:** The mean age of the patients was 59.8 years and 58% (n = 722) were male. The prevalence of genotypes 1 and 2 was 52% and 46%, respectively. The mean liver stiffness value was 11.6 ± 9.8 kPa at baseline and 8.8 ± 7.5 kPa at SVR. LREs developed in 77 (6.2%) patients and consisted of death in 13, HCC in 34, decompensation in 44 and liver transplantation in 2 patients. The multivariable analysis showed that TE-defined cirrhosis at baseline (liver stiffness e 14.5 kPa; hazard ratio [HR] = 2.56; 95% confidence interval [CI] 1.30–5.07) and FIB-4-defined advanced fibrosis stage at SVR (> 3.25) (HR = 3.24; 95% CI 1.45–7.22) were independently associated with an increased risk of developing LREs (all $P < 0.05$), together with male sex (HR = 1.99; 95% CI 1.26–3.14) and lower serum albumin level at SVR (< 4.0 g/dL) (HR = 1.87; 95% CI 1.12–3.13) (all $P < 0.05$). **Conclusion:** The fibrotic burden decreased in patients with CHC after DAA treatment. However, the risk of developing LREs remained even after SVR. Our study showed that an assessment of fibrotic burden before and after DAA treatment is required for predicting outcomes in patients with DAA-treated CHC who achieve SVR.

Disclosures: Sang Hoon Ahn – SL Vaxigen: Advisor, No, Yes; Samil: Advisor, No, Yes; Roche: Advisor, No, Yes; Janssen: Advisor, No, Yes; Inovio: Advisor, No, Yes; Ildong: Advisor, No, Yes; GSK: Advisor, No, Yes; GreenCross: Advisor, No, Yes; Gilead Sciences Inc.: Advisor, Yes, No; GeneOne Life Science: Advisor, No, Yes; Brii: Advisor, No, Yes; Assembly Biosciences: Advisor, No, Yes; Arbutus: Advisor, No, Yes; Aligos: Advisor, No, Yes; Abbvie: Advisor, No, Yes; Vaccitech: Advisor, No, Yes; Vir Biotechnology: Advisor, No, Yes; Yuhan: Advisor, No, Yes;

The following people have nothing to disclose: Seung Up Kim, Won Sohn, Young Seok Kim

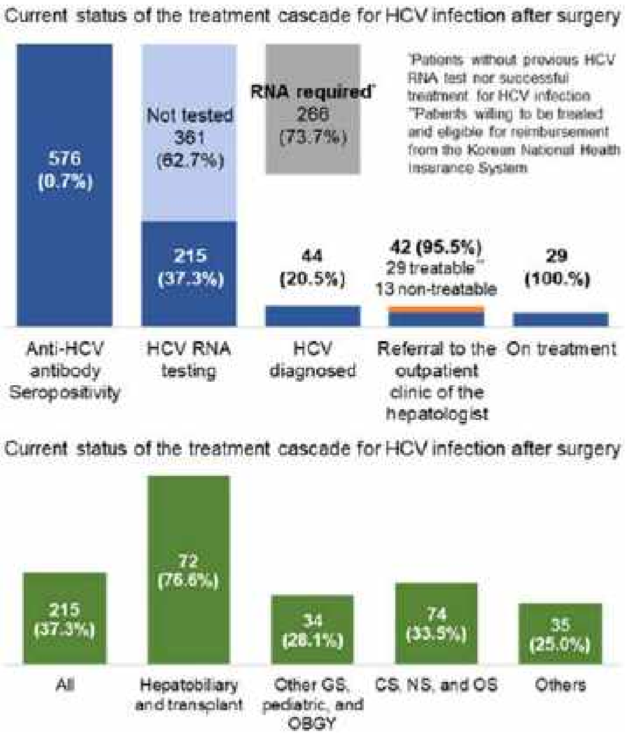
1848-A | SCREENING, CONFIRMATION, AND TREATMENT RATE OF HEPATITIS C VIRUS INFECTION IN PATIENTS UNDERGOING SURGERY AND APPLICATION OF AN EMR-BASED AUTOMATIC ALERT SYSTEM IN A SINGLE TERTIARY ACADEMIC CENTER

Jae Seung Lee[1,2], Hye Won Lee[1,3,4], Beom Kyung Kim[1,2], Jun Yong Park[1,2], Do Young Kim[1,2], Sang Hoon

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

Ahn[1] and Seung Up Kim[1,2], (1)Yonsei University College of Medicine, Seoul, Republic of Korea, (2) Severance Hospital, Seoul, Republic of Korea, (3) Yonsei Liver Center, Severance Hospital, Seoul, South Korea, (4)Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, South Korea

Background: A lack of awareness disturbs proper linkage to care for hepatitis C virus (HCV) infection in patients undergoing surgery. Therefore, we aimed to evaluate the status of HCV screening, confirmation, and treatment rates in patients undergoing surgery in the era of pan-genotypic direct-acting antivirals (DAAs). Additionally, we established and tested an EMR-based automatic alert system for the detection of patients with HCV infection. **Methods:** Patients who underwent surgery in a tertiary academic center between 2019 and 2021 were eligible for this retrospective study. The testing and positivity rates for anti-HCV antibodies and HCV RNA were sequentially analyzed. Additionally, an EMR-based automatic alert system for patients with positive anti-HCV within 3-years before surgery who had yet to be referred to hepatologists was adopted in January 2022 to help surgical departments adequately consult these patients to hepatologists before discharge. **Results:** Between 2019 and 2021, 96894 patients (40121 males, 41.4%) who underwent surgery under general anesthesia were recruited. The median age of the study population was 55.0 years. Of 83920 (86.6%) patients who tested anti-HCV antibody, 576 (0.7%) patients showed positive results with a higher proportion of diabetes mellitus (32.6% vs. 18.5%), hypertension (50.5% vs. 28.6%), liver cirrhosis (13.2% vs. 1.7%) and unfavorable laboratory test results (all $P < 0.05$). HCV RNA was confirmed in 215 (37.3%) patients, with a 20.5% (n = 44) positivity rate. HCV RNA confirmation was required in 266 of 361 (73.7%) patients without HCV RNA test results. Of 44 patients, 42 (95.5%) were referred for treatment, and 29 (69.0%) treatable patients were successfully treated using DAA. HCV RNA confirmation rates were higher in the hepatobiliary and transplant surgery (76.6%) than in the other surgery parts (25.0–33.5%). The newly established automatic alert system alarmed 449 (0.6%) patients from 75,724 discharges after surgery between January 2021 and April 2023. However, only 101 (22.5%) patients were referred to hepatologists even after the automatic notification to the surgical departments. **Conclusion:** Many patients who tested positive for anti-HCV antibodies for surgery still failed to be linked for proper management in the era of pan-genotypic DAA. The attenuated awareness, which continued even after applying an EMR-based automatic alert system, suggests the necessity of comprehensive education with forceful referral or retrospective call-back approach without infringing on the patient's legal privacy.@



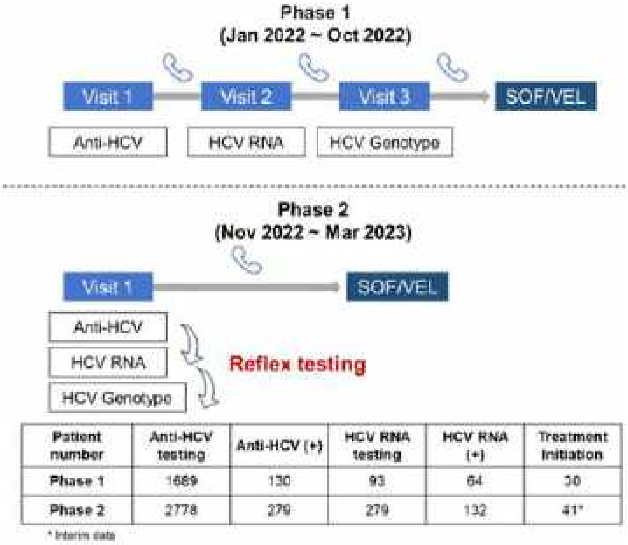
Disclosures: The following people have nothing to disclose: Jae Seung Lee, Hye Won Lee, Beom Kyung Kim, Jun Yong Park, Do Young Kim, Sang Hoon Ahn, Seung Up Kim

1849-A | SIMPLIFIED HEPATITIS C DIAGNOSIS AND TREATMENT STRATEGY ON OUTPATIENT CARE FOR PEOPLE LIVING WITH HIV : A PILOT STUDY IN SOUTHWEST CHINA

Xiao Li[1,2], Xinping Yang[2], Quanying He[2], Yunqiu Yang[2], Shifang Liu[2], Lin Gui[2], Xingqiong Chen[2], Mei Liu[2], Jie Yang[2], Qiong Huang[2], Yanjiang Xu[2], Lihong Gong[2], Xiao Song[1,2], Canzhu Shang[1,2] and Huiqin Li[2], (1) Kunming Medical University,Kunming, Yunnan, China, (2)Yunnan Provincial Infectious Disease Hospital, Kunming, Yunnan, China

Background: The simplification of current hepatitis C (HCV) diagnostic algorithms and service delivery is very crucial to achieving the WHO goal by 2030. To increase timely diagnosis and improve the linkage to care in people living with human immunodeficiency virus (PLWH), HCV reflex testing and a call-back strategy was implemented in a outpatient-clinic of a territorial hospital in Southwest China. **Methods:** The pilot study was conducted in two phases. In Phase 1 (Jan 2022 ~ Oct 2022), the traditional approach to HCV diagnosis including at least 3 visits was adopted. The coordinating

nurses followed up each testing result and called the patients with positive result back for the next visit. In Phase 2(Dec 2022 ~ Mar 2023), reflex testing for HCV RNA and genotype was implemented which only required one visit to confirm HCV diagnosis (Figure 1). 12-week Sofosbuvir/Velpatasvir regimen was administered to HCV viremic patients, and weight-based ribavirin was added for genotype 3 patients. **Results:** In phase 1, a total of 1689 PLWH were included during 10-month study period. With close follow-up by coordinating nurses, 93 anti-HCV positive patients came back for HCV RNA testing and the RNA diagnostic rate was only 71.5% (93/130). Genotype distribution: 10.0% (3/30)GT1b, 33.3% (10/30) GT3a ,43.3% (13/30) GT3b,10.0% (3/30) GT6n ,3.3% (1/30)GT6xa. 30 HCV viremic patients initiated SOF/VEL treatment and achieved SVR12. In phase 2, totally 2778 PLWH were included during 4-month period. The patients of Phase 2 with the "one-visit for diagnosis" strategy, the RNA diagnostic rate increased to 100% (279/279).Phase 2 Genotype distribution: 19.5% (8/41)GT1b, 26.8% (11/41) GT3a ,31.7% (13/41) GT3b,4.8%(2/41)GT6a,12.1% (5/41) GT6n ,2.4% (1/41) GT6u,one person genotyping was not detected. Compared with the Phase 1, the mean time from screening to treatment initiation was shorten from 144 days(144.47 ± 47.29) to 61 days (61.46 ± 25.59), $p < 0.01$. **Conclusion:** The application of the reflex testing significantly increased HCV diagnosis rate and efficiently improved the HCV care cascade efficiently in the HIV outpatient clinic. The simplified HCV diagnosis and treatment strategy could be scaled up for HIV services in China.



Patient number	Anti-HCV testing	Anti-HCV (+)	HCV RNA testing	HCV RNA (+)	Treatment Initiation
Phase 1	1689	130	93	64	30
Phase 2	2778	279	279	132	41*

* Interim data

Figure 1 HCV patient journey in study phase 1 and phase 2

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1850-A | SPECIFIC RISK GROUPS FOR HCV INFECTION: SCREENING DATA FROM LATVIA

Ieva Tolmane[1,2], *Ieva Siksaliete*[3], *Inga Upmace*[4], *Inga Bulmistre*[5], *Agita Jeruma*[1], *Inga Azina*[1] *and Baiba Rozentale*[1], *(1)Riga East University Hospital, (2) University Og Latvia, (3)Riga Stradins University, (4) Balthiv, (5)Diseases Prevention and Control Center*

Background: There are 58 million people living with chronic hepatitis C virus according to WHO data published in 2021. Hepatitis C has lead to approximately 290 000 deaths worldwide in 2019 mainly due to liver cirrhosis and hepatocellular carcinoma. According to previous population screening studies done in Latvia, there is a 2,4% anti-HCV prevalence. There is an anti-HCV screening done in Latvia's psychiatry hospitals reviled a prevalence of 6,8%. The aim of this study was to analyse screening, demographic and risk factor data regarding HCV infection in social care centres and shelters in Latvia. **Methods:** The study was done from October 2020 till October 2022 by HIV Prevention Point employees. Data were obtained using HCV rapid antigen tests and a questionnaire. The participants answered questions concerning demographics and risk factors like sexual activity, intravenous (IV) narcotic use and incarceration. 2838 tests were done in 46 social care centres (SCC) during 61 testing visits. 349 tests were done in 6 shelters during 13 testing visits. Data were analysed using MS Excel and IBM SPSS. **Results:** The mean age in SCC was 58 years (range 16 - 102) and 56 years in shelters (range 20 – 81). 10,3% of SCC residents noted that they were sexually active during the last 12 months. 19% of those who were sexually active used a condom. 5.6% admitted incarceration and 1.2% had IV narcotic use. In shelters 32.7% have been sexually active during the last 12 months of whom 31.6% used condoms. 26.9% admitted incarceration and 6.8% had IV narcotic use. 5.4% of performed tests in SCC were positive for anti-HCV and 12% in shelters. 11% had a history of IV narcotic use ($p < 0.001$) and 21.3% have been incarcerated ($p < 0.001$) of those with a positive anti-HCV test in SCC. 25% had a history of IV narcotic use ($p < 0.001$) and 46.9% have been incarcerated ($p = 0.008$) of those with positive anti-HCV test in shelters. And it is significantly higher rate in comparison to persons not been incarcerated or IV drug users in both groups. **Conclusion:** Residents of SCC and shelters in Latvia have a 2- and 5-times higher prevalence respectively of anti-HCV than the general population of Latvia. However, when compared to Latvia's psychiatry hospitals prevalence is lower in SCC and higher in shelters. The key risk factors in both populations of this study were highlighted as previous incarceration and IV narcotic use. These findings

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correlate with risk factors in the psychiatric hospital patient population and population in total. Both SCC and especially shelter populations are at high risk of HCV infection. Screening tools and primary health care professionals should be made more available for these populations.

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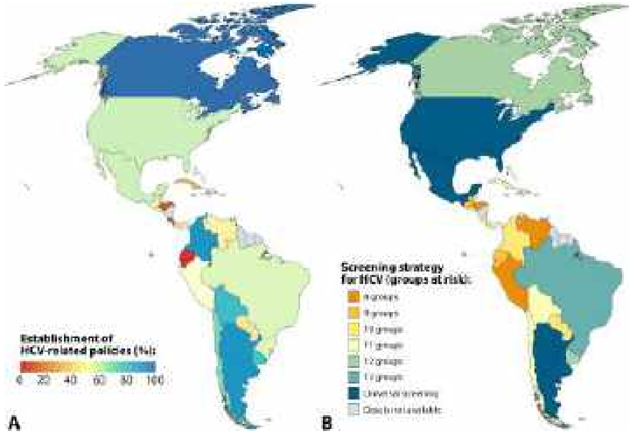
Disclosure information not available at the time of publication: Ieva Siksaliete, Inga Upmace, Inga Bulmistre, Agita Jeruma, Inga Azina, Baiba Rozentale

1851-A | STRATEGIES TO ELIMINATE HEPATITIS C VIRUS INFECTION IN THE AMERICAS

Luis Antonio Diaz[1], Sergio García[1], Gustavo Ayares[1], Javier Uribe[1], Francisco Idalsoaga[2], José Miguel Fuentealba[3], Eduardo Fuentes-López[1], María Paz Medel[1], Carolina A. Ramirez-Cadiz[4], Rayan Khan[4], Mariana Lazo[5], Catterina Ferreccio[6], Manuel Mendizabal[7], Melisa Melisa Dirchwolf[8], Patricia Guerra Salazar[9], Claudia PMS Oliveira[10], Mario G. Pessoa[11], Mario R. Alvares-Da-Silva[12], Giada Sebastiani[13], Mayur Brahmania[14], Alnoor Ramji[15], Mina Niazi[16], Hin Hin Ko[15], Jordan J. Feld[17], Juan Carlos Restrepo[18], Wagner Enrique Ramirez Quesada[19], Omar Alfaro[20], Marlen Ivon Castellanos Fernandez[21], Enrique Carrera Estupiñan[22], Jose Roberto Aguirre[23], Katherine Maldonado[24], Abel Sanchez[24], Marco Sanchez[25], Teresa Andara Sr[26], Graciela Elia Castro-Narro[27], Norberto Carlos Chavez-Tapia[28], Nahum Mendez-Sanchez[29], Enrique Adames-Almengor[30], Julissa Lombardo[31], Marcos Girala Sr[32], Elias Moran[33], P. Martin Padilla-Machaca[34], Javier Diaz Ferrer[35], Martin Tagle[36], Vitoria Mainardi[37], Nelia Hernandez[38], Edmundo Martínez[39], Edilmar Alvarado-Tapias[40], Roberto Leon[41], Andrew Talal[42], Emmanuel Thomas[43], Sandra Springer[44], Mauricio Garcia Saenz de Sicilia[45], Wei Zhang[46], Jasmohan S. Bajaj[47], Elliot B. Tapper[48], Manhal Izzy[49], Robert G. Gish[50], Bashar M. Attar[51], Thomas G. Cotter[52], Michael R. Lucey[53], Patrick S. Kamath[54], Ashwani K. Singal[55], Ramon Bataller[56], Gabriel Mezzano[57], Alejandro Soza[1], Jeffrey V. Lazarus[58], Marco Arrese[59], Juan Pablo Arab[60] and Observatorio Multicéntrico de Enfermedades Gastrointestinales (OMEGA), (1)Pontificia Universidad Católica De Chile, (2)Pontificia Universidad Católica De Chile, Buin, Chile, (3)Universidad Finis Terrae, (4)Western University, (5)Drexel University School of Public Health, (6)Advance Center for Chronic Diseases, Accdis, (7)Hospital Universitario Austral, (8)Hospital Privado De Rosario, (9)Iinstituto De Gastroenterología Boliviano-Japoné, (10)University of Sao Paulo School of Medicine, (11)University of São Paulo School of Medicine (FMUSP), (12)Hospital De Clínicas De Porto Alegre, (13)Mcgill University Health Centre, (14)University of Calgary, (15)Division of Gastroenterology, University of British Columbia, BC, Canada, (16)University of Saskatchewan, (17)Toronto Centre for Liver Disease/Viral Hepatitis Care Network (VIRCAN), University Health Network, Toronto, Canada, (18)Hospital Pablo Tobon Uribe, (19)Clínica Equilibrium, (20)Hospital San Carlos, (21)Institute of Gastroenterology, University of Medical Sciences of Havana, Cuba, (22)Departamento De Gastroenterologia y Hepatologia, Hospital Eugenio Espejo, Quito, Ecuador, (23)Instituto Salvadoreño Del Seguro Social, (24)Hospital Roosevelt, (25)Hospital Escuela Universitario, (26)Instituto Hondureño de Seguridad Social, (27)Medica Sur Clini, (28)Medica Sur, (29)National Autonomous University of Mexico, (30)Hospital Santo Tomas, (31)Hospital Punta Pacífica, (32)Universidad Nacional de Asuncion, (33)Hospital De Clínicas, Universidad Nacional De Asunción, Asuncion, (34)Guillermo Almenara National Ho, (35)Universidad San Martin De Porres, Lima, Peru, (36)Clinica Anglo, (37)Hospital Central De Las Fuerzas Armadas, (38)Clínicas Hospital, Montevideo, Uruguay, (39)Hospital Sotero Del Rio, (40)Hospital De La Santa Creu I Sant Pau, (41)Instituto Médico La Floresta, (42)University at Buffalo, (43)University of Miami Miller School of Medicine, Schiff Center for Liver Diseases, (44)Yale School of Medicine, New Haven, CT, (45)University of Arkansas, (46)MGH, (47)Virginia Commonwealth University and Central Virginia Veterans Healthcare System, Richmond, VA, (48)University of Michigan Medical Center, (49)Vanderbilt University Medical Center, (50)Hepatitis B Foundation, La Jolla, CA, (51)Cook County Health, and Hospital Systems, (52)University of Texas Southwestern Medical Center, Dallas, TX, (53)University of Wisconsin School of Medicine and Public Health, Madison, WI, (54)Mayo Clinic, Rochester, MN, (55)Department of Medicine, University of South Dakota Sanford School of Medicine, Vermillion, SD, USA, (56)Barcelona Clinic, Barcelona, Spain, (57)Hospital Del Salvador, (58)Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Barcelona, Spain, (59)Departamento De Gastroenterologia, Escuela De Medicina, Pontificia Universidad Catolica De Chile, Santiago, Chile; Centro De Envejecimiento y Regeneración (CARE), Facultad De Ciencias Biológicas, Pontificia Universidad Católica De Chile, Santiago, Chile, (60)University of Western Ontario, London, ON, Canada

Background: Although the WHO strategy has the goal to eliminate the hepatitis C virus (HCV) as a public health threat by 2030, the existence of national strategies is variable worldwide. We aimed to assess the establishment of different policies and strategies to eliminate HCV in the Americas. **Methods:** We conducted a 23-item survey about HCV infection among gastroenterologists and hepatologists in the Americas. Questions were classified into four categories: policies and civil society (1 question), diagnosis (6 questions), care management (14 questions), and monitoring systems (2 questions). The survey was carried out using an electronic form between November 2022 – May 2023. Data were collected in a spreadsheet, revised by two independent reviewers, and compared with governmental institutions, regulatory agencies, scientific societies, and scientific publications. We estimated an index obtained from a regression scoring method through exploratory analysis, and row values were normalized from 0 to 100 using a min-max method. **Results:** We obtained 52 responses from 19 out of 21 countries targeted. The median HCV-related policies index was 51.4 [IQR: 27.3–70.1]. The lower establishment of HCV-related policies was observed in Ecuador (0.0), Honduras (6.6), and Costa Rica (9.8), while the highest performance was observed in Argentina (94.1), Colombia (94.7), and Canada (100) (Figure A). Fifteen (78.9%) countries have adopted a national strategic plan to eliminate HCV. Three (15.8%) countries have universal screening for HCV infection (Figure B). After a positive HCV serological test, 10 (52.6%) countries perform reflex testing to confirm HCV diagnosis using the same sample. However, only 7 (36.8%) countries have an alert system for the requesting physician. Twelve (63.2%) countries have a direct referral system for specialized care of HCV-positive cases. There is universal access to direct-acting antivirals (DAAs) in 15 (78.9%) countries. Universal access to DAAs was not widely available in Cuba, Ecuador, Venezuela, and the United States. Seven (36.8%) countries have generic DAAs available. Only 3 (15.8%) countries perform a retrospective search for HCV-positive cases that could have been lost to follow-up. **Conclusion:** Although most countries have adopted a national strategic plan to eliminate HCV, there are several issues and barriers to elimination in the Americas.


Establishment of HCV-related policies (%):
0
20
40
60
80
100
A
Screening strategy for HCV (groups at risk):
Universal screening
Data not available
B

Disclosures: Hin Hin Ko – GSK: Consultant, No, No; Gilead: Consultant, No, No; Ipsen: Consultant, No, No; Abbvie: Consultant, No, No; Sanofi: Consultant, No, No; Celgene: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Eupraxia Pharmaceuticals Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Dr. Falk Pharma.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Escient Pharmaceuticals Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Madrigal Pharmaceutical Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

Jordan J. Feld – AbbVie: Consultant, No, No; AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Eiger: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Consultant, No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GSK: Consultant, No, No; Janssen: Consultant, No, No; Janssen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

Andrew Talal – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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Jasmohan S. Bajaj – Bausch: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Grifols: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Sequana: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

Robert G. Gish – Abbott: Consultant, No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; HepQuantum: Stock – privately held company (individual stocks and stock options), No, No; Ganlantis: Stock – privately held company (individual stocks and stock options), No, No; Eiger: Stock – privately held company (individual stocks and stock options), No, No; Prodigy: Advisor, No, No; Venatorx: Consultant, No, No; Topography Health: Consultant, No, No; Pfizer: Consultant, No, No; Merck: Consultant, No, No; Janssen: Consultant, No, No; Intercept: Speaking and Teaching, No, No; HepQuant: Advisor, No, No; HepaTx: Advisor, No, No; Helios: Consultant, No, No; Gilead Sciences: Consultant, Yes, No; GLG: Consultant, No, No; Genlantis: Consultant, No, No; Genentech: Consultant, No, No; Enyo: Consultant, No, No; Eiger: Advisor, No, No; Dynavax: Consultant, No, No; Arrowhead: Consultant, No, No; Antios: Consultant, No, No; Altimmune: Consultant, No, No; Abbvie: Speaking and Teaching, No, No; Abbott: Consultant, No, No; Eisai: Consultant, No, No; Gilead Sciences: Consultant, No, No; CymaBay: Advisor, No, No; Durect: Advisor, No, No; AstraZeneca: Speaking and Teaching, No, No; BMS: Speaking and Teaching, No, No; Eisai: Speaking and Teaching, No, No; Hepquant: Stock – privately held company (individual stocks and stock options), No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

Michael R. Lucey – target. Pharmasolutions: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Novartis: Advisor, No, Yes;

Ramon Bataller – Abbvie: Speaking and Teaching, No, Yes;

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The following people have nothing to disclose: Luis Antonio Diaz, Sergio García, Gustavo Ayares, Javier Uribe, Francisco Idalsoaga, Eduardo Fuentes-López, María Paz Medel, Carolina A. Ramirez-Cadiz, Rayan Khan, Mariana Lazo, Catterina Ferreccio, Manuel Mendizabal, Melisa Melisa Dirchwolf, Patricia Guerra Salazar, Claudia PMS Oliveira, Mario G. Pessoa, Mario R. Alvares-Da-Silva, Giada Sebastiani, Mayur Brahmania, Alnoor Ramji, Mina Niazi, Juan Carlos Restrepo, Wagner Enrique Ramirez Quesada, Omar Alfaro, Marlen Ivon Castellanos Fernandez, Enrique Carrera Estupiñan, Graciela Elia Castro-Narro, Nelia Hernandez, Wei Zhang, Elliot B. Tapper, Manhal Izzy, Thomas G. Cotter, Ashwani K. Singal, Juan Pablo Arab

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

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

School of Medicine, (2)VA Greater Los Angeles Healthcare System, (3)Greater Los Angeles VA Healthcare System, (4)University of California, Los Angeles

Background: Veterans experiencing homelessness (VEH) face multiple barriers to Hepatitis C (HCV) diagnosis and treatment. We implemented and evaluated a novel universal HCV screening, care linkage, and treatment program for Veterans living at a tiny shelter encampment on the West Los Angeles Veterans Affairs campus. **Methods:** We implemented a low-barrier HCV treatment program for VEH in January 2022 that involved clinical dashboard evaluation and universal HCV screening, a novel e-consult direct-to-treatment program facilitated by pharmacists and referral to Infectious Diseases (ID)/Gastroenterology (GI) clinics (if ineligible for e-consult), and extensive engagement by providers. Veterans admitted to the encampment were assessed for HCV Antibody (HCV Ab) positivity and viremia via a local clinical dashboard developed from the National Hepatitis C Registry and universal HCV screening. Subsequent Veterans with HCV viremia were linked to care via an e-consult program, resulting in immediate treatment or referral to a liver clinic. Direct-acting antivirals (DAA) were delivered weekly to Veterans by medical teams. HCV RNA levels were obtained 12 weeks after the end of treatment (SVR12) to assess for treatment efficacy. Demographics, medical history, healthcare visits, and HIV and Hepatitis B (HBV) serologic results were abstracted from the electronic health record. **Results:** Of the 372 Veterans admitted since January 1, 2022, 59 (16%) had a positive HCV Ab. None had co-infection with HBV, and one had co-infection with HIV. Forty-eight percent (28/59) had HCV viremia. The median age for Veterans with HCV viremia was 64 years; all were male, 36% (11/28) were Black, 11% (3/28) were Hispanic, and 54% (15/28) were White. HCV linkage to care occurred in 75% (21/28) of Veterans (18 via e-consult, 3 via clinic referral). DAA initiation occurred in 71% (20/28). Of those who initiated DAA therapy, were not lost to follow-up, and had SVR12 results, 7 Veterans (100%) achieved SVR. Of Veterans with positive HCV Ab, 56% percent (34/59) were immune to Hepatitis B, and 80% (47/59) were immune to Hepatitis A. Of the 22 patients not immune to HBV, immunization was initiated at the encampment in 32% (7/22) of Veterans. **Conclusion:** In a small cohort, we demonstrate the feasibility of encampment-based HCV screening for VEH and high linkage to care and SVR rates. We also show the successful incorporation of other ID screening and immunization.

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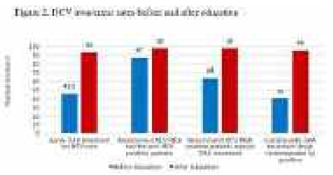
The following people have nothing to disclose: Cassandra Coleman Lautredou, Kimberly Lynch, Katherine Stricker, Peter Capone-Newton, Matthew McCoy, Jenna H Kawamoto, Arpan Arun Patel, Michele Seckington

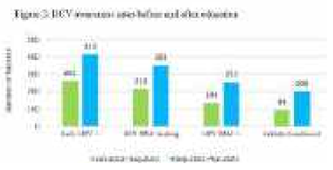
1853-A | SUPPORTING HCV ELIMINATION THROUGH MEDICAL EDUCATION TOURS PROJECT IN SOUTHWEST CHINA

Chunmei Li, Jia Wei and Hui Li, Hospital of Yunnan University

Background: Awareness of HCV disease and treatment rate were still very low in the resource-constrained rural/remote areas. We aimed to evaluate the effectiveness of medical education tours for health care providers (HCPs) disease awareness and the HCV link-to-care rates in county hospitals in Yunnan, China **Methods:** HCV disease specialists from Affiliated Hospital of Yunnan University and Health Commission of Yunnan province gave medical speeches including HCV disease knowledge training, update of HCV guideline and government policy of HCV elimination work among different cities in Yunnan for different levels of hospitals. HCV awareness questionnaires were provided to each attendee before and after education to assess the baseline knowledge and effectiveness of education. With the guidance of experts, HCV micro-elimination model in each area was carried out after education tour. **Results:** From Sep.2022 to Apr. 2023, a total of 5 viral hepatitis education speaker tours were held. Above 500 primary HCPs including Infectious Disease (ID) department and non-ID departments received the education from 11 counties in Yunnan Province (Figure 1). 146 HCPs completed paired surveys before and after education and disease awareness rates were increased significantly after education (Figure 2). In-hospital referral process of anti-HCV positive individual's from non-ID departments to ID department was improved in 14 county hospitals. Before the education tour project, 2237 patients received HCV screening from Jan 2022 to Aug 2022. After the project, 3167 patients received HCV antibody screening from Sep 2022 to Apr 2023. The rate of link-to-diagnosis rate before and after education was 81% (212/261) and 85% (351/431) respectively. The rate of link-to-treatment was increased from 70% (94/134) to 79% (200/253) after education (Figure 3) **Conclusion:** Medical education tours could raise the HCV disease awareness of local HCPs and improved the HCV screening and linkage to care in rural/remote areas.

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





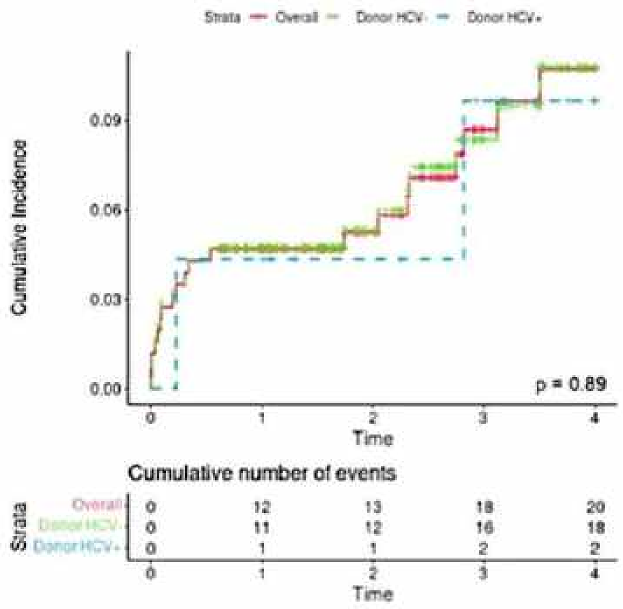
Disclosures: The following people have nothing to disclose: Chunmei Li, Jia Wei, Hui Li

1854-A | SURVIVAL, REJECTION AND EXTRA-HEPATIC MANIFESTATIONS FROM TRANSPLANTATION OF HEPATITIS C + HEARTS: A QUATERNARY CENTER EXPERIENCE

Ritika M. Mazumder, Sarah Khan, Qijun Yang, James Bena, Omar T. Sims and William D. Carey, Cleveland Clinic

Background: Donor organ shortages have consistently afflicted the field of solid organ transplantation. Although direct-acting antiviral (DAA) therapy has enabled successful use of HCV+ organs with favorable initial results, long-term outcome data beyond 12 months post-transplant remains insufficient. This study aimed to assess mortality, rejection rates, and extrahepatic manifestations of Hepatitis C in aviremic recipients of HCV+ hearts. **Methods:** This retrospective cohort study included all adult heart transplants at our center between January 2018 and September 2022. **Results:** A total of 256 heart transplant patients (23 HCV+ donors, 233 HCV- donors) were included. All recipients were HCV aviremic prior to transplant. Over a 4-year follow-up period, there was no statistical difference in survival between HCV+ and HCV- heart recipients (90% vs 89%, p = 0.89, Figure 1). Similarly, a multivariate proportional hazard model of survival showed that donor HCV status was not associated with death (HR 0.81, p = 0.78, Table 1). None of the patients developed fibrosing cholestatic hepatitis. No definitive extra-hepatic manifestations of HCV were noted in HCV+ heart recipients, including nephropathy, neuropathy, cryoglobulinemia or dermatitis. Rates of acute cellular rejection, chronic rejection and antibody-mediated rejection for HCV+ heart recipients were 96%, 13% and 0% respectively. All but one patient developed HCV viremia after receiving an HCV+ organ (96%), and the majority were treated with glecaprevir/pibrentasvir (86%). All viremic patients achieved sustained virologic response with one round of treatment. The median time to HCV clearance was 11.8 (6.0, 13.0) weeks. HCV genotypes 1a (45%) and 3 (32%) were the most prevalent. None of the patients contracted HBV or HIV infections from their high-risk donors. **Conclusion:** For heart transplant recipients, donor HCV status is not associated with mortality over 4 years. Nearly all patients with HCV+ donors acquired HCV and 100% of those infected were cured with a single 12-week course of DAA therapy. Extrahepatic effects of HCV were not encountered. Ongoing work at our institution aims to examine rejection rates in all heart recipients, enabling fair comparisons. Overall, our data suggests long-term safety in utilizing HCV+ hearts for enlarging the pool of limited organs. Future studies may examine variations of DAA therapy, such as shorter treatment durations and preemptive treatment strategies.

Figure 1. Cumulative Incidence of Death at 4-Years (N= 256, Death=20)



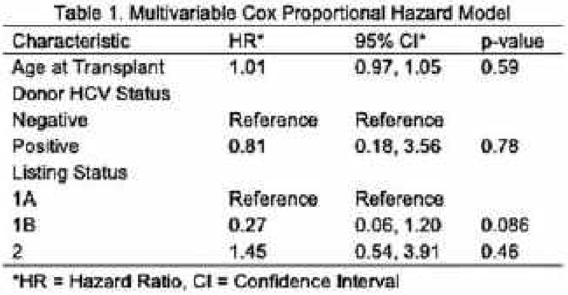


Table 1. Multivariable Cox Proportional Hazard Model

Characteristic	HR*	95% CI*	p-value
Age at Transplant	1.01	0.97, 1.05	0.59
Donor HCV Status			
Negative	Reference	Reference	
Positive	0.81	0.18, 3.56	0.78
Listing Status			
1A	Reference	Reference	
1B	0.27	0.06, 1.20	0.086
2	1.45	0.54, 3.91	0.46

*HR = Hazard Ratio, CI = Confidence Interval

Disclosures: The following people have nothing to disclose: Ritika M. Mazumder
Disclosure information not available at the time of publication: Sarah Khan, Qijun Yang, James Bena, Omar T. Sims, William D. Carey

1855-A | SUSTAINED VIROLOGIC RESPONSE 4 WEEKS AFTER HEPATITIS C TREATMENT HAS A HIGH SENSITIVITY AND POSITIVE PREDICTIVE VALUE FOR CURE

Gia Landry[1,2,3], Frederic McCall III[3], Elizabeth N. Britton[4], Lisa Chang[3] and Kristina Larson[3], (1)Ochsner Health, (2)Louisiana State University, (3)Louisiana Department of Health, (4)Louisiana Department of Health/ Office of Public Health

Background: The United States is starting its plan for nationwide hepatitis C virus (HCV) elimination. Louisiana (LA) is one of a few states to have a statewide HCV elimination program. One part of a successful elimination program will be the sustained virologic response (SVR) rates. It can be difficult in these public health initiatives to have patients get SVR testing 12 weeks after treatment. Therefore, we designed this study to see if SVR 4 weeks after HCV treatment is adequate for determining HCV cure in a large, HCV elimination program. **Methods:** All persons in LA on Medicaid who completed HCV treatment from July 15, 2019 – October 31, 2022 were analyzed. HCV treatment completion was determined by Medicaid claims data. SVR4 and SVR12 were defined as having a negative HCV RNA test 3-6 weeks and e 10 weeks after HCV treatment, respectively. SVR data is based on those with SVR testing. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for SVR4 were calculated using SVR12 as the definition of cure. **Results:** There were 9,582 persons who completed treatment for HCV. 599 persons (6%) had SVR4 testing, 6,669 (70%) had SVR12 testing and 408 (4%) had both SVR 4 and SVR12 testing. SVR4 testing was done at a median of 5 weeks (range of 4-6) and SVR12 testing at a median of 22 weeks (range 12-187). 558 (93%) people achieved SVR4 and 5,976 (90%) people were cured based on SVR12. The test characteristics of SVR4 (Table 1) show a sensitivity of 97% and a positive predictive value of 98%. **Conclusion:** LA's HCV elimination program shows that HCV cure rates can be high (90%) in a public health initiative focused on a more complex Medicaid population. Capturing SVR12 data may be a challenge as only 70% of people had SVR12 testing completed. Although only 4% had SVR4 testing, it is not currently standard of practice, but the sensitivity and PPV were very high, 97% and 98%. This suggests that SVR4 could be used to determine HCV cure. It should be captured more systematically in future elimination programs, as it may be easier to get SVR4 testing done since it is closer to the time of treatment when people are still focused on their HCV as opposed to 12 months later. In fact, many people did not have SVR12 testing done until closer to 22 weeks after treatment was completed. SVR4 may be a better alternative to SVR12 going forward, but additional studies are needed.

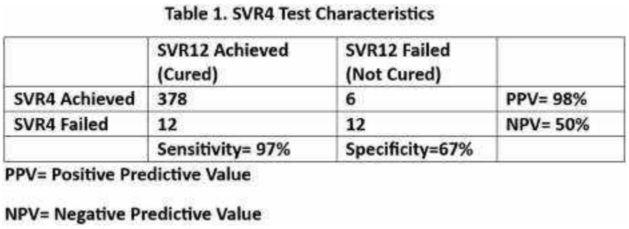


Table 1. SVR4 Test Characteristics

	SVR12 Achieved (Cured)	SVR12 Failed (Not Cured)	
SVR4 Achieved	378	6	PPV= 98%
SVR4 Failed	12	12	NPV= 50%
	Sensitivity= 97%	Specificity=67%	

PPV= Positive Predictive Value

NPV= Negative Predictive Value

Disclosures: Gia Landry – Gilead Sciences, Inc: Speaking and Teaching, No, No; Fujifilm: Speaking and Teaching, No, No;
The following people have nothing to disclose: Frederic McCall
Disclosure information not available at the time of publication: Elizabeth N. Britton, Lisa Chang, Kristina Larson

1856-A | SUSTAINED VIROLOGIC RESPONSE IMPROVED THE LONG-TERM HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH CHRONIC HEPATIC C: A PROSPECTIVE NATIONAL STUDY IN CHINA

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Background: Chronic hepatitis C virus (HCV) infection can severely impair health-related quality of life (HRQoL) in patients. Although achieving sustained virologic response (SVR) is known to improve HRQoL, there is currently a lack of long-term longitudinal studies in real-world settings. We conducted the study to investigate the trends in HRQoL among HCV patients, and to assess the longitudinal impact of antiviral therapy on their well-being. **Methods:** We conducted a prospective observational study at 28 hospitals across China in adults diagnosed with chronic HCV infection. Sociodemographic, clinical characteristics as well as EQ-5D questionnaires were collected. To assess the associations between these variables and changes in HRQoL over time, we applied generalized estimating equation (GEE) models. **Results:** Our study included 456 patients, with a median age of 46.5 years (interquartile range: 36.5-57.0), of which 262 (57.5%) were males and 44 (9.6%) had cirrhosis. Among the 335 patients (73.5%) who received antiviral therapy, 61.8% achieved SVR24. The baseline EQ-5D utility and EQ-VAS were 0.916 ± 0.208 and 80.6 ± 13.0,

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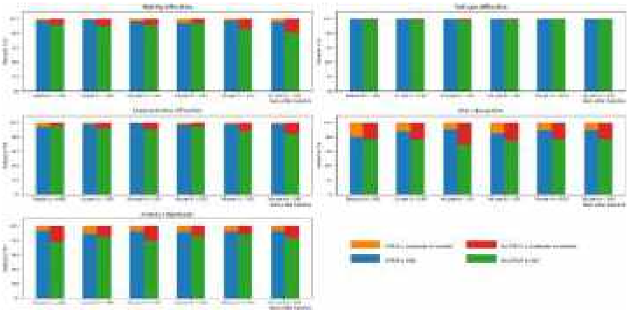
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

respectively. At baseline, there was no significant difference in EQ-5D utility scores between patients with and without SVR (0.959 ± 0.077 and 0.913 ± 0.215, $p = 0.241$), but as the proportion of patients achieving SVR increased over time, these differences became significant. Moreover, EQ-VAS scores were significantly higher in patients with SVR compared to those without SVR, both at baseline and during the follow-up period (baseline: 86.2 ± 12.0 and 80.2 ± 13.0, $p = 0.013$; 5th year: 88.2 ± 11.2, $p = 0.000$). Figure 1 illustrates the proportions of patients who reported moderate or severe problems in individual domains of EQ-5D during follow-up, stratified by SVR status. The differences in proportions between patients with and without SVR became significant over time, particularly in the domains of mobility (MO) and usual activities (UA) (5th year: MO, 8[4.8%] & 8[18.6%], $p = 0.032$; UA, 4 [2.4%] & 7 [16.3%], $p = 0.021$). A higher proportion of patients without SVR reported pain or discomfort compared to those with SVR (1st year: 21[12.2%] & 39[23.9%], $p = 0.005$; 2nd year: 20[9.9%] & 39 [20.2%], $p = 0.000$; 3rd year: 29[15.3%] & 28 [25.0%], $p = 0.047$; 4th year: 19 [10.9%] & 18[22.8%], $p = 0.027$). Using GEE estimation, we found that achieving SVR24 was positively associated with EQ-5D utility ($\beta = 0.039$, 95% CI [0.023, 0.056], $p = 0.000$) and EQ-VAS ($\beta = 5.317$, 95% CI [4.198, 6.438], $p = 0.000$) over time. Age, residence, marital status, occupation, income, cirrhosis and genotype also significantly influenced long-term changes in patients' quality of life. **Conclusion:** Our study suggested that SVR improved long-term HRQoL in HCV patients. Certain sociodemographic factors, as well as the presence of cirrhosis and genotype, significantly influenced long-term changes in patients' quality of life.

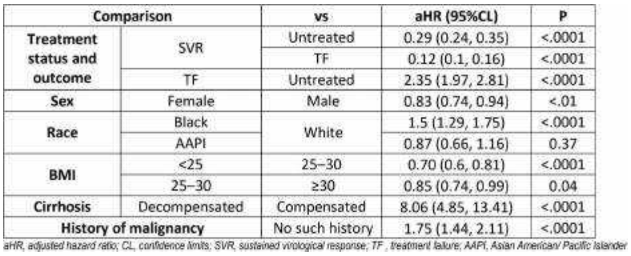


Disclosures: The following people have nothing to disclose: Rui Huang, Huiying Rao

1857-A | SUSTAINED VIROLOGICAL RESPONSE REDUCES RISK OF PORTAL VEIN THROMBOSIS IN HEPATITIS C PATIENTS WITH CIRRHOSIS

Humberto Gonzalez[1], Stuart C. Gordon[2], Yihe G Daida[3], Mark A Schmidt[4], Yueren Zhou[1], Trueman Wu[1], Lora Rupp[1], Sheri Trudeau[1] and Mei Lu[5], (1)Henry Ford Health, (2)Henry Ford Health and Wayne State University School of Medicine, Detroit, MI, USA, (3) Kaiser Permanente Hawai'I, (4)Kaiser Permanente Northwest, (5)156 Pocatello Rd

Background: Portal vein thrombosis (PVT) is a relatively common complication of liver cirrhosis. Prevalence estimates ranging from 10–25% of cirrhotic patients, but there are few studies investigating whether treatment of underlying liver disease affects risk of PVT. We used data on patients with cirrhosis and a history of chronic hepatitis C (HCV) infection to evaluate the impact of antiviral treatment status (treated or untreated) and treatment response (sustained virological response [SVR] or treatment failure) as well as patient demographic and clinical characteristics on risk of PVT. **Methods:** Patients were drawn from the multisite, US-based Chronic Hepatitis Cohort Study. PVT events were identified using ICD-CM codes. Events were excluded if they occurred < 1 month before or < 5 months after other thrombotic events (eg, deep vein thrombosis), malignant neoplasm, gastrointestinal inflammatory conditions (eg pancreatitis), pregnancy/ hormone therapy, or major abdominal surgery. Risk for PVT was assessed using a discrete survival model that include both fixed covariates (age, race, sex, history of thrombotic events, malignant neoplasm, gastrointestinal inflammatory conditions, pregnancy/hormone therapy, and major abdominal surgery) and time-dependent variables (BMI, compensated/decompensated cirrhosis, and treatment status/ response). Time-dependent propensity score weighting was used to address treatment selection bias. Patients were followed until liver transplant (if applicable) or last encounter; death was considered a competing risk. **Results:** A total of 6098 HCV patients with cirrhosis were included, among whom 39% (1798) received antiviral therapy and 55% (2956) achieved SVR; 116 patients developed PVT across 10 years of follow-up. SVR significantly reduced risk of PVT compared to no treatment (aHR = 0.29) and treatment failure (aHR = 0.12). Compared to no treatment, treatment failure was associated with more than twice the risk of PVT (aHR = 2.35). Sex and race were significantly associated with PVT: female patients had lower risk than male patients (aHR = 0.83]; Black patients were at 50% higher risk than whites (aHR = 1.5). Other significant risk factors included BMI (aHR = 0.70 [< 25 vs 25-30] and aHR = 0.85 [25–30 vs e 30), and history of malignancy (aHR = 1.75); Decompensated cirrhosis increased risk more than 8-fold (aHR = 8.06). **Conclusion:** In adjusted analyses, SVR from either interferon-based or direct-acting antiviral therapy is significantly and strongly associated with lower risk of PVT among HCV patients with cirrhosis. Male sex, Black race, and increasing BMI were associated with increased risk. Future studies to elucidate possible mechanisms for these observations are warranted.



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

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

Disclosures: Stuart C. Gordon – AbbVie Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Arbutus: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; CymaBay: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; DURECT: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genfit: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GSK: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Hightide: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Mirum: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
The following people have nothing to disclose: Humberto Gonzalez, Mei Lu
Disclosure information not available at the time of publication: Yihe G Daida, Mark A Schmidt, Yueren Zhou, Trueman Wu, Lora Rupp, Sheri Trudeau

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

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

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

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

Disclosures: The following people have nothing to disclose: Lisa Carpenter, Richard K. Sterling

Disclosure information not available at the time of publication: Shawn Lewis

1859-A | THE RISK OF HEPATOCELLULAR CARCINOMA DEPENDING ON LIVER CIRRHOSIS IN PATIENTS WITH CHRONIC HEPATITIS C: A NATIONAL COHORT STUDY

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

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

Disclosures: The following people have nothing to disclose: Jong-In Chang, Gi Hyeon Seo, Eunju Kim, Young Youn Cho, Hyung Joon Kim

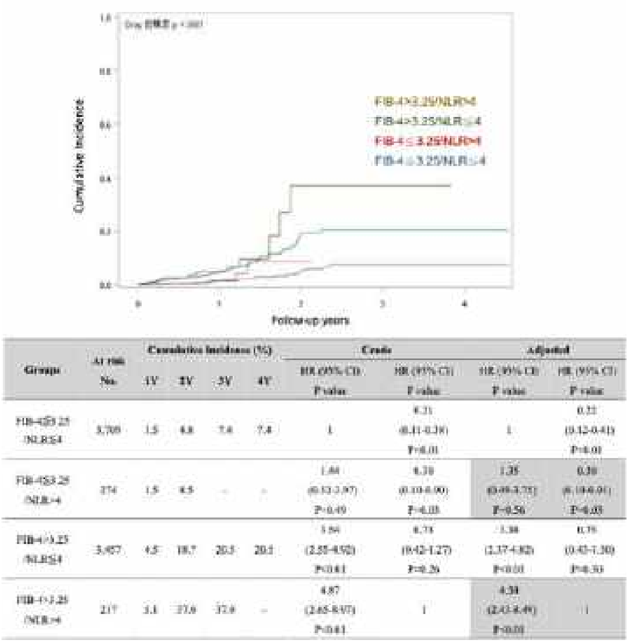
1860-A | ADDITION OF NEUTROPHIL-TO-LYMPHOCYTE RATIO TO PRE-DAA FIB-4 TO PREDICT DE NOVO LIVER COMPLICATIONS IN HEPATITIS C

Chun-Ming Hong[1], Tung-Hung Su[2], Shih-Jer Hsu[1], Tai-Chung Tseng[1], Chen-Hua Liu[2], Hung-Chih Yang[1], Jia-Horng Kao[2], Pei-Jer Chen[2], Pin-Nan Cheng[3], Cheng-Yuan Peng[4], Chun-Yen Lin[5], Han-Chieh Lin[6], Yi-Hsiang Huang[7], Chi-Yi Chen[8], Chih-Lin Lin[9], Pei-Chien Tsai[10], Chia-Yen Dai[10], Wan-Long Chuang[11], Jee-Fu Huang[11], Chung-Feng Huang[10], Ming-Lun Yeh[10], Ming-Lung Yu[11] and Chun-Jen Liu[2], (1)National Taiwan University Hospital, Taiwan, (2)National Taiwan University Hospital, (3)National Cheng Kung University Hospital, Taiwan, (4)China Medical University Hospital, Taiwan, (5)Linkou Chang Gung Memorial Hospital, (6)Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei City, Taiwan, (7)Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, (8)Ditmanson Medical Foundation Chiayi Christian Hospital, Chia Yi, Taiwan, (9)Renai Branch, Taipei City Hospital, Taipei, Taiwan, (10)Hepatobiliary Section, Department of Internal Medicine, and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, (11)Kaohsiung Medical University, Kaohsiung, Taiwan

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

NLR can increase the prediction power of pre-DAA FIB-4 for de novo liver complications such as ascites, hepatic encephalopathy, variceal bleeding, or HCC after SVR. **Methods:** We recruited patients via the platforms of The Taiwan HCV Registry (TACR) and National Health Insurance Registry Database. The inclusion criteria were patients who achieved SVR12 after DAA therapy and were followed for at least 24 months after SVR12. **Results:** Totally 7657 patients were recruited from 2013/12/25 to 2018/12/31. Among these 7657 patients, 3674 patients (48.0%) were FIB-4 > 3.25 and 491 patients (6.4%) were NLR > 4 before DAA therapy. 2281 (29.8%) had prior treatment. 5115 patients (66.8%) were infected with genotype 1, followed by genotype 2 (2269 patients, 29.6%). After two-year of follow-up after SVR 12, 214 patients (2.8%) developed de novo liver complications. Among these 214 patients, 11 (5.1%) were coinfected with HBV. 163 patients (76.2%) were FIB-4 > 3.25 and 17 patients (7.9%) were NLR > 4 at baseline. The cumulative incidence of de novo liver complications in patients with FIB-4 > 3.25 and NLR > 4 was the highest while the cumulative incidence in FIB-4 < 3.25 and NLR < 4 was the lowest. The addition of NLR did not differentiate the cumulative incidence in patients with either FIB-4f 3.25 or FIB-4 > 3.25. **Conclusion:** The overall incidence of de novo liver-associated complications after SVR is low during short-term follow-up. Pre-DAA FIB-4 is associated with de novo liver complications after SVR, though the addition of pre-DAA NLR does not increase the prediction power.

Figure. The cumulative incidence of de novo liver complications.



Groups	At risk No.	Cumulative incidence (%)				Crude		Adjusted	
		1Y	2Y	3Y	4Y	HR (95% CI) P value	HR (95% CI) P value	HR (95% CI) P value	HR (95% CI) P value
FIB-4≦3.25 /NLR≦4	3,709	1.5	4.8	7.4	7.4	1	0.21 (0.11-0.38) P<0.01	1	0.22 (0.12-0.41) P<0.01
FIB-4≦3.25 /NLR>4	274	1.5	8.5	-	-	1.44 (0.52-3.97) P=0.49	0.30 (0.10-0.90) P=0.03	1.35 (0.49-3.73) P=0.56	0.30 (0.10-0.91) P=0.03
FIB-4>3.25 /NLR≦4	3,457	4.5	18.7	20.5	20.5	3.56 (2.35-4.92) P<0.01	0.73 (0.42-1.27) P=0.26	3.38 (2.37-4.82) P<0.01	0.75 (0.43-1.30) P=0.31
FIB-4>3.25 /NLR>4	217	3.1	37.0	37.0	-	4.87 (2.65-8.97) P<0.01	1	4.38 (2.42-8.49) P<0.01	1

Disclosures: The following people have nothing to disclose: Chun-Ming Hong, Tung-Hung Su, Shih-Jer Hsu, Tai-Chung Tseng, Chen-Hua Liu, Hung-Chih Yang, Jia-Horng Kao, Pei-Jer Chen, Pin-Nan Cheng, Cheng-Yuan Peng, Chun-Yen Lin, Han-Chieh Lin, Yi-Hsiang Huang, Chi-Yi Chen, Chih-Lin Lin, Pei-Chien Tsai, Chia-Yen Dai, Wan-Long Chuang, Jee-Fu Huang, Chung-Feng Huang, Ming-Lun Yeh, Ming-Lung Yu, Chun-Jen Liu

1861-A | BEMNIFOSBUVIR AND RUZASVIR ARE POTENT HCV DAAS WITH FAVORABLE ANTIVIRAL PROFILES AGAINST MAJOR HCV NS5A AND NS5B RAVS SUPPORTING USE IN COMBINATION

Qi Huang, Steven Good, Dawei Cai, Nancy Agrawal and Jean-Pierre Sommadossi, Atea Pharmaceuticals, Inc.

Background: Bemnifosbuvir (BEM), an oral prodrug of a guanosine nucleotide analog, has demonstrated highly potent pan-genotypic best-in-class *in vitro* and clinical antiviral activities against all hepatitis C virus (HCV) genotypes (GTs 1-4) tested. Ruzasvir (RZR), a potent NS5A inhibitor, has shown broad genotypic *in vitro* antiviral activities (EC_{50} **d** 10 pM) against GTs 1-6. Viral resistance has emerged as an important consideration for direct-acting antiviral (DAA) drug use since it may impact effectiveness for treatment of HCV infection. We aim to profile the antiviral activity of each of BEM and RZR against a panel of previous NS5A Resistance-Associated Variants (RAVs) selected *in vitro* or identified in HCV patients who have failed treatment with currently available DAAs. **Methods:** The antiviral effects of BEM, RZR and current Standard of Care (SOC) DAAs sofosbuvir and velpatasvir (component of EPCLUSA) against a set of selected, clinically relevant NS5A and NS5B RAVs were determined in transient replicon assays. **Results:** BEM is at least 10-fold more potent than sofosbuvir (SOF) across all genotypes tested and is not resistant to sofosbuvir RAVs (S282T, L159F/S282T, Figure 1A). BEM also retains antiviral activity against all GT1a and GT3a NS5A RAVs tested (Figure 1B). In GT- 1a, RZR is 10-fold more potent than velpatasvir (VEL), and it retains single-digit pM antiviral activity against RAVs (M28V +Q30R, M28T+T64A, L31M+H58P) selected by previous NS5A inhibitors, while velpatasvir is 10 time less potent against selected double mutants (M28V+Q30R, M28T+T64A). In GT-3a, the most difficult to treat genotype, RZR is 6 times more potent than velpatasvir, and retains sub-nM potency against NS5A RAVs (such as A30K, Y93H) which were treatment-emergent in HCV GT3 patients failing DAAs (Figure 1C). The combination of BEM and RZR resulted in additive to synergistic antiviral effects. The antiviral potency of RZR is not affected by signature RAVs emerging with

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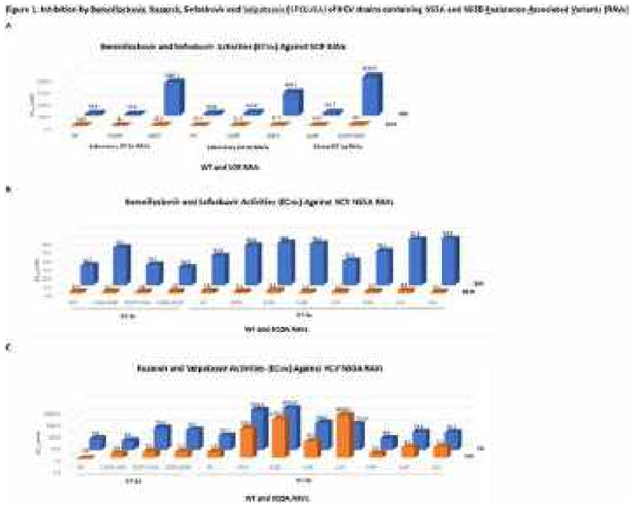
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

other classes of HCV DAAs against NS3/4A protease and NS5B polymerase (nucleoside and non-nucleoside) inhibitors. **Conclusion:** Given the highly potent pan-genotypic antiviral activity of BEM and RZR, the high resistance barrier of BEM, the complementary mechanisms of action of BEM and RZR, the clinically demonstrated safety and efficacy of each agent when administered individually, and the lack of drug-drug interaction(DDI) between BEM and RZR, combination treatment with these two agents for HCV infections is highly attractive and is currently being evaluated in a Phase 2 clinical trial. The combination of BEM/RZR should have a more compelling antiviral profile against major HCV NS5A RAVs than current SOCs.



Disclosures: Qi Huang – Atea Pharmaceuticals, Inc.: Employee, Yes, No;
Steven Good – Atea Pharmaceuticals, Inc.: Employee, Yes, No;
Dawei Cai – Atea Pharmaceuticals, Inc.: Employee, Yes, No;
Nancy Agrawal – Atea Pharmaceuticals, Inc.: Employee, Yes, No;
Jean-Pierre Sommadossi – Atea Pharmaceuticals, Inc.: Employee, Yes, No;

1862-A | CHARACTERISTICS OF HEPATITIS C VIRUS RESISTANCE IN A TERTIARY CENTER IN FRANCE – A 6 YEARS EXPERIENCE

Simona Tripon[1], Mira Kayal[1], Aurélie Velay[1], Thibaut Goetsch[1], Francois Habersetzer[1], Robert Bader[2], Dominique Paya[1], Martine Alt-Tebacher[1], Izabelle-Ana Amaritei[3], Frederic Chaffraix[1], Carine Wiedemer[1], Thomas F. Baumert[4] and Michel Doffoel[1], (1)Nouvel Hôpital Civil, Hôpitaux Universitaires De Strasbourg, (2) Hôpital Emile Muller, Groupement Hospitalier Régional Mulhouse Sud Alsace (GHRMSA), (3)Hôpital Louis Pasteur, Colmar, (4)Institut Hospitalo-Universitaire (IHU), Pôle Hépato-Digestif, Hôpitaux Universitaires De Strasbourg, 67000 Strasbourg, France

Background: Despite the excellent efficacy of direct-acting antiviral (DAA), in some patients, virological failure can occur associated with resistance –associated substitutions (RASs). This study aimed to describe the RASs characteristics and evaluate clinical factors associated with RASs selection after 6 years of experience with DAA treatment, in a tertiary center in France. **Methods:** We performed a retrospective analysis based on data presented at the multidisciplinary team meetings of our tertiary care center between July 2015 and August 2021. From a total of 1593 patients, 55 experienced RAS mutations. The RASs in non-structural protein (NS)3, NS5A, and NS5B were determined by direct sequencing. **Results:** In our population, 64% of patients had a 1st generation DAA, 36% -2nd DAA generation as the first line treatment, 9% had **e** 2 lines of DAA regiments and 16% had INF before DAA. According to the RASs : 81% were NS5A, 38% NS3, 7% NS5B and 22% were mixed NS5A+NS3. Y93H and L31M in NS5A were more frequently detected in 47% and 18% of patients, respectively V170I in NS3 in 24%. Patients with cirrhosis had more frequent genotype 1b, 50% vs. 16% ($p = 0.013$) and NS3 –RASs 53.3% vs. 20% ($p = 0.024$). Y93H-RAS in NS5A was more present in older patients (> 60 y) 60% vs. 40% ($p = 0.06$) and after 1st generation DAA regimens, 52 %vs 48% ($p = 0.04$). NS5A RASs was associated with HCV genotype 3 ($p = 0.04$). Moreover, in multivariate logistic regression adjusted analyses, having genotype 3 seem to be more associated with NS5A RAS, aOR 5.57 95%CI 0.79-39.17; $p = 0.08$). **Conclusion:** In our cohort, failure to DAA treatment leads to more frequent RASs in the NS5A region, especially in patients with genotype 3 HCV infection.
Disclosures: Thomas F. Baumert – Alentis Therapeutics: Advisor, No, No;
The following people have nothing to disclose: Simona Tripon
Disclosure information not available at the time of publication: Mira Kayal, Aurélie Velay, Thibaut Goetsch, Francois Habersetzer, Robert Bader, Dominique Paya, Martine Alt-Tebacher, Izabelle-Ana Amaritei, Frederic Chaffraix, Carine Wiedemer, Michel Doffoel

f 1863-A | DAA TREATMENT FAILURE AND RETREATMENT STRATEGIES FOLLOWING NAT+ HCV SOLID ORGAN TRANSPLANTATION IN HCV-NEGATIVE RECIPIENTS: A CASE SERIES

Alicia B. Carver[1], Morgan Lange[2], Alysa Martin[3], Claire Ozoral[4], Kristen Whelchel[1] and Roman Perri[1], (1)

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

Vanderbilt University Medical Center, (2)The Medical University of South Carolina, (3)University of Rochester Medical Center, (4)Ochsner Health

Background: The practice of transplanting solid-organs from hepatitis C virus (HCV) Nucleic Acid Testing (NAT)+ donors into HCV-negative recipients has become more prevalent as supporting data continues to emerge. Given the high sustained virologic response (SVR) rates of direct-acting antivirals (DAAs), little data exists regarding retreatment strategies for patients that fail to achieve SVR. This multi-site case series describes HCV-negative solid-organ transplant (SOT) recipients that failed DAA therapy following HCV NAT+ SOT, retreatment strategies, and subsequent SVR rates. **Methods:** This was a multi-site retrospective case series of patients that failed DAA treatment following HCV NAT+ SOT between September 2016 and September 2022 at three tertiary medical centers in the United States. **Results:** Nine patients were included (male, 78%; white, 78%; median [interquartile range (IQR)] age 66 years [57-70]) and are described in Table 1. The majority received an HCV NAT+ kidney (78%), just over half were genotype 1 (56%), and sofosbuvir/velpatasvir (SOF/VEL) x12 weeks was the initial DAA course most frequently (44%) prescribed. Baseline resistance testing was not completed. The median [IQR] time to treatment initiation following SOT was 26 days [20-40]. Two patients (ID 6, ID 9) never achieved a viral load of < 15 IU/mL or undetectable and 2 patients (ID 2, ID 5) never achieved normalization of alanine transaminase (ALT) while receiving the initial DAA course. The median [IQR] time to retreatment following positive viral load was 28 days [18-73]. The majority (67%) received retreatment with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) x12 weeks. One patient (ID 5) prescribed SOF/VEL/VOX + ribavirin (RBV) x12 weeks with emergent M28I/K and L31L/P mutations failed to achieve a viral load of < 15 IU/mL or undetectable or normalization of ALT during 12 weeks of treatment. Treatment was extended to 24 weeks and SVR achieved. One patient (ID 8) prescribed SOF/VEL/VOX x12 weeks failed to achieve a viral load of < 15 IU/mL or undetectable until week 11 of treatment. Treatment was extended to 24 weeks and SVR achieved. Only 1 patient (ID 6) failed to achieve SVR following DAA retreatment with SOF/VEL/VOX x12 weeks. This patient was retreated with sofosbuvir (SOF) + GLE/PIB + RBV x24 weeks and achieved SVR. **Conclusion:** HCV-negative patients that failed DAA therapy following NAT+ HCV SOT are described. All patients achieved SVR following one or more DAA retreatment courses.

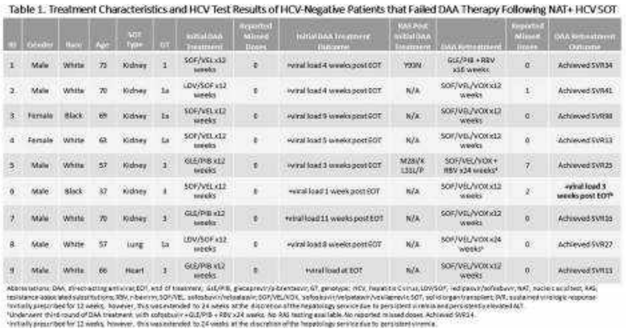


Table 1. Treatment Characteristics and HCV Test Results of HCV-Negative Patients that Failed DAA Therapy Following NAT+ HCV SOT

ID	Gender	Race	Age	SOT Type	GT	Initial DAA Treatment	Reported Missed Doses	Initial DAA Treatment Outcome	RAS Post Initial DAA Treatment	DAA Retreatment	Reported Missed Doses	DAA Retreatment Outcome
1	Male	White	73	Kidney	1	SOF/VEL x12 weeks	0	+viral load 4 weeks post EOT	Y93N	GLE/PIB + RBV x16 weeks	0	Achieved SVR34
2	Male	White	70	Kidney	1a	LDV/SOF x12 weeks	0	+viral load 4 weeks post EOT	N/A	SOF/VEL/VOX x12 weeks	1	Achieved SVR41
3	Female	Black	69	Kidney	1a	SOF/VEL x12 weeks	0	+viral load 9 weeks post EOT	N/A	SOF/VEL/VOX x12 weeks	0	Achieved SVR88
4	Female	White	62	Kidney	1a	SOF/VEL x12 weeks	0	+viral load 5 weeks post EOT	N/A	SOF/VEL/VOX x12 weeks	0	Achieved SVR13
5	Male	White	57	Kidney	3	GLE/PIB x12 weeks	0	+viral load 3 weeks post EOT	M28I/K L31L/P	SOF/VEL/VOX + RBV x24 weeks[a]	7	Achieved SVR25
6	Male	Black	37	Kidney	3	SOF/VEL x12 weeks	0	+viral load 1 week post EOT	N/A	SOF/VEL/VOX x12 weeks	2	+viral load 3 weeks post EOT[b]
7	Male	White	70	Kidney	3	GLE/PIB x12 weeks	0	+viral load 11 weeks post EOT	N/A	SOF/VEL/VOX x12 weeks	0	Achieved SVR26
8	Male	White	57	Lung	1a	LDV/SOF x12 weeks	0	+viral load 8 weeks post EOT	N/A	SOF/VEL/VOX x24 weeks[c]	0	Achieved SVR27
9	Male	White	66	Heart	3	GLE/PIB x12 weeks	0	+viral load at EOT	N/A	SOF/VEL/VOX x12 weeks	0	Achieved SVR11

Abbreviations: DAA, direct-acting antiviral; EOT, end of treatment; GLE/PIB, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; NAT, nucleic acid test; RAS, resistance-associated substitutions; RBV, ribavirin; SOF/VEL, sofosbuvir/velpatasvir; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SOT, solid organ transplant; SVR, sustained virologic response

[a] Initially prescribed for 12 weeks, however, this was extended to 24 weeks at the discretion of the hepatology service due to persistent viremia and persistently elevated ALT.

[b] Underwent third round of DAA treatment with sofosbuvir + GLE/PIB + RBV x24 weeks. No RAS testing available. No reported missed doses. Achieved SVR14.

[c] Initially prescribed for 12 weeks, however, this was extended to 24 weeks at the discretion of the hepatology service due to persistent viremia.

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Disclosure information not available at the time of publication: Alysa Martin, Kristen Whelchel, Roman Perri

1864-A | DIRECT-ACTING ANTIVIRALS HAVE SUBSTANTIALLY MODIFIED THE PROFILE OF CHRONIC HEPATITIS C PATIENTS WITH CIRRHOSIS IN SOUTH CHINA: A MULTICENTER STUDY

Jianping Li[1], Songlian Liu[1], Ying Tan[1], Wenyu Wang[1], Shi Ouyang[2], Ganqiu Lin[1], Aiqi Lu[1], Binbin Chen[1], Zhiwei Xie[1], Chunlan Zhang[1], Yujuan Guan[1] and Xujing Liang[3], (1)Guangzhou Eighth People's Hospital, Guangzhou Medical University, (2)The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhuo, China, (3)The First Affiliated Hospital of Jinan University

Background: In patients with cirrhosis due to hepatitis C virus (HCV), a sustained virologic response (SVR) to antiviral therapy is associated with reductions in the incidence of hepatic decompensation, hepatocellular carcinoma, all-cause mortality and liver-related mortality. We aimed to evaluate the efficacy, safety and changes in noninvasive tests (NITs) in this population in South China. **Methods:** This retrospective multicenter study enrolled patients with Chronic hepatitis C (CHC) and cirrhosis who were treated with Direct-acting antivirals (DAAs). Patients with decompensated cirrhosis (DCC) received additional ribavirin (RBV). In the cases where RBV was not tolerated, the treatment duration was extended to 24weeks according to the guideline. Virological indicators, liver and renal function indexes were assessed at baseline, the week 4, the end of treatment, and 12 weeks of follow-up. **Results:** A total of 128 patients were enrolled from Jan. 2016 to Dec. 2022. The patients were from Guangzhou Eighth People’s Hospital, The First Affiliated Hospital of Jinan

University, and The Fifth Affiliated Hospital of Guangzhou Medical University. 66 cases had compensated cirrhosis (CC) and 62 cases had DCC. Baseline characteristics were showed in Table 1. All patients completed the treatment, primarily with the regimen of Sofosbuvir and Velpatasvir. RBV was used in 81 (63.3%) patients. At the end of treatment, undetectable levels of HCV RNA were achieved in 125 cases (97.7%). The SVR12 rate was 94.5%. The SVR12 rates were high across genotypes (GT) with 100% for GT 1, GT 2 and GT unknown, 92.9% for GT 3a, 90.3% for GT 3b, and 93.5% for GT 6a. With different Child-Turcotte-Pugh (CTP) scores, the SVR12 rates were 97.0% for CTP A, 90.2% for CTP B, and 95.2% for CTP C. Notably, patients with CC showed significant improvements in ALB (from 40.7 ± 4.2 to 44.3 ± 3.7 g/L) ($P < 0.001$), ALT (from 81.6 ± 67.4 to 30.7 ± 24.8 U/L) ($P < 0.001$), APRI (from 1.6 ± 1.2 to 0.7 ± 0.5) ($P < 0.001$) and FIB-4 (from 3.9 ± 2.2 to 2.7 ± 1.5) ($P = 0.002$) after treatment. Additionally, patients with DCC showed a significant improvement in CTP score after treatment. All 66 CTP A patients remained in CTP A, while in the group CTP B, 22 (53.7%) improved to CTP A, 18 (43.9%) remained in CTP B and 1 (2.4%) worsened to CTP C. In the group CTP C, 9 (42.6%) improved to CTP A ,10 (47.6%) improved to CTP B, and 2(9.5%) remained in CTP C. Renal function remained stable throughout the treatment. The most common adverse events were fatigue (21.9%) and anemia (19.5%). 7 cases relapsed, 4 of them were successfully rescued and achieved SVR12, while 3 cases were lost to follow-up. **Conclusion:** This study shows that DAA treatment has good efficacy and safety in CHC with cirrhosis. Patients with CC show significant improvements in ALB, ALT, APRI and FIB-4 scores after treatment. Patients with DCC show a significant improvement in CTP score after treatment.

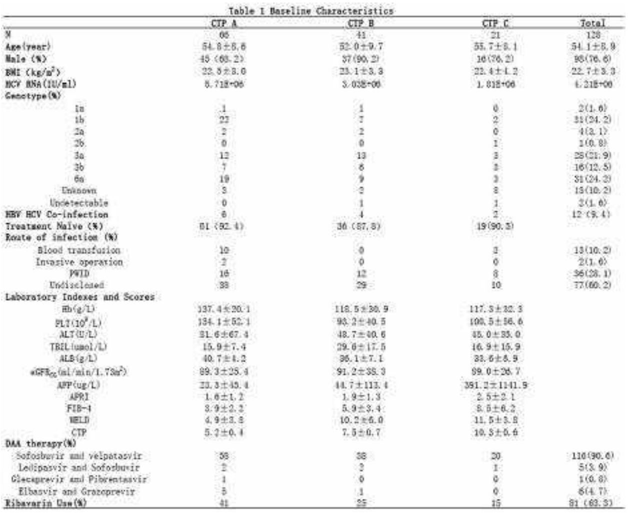

Table 1 Baseline Characteristics

	CTP A	CTP B	CTP C	Total
N	66	41	21	128
Age(year)	54.8±8.6	52.0±9.7	55.7±8.1	54.1±8.9
Male (%)	45 (68.2)	37(90.2)	16(76.2)	98(76.6)
BMI (kg/m²)	22.5±3.0	23.1±3.3	22.4±4.2	22.7±3.3
HCV RNA(IU/ml)	5.71E+06	3.03E+06	1.81E+06	4.21E+06
Genotype(%)				
1a	1	1	0	2(1.6)
1b	22	7	2	31(24.2)
2a	2	2	0	4(3.1)
2b	0	0	1	1(0.8)
3a	12	13	3	28(21.9)
3b	7	6	3	16(12.5)
6a	19	9	3	31(24.2)
Unknown	3	2	8	13(10.2)
Undetectable	0	1	1	2(1.6)
HBV HCV Co-infection	6	4	2	12 (9.4)
Treatment Naive (%)	61 (92.4)	36 (87.8)	19(90.5)	
Route of infection (%)				
Blood transfusion	10	0	3	13(10.2)
Invasive operation	2	0	0	2(1.6)
PWID	16	12	8	36(28.1)
Undisclosed	38	29	10	77(60.2)
Laboratory Indexes and Scores				
Hb(g/L)	137.4±20.1	118.5±30.9	117.3±32.3	
PLT(10^9/L)	134.1±52.1	93.2±40.5	100.5±56.6	
ALT(U/L)	81.6±67.4	48.7±40.6	45.0±35.0	
TBIL(umol/L)	15.9±7.4	29.6±17.5	46.9±15.9	
ALB(g/L)	40.7±4.2	36.1±7.1	33.6±6.9	
$eGFR_{CG}$(ml/min/1.73m²)	89.3±25.4	91.2±35.3	89.0±26.7	
AFP(ug/L)	23.3±45.4	44.7±113.4	381.2±1141.9	
APRI	1.6±1.2	1.9±1.3	2.5±2.1	
FIB-4	3.9±2.2	5.9±3.4	8.5±6.2	
MELD	4.9±3.8	10.2±6.0	11.5±3.8	
CTP	5.2±0.4	7.5±0.7	10.3±0.6	
DAA therapy(%)				
Sofosbuvir and velpatasvir	58	38	20	116(90.6)
Ledipasvir and Sofosbuvir	2	2	1	5(3.9)
Glecaprevir and Pibrentasvir	1	0	0	1(0.8)
Elbasvir and Grazoprevir	5	1	0	6(4.7)
Ribavarin Use(%)	41	25	15	81 (63.3)

Disclosures: The following people have nothing to disclose: Jianping Li, Songlian Liu, Ying Tan, Wenyu Wang, Shi Ouyang, Ganqiu Lin, Aiqi Lu, Binbin Chen, Zhiwei Xie, Chunlan Zhang, Yujuan Guan, Xujing Liang

1865-A | DRUG DRUG INTERACTIONS BETWEEN ANTIPSYCHOTICS AND PANGENOTYPIC DAA IN PATIENTS RECEIVING OPIOID SUBSTITUTE THERAPY

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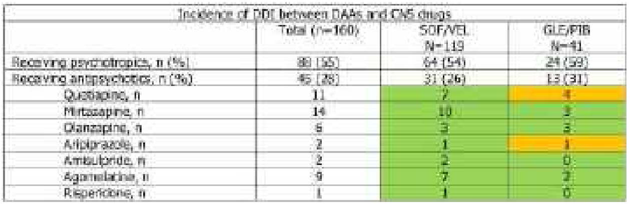
Background: Previous studies have shown high efficacy associated with new generation of pangenotypic direct acting antivirals (DAAs). Despite having high cure rate and well tolerated safety profile, DAAs are linked to potential drug drug interactions (DDI) with concomitant medications. Patients received opioid substitute therapy and infected with HCV are often prescribed with antipsychotics as comedication. The aim of current study is to describe the efficacy of pangenotypic DAA in Asian patients who receive opioid replacement therapy and assess their associated risk of DDI with antipsychotics. **Methods:** This is a retrospective observational study reviewing HCV adult patients treated in two addiction centers between Jan 2020 and Dec 2021 with pangenotypic DAAs. Demographic variables collected including age, baseline fibrosis, presence of ongoing recreational drug use, neurological comorbidities, type of DAA prescribed and presence or absence of psychiatric co-medication. DDI between concomitant medication and DAA were assessed using Liverpool database. Baseline demographic and clinical characteristics were summarized using descriptive statistics. **Results:** A total of 160 patients were included, 119 patients received SOF/VEL and 41 patients received GLE/PIB. Patient characteristics: mean age of 49 years, 39% patients had positive urine test for recent recreational drug use, 69 % received methadone maintenance therapy. The distribution of HCV genotypes- GT 6 (39%), GT 1a (19%), GT 1b (19%), GT 2 (12%), GT 3 (7%). 140 patients completed DAA treatments and had SVR 12 obtained; the SVR 12 per protocol was 98%. Eighty-eight patients (55%)

received psychotropics during HCV treatment and 28% received antipsychotics. The most prescribed antipsychotics were mirtazepine (50%), quetiapine (39%), and agomelatine (20%). There were no DDI between SOF/VEL and prescribed antipsychotics while DDI occurs in 16% (5/31) of patients treated with GLE/PIB with antipsychotics. (Table 1) **Conclusion:** Current study showed pangenotypic DAAs are effective in Asian HCV population receiving opioid substitute therapy. Similar to western data, antipsychotics are frequently prescribed in this cohort. SOF/VEL is associated with lower incidence of DDI with CNS drugs compared to GLE/PIB. A careful evaluation of DDI prior to DAA initiation is important to minimize potential risk and optimize treatment outcome.



Incidence of DDI between DAAs and CNS drugs

	Total (n=160)	SOF/VEL N=119	GLE/PIB N=41
Receiving psychotropics, n (%)	88 (55)	64 (54)	24 (59)
Receiving antipsychotics, n (%)	45 (28)	31 (26)	13 (31)
Quetiapine, n	11	7 🟩	4 🟧
Mirtazapine, n	14	10 🟩	3 🟩
Olanzapine, n	6	3 🟩	3 🟩
Aripiprazole, n	2	1 🟩	1 🟧
Amisulpride, n	2	2 🟩	0 🟩
Agomelatine, n	9	7 🟩	2 🟩
Risperidone, n	1	1 🟩	0 🟩

Disclosures: The following people have nothing to disclose: Chihhao Chang, Yea-Yuan Chang, Han-Ting Wei, Chien-Chun Wang

1866-A | EFFECTIVENESS AND SAFETY OF SOFOBUVIR/VELPATASVIR/VOXILAPREVIR AS A RESCUE THERAPY FOR CHRONIC HEPATITIS C PATIENTS WITH FAILED PREVIOUS DIRECT-ACTING ANTIVIRALS TREATMENT IN SOUTHWEST CHINA

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Background: The effectiveness and safety of sofobuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) as a rescue therapy for chronic hepatitis C (CHC) patients in China who failed previous direct-acting antivirals (DAA) treatment remains limited. **Methods:** Patients with hepatitis C who failed previous DAA receiving SOF/VEL/VOX for rescue therapy from Jan. 2022 to Mar. 2023 were recruited. The primary efficacy endpoint was the sustained virological response at post-treatment week 12 (SVR12). Clinical and laboratory data and adverse events (AEs) were collected during treatment period. **Results:** A total of 12 CHC patients receiving SOF/VEL/VOX rescue therapy were collected. The median age was 51 (48-58) years, and 8 patients (66.7%) were males. 8 patients (66.7%) had drug injection history and 2 of them were co-infected with HIV. 6 patients (50.0%) had liver cirrhosis. The previous failed DAA regimen include sofosbuvir/velpatasvir (SOF/VEL, n = 9, 75.0%), sofosbuvir plus coblopasvir (SOF plus CLP, n = 3, 25.0%). The median interval between virological relapse and previous DAA cessation was 9 (3-11) months. The median HCV RNA was 6.5 (5.9-6.9) $\log_{10}$IU/mL at baseline of rescue therapy and the most common HCV GT was GT 3b (n = 10, 83.3%). All patients with GT 3b received SOF/VEL/VOX plus ribavirin (RBV) combination therapy, and the other 2 patients received SOF/VEL/VOX monotherapy. Till now, 9 patients completed 12 weeks of SOF/VEL/VOX treatment and 12 weeks of follow-up, 2 patients were still under treatment, and 1 patient was lost to follow-up. All the 9 patients who completed the 12 weeks of SOF/VEL/VOX treatment achieved SVR12. Median ALT significantly declined from 134.7 (51.0-262.5) IU/L at baseline to 25.5 (9.6-40.4) IU/L at the end of treatment ($P = 0.013$). No special AE was reported during treatment and no patient discontinued treatment. **Conclusion:** SOF/VEL/VOX was effective and well-tolerated for difficult-to-treat DAA experienced CHC patients in China, including those with GT3b and cirrhosis.

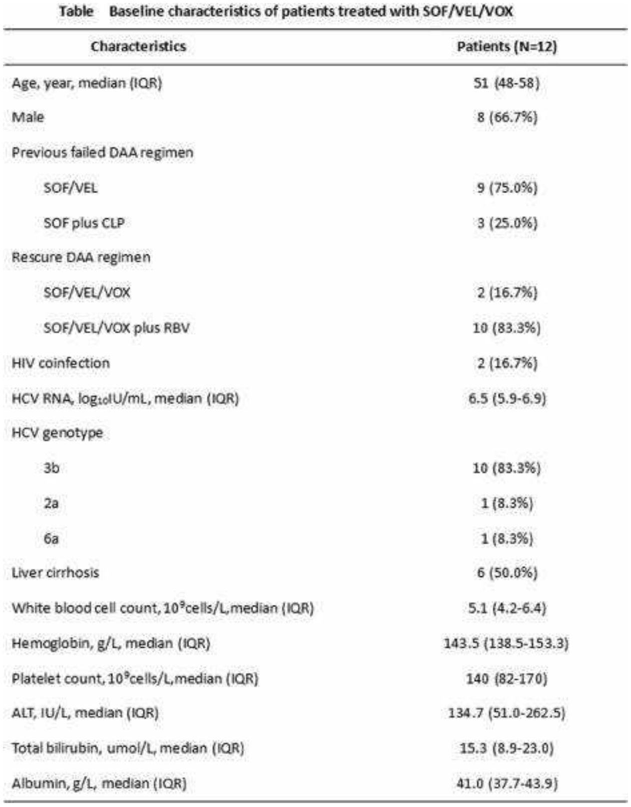

Table Baseline characteristics of patients treated with SOF/VEL/VOX

Characteristics	Patients (N=12)
Age, year, median (IQR)	51 (48-58)
Male	8 (66.7%)
Previous failed DAA regimen	
SOF/VEL	9 (75.0%)
SOF plus CLP	3 (25.0%)
Rescure DAA regimen	
SOF/VEL/VOX	2 (16.7%)
SOF/VEL/VOX plus RBV	10 (83.3%)
HIV coinfection	2 (16.7%)
HCV RNA, $\log_{10}$IU/mL, median (IQR)	6.5 (5.9-6.9)
HCV genotype	
3b	10 (83.3%)
2a	1 (8.3%)
6a	1 (8.3%)
Liver cirrhosis	6 (50.0%)
White blood cell count, 10^9cells/L, median (IQR)	5.1 (4.2-6.4)
Hemoglobin, g/L, median (IQR)	143.5 (138.5-153.3)
Platelet count, 10^9cells/L, median (IQR)	140 (82-170)
ALT, IU/L, median (IQR)	134.7 (51.0-262.5)
Total bilirubin, umol/L, median (IQR)	15.3 (8.9-23.0)
Albumin, g/L, median (IQR)	41.0 (37.7-43.9)

Disclosures: The following people have nothing to disclose: Yan Guo, Yan Zhu, Jianqiong Guo, Yanyan Wu, Qing Mao, Jie Xia, Ming Liu

1867-A | EFFICACY AND SAFETY OF SOF/VEL TREATMENT IN RECENTLY ACQUIRED HEPATITIS C VIRUS INFECTION AMONG PEOPLE LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS: A SINGLE-CENTER STUDY IN SOUTHWEST CHINA

Qing Lin[1], Zhenglin Wang[1], Xiaohui Cheng[1], Fang Wang[1], Zheng Tang[1], Xinyue Huang[2], Zehu Deng[1] and Yiping Yang[1], (1)The People's Hospital of Jiulongpo District ,Chongqing,China, (2)Tongguanyi Town Health Center of Jiulongpo District, Chongqing,China

Background: HIV/HCV coinfection is a global health problem with overlapping modes of transmission. Epidemic outbreaks of recently acquired HCV infection in people living with HIV (PWLH) have been observed globally. However, little is known about the diagnosis and treatment of recently acquired HCV in PWLH in China. **Methods:** We retrospectively reviewed the recently acquired HCV patients in the HIV outpatient clinic of People's Hospital of Jiulongpo District, Chongqing from May 2021 to January 2023. **Results:** In total, 42 recently acquired HCV patients were identified from the PLWH cohort (n = 1623). All the patients were anti-HCV negative upon HAART initiation and were symptomatic or abnormal liver function during routine visits and confirmed HCV infection by Anti-HCV and HCV RNA testing. The baseline characteristics are summarized in table 1. 40(95%) patients who were taking EFV/TDF/3TC or AZT/3TC/LPVr switched to B/F/TAF regimen before anti-HCV treatment. All the patients received 12-week SOF/VEL (400 mg sofosbuvir plus 100 mg velpatasvir) treatment, weight-based ribavirin was added for genotype 3 patients. All the patients completed anti-HCV treatment and follow up. At post-treatment week 12, 42 (100%) patients were HIV RNA undetectable, 41 (98%) achieved HCV sustained virological response (SVR), and ALT concentrations declined into the normal range in 36 (86%) patients. The only patient who didn't achieve SVR12 was a 46-year-old male with HCV genotype 3. The 5 HBV/HCV/HIV co-infection patients maintained HBV DNA undetectable during treatment. SOF/VEL treatment was well tolerated. No serious adverse event (AE) reported, and no patient discontinued treatment prematurely due to AE. **Conclusion:** The 12-week treatment with SOF/VEL was well tolerated and highly effective in recently required HCV infection in PWLH. Regular HCV screening and prompt anti-HCV treatment might effectively prevent HCV transmission in PWLH.

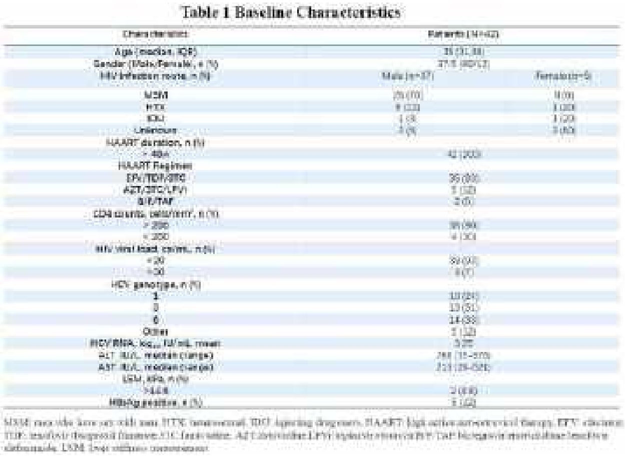

Table 1 Baseline Characteristics

Disclosures: The following people have nothing to disclose: Qing Lin, Zhenglin Wang, Xiaohui Cheng, Fang Wang, Zheng Tang, Xinyue Huang, Zehu Deng, Yiping Yang

1868-A | EFFICACY AND SAFETY OF SOFOSBUVIR/VELPATASVIR WITH OR WITHOUT RIBAVIRIN IN HCV-INFECTED CHINESE PATIENTS: A PROSPECTIVE COHORT STUDY

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Background: Sofosbuvir/velpatasvir (SOF/VEL) is a highly effective pan-genotype, one single tap antiviral regiment in patients chronically infected with hepatitis C virus (HCV). But real-world data on its efficacy and safety remains scarce in Southwest China, a region with diverse HCV genotypes (GT), especially high proportion of HCV GT3. **Methods:** In this prospective observational cohort study, we recruited patients from West China Hospital and Public Health Clinical Center of Chengdu in Southwest China. Patients included adults chronically infected with any HCV genotype, either with or without cirrhosis, HCC, HIV/HBV coinfection. Patients were administered with a single table regimen SOF / VEL (400/100 mg) once daily for 12 weeks, with or without ribavirin (RBV). The usage of RBV was depended on GT3, cirrhosis and poor liver function. All

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HCV patients reaching 12 weeks post-treatment were assessed for SVR12 (defined as HCV RNA less than 15 IU/mL at 12 weeks after treatment cessation). Adverse events (AEs) were also evaluated during treatment. **Results:** This study included 452 patients. HCV genotype: GT1 40.3% (182/452), GT2 7.3% (33/452), GT3 37.4% (169/452), GT6 11.3% (51/452) and GT uncertain 3.8% (17/452). RBV was administrated to 36.7% (166/452) patients. The overall SVR12 rate was 99.1% (448/452). The SVR12 for patients infected with HCV GT3, patients with cirrhosis or HCC, or patients with HBV/HIV coinfections was 99.4% (168/169), 100% (62/62), and 97.6% (40/41), respectively. The SVR12 was 98.8% (164/166) for patients who had received RBV. Among patients who received RBV, 88.0% (146/166) were infected with HCV GT3, 18.1% (30/166) had cirrhosis, and 7.2% (12/166) were coinfected with HBV/HIV. After SOF/VEL ± RBV therapy, ALBI representing liver function showed a significant decrease from baseline to SVR12(-2.91 *vs.* -3.11 $P < 0.001$), while both FIB4 (3.67 *vs.* 2.81, $P = 0.004$) and APRI (1.42 *vs.* 0.71, $P < 0.001$) used for liver fibrosis evaluation also showed a significant decrement from baseline to SVR12. None of the involved patients experienced any grade 3-5 AEs. **Conclusion:** Although included high proportion of patients with HCV GT3b, cirrhosis, HCC, or HBV/HIV coinfections, SOF/VEL with or without RBV was highly effective and well tolerated in patients with chronic HCV infection in Southwest China.

Disclosures: The following people have nothing to disclose: Jiayi Wang, Lingyao Du, Chen Zhou, Yilan Zeng, Enqiang Chen, Dong-Mei Zhang, Xing Cheng, Xiaona Song, Ning Han, Miao Liu, Han Chen, Hong Tang

1869-A | EFFICACY OF SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR IN NAÏVE CHRONIC HEPATITIS C PATIENTS: REAL LIFE STUDY

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Background: Pan-genotypic Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX) for 8-12 weeks has been shown highly effective, safe, and well-tolerated in treating patients with chronic hepatitis C (CHC)) in POLARIS studies, however, there are no real-world setting data are available especially in treating naïve patients. This is the first opportunity from all over the world to demonstrate SOF/VEL/VOX efficacy and safety in Real World setting for the naive patients. **Methods:** On June 1, 2022, Turkey's reimbursement guidelines for CHC treatments were updated. With this change, SOF/VEL/VOX was approved to use pan-genotypically for noncirrhotic naïve patients, cirrhotic naïve patients, treatment experienced patients for 8, 12 and 12weeks respectively. The patients who treated with SOF/VEL/VOX were included in a database within the scope of the HEP-C II TURKEY STUDY. We presented preliminary results of naïve CHC patients. **Results:** Of the 127 patients 92.9% (n = 118) were naïve and 9 were treatment experienced, 48 naïve patients (40.7%) were treated with 8 weeks of SOF/VEL/VOX. Of these 48 patients 45.8% were female, median age was 59.5 (24-85), 70.0% were genotype 1 and 95.5% were genotype 1b, 2.1% were compensated cirrhotic. Median HCVRNA at the time of diagnosis were 918.000 IU/mL (19.426 – 10.000.000). Undetectable HCVRNA levels at the 1st month, end of the of treatment were 83.3% and 100% respectively and the rate of response, SVR12 were 97.9% (47/48). One relapsed patient was genotype 4. Median ALT levels were 32.0, 19.0 and 15.5 IU/L at diagnosis, end of the treatment and at the SVR12 follow-up respectively. There were not any treatment interruption or adverse event leading to treatment cessation. **Conclusion:** SOF/VEL/VOX combination treatment is safe and presenting high SVR12 rates for the naïve CHC patients, further results with the high number of patients will be needed to prove this preliminary results.

Disclosures: The following people have nothing to disclose: Hatice Rahmet Guner, Tansu Yamazhan, Oguz Karabay, Ayse Inci, Gurdal Yilmaz, Ozlem Altuntas Aydin, Yesim Caglar, Ilknur Senel, Arzu Altuncekic Yildirim, Esra Yerlikaya Zerdali, Bengu Gireniz Tatar, Fehmi Tabak

1870-A | ELIMINATING HepC IN CHILDREN; CARE CLOSER TO HOME

Deirdre A. Kelly[1], Maxine Brown[2], Palaniswamy Karthikeyan[3], Sanjay Bansal[4], William Irving[5], Ivana Carey[6], Paddy McMaster[7], Alasdair Bamford[8], Siske Struik[9], Anthi Thangarajah[10], Caroline Foster[11], Sarah Tizzard[12], Alison Tennant[2], Tayebah Abbasi[2], Joanne

Crook[13], Penny North-Lewis[14], Rebecca Cooper[15], Carla Lloyd[2] and Graham R. Foster[16], (1)Birmingham Women's & Children's Hospital NHS Trust and University of Birmingham, (2)Birmingham Women's and Children's Hospital, (3)Leeds Teaching Hospitals NHS Trust, Leeds Children's Hospital, (4)King's College Hospital, (5)Nottingham University, (6)Institute of Liver Studies, Kings College Hospital, London, United Kingdom, (7)North Manchester General Hospital, (8) Great Ormond Street Hospital, (9)Cardiff and Value University, (10)Chelsea and Westminster Hospital, London, United Kingdom, (11)Imperial College Hospital, London, (12)St George's Hospital,London, (13)King's College Hospital, London, (14)Leeds General Infirmary, (15)Children's Liver Disease Foundation, (16)Queen Mary University Hospital

Background: Hepatitis C virus (HCV) infection is a major global health problem in adults & children. Direct Acting Anti-viral therapies (DAA) achieve cure rates of 99% in adults and adolescents, were licensed for children 3–12 yrs in 2020. Prescribing and reimbursement for HCV therapy is centralized in England by NHS England (NHSE)r To ensure equitable access, safe & convenient supply during COVID lockdown, a virtual national treatment pathway for children with HCV in England & Wales which provided care to children nearer to home, was established in April 2021. We evaluated its feasibility, efficacy & treatment outcomes. **Methods:** A paediatric Multidisciplinary Team Operational Delivery Network (pMDT ODN), funded & supported by NHSE, with relevant paediatric specialists provided a single point of contact for referrals. Referral & treatment protocols were agreed for HCV therapy approved by MHRA. On referral the pMDT ODN agreed the most appropriate DAA therapy based on clinical presentation, genotype, patient preferences, & ability to swallow tablets. Treatment was prescribed in association with the local paediatrician & pharmacist, with no need for families to travel to national centres. All children in England & Wales were eligible for NHS funded therapy. Referral centres were approved by the pMDT ODN to dispense medication with funding reimbursed by NHSE. Demographic, clinical data, treatment outcomes, Sustained viral response at 12 weeks (SVR12) and 12m (12mSVR) were collected. Feedback on feasibility & satisfaction on the pathway was sought from referrers. **Results:** 92 children referred April 2021 to March 2023: 85–England; 7–Wales; median (range) age: 8.7 years (3–16); 49 (53%) male; with genotypes 3(45); 1 (45); 2 (3) and 4 (4). Route of transmission where known was vertical; No child had cirrhosis. DAA therapy prescribed Sofosbuvir/Ledipasvir (Harvoni): tablets (33); granules (11) Glecaprevir/Pibrentasvir (Maviret) : tablets (6) ; granules (7) Sofosbuvir/Velpatisvir (Epclusa) : tablets (33) ; granules (2) 68 were treated, 62 completed treatment & cleared virus; 53 achieved SVR 12; 22 achieved 12m SVR Referrers found the virtual process easy to access, valuing opportunity to discuss their patient's therapy with the virtual MDT & many found it educational. There were initial difficulties in providing the medication due to manufacturing delays for granule formulations and pharmacy issues such as confusion with adult packaging. **Conclusion:** The National HCV pMDT ODN delivers high quality treatment & equity of access for children & young people, 3– 18 yrs with HCV in England and Wales, enabling care close to home with 100% cure rates and contributing to the goal of eliminating HCV in the UK by 2025

Disclosures: The following people have nothing to disclose: Deirdre A. Kelly, Maxine Brown, Palaniswamy Karthikeyan, Sanjay Bansal, William Irving, Ivana Carey, Paddy McMaster, Alasdair Bamford, Siske Struik, Anthi Thangarajah, Caroline Foster, Sarah Tizzard, Alison Tennant, Tayebah Abbasi, Joanne Crook, Penny North-Lewis, Rebecca Cooper, Carla Lloyd, Graham R. Foster

1871-A | ESTABLISHMENT OF A STANDARDIZED CLINICAL PATHWAY TO HCV : PRIMARY HOSPITAL CONTRIBUTE HCV ELIMINATION

Guo Li[1], Gao Bihua[1], Wu Wenbin[1] and Cailian Cai[2], (1) Beihai City People's Hospital, (2)Guangxi Medical University

Background: There is a big gap in HCV awareness and it is a big challenge to HCV elimination ,esp. in primary care physicians(PSP) in China. We aimed to work out a standardized clinical pathway for HCV patients screening -diagnosis and treatment in a primary hospital. We collaborate with other departments, including non-ID clinical departments and clinical laboratories and IT departments on this. **Methods:** We initiated the HCV elimination project in primary hospitals 6 months ago. We conducted education forums for PCP and produced soerials for them on this topic. We have increased awareness of HCV and HCV linkage to care,including free diagnosis, lectures, dissemination of information and other forms of publicity. We havme education mate also worked with the IT department to build a platform for the project. All in-hospital patients at high risk of HCV infection are alerted through the system to undergo HCV screening with HCV-Ab testing. All the patients with HCV-Ab (+) will be reminded to complete the HCVRNA testing by the clinical lab and referred to hepatologists automatically. Once the hepatologists are given the request, they should make a diagnosis and conduct appropriate treatment for the patients promptly. **Results:** Over the

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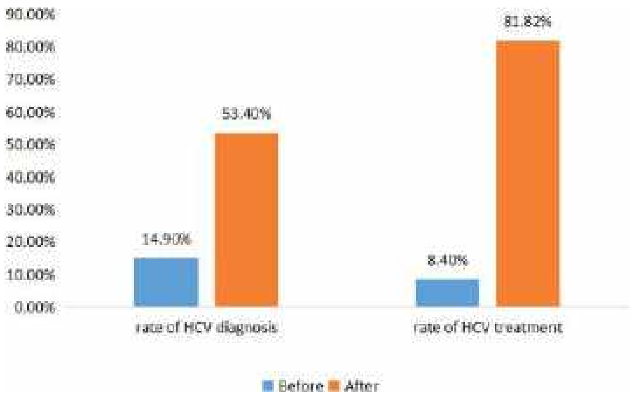
past 6 months, 90% (24220/26912) patients were screened for HCV-Ab, including in-hospital and clinic, 0.41% (111/26912) of them are HCV-Ab (+), 36.9% (41/111) of them accepted HCVRNA test and 53.6% (22/44) were diagnosed with HCV infection, 81.82% were treated with DAA. The rate of diagnosis and treatment has increased significantly compared to the last years (53.4% vs. 14.9%; 81.82% vs. 8.4%). **Conclusion:** Establishment of standardized clinical pathways in collaboration with non-ID departments can approach HCV elimination in primary hospitals.



Disclosures: The following people have nothing to disclose: Guo Li, Gao Bihua, Wu Wenbin, Cailian Cai

1872-A | EVALUATION OF HEPATITIS C TREATMENT AND CARE MODEL IN PRIMARY HEALTHCARE CENTERS IN THE COUNTRY OF GEORGIA

Tengiz Tsertsvadze[1,2], Nikoloz Chkhartishvili[1], Akaki Abutidze[1,2], Lali Sharvadze[2,3], Senad Handanagic[4], Shaun Shadaker[4], Ekaterine Adamia[5] and Tamar Gabunia[5], (1)Infectious Diseases, AIDS and Clinical Immunology Research Center, (2)Ivane Javakhishvili Tbilisi State University, (3)Hepatology Clinic Hepa, (4)Centers for Disease Control and Prevention, Division of Viral Hepatitis, National Center for HIV, Hepatitis, Std&tb Prevention, (5)Ministry of IDPs from the Occupied Territories, Labour, Health and Social Affairs of Georgia

Background: In April 2015, with a partnership with Gilead Sciences and technical assistance from U.S. CDC, Georgia launched the world's first hepatitis C elimination program. By the end of April 2023, more than 82,000 patients with current hepatitis C virus (HCV) infection initiated treatment, achieving > 98% cure rates. Broad access to direct acting antivirals (DAAs) resulted in rapid increase in treatment uptake in 2016, which has since declined due to barriers in diagnosis and linkage to care. To address this issue Georgia initiated service decentralization in 2018 by integrating HCV screening and treatment in primary healthcare centers (PHCs). We report preliminary results of an integrated model of HCV care in PHCs **Methods:** By April 30, 2023, a total of 10 PHCs were providing HCV care services throughout the country. The integrated model was based on "one stop shop" approach, where patients receive all HCV screening, treatment and care services in selected PHCs. PHCs provided care to HCV treatment-naïve patients with no or mild fibrosis (FIB-4 score < 1.45) using simplified diagnostics and a treatment monitoring approach, while persons with advanced liver fibrosis/cirrhosis were referred to specialized clinics. Patients received Sofosbuvir/Ledipasvir and/or Sofosbuvir/Velpatasvir for 12 weeks. Sustained virologic response (SVR) was defined as undetectable HCV RNA at 12-24 weeks after end of therapy. The Extension for Community Healthcare Outcomes (ECHO) telemedicine model was used to train and support primary healthcare providers. Regular teleECHO videoconferencing was conducted to provide primary care providers with advice and clinical mentoring. **Results:** Among persons diagnosed with current HCV infection, 1,756 were evaluated for FIB-4 score. A total of 1,159 patients initiated treatment, and of them 1,075 (92.8%) completed treatment. Of 1,051 patients eligible for SVR testing, 835 (79.4%) had been tested at the time of analysis, and 821 (98.3%) achieved SVR. **Conclusion:** Our study shows the feasibility and effectiveness of integrating a simplified HCV diagnostic and treatment model in PHCs. Countrywide expansion of this model is warranted to bridge the gaps in the HCV care continuum and ensure high rates of treatment uptake towards achieving elimination targets.

Disclosures: The following people have nothing to disclose: Tengiz Tsertsvadze, Nikoloz Chkhartishvili, Akaki Abutidze, Lali Sharvadze, Senad Handanagic, Shaun Shadaker, Ekaterine Adamia, Tamar Gabunia

1873-A | EVOLUTION OVER TWO YEARS OF THE ANNUAL INCIDENCE OF HCV VIRAL LOAD DETECTED BY RAPID RT PCR (XPERT HCV VIRAL LOAD FINGERSTICK ASSAY) DIRECTLY ON SITE IN 3 ADDICTION CENTERS

Denis Ouzan[1,2], Nicolas Camerlo[3], Justine Dupuis[4], Joris Herin[5], Teresa Namouni[6], Bruno Blasi[3], G Ozenda[7], Maela Lebrun[5], Perrine Roux[8] and Stephane Chevaliez[9], (1)Rhecca, (2)Institut Arnault Tzanck, (3)Lou Passagin, (4)Bus 31/ 32, (5)Bus 31/32, (6)Emergence, (7)Csapa Olivetto, (8)Inserm, (9)Service De Virologie, Hôpital Henri Mondor

Background: Eradication of HCV infection requires elimination of this infection among people who inject drugs (PWID). However, the number of patients screened and treated for hepatitis C in PWID remains low. Many patients are lost of follow-up after serological diagnosis. The measurement of the viral load by rapid RT-PCR from capillary blood (Xpert® HCV Viral Load Fingerstick) allows to obtain a result in 1 hour. Measuring the evolution of the annual incidence of rapid PCR in our centers was used to define the evolution of HCV infection in these addiction centers. The objective of our study was to measure the annual incidence of C viral load over the last 2 years in anti HCV-positive PWID followed up in 3 French Harm reduction centers and Needle exchange structures (CAARUD/CSAPA) and the proportion of patients treated annually. **Methods:** From March 1, 2021, all HCV seropositive PWID (previously known positive for serology or determined using a Rapid Antigenic Detection Testing (RADT) targeting HCV, HBV, and HIV) followed in 3 CAARUD/CSAPA (2 in Nice, 1 in Marseille) were offered a rapid RT- PCR using the molecular Point of Cares Testing (POCT) (Xpert HCV Viral Load Fingerstick). If the HCV PCR was positive, treatment was proposed. **Results:** From March 2021 to February 2023 , 303 PWID were included :183 during the first year (March 2021 to February 2022) and 120 during the second year (March 2022 to February 2023): 80 % men with an average age of 44 years, 65 without social rights, 68 with precarious housing and 42 homeless, 143 declared having injected: heroin, crack, other, 119 inhaled: cocaine, crack, other, 167 having multiple addictions which cannabis 75 and drugs 52 and 180 excessive alcohol consumption. 153 were receiving substitution treatment. HCV serology was documented in 180/ 183 PWID seen during the first year and in 118 /120 PWID seen during the second year and was positive in respectively 85 (47 %) and 60 (51%) of them. During the first year 82/85 anti-HCV+ PWID agreed to perform a rapid RT-PCR which was positive in 29, i.e. annual incidence of 16%. Anti-HCV treatment was initiated in 18 of the 29 patients whose RT-PCR was positive. During the second year 59/60 anti-HCV+ PWID agreed to perform a rapid RT-PCR which was positive in 25, i.e. annual incidence of 21% and treatment was initiated in 12 of the 25 PCR positive patients. 6/11 in the first and 12/25 in the second year of the PCR positive patient could not be treated because they did not have access to social rights. **Conclusion:** The annual incidence of C viral load over the last 2 years in anti HCV-positive PWID followed up in 3 French Harm reduction centers remain relatively high . The introduction of rapid PCR allow a virological diagnosis in almost all anti-HCV+ PWID . Despite the implementation of rapid PCR, there is still a long way to go to achieve viral eradication in these centers. To achieve this goal it would be necessary to treat all PCR positive PWID.

Disclosures: The following people have nothing to disclose: Denis Ouzan, Stephane Chevaliez

Disclosure information not available at the time of publication: Nicolas Camerlo, Justine Dupuis, Joris Herin, Teresa Namouni, Bruno Blasi, G Ozenda, Maela Lebrun, Perrine Roux

f 1874-A | FREQUENCIES OF UNUSUAL HCV GENOTYPES AND SUBTYPES IN EUROPEAN DAA-EXPERIENCED PATIENTS AND REAL-WORLD RETREATMENT OUTCOMES

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Background: The approval of direct acting antivirals (DAAs) has revolutionized treatment of chronic HCV infection and the WHO has set the goal to eliminate HCV by 2030. However, sustained virological response (SVR) rates were lower in patients with unusual HCV genotypes (GT), which are uncommon in industrialized countries, and second generation DAAs are not available in low-income countries. This study investigated the prevalence of unusual GT and resistance-associated substitutions (RASs) among European DAA failure patients. **Methods:** A total of 1376 patients with DAA treatment failure were identified from the European Resistance database between 2014 and 2023 and included in the study. We amplified and sequenced the HCV NS3, NS5A and NS5B genes and re-evaluated subtypes sequence-based. RASs that conferred >2-fold increased DAA susceptibility were analyzed. **Results:** The frequency of unusual subtypes among DAA-failure patients was 4% (60/1376). The majority of patients with unusual GT were infected with unusual GT4 subtypes (47%, 28/60; subtypes 4b, 4c 4f, 4n, 4o, 4r, 4v) and GT3 subtypes (25%, 15/60; 3b, 3g, 3h, 3i, 3k). Among them, GT4r (n = 17) and GT3b (n = 8) were the most frequent, which were detected especially after failure to LDV/SOF (GT4r) or after DCV/SOF or VEL/SOF failure (GT3b), respectively. In addition, 12% (7/60) of DAA failures were infected with unusual GT6 (6e, 6f, 6n, 6r), 10% (6/60) with GT1 (1c, 1e, 1l) and 3% each (2/60) with GT2k and GT5a, respectively. Most patients (78%, n = 47/60) with unusual GT had failed to first generation DAA treatment (LDV/SOF, DCV/SOF, 2D/3D, SOF/RBV, GZR/EBR), whereas only 22% (13/60) had not responded to second generation DAAs (VEL/SOF, G/P). NS5A RASs at positions 28, 30 and 31 were common in patients with unusual GT1 (100%, n = 5/5), GT3 (80%, n = 12/15), GT4 (96%, 24/25) after NS5A inhibitor (NS5Ai) failure. Y93H was detected in only 16% (7/43) of patients with unusual GT after NS5Ai failure, whereas typically > 70% of patients with GT1b or GT3a harboured Y93H after NS5Ai failure. Overall, 75% (45/60) of patients had started retreatment, most with VOX/VEL/SOF (n = 27), and across all regimens 95% (40/42 with completed follow-up) had achieved SVR. **Conclusion:** Of European DAA failure patients, 4% were infected with an unusual HCV genotypes. Retreatment with second generation regimens resulted in an SVR rate of 95%. The limited global availability of these regimens could result in HCV elimination targets being delayed.

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1875-A | HEPATITIS C VIRUS SUSTAINED VIROLOGIC RESPONSE (SVR) RATES ARE DISSIMILAR FOR PATIENTS WHO RECEIVED A SINGLE 84-DOSE FILL OF SOFOSBUVIR / VELPATASVIR COMPARED TO PATIENTS WHO RECEIVED A 28-DOSE PRESCRIPTION WITH TWO REFILLS

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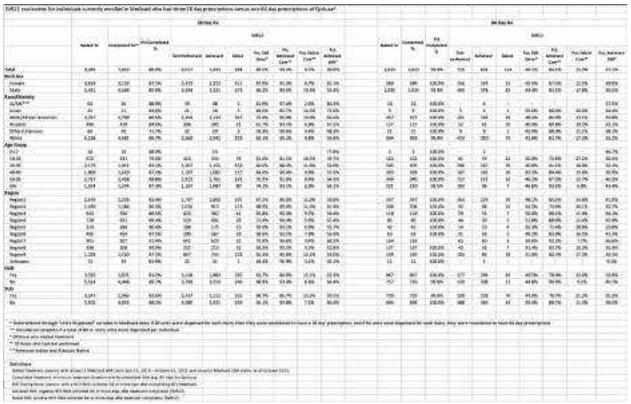
Background: The goal of Hepatitis C Virus (HCV) elimination has been prioritized globally by the World Health Organization and the United States has begun its planning for nationwide elimination. Louisiana (LA) stands out as one of the few states that has implemented a comprehensive HCV elimination program throughout the state. Due to the global Covid-19 pandemic and difficulty accessing in-person care, LA Medicare allowed prescribers to write 84-dose fills to limit patients from leaving home and to limit barriers to treatment. In this abstract we are examining how prescribing methods may effect cure rates. **Methods:** All persons in LA on Medicaid who initiated HCV treatment from July 15, 2019 – October 31, 2022 were analyzed. Test of Cure (TOC) is defined as the HCV RNA test result **e** 84 days after anticipated last HCV medication dose. Cure is defined as an undetectable TOC result. Treatment failure is defined as a detectable TOC result. **Results:** Of the 10,673 LA Medicaid patients analyzed, 9,049 (84.78%) of the patients were prescribed a 28 dose prescription with two refills and 1,624 (15.22%) of the patients were prescribed a single 84 dose fill of medication. Of those prescribed a 28-

dose fill with two refills and filled at least one dose; 6017 (66.5%) received an TOC. 5,433(60.0%) had a documented cure in LA Medicaid records, and 584(6.5%) had a documented treatment failure in LA Medicaid records. 7,819 of the 9,049 (86.4%) picked up all 84 doses. For those who filled an 84-dose prescription; 716 (44.1%) received a TOC. 602 (37.1%) had a documented cure in LA Medicaid records and 114 (7.0%) had a documented treatment failure in LA Medicaid records. 100% of claims picked up all 84 doses of medication. Please see the table for more detailed data. **Conclusion:** While patients who were prescribed a 28 dose-fill with 2 refills were more likely to have a documented TOC compared to those prescribed a single 84-dose fill, treatment failure rates were similar between the two groups (6.5% vs 7.0%). Cure rates are drastically lower in the 84 dose fill group, but that is largely driven by the decrease in TOC testing for that group. When considering only those who did receive a TOC, cure rates are 84.1% for those with a single 84 dose fills and 90.3% for those with a 28-dose fill with 2 refills. TOC with positive HCV RNA results may also be contributed to reinfection instead of treatment failure as some TOC labs were not obtained until years after treatment. Over a third of the medicaid claims had documented Opioid or Substance use disorder in their records, which may have also contributed to reinfection of HCV and makes us consider reinfection of HCV instead of true treatment failure. Overall, low return rates for TOC limited the data we have, and the small proportion of those who were prescribed a single 84-dose fill limit the power of the data we collected. Further studies may help direct future elimination efforts in how to most effectively prescribe HCV medications to improve TOC and cure rates.



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f 1876-A | HEPATOCELLULAR CARCINOMA ASSOCIATED WITH CHRONIC HEPATITIS C, CLINICAL PROFILE, MANAGEMENT OUTCOMES AND SURVEILLANCE STRATEGY OF THE PUNJAB HCV MODEL: REAL WORLD DATA FROM THE PUBLIC HEALTH PERSPECTIVE

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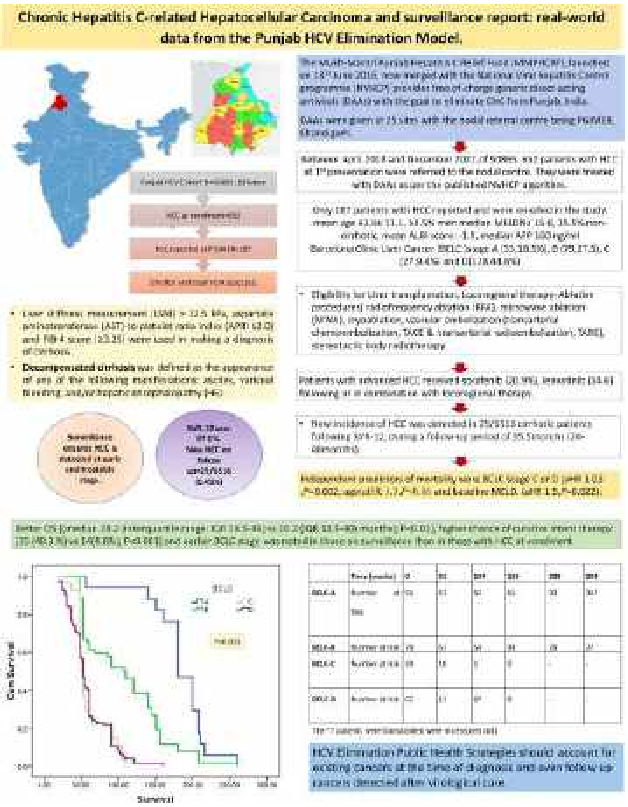
Background: The Punjab HCV Model, a decentralized multicentric public health cohort, has resulted in cure rates of 91.6% using free-of-charge generic direct-acting antiviral agents (DAAs) in patients with chronic hepatitis C (CHC) infection. Real world data on the risk of hepatocellular carcinoma (HCC) in CHC patients with or without cirrhosis, and benefit of surveillance in a population-based cohort is needed to guide health policy. **Methods:** The association of hepatocellular carcinoma with CHC at first enrolment, clinical course, outcomes and new incidence of HCC following post sustained virological response (SVR-12) surveillance was assessed between December 2017 and December 2022. The treatment given and outcomes were recorded (Figure1). **Results:** Of the 51865 viremic patients with CHC in the Punjab Model cohort, 652 patients with HCC at 1st presentation were reported, of whom 287 referred patients (mean age 63.6 ± 11.1 years, 58.5% men median MELDNa 15.6, 15.5% non-cirrhotic, mean ALBI score: -1.9, median AFP 160 ng/ml) managed at the nodal centre PGIMER, Chandigarh were enrolled. The patients with HCC were classed as BCLC stage A (53,18.5%), B (79,27.5%), C (27,9.4%) and D(128,44.6%). About 22% had decompensation including ascites(20.9%) and variceal bleeding (3.2%), at enrolment. HCC characteristics were as follows; 193, 67.2%-single nodule, mean size as 4.4 ± 2 cm, 50 (17.4%)-tumoral portal vein thrombosis. The SVR-12 was 87.1%, which is lower than the Punjab cohort cure rate of 91.6%. 220 (76.4%) patients died, and 7 (2.4%) underwent liver transplantation.

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

Ablative procedures included radiofrequency ablatio (7), microwave ablation (5) and cryoablation (2). In intermediate HCC, transarterial (TA) chemoembolization (95), transarterial radioembolization (32), bland embolization (2) and stereotactic body radiation (SBRT-6) were done. Patients with advanced HCC received sorafenib (20.9%), lenvatinib (14.6) following or in combination with locoregional therapy. Independent predictors of mortality were BCLC Stage C or D (aHR 1.03 ,95%CI:1.008-1.28, $P=0.002$, age(aHR 1.3 ,95% CI:1.2-1.8,$P<0.01$ and baseline MELD. (aHR 1.5 , 95% CI:1.2-1.8, $P=0.022$). New incidence of HCC was detected in 29/6516 (0.45%) cirrhotic patients following SVR-12; during a follow-up period of 35.5months (24-48months). Better overall survival [(median 28.2 (interquartile range; IQR 18.5-45) vs 20.2 (IQR 12.5-40) months); $P<0.01$], higher chance of curative intent therapy [15 (48.3 %) vs 14(4.8%); $P<0.001$] and earlier BCLC stage was noted in those on surveillance than in those with HCC at enrolment, suggesting clinically meaningful lead time and better outcomes with the surveillance. **Conclusion:** The Punjab HCV Model demonstrates patients with CHC should remain on strict HCC surveillance following virological cure to provide survival benefit. The population cohort data provides unique insight to manage HCV-HCC and guides future heath policy.



Chronic Hepatitis C-related Hepatocellular Carcinoma and surveillance report: real-world data from the Punjab HCV Elimination Model.

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1877-A | INCIDENCE OF LIVER ENZYME ELEVATION IN HCV-NONVIREMIC RECIPIENTS WHO UNDERWENT THORACIC ORGAN TRANSPLANTATION WITH HCV-VIREMIC ORGANS

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Background: The use of HCV-viremic donor organs in HCV-nonviremic recipients has helped address the shortage in available donor grafts. Despite the risk of HCV transmission, there is a high rate of sustained viral response (SVR) with direct-acting antiviral (DAA) agents. While fibrosing cholestatic hepatitis and liver failure is rare, the incidence of liver enzyme elevation in the post-operative period and prior to initiation of DAA therapy has not been described in patients undergoing thoracic organ transplantation. **Methods:** This retrospective single center study evaluated patients who underwent lung or heart transplantation with an HCV-viremic organ from April 2019 to August 2022. Hepatitis B surface antigen or HIV antibody positive recipients were excluded. Lamivudine was initiated in patients who received hepatitis B core antibody positive organs. The degree of liver enzymes elevation was classified as mild (ALT > 1 to < 3x the upper limit of normal (ULN) and/or total bilirubin (TB) < 2x ULN), moderate (ALT 3-5x ULN and/or TB 2-4x ULN) or severe (ALT > 5x ULN and/or total bilirubin > 4x ULN). All patients were evaluated for DAA therapy post-transplant. **Results:** 44 patients underwent transplantation with an HCV-viremic donor heart (n = 18) or lung (n = 26) during the study period. 57% were male with a mean age of 58 years of age. 9% of donor organs were hepatitis B core antibody positive. HCV viremia occurred universally post-transplant with genotype 1A being the most prevalent (73%). Elevation in liver enzymes also occurred in all patients post-operatively (25% mild, 34% moderate, 41% severe). Of the patients with severe elevation in liver enzymes, n = 19 (95%) occurred while critically ill in the ICU. No patients underwent liver biopsy. Three patients died from etiologies unrelated to hepatitis C exposure prior to initiation of DAA therapy. The median time between transplantation and initiation of HCV therapy was 42 days. All patients who underwent DAA therapy reached SVR. **Conclusion:** Post-transplant liver enzyme elevation occurs commonly in patients who undergo thoracic transplantation with HCV-viremic organs. Moderate to severe levels of enzymes elevation can present in critically ill patients, but are not associated with poor hepatic outcomes. This study is the first to describe the incidence of liver enzyme elevation in this population and further supports the utility of HCV-viremic organs in patients awaiting heart and lung transplantation.

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1878-A | INDIVIDUALIZED HCV TREATMENT FOR PWIDS ON OPIOID AGONIST THERAPY LED TO EXCELLENT ADHERENCE THROUGHOUT THE COVID19 PANDEMIC

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Background: Directly observed therapy (DOT) with DAAs (direct-acting antivirals) is successful in eliminating HCV in PWIDs (people who inject drugs) on opioid agonist therapy (OAT): DAAs are prescribed via a low-threshold facility (LTF), and supervised DAA administration alongside OAT is performed at a pharmacy or LTF. In PWIDs with good adherence, DOT distribution intervals may be extended from daily to once weekly. We present one of the scarce HCV elimination projects for PWIDs that was continued throughout the COVID19 pandemic using the concept of DOT. **Methods:** We included 239 PWIDs on OAT starting DOT with DAAs 03/2020-10/2022 ("COVID" period), and a control group of 441 PWIDs receiving DOT 09/2014-03/2020 ("pre-COVID" period). We compared socio-economic characteristics, DOT distribution intervals, and SVR12 (sustained virologic response at week 12) rates of the two groups. **Results:** Pre-COVID, 348 (78.9%) PWIDs underwent daily DOT, while 19 (4.3%) and 74 (16.8%) were on 2-3 times/week and once weekly OAT/DAA dispensation schedules, respectively. During COVID, merely 75 (31.4%, $p < 0.001$) PWIDs were on daily OAT/DAA distribution, while 60 (25.1%, $p < 0.001$) and 104 (43.5%, $p < 0.001$) had 2-3 times/week and once weekly intervals, respectively. Missed visits (59 [0.8%] vs. 84 [0.4%] pre-COVID; $p = 0.239$) and SVR12 rates (167/168 [99.4%] vs. 402/405 [99.3%] pre-COVID according to modified intention-to-treat analysis; $p = 0.849$) were comparable among the groups. Loss of follow-up after end of treatment was more frequent during COVID (28.5% vs. 7.5% pre-COVID; $p < 0.001$), while mortality was similar (1.3% vs. 0.7% pre-COVID; $p = 0.444$). During COVID, socioeconomic status was equal or lower than pre-COVID (unemployment: 83.7% vs. 67.3%, $p = 0.967$; homelessness: 38.5% vs. 35.1%, $p = 0.227$; habitual alcohol consumption: 29.3% vs. 10.7%, $p < 0.001$; ongoing intravenous drug use: 64.0% vs. 57.8%, $p = 0.616$). No treatment interruptions or COVID19-associated deaths occurred among the study cohort. **Conclusion:** Initially, DOT was established to overcome suboptimal adherence to medical therapy in PWIDs with frequent ongoing substance use disorder, high prevalence of psychiatric comorbidities, and low socioeconomic status. Our data suggest that DOT is highly effective even with extended OAT/DAA dispensation intervals. The success of DOT seems to depend on the streamlined linkage to care and access to DAA achieved via a single visit to an LTF rather than the strict daily supervised ingestion of OAT/DAA.

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1879-A | LACK OF PHARMACOKINETIC DRUG-DRUG INTERACTION BETWEEN BEMNIFOSBUVIR AND RUZASVIR IN HEALTHY PARTICIPANTS

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Background: Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent, pan-genotypic inhibitors of HCV NS5B polymerase and NS5A protein, respectively. Combinations of BEM with daclatasvir, and RZR with uprifosbuvir were safe and well-tolerated, and independently achieved high sustained virologic response rates (SVR) in HCV-infected participants. *In vitro*, BEM is 10 times more potent than sofosbuvir and retains activity against sofosbuvir-resistant mutations. BEM and RZR exhibited synergistic anti-HCV activity *in vitro.* Cumulative data suggest that, while having a low drug-drug interaction (DDI) potential, the combination of BEM and RZR could be highly efficacious with a shorter treatment duration in a broad patient population. Here we report the results from a pharmacokinetic (PK) DDI study between BEM and RZR in healthy participants. **Methods:** Two groups of healthy participants (n = 16/group) were enrolled and received BEM 550 mg once daily (QD) or RZR 180 mg QD, alone, for 6 days. Starting on day 7, both groups received BEM+RZR QD for 12 days. Dosing occurred under fasting conditions from days 1-12 and with a low- or moderate-fat meal from days 13-18. Intensive PK sampling was performed over 24 h on days 6, 12 and 18, and plasma concentrations of BEM and metabolites and RZR were quantitated using validated bioanalytical methodologies. DDIs were assessed by comparing PK results on day 12 (combined) to day 6 (alone), whereas food effect assessed by comparing PK results on day 18 (fed) to day 12 (fasted). **Results:** All subjects completed the study. Adverse events were mild and non-serious. Co-administered RZR did not significantly alter the plasma PK of BEM: Maximum plasma concentration (Cmax) and area under the curve (AUC) of the parent drug of BEM (AT-511) and the circulating nucleoside metabolite AT-273, surrogate of the intracellular active triphosphate metabolite of BEM, were similar between BEM dosed alone and in the presence of RZR. Likewise, co-administered BEM had no marked effect on the plasma PK of RZR. In addition, a low- and moderate – fat meal did not affect the plasma exposure of AT-273 while slightly increased that of RZR. **Conclusion:** This study reports the first combination results of BEM and RZR in humans. The study drugs were well tolerated. Plasma PK of BEM and RZR was not altered when co-administered, indicative of a lack of PK DDI between the two drugs, and also the absence of a food effect. These results support the evaluation of a combination of these highly potent molecules as a potential novel combination for the treatment of HCV.

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Arantxa Horga – Atea Pharmaceuticals, Inc.: Employee, Yes, No;

Janet Hammond – Atea Pharmaceuticals, Inc.: Employee, Yes, No;

1880-A | LONG-ACTING TREATMENT FOR HEPATITIS C: HIGH ACCEPTABILITY AND FEASIBILITY AMONG PROVIDERS AND POLICYMAKERS IN LOW- AND MIDDLE-INCOME COUNTRIES

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Background: Although treatment for hepatitis C virus (HCV) with daily oral antiviral regimens is highly efficacious, suboptimal linkage and adherence may limit treatment success, particularly in patients with socioeconomic barriers or co-morbidities. Long-acting treatment (LAT) formulations are currently under early development as a strategy to improve HCV treatment outcomes. However, provider acceptability and health system feasibility for HCV LAT in low- and middle-income countries (LMICs) have not been evaluated. **Methods:** We conducted an online survey of HCV treatment prescribers and policymakers in LMICs regarding acceptability and feasibility of potential HCV LAT formulations, including one-time intramuscular injection, subdermal implant, and transdermal patch. Respondents were solicited from October 2022 to February 2023 via social media and targeted communications to provider networks, professional societies, and governmental contacts. **Results:** Overall, 122 providers and 50 policymakers from 42 LMICs completed the survey. Among providers, 113 (93%) expressed willingness to prescribe LAT, of which 63 (56%) would prescribe LAT for all patients and 50 (44%) would prescribe LAT based on risk factors or patient preference. If efficacy, safety, and cost were similar, 88 (72%) providers preferred LAT compared to oral treatment, of which 59 (67%) preferred injection, 21 (24%) preferred patch, and 8 (9%) preferred implant. Only 24 (20%) would still prescribe LAT if it were more costly than oral treatment. Reasons ranked most important for prescribing LAT were improved patient satisfaction or quality of life and improved adherence or treatment success. Patient characteristics ranked most important for prescribing LAT were non-routine engagement in medical care, HIV co-infection, previous HCV treatment failure, marginalized socioeconomic or ethnic background, incarceration, or housing instability. In regression analysis, no provider characteristics were associated with preference for LAT over oral treatment. Among policymakers, 42 (84%) reported high likelihood that LAT would be included in treatment guidelines and 39 (79%) reported high likelihood LAT would ultimately be included in national drug formularies (78%) if efficacy, safety, and cost were similar to oral treatment. **Conclusion:** There was high acceptability and perceived feasibility of HCV LAT if provided at comparable efficacy, safety, and cost as current oral treatment. Further characterizations of optimal patient populations, treatment settings, patient preferences, and health system preparedness are critical to inform development of HCV LAT options.

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1881-A | LONG-TERM SAFETY AND EFFICACY OF SOFOSBUVIR-BASED DIRECT-ACTING ANTIVIRALS IN PEDIATRIC PATIENTS WITH HEPATITIS C VIRUS

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Background: Direct-acting antivirals (DAAs) have revolutionized the treatment landscape for children with chronic hepatitis C virus (HCV) infection compared with pegylated interferon + ribavirin (RBV), which has suboptimal efficacy, extensive side effects, and negative impacts on growth. DAAs have shown high sustained virologic response (SVR) rates and favorable safety profiles in children, but data describing long-term outcomes are limited. Herein, we describe final follow-up data from study GS-US-334-1113 (NCT02510300) describing virologic outcomes and effects on growth and sexual development in children with chronic HCV infection. **Methods:** Children with chronic HCV infection who received sofosbuvir (SOF)+RBV, ledipasvir (LDV)/SOF ± RBV, SOF/velpatasvir (VEL), or SOF/VEL/voxilaprevir (VOX) in prior clinical trials were eligible to enroll in this 5-year registry study. Study baseline for enrollees was the day of their last visit in the parent trial. Every 6 to 12 months, we assessed the durability of SVR by measuring HCV RNA, and we evaluated the effects of DAAs on growth and sexual development by measuring weight, height, and body mass index (BMI) percentiles and z-scores (calculated using the 2000 CDC reference charts) and Tanner pubertal stage. **Results:** A total of 461 patients were enrolled between October 2015 and June 2021; 20% were treated with SOF+RBV, 42% with LDV/SOF ± RBV, 34% with SOF/VEL, and 4% with SOF/VEL/VOX in parent trials. Among 426 patients with **e** 1 postbaseline measurement, 58% were female, 80% were White, and the HCV genotype (GT) distribution was 66% GT1, 9% GT2, 21% GT3, 3% GT4, and 1% GT6. At enrollment, the median age (range) was 12 (3–18) years, and the mean (SD) weight, height, and BMI z-scores were 0.2 (1.23), −0.2 (1.05), and 0.4 (1.12), respectively. The median (range) follow-up was 193 (9–325) weeks. All but 2 patients achieved SVR in parent trials, and 100% of these patients maintained SVR throughout the registry study, with a median (range) SVR duration of 207 (30–341) weeks. Treatment with SOF-based DAAs had little impact on growth at week 240, and the mean changes (SD) in z-scores for weight, height, and BMI were 0.1 (0.71), 0.0 (0.67), and 0.1 (0.70), respectively. DAA treatment did not impact sexual development as assessed by Tanner stage. **Conclusion:** HCV treatment with SOF-based regimens resulted in durable SVR in children and had no impact on growth or sexual development up to 5 years posttreatment.

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1882-A | LONG-TERM SURVIVAL AND HEPATOCELLULAR CARCINOMA DEVELOPMENT IN HEPATITIS C VIRUS PATIENTS WITH DECOMPENSATED CIRRHOSIS AFTER DIRECT-ACTING ANTIVIRAL TREATMENT: A LONG-TERM FOLLOW-UP STUDY OF JAPANESE PHASE 3 TRIAL COHORT

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Background: Approximately 90% of hepatitis C virus (HCV) patients with decompensated cirrhosis can achieve sustained virologic response (SVR) by direct-acting antiviral (DAA) treatment. However, the long-term survival and hepatocellular carcinoma (HCC) development in patients with decompensated cirrhosis following DAA treatment is unclear. **Methods:** This study included 99 of the 102 patients who participated in the Japanese phase 3 trial on the effect of sofosbuvir and velpatasvir (SOF/VEL) with or without ribavirin (RBV) treatment in HCV patients with decompensated cirrhosis and who agreed to a long-term follow-up study. In the trial, patients started SOF/VEL with or without RBV treatment for 12 weeks between January 2017 and August 2017 at 33 Japanese hospitals. Decompensated cirrhosis was defined as Child-Pugh class B (CP-B) or CP-C at screening. We collected laboratory and clinical data at baseline, end of the treatment (EOT), 12 weeks after the EOT, 24 weeks after the EOT, 1 year after the EOT and every 1 year thereafter. Incidence rates of and baseline factors associated with overall survival and HCC development after DAA treatment were examined by Cox proportional hazard analysis. **Results:** The median age was 67 years, 40% of the patients were male, and seven patients had a history of HCC. The proportions of patients with CP-A, CP-B and CP-C at baseline were 12%, 77%, and 10%, respectively. The median observation period of this study was 58.7 months from the start of DAA. The percentage of patients with CP-A after starting DAA treatment was 22.2% (20/90) at the EOT, 43% (33/77) at 1 year after the EOT, 48% (36/75) at 3 years after the EOT, and 54% (27/50) at 5years after the EOT. Nineteen patients died, and the 3-year and 5-year overall survival rates were 92.4% and 76.6%, respectively. On multivariate analysis, higher γ-glutamyl transpeptidase levels (hazard ratio (HR): 1.020, $p = 0.009$), higher total bilirubin levels (HR: 1.941, $p < 0.001$), and lower albumin levels (HR: 0.164, $p = 0.010$) were significant baseline factors for overall survival after DAA treatment. For HCC development, 34 patients experienced HCC occurrence, and three patients experienced HCC recurrence. Cumulative HCC occurrence and HCC recurrence rates at 3 years were 28.4% and 57.1%, respectively. On univariate analysis, the presence of a history of HCC (HR: 2.898, $p = 0.050$) and lower albumin levels (HR: 0.363, $p = 0.025$) were significant baseline factors for HCC development after DAA treatment. **Conclusion:** In patients with decompensated cirrhosis, improvement in liver function is maintained over the long term after DAA treatment, and long-term survival is favorable. On the other hand, the risk of HCC development is high even after DAA treatment, continuous HCC surveillance is necessary in the long term.

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1883-A | MARCHING TOWARDS ELIMINATION: REDUCTIONS IN COMMUNITY VIRAL LOAD IN A RURAL APPALACHIAN COUNTY WITH AN ONGOING HCV TREATMENT TRIAL

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Background: As we march towards the 2030 hepatitis C virus (HCV) elimination goal set forth by the World Health Organization, innovative programs are necessary to reach those at greatest risk for transmitting the virus. The Kentucky Viral Hepatitis Treatment (KeY Treat) project sought to enroll chronically infected individual's in a treatment trial where medical care and medication (sobosbuvir/velpatasvir) were provided free of charge in a rural Appalachian Kentucky county. **Methods:** The goal of this analysis was to determine the potential effectiveness of the KeY Treat intervention in reducing community viral load by examining the proportion of viremic individual's screening for study participation over time. We hypothesized that the proportion of viremic individual's would decrease over time as those achieving SVR in the community increased. Multiple logistic regression was utilized to analyze the proportion of viremic individual's by time (seven 6-month periods), adjusting for prior knowledge of HCV exposure, people who inject drugs (PWID), gender and age. **Results:** 748 screened in-person for the study; of those, 76.9% ($n = 575$) were anti-HCV-positive. Of the Ab-positive 64.9% ($n = 373$) were

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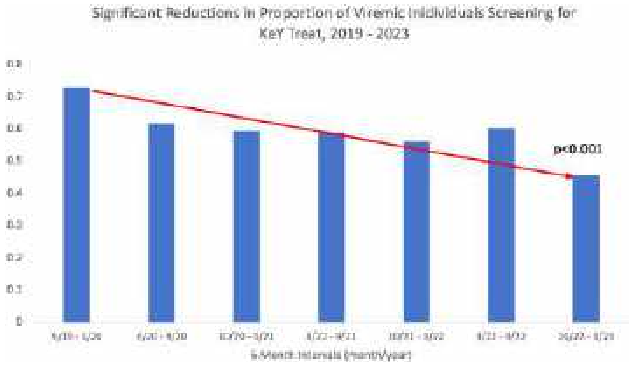
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

viremic and the proportion of viremic individual's significantly decreased over time ($p < 0.001$). In the multivariable model, compared to the first six months of recruitment (pre-COVID), the odds of being viremic were significantly lower at all follow-up periods, but especially the final 6 months of recruitment, from October 2022 to March 2023 where the odds were 69% lower. Age and PWID status were not associated with the presence of a chronic infection, but women were 39% less likely to be viremic at screening than men. **Conclusion:** These data point to a reduction in the proportion of viremic individual's over time, suggesting that the community viral load may have been significantly reduced as a result of an increase in the number of cured individual's in the county. These results held even after adjustment for PWID, gender and age. Continued treatment of those at greatest risk for HCV viral transmission is necessary to eliminate the virus from this high-risk community.



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1884-A | PATIENTS WITH HEPATITIS C SUCCESSFULLY TREATED WITH SOFOSBUVIR/VELPATASVIR BY NON-SPECIALISTS IN FRANCE: FINAL ANALYSIS OF HELIOS-3

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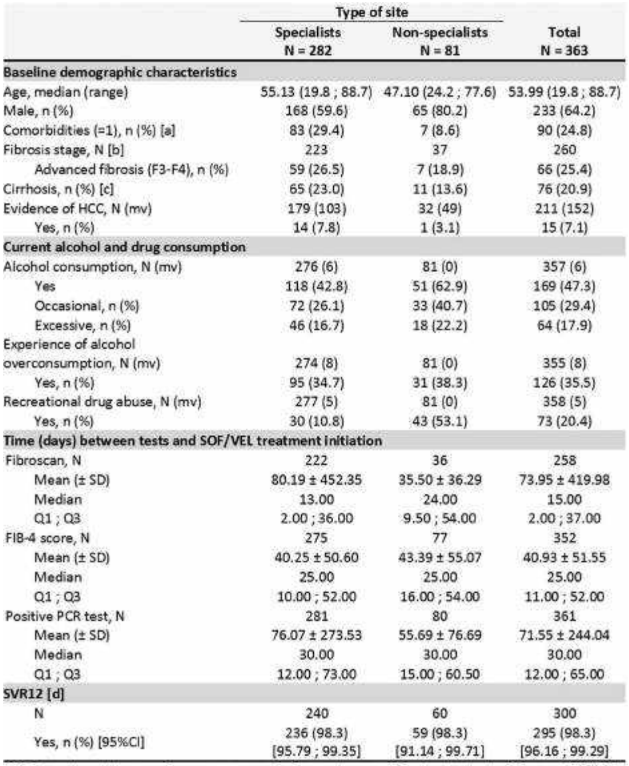
Background: Sofosbuvir/Velpatasvir (SOF/VEL) is a curative treatment for hepatitis C virus (HCV) infection. In France, prescribing rights were extended in May 2019 to non-specialists including physicians working in prisons, addiction centers, and psychiatric hospitals. For rapid treatment initiation, a Test and Treat (TnT) approach is followed, with severe patients (cirrhosis, treatment failures, comorbidities) referred to specialists. The main objective of this study was to evaluate the effectiveness and safety of the SOF/VEL TnT strategy for 12 weeks in HCV patients after prescription expansion. **Methods:** This French, multi-center, prospective, non-interventional study included adults with chronic HCV infection, treated with SOF/VEL for 12 weeks by specialists or non-specialists. Study data (e.g., patient characteristics, fibrosis evaluation) were collected from patients' medical records. The primary endpoint was the proportion of patients with sustained virologic response 12 weeks after end of treatment (SVR12). Secondary endpoints included safety profile, time between diagnostic tests and treatment start, and demographic characteristics of patients treated with SOF/VEL. **Results:** A total of 363 patients met the eligibility criteria and received at least one dose of SOF/VEL. Median age was 53.99 years (range, 19.8 to 88.7) and 233 (64.2%) patients were male. Among them, 282 (77.7%) were treated by specialists, 81 (22.3%) by non-specialists. The specialist group had more patients with comorbidities (29.4% vs 8.6%) and advanced fibrosis (26.5% vs 18.9%), whereas the non-specialist group had more patients reporting alcohol consumption (62.9% vs 42.8%) and drug abuse (53.1% vs 10.8%). Among patients eligible for SVR12 analysis (300 patients), SVR12 rate was 98.3% (95%CI, 95.79%-99.35%) in the specialist group and 98.3% (95%CI, 91.14%-99.71%) in the non-specialist group. Overall, adverse events considered related to SOF/VEL occurred in 16 patients (specialist group, 7; non-specialist group, 9). One event in the non-specialist group led to treatment discontinuation. Median time between PCR positive test and treatment was 30 days in both groups. Median time between fibrosis evaluation by Fibroscan and treatment was longer in the non-specialist group (24 d vs 13 d). FIB-4 was also calculated and median time to treatment was 25 days in both groups. **Conclusion:** This study shows that non-specialists successfully treat chronic HCV infection with SOF/VEL for 12 weeks with a TnT approach. SOF/VEL prescription expansion could therefore be considered in other countries as a tool to reach WHO HCV elimination targets by 2030.



	Type of site		
	Specialists N = 282	Non-specialists N = 81	Total N = 363
Baseline demographic characteristics			
Age, median (range)	55.13 (19.8 ; 88.7)	47.10 (24.2 ; 77.6)	53.99 (19.8 ; 88.7)
Male, n (%)	168 (59.6)	65 (80.2)	233 (64.2)
Comorbidities (=1), n (%) [a]	83 (29.4)	7 (8.6)	90 (24.8)
Fibrosis stage, N [b]	223	37	260
Advanced fibrosis (F3-F4), n (%)	59 (26.5)	7 (18.9)	66 (25.4)
Cirrhosis, n (%) [c]	65 (23.0)	11 (13.6)	76 (20.9)
Evidence of HCC, N (mv)	179 (103)	32 (49)	211 (152)
Yes, n (%)	14 (7.8)	1 (3.1)	15 (7.1)
Current alcohol and drug consumption			
Alcohol consumption, N (mv)	276 (6)	81 (0)	357 (6)
Yes	118 (42.8)	51 (62.9)	169 (47.3)
Occasional, n (%)	72 (26.1)	33 (40.7)	105 (29.4)
Excessive, n (%)	46 (16.7)	18 (22.2)	64 (17.9)
Experience of alcohol overconsumption, N (mv)	274 (8)	81 (0)	355 (8)
Yes, n (%)	95 (34.7)	31 (38.3)	126 (35.5)
Recreational drug abuse, N (mv)	277 (5)	81 (0)	358 (5)
Yes, n (%)	30 (10.8)	43 (53.1)	73 (20.4)
Time (days) between tests and SOF/VEL treatment initiation			
Fibroscan, N	222	36	258
Mean (± SD)	80.19 ± 452.35	35.50 ± 36.29	73.95 ± 419.98
Median	13.00	24.00	15.00
Q1 ; Q3	2.00 ; 36.00	9.50 ; 54.00	2.00 ; 37.00
FIB-4 score, N	275	77	352
Mean (± SD)	40.25 ± 50.60	43.39 ± 55.07	40.93 ± 51.55
Median	25.00	25.00	25.00
Q1 ; Q3	10.00 ; 52.00	16.00 ; 54.00	11.00 ; 52.00
Positive PCR test, N	281	80	361
Mean (± SD)	76.07 ± 273.53	55.69 ± 76.69	71.55 ± 244.04
Median	30.00	30.00	30.00
Q1 ; Q3	12.00 ; 73.00	15.00 ; 60.50	12.00 ; 65.00
SVR12 [d]			
N	240	60	300
Yes, n (%) [95%CI]	236 (98.3) [95.79 ; 99.35]	59 (98.3) [91.14 ; 99.71]	295 (98.3) [96.16 ; 99.29]

HCC, hepatocellular carcinoma ; mv, missing values ; SD, standard deviation ; SOF/VEL, Sofosbuvir/Velpatasvir

[a] Comorbidities were: diabetes, non-alcoholic fatty liver disease, arterial hypertension, renal insufficiency, dialysis, renal transplantation

[b] Advanced Fibrosis assessed by Fibroscan

[c] Fibrosis stage F4 determined by Fibroscan, Fibrotest, Fibrometer, or FIB-4

[d] SVR12, sustained virologic response rate 12 weeks after discontinuation of SOF/VEL where virologic response is defined as HCV RNA < 25 IU/mL (lower limit of quantification)

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1885-A | PEER EDUCATION AND PSYCHOLOGICAL INTERVENTION FOR HCV ELIMINATION AMONG HIGH-RISK GROUPS: A PROSPECTIVE REAL WORLD STUDY IN METHADONE CLINIC

Shan Shi[1], Likui Wei[1], Hangfeng Liu[1], Ruyi Luo[1], Lanjuan Li[1], Rongjian Li[2], Cailian Cai[3], Xiaoting Li[3] and Minghua Su[3], (1)Nanning Red Cross Hospital, (2) Guangxi Zhuang Autonomous Region Center for Disease Control and Prevention, (3)The First Affiliated Hospital of Guangxi Medical University

Background: HCV elimination in methadone clinic is very important in China. But it is still a big challenge in patient education. Peer education and psychological interventions may be a strategy for health promotion in this population for HCV infection. We aim to explore a new model for HCV elimination in methadone clinic in Guangxi Province of China (Connection Project) **Methods:** A multi-collaborative approach was used for MT patients and HCV patients were recruited from methadone clinics from October 2022 to April 2023. The co-operation network consists of local centers for Disease Control and Prevention (CDC) and hepatology hospital and methadone clinics. The CDC is responsible for funding and building the patient network. Leaded by CDC, hepatologists collaborate with the health care professionals (HCPs) from methadone clinics, including physicians and nurses. Hepatology specialists educate methadone providers about HCV disease and conduct DAA treatment and follow-up for HCV RNA positive patients. Methadone health care providers are responsible for HCV antibody screening, HCV RNA testing, providing psychological intervention to patients, inviting the patients who have been cured of HCV treatment to communicate with patients who have not been treated for HCV, and facilitating referral of patients to receive treatment at MT or hepatologists for DAA treatment. **Results:** 3 HCV educations for HCPs (84 participants) and 12 psychological intervention classes for patients (120 participants) were conducted in one pilot methadone clinic of the Connection Project totally. 1,500 learning education materials were produced and handed out for the project. At the methadone clinic, there were 412 patients. The mean age was 50.28 (+/-7.19) years, 80.8% were male, 95% had medical insurance, 5% had cirrhosis. Most of them have comorbidities, including HIV infection, mental illness and diabetes. 96% (395/412) of them are HCV-Ab (+), and 58% (231/395) are HCV RNA (+) The main genotypes were 3b and 6a (30% and 30% respectively). Within six months of the start of the program, 38 patients had been referred and 27 had received HCV antiviral treatment, and they are still in the process of treatment and follow-up. Others are on the waiting list for health insurance approval. **Conclusion:** Peer education may be a strategy to HCV elimination in methadone clinics. Psychological intervention plays a key role in referral. The model is being extended to other methadone clinics in the province to help HCV elimination.

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1886-A | PEOPLE WITH HIV/HCV CO-INFECTION HAVE COMPARABLE SVR AND IMPROVEMENTS IN LIVER FUNCTIONS USING MINIMAL MONITORING STRATEGY: SECONDARY ANALYSES FROM THE MINMON TRIAL

Emmanuel Thomas, Miami, Dimas Kliemann, Hospital Nossa Senhora Da Conceição - Ghc, Kevin Wongsodirdjo, Cbar | Harvard T.H. Chan School of Public Health, Tanyaporn Wansom, Baylor College of Medicine, Estevão Nunes, Instituto Nacional De Infectologia, Laura Smeaton, Harvard School of Public Health, Susanna Naggie, Duke Clinical Research Institute, Durham, NC, David L. Wyles, Denver Health Medical Center, Sunil S. Solomon, The Johns Hopkins University School of Medicine and Mark S. Sulkowski, Johns Hopkins Medicine

Background: Simplified HCV treatment strategies allow for greater access in many settings. Current AASLD/IDSA simplified guidelines suggest that persons with HIV (PWH) are eligible for this approach. We compared markers of liver disease before and after treatment in both people with HCV only and HIV & HCV (HIV/HCV) treated using a minimal monitoring approach. **Methods:** ACTG A5360 was a single-arm, open-label trial to evaluate safety/efficacy of a minimal monitoring (MINMON) approach to HCV therapy in HCV treatment-naïve persons from 5 countries who had no evidence of decompensated cirrhosis. All participants received 84 tablets of sofosbuvir/velpatasvir at entry with the next scheduled in-person visit being at Week 24 to ascertain sustained virologic response (SVR). ALT, FIB-4 and Liver Stiffness Measurement by Fibroscan® (optional) were measured at baseline and week 24. Distribution of changes in ALT between baseline and SVR by HIV status were summarized; changes in FIB-4 and LSM were also quantified. Analyses included 379 of 399 participants who achieved SVR. **Results:** Median age of 379 participants was 47 years and 35% were assigned female sex at birth, 41% had HIV and 8% had compensated cirrhosis. SVR in HCV and HIV/HCV were 95.3% and 94.6%, respectively. The median ALT at baseline was 53 IU/L for the entire cohort. Overall, ALT had a median change

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

of -33 IU/L (IQR: -70, -19); improvements were similar in each group based on HIV status (Table 1). FIB-4 median change of -0.10 (IQR: -0.39, 0.09) and -0.11 (IQR: -0.53, 0.07) in HCV and HIV/HCV, respectively. In the subset of 142 patients with LSM, the median score changed from 6.4 kPa at baseline to 5.4 kPa at SVR. **Conclusion:** Among participants treated with minimal monitoring, these data suggest similar improvement in liver disease measured among people with and without HIV. Cumulatively with the SVR data, these data further strongly support the inclusion of PWH for curative HCV treatment using minimal or simplified monitoring strategies as indicated in recent guidelines.

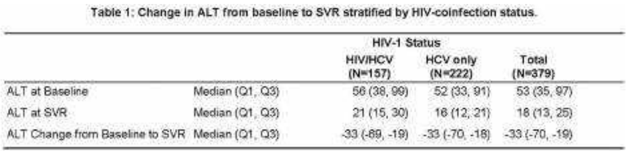
Table 1: Change in ALT from baseline to SVR stratified by HIV-coinfection status.

		HIV-1 Status		
		HIV/HCV (N=157)	HCV only (N=222)	Total (N=379)
ALT at Baseline	Median (Q1, Q3)	56 (38, 99)	52 (33, 91)	53 (35, 97)
ALT at SVR	Median (Q1, Q3)	21 (15, 30)	16 (12, 21)	18 (13, 25)
ALT Change from Baseline to SVR	Median (Q1, Q3)	-33 (-69, -19)	-33 (-70, -18)	-33 (-70, -19)

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1887-A | POSTTREATMENT CHILD-PUGH CLASS STRATIFIES PATIENT SURVIVAL AFTER DIRECT-ACTING ANTIVIRAL TREATMENT IN HEPATITIS C VIRUS-ASSOCIATED DECOMPENSATED CIRRHOSIS

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Background: The prognosis of cirrhosis is clearly stratified by Child-Pugh (CP) class. Although direct-acting antiviral (DAA) treatment has recently been used to eliminate hepatitis C virus (HCV), it is not clear whether CP class stratifies the prognosis of decompensated cirrhotic patients treated with DAA. **Methods:** This study prospectively registered 206 HCV-associated decompensated cirrhotic patients who started DAA from February 2019 to December 2021 at Japanese institutions. Decompensated cirrhosis was defined as CP-B or CP-C or CP-A with previous decompensating events. All patients were treated with sofosbuvir and velpatasvir (SOF/VEL) for 12 weeks. Factors associated with liver transplantation (LT)-free survival and changes in CP class after SOF/VEL treatment were examined. **Results:** The median age was 68 years, and the proportions of patients with CP-A, CP-B and CP-C were 10%, 76% and 15%, respectively. The sustained virologic response rate was 91% in an intention-to-treat fashion. During 28 months from the start of SOF/VEL, 26 patients died (13 liver failure, 4 hepatocellular carcinoma, 1 varix rupture, 8 non-liver-related cause) and two patients underwent LT. The 3-year LT-free survival rate was 83%. In a multivariate Cox proportional hazards model, alanine aminotransferase level ($p = 0.046$), creatinine level ($p = 0.001$) and CP-C at 12 weeks after the end of treatment (EOT) ($p < 0.001$) were significantly associated with LT-free survival after SOF/VEL treatment, while baseline CP class was not. The 3-year LT-free survival rates were 91%, 86% and 52% for patients with CP-A, CP-B and CP-C at 12 weeks after the EOT, respectively (CP-A vs. CP-B; $p = 0.269$, CP-A vs. CP-C; $p < 0.001$, CP-B vs. CP-C; $p < 0.001$), indicating that not becoming to CP-C at 12 weeks after the EOT is important for patient prognosis. We evaluated CP changes in 193 patients for whom CP class both at baseline and 12 weeks after the EOT could be assessed. Among 17 patients with baseline

CP-A, two deteriorated to CP-B, but no patients deteriorated to CP-C at 12 weeks after the EOT. Among 150 patients with baseline CP-B, 60 improved to CP-A and seven deteriorated to CP-C at 12 weeks after the EOT. Among 26 patients with baseline CP-C, one and 14 improved to CP-A and CP-B, respectively, and 11 remained in CP-C at 12 weeks after the EOT. When we examined baseline factors associated with CP-C at 12 weeks after the EOT among patients with CP-B or CP-C at baseline, the presence of hepatic encephalopathy ($p = 0.020$) and total bilirubin levels ($p = 0.002$) were significant in multivariate logistic regression analysis. **Conclusion:** The prognosis of decompensated cirrhotic patients who underwent DAA treatment was clearly stratified by CP class at 12 weeks after the EOT. Baseline hepatic encephalopathy and total bilirubin levels were associated with CP-C at 12 weeks after the EOT.

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1888-A | PROGRESS TOWARDS ACHIEVING HEPATITIS C ELIMINATION IN THE COUNTRY OF GEORGIA, APRIL 2015 – APRIL 2023

Tengiz Tsertsvadze[1,2], *Amiran Gamkrelidze*[3], *Nikoloz Chkhartishvili*[1], *Akaki Abutidze*[1,2], *Lali Sharvadze*[2,4], *Maia Butsashvili*[5], *Jaba Zarkua*[6], *Shaun Shadaker*[7], *Irina Tskhomelidze*[7], *Ekaterine Adamia*[8], *Senad Handanagic*[7] *and Tamar Gabunia*[8], *(1)Infectious Diseases, AIDS and Clinical Immunology Research Center, (2)Ivane Javakhishvili Tbilisi State University, (3)National Center for Disease Control and Public Health, (4)Hepatology Clinic Hepa, (5)Health Research Union, (6)Medical Center Mrcheveli, (7)Centers for Disease Control and Prevention, Division of Viral Hepatitis, National Center for HIV, Hepatitis, Std&tb Prevention, (8)Ministry of IDPs from the Occupied Territories, Labour, Health and Social Affairs of Georgia*

Background: The country of Georgia launched the world's first national hepatitis C elimination program in April 2015. Key strategies include nationwide screening, active case finding, linkage to care, decentralized care, and provision of treatment for all persons with hepatitis C virus (HCV) infection, along with effective prevention interventions. The elimination program aims to achieve the following targets: a) diagnose 90% of HCV-infected persons, b) treat 95% of those diagnosed, and c) cure 95% of those treated. We report progress toward elimination targets of the elimination program. **Methods:** The estimated number of persons with HCV infection was based on a 2015 population-based national seroprevalence survey, which showed that 5.4% of the general adult population had current HCV infection (approximately 150,000 persons). We analyzed data in the national HCV screening and treatment databases during April 2015-April 2023. **Results:** As of April 30, 2023, 157,198 adults screened positive for HCV antibodies. Of those, 130,955 (83.3%) received HCV RNA or core antigen testing, of whom 102,354 (78.2%) tested had current HCV infection, and 82,203 (80.3%) of them initiated treatment. Of 58,074 persons who were evaluated for sustained virologic response (SVR), 57,478 (99.0%) had no detectable HCV RNA. Based on the 90-95-95 program goals, Georgia has diagnosed 68.2% of the estimated 150,000 adults with current HCV infection, treated 64.1% of the target 128,250 (95% of 150,000), and cured 47.2% of the target 121,837 (95% of 128,250). Treatment effectiveness was comparable among persons with advanced fibrosis (FIB-4 score F3 or F4) with 98.4% achieving SVR, and among patients with mild or no liver fibrosis (FIB-4 score d F2), SVR = 99.3%, $p < 0.0001$. **Conclusion:** Georgia has made substantial progress towards eliminating hepatitis C. Over 68% of persons with current HCV infection have been diagnosed, and most have initiated treatment and experienced high cure rates regardless of fibrosis status. Challenges remain in identifying and linking to care persons with current HCV infection in Georgia. The Nationwide integrated, decentralized model of HCV treatment, which is already implemented in many locations, will be critical to improve linkage to care and close gaps in the HCV cascade of care.

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1889-A | REAL WORLD EXPERIENCE IN TREATMENT OF CHRONIC HEPATITIS C IN PATIENTS WITH CIRRHOSIS AT A SAFETY-NET HOSPITAL

Francois Rollin, Jennifer E. Lom, Maeve McNamara, Lana Aleuy, Siri Chirumamilla, Alexander Molinari, Lesley S. Miller and Shelly-Ann Fluker, Emory University School of Medicine

Background: Outside of clinical trials, there is limited data on the safety and efficacy of direct acting antivirals (DAAs) in patients with chronic hepatitis C (HCV) with cirrhosis. The CREST study recently described real world experience with glecaprevir/pibrentasvir in Canada, Israel, and Europe in treatment naïve patients with compensated cirrhosis. We sought to add to this knowledge by evaluating a large cohort of medically underserved patients in the US (United States) with compensated and decompensated cirrhosis treated with a variety of DAA regimens. **Methods:** We performed a retrospective chart review of patients with HCV cirrhosis treated with DAAs at the Grady Liver Clinic (GLC). The GLC is a primary care-based HCV treatment clinic at a safety net hospital in Atlanta, GA. We reviewed electronic health record charts of patients treated at the GLC between 2015 and 2019. Charts were abstracted for patient demographics and characteristics, treatment regimen, and treatment outcomes. We performed an intention to treat (ITT) analysis for all patients who took at least one dose of a DAA regardless of completion, and a per protocol (PP) analysis of those who completed treatment and were tested for sustained virologic response (SVR). **Results:** 451 patients with cirrhosis were treated during the study period. The median age was 62 and they were primarily male (59.0%), black (82.0%), and 90.5% had compensated cirrhosis. The primary HCV genotype was 1 (90.0%). Patients were treated according to AASLD guidelines, and we compared outcomes for compensated vs. decompensated cirrhosis. The most common regimens were ledipasvir/sofosbuvir (65.9% vs. 34.8%), sofosbuvir/velpatasvir (13.4% vs. 11.63%), glecaprevir/pibrentasvir (2.21% vs. 0%), and sofosbuvir/velpatasvir/voxilaprevir (2.7% vs. 0%). The majority of both groups had a high rate of adherence with no missed doses (66.4% vs. 65.1%) or 1 - 7 d missed (23.3% vs. 20.9%). The most common adverse effects between both groups were fatigue (33.3% vs. 39.0%), headache (30.3% vs. 29.3%), and nausea (11.6% vs. 14.6%). In the ITT analysis, 88.5% of compensated and 86.0% of decompensated achieved SVR and in the PP analysis, 94.0% of compensated and 90.2% of decompensated achieved SVR. For the entire cohort, ITT SVR was 88.2% and PP SVR was 93.6%. **Conclusion:** In this retrospective study, patients with compensated and decompensated HCV cirrhosis at a safety-net HCV clinic achieved high SVR rates using a variety of DAAs. Our study is among the first to report such results from a real-world cohort of medically underserved patients in the US.

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Disclosure information not available at the time of publication: Francois Rollin, Jennifer E. Lom, Maeve McNamara, Alexander Molinari, Lesley S. Miller

1890-A | REAL-WORLD EFFECTIVENESS AND SAFETY OF SOFOSBUVIR/VELPATASVIR (SOF/VEL) IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS (HCV) GENOTYPE 3b

Zhiyan Nan, China Medical University and Aihua Jiang, Infectious Hospital of Fushun

Background: To analyze the effectiveness and safety of SOF/VEL in real-world treatment of patients with HCV genotype 3b infection. **Methods:** A retrospective study of 22 patients with HCV genotype 3b admitted to our hospital from January 2020 to January 2023. Patients were treated with SOF/VEL for 12 weeks, and patients with hepatitis C cirrhosis, both hepatic compensated and decompensated, received a 12-week regimen of SOF/VEL ± ribavirin (RBV) to observe SVR12 and adverse events. **Results:** At the end of treatment, the sustained virological response rate (SVR12) was 95.4% in 22 patients, including 5 patients with compensated cirrhosis with 100% SVR12 and 5 patients with decompensated cirrhosis with 100% SVR12;there were no serious adverse events and death. **Conclusion:** SOF/VEL ± RBV regimen for genotype 3b HCV infection can achieve high sustained virological response (SVR) rates, especially in patients with cirrhosis, including compensated and decompensated stages, can still achieve good effectiveness and safety, but further sample size expansion is needed to validate.

Disclosures: The following people have nothing to disclose: Zhiyan Nan, Aihua Jiang

1891-A | REAL-WORLD EFFECTIVENESS OF VOXILAPREVIR/VELPATASVIR/SOFOSBUVIR IN DAA FAILURE PATIENTS: AN INTEGRATIVE ANALYSIS

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Background: The currently approved re-treatment regimen for prior DAA failure is a combination of voxilaprevir/velpatasvir/sofosbuvir (VOX/VEL/SOF), although data on its clinical use especially in difficult-to-treat patients are limited. The aim of the present study was to analyze the effectiveness of VOX/VEL/SOF in a real-world setting. **Methods:** All patients with HCV, starting antiviral treatment with VOX/VEL/SOF between 2016 and 2021 in 227 centers of the European Resistance study group in Austria, Belgium, Germany, Italy, Spain and Switzerland were enrolled in a retrospective multicenter real-life study. Sustained virological response (SVR) was defined as undetectable HCV RNA 12 (SVR12) weeks after the end-of-treatment. **Results:** A total of 746 patients were included: median age was 55 (21-84) years and 79% were male. Most were infected with HCV genotype (GT) 1 (56%) or 3 (32%). 87% of patients carried resistance associated substitutions (RAS) in the NS3, NS5A and NS5B region. The most common prior DAA combinations were ledipasvir/sofosbuvir (LDV/SOF), velpatasvir/sofosbuvir (VEL/SOF) and glecaprevir/pibrentasvir (G/P). Overall, per protocol (PP) SVR was 96.4% (683/716). Treatment effectiveness was significantly lower in patients with advanced liver disease ($p < 0.001$), hepatocellular carcinoma (HCC; $p < 0.001$), higher baseline alanine aminotransferase (ALT) levels ($p = 0.02$), HCV GT 3 ($p < 0.001$) and prior VEL/SOF experience ($p = 0.01$). However, in a multivariate analysis only HCV GT 3, HCC and liver cirrhosis turned out to be independent predictors of a treatment failure. RASs as well as the presence of rare genotypes did not impact treatment outcome of VOX/VEL/SOF. RBV was added in 8% of treatment courses and increased overall SVR rates (97%) as well as SVR rates in difficult-to-treat patients with HCV GT 3a (100%), liver cirrhosis (92.6%) and liver cancer (90%) insignificantly. Moreover, treatment effectiveness of rescue therapy with G/P+SOF, which was initiated in 9 patients after VOX/VEL/SOF failure, was found to be high (SVR 12: 100%). **Conclusion:** VOX/VEL/SOF represents an effective retreatment for patients with HCV and prior DAA treatment failure. The addition of ribavirin or alternative retreatment with G/P+SOF, which was found to be effective in VOX/VEL/SOF treatment failures, may be considered in difficult-to-treat patients with HCV GT 3a, liver cirrhosis and liver cancer.

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1892-A | SAFETY AND IMMUNOGENICITY OF COVID-19 VACCINE IN PATIENTS WITH HCV RELATED LIVER DISEASE

Zhang Jing and Haiqing Guo, Beijing Youan Hospital Capital Medical University, Beijing, China

Background: Due to the high mortality of patients with severe liver disease who infected with SARS-CoV-2, vaccination was strongly recommended to those patients. However, there was little data on safety and antibody level after whole course vaccination by domestic vaccine. The present study evaluated the safety and immunogenicity of domestic COVID-19 vaccine in patients with HCV related liver disease aimed to provide evidence of vaccination strategy adjustment. **Methods:** This observational study recruited 211 patients with HCV related liver disease who never infected with SARS-CoV-2. All patients received 3 doses of domestic COVID-19 vaccines within 7 months. The adverse reactions of vaccination were recorded. Liver function before and after vaccination, serum level of neutralizing antibody after the whole course vaccination were determined. **Results:** Among them, 81 were chronic hepatitis C, 117 were cirrhosis and 13 were hepatocellular carcinoma (HCC). Patients with cirrhosis and HCC were analyzed as one group. No serious adverse events were reported by patients. Hemoglobin, bilirubin, albumin, creatinine and prothrombin time worsened after vaccination but hadn't clinical significance. The negative response rate (40.8%) of cirrhosis and HCC group was comparable to chronic hepatitis C group (32.1%, p = 0.206). However, neutralizing antibody titer (median titer 24.2, range 11.2-65.5 IU/ml) was significantly lower in patients with cirrhosis and HCC than chronic hepatitis C (median titer 38.9, range 16.0-198.9 IU/ml, p = 0.031). **Conclusion:** The domestic COVID-19 vaccine appears to be safe and has a certain protective effect in patients with HCV related liver disease.

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1893-A | SAFETY AND TOLERABILITY OF AN ORAL CONTRACEPTIVE CONTAINING LOW-DOSE ETHINYL ESTRADIOL COMBINED WITH GLECAPREVIR/PIBRENTASVIR TREATMENT IN HEALTHY PREMENOPAUSAL WOMEN: RESULTS OF A PHASE 1 STUDY

Dee-Dee Shiller[1], Betty B. Yao[1], Mong-Jen Chen[1], Amelia Orejudos[1], Nael M. Mostafa[1], John F. Marcinak[1], Margaret Burroughs[1] and Craig Boyle[2], (1)Abbvie, Inc., (2)PPD Phase 1 Clinic

Background: Glecaprevir/pibrentasvir (GLE/PIB) is an approved and guideline-recommended treatment for chronic hepatitis C virus infection. Current product labels do not recommend co-administration of GLE/PIB with ethinyl estradiol (EE)-containing medications such as oral contraceptives (OC) due to alanine aminotransferase (ALT) elevations observed in an earlier study. Specifically, Grade 2-3 ALT elevations were reported in 2/12 women co-treated with 35 µg/250 µg EE/norgestimate for 11 days; however, no Grade e 2 ALT elevation was reported in 14 women co-treated with low-dose EE (20 µg) and 100 µg levonorgestrel (LNG) for 11 days. Therefore, this Phase 1, single-arm, open-label study was designed to assess the safety of GLE/PIB co-administered with an OC containing low-dose EE and LNG, with a larger sample size and longer treatment duration than the earlier study. **Methods:** Healthy premenopausal women aged 18-49 years received 20 µg/100 µg EE/LNG alone during cycles 1-2, followed by co-administration with 300 mg/120 mg GLE/PIB during cycles 3-4. The main safety event of special interest was confirmed Grade e 2 ALT elevation. Adverse events (AEs) and steady-state trough concentrations of EE/LNG and GLE/PIB were also assessed. **Results:** Of 85 enrolled women, 72 received combined GLE/PIB+EE/LNG treatment and 66 completed the study; 16 discontinued the study due to non-safety reasons and 3 due to AEs deemed unrelated to GLE/PIB. No serious or Grade e 3 AEs were reported. No AEs of Grade e 2 ALT or aspartate aminotransferase (AST) elevation were reported. No ALT levels observed met the safety criterion of special interest of confirmed Grade e 2 elevation. Two women had Grade 2 bilirubin increase (EE/LNG, n = 1; EE/LNG +GLE/PIB, n = 1), which was considered representative of isolated hyperbilirubinemia, as neither woman had ALT/AST elevation reported during the study. EE/LNG and GLE/PIB concentrations (e 20-hour interval, binned data) were within the expected ranges. **Conclusion:** No Grade e 2 ALT elevation or evidence of drug-induced liver injury was observed during combined treatment with low-dose EE-containing OC and GLE/PIB in this robust Phase 1 study with a 2-cycle treatment duration and sample size of 72 women receiving the combined treatment. The combined treatment was generally well tolerated in this study, with no pattern to reported AEs and no new safety issues identified. *Note: Glecaprevir was identified by AbbVie and Enanta.*

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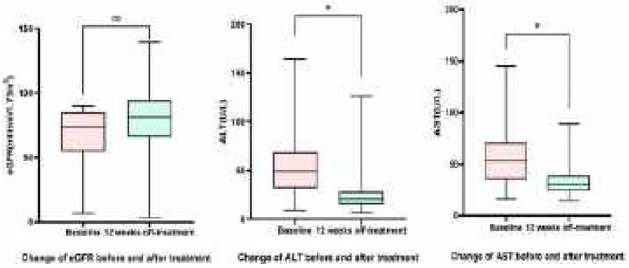
1894-A | SOFOSBUVIR/VELPATASVIR WITH OR WITHOUT RIBAVIRIN FOR CHRONIC HEPATITIS C VIRUS INFECTED PATIENTS WITH LIVER CIRRHOSIS AND CHRONIC KIDNEY DISEASE: REAL-WORLD EXPERIENCE FROM SOUTHWEST CHINA

Yang Yong Rui, Kang Huang, Zhirong Zhao, Jinsong Bai, Lei Wu, Junyi Li, Shenghao Li, Liu Li, Haiwen Li and Yingrong Du, The Third People's Hospital of Kunming City

Background: Evidence of direct-acting antiviral (DAA) treatment for refractory chronic hepatitis C (CHC) patients with liver cirrhosis and chronic kidney disease (CKD) was limited . We aimed to evaluate the safety and effectiveness of Sofosbuvir/Velpatasvir (SOF/VEL) with or without Ribavirin (RBV) treatment in this special population in Southwest China. **Methods:** From June 2018 to March 2023, CHC patients with liver cirrhosis (diagnosed by imaging examination and clinical manifestation) and CKD (eGFR < 90 ml/min/1.73m2) at The Third People's Hospital of Kunming City were retrospectively enrolled. All patients received SOF/VEL ± RBV (dosage of RBV depending on weight and renal function) for 12 weeks. The primary endpoints were change of renal function during treatment. Sustained virologic response at 12 weeks off-therapy (SVR12,defined as HCV RNA < 20 IU/mL), change of liver function and adverse events (AEs) were also assessed. **Results:** A total of 65 CHC patients with liver cirrhosis and CKD were included. The mean age was 52.31 ± 8.02 years and 76.92% (50/65) were male. HCV genotype distribution: 6.15%(4/65) patients were GT2a, 28 %(18/65) were GT3a, 55%(36/65) were GT3b,.4.6%(3/65) were GT6n and 6.15%(4/65) were unknown genotype. Baseline CKD stage: 49 (75.4%) in CKD stage 2, 12 (18.5%) in stage 3, 2 (3%) in stage 4 and 2 (3.1%) in stage 5. Cirrhosis status: 41.54% (27/65) were compensated cirrhosis(CC) and 58.46% (38/65) were decompensated cirrhosis (DCC). Regarding the safety profile, mean eGFR increased significantly from 68.45 ± 20.56 ml/min/1.73m^2 at baseline to 84.24 ± 56.97ml/min/1.73m^2 at the end of treatment ($P = 0.073$). There were no patients in CKD stage 1 at baseline but 21.5% (14/65) of patients improved to stage 1 after 12 weeks off-treatment. For liver function, mean ALT (from55.57 ± 38.18 U/L to 25.23 ± 20.97 U/L, $P < 0.05$) and AST (from 59.38 ± 33.24 U/L to 35.54 ± 18.99 U/L, $P < 0.05$) also decreased significantly after treatment. 38.5% (25/65) patients reported AEs during treatment (including 20 hemolysis,1 pruritus, 1 rash, 2 dizziness and 2 fatigue) and recovered after supportive treatment. No serious AEs were reported. For the efficacy profile, 96.9% (63/65) patients achieved SVR12 after SOF/VEL ± RBV for 12 weeks, including 100%(18/18) in GT3a , 94.44% (34/36) in GT3b, 100% (11/11) in other GTs patients with CKD. 100% (27/27) patients with CC and 94.74%(36/38) patients with DCC achieved SVR12. 2 patients with GT3b and DCC with CKD stage 2 failed treatment. **Conclusion:** SOF/VEL ± RBV treatment was effective and well tolerated in CHC patients with liver cirrhosis and CKD. Both renal and liver function were improved after DAA treatment.



Disclosures: The following people have nothing to disclose: Yang Yong Rui, Kang Huang, Zhirong Zhao, Jinsong Bai, Lei Wu, Junyi Li, Shenghao Li, Liu Li, Haiwen Li, Yingrong Du

1895-A | STANDARD VERSUS MINIMAL MONITORING FOR HEPATITIS C DIRECT ACTING ANTIVIRAL (DAA) THERAPY AT AN ACADEMIC MEDICAL CENTER

Anita Yang, University of North Carolina Health, Jane Giang, University of North Carolina at Chapel Hill and Neel Swamy, University of North Carolina Eshelman School of Pharmacy

Background: Several publications have shown safety and efficacy data with minimal Hepatitis C Virus (HCV) monitoring during treatment with direct acting antivirals (DAA). However, many practices have not implemented this change. The coronavirus disease 2019 (COVID-19) pandemic has shifted care from an in-person to virtual platform in a short period of time. Despite these events, there continues to be limited real-world data regarding the impact of minimal HCV monitoring approaches. Thus, the purpose of this study was to assess if minimal monitoring approaches in HCV direct acting antiviral (DAA) therapy can overcome clinic and patient burden while maintaining undetectable HCV RNA 12 weeks after the end of treatment (SVR12). **Methods:** A 12-month, single-center retrospective chart review was conducted in treatment-naïve HCV-infected adults who received DAA therapy from May 1st, 2020, to April 30th, 2021. Patients in Cohort 1 had standard monitoring with > 1 in-person clinic visit during DAA treatment. Patients in Cohort 2, minimal monitoring, had entirely virtual visits during treatment. Both groups received telephonic touch points throughout DAA treatment from a Clinical Pharmacist Practitioner (CPP) and Nurse

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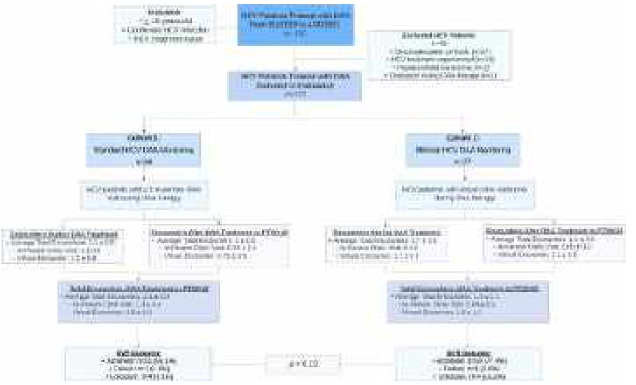
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Care Coordinator (NCC). The primary outcome was SVR12 rate. Student t-tests were conducted for continuous variables and chi-square tests for categorical variables. **Results:** From 5/1/2020 to 4/30/2021, 133 HCV patients met inclusion criteria and were treated with DAA (Cohort 1: n = 56; Cohort 2: n = 77). There were no differences in baseline demographics and most patients received Epclusa or Mavyret for 8-12 weeks. Total encounters remained significantly higher in Cohort 1 compared to Cohort 2 (Cohort 1: 3.1 ± 1.0 vs Cohort 2: 2.8 ± 1.2; p = 0.047), whereas Cohort 2 had more telephonic CPP and NCC touch points (Cohort 1: 2.1 ± 1.2 vs Cohort 2: 2.5 ± 1.9; p = 0.045). Although Cohort 2 had non-significantly higher loss to follow-up rates (Cohort 1: 7.1% vs Cohort 2: 18.2%; p = 0.06), ultimately, there were no differences in SVR rate between cohorts (Cohort 1: 91.1% vs Cohort 2: 77.9%; p = 0.13). **Conclusion:** This single-center study demonstrates that minimal monitoring during HCV treatment through post-treatment week 12 is as effective in achieving SVR cure rates compared to standard monitoring. Eliminating required in-person clinic visits during DAA therapy alongside a collaborative approach may play a major role in overcoming barriers to HCV care in select patients.



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1896-A | THE EFFICACY AND SAFETY OF 12-WEEK SOF/VEL REGIMEN COMBINED WITH PROPHYLACTIC USE OF TAF FOR TREATMENT-NAIVE genotype1-6 HCV/HBV CO-INFECTION ADULT PATIENTS WITH OR WITHOUT COMPENSATED CIRRHOSIS IN CHINA: A MULTI-CENTER PROSPECTIVE, SINGLE-ARM, OPEN-LABEL TRIAL

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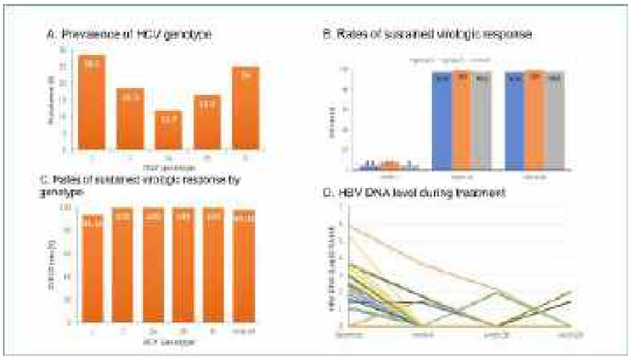
Background: When humans are co-infected with the Hepatitis B virus (HBV) and Hepatitis C virus (HCV), HCV can inhibit the replication of HBV in HCV/HBV co-infected patients. Therefore, it may put patients at increased risk of HBV reactivation after they receive anti-HCV therapy. This study will evaluate the safety and efficacy of SOF/VEL in Chinese patients with HBV/HCV co-infection and assess the preventive effect of TAF on HBV reactivation during direct-acting antiviral (DAA) treatment. **Methods:** We performed a multicenter, prospective, single-arm, open clinical trial to evaluate the safety and efficacy of SOF/VEL 12-week regimen and prophylactic use of TAF in patients with GT1-6 HCV/HBV co-infection in China. All patients included in the study were divided into a non-cirrhotic group (group 1) and a compensated cirrhotic group (group 2). Patients were given 7 months of TAF (from day 0 to week 28) and 3 months of SOF/VEL (from week 4 to week 16) antiviral therapy. The primary endpoint of the study was the proportion of subjects achieving sustained virological response to HCV 12 weeks (SVR12) after discontinuation of SOF/VEL therapy. **Results:** 60 patients (47 patients in group 1, 13 patients in group 2) with hepatitis B and C co-infection were included in the study, with 17 (28.3%), 11 (18.3%), 7 (11.7%), 10 (16.4), and 15 (25%) patients with HCV genotypes 1, 2, 3a, 3b, and 6, respectively (Figure A). 59 patients achieved SVR12, and 1 patient (group 1, HCV genotype 1b) converted to HCV RNA positive after 12 weeks end of SOF/VEL treatment, with an overall SVR12 of 98.3% (Figure B and C). 28 patients were HBV DNA positive at baseline and 2 patients were HBV DNA positive at week 28. HBV DNA decreased after antiviral therapy in all patients and no HBV reactivation occurred (Figure D). No deaths and 6 adverse events (5 in group 1, 1 in group 2) occurred. There was no significant difference in the degree of decrease in liver stiffness between group 1 and group 2 patients after 16 weeks of antiviral therapy [6.9 (5.6-9.8) vs 6.8 (5.7-8.9), p = 0.690], [20.5 (16.4-37.1) vs 17.2 (10.9-24.9), p = 0.246]. **Conclusion:** In the present study, the HCV genotype distribution rates differed significantly from those previously reported for HCV genotypes. Patients demonstrated high SVR rates after 12 weeks of SOF/VEL combined with TAF anti-HCV therapy, and all patients did not experience HBV DNA reactivation during the treatment period. Although there was an overall decrease in liver stiffness measurement values in both groups, the difference was not statistically significant. Most patients did not experience significant adverse events during treatment. (ClinicalTrials.gov no: NCT04997564).

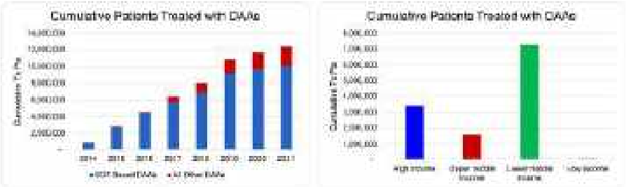


Disclosures: The following people have nothing to disclose: Hongyu Chen, Xiaoyuan Xu, Qian Kang, Yifan Han, Jiali Pan, Zhan Zeng, Yanyan Yu

1897-A | TOTAL HCV PATIENTS TREATED WITH DIRECT ACTING ANTIVIRALS SINCE 2014

Alexis Voeller, Devin Razavi-Shearer, Sarah Blach, Ivane Gamkrelidze, Kathryn Razavi-Shearer and Homie Razavi, Center for Disease Analysis Foundation

Background: With the second generation direct-acting antiviral (DAAs) treatments taking over as the gold standard for hepatitis C virus (HCV) treatment circa 2014, there has been an exponential increase in HCV treatment patterns globally. The aim of this analysis is to quantify the increase in cumulative HCV treatment in 2014-2021. **Methods:** Experts in over 100 countries provided HCV treatment data from 2014-2021 via the Polaris Observatory annual surveys. These surveys included regimen data starting in 2019. Prior to that, the average sustained viral response (SVR) rate was used to determine the percentage of all patients treated with DAAs in each country. National registration dates of sofosbuvir (SOF), ombitasvir + paritaprevir + ritonavir, glecaprevir + pibrentasvir, and elbasvir + grazoprevir based treatments were used to allocate treated patients to specific regimens. Outside of Egypt and Georgia, most treated patients were in high-income countries in years 2014-2018 where drug sales data were available and analyzed to determine annual treated patients by regimen. **Results:** Between 2014-2021, 12.4 million HCV patients have been treated cumulatively, globally with DAAs, of which, 10.1 million were treated with SOF based regimens accounting for an estimated 81% of the total. The increase in treatment was accompanied by an increase in the use of other DAAs over the past 4 years. Most HCV treatments were in lower-middle income countries (7.3 million) with high income countries following (3.4 million). The peak in percentage of SOF based regimens in 2019 was due to the substantial uptake in HCV treatment in the Egyptian elimination program. **Conclusion:** The access to DAAs in low- and middle-income countries (LMIC) has had a profound impact on the total number of HCV patients treated globally with generic sofosbuvir + daclatasvir being the preferred treatment. With 89% of all HCV infections in LMIC, immediate access to generic versions of the latest drugs is needed to achieve the global elimination targets. The high-income countries have been very proactive in treating their HCV infected populations and removing all restrictions. For the global elimination of HCV, there needs to be a continued exponential increase in cumulative treated patients in LMIC along with continued expansion of generic access to medications.



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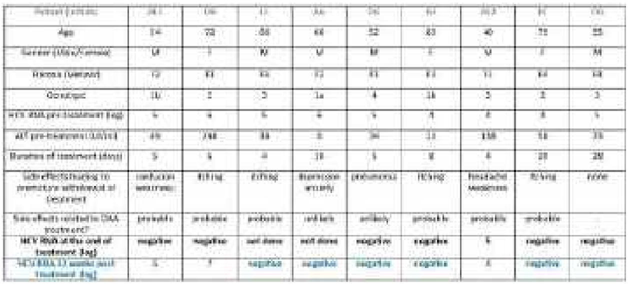
1898-A | TOWARDS ULTRA-SHORT THERAPY TO ERADICATE HCV INFECTION?

Alberto Grassi[1], Natascia Celli[2], Silvana Maccariello[2], Gabriele Donati[3], Angela Fabbri[2] and Giorgio Ballardini[2], (1)Internal Medicine Unit, Cervesi Hospital, Cattolica (RN), Italy, (2)Internal Medicine, Infermi Hospital, Rimini, Italy, (3)Internal Medicine, San Marino Hospital, RSM

Background: Direct Antiviral Agents (DAA) permit HCV eradication with short-time therapy (8-12 weeks) in the vast maiority of cases. **Methods:** From 2018 to 2022, 271 HCV-RNA positive patients completed antiviral treatment with glecaprevir/pibrentasvir (G/P) and 12 weeks post treatment follow up. **Results:** Sustained virological response (SVR) was globally obtained in 267 patients (98.5%). Nine patients (3.3%) prematurely suspended treatment, mainly for side effects: six of them anyway resulted SVR, two were HCV RNA negative at the end of treatment but relapsed 12 weeks later and one resulted non responder. Clinical data of patients are reported in the table. **Conclusion:** There is general agreement about the fact that at least 8 weeks of therapy are necessary to achieve definitive HCV eradication. In this series of patients, HCV eradication was obtained with (even extremely) reduced duration of treatment (4-28 d only) with G/P. Nowadays, probably, the real impact of DAA in HCV replication is not yet completely known. More studies about this topic would be important to eventually permit ultra-short scheduled of treatment to eradicate HCV infection: this could have paramount impact in the WHO program to eliminate HCV infection within 2030.



Disclosures: Alberto Grassi – Abbvie: Advisor, Yes, Yes; The following people have nothing to disclose: Natascia Celli, Silvana Maccariello, Gabriele Donati, Angela Fabbri, Giorgio Ballardini

1899-A | TREATING CHRONIC HEPATITIS C VIRUS-INFECTED PATIENTS IN SARS-COV-2 GLOBAL PANDEMIC ERA IN AN URBAN MEDICAL CENTER IN TAIWAN: 'CALL-BACK' STRATEGY NEEDED

Hsin-Ju Tsai, Cheng-Che Chen, Teng-Yu Lee, Shao-Wu Lee, I-Ta Lu, Chung-Hsin Chang and Sheng-Shun Yang, Taichung Veterans General Hospital

Background: Hepatitis C virus (HCV) can be eliminated by all-oral direct-acting antivirals (DAA) nowadays, here we report real-world data on the effectiveness and safety of pangenotypic DAAs namely sofosbuvir/velpatasvir (SOF/VEL) and glecaprevir/pibrentasvir (G/P) in a hospital applying 'call-back' strategy during SARS-CoV-2 global pandemic era. **Methods:** A total of 832 chronic HCV-infected patients with different liver disease severity completed 8 or 12 weeks DAAs treatment are retrospectively enrolled. The effectiveness was determined by a sustained virologic response at off-treatment 12 weeks (SVR12). Baseline patient characteristics, laboratory data, and adverse events were analyzed and compared between two antiviral regimens and 'call-back' vs. 'non-call-back' populations. **Results:** By per-protocol analyses, the overall SVR12 rate was 98.0% with SOF/VEL 98.9% vs. G/P 97.2%, 'call-back' 98.6% vs. 'non-call-back' 97.8% respectively (Table 1 & 2). Twenty patients died and 14 patients discontinued treatment due to non-virologic causes throughout the antiviral therapy course, none with SVR12 data available. The median age was 64.0 (vs. 59.0, $p < 0.001$), > 65 y/o 45.9% (vs. 32.4%, $p < 0.001$), fewer male patients (48.5% vs. 56.2%, $p = 0.044$), more treatment-experienced (9.5% vs 5.2%, $p = 0.021$), less FIB-4 < 1.45 and more FIB-4 > 3.25 (26.2% vs. 36.6%, and 31.9% vs. 24.0%; $p = 0.008$) in 'call-back' compared to 'non-call-back' subjects. Aged, history of HCC, more genotype 1b and less genotype 2, higher FIB-4 scores, poorer laboratory data (AST, ALT, T. bil., INR, and albumin), while less CKD subjects noted in patients receiving SOF/VEL compared to G/P (Table 1). A total of 332 (40.4%) experienced any adverse event, of them fatigue (19.6%) and pruritus (15.4%) were the most common AEs in SOF/VEL and G/P respectively (Table 1). Elevated ALT or T. bil. level during the treatment course was mild and did not lead to treatment discontinuation. **Conclusion:** Real-world data in HCV management were heterogeneous and we found several baseline patient characteristics which might lead to different pangenotypic DAA choices by the physicians. While in our 'call-back' cohort, age, female, prior antiviral treatment failure, and FIB-4 score were significantly more or higher than the 'non-call-back' cohort, and both with the same favorable SVR12 rate and tolerable AEs to the two pangenotypic DAA regimens.

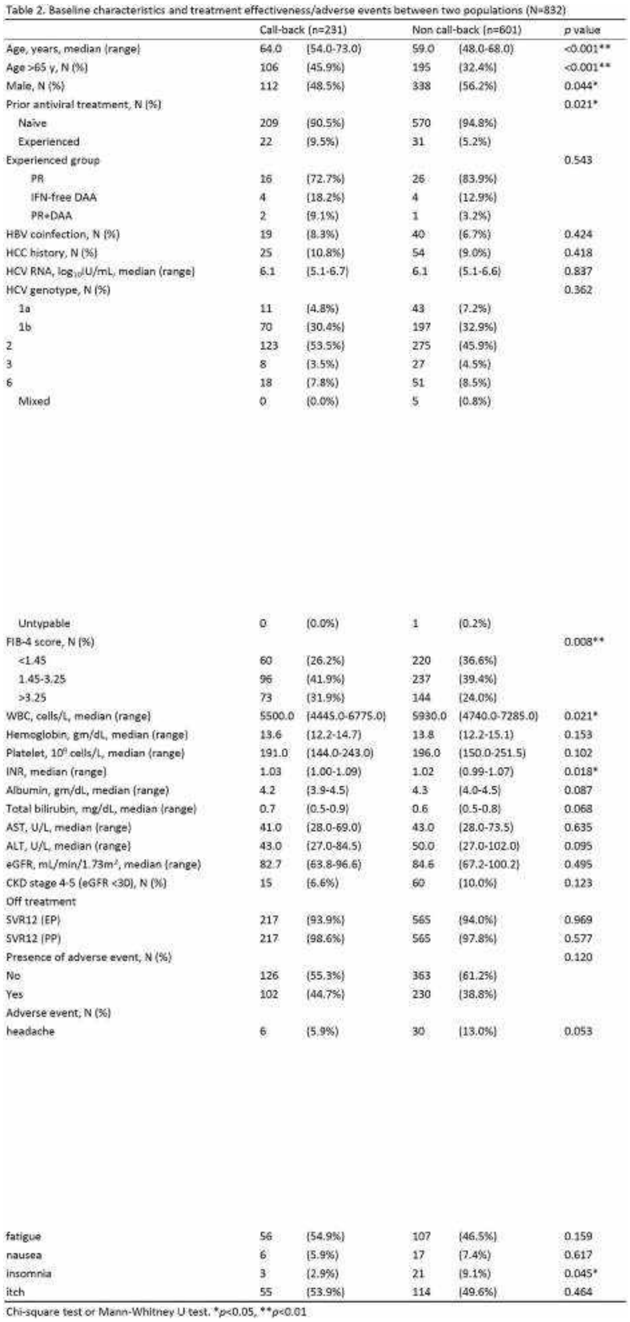


Table 2. Baseline characteristics and treatment effectiveness/adverse events between two populations (N=832)

	Call-back (n=231)		Non call-back (n=601)		p value
Age, years, median (range)	64.0	(54.0-73.0)	59.0	(48.0-68.0)	<0.001**
Age >65 y, N (%)	106	(45.9%)	195	(32.4%)	<0.001**
Male, N (%)	112	(48.5%)	338	(56.2%)	0.044*
Prior antiviral treatment, N (%)					0.021*
Naive	209	(90.5%)	570	(94.8%)	
Experienced	22	(9.5%)	31	(5.2%)	
Experienced group					0.543
PR	16	(72.7%)	26	(83.9%)	
IFN-free DAA	4	(18.2%)	4	(12.9%)	
PR+DAA	2	(9.1%)	1	(3.2%)	
HBV coinfection, N (%)	19	(8.3%)	40	(6.7%)	0.424
HCC history, N (%)	25	(10.8%)	54	(9.0%)	0.418
HCV RNA, log_{10}IU/mL, median (range)	6.1	(5.1-6.7)	6.1	(5.1-6.6)	0.837
HCV genotype, N (%)					0.362
1a	11	(4.8%)	43	(7.2%)	
1b	70	(30.4%)	197	(32.9%)	
2	123	(53.5%)	275	(45.9%)	
3	8	(3.5%)	27	(4.5%)	
6	18	(7.8%)	51	(8.5%)	
Mixed	0	(0.0%)	5	(0.8%)	
Untypable	0	(0.0%)	1	(0.2%)	
FIB-4 score, N (%)					0.008**
<1.45	60	(26.2%)	220	(36.6%)	
1.45-3.25	96	(41.9%)	237	(39.4%)	
>3.25	73	(31.9%)	144	(24.0%)	
WBC, cells/L, median (range)	5500.0	(4445.0-6775.0)	5930.0	(4740.0-7285.0)	0.021*
Hemoglobin, gm/dL, median (range)	13.6	(12.2-14.7)	13.8	(12.2-15.1)	0.153
Platelet, 10^9 cells/L, median (range)	191.0	(144.0-243.0)	196.0	(150.0-251.5)	0.102
INR, median (range)	1.03	(1.00-1.09)	1.02	(0.99-1.07)	0.018*
Albumin, gm/dL, median (range)	4.2	(3.9-4.5)	4.3	(4.0-4.5)	0.087
Total bilirubin, mg/dL, median (range)	0.7	(0.5-0.9)	0.6	(0.5-0.8)	0.068
AST, U/L, median (range)	41.0	(28.0-69.0)	43.0	(28.0-73.5)	0.635
ALT, U/L, median (range)	43.0	(27.0-84.5)	50.0	(27.0-102.0)	0.095
eGFR, mL/min/1.73m^2, median (range)	82.7	(63.8-96.6)	84.6	(67.2-100.2)	0.495
CKD stage 4-5 (eGFR <30), N (%)	15	(6.6%)	60	(10.0%)	0.123
Off treatment					
SVR12 (EP)	217	(93.9%)	565	(94.0%)	0.969
SVR12 (PP)	217	(98.6%)	565	(97.8%)	0.577
Presence of adverse event, N (%)					0.120
No	126	(55.3%)	363	(61.2%)	
Yes	102	(44.7%)	230	(38.8%)	
Adverse event, N (%)					
headache	6	(5.9%)	30	(13.0%)	0.053
fatigue	56	(54.9%)	107	(46.5%)	0.159
nausea	6	(5.9%)	17	(7.4%)	0.617
insomnia	3	(2.9%)	21	(9.1%)	0.045*
itch	55	(53.9%)	114	(49.6%)	0.464

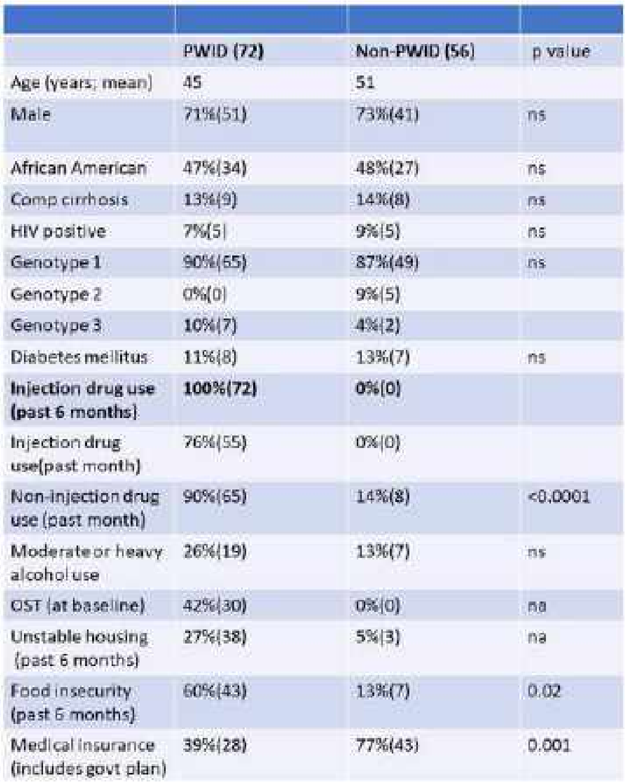
Chi-square test or Mann-Whitney U test. *p<0.05, **p<0.01

Disclosures: The following people have nothing to disclose: Hsin-Ju Tsai, Cheng-Che Chen, Teng-Yu Lee, Shao-Wu Lee, I-Ta Lu, Chung-Hsin Chang, Sheng-Shun Yang

f 1900-A | TREATMENT OF RECENT INJECTION DRUG USERS WITH CHRONIC HCV INFECTION IN U.S. LIVER REFERRAL CLINICS: A PROSPECTIVE, OBSERVATIONAL COHORT STUDY AND CONTEMPORANEOUS THERAPY COHORT WITHOUT INJECTION DRUG USE

Brian Pearlman[1,2,3], Michael Perrys[1], Carole Ehleben[2] and Andrew Hinds[2], (1)Medical College of GA, (2) Wellstar, (3)Emory

Background: It is estimated that nearly 3.7 million people, or 1.5% of the U.S. population injected drugs in 2018, which is five times more prevalent than had been in 2011. With the advent of COVID, those numbers are expected to be even higher. Although there have been studies of people who inject drugs (PWID's) who underwent successful HCV treatment in opiate substitution therapy (OST) clinics/harm reduction centers, correctional settings, mobile health units and primary care clinics, few have studied active injection drug users at liver referral clinics, and the relative success in this setting has been questioned. **Methods:** Chronically HCV-infected participants were recruited and treated at two liver referral clinics in GA, but had been referred from OST clinics, primary care + GI clinics, neighboring hospitals, and correctional centers. Once consented, each participant was assigned to a nurse navigator was responsible for all subjects' appointments, and med supplies. Drug testing was mandated at specified intervals. Patients with recent injection drug use (within 6 mo) were assigned to the PWID arm, and those who hadn't injected within 6 months but agreed to be in the study and signed consents, were assigned to the non-PWID arm. Both groups were treated with velpatasvir (100 mg) and sofosbuvir (400 mg) once daily for 12 weeks (brand or branded generic). Adherence was assessed by pill counts. Mandatory treatment visits were scheduled for baseline, 4 and 12 weeks (+/- 2 weeks) and follow-up (FU) week 12 (+ 4 mo). Long-term FU was flexible and could be virtual, but was mandated once yearly with HCV RNA testing. **Results:** Between March, 2018 and September, 2020, 128 subjects were enrolled, 72 PWIDS and 56 non-PWIDS. Baseline characteristics are shown in the Table. In PWID and non-PWID, respectively, SVR rates (ITT) were 94%(68) and 96%(54) ($p = 0.62$), and SVR rates (as treated) were 97%(70) and 100%(56) ($p = 0.09$); adverse events were 46%(33) and 41%(23), and serious adverse events were 4%(3) and 7%(4), including one drug overdose/death and one suicide in the PWID arm. The FU period was 32 months (mean). Adherence differed between PWID group (73%) and non-PIWD (95%) ($p = 0.007$). Reinfection rate was 2% in the PWID and 0% in the non-PWID groups. Moderate alcohol use declined in the PWID group but increased in the non-PWID group. In the PWID group, relative to baseline at the end of FU, the OST rate increased (42% to 68%), and the rates of other drug use and injection drug use in the preceding month and six month period likewise declined (76% to 58% and 100% to 79%, respectively). **Conclusion:** Active PWIDS were successfully treated in liver referral clinics with comparable rates of SVR as concurrently treated non-PWIDS (non-significant differences) . Using a nurse navigator, retention rates were excellent. In the PWID arm, alcohol and drug use diminished and OST increased during follow-up. Reinfection was rare and consistent with PWID reinfection rates globally.



	PWID (72)	Non-PWID (56)	p value
Age (years; mean)	45	51	
Male	71%(51)	73%(41)	ns
African American	47%(34)	48%(27)	ns
Comp cirrhosis	13%(9)	14%(8)	ns
HIV positive	7%(5)	9%(5)	ns
Genotype 1	90%(65)	87%(49)	ns
Genotype 2	0%(0)	9%(5)	
Genotype 3	10%(7)	4%(2)	
Diabetes mellitus	11%(8)	13%(7)	ns
Injection drug use (past 6 months)	**100%(72)**	**0%(0)**	
Injection drug use(past month)	76%(55)	0%(0)	
Non-injection drug use (past month)	90%(65)	14%(8)	<0.0001
Moderate or heavy alcohol use	26%(19)	13%(7)	ns
OST (at baseline)	42%(30)	0%(0)	na
Unstable housing (past 6 months)	27%(38)	5%(3)	na
Food insecurity (past 6 months)	60%(43)	13%(7)	0.02
Medical insurance (includes govt plan)	39%(28)	77%(43)	0.001

Disclosures: Brian Pearlman – Gilead: Speaking and Teaching, Yes, No; Abbvie: Speaking and Teaching, Yes, No;
The following people have nothing to disclose: Michael Perrys, Carole Ehleben, Andrew Hinds

1901-A | CELL-FREE NUCLEIC ACIDS VARY BY DISEASE SEVERITY AND BODY COMPARTMENTALIZATION IN CHRONIC HEPATITIS C VIRUS INFECTION

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Background: Circulatory cell-free nucleic acids (ccfNAs), comprised of both ccfDNAs and ccfRNAs, play roles in signaling, immunity, and gene regulation. ccfNAs are an active area of research given their role in disease progression and ease of measurement. The aim of this study is to explore composition and concentration of ccfNAs in both portal vein and peripheral plasma, before and after HCV clearance. **Methods:** HCV patients had a liver biopsy with portal vein cannulation before (HCVi, n = 29) and 1 year after DAA therapy (SVR, n = 23) (NCT02400216). Peripheral blood was collected from HCVi patients, before and 1 year after DAA therapy. Total ccfRNAs and ccfDNAs were extracted from plasma and measured using a TBS-380 Mini-Fluorometer. For significance $p < 0.05$. **Results:** Concentrations of ccfNAs were lower after SVR in portal plasma compared to peripheral plasma (median 83.11 vs. 108.9 ng/ml plasma, n = 22 pairs). During HCVi, portal (median 99.92 vs. 210.1 ng/ml plasma, n = 13 cirrhotic and 15 non-cirrhotic) and peripheral (median 100.5 vs. 210 ng/ml plasma) ccfNA levels were lower in cirrhotic (C) compared to non-cirrhotic (NC) patients. ccfRNA concentration was lower in portal plasma (median 84.87 vs. 108.4 ng/ml plasma, n = 23 pairs) compared to peripheral plasma after HCV clearance. During HCVi, both peripheral (median 203.435 vs. 82.40 ng/ml plasma, n = 15 NC and 13 C) and portal ccfRNA (median 207.6 vs. 81.88 ng/ml plasma, n = 15 NC and 13C) concentrations were higher in non-cirrhotic compared to cirrhotic patients. After SVR, ccfDNA concentrations reduced (median 5.980 vs. 12.86, n = 21 pairs) in portal plasma compared to HCVi patients. There were correlations between portal and peripheral ccfRNAs (r = 0.9299, and r = 0.8854) and between portal and peripheral ccfDNAs (r = 0.4800, and 0.4839) during both HCVi and after SVR. The concentration of ccfRNA was higher than its accompanying ccfDNA in all patients (HCVi and after SVR) and all body compartments (peripheral and portal plasma) (n = 29 HCV and 23 SVR). **Conclusion:** The concentration and pattern of ccfNAs differ between mild and severe forms of liver disease as well as in different compartments of the body, with ccfRNA concentrations being higher than ccfDNA concentrations. After SVR, significant reduction of portal ccfRNAs compared to peripheral suggests that a deeper understanding of cell-free nucleic acids will provide insight into disease pathogenesis.

Disclosures: The following people have nothing to disclose: Nicole San-Dee Minerva, Rownock Afruza, Christina Park, Moumita Chakraborty, Adekanyinsola Onitiri, Maleeha F Ahmad, Rabab Ali, Ohad Etzion, David E Kleiner, Christopher Koh, Theo Heller

Disclosure information not available at the time of publication: Elliott Levy

1902-A | DIRECT-ACTING ANTIVIRALS INDUCE LYMPHOPROLIFERATIVE DISEASE RESPONSE IN HEPATITIS C VIRUS-INFECTED PATIENTS WITH INDOLENT B-CELL NON-HODGKIN'S LYMPHOMA: A PROSPECTIVE OBSERVATIONAL STUDY

Monica George, Khalis Mustafayev, Sairah Ahmed, Sheeba K. Thomas, Ying Jiang, Krina Patel and Harrys A. Torres, The University of Texas MD Anderson Cancer Center

Background: Chronic hepatitis C virus (HCV) infection has been associated with an increased risk of different types of B-cell non-Hodgkin's lymphoma (NHL). Case reports and retrospective case series have suggested that HCV eradication with direct-acting antivirals (DAA) favorably impacts the oncologic outcome of patients with indolent NHL. We aim to prospectively evaluate the oncologic impact of DAA treatment on HCV-infected patients with indolent NHLs not yet requiring initiation of systemic cancer therapy. **Methods:** HCV-infected patients with NHL seen at MD Anderson Cancer Center between 01/01/2014 and 01/31/2021 were enrolled in a prospective observational study. Only chemotherapy naïve patients treated with DAAs were further analyzed. The primary endpoints were lymphoproliferative disease responses classified as complete response, partial response, stable disease, and progressive disease. The secondary endpoints were overall survival (OS) and progression-free survival (PFS) at 2 years after achieving sustained virologic response at week 12 without DAAs (SVR12). Response evaluation was based on the 2014 Lugano criteria. **Results:** Forty HCV-infected patients with indolent NHL were enrolled. Seven of them fulfilled the study criteria and were

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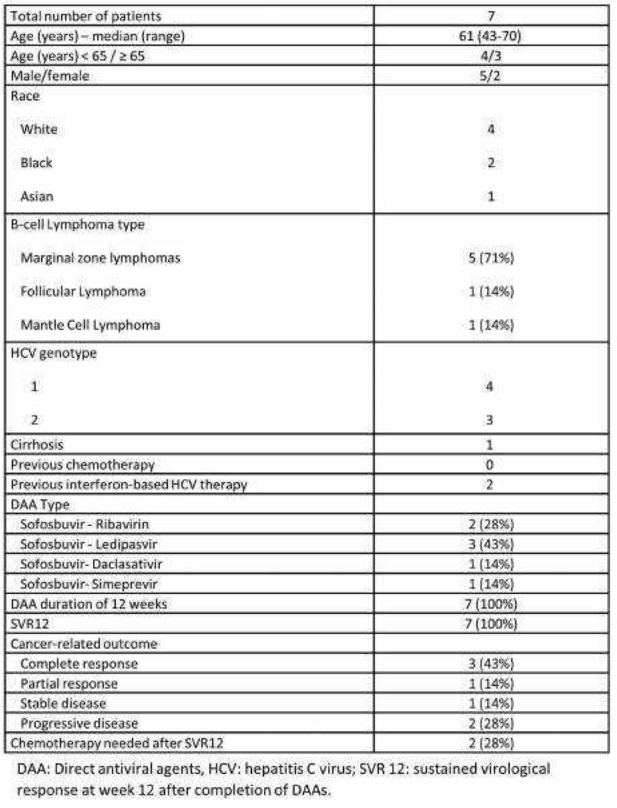
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

further analyzed. Most patients had HCV genotype 1 (4/7, 57%), and were less than 65 years of age (4/7, 57%), male (5/7, 71%), white (4/7, 57%), and non-cirrhotic (6/7, 86%). Two patients had failed prior interferon-based treatment (follicular lymphoma [n = 1] and marginal zone lymphoma [n = 1]). All patients were treated with a sofosbuvir-based regimen, with an SVR12 rate of 100%. The total follow-up period from DAA initiation was 32 months (range 32-60 mo). At 2 years after achieving SVR12, most patients (4/7, 57%) experienced either complete or partial response, 2 had NHL progression requiring chemotherapy, and 1 had stable disease (Table 1). Two years after SVR12, rates of OS and PFS were 100% and 71% respectively. **Conclusion:** This is the first prospective study evaluating the impact of treatment with DAAs alone on the oncologic outcomes of HCV-infected patients with indolent NHL. Most patients experienced lymphoproliferative disease response after HCV eradication.

Table 1. Characteristics of HCV-infected patients with Indolent B-Cell Non-Hodgkin's Lymphoma treated with direct-acting antivirals without cancer treatment.



Total number of patients	7
Age (years) – median (range)	61 (43-70)
Age (years) < 65 / ≥ 65	4/3
Male/female	5/2
Race	
White	4
Black	2
Asian	1
B-cell Lymphoma type	
Marginal zone lymphomas	5 (71%)
Follicular Lymphoma	1 (14%)
Mantle Cell Lymphoma	1 (14%)
HCV genotype	
1	4
2	3
Cirrhosis	1
Previous chemotherapy	0
Previous interferon-based HCV therapy	2
DAA Type	
Sofosbuvir - Ribavirin	2 (28%)
Sofosbuvir - Ledipasvir	3 (43%)
Sofosbuvir- Daclasativir	1 (14%)
Sofosbuvir- Simeprevir	1 (14%)
DAA duration of 12 weeks	7 (100%)
SVR12	7 (100%)
Cancer-related outcome	
Complete response	3 (43%)
Partial response	1 (14%)
Stable disease	1 (14%)
Progressive disease	2 (28%)
Chemotherapy needed after SVR12	2 (28%)

DAA: Direct antiviral agents, HCV: hepatitis C virus; SVR 12: sustained virological response at week 12 after completion of DAAs.

Disclosures: Sheeba K. Thomas – BMS Acerta Pharma X4 Pharma Genentech Cellectar Biosciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Astra Zeneca Cellectar Biosciences: Consultant, No, No;

Harrys A. Torres – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Merck & Co., Inc: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;

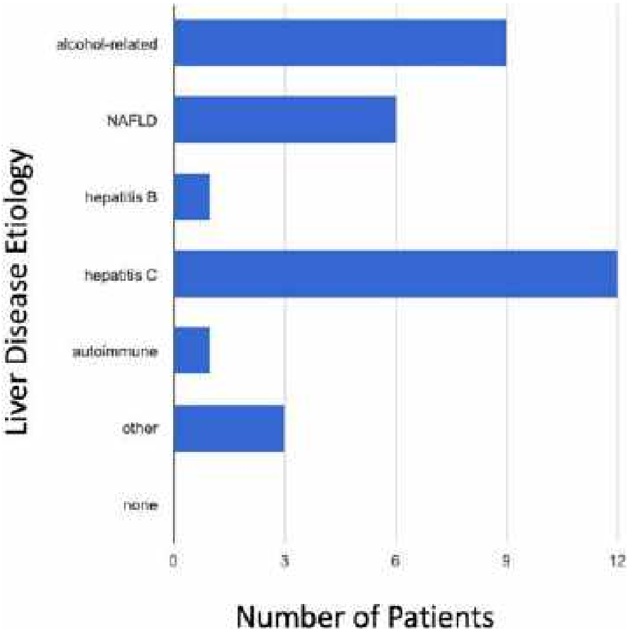
The following people have nothing to disclose: Monica George, Khalis Mustafayev, Sairah Ahmed, Ying Jiang, Krina Patel

1903-A | IS CHRONIC HEPATITIS C INFECTION ASSOCIATED WITH AN INCREASED RISK OF DISSEMINATED COCCIDIOIDOMYCOSIS? A RETROSPECTIVE ANALYSIS

Humzah Iqbal, Nam Huynh, Geetha Sivasubramanian and Marina M. Roytman, UCSF Fresno

Background: Coccidioidomycosis, a fungal infection caused by *Coccidioides spp.* is endemic to the southwestern United States. Most cases are limited to the respiratory system, however a small subset of patients may develop disseminated coccidioidomycosis (DCM). Liver cirrhosis is associated with an increased risk for infections, with some studies suggesting it may be a risk factor for developing DCM as well as worse outcomes. There is a paucity of literature regarding DCM in patients with chronic liver disease. Our study explored risk factors and attributes of patients with chronic liver disease who developed DCM. **Methods:** We conducted a retrospective study including patients over the age of 18 from January 2010 to December 2020 with chronic liver disease who developed DCM. DCM was defined as positive serum *Coccidioides* immunoglobulin G (IgG) titers, culture, or polymerase chain reaction (PCR) along with compatible clinical syndrome with evidence of extrapulmonary coccidioidal infection. Data were collected at the time of DCM diagnosis and included age, gender, ethnicity, type of liver disease, co-morbidities, hepatitis B (HBV) and hepatitis C (HCV) viral loads, presence of cirrhosis and site of coccidioidal dissemination. **Results:** We identified 32 patients with chronic liver disease who developed DCM. Median age at diagnosis was 49 years and 87.5% were men. Hispanic patients accounted for 65.6%, while 12.5% were Black, 12.5% Caucasian, and 6.3% were Asian. Causes of liver disease included: HCV in 37.5%, alcohol-related liver disease (ALD) in

28.1 % and metabolic associated liver disease (MAFLD) in 18.8% of patients. Of the patients with chronic HCV, 83% had a positive viral load, and 25% had progressed to cirrhosis. Diabetes was noted in 16.7% of patients with chronic HCV, compared to 47% in all patients. Sites of coccidioidal dissemination included central nervous system (CNS) (34.4%), bone (31.3%), visceral organ (28.1%), skin/soft tissue (18.8%), hematogenous (6.3%), and multiple sites (15.6%). **Conclusion:** Although ALD and MAFLD are known to be the most common driving factors of liver disease in our population, our study found that DCM is more commonly seen in patients with chronic HCV. Majority of patients had a positive viral load bringing up a possibility of immune dysfunction in patients with active HCV potentially playing a role in developing DCM. Further studies are needed to determine if chronic HCV predisposes patients to coccidioidal dissemination to the CNS.



Disclosures: The following people have nothing to disclose: Humzah Iqbal, Nam Huynh, Geetha Sivasubramanian, Marina M. Roytman

1904-A | LOCAL ELIMINATION PROGRAMS LEADING TO GLOBAL ACTION IN HCV(LEGA-C): OUTCOME OF STUDIES AND THE IMPACT FOCUSING ON ACTIVITIES WITHIN UNITES STATES

Kyung Min Kwon and Efe Johnson, Gilead Sciences, Inc.

Background: Since 2016 Gilead Sciences, Inc., has committed to support studies and grants for programs focused on hepatitis C virus (HCV) elimination under LEGA-C (Local Elimination programs leading to Global Action in HCV) initiative. Focusing on Investigator Sponsored Studies (ISR) and collaborative studies under LEGA-C initiative, > 120 studies in > 30 countries were funded from Gilead until now. Here we aim to report the relative impact of these studies that took place in the United States. **Methods:** We aim to measure the impact of these studies from 3 aspects; scientific communications, number of individual/patients reached and the changes made in guidelines. We describe the types of studies supported, the populations and the treatment patterns emerging from the studies. To assess the potential impact in science, we catalogued the number and impact factors (IF) of studies' publications and the numbers of citations of study papers. For the measurable impact made to patients' lives, we collected the number of individual's reached within each presentation/publication. To gauge potential impacts, we reviewed recent AASLD and EASL guidelines to identify mentions of LEGA-C supported studies in the US. **Results:** Globally, total of 120 studies were conducted in 6 continents. 67 studies were conducted in the United States as of July 2022.

The types of approaches varied in ways to overcome the barriers of screening and linkage to care ; Test and treat (n = 10), Simplified screening/Minimal monitoring (n = 4), epidemiology (n = 3), outreach/callback (n = 3), modeling/cost effectiveness (n = 4), and patient/HCP education (n = 2).

Of the 67 studies, 30 (45%) focused on special populations such as persons who inject drugs (n = 14), men who have sex with men (n = 3), persons with concomitant HIV infection (n = 6), and homeless population (n = 4).

Roughly 200,000 individual's were reached with the studies and among those who were identified as HCV infected, 1941 patients were treated with DAAs.

Publications include 32 journal articles with mean IF of 9.2 (1.4 - 45.0). 26 papers were cited a total of 335 times.

Changes in clinical practices were made with 2 studies on EASL and AASLD recommendations regarding universal HCV screening in pregnancy women and implementation of minimal monitoring to reduce the time to treat.

AASLD 2019 HCV screening guidance and the EASL 2020 acute HCV treatment guideline cited the LEGA-C–supported paper on cost-effectiveness of universal screening of pregnant women for HCV infection, recommending that such screening be adopted. **Conclusion:** Since 2016, LEGA-C initiative has supported 67 studies in the US that led to advance in science,

identified and linked patients for appropriate care and updated clinical practice. This is a good example of industry and Academia/Community/Public that leads to impact and synergy. The ongoing LEGA-C initiative is demonstrably contributing to the understanding, treatment, and ultimate elimination of HCV.
Disclosures: Kyung Min Kwon – Gilead Sciences Inc.: Employee, Yes, No;
Efe Johnson – Gilead Sciences Inc.: Employee, Yes, No;

1905-A | MODELING HCV KINETICS FROM INOCULATION TO STEADY STATE IN SCID HUMANIZED MICE PREDICTS A PARTIAL BLOCK OF VIRAL PRODUCTION POSSIBLY DUE TO AN EARLY STAGE OF INNATE IMMUNE RESPONSE

Ari Josephson[1], Yuji Ishida[2,3], Zhenzhen Shi[1], Adquate Mhlanga[1], Chise Tateno[2,4], Jordan J. Feld[5], Harel Dahari[1] and Kazuaki Chayama[2,6,7], (1)The Program for Experimental and Theoretical Modeling, Division of Hepatology, Department of Medicine, Stritch School of Medicine, Loyola University Chicago, Maywood, Illinois, USA, (2)Hiroshima Institute of Life Sciences, (3)R&D, Phoenixbio Co., Ltd., (4)Phoenixbio Co., Ltd., (5)Viral Hepatitis Care Network (VIRCAN), Toronto, Canada, (6) Collaborative Research Laboratory of Medical Innovation, Hiroshima University, (7)Riken Center for Integrative Medical Sciences

Background: Understanding of HCV early evolution and the interplay between HCV and the mammalian host will help to identify key aspects of early HCV infection that is crucial for the design of an urgently needed prophylactic HCV vaccine. In this study, we investigated HCV kinetics from inoculation to steady state in uPA-SCID chimeric mice with humanized livers and developed a mathematical model to provide insights into early HCV-host dynamics. **Methods:** Five PXB uPA-SCID mice with hepatocyte donor: JFC (1 y, male Caucasian) and human albumin > 9mg/mL, inoculated intravenously with HCV (genotype 1a)-infected serum of 1x10^6 copies/animal. Viral levels were frequently measured from blood samples up to 35 days post infection (p.i.). We modified our previous HCV acute mathematical model in chimpanzees (Gastroenterology.2005;128(4):1056-66) to account for the lack of adaptive immune response and hepatocytes proliferation in the uPA-SCID mouse model. **Results:** After an initial rapid viral decline, the virus resurged in a biphasic manner i.e., rapid phase during the first 2 to 6 days p.i. followed by a slower phase, with a transient decline (in 3 mice) in between), that eventually stabilized at high steady state levels [Fig. 1]. The modified model was able to account for the initial rapid viral decline, assuming that the inoculated virus was less infectious (~100-fold) compared to the newly produced virions from infected human hepatocytes. Modeling suggests that the biphasic viral increase (with [Fig. 1a] or without [Fig. 1b] a transient decline), can be best explained by assuming blockage in viral production [Fig. 1, solid lines] over blocking of infection [Fig. 1: dashed lines]. **Conclusion:** The multiphasic HCV kinetic patterns observed in uPA-SCID mice were reminiscent of our previously reported early acute HCV kinetics in chimpanzees (ibid). The biphasic viral increase seen in mice can be explained by a partial block of virion production possibly due an early stage of innate immune response, reminiscent of the observed biphasic increase in chimpanzees that was suggested due to an endogenous type I interferon response (ibid). The nature of the innate immune response in humanized mice requires further study.

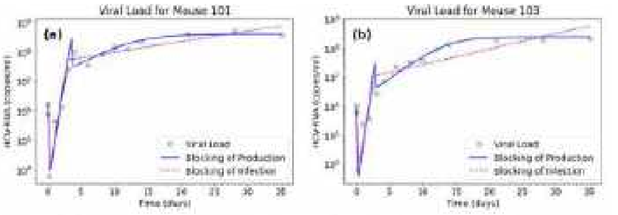


Fig 1: Modeling fit curves (lines) with measured HCV viral load (symbols) in uPA/SCID humanized mice. (a) representative mouse (out of 3) with an observed transient viral decline. (b) representative mouse (out of 2) without an observed transient viral decline. Model parameter estimates in (a) and (b) respectively were: HCV clearance rate constant 21.2 and 20.8 day^{-1}, viral production of 51.5 and 188 copies/cell, blocking of virion production of 92.5% and 91% that was initiated 3.5 and 2.8 days p.i.. Blocking of infection (dashed lines) was ruled out due to poor goodness of fit compared to blocking of viral production (solid lines). Modeling fits were done using Python 3.7.3.

Disclosures: Jordan J. Feld – AbbVie: Consultant, No, No; AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Eiger: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Consultant, No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GSK: Consultant, No, No; Janssen: Consultant, No, No; Janssen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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Disclosure information not available at the time of publication: Ari Josephson, Zhenzhen Shi, Adquate Mhlanga

2000-A | 3D SPATIAL BIOLOGY ASSESSMENT OF LIVER BIOPSIES FROM PATIENTS WITH NASH AND NAFLD

Alexandra Alvarsson[1], Brandy Olin[1], Caleb Stoltzfus[1], Rohit Loomba[2], Seema Singh[2], Mark A Valasek[2] and Nicholas Reder[1], (1)Alpenglow Biosciences, (2) University of California, San Diego

Background: Liver fibrosis and steatosis are hallmark features of non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD). 2D histopathological examination of biopsies is the gold standard for the assessment of steatosis and fibrosis in liver disease. However, this traditional method is subject to significant undersampling, interobserver variability and interpretative errors. Here we present a method for comprehensive 3D assessment of intact biopsies to evaluate the severity of liver damage based on the quantity and spatial distribution of fibrosis and steatosis. **Methods:** Formalin-fixed paraffin embedded liver biopsies were obtained from human subjects with/without varying degrees of NASH and NAFLD. The samples were processed using a modified iDISCO+ protocol, stained with To-Pro-3 and eosin and optically cleared. Entire biopsies (average dimensions: 0.5 x 1 x 10 mm) were imaged using an open-top light-sheet microscope (3D*i*, Alpenglow Biosciences) at a resolution of 2 µm/px. High-resolution images (0.33 µm/px) were acquired from select regions of interest to capture specific pathological features. Steatosis, fibrosis, hepatocyte ballooning and inflammation were segmented across complete 3D datasets using Aivia. CytoMAP and python were used to quantify and localize the radius, volume and clustering of lipid droplets, the degree of fibrosis, and their spatial relationships. **Results:** High field of view images of entire biopsies were obtained within 11-63 min depending on sample volume. Steatosis and fibrosis were readily visualized and recognizable in 2D optical sections of the 3D datasets, and we found that their 3D distribution varied substantially throughout the volume of each biopsy. This variability may cause sampling and interpretative errors when biopsies are processed using conventional 2D histology. Qualitative pathologist 3D assessment revealed a preponderance of fine collagen fibers interdigitating with larger fat droplets in the lobules of NASH biopsies. **Conclusion:** This novel method enables identification and quantification of pertinent parameters such as the percentage of fibrosis and steatosis across an entire biopsy. Further sampling and 3D reconstruction may enable us to develop a new and more accurate scoring system which can correlate better with clinical disease severity. Quantitative assessments, including zonal variation in collagen fiber size and fat-collagen distance measurements, are underway.

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2001-A | A MULTI-OMICS STUDY REVEALS A MECHANISTIC LINK BETWEEN ADENOSINE DEAMINASE 2 AND LIVER FIBROSIS IN NONALCOHOLIC FATTY LIVER DISEASE

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Background: Adenosine deaminase 2 (ADA2) is an ecto-enzyme secreted by monocytes and macrophages that catalyzes the conversion of extracellular adenosine to inosine, thus regulating circulating ATP, AMP, and adenosine. We have previously discovered a correlation between serum ADA2 enzymatic activity and fibrosis in patients with nonalcoholic fatty liver disease (NAFLD). The mechanism underscoring this link remains elusive. In this study we use a multi-omics approach to determine the relationship of ADA2 activity with metabolic and inflammaotry pathways associated with macrophage activation and fibrosis. **Methods:** Individual's with NAFLD were identified based on the liver-to-spleen density ratio on CT scan and medical history from the Multi-Ethnic Study of Atherosclerosis (MESA). Serum ADA2 activity and biochemical components of Enhanced Liver Fibrosis (ELF) score were measured in serum samples from exam 5. Serum proteomics from SomaScan, metabolomics from mass spectrometry, and peripheral blood mononuclear cell (PBMC) transcriptomics from RNA-seq were obtained through the Trans-Omics for Precision Medicine (TOPMed) Whole Genome Sequencing Program. We used multiple regression models and clustering analysis to determine how ADA2 activity is related to liver fibrosis, purine metabolism, cytokine/chemokine profiles, and PBMC transcriptomics. **Results:** From a total of 427 participants with NAFLD, we demonstrate an association between circulating ADA2 activity and ELF score ($r = 0.484$; $p < 0.0001$), a non-invasive marker of fibrosis. Using hypothesis-free clustering analysis, high ADA2 activity was associated with high inosine and its downstream metabolites, hypoxanthine, and xanthine. Based on serum proteomics data, high ADA2 activity was associated with elevated levels of IL13, IL23, but reduced levels of IL10, suggesting a proinflammatory phenotype. PBMC transcriptomics data further revealed upregulation of interferon (IFN)-induced genes (IFI27, IFIT3, IFI6, IGLV7-46), and cell migration regulators (CXCL10, CCR9, ITGA1, MIF). Monocyte subset transcriptome analysis trended toward NF-kB activation. Finally, we evaluated the impact of ADA2 on glycolysis and the Krebs cycle using both cluster analysis and regression, and determined that ADA2 is associated with increased circulating Krebs cycle metabolites and decreased glycolytic metabolites. **Conclusion:** We developed a multi-omics approach to determine the impact of ADA2 on liver fibrosis in NAFLD. Elevated ADA2 activity in the circulation is associated with increased purine metabolites with a shift toward an accumulation of inosine and its downstream metabolites. There is also an association with proinflammatory cytokines, activation of IFN genes, and chemokine-mediated immune cell migration. These findings support emerging mechanistic framework of how ADA2 regulates inflammation and provides insight on how ADA2 may be implicated in liver fibrosis.

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2002-A | A NOVEL PATIENT DECISION AID SYSTEM FOR EARLY RISK STRATIFICATION IN NAFLD: METHODOLOGY, AND RESULTS

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Background: Nonalcoholic fatty liver disease (NAFLD) affects billions worldwide, however, most individual's are asymptomatic until a late-stage of the disease. This makes early identification and risk stratification challenging at both the individual level for clinicians and the population health level. Current methods for identifying NAFLD are limited by access, cost and are often invasive. Patient Decision Aid Systems (PDAS) aim to improve outcomes through early risk stratification. The objective of this study was to develop a PDAS for early risk stratification of patients with NAFLD. **Methods:** This study includes 940 individual's from Houston and Galveston County, Texas who completed a survey questionnaire regarding clinical and lifestyle variables deemed important to metabolic disease. as a part of the Screening for Undiagnosed Nonalcoholic Steatohepatitis and NAFLD (SUNN-1) study. A number of classification models were tested on data contained in SUNN-1. These classifiers included logistic regression, support vector machine, neural network, decision tree, random forest and XGBoost (eXtreme Gradient Boosting). XGBoost was the most performant and was selected for fine tuning. As a result, an XGBoost-based PDAS was developed using data in SUNN-1. Features were selected through iterative feature exclusion and model re-training ordered by feature information gain. The PDAS was designed to separate NAFLD from non-NAFLD individual's, with its performance evaluated using the Area Under the Receiver Operating Characteristic (AUROC) curve. **Results:** In the subsection of the population included in SUNN-1, the median age group was 40-49 years of age with the majority of

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

patients between 40 and 59 years of age. Of the population that was surveyed, 2 in 3 were female and 61% were Hispanic. 80% of those who took the survey were classed as either overweight or obese and 1 in 4 were diabetic. The model demonstrated an AUROC of 0.81 on test data, indicating its effectiveness in identifying NAFLD patients who have entered severe steatosis (S3). The chosen model identified S3 positive patients with 0.7 precision and 0.7 recall. In identifying negative cases, the model scored 0.77 and 0.77 precision and recall respectively. The average accuracy across both classes was 0.74. **Conclusion:** The developed PDAS shows promise for early risk stratification of NAFLD patients based on results. Importantly, the developed PDAS offers tremendous potential to screen for NAFLD in the general population and improves upon previous machine learning developed models for population screening which require input from a treating clinician in the form of physical examination findings and blood testing. If prospectively validated, this novel tool offers potential to improve patient outcomes and doctor-to-patient time efficiency at the population level.

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2003-A | A PUBLIC HEALTH INITIATIVE FROM THE AMERICAN LIVER FOUNDATION DEMONSTRATES THE FEASIBILITY OF A SCREENING PROGRAM FOR FATTY LIVER DISEASE

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

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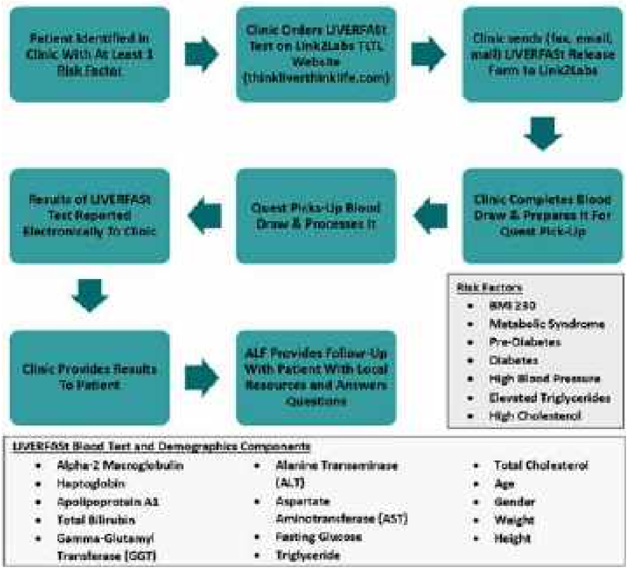
Background: Nonalcoholic fatty liver disease (NAFLD) prevalence is estimated to be 80-100 million in the US. NAFLD is highly under-diagnosed due to inadequate screening programs, and as a result can progress to non-alcoholic steatohepatitis (NASH), liver cirrhosis, liver cancer, the need for liver transplantation,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

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


Patient Identified In Clinic With At Least 1 Risk Factor
Clinic Orders LIVERFASt Test on Link2Labs TLTL Website (thinkliverthinklife.com)
Clinic sends (fax, email, mail) LIVERFASt Release Form to Link2Labs
Clinic Completes Blood Draw & Prepares It For Quest Pick-Up
Quest Picks-Up Blood Draw & Processes It
Results of LIVERFASt Test Reported Electronically To Clinic
Clinic Provides Results To Patient
ALF Provides Follow-Up With Patient With Local Resources and Answers Questions
Risk Factors
BMI ≥30
Metabolic Syndrome
Pre-Diabetes
Diabetes
High Blood Pressure
Elevated Triglycerides
High Cholesterol
LIVERFASt Blood Test and Demographics Components
Alpha-2 Macroglobulin
Haptoglobin
Apolipoprotein A1
Total Bilirubin
Gamma-Glutamyl Transferase (GGT)
Alanine Transaminase (ALT)
Aspartate Aminotransferase (AST)
Fasting Glucose
Triglyceride
Total Cholesterol
Age
Gender
Weight
Height

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2004-A | Agile3+ AND Agile4: TWO DIAGNOSTIC SCORES THAT SYNERGIZE FOR THE PROGNOSTIC ASSESSMENT IN NAFLD

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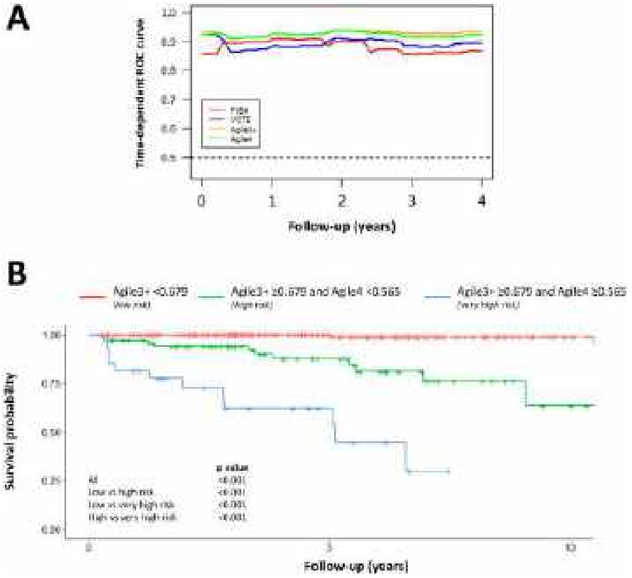
Laboratoire Hifih, Sfr Icat 4208, Université D'angers, Angers, France, (3)Echosens, (4)Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

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



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

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The following people have nothing to disclose: Clemence Canivet, Adrien Lannes, Isabelle Fouchard Hubert, Frederic Oberti, Marine Roux

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

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

Background: Efficacy studies in animal models of non-alcoholic steatohepatitis (NASH) include histopathological endpoints. Clinical-derived NAFLD Activity Scoring (NAS) and Fibrosis Staging system, outlined by Kleiner et al., is reproducible in preclinical models of NASH. Manual histopathological scoring is prone to observer variability which can influence robustness and reproducibility of study results. To enable objective and unbiased histopathological assessment in liver biopsies, we developed GHOST, an deep learning-based digital imaging analysis pipeline for automated NAS and fibrosis scoring. **Methods:** Liver biopsies were obtained from two NASH rodent models, GAN diet-induced obese (GAN DIO-NASH) mouse and choline-deficient L-amino acid-defined high-fat diet (CDAA-HFD) rat. Age-matched chow-fed mice and rats served as normal controls. Automated GHOST deep learning computational analysis of NAS and fibrosis scores was performed on hematoxylin-eosin (HE) and picrosirius red (PSR) stained sections. GHOST module was extended to enable automated analysis of fibrosis severity in CDAA-HFD rats using the Ishak fibrosis scoring system. All GHOST data were validated by manual scoring by expert histopathologists. Quantitative morphometrics, derived from scoring variables, includeddensity of hepatocytes with lipid droplets, number of inflammatory foci, and %-area of fibrosis. **Results:** GHOST accurately and reproducibly detected hepatic central veins and portal areas in GAN DIO-NASH mice and CDAA-HFD rats , enabling segmentation of zones for clinical histopathological scoring. In HE stained sections, hepatocytes, inflammatory cells, and ballooned hepatocytes were identified. Inflammatory foci were considered as clusters of **e** 4 inflammatory cells. NAS was computed and validated using 338 mouse liver biopsies with a Cohen´s Kappa value of 0.72, indicating agreement between AI-assisted and manual scoring of NAS. PSR-stained collagen fibers were localized in the sinusoidal and periportal space by GHOST, identifying collagen forming bridges and branch points. Kleiner fibrosis stage was computed and validated using 537 mouse liver biopsies, achieving a Kappa value of 0.84 between AI and manual scores. For Ishak scores, PSR-stained sections were segmented into smaller tiles, classified using convolutional neural network (CNN) analysis. The output of the CNN model was used in a machine learning algorithm to predict fibrosis stage achieving Kappa value of 0.82, based on86 liver biopsies from CDAA-HFD rats. **Conclusion:** Accuracy of GHOST-automated histopathological scoring in the GAN DIO-NASH and CDAA-HFD models of NASH was in close agreement with expert histopathologist assessment. Using GHOST for automated assessment of NAS and fibrosis scores provides fast, accurate and reproducible histopathological scoring, hence highly instrumental for the assessment of test drug effects in preclinical models of NASH.

Disclosures: Anitta Kinga Sarvari – Gubra: Employee, Yes, No; Gubra: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;
Susanne E. Pors – Gubra: Employee, Yes, No;
Michael Feigh – Gubra: Employee, Yes, No; Gubra: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No; Gubra: Executive role , Yes, No;
The following people have nothing to disclose: Jacob Nøhr-Meldgaard, Denise Oró Bozzini, Henrik B. Hansen
Disclosure information not available at the time of publication: Casper Salinas

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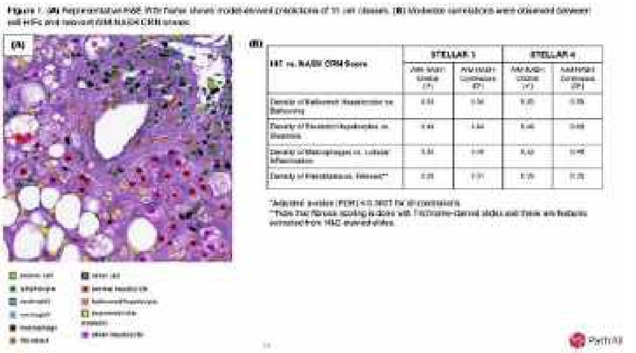
2006-A | AI-BASED CELLULAR-LEVEL CHARACTERIZATION OF TISSUE MICROARCHITECTURE IN NON-ALCOHOLIC STEATOHEPATITIS

Neel Patel[1], Pratik Mistry[1], Adam Stanford-Moore[1], Robert Egger[1], Michael G. Drage[1], Murray Resnick[1], Jonathan Glickman[1], John Abel[1], Nidhi Chandra[1], Dinkar Juyal[1], Dana Lau-Corona[1], Ilan Wapinski[1], Timothy R. Watkins[2], Andrew N. Billin[2] and Janani Iyer[1], (1)Pathai, Inc., (2)Gilead Sciences, Inc.

Background: Non-alcoholic steatohepatitis (NASH) is traditionally evaluated via ordinal scoring of tissue patterns in liver biopsies. While these scoring systems facilitate pathologist evaluation, they do not afford the granularity and sensitivity required to detect subtle yet meaningful histologic changes. To address this unmet need, we trained machine learning (ML) models to characterize the morphological architecture of H&E NASH liver biopsies at the cellular level, and tested the biological validity of model-generated, quantitative Human Interpretable histologic Features (HIFs) by comparing them against ML-derived NASH Clinical Research Network (CRN) scores. **Methods:** An ML model was trained using whole slide images (WSIs) of H&E NASH biopsies to detect all cell nuclei present and assign a cell label (Fibroblast, Macrophage, Lymphocyte, Neutrophil, Eosinophil, Plasma Cell, Ballooned Hepatocyte, Normal Hepatocyte, Other Hepatocyte, Macrovesicular Steatotic Cell, or Other cell; Fig. 1A) to each nucleus. We deployed the resulting cell model alongside a previously developed ML-based Tissue Model on WSIs from a subset of enrolled participants in the Stellar-3 (ST3; Baseline [BL] N = 391, Week 48 [Wk48] N = 384) and Stellar-4 (ST4; BL N = 1117, Wk48 N = 548) clinical trials to characterize tissue composition in the form of cellular HIFs. In addition, ordinal and continuous ML-derived NASH CRN scores for each sample were generated via the AI-based Measurement of NASH Histology tool (AIM-NASH, PathAI, Inc.; previously described). We used Kendall's tau (T) or Pearson's correlation (R) to measure the association between cellular composition of tissue samples and AIM-NASH scores. **Results:** We found moderate correlations between cell HIFs and AIM-NASH CRN ordinal and continuous scores in BL WSIs from both ST3 and ST4 (Fig.1B). The cell density features that best correlated with the AIM-NASH CRN components were Ballooned Hepatocytes with Ballooning Grade, Steatotic Hepatocytes with Steatosis Grade, Macrophages with Lobular Inflammation Grade, and Fibroblasts with Fibrosis Stage (FDR-corrected $p < 0.001$ for these comparisons), suggesting that the ML model is accurately capturing relevant cellular histology. **Conclusion:** Here we report an ML model that delivers insight into the cellular architecture of NASH liver biopsies. We found biological validity of model predictions by showing correlations of quantitative HIFs with the gold standard NASH CRN grading and staging system. Future work should aim to characterize the cellular patterns that uniquely predict histologic response to individual drug classes or indicate mechanisms of action, in addition to interrogating the spatial relationships between these cell types in advancing versus regressing fibrosis in NASH.



Disclosures: Neel Patel – PathAI, Inc: Employee, Yes, No;
Pratik Mistry – PathAI, Inc.: Employee, Yes, No;
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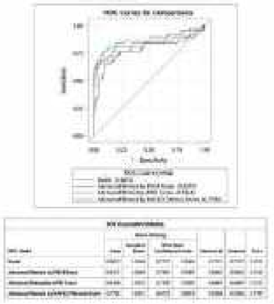
The following people have nothing to disclose: Nidhi Chandra

2007-A | ALANINE TRANSAMINASE LEVEL DOES NOT AFFECT THE PREDICTABILITY OF CLINICALLY SIGNIFICANT OR ADVANCED FIBROSIS BETWEEN NONINVASIVE SCORING SYSTEMS

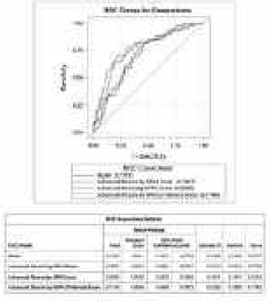
Maham Ghani[1], Salima Makhani[1], Alexa Giammarino[1], Ethan Berman[1], Justin Lin[2], Jeffrey Lowell[1], Mark Patrick Cubillan[2], Pratik Patel[3], Hassam Ali[4], Michael Ramada[1], James S. Park[3] and Sanjaya Kumar Satapathy[5], (1)Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, (2)Northshore University Hospital/Long Island Jewish Hospital, (3)Northwell Health, Forest Hills, NY, (4)East Carolina University, (5) Division of Hepatology, Northwell Health, and Donald and Barbara Zucker School of Medicine at Hofstra/ Northwell, Hempstead, NY, USA.

Background: Serum alanine transaminase (ALT) levels are regarded as a sensitive and reliable marker of liver disease, however patients with chronic liver disease can have normal or slightly elevated ALT. Non-invasive validated scoring systems such as FIB-4, APRI and NAFLD fibrosis score (NFS) can assist in predicting severity of disease. Our study aims to determine whether stratification by ALT level can improve accuracy of non-invasive fibrosis scores. **Methods:** We retrospectively analyzed 444 biopsy proven NAFLD cases from 2015-2020. Fibrosis score > 1 was defined as clinically significant fibrosis and while a score > 2 was defined as advanced fibrosis. Performances of each score for advanced fibrosis were determined for low ALT (< 40 U/L) and high ALT (> 40 U/L) levels by calculating the area under the receiver operating characteristic (ROC) curve and their 95% confidence intervals (CI). We used two-sided tests with $\alpha = 0.05$. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). **Results:** Of 444 biopsy proven NAFLD patients, 187 had serum ALT levels < 40 whereas 257 had serum ALT levels > 40. The average APRI, FIB4 and NFS for all patients were 0.77, 1.81, and -0.96, respectively; for the normal ALT cohort were 0.36, 1.57, and -0.27 respectively; and for the elevated ALT cohort were 1.08, 1.99, and -1.46, respectively. In the advanced fibrosis cohort, there were 37 patients in the normal ALT cohort and 77 patients in the elevated ALT cohort. ROC scores for the FIB4, APRI, and NFS in clinically significant fibrosis were approximately 0.83 (95% CI 0.74-0.93, p = 0.21), 0.83 (95% CI .73-94, p = 0.21), and 0.78 (95% CI .67-0.89 p = 0.18), for the normal ALT cohort and 0.76 (95% CI 0.70-0.83, p = 0.22), 0.70 (95% CI 0.63-0.77, p = 0.16), 0.71 (95% CI 0.65-0.78, p = 0.18) for the elevated ALT cohort. When stratifying for advanced fibrosis, defined as fibrosis score > 2, ROC scores for the FIB4, APRI, and NFS were approximately 0.88 (95% CI 0.77-0.98, p = 0.18), 0.86 (95% CI .74-97, p = 0.17), and 0.86 (95% CI .75-0.96 p = 0.17), for the normal ALT cohort and 0.84 (95% CI 0.78-0.90, p = 0.18), 0.76 (95% CI 0.69-0.84, p = 0.14), 0.80 (95% CI 0.72-0.87, p = 0.15) for the elevated ALT cohort. **Conclusion:** Our analysis demonstrated that all three non-invasive fibrosis scores (FIB-4, APRI, and NFS) are highly predictive for fibrosis, regardless of normal or elevated serum ALT level. FIB-4, APRI and NFS equally predict both clinically and advanced fibrosis in patients with normal ALT level levels. FIB-4 and the NFS are slightly better predictors of the degree of fibrosis in patients with elevated ALT levels. Larger prospective studies are needed to validate the stratification of non-invasive fibrosis scores based on serum ALT level.

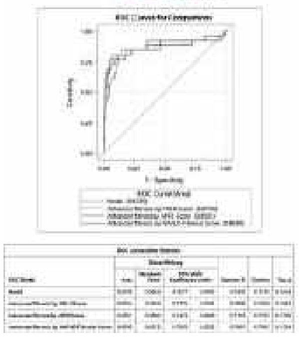
ROC Curves of Normal ALT Cohort in Clinical Significant Fibrosis



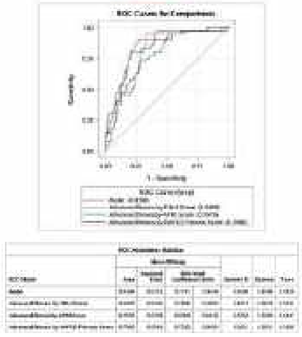
ROC Curves of Elevated ALT Cohort in Clinically Significant Fibrosis



ROC Curves of Normal ALT Cohort in Advanced Fibrosis



ROC Curves of Elevated ALT Cohort in Advanced Fibrosis

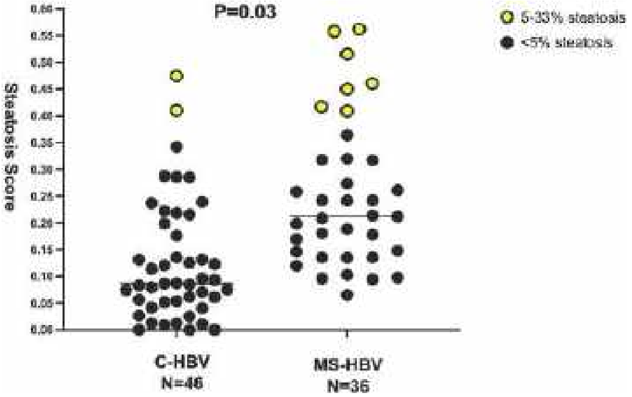


Disclosures: The following people have nothing to disclose: Maham Ghani, Salima Makhani, Alexa Giammarino, Ethan Berman, Justin Lin, Jeffrey Lowell, Mark Patrick Cubillan, Pratik Patel, Hassam Ali, Michael Ramada, James S. Park, Sanjaya Kumar Satapathy

2008-A | APPLICATION OF LIVERFAST BIOMARKERS TO PREDICT STEATOSIS IN CHRONIC HEPATITIS B PATIENTS WITH METABOLIC SYNDROME

Mati Ullah Dad Ullah[1], Mansoor Rahman[1], Mehdi Sakka[2], Rana Alkouri[2], Muhammad Asad Raza[1], Mukarram Jamat Ali[1], Karen Campoverde Reyes[1], Maxime Deregnaucourt[2], Dominique Bonnefont-Rousselot[2,3], Ronald Quiambao[4], Mona Munteanu[4] and Daryl T. Y. Lau[1], (1)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (2) Metabolic Biochemistry Department, Pitié-Salpêtrière Hospital, Public Assistance Paris Hospitals,Aphp Sorbonne University, France, (3)Pharmacy Training and Research Unit (UFR), Paris Cité University; Cnrs, Inserm, Utcbs, France, (4)Fibronostics US Inc, USA

Background: Chronic hepatitis B (CHB) and nonalcoholic fatty liver disease (NAFLD) are both common liver conditions. Approximately 30-40% patients with CHB also have NAFLD. Patients with coexisting CHB and NAFLD have high risk of liver disease progression and hepatocellular carcinoma. In this study, we evaluated LIVERFASt as a noninvasive biomarker in detecting hepatic steatosis among CHB patients with and without metabolic syndrome. We also correlated LIVERFASt steatosis scores with the Controlled Attenuation Parameter (CAP) scores of FibroScan. **Methods:** This is a retrospective, cross-sectional study in a single tertiary liver center. We identified 82 patients who met the study criteria and had available fasting sera in the biorepository. The MS-HBV group consisted of 36 (44%) CHB patients with metabolic syndrome or known diabetes mellitus; the C-HBV group had 46 (56%) patients with CHB alone. Metabolic syndrome was defined according to the criteria of the national cholesterol education program. LIVERFASt ™ (Fibronostics) scores were computed for each sample using the defined clinical and laboratory values. Medical chart review was performed to record demographics, clinical and HBV status. **Results:** Asians were predominant in both the MS-HBV (83%) and C-HBV (67%) groups with similar mean age of 50 and 46 years, respectively. BMI (28 vs. 25 kg/m^2, $p = 0.001$), HbA1c (6.1 vs. 5.2%, $p < 0.0001$), ALT (42 vs. 27 U/L, $p = 0.002$) and AST (30 vs. 25 U/L, $p = 0.01$) were significantly higher in the MS-HBV group. The proportions of patients on antiviral therapy for CHB in the MS-HBV (42%) and C-HBV (37%) groups were similar. About 15% of patients in each group had HBV DNA levels > 2000 IU/ml. 7 (19%) patients in MS-HBV and only 2 (4%) patients in C-HBV groups were identified to have steatosis ($p = 0.03$) [Figure]. LIVERFASt steatosis score most strongly correlated with BMI ($r = 0.58$, $p < 0.00001$), followed by HbA1c ($r = 0.32$, $p = 0.004$) and lipo-protein insulin resistance index (LP-IR) ($r = 0.33$, $p = 0.002$). In a linear regression model, steatosis can be predicted using the formula: *Steatosis score = (0.02199 x BMI)-0.3985*. Fewer than 10% of subjects in each group had advanced fibrosis. There was no significant correlation between steatosis and fibrosis scores. 54 (66%) patients had BMI change < 2 kg/m^2 and had FibroScan with CAP in an average follow up of 2 years. Their steatosis scores significantly correlated with their CAP scores ($r = 0.56$, $p = < 0.00001$). **Conclusion:** LIVERFASt has prognostic value in detecting steatosis among CHB patients with metabolic syndrome. LIVERFASt steatosis score had the strongest correlations with BMI and CAP score by fibroScan in this study. Noninvasive methods to identify patients with NAFLD are important for timely interventions and management. These positive observations and the steatosis prediction model need to be validated with larger, racially diverse cohorts of chronic hepatitis B patients in further studies.



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The following people have nothing to disclose: Mati Ullah Dad Ullah, Mukarram Jamat Ali

Disclosure information not available at the time of publication: Mansoor Rahman, Mehdi Sakka, Rana Alkouri, Muhammad Asad Raza, Karen Campoverde Reyes, Maxime Deregnaucourt, Dominique Bonnefont-Rousselot, Mona Munteanu, Daryl T. Y. Lau

2009-A | ARTIFICIAL INTELLIGENCE/NEURAL NETWORK SYSTEM THAT ACCURATELY DIAGNOSES HEPATOCELLULAR CARCINOMA IN NONALCOHOLIC STEATOHEPATITIS

Kanji Yamaguchi[1], Toshihide Shima[2], Yasuhide Mitsumoto[3], Yuya Seko[1], Yoshito Itoh[1] and Takeshi Okanoue[3], (1)Kyoto Prefectural University of Medicine, (2)Saiseikai Suita Hospital, Suita, Osaka, Japan, (3) Saiseikai Suita Hospital

Background: The aim of this study was to develop a novel noninvasive test using an artificial intelligence/neural network system (called HCC-Scope) to diagnose early stage hepatocellular carcinoma (HCC) in nonalcoholic steatohepatitis (NASH). **Methods:** One hundred and seventy-five NASH patients and 55 patients with NASH-HCC were enrolled for training and validation studies. Of the 55 NASH-HCC, 27 had very early stage HCC, and six had early stage HCC based on the Barcelona Clinic Liver Cancer staging system. Diagnosis with HCC-Scope was performed based on 12 items: age, sex, height, weight, aspartate aminotransferase level, alanine aminotransferase level, gamma-glutamyl transferase level, cholesterol level, triglyceride level, platelet count, diabetes status, and immunoglobulim M-free apoptosis inhibitor of macrophage level. The FMVWG2U47 hardware (Fujitsu Co. Ltd, Tokyo) and the originally developed software were used. **Results:** HCC-Scope had 100.0% sensitivity, 100.0% specificity, 100.0% positive predictive value (PPV), and 100.0% negative predictive value (NPV) for differential diagnosis between non-HCC and HCC in a training study with and without gray zone analysis. It was also excellent in the validation study (95.0% sensitivity, 100.0% specificity, 100.0% PPV, and 97.1% NPV with gray zone analysis and 95.2% sensitivity, 100.0% specificity, 100.0% PPV, and 97.1% NPV without gray zone analysis). HCC-Scope had significantly higher sensitivity (85.3%) and specificity (85.1%) than alpha-fetoprotein (AFP) level, AFP-L3 level, des-gamma-carboxy prothrombin (DCP) level, and the gender–age–AFP-L3–AFP–DCP (GALAD) score. **Conclusion:** HCC-Scope is easy to use and can accurately differentially diagnose between non-HCC NASH and NASH-HCC, including very early stage NASH-HCC.

Disclosures: Yuya Seko – Mitsubishi Tanabe Pharma Corporation: Speaking and Teaching, No, No; AbbVie Inc.: Speaking and Teaching, No, No; Gilead Sciences Inc.: Speaking and Teaching, No, No; Novo Nordisk Pharma Ltd.: Speaking and Teaching, No, No; Kowa Company, Ltd.: Speaking and Teaching, No, No; Merck Sharp and Dohme: Speaking and Teaching, No, No; EA Pharma Co.,Ltd.: Speaking and Teaching, No, No; ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, No, No; Dainippon Sumitomo Pharma Co., Ltd: Speaking and Teaching, No, No;
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institution receives the research grant and manages the funds), No, No; Takeda Pharmaceutical Company Limited.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Mitsubishi Tanabe Pharma Corporation: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Chugai Pharmaceutical Co., Ltd.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Novo Nordisk Pharma Ltd.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Bayer Yakuhin, Ltd.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Parexel International Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pfizer Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol-Myers Squibb Company: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Kowa Company, Ltd.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, No, No; Daiichi Sankyo Company, Ltd.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Nippon Boehringer Ingelheim Co., Ltd.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences Inc.: Speaking and Teaching, Yes, No; AbbVie Inc.: Speaking and Teaching, No, No; Zeria Pharmaceutical Co., Ltd.: Speaking and Teaching, No, No; Daiichi Sankyo Company,Ltd.: Speaking and Teaching, No, No; Mitsubishi Tanabe Pharma Corporation: Speaking and Teaching, No, No; Viatris Inc.: Speaking and Teaching, No, No; Sumitomo Pharma Co.,Ltd.: Speaking and Teaching, No, No; Kowa Company, Ltd.: Speaking and Teaching, No, No; TAIHO Phamaceutical Co., Ltd.: Speaking and Teaching, No, No; Ono Pharmaceutical Co., Ltd.: Speaking and Teaching, No, No; Mochida Pharmaceutical Co., Ltd.: Speaking and Teaching, No, No; Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, No, No; Tumura & Co.: Speaking and Teaching, No, No; Chugai Pharmaceutical Co., Ltd.: Speaking and Teaching, No, No; Toray Industries, Inc.: Speaking and Teaching, No, No; Bristol-Myers Squibb Company: Speaking and Teaching, Yes, No; Merck Sharp and Dohme: Speaking and Teaching, No, No; ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, No, No; Eli Lilly and Company: Speaking and Teaching, No, No; Eisai Co., Ltd.: Speaking and Teaching, No, No; AstraZeneca plc: Speaking and Teaching, Yes, No; Takeda Pharmaceutical Company Limited.: Speaking and Teaching, No, No; Novo Nordisk Pharma Ltd.: Advisor, Yes, No;

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

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

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

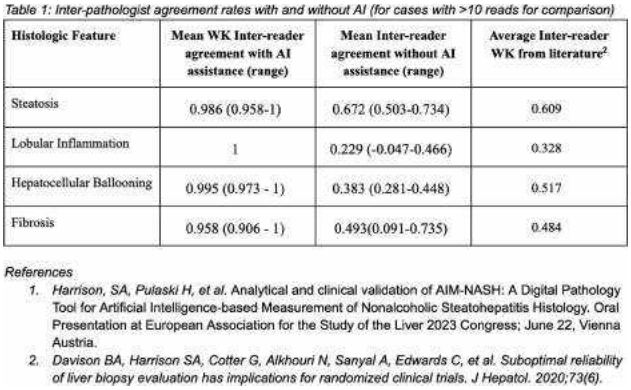

Table 1: Inter-pathologist agreement rates with and without AI (for cases with >10 reads for comparison)

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

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2. *Davison BA, Harrison SA, Cotter G, Alkhouri N, Sanyal A, Edwards C, et al. Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials. J Hepatol. 2020;73(6).*

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Quentin M. Anstee – AstraZeneca, Boehringer Ingelheim, Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Alimentiv, Akero, AstraZeneca, Axcella, 89Bio, Boehringer Ingelheim, Bristol Myers Squibb, Galmed, Genfit, Genentech, Gilead, GlaxoSmithKline, Hanmi, HistoIndex, Intercept, Inventiva, Ionis, IQVIA, Janssen, Madrigal, Medpace, Merck, NGMBio, Novartis, Novo: Consultant, No, No; Fishawack, Integritas Communications, Kenes, Novo Nordisk, Madrigal, Medscape, Springer Healthcare: Speaking and Teaching, No, No; Elsevier Ltd: Royalties or patent beneficiary, No, Yes;
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The following people have nothing to disclose: Vlad Ratziu

2011-A | ASSESSING THE REPEATABILITY AND REPRODUCIBILITY OF LIVERMULTISCAN METRICS cT1 AND PDFF

Cayden Beyer[1], Anneli Andersson[1], Elizabeth Shumbayawonda[2], Andrea Dennis[1] and Kathleen E. Corey[3], (1)Perspectum Ltd, (2)Perspectum Ltd., (3) Massachusetts General Hospital, Somerville, MA

Background: Multi-parametric magnetic resonance imaging (mpMRI)-derived metrics iron-corrected T1 (cT1) and proton density fat-fraction (PDFF) have proven to be excellent non-invasive biomarkers for diagnosis and monitoring of non-alcoholic steatohepatitis (NASH). They are both commonly utilized as efficacy endpoints in NASH trials to assess therapy-induced changes in liver health, and cT1 additionally predicts clinical outcomes. Here we assess the robustness of both metrics by investigating their test-retest variability in a NASH population. **Methods:** Patients were recruited at Massachusetts General Hospital. All participants underwent two LiverMultiScans within the same scanning session, five minutes between scans without exiting the scanner, (timepoints A and B, respectively) to assess the measurement variability of cT1 and PDFF. Additionally, patients histologically classified as having at-risk NASH (NAS > = 4 and fibrosis > = 2) were invited back for a third scan 2-4 weeks after their first visit (timepoint C) to test the biological/physiological variability. Bland-Altman analysis was performed, and the coefficient of variance (CoV), repeatability coefficient (RC), bias and upper/lower limits of agreement (LoA) were calculated, PDFF values are reported in relative percentages, rather than absolute. **Results:** Of the patients included in this study (n = 22; age = 48 years; BMI = 36.1 kg/m^2; cT1 = 858 ms; PDFF = 12.8%; 50% female, 41% diabetic), 7 had histologically confirmed at-risk NASH and were scanned 2-4 weeks following the initial scan. cT1 demonstrated high repeatability across timepoints A and B (CoV: 1.5%; RC: 32.1ms; bias: -6.2ms; 95% LoA: –36.6 to 24.2ms), and high reproducibility across timepoints A and C (CoV: 2.6%; RC: 65.2ms; bias: 6.3 ms; 95% LoA: –63.8 to 76.5ms). PDFF also demonstrated high repeatability across timepoints A and B (CoV: 1.9%; RC: 5.1%; bias: 1.1%; 95% LoA: –3.7 to 5.8%%), and high reproducibility across timepoints A and C (CoV: 6.9%; RC: 19.5%; bias: -1.1%; 95% LoA: –22.0 to 19.7%). **Conclusion:** Both cT1 and PDFF are used as efficacy endpoints in clinical trials with meaningful changes aligning with approved endpoints of NASH resolution and/or fibrosis regression reported to be > 80 ms for cT1 and **e** 30% relative change for PDFF. In this study of test-re-test variability, both metrics showed measurement variability well under the clinical meaningful change thresholds, both within session and two-weeks later With excellent repeatability and reproducibility, and proven correlations with respective histopathological features of NASH, cT1 and PDFF represent robust and reliable metrics for characterizing and assessing changes in liver tissue.

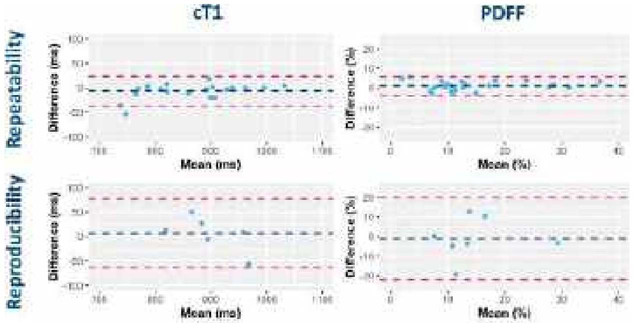

Figure 1. Bland-Altman plots showing the cT1 and PDFF differences between baseline (timepoint A) and follow up (timepoint B for repeatability and timepoint C for reproducibility). The dashed lines represent the the upper 95% LoA (top), the mean (middle) and the lower 95% LoA (bottom).

Disclosures: Cayden Beyer – Perspectum Ltd: Employee, Yes, No;

Elizabeth Shumbayawonda – Perspectum Ltd.: Employee, Yes, No;

Kathleen E. Corey – Intercept: Consultant, No, No; Theratechnologies: Consultant, No, Yes; Medscape: Speaking and Teaching, No, No;

Disclosure information not available at the time of publication: Anneli Andersson, Andrea Dennis

2012-A | ASSESSMENT OF HEPATIC FIBROSIS SCREENING IN PRIMARY CARE USING AUTOMATIC CALCULATION OF THE FIB-4 SCORE, FOLLOWED IN SECOND LINE BY AN ELF (ENHANCED LIVER FIBROSIS) TEST

Denis Ouzan, Institut Arnault Tzanck; Rhecca, Guillaume Penaranda, Hopital Europeen, Malik Jlaiel, Bioesterel BIO Group and Jeremie Corneille, Bioesterel Biogroup

Background: Screening for liver fibrosis in the general population is a public health issue. We have shown in a previous study that FIB-4, a simple score combining age, ALT, AST, and platelet, can detect liver fibrosis in general practice and identify a possible cause of liver disease (1). The objective of our work was to evaluate the screening of hepatic fibrosis in general practice using the FIB-4 score automatically calculated, followed in second line if **e** 1.3 by an ELF test. **Methods:** The FIB-4 score was calculated from March to September 2022 in all consecutive patients seen by 15 general practitioners, outside the emergency. When the FIB-4 was **e** 1.3, it was defined as positive and ELF test was systematically performed. FIB-4 positivity was confirmed when the ELF test was **e** 9.8. **Results:** Among the 3427 patients included, 869 (25%) had a positive FIB4 score: 784 (22.5%) at intermediate (FIB-4:1.3-2.67) and 85 (2.5 %) at high risk of fibrosis (FIB-4 > 2.67). Among the 869 FIB-4 positive patients, 509 (59%) were confirmed by the ELF test. FIB-4 positivity was significantly linked to age over 65 years, AST, AST/ALT ratio and platelets levels $p < 0.001$. Confirmation by ELF was observed in 80% of the patients at high risk and 56 % at intermediate risk of fibrosis ($p < 0.0001$). Clinical information's were collected in 755/869 (87%) FIB-4 positive patients. The percentage of confirmation was significantly higher in patients over 65 years (84 vs 58%, $p < 0.0001$), in those with FIB-4 > 2.67 (80 vs 56%, $p < 0.0001$), BMI > 25 (47 vs 38%, $p = 0.010$), and with a diabetes (24 vs 14%, $p = 0.001$), but not in those with excessive alcohol consumption (14 vs 15%, $p = 0.8284$). In patients without known liver disease (92%), the general practitioner defines a cause of liver disease in 27% of cases: NAFLD 67 %, Alcohol 23%, FLD+ Alcohol 9%, other 5% and requires a specialized advice in 1/2 cases. **Conclusion:** Liver fibrosis was suspected by FIB4 score in 25 % of patients who consulted a general practitioner. The ELF test performed as a second-line test improves the screening of hepatic fibrosis by FIB-4 in primary care and in

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particular for FIB-4 indetermined results which are confirmed in one out of two cases. The FIB-4 score, automatically generated, represents a warning that allows the general practitioner to identify a risk factor and a cause of liver disease on which it can intervene at an early stage. (1) Ouzan D et al. Prospective screening for significant liver fibrosis by FIB-4 in primary care patients without known liver disease. Eur J Gastroenterol Hepatol 2021;33:986-991.

Disclosures: The following people have nothing to disclose: Denis Ouzan

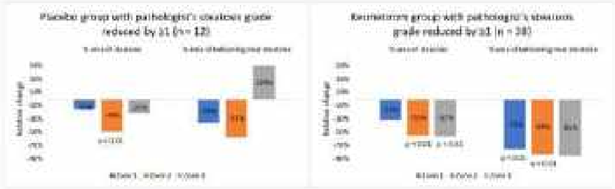
Disclosure information not available at the time of publication: Guillaume Penaranda, Malik Jlaiel, Jeremie Corneille

2013-A | ASSESSMENT OF RESMETIROM-MEDIATED REDUCTIONS OF STEATOSIS AND CONCOMITANT BALLOONING UTILIZING QUANTITATIVE SECOND HARMONIC GENERATION IMAGING

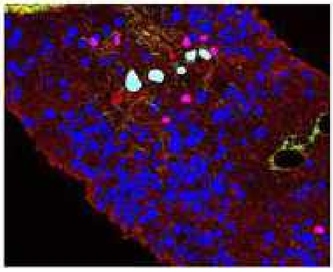
Dean Tai[1], *Rebecca A. Taub*[2], *Ya-Yun Ren*[3], *Elaine Lay Khim Chng*[1] *and Stephen A Harrison*[4], *(1)Histoindex Pte Ltd, Singapore, (2)Madrigal Pharmaceuticals, (3) Histoindex Pte Ltd, (4)Pinnacle Clinical Research Center, San Antonio, TX*

Background: Resmetirom is an oral, liver-targeted thyroid hormone receptor-β selective agonist that reduces biopsy component scores. As shown in a previous analysis of qSteatosis and qFibrosis in a Phase 2 serial liver biopsy study, reduction of collagen near steatosis associates with steatosis improvement in Zone 2. The aim of this analysis was to study the association between ballooning reduction and steatosis reduction in the resmetirom versus placebo group using second harmonic generation (SHG)/two-photon excited fluorescence (TPEF) microscopy imaging of paired biopsy samples with artificial intelligence (AI)-based algorithms. **Methods:** 102 paired biopsy samples from a 36-week, randomized, double-blind, placebo-controlled Phase 2 study with resmetirom (NCT02912260) were imaged using SHG/TPEF. Ballooning and steatosis were estimated as a continuous variable using an AI-based algorithm. Resmetirom-mediated changes of ballooning in relation to steatosis reduction were evaluated by simultaneous measurement of ballooning and hepatic fat in selected areas around the fat vacuoles in liver regions: portal tract (Zone 1), central vein (Zone 3), and transitional (Zone 2). **Results:** In patients who showed a reduction in steatosis grade, resmetirom-treated patients ($n = 38$) showed a decrease in percentage area of steatosis according to qSteatosis across all 3 zones with significance observed in Zone 1 and 2; as compared to placebo-treated patients ($n = 13$) who only showed significance in Zone 2. Concomitant analysis of ballooning around the steatosis revealed some ballooning reduction in Zones 1 and 2 for the placebo group, but these were not statistically significant. The resmetirom group clearly showed a significant ballooning reduction across all zones with significance in Zones 1 and 2. A relative decrease of 55% for percentage area of steatosis was associated with a relative decrease of 83% for percentage area of ballooning near steatosis in Zone 2 ($p < 0.01$). Similar observation of concomitant reduction in ballooning (85%) near steatosis (57%) was seen for Zone 3 too ($p < 0.01$). **Conclusion:** Qualitatively, a clear difference can be seen in the pattern of co-localization analysis of steatosis and ballooning in resmetirom-treated patients versus placebo-treated patients. The use of a continuous variable (qBallooning, qSteatosis) provides quantitation of zonal changes in ballooning and steatosis in serial liver biopsy studies which cannot be captured using the NASH CRN system.

Figure: Steatosis and ballooning co-localization plots for resmetirom-treated (right) versus placebo-treated groups (left) in patients whose steatosis reduced from baseline to end-of-treatment.



SHG/TPEF image showing co-localization of ballooned hepatocytes (pink) in close proximity to steatotic vacuoles (blue) versus ballooned hepatocytes (white) further away from steatotic vacuoles.



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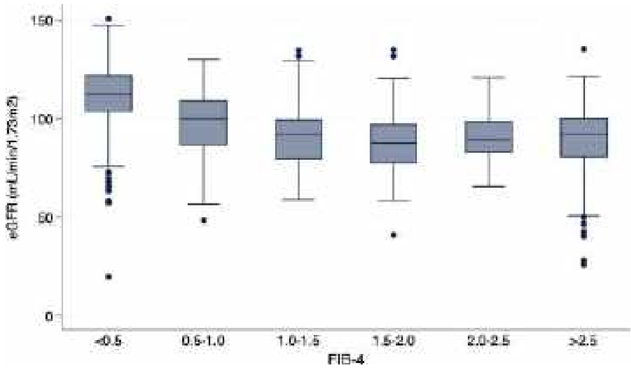
Hightide: Consultant, No, No; HistoIndex: Consultant, No, No; Intercept: Consultant, No, No; Madrigal: Consultant, No, No; Medpace: Consultant, No, No; Metacrine: Consultant, No, No; NGM Bio: Consultant, No, No; Northsea: Consultant, No, No; Novartis: Consultant, No, No; Novo Nordisk: Consultant, No, No; Nutrasource: Consultant, No, No; Perspectum: Consultant, No, No; Poxel: Consultant, No, No; Sagimet: Consultant, No, No; Sonic Incytes: Consultant, No, No; Terns: Consultant, No, No; Viking: Consultant, No, No; Pinnacle Clinical Research: Executive role , No, No;

The following people have nothing to disclose: Dean Tai, Ya-Yun Ren, Elaine Lay Khim Chng

2014-A | ASSOCIATION BETWEEN RENAL FUNCTION AND NONALCOHOLIC STEATOHEPATITIS (NASH) SEVERITY: COMBINED DATA FROM MULTIPLE THERAPEUTIC TRIALS INCLUDING MORE THAN 6,000 PATIENTS (IN COLLABORATION WITH NAIL-NIT CONSORTIUM)

Stephen A Harrison[1], Julie Dubourg[2], Sophie Jeannin[2], Naim Alkhouri[3], Jörn M. Schattenberg[4] and Mazen Noureddin[5], (1)Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom, (2) Summit Clinical Research, San Antonio, TX, (3)Arizona Liver Health, Phoenix, AZ, (4)I. Department of Medicine, University Medical Centre Mainz, Johannes Gutenberg University, Mainz, Germany, Mainz, Germany, (5) Houston Research Institute, Houston, TX

Background: Previous reports have identified an association between chronic kidney disease (CKD) and nonalcoholic fatty liver disease (NAFLD). The prevalence and incidence of these two chronic conditions are rapidly increasing worldwide. Both conditions share cardiometabolic comorbidities including type 2 diabetes, obesity, hypertension, and metabolic syndrome. We aimed to assess the association between non-invasive biomarkers of fibrosis and NASH with renal function. **Methods:** We combined screening data from 8 NAFLD/NASH non-cirrhotic phase 2 trials. Estimated glomerular filtration rate (eGFR) was used as a marker of renal function with 5 categories (G1 **e** 90; G2 60-89; G3a: 45-59; G3b: 30-44; G4: 15-29; G5 < 15) where CKD is defined by eGFR < 60 mL/min/1.73m^2. We performed univariate linear regression analyses to describe the potential associations between noninvasive biomarkers and renal function. **Results:** Out of 6,558 patients, 5,343 with eGFR and non-invasive biomarkers data were included. Due to the clinical trials settings most patients were G1 (64%) or G2 (32%). A small proportion of patients were G3a (3%), G3b (< 1%) or G4 (< 1%). Liver biopsies were performed in 2,185 of these patients. Among patients without CKD, 59%, 40% and 32% had NASH, at-risk NASH (NASH + NAS **e** 4 + Fibrosis Stages 2 or 3), and advanced fibrosis (Fibrosis stages 3 or 4), respectively. This rises to 66%, 49% and 42% in patients with CKD. In univariate regression analysis, Fib-4 ($p < 0.001$, Figure), FibroScan liver stiffness measurement (LSM) ($p < 0.001$), AST ($p < 0.001$), ALT ($p < 0.001$) and type 2 diabetes ($p < 0.001$) were significantly associated with eGFR. **Conclusion:** A decrease in renal function is associated with higher NASH severity based both on non-invasive biomarkers and liver biopsy. Considering the low representation of CKD patients in this clinical trial population, further analyses are required to further confirm and explore this association. Enrichment with CKD population could be considered to help mitigate the high liver biopsy screen failure rate observed in NASH clinical trials.



Disclosures: Stephen A Harrison – Terns: Consultant, No, No; Viking: Consultant, No, No; Pinnacle Clinical Research: Executive role , No, No; Northsea: Consultant, No, No; Novartis: Consultant, No, No; Novo Nordisk: Consultant, No, No; Perspectum: Consultant, No, No; Poxel: Consultant, No, No; Sagimet: Consultant, No, No; Sonic Incytes: Consultant, No, No; Hepta Bio: Consultant, No, No; Hightide: Consultant, No, No; HistoIndex: Consultant, No, No; Intercept: Consultant, No, No; Madrigal: Consultant, No, No; Medpace: Consultant, No, No; NGM Bio: Consultant, No, No; Altimmune: Consultant, No, No; AstraZeneca: Consultant, No, No; Axcella: Consultant, No, No; Chronic Liver Disease Foundation: Consultant, No, No; Echosens: Consultant, No, No; Genfit: Consultant, No, No; Gilead: Consultant, No, No; GSK: Consultant, No, No; Hepion: Consultant, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; 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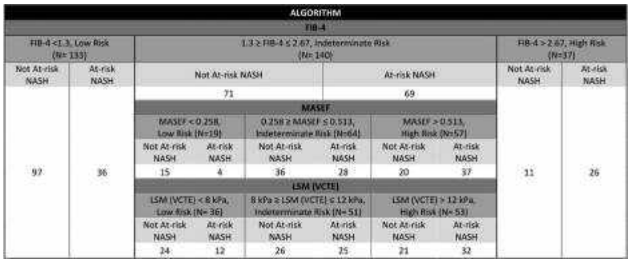
The following people have nothing to disclose: Sophie Jeannin

Disclosure information not available at the time of publication: Mazen Noureddin

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

Mazen Noureddin[1,2], Emily Truong[3,4], Rebeca Mayo[5], Ibon Martínez-Arranz[5], Itziar Mincholé[5], Jesus M. Banales[6,7], Marco Arrese Jimenez[8], Kenneth Cusi[9], Maria Teresa Arias[10], Radan Bruha[11], Manuel Romero-Gómez[12], Paula Iruzubieta[10], Rocio Aller[13], Javier Ampuero[14], Jose Luis Calleja[15], Luis Ibáñez Samaniego[16], Patricia Aspichueta[17,18,19], Antonio Marín-Duce[20], Tatyana Kushner[21], Pablo Ortiz[5], Stephen A Harrison[22], Quentin M. Anstee[23], Javier Crespo Garcia[10], José M Mato[24] and Arun Sanyal[25], (1) Houston Liver Institute, Houston, TX, (2)Houston Research Institute, Houston, TX, (3)Department of Medicine, (4)Cedars-Sinai Medical Center, Los Angeles, CA, (5)OWL Metabolomics, Derio, Spain, (6) Biodonostia Research Institute, Donostia University Hospital, University of the Basque Country (UPV-EHU), Ciberehd, Ikerbasque, Donostia, Spain, (7)Department of Biochemistry and Genetics, School of Sciences, University of Navarra, Pamplona, Spain, (8)Pontificia Universidad Católica De Chile, (9)Division of Endocrinology, Diabetes and Metabolism, University of Florida, Gainesville, FL, USA, (10)Marqués De Valdecilla University Hospital, Cantabria University, Idival, Santander, Spain, (11)General University Hospital and the First Faculty of Medicine, Charles University, Prague, Czech Republic, (12)Ucm Digestive Diseases, Virgen Del Rocio University Hospital, Instituto De Biomedicina De Sevilla, Ciberehd, University of Seville, Sevilla, Spain, (13)Clinic University Hospital, University of Valladolid, Valladolid, Spain, (14)Virgen Del Rocío University Hospital, Sevilla, Spain, (15) Puerta Del Hierro University Hospital, Madrid, Spain, (16)Gregorio Marañón University Hospital, Madrid, *Spain, (17)Department of Physiology, Faculty of Medicine and Nursing, University of the Basque Country Upv/EHU, Leioa, Spain, (18)Biocruces Bizkaia Health Research Institute, Barakaldo, Spain, (19) National Institute for the Study of Liver and Gastrointestinal Diseases (CIBERehd, Instituto de Salud Carlos III), Madrid, Spain, (20)Príncipe De Asturias University Hospital, Alcalá University, Madrid, Spain, (21)Icahn School of Medicine at Mount Sinai, New York, NY, (22)Pinnacle Clinical Research Center, San Antonio, TX, (23)Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom, (24)CIC Biogune, Basque Research and Technology Alliance (BRTA), Derio, Spain, (25) Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA*

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



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<tr><th colspan="6">MASEF</th></tr>
<tr><th colspan="2">MASEF < 0.258,
Low Risk (N=19)</th><th colspan="2">0.258 ≥ MASEF ≤ 0.513,
Indeterminate Risk (N=64)</th><th colspan="2">MASEF > 0.513,
High Risk (N=57)</th></tr>
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<tr><th colspan="6">LSM (VCTE)</th></tr>
<tr><th colspan="2">LSM (VCTE) < 8 kPa,
Low Risk (N= 36)</th><th colspan="2">8 kPa ≥ LSM (VCTE) ≤ 12 kPa,
Indeterminate Risk (N= 51)</th><th colspan="2">LSM (VCTE) > 12 kPa,
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2016-A | AUTOMATED AI-BASED MORPHOMETRIC ANALYSIS OF FIBROSIS REVEALS SIGNIFICANT FIBROSIS CHANGES IN T2DM VS NON-T2DM NASH PATIENTS WITH ADVANCED FIBROSIS

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

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

Disclosures: Cindy Serdjebi – Biocellvia: Employee, Yes, No; Biocellvia: Stock – privately held company (individual stocks and stock options), Yes, No;

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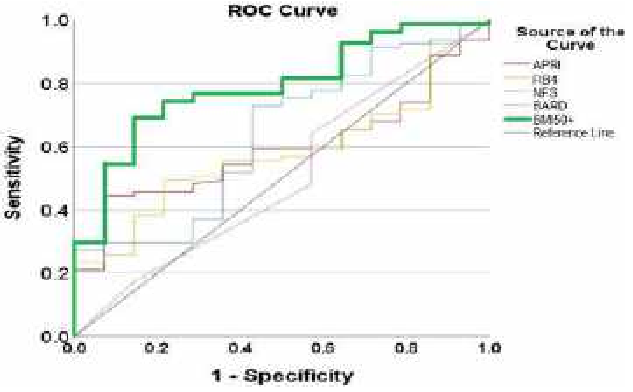
2017-A | BMI50+-FIBROSIS SCORE – A NEW NON-INVASIVE TEST FOR LIVER FIBROSIS IN PATIENTS WITH OBESITY AND A BMI > 50 KG/mβ

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

Background: Liver fibrosis is a hallmark of chronic liver disease. Especially in non-alcoholic fatty liver disease (NAFLD), awareness of liver fibrosis is key for patient stratification and planning of follow-up care. Current non-invasive tests (NIT) for liver fibrosis show poor performance in patients with obesity and to date no NIT was validated in the rapidly growing cohort of patients with clinically severe obesity, defined by a body mass index (BMI) over 50 kg/m². **Methods:** In this prospective, single-center cohort study, 95 patients scheduled for bariatric surgery were included (liver disease no other than NAFLD, BMI > 50 kg/m²). Liver biopsies were performed during surgery. Liver fibrosis was histologically determined according to Kleiner. AST-to-platelet ratio index (APRI), Fibrosis-4 score (FIB-4), NAFLD fibrosis score (NFS) and BMI, AST/ALT-ratio and diabetes score (BARD) with standard and optimized thresholds, determined by maximum Youden-Index, were calculated. Accuracy, sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated for each NIT. Multiple regression analysis of clinical variables were used to identify predictive factors in our cohort. **Results:** Commonly used NITs showed weak prediction of liver fibrosis in our cohort, with area under the receiver operating characteristic curve (AUROC) of .70. ANOVA analyses identified five variables (presence of dyslipidemia, presence of diabetes, serum levels of ALT, AST and creatinine) significantly differing among stage of fibrosis. This resulted through multiple regression in the BMI50+-Fibrosis score (BMI50+) with an AUROC of .79. Sensitivity was 0.4 for APRI, 0.49 for FIB-4, 0.73 for NFS, 0.64 for BARD and 0.74 for BMI50+. Specificity was 0.93 for APRI, 0.71 for FIB-4, 0.57 for NFS, 0.43 for BARD and 0.79 for BMI50+. Accuracy in predicting fibrosis for established NITs ranged between 48 - 71%. Our score had the best accuracy (75% correctly classified patients) and best NPV for prediction of any degree of fibrosis. **Conclusion:** Performance of established NITs is weak in patients with a BMI over 50 kg/m². The BMI50+-Fibrosis score is a useful tool for this setting. A prospective evaluation of our score should be done in further studies.



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2018-A | CELL FREE MESSENGER RNA PROFILES INDICATIVE OF SHARED PATHOLOGY BETWEEN NON-ALCOHOLIC FATTY LIVER DISEASE AND ALZHEIMER'S DISEASE

Naga P. Chalasani[1], Shusuke Toden[2], Rhys De Sota[2] and John J Sninsky[2], (1)Indiana University School of Medicine, (2)Molecular Stethoscope

Background: Emerging evidence indicates that nonalcoholic fatty liver disease (NAFLD) is associated with increased rates of dementia and poor cognitive performance. Cell-free RNA carriers in blood are expected to be involved in intercellular communication and provide signals of disrupted cellular homeostasis. We reported development of cell-free messenger RNA sequencing (cf-mRNA RNA-Seq) machine learning assays for NAFLD and Alzheimer's Disease (AD). Here we interrogated genes and pathways that are dysregulated in common for NAFLD and AD cell-free secretome. **Methods:** Cf-mRNA RNA-Seq was performed on 441 serum and plasma samples from NAFLD (176 NAFLD vs 23 healthy controls) and AD (126 AD vs 116 non cognitively impaired (NCI)) studies. Tissue-specific cf-mRNA content was evaluated using GTEx. Independent differential expression analysis was performed using DE-Seq2 and pathway analysis (GO, Reactome and KEGG) was conducted using differentially expressed genes in the studies. We evaluated genes that are dysregulated in both AD and NAFLD and validated these cf-mRNA genes in a tissue sequencing dataset. **Results:** Differentially expressed genes in cf-mRNA between NAFLD and healthy controls (2498 genes) as well as between AD and NCI (2591 genes) were identified. 296 genes were commonly dysregulated in both AD and NAFLD (198 up- and 98-downregulated). Pathway analysis revealed that Rho GTPase signaling pathway was the most dysregulated pathway for genes that are dysregulated in both diseases. Key dysregulated genes in AD in this pathway for cf-mRNA include RHOA, RAC1, ROCK1 and ROCK2. We confirmed dysregulation of a subset of Rho GTPase genes from a prior study of brain tissue. Furthermore, plasma cf-mRNA APOE expression was inversely correlated with plasma cf-mRNA RHOA expression. Finally, we identified dysregulation of other therapeutically targetable gene pathways for NAFLD and AD, such as GLP-1. **Conclusion:** Insight into common dysregulated genes and pathways in the extracellular compartment of disparate diseases potentially can inform the repurposing of pharmacotherapies. We identified cf-mRNA genes that are dysregulated in both AD and NAFLD, in particular, Rho GTPase signaling genes. Rho GTPase signaling pathway is currently being targeted by pharmacotherapies such as statins for both NAFLD/NASH and AD. Besides the pharmacotherapies already being considered for these two diseases, our study may provide insight into other pathways that merit consideration.

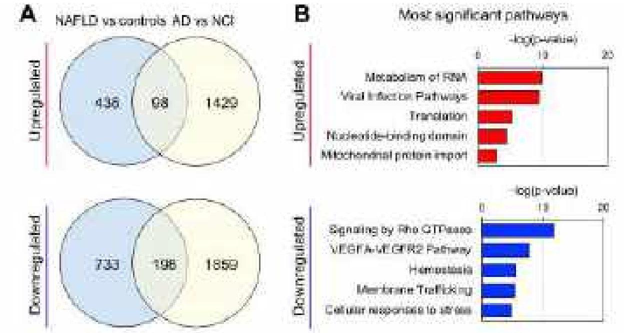


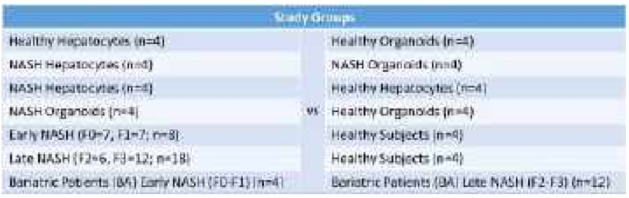
Figure 1: Identification of cf-mRNA dysregulated genes between NAFLD and AD. A) Overlap of genes between NAFLD vs controls, AD vs NCI (Upregulated genes (top), Downregulated genes (bottom)). B) Most significant pathways for genes that are upregulated in both NAFLD and AD (top) and downregulated in NAFLD and AD (bottom).

Disclosures: Shusuke Toden – Molecular Stethoscope: Employee, No, No;
Rhys De Sota – Molecular Stethoscope: Employee, No, No;
John J Sninsky – Molecular Stethoscope: Employee, Yes, No;
The following people have nothing to disclose: Naga P. Chalasani

2019-A | CHARACTERIZATION OF EXTRACELLULAR VESICLES PROTEOME FROM HUMAN HEPATOCYTES, NASH ORGANOIDS AND BLOOD FROM NASH PATIENTS IDENTIFIES NOVEL POTENTIAL BIOMARKERS

Ola Leszczynska[1], Benedikt Kaufmann[1], Christian Stoess[1], Hana Sung[1], Andrea D. Kim[1], Agustina Reca[1], Trevor Crafts[2], Bruce Wolfe[2] and Ariel E. Feldstein[1], (1) University of California, San Diego, (2)Oregon Health and Science University, Portland

Background: Nonalcoholic fatty liver disease (NAFLD) is currently one of the most common forms of chronic liver disease globally. The lack of effective treatments for NASH and the current requirement for an invasive liver biopsy for its diagnosis makes the discovery of reliable, noninvasive biomarkers urgently needed. In this study, we aimed to investigate the protein profile of extracellular vesicle (EV) release by primary human hepatocytes and human organoids and compared their profiles to those of circulating EVs from patients with the spectrum of NAFLD. **Methods:** EVs from the serum of healthy (n = 4) and NASH (n = 33; fibrosis stage: F0 = 7, F1 = 7, F2 = 6, F3 = 12) subjects, EVs supernatants from normal primary human hepatocytes (PHH), and human liver organoids (HLO) cultured in normal or NASH media were characterized. Quantification of EV populations was determined via NanoView® chip analysis using established EV protein markers including CD9, CD81, CD63, and the ASGPR1-hepatocyte-specific marker. Additional characterization of EVs was performed via Cryo-EM and Western blotting. The multiplex aptamer-based protein array SOMAScan® platform was performed to establish the EV proteome. The top 40 most differentially expressed proteins in early NASH versus healthy controls and late NASH vs healthy controls were clustered using unsupervised complete linkage clustering. **Results:** The number of EVs derived from NASH stimulated PHHs and HLOs increased compared to those from healthy cultures, and were quantified for hepatocyte marker ASGPR1 (PHH: Healthy 9.2×10^{5} vs NASH 4.51×10^{6} p **d** 0.001; HLO: Healthy 7.4×10^{5} vs NASH 6.14×10^{6} p **d** 0.0001) and tetraspanins markers CD9 (PHH: Healthy 1.71×10^{8} vs NASH 1.76×10^{8}, p **d** 0.05), CD63 (PHH: Healthy 1.79×10^{8} vs NASH 1.87×10^{8}; HLO: Healthy 7.7×10^{7} vs NASH 1.45×10^{8}, p **d** 0.05), and CD81 (PHH: Healthy 1.9×10^{8} vs NASH 1.95×10^{8}, p **d** 0.05; HLO: Healthy 3.2×10^{8} vs NASH 4.1×10^{8}, p **d** 0.001). Cryo-EM confirmed the EV ultrastructure and showed no specific changes in EV morphological features present among study groups. The average size of circulating EV did not differ between NASH and healthy control samples. Differential protein expression datasets were analyzed between various groups as depicted in Table 1. **Conclusion:** In this report, we have characterized the EV proteome from supernatants of primary human hepatocytes, human liver organoids, and blood samples of patients with NASH allowing for the identification of novel cell-type specific and disease-related biomarkers.



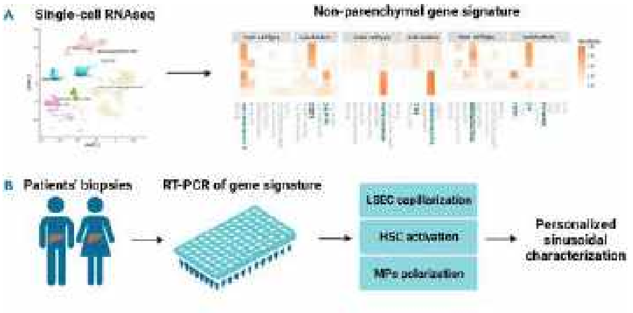
Study Groups		
Healthy Hepatocytes (n=4)		Healthy Organoids (n=4)
NASH Hepatocytes (n=4)		NASH Organoids (n=4)
NASH Hepatocytes (n=4)		Healthy Hepatocytes (n=4)
NASH Organoids (n=4)	vs	Healthy Organoids (n=4)
Early NASH (F0=7, F1=7; n=8)		Healthy Subjects (n=4)
Late NASH (F2=6, F3=12; n=18)		Healthy Subjects (n=4)
Bariatric Patients (BA) Early NASH (F0-F1) (n=4)		Bariatric Patients (BA) Late NASH (F2-F3) (n=12)

Disclosures: Ariel E. Feldstein – Novo Nordisk: Executive role , No, No;
The following people have nothing to disclose: Ola Leszczynska, Benedikt Kaufmann, Christian Stoess, Hana Sung, Andrea D. Kim, Agustina Reca, Trevor Crafts, Bruce Wolfe

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

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

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



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

Disclosures: Jordi Gracia-Sancho – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Inventiva: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Gat therapeutics: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Barcelona Liver Bioservices: Stock – privately held company (individual stocks and stock options), No, No; Quinton International: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
The following people have nothing to disclose: Anabel Fernandez-Iglesias, David Sanfeliu-Redondo
Disclosure information not available at the time of publication: Sergi Guixé-Muntet

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

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

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

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

Disclosures: Mikael Fredrik Forsgren – AMRA Medical AB: Employee, Yes, No;

The following people have nothing to disclose: Domenico Chavez, Mohammad S. Siddiqui

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

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

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

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

MAFLD-TT-F0F1. **Conclusion:** Metabolomics and transcriptomic analysis allow us to discriminate MAFLD-HCC according to fibrosis severity. Our findings identified that CHKA and MBOAT7 could be proposed as biomarkers to MAFLD-HCC patients without or with low level of fibrosis. In addition, the different expression of CHKA support the idea that choline could be used as a more efficient tracer of PET-scan in MAFLD-HCC patients.

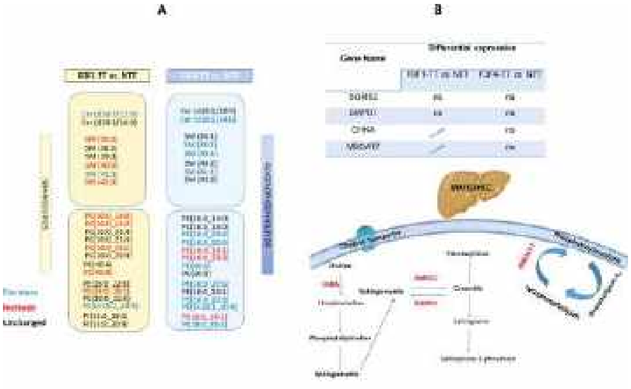


Fig. 1. (A) Two different lipid profiles of MAFLD-HCC according to fibrosis severity revealed by LC-MS. (B) SGMS2, SMPD1, CHKA and MBOAT7 gene expression level of MAFLD-HCC versus MAFLD-NTT in F0F1 and F3F4 by qRT-PCR.

Disclosures: The following people have nothing to disclose: Jihan Sun, Fatima Dahboul, Estelle Pujos-Guillot, Stéphanie Durand, Mélanie Petera, Delphine Centeno, Benoit Colsch, Zoulim Guillaume, Aicha Demidem, Armando Abergel

2023-A | CIRCULATING HEPATIC EXOSOMAL miR122 AS A BIOMARKER OF NAFLD/NASH ACTIVITY

Susan D Rouster, Carrie Jennings and Kenneth E Sherman, University of Cincinnati

Background: NAFLD/NASH is an important contributor to liver-related morbidity and mortality. There is a need for new biomarkers to define disease activity and disease stage. Hepatic exosomes or extracellular vesicles are lipid products of cell membranes. Isolation and evaluation of circulating hepatic microRNAs such as miR122 enveloped by exosomes may provide non-invasive measures to better assess disease and effect of treatment interventions. **Methods:** Serum samples from an IRB approved biorepository at the University of Cincinnati were utilized for this analysis. Clinical data and samples were available for both participants with NAFLD/NASH (NA) and healthy controls (HC). Hepatic exosomal RNA was isolated from serum using the Qiagen (Germantown, MD) miRNeasy Serum Advanced kit, with RNA spike-ins to monitor RNA isolation quality. RNA was then subjected to reverse transcription using the miRCURY LNA RT kit, including additional synthetic spike-ins to monitor cDNA synthesis and presence of inhibition. The resulting cDNA template was then amplified by qPCR using the Qiagen miRCURY LNA SYBR Green kit and miRNA PCR assays for each target (spike-ins, reference miRNA (*C. eleg* miR39), and liver-specific miRNA 122). Relative expression was determined using the $2^{-\Delta\Delta CT}$ method compared to the reference miRNA and reported as fold change from the HC group. **Results:** The study set included 27 participants with NAFLD/NASH and 8 healthy controls. The mean age of NAFLD/NASH participants was 56 years and mean age of HC was 44 years. Most participants were white, non-Hispanic (94%) and female (69%). The NA subjects had a mean BMI of 35.2, and an ALT of 47.8 U/L. The mean NASH Fibrosis Score (NFS) was 0.30. The mean hepatic exosomal miR122 fold change among NA was 17.6 (range 0.02 to 198.97) compared to HC. (ANOVA $<$ 0.05, One-tailed test). A linear regression model was utilized to explore factors associated with miR122 from hepatic exosomes, and yielded an $R^2 = 0.62$. ALT and AST were highly associated with exosomal miR122. BMI, FIB4, race, age, and gender were not significant factors in the model. Subjects with F3 liver fibrosis had a 43.1-fold increase in exosomal miR122 while F4 cirrhotic patients had only a 3.78 increase over the index controls. **Conclusion:** Exosomal miR122 may represent NAFLD/NASH inflammatory activity which declines once cirrhosis is established. Further exploration of this biomarker in defining disease activity may help identify candidates for therapeutic interventions that target the active necroinflammatory process.

Disclosures: Kenneth E Sherman – AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Helio: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Zydus: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Calliditas: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or

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

named investigator even if that individual's institution receives the research grant and manages the funds), No, No; MedPace: Consultant, No, No; Horizon: Consultant, No, No; Inovio: Consultant, No, Yes; Axcella: Consultant, No, Yes;
The following people have nothing to disclose: Susan D Rouster
Disclosure information not available at the time of publication: Carrie Jennings

2024-A | CIRCULATING SHORT-CHAIN FATTY ACIDS AND SEVERITY OF THE NON-ALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

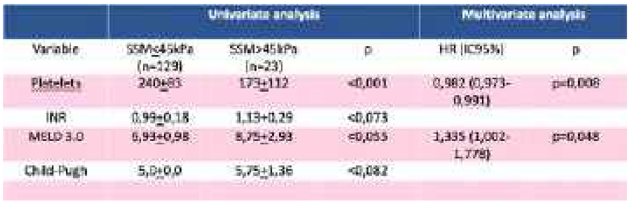
Chia-Yen Dai[1], Wei-Wen Hung[2], Hui-Ju Tsai[2,3], Wei-Chun Hung[3] and Yi-Chun Tsai[2,3], (1)Kaohsiung Medical University Hospital, Kaohsiung Medical University, (2) Kaohsiung Medical University Hospital, (3)Kaohsiung Medical University

Background: Non-alcoholic fatty liver disease (NAFLD) is a major global health concern. The increasing prevalence of NAFLD has been related to type 2 diabetes mellitus (T2D). The gut microbiota has frequently been linked to metabolic diseases such as NAFLD, diabetes, and obesity, and dysregulation of the intestinal microbiota (gut dysbiosis) can cause NAFLD. Short-chain fatty acids (SCFAs) are volatile fatty acids produced by intestinal bacteria to metabolize dietary fiber which involve glucose metabolism, insulin sensitivity, and lipogenesis through diverse pathways, thereby affecting the development of diabetes and obesity. The relationship between short-chain fatty acids (SCFAs) and NAFLD severity is ambiguous in T2D subjects. This study aimed to explore the association between SCFAs with the severity of NAFLD in T2D patients in Taiwan. **Methods:** We employed echography to examine the severity of hepatic steatosis. The serum levels of 9 SCFAs, namely formate, acetate, propionate, butyrate, isobutyrate, methylbutyrate, valerate, isovalerate and methylvalerate were measured using liquid chromatography mass spectrometry (LC-MS). Demographic data including the history of tobacco smoking, alcohol consumption and clinical data were collected through interviews and medical records at enrollment. **Results:** A total of 259 T2D patients (mean age: 61.4 ± 10.6 years; ranged from 25.4 to 88.1 years; 142 had no or mild NAFLD, and 117 had moderate to severe NAFLD) was enrolled in this cross-sectional study. The participants with moderate to severe NAFLD had lower levels of formate, isobutyrate and methylbutyrate than the those who without NAFLD or with mild NAFLD. Lower circulating levels of isobutyrate and methylbutyrate were associated with an increased severity of NAFLD. After adjusting for age, BMI **e** 27 kg/m2, T2D duration, Hb, GOT, GPT, log-formed TG, metformin usage, habit of smoking, alcohol drinking, history of hypertension, gout, and hyperlipidemia, the patients with low levels of circulating isobutyrate (odds ratio (OR): 0.17, 95% confidence index (CI): 0.03-0.86) and methylbutyrate (OR: 0.25, 95% CI: 0.08-0.76) levels had an increased risk of moderate to severe NAFLD. Negative correlations between circulating isobutyrate and methylbutyrate levels and the severity of NAFLD were found in men but not in women. In addition, a negative correlation between NAFLD severity with circulating isobutyrate and methylbutyrate levels was found independently of a glycated hemoglobin (HbA1C) level of 7.0%. **Conclusion:** Circulating levels of isobutyrate and methylbutyrate were significantly and negatively correlated with NAFLD severity in the enrolled T2D patients. SCFAs may be related to NAFLD severity in T2D patients.
Disclosures: The following people have nothing to disclose: Chia-Yen Dai, Wei-Wen Hung, Hui-Ju Tsai, Wei-Chun Hung, Yi-Chun Tsai

2025-A | CLINICAL UTILITY OF LIVER AND SPLEEN ELASTOGRAPHY IN THE MANAGEMENT OF PATIENTS LIVING WITH LIVER DISEASE

Carmen Lara Romero[1], Maria Del Barrio[2], Maria Del Carmen Rico[1] and Manuel Romero-Gómez[3], (1) Hospital Universitario Virgen Del Rocio, (2)Hopsital Universitario Marqués De Valdecilla, (3)Ucm Digestive Diseases, Virgen Del Rocio University Hospital, Instituto De Biomedicina De Sevilla, Ciberehd, University of Seville, Sevilla, Spain

Background: Portal hypertension (PH) is responsible for the progression of liver diseases and the development of complications. In patients with liver elastography < 10 kPa, advanced liver disease is ruled out according to Baveno VII consensus. Aims: a) To analyze the prevalence of portal hypertension and porto-sinusoidal vascular disease (PSVD) in patients with liver disease; b) Identify non-invasive parameters of suspicion of PSVD and/or hidden PH; c) Assess the clinical impact of the presence of elevated spleen stiffness in the development of complications. **Methods:** Prospective cohort of 276 consecutive patients seen in a hepatology consultation who underwent liver and splenic transient elastography (Fibroscan 630, Echosens, France). Thresholds for advanced disease were spleen stiffness measurement (SSM) > 45 kPa and Liver stiffness measurements (LSM) > 10kPa. It was evaluated: hepatic, renal, metabolic function, concomitant treatment, ultrasound, endoscopy, liver histology and portal hemodynamic. Statistical analysis: t-student, ANOVA, Chi-square, Spearman's coefficient, U-Mann-Whitney, Wilcoxon, logistic regression, and linear correlation. **Results:** SSM > 45kPa in 23 cases of 154 with LSM < 10kPa (14.9%) versus 56 of 122 with LSM > 10kPa (45.9%); p < 0.001). The predictive parameters of SSM > 45 kPa in patients with LSM < 10 kPa are collected in the table (platelets, INR, Child-Pugh and MELD3.0). In the multivariate analysis, the platelet count and MELD 3.0 were independently related to SSM > 45kPa and LSM < 10kPa. The rate of decompensation (hepatic encephalopathy, ascites, or variceal bleeding) was 1.5% in patients with LSM < 10 kPa and SSM < 45kPa (2/131), versus 13% (3/23) in patients with LSM < 10kPa and SSM > 45kPa, 15.4% (10/65) in patients with LSM > 10kPa and SSM < 45kPa and 44% (24/54) in patients with LSM > 10kPa and SSM > 45kPa; p < 0. 0001. **Conclusion:** The SSM can detect up to 15% of cases of occult PH/PSVD in patients with LSM < 10kPa and SSM > 45kPa. In patients with LSM < 10kPa, a decrease in platelet count or an increase in MELD 3.0 should lead to suspicion of PH. The presence of altered SSM is associated with an increased risk of liver events. The implementation of SSM will improve the management of patients with liver disease.



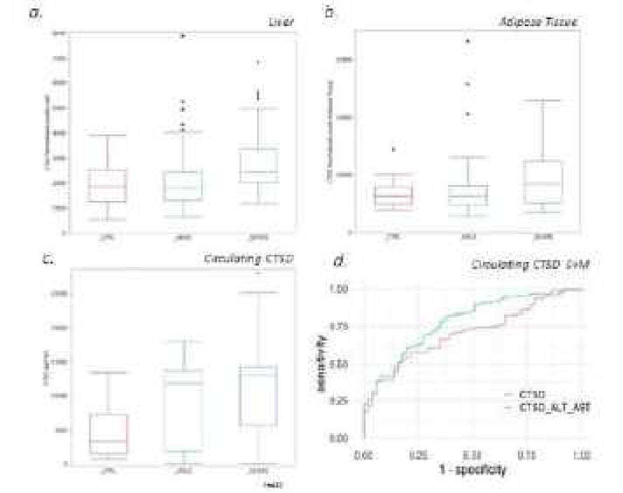
	Univariate analysis			Multivariate analysis	
Variable	SSM≤45kPa (n=129)	SSM>45kPa (n=23)	p	HR (IC95%)	p
Platelets	240±83	173±112	<0,001	0,982 (0,973-0,991)	p=0,008
INR	0,99±0,18	1,13+0,29	<0,073		
MELD 3.0	6,93±0,98	8,75±2,93	<0,053	1,335 (1,002-1,778)	p=0,048
Child-Pugh	5,0±0,0	5,75±1,36	<0,082		

Disclosures: Manuel Romero-Gómez – Gilead, Intercept, Siemens; co-inventor of Hepamet Fibrosis Score, DeMILI, and DeMILI 3.0: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; AbbVie, Alphasigma, Allergan, AstraZeneca, Axcella, BMS, Boehringer-Ingelheim, Gilead, Intercept, Inventia, Kaleido, MSD, Novo-Nordisk, Pfizer, Prosciento, RubiÃ³, Siemens, Shionogi, Sobi, and Zydus: Advisor, Yes, No;
The following people have nothing to disclose: Carmen Lara Romero, Maria Del Barrio, Maria Del Carmen Rico

2026-A | COMBINED HEPATIC AND ADIPOSE TISSUE TRANSCRIPTOMICS HIGHLIGHTS CIRCULATING NASH BIOMARKERS

Marica Meroni[1], Emilia Rita De Caro[1], Federica Chiappori[2], Miriam Longo[3], Erika Paolini[4], Ettore Mosca[2], Ivan Merelli[2], Rosa Lombardi[5], Sara Badiali[1], Marco Maggioni[6], Alessandro Orro[2], Alessandra Mezzelani[2], Luca Valenti[7], Anna Ludovica Fracanzani[5] and Paola Dongiovanni[6], (1)Fondazione Irccs Cà Granda Ospedale Maggiore Policlinico Milano (ITALY), (2)National Research Council (ITB-CNR), 20054 Segrate, Italy, (3)Fondazione Italiana Fegato, (4) Fondazione Irccs Cà Granda Ospedale Maggiore Policlinico, Milan, Italy., Milano, MI, Italy, (5)Università Degli Studi Di Milano, (6)Fondazione Irccs Cà Granda Ospedale Maggiore Policlinico, (7)Department of Transfusion Medicine and Haematology, Fondazione Irccs Ca' Granda Ospedale Maggiore Policlinico

Background: Obesity represents the main contributor to nonalcoholic fatty liver disease (NAFLD) and adipose tissue is strongly interlaced with the liver in the disease pathogenesis and progression. Previous studies were restricted to investigate the hepatic transcriptome across the entire spectrum of NAFLD, whereas the transcriptomic changes which occur in visceral adipose tissue (VAT) in relation to liver damage have been poorly investigated. Therefore, we aimed to compare hepatic and VAT transcriptome in NAFLD patients with the purpose to identify shared gene pathways and biomarkers useful for the diagnosis of advanced liver damage. **Methods:** We performed high-throughput RNA-sequencing in 167 hepatic samples from and in a subset of 79 matched adipose tissues, isolated from obese individual's who underwent bariatric surgery. Patients were subdivided in normal liver, mild and severe NAFLD, according to histology and NAFLD activity score (NAS). Circulating cathepsin D (CTSD), a marker of autophagy-lysosomal pathway was assessed by ELISA in serum samples collected at the time of the biopsy. **Results:** We identified a specific transcriptomic signature that may discriminate patients with mild and severe NAFLD, including 424 deregulated genes in liver and 209 in VAT. According to pathway and network analyses, inflammation, ECM remodeling and mitochondrial dysfunction were upregulated whereas oxidative phosphorylation was downregulated in both tissues. We highlighted 13 genes commonly deregulated in both tissues and among them, CTSD showed the most robust diagnostic accuracy in discriminating mild and severe NAFLD. In 52 of 167 obese subjects and in a validation cohort of 432 histologically-characterized NAFLD patients, increased serum CTSD was associated with steatosis, inflammation, steatohepatitis (NASH), fibrosis and NAS > 5. The area under the curve (AUC) adjusted for transaminases to foresee severe NAFLD *versus* mild and normal liver was 0.78 and 0.87, respectively. **Conclusion:** CTSD may be a possible biomarker of severe NAFLD since its hepatic/adipose tissue expression as well as circulating levels correlated with liver damage thus allowing to discriminate advanced disease.



Serum cathepsin D (CTSD) as possible biomarker to detect severe NAFLD. CTSD expression is stratified according to the severity of NAFLD in both liver (A) and adipose tissue (B). Boxes span from 25th to 75th percentile, while whiskers indicate the 10th and 90th percentile. Normal liver (CTRL) is plotted in red, mild in green, while Severe NAFLD in blue. CTSD serum concentration was evaluated in n=432 patients (Liver Clinic cohort) (C). p<0.05 at one-way ANOVA. ROC curves describe the accuracy of circulating CTSD (pg/mL) in foreseeing severe NAFLD from mild NAFLD (S+M) (D), obtained considering CTSD alone, or in a generalized linear model with transaminases (ALT and AST).

Disclosures: The following people have nothing to disclose: Marica Meroni, Emilia Rita De Caro, Federica Chiappori, Miriam Longo, Erika Paolini, Ettore Mosca, Ivan Merelli, Rosa Lombardi, Sara Badiali, Marco Maggioni, Alessandro Orro, Alessandra Mezzelani, Luca Valenti, Anna Ludovica Fracanzani, Paola Dongiovanni

2027-A | COMPARATIVE EFFICACY OF FIBROSIS-4, LIVER STIFFNESS MEASUREMENT, AND FIBROSCAN-AST SCORE TO PREDICT MAJOR LIVER-RELATED OUTCOMES IN NON-ALCOHOLIC FATTY LIVER DISEASE: AN INTERNATIONAL MULTICENTER STUDY

Yu JUN Wong[1,2], Esteban Urias[3], Michael W Song[4], Tanvi Goyal[3], Wei Xuan Tay[5], Nicole Xinrong Han[5], Jing Hong Loo[5], Tian Yu Qiu[5], Majd Aboona[6], Claire Faulkner[6], Karn Wijarnpreecha[7], Yiong Huak Chan[8] and Vincent Chen[9], (1)Department of Gastroenterology & Hepatology, Changi General Hospital, (2)Duke-Nus Medical School, Singhealth, (3)University of Michigan, (4)University of Michigan, Ann Arbor, (5)Changi General Hospital, (6)University of Arizona College of Medicine, Phoenix, AZ, (7)University of Arizona College of Medicine Phoenix, Phoenix, AZ, (8)Yong Loo Lin School of Medicine, National University of Singapore, Singapore, (9)University of Michigan Medical Center

Background: Non-invasive tests (NITs) such as FIB-4, liver stiffness measurement (LSM) by vibration controlled transient elastography (VCTE), and FibroscanAST (FAST) are frequently used for risk stratification in non-alcoholic fatty liver disease. However, when NITs yield discordant results, it remains unclear as to how such discrepancies should be interpreted. Furthermore, data on the impact of FAST score on the longitudinal outcomes of NAFLD patients remained unclear. We aim to evaluate the comparative performance of FIB-4, LSM and FAST score to predict 3-year clinical outcomes in NAFLD patients. **Methods:** We included consecutive adult NAFLD patients with VCTE performed between 2015-2022 from USA and Singapore. NAFLD patients stratified based on baseline FIB-4, LSM and FAST score were followed-up until clinical outcomes such as major liver-related outcomes (MALO: defined as liver-related events or death), liver-related events, death and major adverse cardiac events (MACE). **Results:** A total of 1,837 NAFLD patients (63% with obesity and 39% with diabetes) with VCTE were followed-up for median 3.5 years. Overall incidence rate per 1000 person-years for MALO, death and MACE was 6.3, 4.9, and 1.8, respectively. FIB-4 stratified NAFLD patients into low-risk (<1.3), intermediate-risk (1.3-2.67) and high-risk (>2.67) in 58.8%, 31.7% and 9.5%, respectively. No MALO occurred with baseline FIB-4 <1.3, regardless of LSM and FAST score. In fact, 10% of low-risk NAFLD patients by FIB-4 were misclassified as "high-risk" by VCTE. Higher FIB-4 was associated with higher risk of MALOs within each LSM category. FIB-4 was more accurate to predict the occurrence of MALO than LSM (*tAUC at 3 y: FIB4: 0.90 vs 0.79, p = 0.023; 5 y: FIB4: 0.89 vs 0.80 p = 0.035*) or FAST score (*tAUC at 3 y: FIB4: 0.90 vs 0.78, p = 0.014; 5 y: FIB4: 0.89 vs 0.72 p < 0.001*). All 3 scores had limited ability to predict MACE (*tAUC: 0.58-0.68*). Using NITs to identify low-risk NAFLD patients to be discharged to primary care, sequential FIB4/LSM testing identified 77.5% of low-risk patients, but missed 11.8% of MALO. Combination of FIB4/LSM reduces the missed MALO to 0%, but substantially reduced the proportion of low-risk patients identified to 41.3%. FAST score identified similar number of low-risk patients to combine FIB-4/LSM but missed more (22.2%) of MALO. **Conclusion:** In this multicenter international study, FIB-4 has good negative predictive value to identify low-risk NAFLD patients to be monitored in primary care setting. LSM results in false positive in 10% of low-risk NAFLD (FIB-4 <1.3) in whom none developed MALO or LRE, suggesting that LSM is not always superior in the setting of discordant NIT result. In moderate/high-risk NAFLD patients, FIB-4 and LSM synergistically predicted the risk of MALO, even among "high-risk" patients by VCTE. Our findings support the sequential approach of FIB-4 followed by VCTE as recommended by current guidelines.

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The following people have nothing to disclose: Esteban Urias, Karn Wijarnpreecha
Disclosure information not available at the time of publication: Michael W Song, Tanvi Goyal, Wei Xuan Tay, Nicole Xinrong Han, Jing Hong Loo, Tian Yu Qiu, Majd Aboona, Claire Faulkner, Yiong Huak Chan

2028-A | COMPARISON OF MAST, FAST, AND FIB-4 AS NONINVASIVE PREDICTORS OF FIBROTIC-NASH AND NASH

Xiao die Wei[1], Jing Zhang[2], Shi Qi[3], Xinxin Wang[4], Qiqige WuYun[5] and Nengwei Zhang[5], (1)Department of Hepatology, Beijing Youan Hospital, Capital Medical University, (2)Beijing Youan Hospital, Capital Medical University, (3)Department of Radiology, Beijing Youan Hospital, Capital Medical University, (4)Department of Pathology, Beijing Youan Hospital, Capital Medical University, (5)Department of Surgery, Capital Medical University Affiliated Beijing Shijitan Hospital

Background: Non-alcoholic steatohepatitis (NASH) and fibrotic NASH are key events in the course of non-alcoholic fatty liver disease (NAFLD). Recently, two predictors based on images have been proposed as non-invasive tests (NITs) with perfect efficiency, such as magnetic resonance imaging [MRI]- AST(MAST) and FibroScan-AST (FAST score), although they were not verified widely. This study aimed to validate their diagnostic accuracy and compare to fibrosis-4 (Fib-4) for detecting NASH and fibrotic NASH. **Methods:** The study involved 108 patients with biopsy-proven NAFLD undergoing contemporaneous Magnetic Resonance Elastography (MRE), MRI proton density fat fraction (MRI-PDFF), and FibroScan. NASH was diagnosed according to Non-alcoholic steatohepatitis-Clinical Research Network-Histologic Scoring System. Fibrotic-NASH was defined as NASH with fibrosis **e** 2 stage. **Results:** Of the entire cohort, 55.6% (n = 60) were male, with a median age of 38 (interquartile range: 31-48) years. The proportions of NASH and Fibrotic-NASH were 64.8% and 25.9%, respectively. For Fibrotic NASH detection, MAST (AUC 0.810, 95%CI 0.719-0.900) were comparable to FAST (AUC 0.782, 95%CI 0.689-0.874, p = 0.347) and both better than of FIB-4(0.626, 95%CI 0.502-0.751, both p < 0.001). When used as the rule-in criteria, the positive predictive value (PPV) of MAST (63.6%) was higher than that of FAST (40.0%) and FIB-4(50.0%). When used as the rule-out criteria, the NPV of MAST, FAST and FIB-4 were 58.8%, 27.5% and 47.6%, respectively. For the diagnosis of NASH, AUCs (95% CI) of MAST, FAST, and FIB-4 were 0.803 (0.719-0.886), 0.799 (0.708-0.892), and 0.635 (0.526-0.745), respectively (p = 0.930,0.002). When used as the rule-in criteria, PPV of MAST, FAST and FIB-4 were 100.0%, 83.3% and 83.3%, respectively.When used as the rule-out criteria, the NPV of was MAST, FAST and FIB-4 were 91.2% , 66.7% and 81.0% , respectively. **Conclusion:** The MAST score was better than FAST and FIB-4 for identifying patients of Fibro-NASH and NASH.

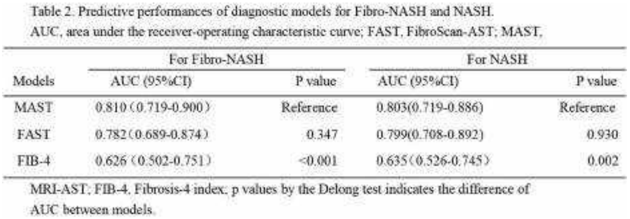


Table 2. Predictive performances of diagnostic models for Fibro-NASH and NASH.
AUC, area under the receiver-operating characteristic curve; FAST, FibroScan-AST; MAST,

	For Fibro-NASH		For NASH	
Models	AUC (95%CI)	P value	AUC (95%CI)	P value
MAST	0.810（0.719-0.900）	Reference	0.803(0.719-0.886)	Reference
FAST	0.782（0.689-0.874）	0.347	0.799(0.708-0.892)	0.930
FIB-4	0.626（0.502-0.751）	<0.001	0.635（0.526-0.745）	0.002

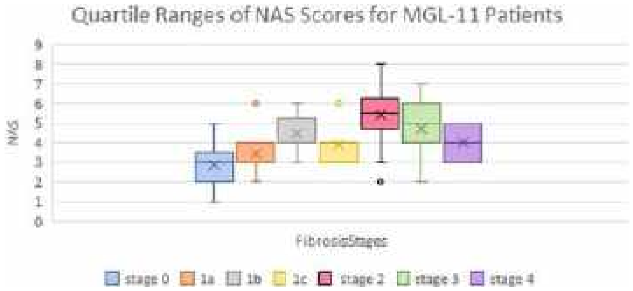
MRI-AST; FIB-4, Fibrosis-4 index; p values by the Delong test indicates the difference of AUC between models.

Disclosures: The following people have nothing to disclose: Xiao die Wei, Jing Zhang, Shi Qi, Xinxin Wang, Qiqige WuYun, Nengwei Zhang

2029-A | COMPARISONS OF LIVER BIOPSY FIBROSIS STAGING WITH NAFLD ACTIVITY SCORE (NAS)

Kirstan Franklin[1], Joshua T. Ghansiam[1], Jasmine Tidwell[1], Gabrielle Bachtel[1], Austin Vaughn[1] and Guy W. Neff[2], (1)Covenant Metabolic Specialists, LLC, (2) Tampa General Medical Group, Bradenton, FL

Background: The global incidence of NAFLD and NASH is increasing. Determining the severity and depth of these disorders is confounded by an assortment of conflicts about non-invasive testing (NIT) techniques and tissue demands. The liver biopsy process provides fibrosis, inflammation, steatosis grade, and ballooning in the liver, all of which translate to the NAFLD Activity Score (NAS). Identifying non-histologic pathways is imperative with the vast number of forthcoming patients in need of therapy. This project aims to compare liver biopsies fibrosis staging with resulted NAS in order to identify any correlations between the two sets of data. **Methods:** Data taken from our clinic over the previous 36 months was collected. Comparisons were done using subjects who had liver biopsies to see if fibrosis staging has any link to NAS. Data collected biopsy results to evaluate fibrosis and NAS values. **Results:** 86 patients had biopsies done and were chosen for analysis. Patients were categorized numerically according to their Fibrosis Staging, which varied from 0 to 4, and their NAS scores were compared. Though the data showed a favorable trend between liver fibrosis staging and computed NAS from stage 0 to 2, it was lost at stages 3 and 4. The broken trend might be due to the lack of patients with fibrosis stage 4 compared to the more abundant data for lower stages. **Conclusion:** The data examined and evaluated showed an optimal analysis to fibrosis staging and NAS up until stage 2, showing the presence of NAFLD and NASH. More research is needed to understand whether NAS characteristics are associated with particular indications based on fibrosis stage.



Disclosures: The following people have nothing to disclose: Kirstan Franklin

Disclosure information not available at the time of publication: Joshua T. Ghansiam, Jasmine Tidwell, Gabrielle Bachtel, Austin Vaughn, Guy W. Neff

2030-A | CONNEXIN 32 EXPRESSION AND ALPHA-SYNUCLEIN ACCUMULATION IN BALLOONING CELLS OF NON-ALCOHOLIC STEATOHEPATITIS (NASH) AND OTHER INFLAMMATORY LIVER DISEASES

Koichi Tsuneyama, Tokushima University Graduate School and Mayuko Ichimura-Shimizu, Department of Pathology and Laboratory Medicine, Institute of Biomedical Sciences, Tokushima University Graduate School, Japan

Background: Ballooning is a crucial pathological finding in the diagnosis of non-alcoholic steatohepatitis (NASH). However, it is often challenging to differentiate it from glycogen retention, hydropic degeneration, or fatty degeneration, making the diagnosis difficult. Cytokeratin 8/18 has been used to identify ballooning cells, but its effectiveness in detecting them accurately is limited. Therefore, there is a need for a marker that can precisely identify ballooning cells. Alpha-synuclein, a protein deposited in neurons in Parkinson's disease, has been found in various organs besides neurons. In our recent study (Kakimoto, et al., Pathol Res Pract 247 (2023) 154525), we reported that polyclonal antibodies against phosphorylated alpha-synuclein and ubiquitin selectively react with acidophilic aggregates in ballooning cells. The absence of a positive reaction with a monoclonal antibody against phosphorylated alpha-synuclein suggests that the acidophilic aggregates in ballooning cells may be denatured alpha-synuclein products degraded through the ubiquitin pathway. In this study, we compared the expression of connexin 32 and alpha-synuclein in the livers of patients with NASH and other inflammatory liver diseases. **Methods:** We utilized liver biopsy tissue samples from 20 patients with NASH, 10 patients with primary biliary cholangitis (PBC), and 10 patients with chronic hepatitis C. Immunohistochemical analysis was performed using polyclonal antibodies against phosphorylated alpha-synuclein and monoclonal antibodies against connexin 32. **Results:** Connexin 32 expression was uniformly observed on hepatocyte membranes in all PBC cases (10/10). However, in NASH, its expression was heterogeneous, showing attenuation or loss in 80% (16/20) of hepatocytes with fatty degeneration. Connexin 32 was strongly expressed in a portion of the hepatocyte membrane in many hepatocytes exhibiting ballooning. In chronic hepatitis C, 20% (2/10) of the cases showed heterogeneous expression of Connexin 32. The polyclonal alpha-synuclein antibody exhibited strong reactivity with eosinophilic aggregates in ballooning cells in NASH, but no positive reactions were observed in PBC or chronic hepatitis C. **Conclusion:** Although alpha-synuclein is physiologically taken up by hepatocytes through connexin 32, the expression of connexin 32 is heterogeneous in NASH, resulting in variations in alpha-synuclein uptake by hepatocytes from cell to cell. Abnormal accumulation of alpha-synuclein in neurons is known to contribute to Parkinson's disease and Lewy body dementia. Abnormal accumulation of alpha-synuclein in ballooning cells highlighted the importance of understanding the brain-liver association mediated by alpha-synuclein.

Disclosures: The following people have nothing to disclose: Koichi Tsuneyama, Mayuko Ichimura-Shimizu

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

2031-A | COST-EFFECTIVENESS OF DIFFERENT MODALITIES OF DIAGNOSING AND MONITORING INCREASED BURDEN OF NON-ALCOHOLIC LIVER DISEASE (NAFLD)

Abdullah Mubarak, Caleb Keng, James Gray, Sai Priya Metla and Mahnoor Fatima, Liver Center of Texas

Background: Early diagnosis of non-alcoholic steatohepatitis (NASH) and adequate staging of liver fibrosis can help manage patients at risk for NAFLD. A biopsy remains the gold standard for diagnosing NAFLD, but it is invasive in nature and expensive. The new Liver MultiScan (LMS) is an MRI scan used to diagnose NAFLD and can measure fat content and inflammation. Cost-effectiveness in diagnosing liver disease has been a recent concern, sparking ideas about moving away from biopsies to more non-invasive tools to diagnose NAFLD. **Methods:** 30 patients diagnosed with similar stages of NASH and received an LMS and Fibroscan from January 2021 and December 2022 were included in the analysis. 11 of the patients received a biopsy prior to receiving imaging. The standard deviation (SD) of LMS and fibroscan measurements of fat content and liver fibrosis were respectively compared. Secondly, the spreads of biopsy and non-biopsy patient groups on LMS fat content and fibrosis measurements were compared. Data from Healthcare Bluebook and online sources was used in identifying the average costs of various tools for monitoring NAFLD to address concerns about cost-effectiveness. **Results:** There are significant differences in the variability of the measurement of fat content between LMS and Fibroscan imaging with LMS results showing a significantly lower SD. There are significant differences in the variability of the measurement of liver fibrosis between LMS and Fibroscan imaging with Fibroscan results showing a significantly lower SD. Figure 1 shows that the spreads of the biopsy and non-biopsy data sets are similar in measuring fat content. The similar distribution of data suggests that datasets have similar variability. Figure 2 shows that the spreads of the biopsy and non-biopsy data sets are similar in measuring liver fibrosis. The similar distribution of data suggests that datasets have similar variability. Figure 3 shows the approximate costs for monitoring NAFLD: liver biopsy, $4000; liver multi scan, $1182; liver fibroscan, $135; and FIB-4, $14 (no data reported with FIB-4 in our analysis). **Conclusion:** Based on the spreads of fat content and liver fibrosis when biopsy and non-biopsy patients were compared, we concluded that non-invasive monitoring is cost-effective and a liver biopsy may not be necessary in most cases if LMS can identify NASH and NAFLD in a reliable way. There is not enough evidence to suggest that liver biopsies are obsolete, but the findings are consistent with past literature on the potential benefits of using non-invasive tools to diagnose NAFLD.

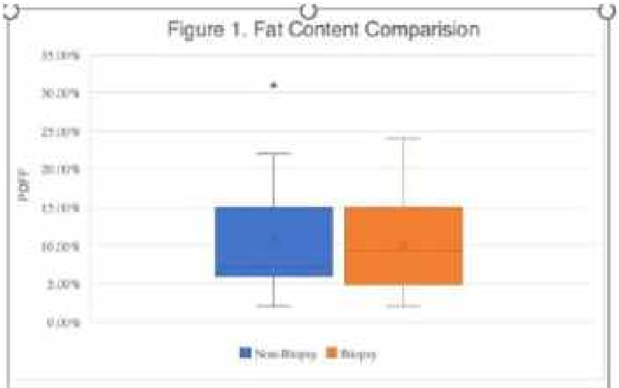


Figure 1. Fat Content Comparision

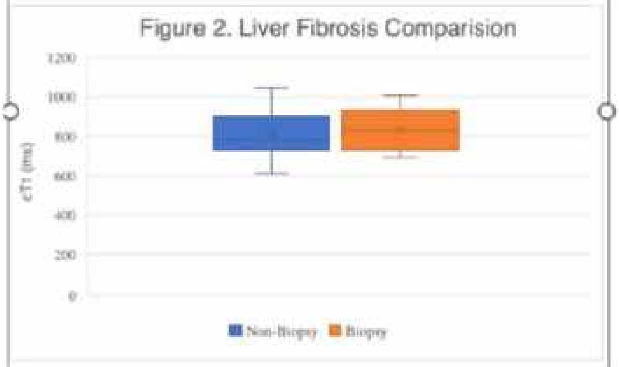
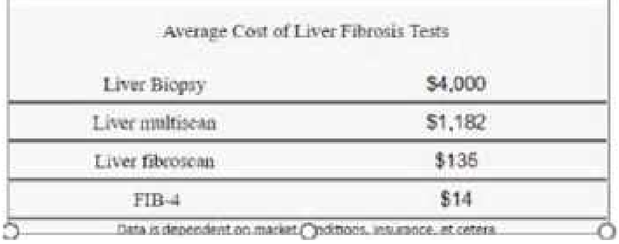


Figure 2. Liver Fibrosis Comparision


Average Cost of Liver Fibrosis Tests

Liver Biopsy	$4,000
Liver multiscan	$1,182
Liver fibroscan	$135
FIB-4	$14

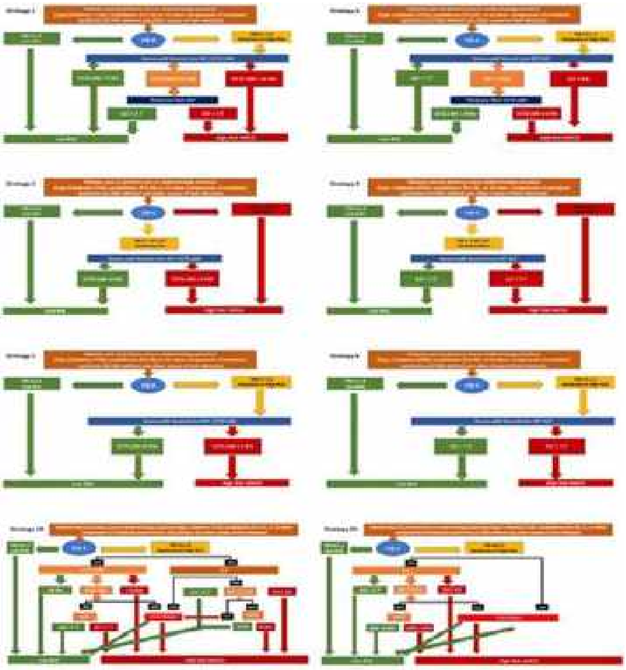
Data is dependent on market conditions, insurance, et cetera.

Disclosures: The following people have nothing to disclose: Abdullah Mubarak, Caleb Keng, James Gray, Sai Priya Metla, Mahnoor Fatima

2032-A | COST-EFFECTIVENESS OF IDENTIFYING HIGH-RISK NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) PATIENTS IN THE UNITED STATES (U.S)

Zobair M. Younossi[1,2,3], James M. Paik[2], Linda Henry[4], Richard F. Pollock[5], Maria Stepanova[4] and Fatema Nader[4], (1)Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, (2) Center for Liver Disease, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, VA, (3) Inova Medicine, Inova Health System, Falls Church, VA, (4)Center for Outcomes Research in Liver Diseases, Washington, DC, (5)Covalence Research Ltd

Background: American Association for the Study of Liver Diseases (AASLD), American Association of Clinical Endocrinologist (AACE), and European Association for the Study of the Liver (EASL) have established pathways to use non-invasive test (NITs) to identify high risk NAFLD. The cost-effectiveness of these pathways has not been established. Aim: To estimate the cost-effectiveness of different strategies to identify NAFLD with advanced fibrosis (AF) (**e** F3) using NITs. **Methods:** A cost-utility model for patients seen at primary care or endocrinology practices consists of a decision tree and Markov model. If patients had type 2 diabetes (T2D), prediabetes (Pre-D), or **e** 2 other components of metabolic syndrome (**e** 2-MS) without any other causes of liver diseases (viral hepatitis, alcoholic liver disease, excessive alcohol use), they entered a decision tree with 6 NIT screening strategies using first line and second line NIT testing. Markov model was used to simulate the natural history of NAFLD/NASH. Costs and health effects of 6 screening strategies were compared to no screening (Figure). The decision tree distributes patients between true and false positive and negative diagnoses based on the sensitivity and specificity of the diagnostic pathways. Prevalence of AF (12.20% in T2D, 4.87% Pre-D, and 4.91% **e** 2-MS) was obtained from the nationally representative sample of the U.S. population (National Health and Nutrition Examination, 2017-2020). The Markov model reflects the subsequent progression or regression across 10 health state and death in each year over 20-year time horizon. Direct medical costs were obtained from the Center for Medicare and Medicaid Services Fee Schedule 2023 and published data. Costs were reported in 2023 US dollars and a discount rate of 3.5%. Utility scores were based on EQ5D scores of patients with NAFLD and different disease stage. The results were a weighted average with weights equal to the distribution of T2D, Pre-D and **e** 2-MS (24.6%, 44.6%, and 30.8%). An additional scenario analysis was simulated considering the availability of VCTE and ELF tests at primary care, endocrinology and GI/Hepatology care in the U.S. **Results:** The decision tree that reported the lowest false positive diagnosis of AF was observed in strategy 1 (7.7%) versus strategy 2, 3, and 5 (11.7-12.7%), and strategy 4 and 6 (16.9-17.3%). In contrast, true positive (3.9-4.4%) and false negative (2.4-2.7%) were similar across the 6 strategies. The cost-utility model showed that all screening options were cost-effective as compared to no screening due to higher long-term cares cost of no screening arm (Table). Our findings remained robust in the additional scenario sensitivity analysis. **Conclusion:** In this economic evaluation, guidelines to identify high risk NAFLD appear to lead to net cost savings. While the results are specific to the U.S, the model can easily be adapted for other countries.



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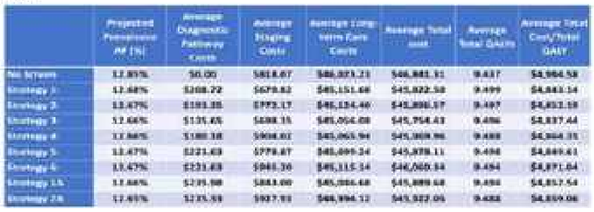


Disclosures: Zobair M. Younossi – Bristol Myers Squibb: Consultant, No, No; Gilead: Consultant, No, No; Intercept: Consultant, No, No; Novo Nordisk: Consultant, No, No; Terns: Consultant, No, No; Merck: Consultant, No, No; Quest: Consultant, No, No; Siemens: Consultant, No, No; Madrigal: Consultant, No, No;

The following people have nothing to disclose: James M. Paik, Linda Henry, Maria Stepanova

Disclosure information not available at the time of publication: Richard F. Pollock, Fatema Nader

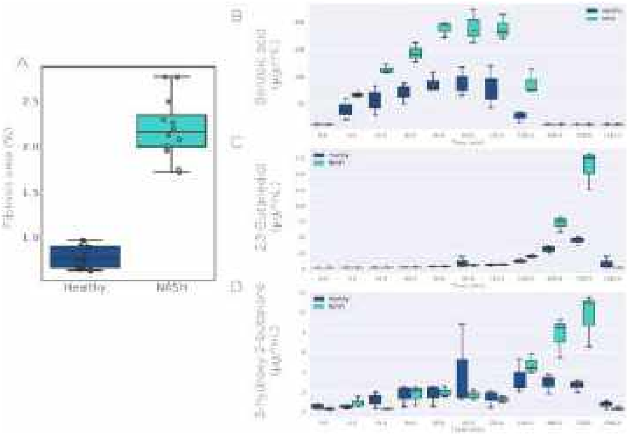
2033-A | DETECTION OF NASH INDUCED METABOLIC ALTERATIONS FOR FUNCTIONAL NON-INVASIVE DIAGNOSTICS

Giuseppe Ferrandino, Federico Ricciardi, Antonio Murgia, Max Allsworth, Billy Boyle, Karina Joyce and Olga Gandelman, Owlstone Medical

Background: Diagnosis and staging of non-alcoholic steatohepatitis (NASH) relies on liver biopsy, an invasive procedure that can lead to complications. Furthermore, histopathology analysis of liver biopsy provides only information on anatomical alterations, lacking insights into the functional impact of the disease on hepatic metabolic capacity. These limitations hinder

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

the efficacy evaluation of experimental drugs for NASH treatment. By using a rat model, we explored pharmacokinetic alterations induced by NASH that can be exploited for functional, non-invasive diagnostic purposes. **Methods:** A total of 12 Wistar Han rats were fed a normal diet (ND) and 12 a choline deficient high fat diet (CDHFD). After 8 weeks, liver fibrosis was assessed by liver biopsy. After 10 weeks, rats were split in four groups of 3 ND, and 3 CDHFD and orally administered by gavage with emulsions containing 2-pentanone, 2-butanol, benzyl alcohol, or other compounds, all known to be metabolized in the liver by specific metabolic pathways. Blood samples were collected before, and at different timepoints after administration, and expected bioproducts were quantified by mass spectrometry. **Results:** Rats fed a CDHFD showed 3 times higher area of liver fibrosis compared to ND rats (Fig. 1A), and impaired body weight gain as expected. Before administration all the assessed compounds showed levels close to background. Benzoic acid, a metabolic product of benzyl alcohol, generated by the alcohol dehydrogenase (ADH) pathway, and further metabolized to hippuric acid, showed a spike in blood 5 minutes after benzyl alcohol administration, with levels of 2-folds higher in CDHFD rats, up to 4 hours (Fig. 1B). Similarly, 2,3-Butanediol and 3-hydroxy-2-butanone, metabolic products of 2-butanol generated by ADH/CYPs pathways, showed higher levels, up to 3-fold increase in CDHFD 8 and 12 hours after administration of 2-butanol (Fig. 1C-D). A similar alteration was observed for 2-3 pentanediol, a metabolic product of 2-pentanone. **Conclusion:** The results reported here show that metabolic alterations induced by NASH cause changes in blood concentration of hepatic xenobiotic products. These changes could be used for diagnostic purposes. The assessed compounds are generally recognized as safe (GRAS), can be administered in large doses to humans, and are detectable in breath. Therefore, this approach has a translational application for NASH detection using a breath test.



Disclosures: Giuseppe Ferrandino – Owlstone Medical LTD: Employee, Yes, No;

Disclosure information not available at the time of publication: Federico Ricciardi, Antonio Murgia, Max Allsworth, Billy Boyle, Karina Joyce, Olga Gandelman

2034-A | DEVELOPMENT AND VALIDATION OF A NEW IMAGING BIOMARKER COMBINING DEMILI AND MRE TO IDENTIFY AT RISK NONALCOHOLIC STEATOHEPATITIS (AT-RISK NASH) PATIENTS

Isabel Fernandez-Lizaranzu[1], Rebeca Siguenza[2], Jiaxu Liang[1], Carmen Lara Romero[1], Sheila Gato[1], Rocio Montero-Vallejo[3], Maria Jesus Pareja[4], Rocio Aller[5], Javier Castell[6] and Manuel Romero-Gómez[7], (1) Instituto De Biomedicina De Sevilla, Ibis/Hospital Universitario Virgen Del Rocío/Csic/Universidad De Sevilla. Digestive Diseases Ucm and Ciberehd, (2) University Hospital Valladolid, (3)Instituto De Biomedicina De Sevilla, Ibis/Hospital Universitario Virgen Del Rocío, Huvr /Csic/Universidad De Sevilla Sevilla, Spain/Centro De Investigación Biomédica En Red (Ciberehd), Madrid, Spain, (4)Pathological Anatomy Service. Virgen Del Rocío University Hospital. Seville, Spain., (5)Digestive Diseases Department. Valladolid University Hospital. Department of Medicine. University of Valladolid, Valladolid, Spain, (6) Department of Diagnostic Radiology. Virgen Del Rocío University Hospital. Seville, Spain, (7)Ucm Digestive Diseases, Virgen Del Rocio University Hospital, Instituto De Biomedicina De Sevilla, Ciberehd, University of Seville, Sevilla, Spain

Background: Non-alcoholic steatohepatitis at risk (NASH with Fibrosis **e** 2) is a clinical priority, as these patients are at the highest risk of disease progression and will benefit most from pharmacologic treatment. In this study, we combined DeMILI 3.0 (Detection of metabolic liver injury method based on magnetic resonance imaging, MRI), that has shown promising accuracy in the identification of NASH, with Magnetic Resonance Elastography (MRE) to identify at-risk NASH patients and we compared it with available methods: FAST (FibroScan-aspartate aminotransferase scores), MAST (MRI-aspartate aminotransferase score) and MEFIB (MRE and FIB-4). **Methods:** Eighty-four patients recruited between 2020 and 2022 at 'Virgen del Rocio' University Hospital (Seville, Spain) were included as a prospective cohort. Main characteristics: 50% female, median age of 59 (±12) years, 32% (n = 27) patients were at-risk NASH. All patients underwent MRI, liver biopsy and laboratory testing. NASH and fibrosis were scored based on the SAF Histologic System. To identify at-risk NASH patients, a score was developed using Logistic Regression. MRE and DeMILI were conducted using a 3.0T scanner without contrast medium and four sequences were performed: SSFSE-T2 (Single Shot Fast Spin Echo T2-weighted), FAST-STIR (Fast Short inversion Time Inversion Recovery) and DYNAMIC, and MRE-SE-EPI (spin-echo echo planar imaging based MRE). To compute our score, liver ROIs (Regions of Interest) where selected at the MRI, then computed to obtain a NASH score for DeMILI and measured to obtain the mean liver stiffness values for MRE. DeMILI-MRE score were also calculated in an external validation cohort (n = 29) at Valladolid Clinical University Hospital (Valladolid, Spain). The diagnostic accuracy was evaluated by AUROC (the area under the receiver operating characteristic curves) and compared to FAST, MAST and MEFIB score using DeLong method. **Results:** In the derivation cohort (n = 27), DeMILI-MRE score demonstrated a high performance and discrimination with the optimal cut-off: -0.97, AUROC = 0.80 (95%CI 0.70-0.88), with a sensitivity (SE) of 81% and a specificity (SP) of 72%. In the validation cohort (n = 29), the DeMILI-MRE score showed AUROC = 0.76 (95%CI 0.57-0.90), SE = 85% and SP = 69%. Based on diagnostic criteria, all scores were transformed into categorical variables, the AUROC of DeMILI-MRE index > -0.97 was 0.77 (95% CI: 0.66-0.85), which exhibited better discrimination of at-risk NASH than MEFIB positive (MRE > 3.3kPa and FIB-4 > 1.6): AUROC = 0.64 (95% CI: 0.53-0.75), FAST score (> 0.67): AUROC = 0.60 (95%CI 0.49-0.71), and MAST score (> 0.242): AUROC = 0.60 (95% CI :0.48-0.71). **Conclusion:** Initial results with limited cohorts show that DeMILI-MRE score showed a good diagnostic performance identifying non-invasively at-risk NASH patients with the optimal cut-off -0.97. It seems to outperform previous biomarker scores.

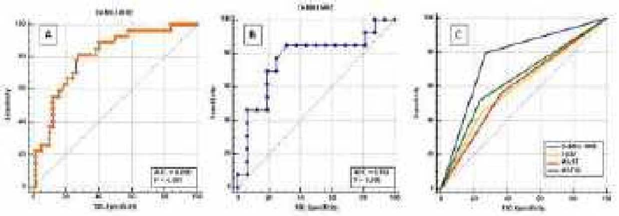


Figure: ROC curves of DeMILI-MRE score at (A) the derivation cohort (n=27), (B) the validation cohort (n=29); and (C) comparison of the diagnostic performance of different scores to identify at-risk NASH

Disclosures: Manuel Romero-Gómez – Gilead, Intercept, Siemens; co-inventor of Hepamet Fibrosis Score, DeMILI, and DeMILI 3.0: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; AbbVie, Alphasigma, Allergan, AstraZeneca, Axcella, BMS, Boehringer-Ingelheim, Gilead, Intercept, Inventia, Kaleido, MSD, Novo-Nordisk, Pfizer, Prosciento, RubiÃ³, Siemens, Shionogi, Sobi, and Zydus: Advisor, Yes, No;

The following people have nothing to disclose: Isabel Fernandez-Lizaranzu, Rebeca Siguenza, Carmen Lara Romero, Rocio Montero-Vallejo

Disclosure information not available at the time of publication: Jiaxu Liang, Sheila Gato, Maria Jesus Pareja, Rocio Aller, Javier Castell

2035-A | DEVELOPMENT OF A NON-INVASIVE DIAGNOSIS FOR FATTY LIVER IN CHILE: PRELIMINARY RESULTS

Maria Spencer Sandino[1,2], Franco Godoy[1,2], Claudio Vargas[3], Felipe Elorrieta[4], Laura Huidobro[2,5], Francisco Barrera[6] and Catterina Ferreccio[1,2], (1)Pontificia Universidad Católica De Chile, (2)Advance Center for Chronic Diseases, Accdis, (3)Hospital Posta Central, (4)Universidad De Santiago De Chile, (5)Universidad Católica Del Maule, (6)The University of Sydney

Background: Non-alcoholic fatty liver disease (NAFLD) is the most frequent chronic liver disease. NAFLD prevalence is estimated at 40% in Latin America and 47.5% in Chile in 2019. NAFLD causes 4,000 deaths in adults, representing 5% of total annual deaths, and Non-Alcoholic Steatohepatitis(NASH) is the primary cause of liver transplantation. NAFLD could be controlled if detected at earlier stages. Imaging techniques, biomarkers, and anthropometric measurements are the most commonly used diagnostic methods. However, imaging techniques are expensive and not accessible in poor areas in Latin America. This study aims to develop an algorithm that can identify the risk of NAFLD in a low-resource setting when no images are available. **Methods:** The study is nested in the MAUCO cohort, including 349 participants of the MAUCO+ lifestyle intervention aimed at preventing NAFLD and cardiovascular diseases, which included participants aged 45-60 years, with varying degrees of fatty liver; who were not taking medications that affect muscle mass or liver function, did not have severe disease or physical condition that could interfere the intervention. We analyzed the baseline data of all participants pre-intervention, including abdominal ultrasound (US), FibroScan, weight, height, waist circumference, AST, ALT, GGT, lipids, blood sugar, insulin, hemoglobin A1c, HOMA-IR, platelet count, and high-sensitivity C-reactive protein. We used ordinal logistic regression to predict the risk of fatty liver and its severity (0 = no risk, 1 = mild risk, and 2 = severe risk), with FibroScan as the gold standard. To evaluate the predictive performance, we validated our findings in five independent datasets using the k-fold cross-validation method in R. **Results:** Our model selected as predictors: sex, waist circumference, ALT, GGT, insulin, glycemia, and high-sensitivity C-reactive protein > 0.2 mg/dL. The algorithm predicts the absence of fatty liver with a specificity of 84%; the sensitivity for mild and moderate or severe fatty liver was 62% and 60%, and its corresponding specificity was 56% and 81%; Youden´s accuracy was 18% for mild disease and 41% for moderate or severe fatty liver. **Conclusion:** Our algorithm was easy and feasible for screening fatty liver, that is suitable for implementing in virtual platforms, but its accuracy needs improvement. The following steps are to improve the sensitivity of the gold standard by adding the measurement of liver fibrosis and to improve the sensitivity of the algorithm, including percentage of body fat, and evaluate a new version in a sample of 1,000 participants, which will be available for the 2023 AASLD Conference.

Disclosures: The following people have nothing to disclose: Maria Spencer Sandino, Franco Godoy, Claudio Vargas, Felipe Elorrieta, Laura Huidobro, Francisco Barrera, Catterina Ferreccio

2036-A | DEVELOPMENT OF A NOVEL CLINICAL SCREENING TOOL TO PREDICT LIVER FIBROSIS

Madeleine Haff[1], Na Wang[2], Emily Kate Sisson[2] and Michelle Long[1,3], (1)Boston Medical Center, Boston, MA, (2)Boston University, (3)Novo Nordisk

Background: Nonalcoholic fatty liver disease (NAFLD) is a major contributor to liver disease in the United States, and non-invasive tools such as vibration-controlled transient elastography (VCTE) estimate the risk of liver fibrosis and help guide patient care. Unfortunately VCTE is not readily available to all patients, as it requires specialized equipment and expertise. In our study, we developed a screening index that uses patient data that is readily available in the clinic to predict odds of significant fibrosis on VCTE. **Methods:** Logistic Least Absolute Shrinkage and Selection Operator (LASSO) regression was used to select clinical factors that best predict fibrosis (VCTE > 8 kPa) in 3013 participants in the Framingham Heart Study cohort. We excluded participants who had significant alcohol use, missing covariates, no VCTE, or unreliable or ineligible liver stiffness measurements. To evaluate predictive performance, we randomly split 70% as training data and 30% as test data for 100 times. We then used Delong's test based on area under the curve (AUC) to assess whether other additional clinically meaningful factors improved the predicted probability of the simple screening index, then used net reclassification index (NRI) to evaluate strength of model improvement. **Results:** In our cohort of 3013 participants, 54.8% were women and the mean age was 54.3 years (Standard Deviation (SD) 9.1). Mean Body Mass Index (BMI) was 28.4 kg/m^2 (SD 5.6), prevalence of diabetes was 8.2%, and the prevalence of suspected significant fibrosis (liver stiffness > 8.0 kPa) was 9.8%. In our analysis, among available patient characteristics, the most selective variables were BMI and having diabetes, along with systolic blood pressure (SBP), age, and sex. These characteristics formed our base model for predicting significant fibrosis, with AUC 0.7048. When alanine transaminase (ALT) or aspartate transaminase (AST) were added to the model, this significantly improved the predictive probability of the base model. This effect was strongest with AST, with AUC 0.7240 with p value 0.0044. The NRI indicated that 6.95% (95 CI 2.22-11.7%) of participants were correctly recategorized when AST was added to the model, with p value 0.0042. **Conclusion:** We developed a new screening index to predict significant liver fibrosis based on easily-measured patient demographic and biometric data (BMI, diabetes, SBP, age, sex, and AST). This tool may help identify patients at risk for complications of NAFLD, especially where VCTE is not available. Future studies are needed to validate this screening index and compare to existing indices.

Disclosures: Michelle Long – Novo Nordisk: Employee, Yes, No; Novo Nordisk: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

The following people have nothing to disclose: Madeleine Haff

Disclosure information not available at the time of publication: Na Wang, Emily Kate Sisson

2037-A | DIAGNOSTIC ACCURACY OF VCTE AND 2D-SWE IN BIOPSY-PROVEN NAFLD AND PERFORMANCE OF TWO-STEP APPROACHES TO PREDICT ADVANCED FIBROSIS

Madalina-Gabriela Taru[1,2], Dan-Corneliu Leucuta[2], Lidia Neamti[2], Anca Maniu[3], Vlad Taru[4], Bobe Petrushev[3], Ioana Rusu[3], Cristian Tefas[2,3], Petra Fischer[2], Andreea-Ioana Terec[5], Lucia Maria Procopciuc[2], Bogdan Procopet[2], Horia Stefanescu[3] and Monica Lupsor-Platon[2,3], (1)Department of Medical and Surgical Sciences, University of Bologna, 40126 Bologna, Italy, (2)Luliu Hatieganu University of Medicine and Pharmacy, 400012 Cluj-Napoca, Romania, (3) Octavian Fodor Regional Institute of Gastroenterology and Hepatology, 400162 Cluj-Napoca, Romania, (4) Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, (5)Niculae Stăncioiu Heart Institute, 400001, Cluj-Napoca, Romania

Background: Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) pose significant challenges to the healthcare system, and the

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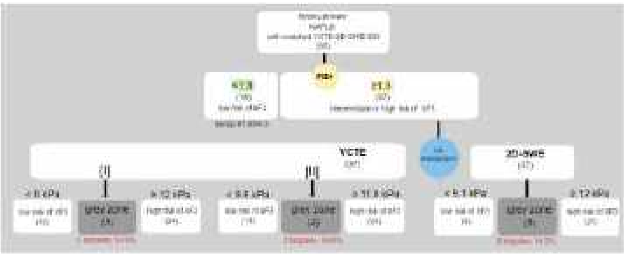
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

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



Disclosures: The following people have nothing to disclose: Madalina-Gabriela Taru, Dan-Corneliu Leucuta, Lidia Neamti, Anca Maniu, Vlad Taru, Bobe Petrushev, Ioana Rusu, Cristian Tefas, Petra Fischer, Andreea-Ioana Terec, Lucia Maria Procopciuc, Bogdan Procopet, Horia Stefanescu, Monica Lupsor-Platon

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

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

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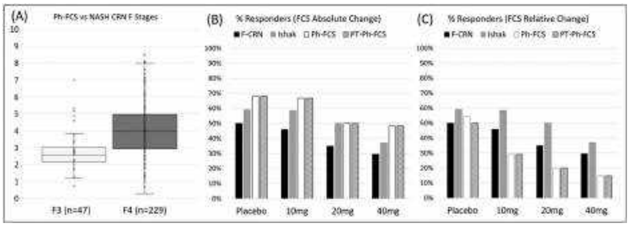
22, 24, 20, 27 for the placebo,10mg, 20mg, 40mg groups following removal of images considered non-evaluable for FibroNest algorithms (i.e., DBA < 5). Responders were identified with a 1-unit reduction for the histological stage (Fig. B-C). Using an absolute reduction of 0.3 (4-fold higher than the analytical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

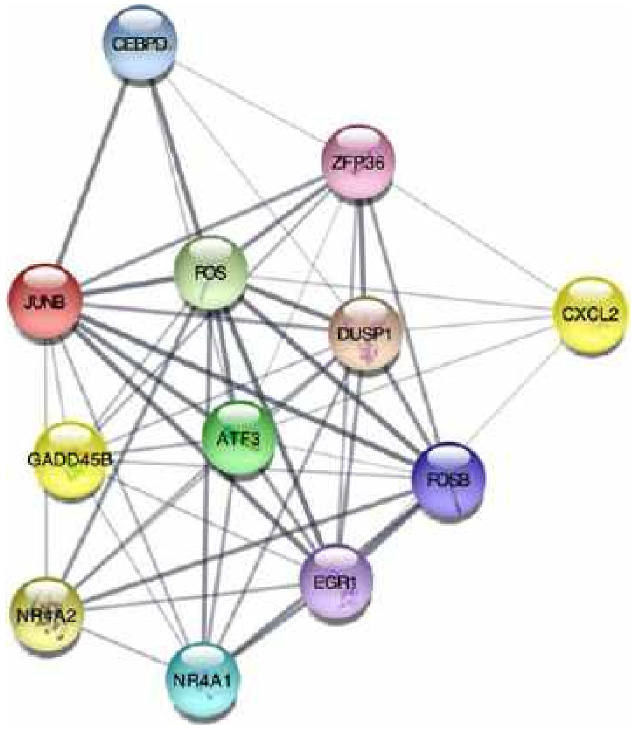


Disclosures: Li Chen – PharmaNest Inc: Employee, Yes, No; PharmaNest: Stock – privately held company (individual stocks and stock options), Yes, No;
Anne Minnich – Bristol Myers Squibb: Consultant, No, No;
Edgar D. Charles – Bristol Myers Squibb: Employee, Yes, No; Bristol Myers Squibb: Stock - publicly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

2039-A | DISCOVERY OF A 12-GENE SIGNATURE UNVEILS NEW CANDIDATE BIOMARKERS FOR NON-ALCOHOLIC FATTY LIVER DISEASE PROGRESSION

Maria Jimenez Ramos, Timothy James Kendall, Lucia Bandiera, Filippo Menolascina and Jonathan A Fallowfield, University of Edinburgh

Background: Non-alcoholic fatty liver disease (NAFLD) represents a global healthcare challenge, with an estimated prevalence of 32.4% worldwide and death rates predicted to increase in the coming years. To date, there are no qualified non-invasive biomarkers. We interrogated the human NAFLD RNA-sequencing (RNA-seq) database from SteatoSITE (https://steatosite.com/) to identify gene expression patterns across the NAFLD spectrum and link them to decompensation and mortality outcomes. **Methods:** We used bulk RNA-seq data generated from n = 579 NAFLD samples and n = 34 normal liver controls. Samples had been defined histologically as isolated steatosis or fibrosis stages F0/F1, F2, F3 and F4. Differentially expressed genes were subjected to Gene Set Enrichment Analysis (GSEA) to identify enriched biological processes/pathways. The common genes were uploaded to the STRING database in Cytoscape with a confidence score **e** 0.4. The most significant module was isolated from the major protein-protein interaction (PPI) network via the Molecular Complex Detection (MCODE) plugin. Gene Ontology (GO) annotations were determined for these hub genes. Through Kaplan-Meier analysis, we evaluated the link between the hub genes and both all-cause mortality and decompensation events. **Results:** GSEA of the dysregulated genes (274 in isolated steatosis, 232 in F0/F1, 477 in F2, 1113 in F3 and 2669 in F4) identified enriched pathways linked to extracellular matrix, cytokine-cytokine receptor interaction and metabolic pathways. 79 genes, shared among all NAFLD stages, were used to generate a PPI network. From these, MCODE identified one module comprising 12 hub genes (Figure) with significant network connectivity; some implicated in NAFLD pathobiology or liver fibrogenesis. These genes were linked to two key GO terms: p38 MAPK cascade and integrated stress response signalling. Network members were also significantly associated with risk of clinical outcomes, such as all-cause mortality (FOSB, EGR1, CEBPD, ZFP36, JUNB) and decompensation events (FOS, EGR1, NR4A1, JUNB). **Conclusion:** We used integrated bioinformatics analysis to identify a 12-gene signature associated with progression of NAFLD. Some of these genes exhibit significant correlations with all-cause mortality and decompensation events and may thus represent potential biomarker candidates or tractable therapeutic targets for NAFLD. External validation is required to confirm and further establish the significance of our observations.



Disclosures: The following people have nothing to disclose: Maria Jimenez Ramos, Timothy James Kendall Disclosure information not available at the time of publication: Lucia Bandiera, Filippo Menolascina, Jonathan A Fallowfield

2040-A | DISCOVERY OF AN EARLY DIAGNOSTIC BIOMARKER OF NONALCOHOLIC STEATOHEPATITIS (NASH)

Tanya Nguyen and Carla Nieser, Sapient

Background: Nonalcoholic steatohepatitis (NASH) is a complex, multifactorial disease. Our understanding of the pathophysiology that underlies progression from NAFLD to NASH is still incomplete, limiting development of mechanism-based therapies to treat NASH and slow disease progression. Herein we describe the discovery of a small molecule biomarker revealing potential drug targets, and that provides an early diagnostic for NASH by predicting disease development more than 10 years in advance. **Methods:** We applied next-generation high-throughput liquid chromatography-mass spectrometry (LC-MS) based methods for non-targeted metabolomics analysis to broadly measure > 45,000 small molecule biomarkers across samples derived from more than 10,000 individual’s in multiple independent studies around the world. Biocomputational analysis identified a number of molecules that are highly increased in individual’s who go on to develop

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

clinically apparent liver disease, and are increased with NASH score in an independent NASH registry study. These molecules were examined in a preclinical model distinguishing NASH from NAFLD to validate the mechanistic connection of the molecules with NASH. The validated biomarker was further investigated using Sapient's Human Biology Database, comprised of data from more than 100,000 biosamples across a large, diverse population. A genome-wide association study (GWAS) was performed to determine the genetic loci associated with the circulating level of the biomarker in humans. Mendelian randomization was further performed to evaluate the causal relationship between the biomarker and liver damage as indicated by alanine transaminase (ALT). **Results:** Through this large-scale population-level analysis with independent datasets, a single molecule was found to be robustly elevated with disease severity in patients with biopsy-proven NASH and was prioritized as a key diagnostic biomarker for subsequent validation in preclinical and human studies. Translation of the biomarker to a preclinical model found the molecule to be highly conserved, with animals that went on to develop NASH having a marked elevation in the biomarker even prior to pathologic evidence of liver inflammation. Biological validation in Sapient's Human Biology Database found this biomarker to be elevated > 10 years prior to formal diagnosis of NASH . The biomarker is causal to liver damage measured by ALT. It is stable over time and geographic location, but changes dynamically in obese patients after bariatric surgery with improvement in NASH. **Conclusion:** This biomarker has been validated in tens of thousands of individual's from around the world and found to represent a robust, non-invasive early diagnostic biomarker for NASH. Equally important, the biomarker may be causal to NASH and reveal new pathways that drive the development of liver disease that may represent new biological targets for NASH therapeutics.

Disclosures: The following people have nothing to disclose: Tanya Nguyen, Carla Nieser

2041-A | ECONOMIC IMPACT OF NON-INVASIVE TESTS FOR THE IDENTIFICATION OF PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

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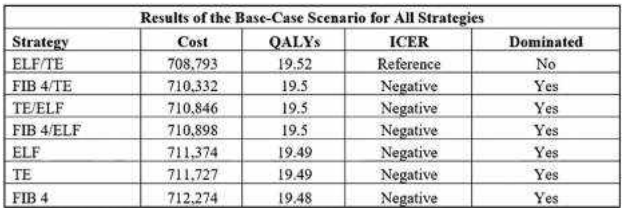
Background: Noninvasive tests (NITs) may facilitate detection of advanced fibrosis (AF) in nonalcoholic fatty liver disease (NAFLD) in the primary care setting (PCP) and may enable more efficient identification of afflicted patients. We developed a health economic model to evaluate the comparative effectiveness of diagnostic strategies employing currently available NITs. **Methods:** We developed a decision analytic model to assess the cost-effectiveness of diagnostic strategies to detect AF comparing the following 8 strategies: 1) FIB-4 only, 2) Enhanced Liver Fibrosis (ELF) only, 3) Transient Elastography (TE), 4) FIB-4 followed by ELF for indeterminant FIB-4 (FIB4/ELF), 5) FIB-4 followed by TE for indeterminant FIB-4 (FIB4/TE), 6) ELF followed by TE for indeterminant ELF (ELF/TE), 7) TE followed by ELF for indeterminant TE (TE/ELF), and 8) FIB-4 followed by ELF for indeterminant FIB-4 (FIB4/ELF). The downstream consequences following NITs were modeled according to AASLD 2023 guidelines. We employed a Markov state transition model to depict disease progression and long-term outcomes for a lifetime horizon. The primary outcomes were quality adjusted life years (QALYs) and cost in 2022 USD. **Results:** The results of the base-case scenario revealed that ELF/TE had the highest benefits (19.52 QALYs) and the lowest expected cost ($708,793) per patient. The FIB-4/TE, TE/ELF, & FIB4/ELF strategies yielded lower expected effectiveness (19.5; 19.5; 19.5 QALYs, respectively) and higher expected costs ($710,332, $710,846, $710,898, respectively) than ELF/TE. ELF, TE, and FIB-4 also yielded lower QALYs (19.49; 19.49; 19.48, respectively) at a higher cost per patient (711,374; 711,727; 712,274, respectively) compared with ELF/TE. Thus, the ELF/TE strategy had superior clinical outcomes and cost savings, thereby representing the dominant strategy. When the sensitivity of ELF was independently varied from 0 to 100%, ELF/TE was the most cost-effective strategy when ELF sensitivity exceeded 71.5%. In a probabilistic sensitivity analysis, the ELF/TE strategy remained cost-effective for all iterations when the willingness-to-pay threshold was varied from $0 to $200,000 USD. **Conclusion:** This study reveals that the ELF/TE strategy is the most cost-effective option to identify AF in NAFLD. Adoption of a cost-effective NIT strategy may facilitate effective use of scarce health-care resources along with efficient AF detection for patients who present to PCPs.



Results of the Base-Case Scenario for All Strategies

Strategy	Cost	QALYs	ICER	Dominated
ELF/TE	708,793	19.52	Reference	No
FIB 4/TE	710,332	19.5	Negative	Yes
TE/ELF	710,846	19.5	Negative	Yes
FIB 4/ELF	710,898	19.5	Negative	Yes
ELF	711,374	19.49	Negative	Yes
TE	711,727	19.49	Negative	Yes
FIB 4	712,274	19.48	Negative	Yes

Disclosures: Donald B Chalfin – Siemens Healthineers: Employee, Yes, No;
David Eric Bernstein – Ocelot Bio: Consultant, Yes, No;

Disclosure information not available at the time of publication: Maria X Sanmartin, Pina C Sanelli, Artem T Boltyenkov

2042-A | EICOSANOID LIPIDOMICS IMPROVES CARDIOVASCULAR RISK PREDICTION IN A PROSPECTIVE COHORT WITH BIOPSY-PROVEN NONALCOHOLIC FATTY LIVER DISEASE: A PILOT ANALYSIS

Robert M Wilechansky, Alessandra Grossman, Oluwafemi Balogun, Kathleen E. Corey and Tracey G. Simon, Massachusetts General Hospital

Background: Eicosanoid lipid species have been associated with cardiovascular disease (CVD) and may be useful biomarkers to identify patients with metabolic syndrome at risk for incident CVD. Given the overlap between metabolic syndrome and non-alcoholic fatty liver disease (NAFLD), it is possible that eicosanoids may also predict CVD events in patients with NAFLD, though this has not yet been elucidated. **Methods:** Targeted lipidomics analysis of 35 eicosanoid lipids was performed in a prospective cohort with biopsy-proven NAFLD and no CVD at baseline (n = 157). Principal component analysis identified a subset of ten lipids that explained most of the variation in the data. Multivariable (MV)-adjusted Cox proportional hazards regression identified lipids associated with incident CVD events (myocardial infarction, heart failure, stroke, peripheral vascular disease, arrhythmia) after adjusting for aspirin use and the ACC/AHA 10-year ASCVD risk score. Hazard ratios reflect a 1-standard deviation change in lipid concentration; false discovery rate (FDR) < 0.2 defined significance. To test the utility of clinical factors and eicosanoids for predicting incident CVD, we used a series of variable selection methods to construct MV models combining the ACC/AHA ASCVD risk score (base model) with clinical factors and eicosanoids. Models were optimized by 15-fold cross-validation and compared to the base model by C-index, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). **Results:** The cohort consisted of 52% women with a median follow-up of 9.4 years. After MV adjustment, two eicosanoid lipids were associated with incident CVD: 9-HETE (aHR 0.29, 95% CI 0.09-0.95, FDR = 0.15) and 11-HETE (aHR 5.38, 95% CI 1.1-26.3, FDR 0.15). There was a borderline association with 14-HDoHE (aHR 1.77, 95%CI 0.91-3.45, FDR 0.22). The base model for predicting incident CVD yielded a C-index of 0.71. The LASSO-Cox method had the highest C-index of 0.74 and included liver fibrosis severity, aspirin use, 11-HETE, and 14-HDoHE with the base model. The LASSO-Cox model resulted in NRI 0.39 (95% CI 0.22-0.59) and IDI 0.13 (95% CI 0.065-0.24), both $p < 0.0001$ compared to the base model. **Conclusion:** Targeted lipidomics identified eicosanoids associated with incident CVD risk in a prospective cohort of patients with biopsy-proven NAFLD. Eicosanoid lipidomics may be a valuable tool in combination with liver-specific factors for improving CVD risk prediction in NAFLD.

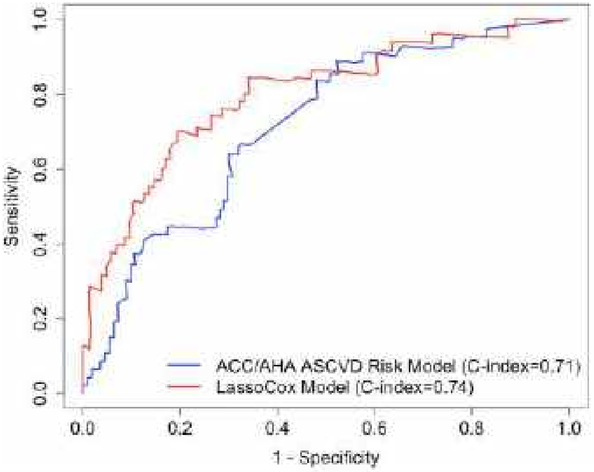


Figure 1: Receiver operating characteristic curves illustrating discriminatory ability of the base model (ACC/AHA ASCVD 10-year risk score) compared to the LASSO-Cox model (ASCVD Risk, fibrosis stage, aspirin use, 11-HETE, 14-HDoHE) in terms of 10-year risk prediction of cardiovascular events. ACC: American College of Cardiology; AHA: American Heart Association; ASCVD: atherosclerotic cardiovascular disease; LASSO: least absolute shrinkage and selection operator.

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Disclosure information not available at the time of publication: Kathleen E. Corey, Tracey G. Simon

2043-A | EVALUATING THE UTILITY OF NON-INVASIVE TESTS AS CONTINUOUS MEASURES OF HEPATIC FIBROSIS IN NAFLD

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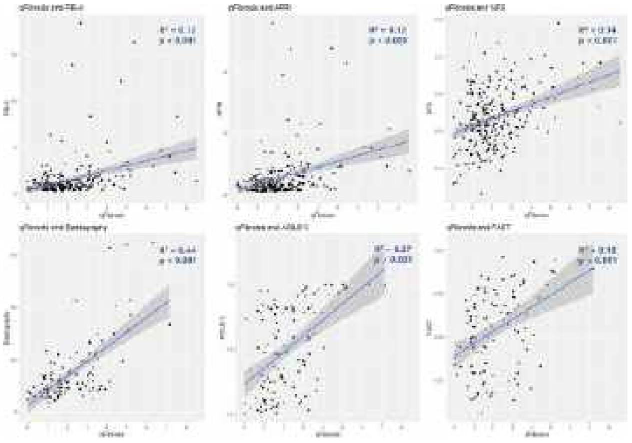
Background: Fibrosis in NASH is the only histological finding that correlates with liver related outcomes, and its improvement is a key outcome measure in assessing therapeutic trials in the disease. Fibrosis on histology is scored according to the Kleiner-Brunt system or the Steatosis-Activity-Fibrosis (SAF) system. However, these scoring systems are limited by their categorical nature, with challenges differentiating patients at the junction between stages. NIT's developed based on these "categorical bins" are only tested for categorical outcomes (eg. Advanced fibrosis). We aimed to correlate common NIT's with a validated novel continuous histological fibrosis score (qFibrosis), to determine the performance of the NIT's as continuous variables. **Methods:** Patients with biopsy-proven NAFLD were enrolled from National University Health System, Singapore. Patients with any other causes for their liver disease were excluded. Their biopsy specimens underwent an artificial intelligence-based quantitative evaluation for fibrosis (qFIBS by HistoIndex®, Singapore). Fibrosis-4 index (FIB-4), AST to Platelet Ratio Index (APRI), NAFLD Fibrosis Score (NFS), as well as vibration-controlled transient elastography (VCTE), AGILE 3+ and FibroScan-AST (FAST) score were measured. The relationship between histological scoring for fibrosis and qFib, as well as the relationship between NITs and qFib was evaluated by simple linear regression analysis. **Results:** 248 multi-ethnic Asian patients with biopsy-proven NAFLD were recruited to undergo qFIBS and non-invasive tests from 2014 to 2021. qFibrosis and histological score for fibrosis had a linear relationship with an R^2 of 0.39 ($p < 0.001$). qFibrosis was significantly correlated with all evaluated NITs (all p-values < 0.001), with respective R^2 values of 0.12, 0.12, 0.14, 0.44, 0.27 and 0.18 for FIB-4, APRI, NFS, VCTE, AGILE 3+ and FAST. On scatterplots, confidence intervals for the regression lines appear narrow in the qFibrosis range of 1-3. **Conclusion:** qFibrosis correlates well with pathologist-reported fibrosis scores. NITs may have a role as continuous measures of fibrosis in NAFLD, which may be used as more sensitive indicators of fibrosis progression or regression, or to evaluate response to therapy. Given the narrow confidence intervals at low to intermediate levels of fibrosis, NITs may perform well in such settings, where early intervention has greatest yield. However, serum NITs are limited in assessing stage differences due to their narrow dynamic range. VCTE is moderately correlated and with the highest dynamic range, and may potentially be the most useful NIT for evaluating degree of fibrosis as a continuous variable.



Disclosures: The following people have nothing to disclose: EN Ying Tan, Daniel Q Huang, Dean Tai, Elaine Lay Khim Chng, Yock Young Dan

Disclosure information not available at the time of publication: Xiang Xuan Eunice Tan, Jonathan Lee, Margaret Li Peng Teng, Nur Halisah Jumat, Mark Dhinesh Muthiah

2044-A | EVALUATION OF DIAGNOSTIC PERFORMANCE OF B-MODE ULTRASOUND USING ULTRASOUND-GUIDED ATTENUATION PARAMETER FOR LIVER STEATOSIS ASSESSMENT IN PATIENTS WITH CHRONIC LIVER DISEASE

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Background: B-mode ultrasound (B-USD) is commonly used for diagnosing fatty liver but has limitations in terms of sensitivity. Ultrasound-guided attenuation parameter (UGAP) is a novel ultrasound-based attenuation imaging method for non-invasive quantification of liver fat content. Recent study using a large cohort of patients with chronic liver disease (CLD) showed that the value of UGAP has excellent diagnostic accuracy for liver steatosis assessment according to the value of MRI-PDFF as a reference (*Clin Gastroenterol Hepatol. 2022*). Based on this background, current study was aimed to evaluate the diagnostic performance of B-USD using UGAP for liver steatosis assessment in patients with CLD. **Methods:** We retrospectively enrolled 379 patients with CLD (HCV/HBV/NAFLD/ALD/PBC. AIH/others: 90/99/63/40/31/56) who underwent both B-USD and UGAP. The diagnostic performance of B-USD for liver steatosis assessment, including bright liver (BL), deep attenuation (DA), hepatorenal echo contrast (HRC), and vessel blurring (VB), was independently examined by two experienced observers using UGAP as a reference value. **Results:** Interobserver agreement of two observers using the kappa statistic was analyzed, yielding the following values for BL, DA, HRC, and VB: 0.767, 0.604, 0.788, and 0.506, respectively. These values indicate that the agreement between the observers ranged from moderate to good. According to previous report, the cut-off value of UGAP for the diagnosis of grade 1, grade 2, and grade3 liver steatosis was defined as 0.650, 0.710, and 0.770 dB/cm/MHz, respectively. These cut-off values divided patients into several groups: 177 cases classified as grade 1 or higher (referred to as G1), 103 cases classified as grade 2 or higher (referred to as G2), and 50 cases classified as grade 3 or higher (referred to as G3). The diagnostic performance of four B-USD

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parameters was then assessed according to the value of UGPA as reference for G1, G2, and G3 of fatty liver using diagnostic accuracy, sensitivity, and specificity. The diagnostic accuracy of four parameters for G1 was as follows: 0.718 for BL, 0.662 for DA, 0.715 for HRC, and 0.623 for VB. The sensitivity of four parameters for G1 was as follows: 0.463 for BL, 0.282 for DA, 0.452 for HRC, and 0.198 for VB. The specificity of four parameters for G1 was as follows: 0.941 for BL, 0.995 for DA, 0.946 for HRC, and 0.995 for VB. These data suggest that B-USD has moderate diagnostic accuracy with high specificity and low sensitivity for G1. Specifically, the sensitivity of DA and VB remained low in G2 or G3:0.456 for DA and 0.320 for VB in G2, and 0.780 for DA and 0.540 for VB in G3. **Conclusion:** Our study showed that B-USD exhibits high specificity but low sensitivity in detecting mild steatosis. The data further suggest that UGAP could be an effective and objective tool to improve the sensitivity of B-USD.

Disclosures: The following people have nothing to disclose: Yuichi Yoshida

Disclosure information not available at the time of publication: Ayako Urabe, Masafumi Naito

2045-A | FIBROSCAN-AST (FAST) SCORE IS DIRECTLY RELATED TO PATIENT-REPORTED OUTCOMES, INCLUDING FATIGUE IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE: A GRAPHICAL MODEL ANALYSIS

Ryuki Hashida[1], Takumi Kawaguchi[2], Dan Nakano[1], Tsubasa Tsutsumi[1], Tomoya Sano[1], Keisuke Amano[1], Machiko Kawaguchi[1], Hiroshi Tajima[1], Hiroo Matsuse[1], Lynn Gerber[3], Zobair M. Younossi[4] and Koji Hiraoka[1], (1)Kurume University, (2)Kurume University School of Medicine, (3)Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, (4) Inova Health System

Background: Patients with non-alcoholic fatty liver disease (NAFLD) frequently report fatigue. While this is a patient reported outcome (PROs), it is associated with various factors including pathological findings such as hepatic inflammation and fibrosis. FibroScan-AST (FAST) score is a useful non-invasive tool to identify non-alcoholic steatohepatitis (NASH) patients with significant disease activity and fibrosis. We aimed to investigate the independent factors associated with PROs including fatigue for patients with NAFLD and their FAST scores. **Methods:** We enrolled 116 patients with NAFLD (age 57 [41-67], female/male 44/72). PROs were assessed by the Chronic Liver Disease Questionnaire (CLDQ)-NAFLD/NASH, which consist of 6 domains including fatigue. We defined each of domain scores < 6 were classified into the Impairment group. According to the total and fatigue domain scores of CLDQ-NAFLD/NASH, patients were classified by each domain, impaired PROs/non-impaired PRO (n = 74/42) and impaired fatigue/no fatigue (n = 96/20) groups. A cut-off value of 0.67 in the FAST score was used to categorize a high (significant disease activity) or low FAST score. Independent factors associated with impaired PROs and fatigue were analyzed using logistic regression analysis, decision tree analysis and graphical model. **Results:** Total CLDQ-NAFLD: In logistic regression analysis, the high FAST score was only identified as a negative independent factor for impaired total CLDQ-NAFLD (OR 5.9, 95% CI 1.11-31.20, p = 0.034). Age, gender, body mass index, estimated glomerular filtration rate, hemoglobin, and hemoglobin A1c (HbA1c) were not independent factors for the impairment of Total CLDQ-NAFLD. Decision-tree analysis showed that the FAST score was the initial classifier for the impaired total CLDQ-NAFLD. The impairment of total CLDQ-NAFLD was observed in 94.1 % and 56.5% of patients with a high FAST and a low FAST score, respectively. The graphical model revealed that FAST score, BMI, and age directly interact with impaired total CLDQ-NAFLD. Fatigue: Age and BMI were selected as factors for impairment fatigue in the logistic regression analysis. However, there was no significant factor for impairment fatigue. The high FAST score was the initial classifier for fatigue in decision-tree analysis. Fatigue was observed in 100%and 78.3% of patients with a high FAST and a low FAST score, respectively. The graphical model revealed that FAST score, BMI, eGFR, and age directly interact with fatigue. **Conclusion:** We found that the FAST score directly interacted with total CLDQ-NAFLD and the domain of fatigue. The FAST score may useful tool to assess impaired CLDQ-NAFLD.

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Zobair M. Younossi – Bristol Myers Squibb: Consultant, No, No; Gilead: Consultant, No, No; Intercept: Consultant, No, No; Novo Nordisk: Consultant, No, No; Terns: Consultant, No, No; Merck: Consultant, No, No; Quest: Consultant, No, No; Siemens: Consultant, No, No; Madrigal: Consultant, No, No;

The following people have nothing to disclose: Ryuki Hashida, Dan Nakano, Tsubasa Tsutsumi, Tomoya

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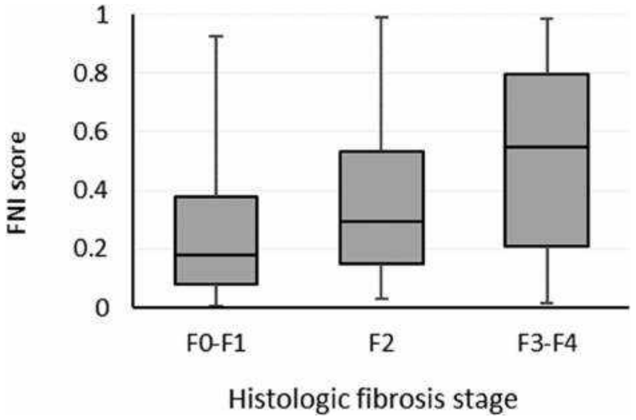
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Sano, Keisuke Amano, Machiko Kawaguchi, Hiroshi Tajima, Hiroo Matsuse, Lynn Gerber, Koji Hiraoka

2046-A | FIBROTIC NASH INDEX (FNI) IN DIABETICS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Pegah Golabi[1,2,3], James M. Estep[1,2,3], Sean Felix[1,2,3], Maria Stepanova[4], Soroor Owrangi[2], Brian P. Lam[1,2,3], Maria João Meneses[5], Andrei Racila[1,2,3], Laurent Castera[6], Maria Paula Macedo[5] and Zobair M. Younossi[1,2,3], (1)Center for Liver Disease, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, VA, (2)Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, (3)Inova Medicine, Inova Health System, Falls Church, VA, (4)Center for Outcomes Research in Liver Diseases, Washington, DC, (5)iNOVA4Health, NOVA Medical School|Faculdade De Ciências Médicas, NMS|FCM, Universidade NOVA De Lisboa; Lisboa, Portugal, (6)Department of Hepatology, Beaujon Hospital, AP-HP, Université Paris Cité, Inserm UMR1149, Clichy, France.

Background: Non-invasive tests (NITs) for identification of fibrosis in NAFLD patients are increasingly used in clinical practice. Performance of these NITs could be affected by presence of type 2 diabetes (T2D). Our aim was to assess performance of FNI score in NAFLD patients with T2D. **Methods:** Clinical and laboratory data for a cohort of patients with NAFLD and T2D were used to calculate FNI scores using their HDL, AST, and HbA1c values [low-risk (**d** 0.10) and high-risk (**e** 0.33)]. Patients' liver biopsy readings, liver stiffness measurements (LSM) by transient elastography, ELF and FIB-4 scores were available. **Results:** There were 531 NAFLD patients with T2D and FNI included: 55 ± 12 years old, 43% male, mean BMI 36.8 ± 9.1, 81% hyperlipidemia, 79% hypertension, mean ELF 9.48 ± 1.10, mean FIB-4 1.43 ± 0.91. Of all patients, 18% had low-risk FNI and 49% high-risk FNI scores. Patients with higher FNI scores had more hyperlipidemia (70% in low-risk vs. 84% in high-risk, $p = 0.0123$). There was significant correlation of FNI with ELF and FIB-4 (Spearman's rho = +0.23 and +0.36, respectively, $p < 0.0001$) and with LSM (rho = +0.31, $p < 0.0001$). In patients with liver biopsy ($n = 236$), there was significant association of FNI scores with histologic fibrosis: FNI (mean ± SD) = 0.26 ± 0.23 in F0-F1 (40% of the sample), 0.38 ± 0.29 in F2 (19%), and 0.52 ± 0.30 in F3-F4 (41%) (Figure). There was also significant association with elevated and high LSM: mean FNI 0.41 ± 0.29 in patients with LSM < 9 kPa vs. 0.50 ± 0.32 in LSM 9 to < 12 kPa vs. 0.56 ± 0.28 in LSM **e** 12 kPa ($p = 0.019$). The predictive performance of FNI for identification of advanced fibrosis (F3-F4) was as follows: area under the ROC curve (AUC) 0.71 (0.65-0.78); for the low-risk cutoff of 0.10, sensitivity (95% CI) 91.7% (84.2-96.3%), specificity 28.6% (21.3-36.8%), PPV 46.8% (43.8-49.8%), NPV 83.3% (71.0-91.1%); for the high-risk cutoff of 0.33, sensitivity 64.58% (54.2 - 74.1%), specificity 64.3% (55.8-72.2%), PPV 55.4% (48.7-61.8%), NPV 72.6% (66.3 - 78.1%). For comparison, ELF had AUC = 0.81 (0.74-0.89), and FIB-4 AUC = 0.83 (0.78-0.88) in the same sample of patients with NAFLD and T2D. **Conclusion:** The FNI score is associated with histologic fibrosis and its NIT surrogates such as ELF, TE and FIB-4 in NAFLD patients with type 2 diabetes.



Disclosures: Laurent Castera – Echosens: Speaking and Teaching, Yes, No; Novo nordisk: Speaking and Teaching, No, No; Echosens: Advisor, Yes, No; Novo nordisk: Consultant, No, No; Gilead: Consultant, Yes, No; MSD: Consultant, No, No; Madrigal: Consultant, No, No; Pfizer: Consultant, No, No; Sagimet: Consultant, No, No;
Zobair M. Younossi – Bristol Myers Squibb: Consultant, No, No; Gilead: Consultant, No, No; Intercept: Consultant, No, No; Novo Nordisk: Consultant, No, No; Terns: Consultant, No, No; Merck: Consultant, No, No; Quest: Consultant, No, No; Siemens: Consultant, No, No; Madrigal: Consultant, No, No;
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Disclosure information not available at the time of publication: Sean Felix, Maria Stepanova, Brian P. Lam, Maria João Meneses, Andrei Racila, Maria Paula Macedo

2047-A | GDF15 IS A NOVEL PREDICTIVE MARKER FOR DEVELOPMENT OF NAFLD-ASSOCIATED LIVER CANCER

Shusuke Kumazaki[1], Hayato Hikita[1], Yuki Tahata[2], Kenji Fukumoto[1], Kazuhiro Murai[1], Takahiro Kodama[2], *Naruyasu Kakita[3], Hirokazu Takahashi[4], Hidenori Toyoda[5], Goki Suda[6], Tomohide Tatsumi[1] and Tetsuo Takehara[2], (1)Osaka University, Graduate School of Medicine, (2)Osaka University Graduate School of Medicine, (3)Kaizuka City Hospital, (4)Saga University, (5)Ogaki Municipal Hospital, (6)Hokkaido University Hospital*

Background: The incidence rate of liver cancer in NAFLD patients is low, and there is a growing need for biomarkers that can effectively narrow down the high-risk patients of liver cancer development. In this study, we investigated whether serum GDF15, which we recently reported as a risk marker for liver cancer development in patients with chronic hepatitis C, is useful as a predictive marker of NAFLD-associated liver cancer. **Methods:** GDF15 levels were measured by ELISA using stocked sera. We investigated the relationship between serum GDF15 levels and hepatocarcinogenesis in 519 biopsy-proven NAFLD patients without a history of liver cancer (biopsy cohort). We also validated using another institutional cohort of 221 patients with clinically diagnosed NAFLD with or without biopsy (validation cohort). **Results:** In biopsy cohort, the median age was 61 years old, and the median observation period was 62 months. The median Fib-4 index was 1.82, 55% were NASH, and 26% had advanced fibrosis(F3-4). Serum GDF15 level was significantly higher in the NASH group than in the NAFL group, and significantly higher in the advanced fibrosis group. The median GDF15 level was 1.22 ng/ml, and total 22 patients developed liver cancer. Multivariate analysis using the Cox proportional hazards model identified Fib-4 (HR:1.68(1.43-1.96)) and GDF15 (HR:1.61(1.36-1.86)) as factors contributing to liver carcinogenesis. Using the Cut off value of serum GDF15 level of 1.75, based on the Youden index, cumulative liver cancer incidence was significantly higher in the high GDF15 group (154 patients), with 5-year liver cancer incidence rates of 9.7% and 0% in the high and low GDF15 groups, respectively. Even among 140 patients with Fib-4 > 2.67, cumulative liver cancer incidence was significantly higher in the high GDF15 group, with 5-year liver cancer incidence rates of 17.0% and 0% in the high and low GDF15 groups, respectively. Furthermore, the GDF15 high group had a significantly higher incidence of decompensated liver events, liver disease-related death, and overall mortality. In the validation cohort, the median observation period was 43 months, and 74 patients were classified in the high GDF15 group (> 1.75 ng/ml). Total 10 patients developed liver cancer. Cumulative liver cancer incidence was significantly higher in the high GDF15 group, with 5-year liver cancer incidence rates of 17.1% and 0.9% in the high and low GDF15 groups, respectively. Among 54 patients with Fib-4 > 2.67, the 5-year incidence of liver cancer in the GDF15 high group was 24.2%, whereas no one from the low GDF15 group developed liver cancer. The incidence rates of decompensated liver events, liver-related deaths, and overall mortality were significantly more frequent in GDF15 high group. **Conclusion:** In NAFLD patients, high serum GDF15 is a risk factor for liver cancer development.

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Disclosure information not available at the time of publication: Naruyasu Kakita, Goki Suda

2048-A | GENETIC ALGORITHMS REVEAL POTENTIAL TO STRATIFY NAFLD HETEROGENEITY

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Background: Non-alcoholic fatty liver disease (NAFLD) affects individual's worldwide. Identification of subtypes within NAFLD is crucial for personalized treatment. **Methods:** Here we employed genetic algorithms to subclassify a cohort of 849 patients previously classified into metabotypes of impaired VLDL secretion (A, n = 541) or increased VLDL secretion (C, n = 308)[1]. We aligned these patient metabotypes with two mouse models, Mat1a-KO and Ldlr-KO. **Results:** Using

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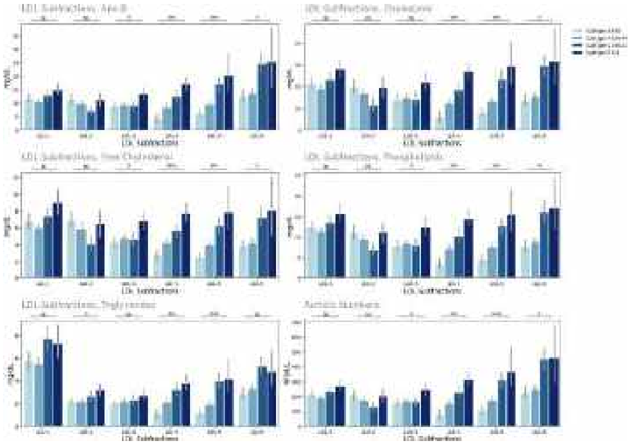
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

genetic algorithms, we successfully subclassified 112 of 541 patients (20.7%) as subtype A-M and 54 of 308 patients (17.5%) as subtype C-L. Notably, the patients stratified as A-M and C-L displayed lipid profiles resembling those observed in the Mat1a-KO and Ldlr-KO mouse models, respectively. Additionally, these stratified patients exhibited distinct lipoprotein profiles. Our findings suggest that utilization of genetic algorithms holds potential in identifying distinct metabotypes with NAFLD. Patients classified as A-M exhibit lower LDL levels than patients classified as C-L, especially in LDL-4, LDL-5 and LDL-6 subfractions. Apo-B: (LDL-4 p = 4.36E-04; LDL-5 p = 9.25E-04; LDL-6 p = 4.99E-02) Phospholipids: (LDL-4 p = 4.35E-04; LDL- 5 p = 9.27E-04; LDL-6 p = 9.97E-03) Particle Numbers: (LDL-4 p = 4.36E-04; LDL-5 p = 4.27E-05; LDL-6 p = 4.99E-02). The same effect was found in HDL subfractions. Apo-A1: (HDL-3 p = 4.27E-02; HDL-4 p = 9.86E-03) Phospholipids: (HDL-3 p = 5.42E-03; HDL-4 p = 7.73E-03). **Conclusion:** Our study demonstrates that the implementation of genetic algorithms enables the subclassification of NAFLD patients into distinct metabotypes associated with relevant mouse models. The characterization of patient subtypes based on genetic profiles and lipidomic patterns provides valuable insights for tailoring personalized treatment strategies. This approach has the potential to identify NAFLD patients who are more likely to respond favorably to pharmacological interventions validated through the use of specific targets. Further investigations are warranted to validate these findings and explore the clinical implications for improved management of NAFLD patients. [1]: Martínez-Arranz I, Bruzzone C, Noureddin M, et al. Metabolic subtypes of patients with NAFLD exhibit distinctive cardiovascular risk profiles. *Hepatology*. 2022;76(4):1121-1134. doi:10.1002/hep.32427



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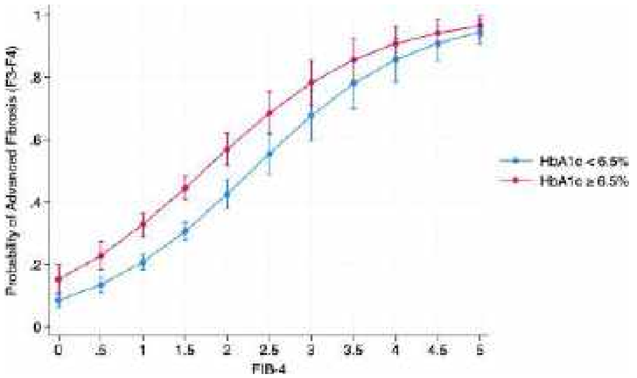
2049-A | GLYCEMIC CONTROL IMPACTS FIB-4 PERFORMANCE TO PREDICT ADVANCED FIBROSIS AND IS INDEPENDENTLY ASSOCIATED WITH THE PRESENCE OF HEPATOCYTE BALLOONING: COMBINED DATA FROM MULTIPLE THERAPEUTIC TRIALS INCLUDING MORE THAN 6,000 PATIENTS (IN COLLABORATION WITH NAIL-NIT CONSORTIUM)

Stephen A Harrison[1], *Julie Dubourg*[2], *Sophie Jeannin*[2], *Naim Alkhouri*[3], *Mazen Noureddin*[4] *and Jörn M. Schattenberg*[5], *(1)Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom, (2) Summit Clinical Research, San Antonio, TX, (3)Arizona Liver Health, Phoenix, AZ, (4)Houston Research Institute, Houston, TX, (5)I. Department of Medicine, University Medical Centre Mainz, Johannes Gutenberg University, Mainz, Germany, Mainz, Germany*

Background: Fib-4 was developed as a non-invasive biomarker to predict advanced fibrosis in other liver disease and was consequently adopted in non-alcoholic fatty liver disease (NAFLD) / nonalcoholic steatohepatitis (NASH) by international guidelines. Fib-4 is recommended as a biomarker to stratify NASH patients according to their risk of advanced disease. We aimed to assess the accuracy of Fib-4 and the impact of glycemic control on its performance in the clinical trial setting. **Methods:** We combined screening data from 7 NASH non-cirrhotic phase 2 trials. Advanced fibrosis was defined as fibrosis stages 3 or 4. Descriptive analysis, univariate and multivariate logistic regression and prediction of probabilities were performed. **Results:** Out of 6,558 patients, 2,123 with centrally read liver biopsy, Fib-4 and glycated hemoglobin (HbA1c) measurements were included. According to the American Association for the Study of Liver Diseases (AASLD) 2023 guidelines, the proportions of patients in the low-risk group (Fib-4 < 1.3), intermediate-risk group (Fib-4 1.3 – 2.66), and high-risk group (Fib-4 e 2.67) were 59%, 37%, and 4%, respectively. In the low-risk group, 20% of patients had advanced fibrosis (17% in HbA1c e 6.5% versus 28 % in HbA1c < 6.5%). In the intermediate-risk group, 47% of patients had advanced fibrosis (56% in HbA1c e 6.5% versus 41% in HbA1c < 6.5%). In the high-risk group, 63% of patients had advanced fibrosis (67% in HbA1c e 6.5% versus 58% in HbA1c < 6.5%). For each Fib-4 value, the probability of advanced fibrosis was increased in patients with HbA1c e 6.5% compared to those with HbA1c < 6.5% (Figure). In univariate analysis, both Fib-4 and HbA1c were associated with the presence of ballooning with increased Fib-4 and HbA1c values corresponding to higher probability of ballooning. After adjustment on age, gender, ethnicity, AST and Fib-4, HbA1c remained significantly associated with the presence of ballooning. For every 1% increase in HbA1c, the adjusted odds of hepatocyte ballooning increased by 1.6 (95% confidence interval: 1.4 – 1.8). **Conclusion:** Glycemic control as assessed by HbA1c is an independent predictor of hepatocyte ballooning and impacts the thresholds of Fib-4 to predict advanced fibrosis. The integration of glycemic control parameters within the Fib-4 score would increase its ability to predict advanced fibrosis in the NASH population.



Disclosures: Stephen A Harrison – Terns: Consultant, No, No; Viking: Consultant, No, No; Pinnacle Clinical Research: Executive role , No, No; Northsea: Consultant, No, No; Novartis: Consultant, No, No; Novo Nordisk: Consultant, No, No; Perspectum: Consultant, No, No; Poxel: Consultant, No, No; Sagimet: Consultant, No, No; Sonic Incytes: Consultant, No, No; Hepta Bio: Consultant, No, No; Hightide: Consultant, No, No; HistoIndex: Consultant, No, No; Intercept: Consultant, No, No; Madrigal: Consultant, No, No; Medpace: Consultant, No, No; NGM Bio: Consultant, No, No; Altimmune: Consultant, No, No; AstraZeneca: Consultant, No, No; Axcella: Consultant, No, No; Chronic Liver Disease Foundation: Consultant, No, No; Echosens: Consultant, No, No; Genfit: Consultant, No, No; Gilead: Consultant, No, No; GSK: Consultant, No, No; Hepion: Consultant, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; 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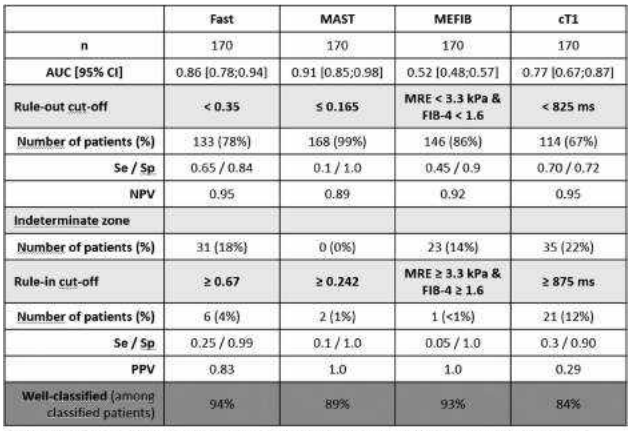
f 2050-A | HEAD-TO-HEAD COMPARISON OF FAST, MAST, MEFIB AND cT1 IN IDENTIFYING AT-RISK NASH PATIENTS IN A LOW-PREVALENCE POPULATION

Mazen Noureddin[1], Naim Alkhouri[2], Cassandra Chaldaureille[3], Julie Foucquier[3], Veronique Miette[3], Laurent Sandrin[3], Celine Fournier[3] and Stephen A Harrison[4], (1)Houston Liver Institute, Houston, TX, (2) Arizona Liver Health, Phoenix, AZ, (3)Echosens, (4) Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom

Background: The recently published AASLD practice guidance on the management of NAFLD patients recommend 4 non-invasive tests and associated cut-off values to rule-in and rule-out presence of "at-risk NASH": FAST, MAST, MEFIB (MRE + FIB-4) and cT1. The aim of this study was to compare the performances of these NITs using liver biopsy (LB) as the reference in a population with low prevalence of at-risk NASH patients. **Methods:** Patients referred for a routine colon cancer screening with no prior history of liver disease or alcohol abuse underwent a LB if LSM by VCTE **e** 7kPa, MRE **e** 3kPa, MRI-PDFF **e** 5% or cT1 **e** 780ms. LB were assessed by two expert pathologists in a double-blind manner with consensus, using the NASH CRN scoring system. At-risk NASH was defined by NAS **e** 4 with at least 1 in steatosis, ballooning, lobular inflammation and fibrosis stage F **e** 2. Diagnostic performances of NITs were assessed using Receiver Operating Curve (ROC). **Results:** 170 patients (40.6% females; mean ± SD age 55.9 ± 6.0 y; mean ± SD BMI 33.1 ± 4.9 kg/m^2) were included in this analysis. At-risk NASH was diagnosed in 11.8% of patients. Area under ROC (AUC) of MAST, FAST, MEFIB and cT1 were 0.91 [0.85;0.98], 0.86 [0.78;0.94], 0.52 [0.48;0.57], 0.77 [0.67;0.87], respectively. FAST outperformed cT1 in terms of AUC ($p = 0.045$), specificity for patients in the rule-out zone and positive predictive value (PPV) for patients with a score above the rule-in cut-off. MAST outperforms FAST, MEFIB and cT1 in terms of AUC ($p = 0.031$, $p < 1.10^{-4}$ and $p = 0.003$, respectively). The sensitivity of MAST and MEFIB at rule-out and rule-in cutoffs were numerically lower than FAST but had higher specificity. Moreover, the rate of at-risk NASH patients with a score above the high cut-off was higher for FAST compared to MAST and MEFIB. The percentage of well-classified patients was significantly higher for FAST compared to cT1 ($p = 0.015$). However, percentage of patients in the indeterminate zone was significantly lower for MAST than FAST, MEFIB and cT1 ($p < 1.10^{-4}$ in all cases) (Table). **Conclusion:** MAST and FAST have demonstrated superior performance in the identification of at-risk NASH patients. However, factors such as cost, and their correlation with histological changes and liver-related outcomes over time should be carefully considered when determining the optimal tests. Furthermore, the potential benefits of sequential testing warrant further investigation to establish their efficacy and reliability.



	Fast	MAST	MEFIB	cT1
n	170	170	170	170
AUC [95% CI]	0.86 [0.78;0.94]	0.91 [0.85;0.98]	0.52 [0.48;0.57]	0.77 [0.67;0.87]
Rule-out cut-off	< 0.35	≤ 0.165	MRE < 3.3 kPa & FIB-4 < 1.6	< 825 ms
Number of patients (%)	133 (78%)	168 (99%)	146 (86%)	114 (67%)
Se / Sp	0.65 / 0.84	0.1 / 1.0	0.45 / 0.9	0.70 / 0.72
NPV	0.95	0.89	0.92	0.95
Indeterminate zone				
Number of patients (%)	31 (18%)	0 (0%)	23 (14%)	35 (22%)
Rule-in cut-off	≥ 0.67	≥ 0.242	MRE ≥ 3.3 kPa & FIB-4 ≥ 1.6	≥ 875 ms
Number of patients (%)	6 (4%)	2 (1%)	1 (<1%)	21 (12%)
Se / Sp	0.25 / 0.99	0.1 / 1.0	0.05 / 1.0	0.3 / 0.90
PPV	0.83	1.0	1.0	0.29
Well-classified (among classified patients)	94%	89%	93%	84%

AUC: Area Under the ROC Curve; CI: confidence interval; Se: sensitivity; Sp: specificity; NPV: negative predictive value; PPV: positive predictive value.

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2051-A | IDENTIFICATION OF NAFLD SUBTYPES BASED ON TRANSCRIPTOME ANALYSIS: IMPLICATIONS FOR TARGETED THERAPIES

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

Background: Non-alcoholic fatty liver disease (NAFLD) is a complex condition with significant heterogeneity. The development of effective NAFLD drugs requires a deeper understanding of the disease's pathophysiology and identification of the appropriate target population based on specific mechanisms of action. This study aimed to propose NAFLD subtypes based on transcriptome analysis, enabling a more targeted approach to treatment selection. **Methods:** Liver tissue transcriptome data from 120 NAFLD patients were analyzed, and an additional validation cohort of 200 patients' transcriptome data from public databases was utilized. Non-negative matrix factorization (NMF) clustering was applied to classify the patients into optimized groups, and distinctive gene signatures representing each subgroup were extracted. **Results:** Three distinct patient groups were identified according to transcriptome analysis in training cohort (n = 120). Group 1 comprised individual's without underlying conditions such as hypertension and diabetes, displaying minimal liver fibrosis. Histologically, most cases were characterized by NAFLD without steatohepatitis or significant fibrosis, with upregulated expression of genes related to de novo hepatic fat synthesis. Group 2 consisted of patients with NAFLD and steatohepatitis, exhibiting advanced fibrosis and increased expression of genes associated with immune response and inflammation. Group 3 predominantly included NASH patients with diabetes and hypertension, as well as the highest fibrosis stage. This group exhibited activation of genes related to reactive oxygen species and fibrosis. Pathway analysis revealed specific upregulated and downregulated pathways in each group, serving as potential biomarker pathways for the three NAFLD subtypes. These findings were further validated in the independent public data cohort of 200 patients. **Conclusion:** Transcriptome analysis enabled the classification of NAFLD patients into three distinct subtypes, characterized by distinct gene expression patterns and specific pathway activation or suppression.

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2052-A | IDENTIFICATION OF NEW SEROLOGICAL BIOMARKERS FOR THE DETECTION OF SIGNIFICANT FIBROSIS

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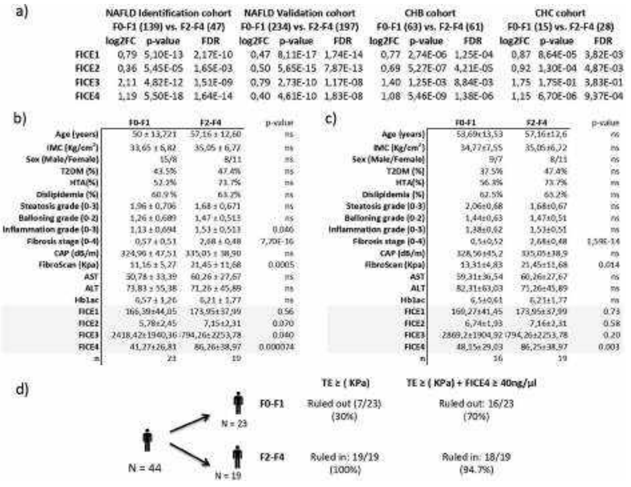
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Sheila Gato-Zambrano[1], Antonio Gil-Gómez[1], Angela Rojas[1], Victor Arroyo[6], Rebeca Siguenza[7], Joaquín Dopazo[5], Jordi Gracia-Sancho[3], Javier Ampuero[1] and Manuel Romero-Gómez[1], (1)Instituto De Biomedicina De Sevilla, Ibis/Hospital Universitario Virgen Del Rocío, Huvr /Csic/Universidad De Sevilla Sevilla, Spain/Centro De Investigación Biomédica En Red (Ciberehd), Madrid, Spain, (2)Biocritic Group/Department of Medicine, Dermatology and Toxicology, Universidad De Valladolid/ Gastroenterology Unit, Hospital Clínico Universitario De Valladolid, 47003, Valladolid, Spain/ Ciberinfec, Instituto De Salud Carlos III, Madrid, Spain, (3)Idibaps & Hospital Clínic Barcelona, Barcelona, Spain/Centro De Investigación Biomédica En Red (Ciberehd), Madrid, Spain., (4)Institute of Health Sciences of Castille and Leon (IECSCYL), 42002 Soria, Spain, (5)Área De Bioinformática. Fundación Progreso y Salud. Junta De Andalucía/ Centro De Investigación Biomédica En Red. Área De Enfermedades Raras (CIBERER), (6)Department of Medicine, Dermatology and Toxicology, Universidad De Valladolid, Valladolid, Spain, (7)Radiology Unit, Hospital Clínico Universitario De Valladolid. 47003 Valladolid, Spain

Background: Significant fibrosis is a clinically relevant endpoint that can be inferred by using a Transient Elastography (TE) cut-off of 8 KPa. This value, however, has low specificity and can lead to a large number of unnecessary referrals to specialized units. Objective: To find serological biomarkers able to improve the specificity of this cut-off to detect significant fibrosis (F2+) in patients with NAFLD and other liver diseases. **Methods:** Potential candidates were identified through the analysis of gene expression of liver biopsies coming from 1) NAFLD patients with or without histologically diagnosed significant fibrosis obtained by microarray [Identification cohort, 3 cohorts, F0-F1 (139) *vs*. F2-F4 (47)] and RNA-seq [Validation cohort, 4 cohorts, F0-F1 (234) *vs*. F2-F4 (197)] and 2) Patients with viral hepatitis induced by HBV [F0-F1 (63) *vs*. F2-F4 (61)] or HCV [F0-F1 (15) *vs*. F2-F4 (28)]. Differences in expression levels were filtered by FDR (**d** 0.05) and through a series of public datasets to retain exclusively secreted proteins able to reach the bloodstream. Common candidates were ranked according to p-value in each dataset and average ranking was used to select the final candidates. Circulating levels of selected candidates were independently validated in serum samples of NAFLD biopsy-proven patients (N = 42) by Enzyme-linked immunosorbent assay (ELISA). **Results:** Gene expression analyses identified 3 potential circulating biomarkers associated to significant fibrosis independent of aetiology (named as FICE1, 2 and 4 for Fibrosis Inducible Circulating Element) and one showing a strong significant association to fibrosis exclusively in NAFLD and CHB (FICE3) (Figure 1a). Preliminary ELISA analysis in NAFLD patients [F0-F1 (23) *vs*. F2-F4 (19)] indicates a significant association to F2+ of circulating levels of biomarkers FICE3 and FICE4 and suggests that circulating FICE2 might also be associated to significant fibrosis (Figure 1b). FICE4 was able to retain a strong association to significant fibrosis in a subanalysis in which only patients with a TE **e** 8 KPa were included [F0-F1 (16) *vs*. F2-F4 (19)] (figure 1c). FICE4 at a cut-off of 40ng/µl combined with TE **e** 8 KPa was able to retain a high ability to rule in significant fibrosis [94.7% (18/19)] compared to TE alone [100% (19/19)] and largely increased the ability to rule out patients without significant fibrosis [70% (16/23) vs 30% (7/23)] (Figure 1d). **Conclusion:** Our analysis has identified at least one circulating biomarker that might be useful to improve the ability of TE **e** 8 KPa to rule in and out the presence of significant fibrosis in patients with NAFLD. Validation in a larger number of samples and additional cohorts in which the leading cause of liver disease is caused by other aetiologies are currently ongoing.



a)

	NAFLD Identification cohort			NAFLD Validation cohort			CHB cohort			CHC cohort		
	F0-F1 (139) vs. F2-F4 (47)			F0-F1 (234) vs. F2-F4 (197)			F0-F1 (63) vs. F2-F4 (61)			F0-F1 (15) vs. F2-F4 (28)		
	log2FC	p-value	FDR	log2FC	p-value	FDR	log2FC	p-value	FDR	log2FC	p-value	FDR
FICE1	0,79	5,10E-13	2,17E-10	0,47	8,11E-17	1,74E-14	0,77	2,74E-06	1,25E-04	0,87	8,64E-05	3,82E-03
FICE2	0,36	5,45E-05	1,65E-03	0,50	5,65E-15	7,87E-13	0,69	5,27E-07	4,21E-05	0,92	1,30E-04	4,87E-03
FICE3	2,11	4,82E-12	1,51E-09	0,79	2,73E-10	1,17E-08	1,40	1,25E-03	8,84E-03	1,75	1,75E-01	3,83E-01
FICE4	1,19	5,50E-18	1,64E-14	0,40	4,61E-10	1,83E-08	1,08	5,46E-09	1,38E-06	1,15	6,70E-06	9,37E-04

b)

	F0-F1	F2-F4	p-value
Age (years)	50 ± 13,721	57,16 ± 12,60	ns
IMC (Kg/cm²)	33,65 ± 6,82	35,05 ± 6,77	ns
Sex (Male/Female)	15/8	8/11	ns
T2DM (%)	43.5%	47.4%	ns
HTA(%)	52.2%	73.7%	ns
Dislipidemia (%)	60.9 %	63.2%	ns
Steatosis grade (0-3)	1,96 ± 0,706	1,68 ± 0,671	ns
Balloning grade (0-2)	1,26 ± 0,689	1,47 ± 0,513	ns
Inflammation grade (0-3)	1,13 ± 0,694	1,53 ± 0,513	0.046
Fibrosis stage (0-4)	0,57 ± 0,51	2,68 ± 0,48	7,70E-16
CAP (dB/m)	324,96 ± 47,51	335,05 ± 38,90	ns
FibroScan (Kpa)	11,16 ± 5,27	21,45 ± 11,68	0.0005
AST	30,74 ± 33,39	60,26 ± 27,67	ns
ALT	73,83 ± 55,38	71,26 ± 45,88	ns
Hb1ac	6,57 ± 1,26	6,21 ± 1,77	ns
FICE1	166,39±44,05	173,95±37,99	0.56
FICE2	5,78±2,45	7,15±2,31	0.070
FICE3	2418,42±1940,36	794,26±2253,78	0.040
FICE4	41,27±26,81	86,26±38,97	0.000074
n	23	19	

c)

	F0-F1	F2-F4	p-value
Age (years)	53,69±13,53	57,16±12,6	ns
IMC (Kg/cm²)	34,77±7,55	35,06±6,72	ns
Sex (Male/Female)	9/7	8/11	ns
T2DM (%)	37.5%	47.4%	ns
HTA(%)	56.3%	73.7%	ns
Dislipidemia (%)	62.5%	63.2%	ns
Steatosis grade (0-3)	2,06±0,68	1,68±0,67	ns
Balloning grade (0-2)	1,44±0,63	1,47±0,51	ns
Inflammation grade (0-3)	1,38±0,62	1,53±0,51	ns
Fibrosis stage (0-4)	0,5±0,52	2,68±0,48	1,59E-14
CAP (dB/m)	328,56±45,2	335,05±38,9	ns
FibroScan (Kpa)	13,31±4,83	21,45±11,68	0.014
AST	59,31±36,54	60,26±27,67	ns
ALT	82,31±63,03	71,26±45,89	ns
Hb1ac	6,5±0,61	6,21±1,77	ns
FICE1	160,27±41,45	173,95±37,99	0.73
FICE2	6,74±1,93	7,16±2,31	0.58
FICE3	2869,2±1904,92	794,26±2253,78	0.20
FICE4	48,15±29,03	86,25±38,97	0.003
n	16	19	

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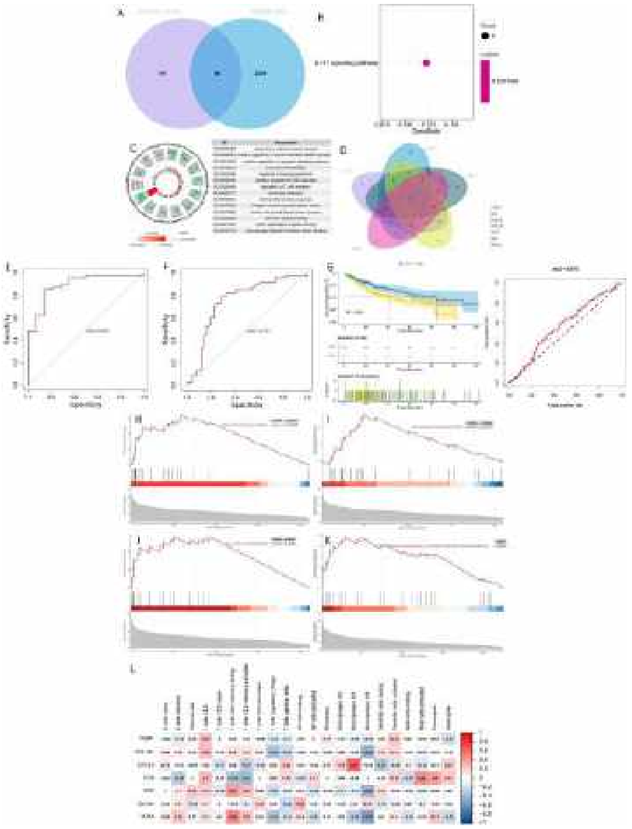
2053-A | IDENTIFICATION OF NOVEL HUB GENES THAT MAY PREDICT THE RISK OF LIVER FIBROSIS PROGRESSING TO HEPATOCELLULAR CARCINOMA IN NON-ALCOHOLIC FATTY LIVER DISEASE

Baiyi Liu[1], Xiaoxiao Wang[1], Rui Jin[2], Zilong Wang[1], Yuyun Song[1], Xiaohe Li[1], Feng Liu[1] and Huiying Rao[1], (1)Peking University People's Hospital, Peking University Hepatology Institute, Beijing Key Laboratory of Hepatitis C and Immunotherapy for Liver Diseases, Beijing International Cooperation Base for Science and Technology on NAFLD Diagnosis, (2)Peking University People's Hospital

Background: Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide and has been increasingly recognized as a contributing factor of hepatocellular carcinoma(HCC), in which liver fibrosis is a crucial stage. At present, the exact pathogenesis of liver fibrosis-related HCC in NAFLD has not been fully elucidated. In this study, we analyze the key genes related to liver fibrosis and HCC in NAFLD, aiming to predict the risk of liver fibrosis progressing to HCC in NAFLD. **Methods:** NAFLD fibrosis and NAFLD-related HCC datasets were selected for identifying differentially expressed genes (DEGs). The common genes of DEGs were taken out for GO and KEGG enrichment analysis, and protein-protein interaction(PPI) network were integrated to explore the potential function of the DEGs and hub genes. According to the hub genes, Lasso Cox regression analyses were performed to determine a gene model that was optimal for risk prediction of the progression of fibrosis to HCC in NAFLD. In order to evaluate the performance of the gene model , two data sets were analyzed, one for NAFLD fibrosis and NAFLD-HCC and the other for NAFLD fibrosis and NASH-HCC. Receiver operating characteristic curves (ROC) were used to evaluate model performance in these two HCC datasets. The enrichment analysis and tumor immune infiltration associated with high and low risk group were performed. **Results:** 559 DEGs in NAFLD fibrosis and 2164 DEGs in NAFLD HCC were identified. A total of 88 common DEGs were found. GO and KEGG enrichment analysis suggested that common DEGs were strongly associated with response to reactive oxygen spices, positive regulation of stress-activated MAPK cascade and apoptotic signaling pathway, IL-17 signaling pathway. Seven genes, including TIPM1, COL1A1, CXCL9, FOS, VWF, CD79A, VCAN, were identified as hub genes by the PPI network and then were used to construct a gene model. By the calculation of the gene model, the area under the receiver operating characteristic curves (AUCs) for risk prediction were 0.893 in the NAFLD-HCC dataset and 0.751 in the NASH-HCC dataset. Also, overall survival in the high-risk group was significantly shorter than that in the low-risk group in TCGA dataset. Gene set enrichment analysis(GSEA) indicated that the PPAR signaling pathway, insulin signaling pathway, fatty acid metabolism were significant up regulation in the high-risk group and negative regulation of intrinsic apoptotic signaling pathway was significant up regulation in the low-risk group. The positive correlation between CXCL9 and Macrophage M1 and negative correlation between VCAN and Macrophage M2 was strongly high in the high-risk group. **Conclusion:** The 7 hub genes may predict the risk of liver fibrosis developing into HCC in NAFLD and may mediate the potential molecular mechanism of NAFLD developing into HCC, which is hopeful to be biomarkers for predicting progression, diagnosis and treatment of diseases.



Disclosures: The following people have nothing to disclose: Baiyi Liu, Xiaoxiao Wang, Rui Jin, Zilong Wang, Yuyun Song, Xiaohe Li, Feng Liu, Huiying Rao

2054-A | IDENTIFYING NOVEL HEPATOCELLULAR CARCINOMA ONCOGENES IN NASH AND NAFLD PUBLIC DATA SETS

Mazen Almasry, University of Wisconsin Hospital and Clinics, Jihad Aljabban, University of North Carolina and

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

Maryam Panahiazar, University of California San Francisco

Background: Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of liver disease worldwide, with an estimated prevalence of 32.4%, which is set only to increase. 20-30% of NAFLD cases will progress to non-alcoholic steatohepatitis (NASH) and, ultimately, to cirrhosis and hepatocellular carcinoma (HCC). HCC may even arise outside the background of cirrhosis in 20% of cases. NAFLD is a growing cause of HCC, which remains a cancer with poor outcomes. Oncogenic changes may be present in earlier stages of NAFLD before cirrhosis. Identifying these changes may help risk stratify patients. **Methods:** We employed the Search Tag Analyze Resource for the GEO platform to search the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) to tag NAFLD and NASH samples. We conducted two separate meta-analyses of data from 62 NAFLD liver biopsies with 83 healthy liver biopsies and 187 NASH liver biopsies with 154 liver biopsies. Samples were taken from series GSE48452, GSE59045, GSE89632, GSE66676, and GSE107321 for the NAFLD meta-analysis and series GSE17470, GSE37031, GSE48452, GSE63067, GSE89632, and GSE83452. Novel HCC genes identified from recent, high-impact papers were compiled and compared to our dataset to characterize undescribed oncogenic changes in NAFLD. **Results:** We have found upregulation of several recently described oncogenes in HCC in our NAFLD and NASH datasets. These genes hold roles in cell division, metabolism, cellular signaling, and inflammation. Upregulated oncogenes included centrin 2 (CETN2, NASH p = 0.0113, NAFLD p = 5.41 E-8), acyl-CoA thioesterase 12 (ACOT12, NASH p = 0.00174, NAFLD p = 0.00661), annexin A4 (ANXA4, NASH p = 0.0401), tripartite motif containing 32 (TRIM32, NAFLD p = 2.21E-5), and the matrix metalloproteinases MMP6 (NASH p = 2.86E-4). **Conclusion:** As global cases of NAFLD expand, so will the consequences of the disease. One of the most morbid outcomes is HCC. Understanding of HCC is burgeoning, and novel oncogenes not previously or well-described in NAFLD may explain increased HCC risk in both the presence or absence of cirrhosis. Oncogenes illustrated in our dataset may serve to risk stratify NAFLD patients and motivate aggressive and earlier intervention.

Disclosures: The following people have nothing to disclose: Mazen Almasry, Jihad Aljabban, Maryam Panahiazar

2055-A | IFN-GAMMA IN THE BLOOD OF NAFL PATIENTS PREDICTS FATTY LIVER DETERIORATION

Ha Neul Kim[1], Hei-Gwon Choi[1], Soon Ok Kim[1] and Eun Hyuk Soo[2], (1)Chungnam National University, (2) Chungnam National University Hospital

Background: Non-alcoholic fatty liver (NAFL) is a liver disease in which fat accumulates more than 5% and is divided into Mild, Moderate, and Severe according to the severity of the fatty liver. There are no blood biomarkers that can identify the severity of fatty liver. NAFL progresses to Non-alcoholic steatohepatitis (NASH) by pro-inflammatory cytokines. It has been reported that interferon-gamma (IFN-γ) may play an important role in the progression of NASH. Therefore, IFN-γ expression was confirmed in the blood of patients according to the severity of fatty liver. **Methods:** The severity of fatty liver in NAFL patients was identified using magnetic resonance imaging (MRI) and Ultrasound (US) (IRB approval number: 2020–06-083). Peripheral blood mononuclear cells (PBMC) were isolated and analyzed using flow cytometry. The expression of IFN-γ was confirmed in the patient's blood and serum, and correlation with NAFLD scores was confirmed. In addition, the patient was followed up to confirm the change in IFN-γ. **Results:** In patients who underwent MRI-PDFF, CD8 T cell expression was increased in severe patients PBMC compared to normal PBMC. CD45^{+}IFN-γ^{+} NK cells increased according to the severity of fatty liver in patients who underwent ultrasound. In fibrosis progression by calculation of NFS, IFN-γ expression was increased. Patients were separated using NFS, in the intermediate group, NK cells, and CD45^{+} IFN-γ cells were increased compared to the F0-F2 group PBMC. CD45^{+}IFN-γ cells in NAFLD patients who followed every three months had a positive correlation with GGT. Serum IFN-γ was expressed low in patients with reduced BMI and correlated with NFS. Conversely, the serum IFN-γ expression of patients with increased BMI showed an increased pattern. BMI and serum IFN-γ levels of the patients followed up showed similar patterns. **Conclusion:** In conclusion, the expression of IFN-γ in the blood can be used as a practical serum biomarker to measure the severity of NAFL.

Disclosures: The following people have nothing to disclose: Ha Neul Kim, Hei-Gwon Choi, Eun Hyuk Soo
Disclosure information not available at the time of publication: Soon Ok Kim

2056-A | IL-18 AND IL-18BP AS NON-INVASIVE BIOMARKERS OF NASH IN A BARIATRIC PATIENT COHORT

Christian Stoess[1], Janset Onyuru[1], Trevor Crafts[2], Ola Leszczynska[1], Alexander Wree[3], Daniel Hartmann[4], Helmut Friess[4], Bruce Wolfe[2], Andrea Stroud[2], Hal Hoffman[1] and Ariel E. Feldstein[1], (1)University of California, San Diego, (2)Oregon Health and Science University, Portland, (3)Charité, Berlin, (4)Technical University of Munich, Munich

Background: Non-alcoholic fatty liver disease (NAFLD) is a prevalent condition in individual's with obesity. A critical stage in the progression of the disease is the transition from hepatic steatosis to non-alcoholic steatohepatitis (NASH). Liver biopsy is currently the gold standard for diagnosing NASH. Non-invasive biomarkers are needed to identify high-risk patients. Interleukin-18 (IL-18) is released during pyroptosis, a lytic cell death known to be involved in the development of NASH. Here, we investigated the role of IL-18 and its antagonist IL-18 binding protein (IL-18BP) as potential non-invasive biomarkers for NASH. **Methods:** A total of 179 serum samples were collected at the preoperative time point. All patients included in the study underwent liver biopsy either by needle sampling or wedge resection during bariatric surgery. Serum samples were measured using the human IL18 Bpa DuoSet ELISA (DY119, R&D Systems) and the human total IL-18 DuoSet ELISA (DY318-05, R&D Systems) according to the manufacturer's instructions. Histologic evaluation was performed by a pathologist according to the NASH Clinical Research Network classification system. **Results:** Serum IL-18 and IL-18BP levels were significantly higher in patients with a NAS score **e** 4 than in subjects with a NAS score <4 ($p<0.05$ and $p<0.001$). Serum IL-18BP alone showed a diagnostic accuracy for NASH with an AUROC of 0.64 (95%CI 0.54-0.74, $p<0.05$) and 0.68 for a NAS score **e** 4 (95%CI 0.59-0.76, $p<0.0001$). Serum IL-18 detected a NAS score **e** 4 with an AUROC of 0.63 (95%CI 0.53-0.72, $p=0.012$). To better understand the association of serum of IL-18 and IL18-BP levels with the different histological components of NASH, we examined correlations with fibrosis, steatosis, inflammation, and ballooning. We observed significantly elevated serum IL18-BP levels in patients with advanced stages of fibrosis compared to patients without fibrosis. Grouping of patients with fibrosis stage 0-1 vs. 2-3 resulted in significant discrimination of these two groups ($p<0.01$). IL-18 and IL-18BP levels were both increased in specimens with advanced lobular inflammation. The association of serum IL-18BP with known markers of NASH progression, including AST, ALT, BMI, and triglycerides was tested. Serum IL-18BP levels showed a moderate correlation with the plasma AST level ($r=0.41$, $p<0.0001$) and ALT ($r=0.36$, $p<0.0001$). Meanwhile, serum IL-18BP levels exhibited a weak correlation with triglycerides ($r=0.25$, $p<0.0001$). Binary logistic regression revealed that IL-18BP independently predicted NASH ($p=0.016$) and a NAS score **e** 4 ($p<0.001$) in our patient cohort whereas IL-18 predicted a NAS score **e** 4 ($p=0.011$). **Conclusion:** IL-18 and IL-18BP are associated with pathological parameters of NASH and can predict a high NAS score in patients with obesity. Both, IL-18 and IL-18BP can potentially serve as biomarkers for NASH.

Disclosures: Hal Hoffman – Novartis and Kiniksa: Consultant, No, No;

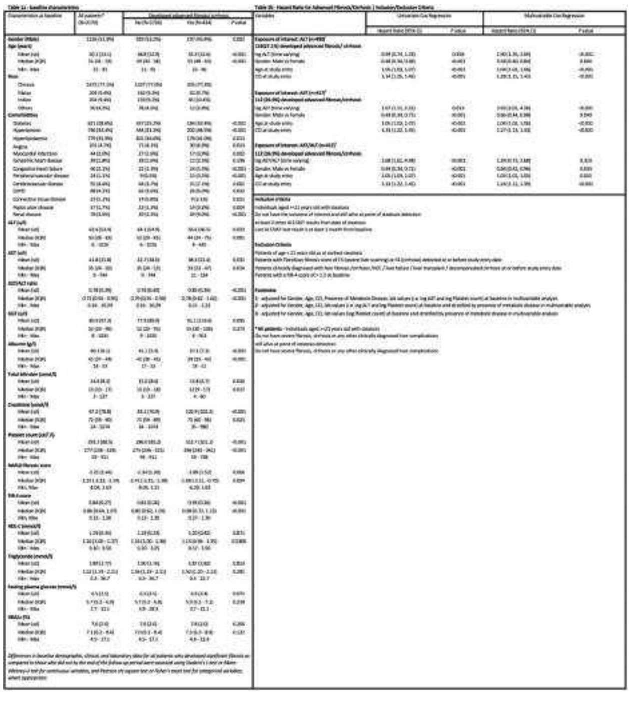
Ariel E. Feldstein – Novo Nordisk: Executive role , No, No;

The following people have nothing to disclose: Christian Stoess, Janset Onyuru, Trevor Crafts, Ola Leszczynska, Alexander Wree, Daniel Hartmann, Helmut Friess, Bruce Wolfe, Andrea Stroud

2057-A | IMPACT OF TIME-VARYING ANALYSIS OF LIVER ENZYMES AND BASELINE FACTORS ON THE DEVELOPMENT OF SIGNIFICANT FIBROSIS IN NAFLD: A SINGAPORE RETROSPECTIVE COHORT STUDY

Ian Yang Liew[1], Hwee Pin Phua[2], Wei-Yen Lim[2], Angela Li Ping Chow[2], Xiu Ying Loo[1], Keivin Wei Wen Sim[1], Eng Sing Lee[3,4] and Kuo Chao Yew[5], (1)Ministry of Health (MOH) Holdings Pte Ltd, Singapore, (2) Department of Preventive and Population Health, Tan Tock Seng Hospital, (3)Clinical Research Unit, National Healthcare Group Polyclinics, (4)Lee Kong Chian School of Medicine, Nanyang Technological University, (5)Department of Gastroenterology and Hepatology, Tan Tock Seng Hospital

Background: Non-alcoholic fatty liver disease (NAFLD) progression to advanced fibrosis is associated with liver complications and mortality{Ye, 2020 #4340}. While liver transaminases are not a perfect screening tool, their use in screening remains relevant, especially for the primary care physician. **Methods:** We conducted a retrospective cohort study to investigate how differences in baseline patient characteristics and changes in liver transaminases can help predict advanced fibrosis in a multi-ethnic Asian population at a tertiary centre. Eligible patients that fulfilled the inclusion and exclusion criteria with a complete set of data were followed up from January 1, 2007 to October 31, 2017. This generated a final cohort comprising 490 patients for alanine aminotransferase (ALT), 417 for aspartate aminotransferase (AST), and 417 for the AST/ALT ratio groups. Hazard ratios and 95% confidence intervals were estimated for ALT, AST, and AST/ALT ratio as factors of significant fibrosis($>$F3 on *fibroscan*, FIB-4$>$1.3) using separate multivariable Cox regression models and treating these as time-varying covariates. **Results:** The median length of follow up for all patients (n = 2170) was 52.6 months (23.0, 81.1). Patients who developed fibrosis (n = 434; 20.0%) exhibited lower baseline ALT, AST and albumin levels, but had higher NAFLD fibrosis score, FIB-4 score, AST/ALT ratio and platelet count (Table 1a). Cox regression analysis showed that ALT and AST were significant predictors (Table 1b) of fibrosis. Specifically, when keeping gender, age, Charlson Comorbidity Index(CCI), presence of metabolic syndrome, baseline AST (log) and platelet count (log) constant, a 10% increase in ALT is associated with 6.3% (95% CI: 2.9% - 9.9%) increase in hazard, while a 10% increase in the AST value is associated with 10.8% (95% CI: 6.9% - 14.9%) increase. Female gender, age and CCI at baseline were also statistically significant risk factors associated with fibrosis. Analysis of the data was limited by missing laboratory data amongst patients due to the retrospective nature of the study. **Conclusion:** This study highlights the importance of assessing changes in liver transaminase levels over time in identifying NAFLD patients at risk of developing fibrosis. Further prospective studies would be necessary to verify the use of these measurements in the prediction of fibrosis in NAFLD patients.

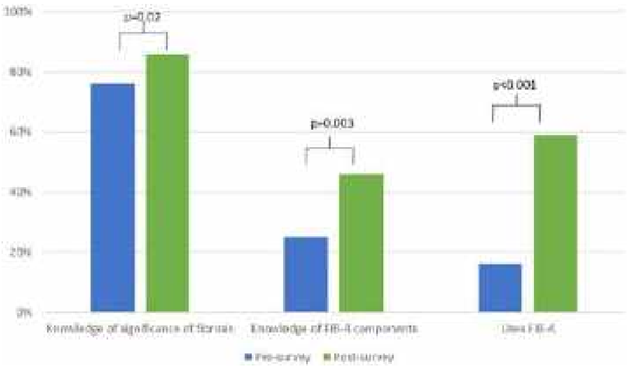


Disclosures: The following people have nothing to disclose: Ian Yang Liew, Hwee Pin Phua, Wei-Yen Lim, Angela Li Ping Chow, Xiu Ying Loo, Keivin Wei Wen Sim, Eng Sing Lee, Kuo Chao Yew

2058-A | IMPROVING PRIMARY CARE PROVIDER AWARENESS AND USE OF FIB-4 RISK-STRATIFICATION FOR NONALCOHOLIC STEATOHEPATITIS (NASH)

Max Lloyd Goldman[1], Rena K. Fox[2], Danielle Brandman[3], Delia Falliers[4], Kendall B Islam[2] and Janet N Chu[2], (1)Kaiser Permanente Northern California, (2) University of California, San Francisco, (3)Weill Cornell Medical College, New York, NY, (4)University of California, Los Angeles

Background: AASLD guidance recommends primary care providers (PCPs) perform fibrosis-4 index (FIB-4) risk assessment to determine the need for specialty management of patients at-risk for NASH. However, few PCPs are aware of or use FIB-4. We implemented AASLD's FIB-4 risk-stratification algorithm and evaluated PCP knowledge and use of FIB-4 pre- and post-intervention. **Methods:** At a large, diverse health system, we conducted a three-part study: 1) a pre-intervention PCP survey to ascertain nonalcoholic fatty liver disease (NAFLD) knowledge and practice patterns, 2) an intervention implementing a FIB-4 risk-stratification referral algorithm in primary care, and 3) a post-intervention PCP survey. During the 18-month intervention, PCPs received an electronic medical record (EMR) notification for each of their patients with diabetes and either a low-risk ($<$1.3) or a high-risk ($>$2.67) FIB-4, including recommendations for patients at low-risk to be managed in primary care and those at high-risk to be referred to hepatology. One year later, a post-intervention survey measured the change in FIB-4 knowledge and use of FIB-4 in managing patients at-risk of NASH. Pre- and post-survey responses were compared using two-sample z-tests for proportions. **Results:** The 88/115 pre- and 69/119 post-intervention survey respondents included PCPs delivering care to 26,602 patients. Among post-survey PCPs, 64% received messages for low- and 54% for high-FIB-4 patients during the intervention. Comparing post- to pre-survey responses, PCP knowledge of fibrosis as a predictor of cirrhosis improved (86% vs. 76%, p = 0.02), knowledge of FIB-4 components increased (46% vs. 25%, p = 0.003), and more PCPs reported now applying FIB-4 for patients with elevated LFTs (59% vs. 16%, p < 0.001). Finally, 46% reported that their likelihood of managing NAFLD patients with low FIB-4 in primary care and/or appropriately referring patients with high FIB-4 to hepatology increased. **Conclusion:** Implementing a FIB-4 risk-stratification algorithm in primary care substantially impacted PCPs' management of NAFLD patients one year later. PCPs demonstrated significantly improved awareness of FIB-4, and most importantly, continued to incorporate FIB-4 risk-stratification into their specialty-referral decision-making, resulting in appropriate referral of high-risk patients to hepatology, while continuing PCP management of low-risk patients. This study provides evidence that PCPs introduced to FIB-4-based risk stratification adopt the strategy, resulting in improved practice patterns.



Disclosures: Max Lloyd Goldman – Novonordisk: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; Eli Lily: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
Rena K. Fox – Gilead Sciences, Inc , NASH Models of Care program, #IN-US-989-5737: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;
The following people have nothing to disclose: Danielle Brandman, Janet N Chu
Disclosure information not available at the time of publication: Delia Falliers, Kendall B Islam

2059-A | INCREASED CARDIOVASCULAR AND KIDNEY DISEASE RISK IN PATIENTS WITH ADVANCED FIBROSIS DUE TO NONALCOHOLIC STEATOHEPATITIS

Kathleen E. Corey[1], *Jun Xu*[2], *Sharlene Lim*[2], *Kaiyi Zhu*[2], *Vladislav A Malkov*[2], *Jason Melehani*[2], *Lisa Boyette*[2], *Timothy R. Watkins*[2] *and Andrew N. Billin*[2], *(1)Massachusetts General Hospital, Somerville, MA, (2) Gilead Sciences, Inc.*

Background: NNASH is associated with increased risks of CVD and CKD. Liver fibrosis stage is an independent predictor of liver-related outcomes in patients with NASH, but the associations of hepatic fibrosis with CVD and kidney disease risk are unclear. Our study aimed to characterize CVD and kidney disease risk in patients with NASH using the SomaSignal® platform. **Methods:** In a phase 2b study (NCT03449446), a subset of participants (pts) with noncirrhotic (F2/F3) or compensated cirrhotic NASH (F4) with paired plasma and liver biopsy samples at baseline were included (N = 175). Liver biopsy fibrosis stage was determined using the NASH CRN system. Risk for future liver events was categorized by baseline ELF scores (low **d** 9.8, high **e** 11.3). SomaSignal® tests (SomaLogic® Colorado) for primary CVD risk (R1123, including MI, stroke, TIA, hospitalization for HF or CV death) and 4-yr kidney disease risk (R1138, probability of progressive chronic renal insufficiency, including 50% decline in eGFR, initiating dialysis or becoming a candidate for kidney transplantation) were performed on baseline plasma samples. The probability of CVD or kidney disease progression was compared between pts by fibrosis stage and ELF risk categories. The fraction of the study population in risk categories for each test was determined. **Results:** At baseline, 16% of noncirrhotic and 21% of cirrhotic pts were characterized by SomaSignal® tests as high risk for primary CVD. By ELF categories, 11% and 33% of pts at low and high risk for liver events, respectively, were characterized as high risk for primary CVD, suggesting that higher risk of liver events may be associated with greater primary CVD risk. 35% of noncirrhotic and 50% of cirrhotic pts were characterized as being at moderate/high 4-yr kidney disease risk. By ELF categories, 29% and 73% of participants at low and high risk for liver events were characterized as being at high 4-yr kidney disease risk, despite the median eGFR being similar between these two groups. **Conclusion:** SomaSignal® results of CVD and kidney disease progression risk suggest that severity of liver fibrosis (by histology or ELF) is associated with an increasing risk for these comorbidities. Individual's with eGFR < 60 mL/min were excluded from the study and yet many participants had 4-yr kidney disease risk scores indicating high risk. Conventional measures of kidney disease risk may under-recognize the risk for progression of CKD. The utility of these tests should be evaluated in larger studies.
Disclosures: Kathleen E. Corey – Intercept: Consultant, No, No; Theratechnologies: Consultant, No, Yes; Medscape: Speaking and Teaching, No, No;
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Sharlene Lim – Gilead Sciences Inc: Employee, No, No; Gilead Sciences Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
Kaiyi Zhu – Gilead Sciences Inc: Employee, No, No; Gilead Sciences Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
Vladislav A Malkov – Gilead Sciences Inc: Employee, No, No; Gilead Sciences Inc.: Stock - publicly traded

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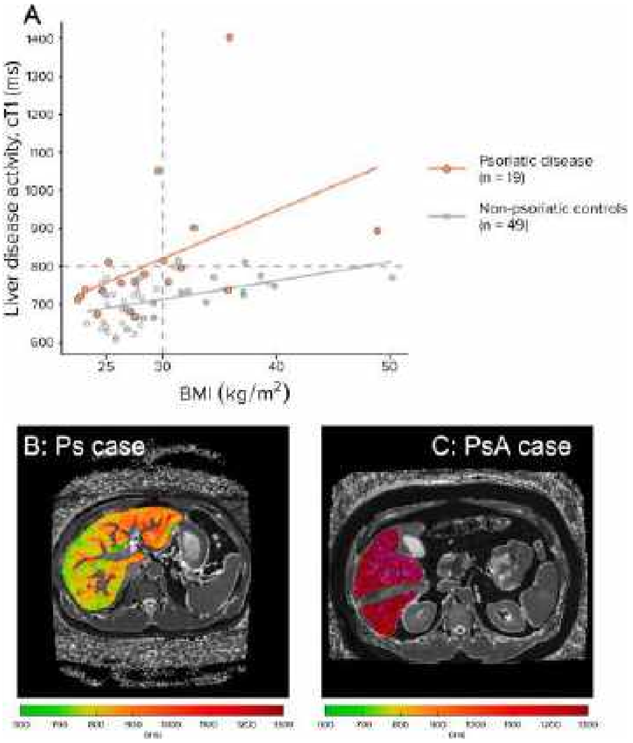
Jason Melehani – Gilead Sciences Inc: Employee, No, No; Gilead Sciences Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
Lisa Boyette – Gilead Sciences Inc: Employee, No, No; Gilead Sciences Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
Timothy R. Watkins – Gilead Sciences Inc: Employee, No, No; Gilead Sciences Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
Andrew N. Billin – Gilead Sciences Inc: Employee, No, No; Gilead Sciences Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;

2060-A | INCREASED LIVER DISEASE ACTIVITY IN PEOPLE WITH PSORIATIC DISEASE AFTER CONTROLLING FOR OBESITY, IDENTIFIED BY QUANTITATIVE MAGNETIC RESONANCE IMAGING

Charlie Diamond[1], Lija James[2], Elizabeth Shumbayawonda[1], Hussein Al-Mossawi[2], Helena Thomaides-Brears[1], Rajarshi Banerjee[1] and Laura Coates[2], (1)Perspectum Ltd., (2)University of Oxford

Background: Psoriatic arthritis and psoriasis (PsA, Ps) are chronic inflammatory conditions of the joints and skin, respectively. Treating with methotrexate (MTX) is associated with hepatotoxicity and liver damage. As risk of psoriatic disease is associated with obesity, this population is also at high risk of fatty liver disease. Magnetic resonance imaging (MRI) provides a non-invasive assessment of liver characteristics, including steatosis and disease activity. Here, we evaluated liver health in participants with PsA and Ps compared to age, sex, and BMI-matched non-psoriatic controls (NCs), using quantitative MRI. **Methods:** Data from 19 participants were collected from an ongoing, prospective study recruiting participants with PsA and Ps on new anti-rheumatic treatments (COLIPSO REC: 20/LO/0616). Retrospective data from 49 NCs (COVERSCAN study, NCT04369807 and UK Biobank application 9914) matched for age, sex, and BMI were included. MRI-derived measures of liver fat (%) and disease activity (cT1) were compared, and prevalence of liver damage from clinical thresholds was assessed with Fisher's exact tests. Wilcoxon rank sum tests were used for continuous variables. Multivariate linear regression estimated the effects of variables influencing cT1. **Results:** In this cohort of middle-aged, overweight people with mild PsA or Ps but no diabetes (age 46 y [IQR: 38 – 59]; 53% male; BMI of 28kg/m^2 [IQR: 25 – 31]; 6 years disease duration [IQR: 3 – 13]; 32% on Methotrexate) liver disease activity (cT1 ^{3}800ms) was more prevalent than the matched NCs (32% vs. 6.1%; p-value: 0.011). Severe liver disease (cT1 ^{3}875ms) was frequent (21% vs. 0% in NCs; p-value: 0.005). The significant increase in liver disease activity in the PsA and Ps patients was equivalent to > 2 NAFLD Activity Score (NAS) points (101ms difference in cT1), after controlling for differences in BMI (figure 1). Non-alcoholic steatohepatitis (NASH), defined as cT1 ^{3}800ms and liver fat ^{3}5%, was more prevalent in the PsA/Ps group (26% vs. 4.1%; p-value: 0.016). Liver health did not differ between patients on MTX from those on other anti-rheumatic treatments (p = 0.34). **Conclusion:** Individual's suffering with PsA/Ps have a significantly higher prevalence of liver disease compared to matched controls, even at higher BMI. The increased liver disease activity in PsA/Ps patients may result from underlying chronic inflammation.



Disclosures: Charlie Diamond – Perspectum Ltd.: Employee, Yes, No;
Elizabeth Shumbayawonda – Perspectum Ltd.: Employee, Yes, No;
Disclosure information not available at the time of publication: Lija James, Hussein Al-Mossawi, Helena Thomaides-Brears, Rajarshi Banerjee, Laura Coates

2061-A | INTEGRATION OF THE ENHANCED LIVER FIBROSIS (ELF) TEST FOR ADVANCED FIBROSIS AND CIRRHOSIS DETECTION IN A REAL-WORLD CLINICAL ENVIRONMENT

Jessica C. Rachman[1], Mina M. Al-Hamadani[1,2], Amberly Komatz[1], Shweta Chakraborty[1], Czarina Mae Morley[1], Ashley M. Goff[1], Jessica N. Wilson[1], Nancy J. Todd[1], Jessica J. Taggart[1], Ryan M. Taylor[1], Nizar T. Talaat[1], Steven A. Weinman[1] and Winston Dunn[1], (1) University of Kansas Medical Center, (2)Medstar Washington Hospital Center / Georgetown University

Background: Nonalcoholic fatty liver disease (NAFLD) affects approximately 26% of the US population, of which 2% develop nonalcoholic steatohepatitis (NASH) with advanced fibrosis or cirrhosis. The study explores the potential of integrating Enhanced Liver Fibrosis (ELF) testing with Vibration-Controlled Transient Elastography (VCTE) in a real-world clinical environment to improve identification of high-risk cases. **Methods:** 359 patients undergoing hepatology evaluation for NAFLD were randomized into the intervention group ($n = 179$) or the control group ($n = 180$). In this design, participants in the intervention group received the ELF test, while participants in the control group did not. The ELF test result was made accessible to the hepatologist before a liver biopsy decision. The primary outcome measured was the rate of advanced fibrosis (**e** F3) diagnoses, determined through either liver biopsy or clinical tool. The secondary outcome was the liver biopsy rate. Diagnosis rates were compared using logistic regression. **Results:** The control group had a mean FIB-4 of 1.50 (SD = 1.40) with 31.3% having type II diabetes. 108 (60.3%) underwent Fibroscan and 37 (20.7%) underwent liver biopsies, with 8 patients (4.5%) showing **e** F3 fibrosis. The intervention group had a mean FIB-4 of 1.49 (SD = 1.17) and a higher type II diabetes incidence of 39.4%. Here, 111 (61.7%) underwent Fibroscan and 40 (22.2%) underwent liver biopsies. No difference in the biopsy rate was observed in the two groups ($p = 0.6283$). However, a higher number of patients in the intervention group (20 patients, 11.1%) compared to the control group (9 patients, 5.0%) had **e** F3 fibrosis (OR 2.672, 95% CI 1.185 – 6.605, $p = 0.0231$). **Conclusion:** This study demonstrates that the integration of ELF testing in a real-world clinical setting, which already includes VCTE, can increase the detection of advanced fibrosis and cirrhosis in NAFLD patients without increasing liver biopsy rates. Importantly, this strategy can enhance patient care by minimizing invasive procedures while maximizing diagnostic capability.

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2062-A | KEY GENE VALIDATION IN HEPATIC FIBROSIS AND HEPATOCELLULAR CARCINOMA IN AFRICAN AMERICANS WITH NAFLD

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Background: Growing prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) is alarming in the USA and has increased to 47.8% of the population. African Americans (AA) with NAFLD have a high risk of progression to fibrosis (28.5%) but this group has been chronically understudied. We identified the key Hepatic Fibrosis and Hepatocellular Carcinoma pathways through global gene expression. In this pilot study, we compare and validate the previously identified signature genes using TaqMan Low-Density Array (TLDA) in the pathogenesis of Hepatic Fibrosis and Hepatocellular Carcinoma from the blood of AA with NAFLD. **Methods:** AA NAFLD research participants (n = 19; mean age: 46.6 ± 8.2) were recruited from the Georgetown University Liver Transplantation Unit, Washington DC, along with healthy AA controls (n = 12; mean age: 35.9 ± 11.1) from the same region. Their sociodemographic, lifestyle exposures, and medical background information were recorded. TaqMan® Array (FAST Plate) for TaqMan® Array Human Liver Cancer 96-well plate, fast (Applied Biosystems, Catalog #4413255, Santa Clara, CA, USA) over the ABI QuantStudio 5 Real-Time PCR System was used to run the QRT-PCRs, coupled with Ingenuity Pathway Analysis (IPA®) validate and visualize the major pathways. **Results:** We identified 13 key genes (e.g., *ADAM17, AKT1, CFLAR, E2F1, EP300, HMBS, RUNX3, SFRP2, STAT3, TCF4, TGFβ1, ITGB1* and *TP53*) that were validated by TLDA method. *TGFβ1* (responsible for liver cell growth and division), *E2F1* (cell proliferation) and *HMBS* (catalyzes synthesis of hydroxymethylbilane synthase) were significantly up and downregulated, respectively. IPA analysis revealed *Hepatic Fibrosis Signaling* as the top canonical pathway with its corresponding bio-functions; viz., Hepatocellular

Carcinoma development, which was further validated by IPA match analysis. **Conclusion:** This pilot study offers an opportunity to gain insight into NAFLD disease dynamics in AA that may help in developing molecular classifiers to identify the disease risks using non-invasive peripheral blood. However, further multiethnic validation using large sample size as well as comparisons of blood and liver biopsies is necessary to strengthen our findings.

Disclosures: The following people have nothing to disclose: Tanmoy Mondal, Coleman I. Smith, Christopher A Loffredo, Ruth Quartey, Charles D. Howell, Brent E. Korba, Kwabi-Addo Bernard, Gail Nunlee-Bland, Leanna Rucker, Gemeyel Moses, Marika Clark, Sharleine Cotin, Jheannelle Johnson, Miranda Newheart, Faith Bentley, Tia Pope, Nacorria Lightsey, Triniti Davis, Oluwaseyi Oyebola, Karma A Matthews, Jasneet Sahota, Somiranjan Ghosh

2063-A | LIPIDOME CHANGES ASSOCIATED WITH A DIET-INDUCED REDUCTION IN HEPATIC FAT AMONG ADOLESCENT BOYS: AN UNTARGETED AND TARGETED LIPIDOMICS ANALYSIS

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Background: Lipid dysregulation is central to non-alcoholic fatty liver disease (NAFLD) onset and progression. However, little is known about lipid partitioning changes that occur with improvement in NAFLD. Using metabolomics, we recently showed that a low-free sugar diet (LFSD) treatment in adolescents with NAFLD was associated with metabolome changes that may indicate improved oxidative stress, inflammation, and lipid metabolism. To further explore these findings, we employed untargeted and targeted lipidomics to examine systemic lipid adaptations associated with the LFSD treatment and improvement of hepatic steatosis in study participants. **Methods:** Fasting plasma samples from 40 adolescent boys (11-16 yrs.) with NAFLD were collected at baseline and after eight weeks following randomization to a low-free sugar diet (LFSD) intervention ($n = 20$; goal: $< 3\%$ total energy intake) or usual diet ($n = 20$). Plasma samples were extracted and analyzed by liquid chromatography with tandem mass spectrometry (LC-MS/MS). Data analysis was performed using Thermo LipidSearch, Skyline, and R Studio version 4.2.3. **Results:** Using LC-MS/MS, a total of 11 lipid classes were measured, and paired t-test analysis revealed that the intervention group had significantly lower levels of cholesterol esters, triacylglycerides (TAGs), diacylglycerides (DAG), lysophosphatidylcholine (LPC), and phosphatidylcholine (PC) species after the diet treatment ($p < 0.05$). Additionally, we identified 274 lipid features with high confidence based on m/z, retention time, and fragmentation. Among these features, 29 were differentially expressed in the intervention group after the eight-week LFSD (adjusted $p < 0.05$). TAGs containing 48-50 carbons and one double bond were significantly decreased. Interestingly, total TAGs were positively correlated with total cholesterol and negatively correlated with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ($p < 0.05$). Oxylipins analysis revealed a significant decrease in the abundance of 8-isoprostane and 14,15-dihydroxy-5Z,8Z,11Z-eicosatrienoic acid (DiHET) after the LFSD intervention. **Conclusion:** We identified novel lipidome changes associated with a LFSD-induced reduction in hepatic steatosis, primarily reflecting changes in lipid species circulating in human plasma. Future studies are needed to elucidate the mechanism of these findings and whether the abundance of these lipids can be used as biomarkers indicative of NAFLD regression.

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Disclosure information not available at the time of publication: Catherine C. Cohen, Xueyun Liu, Chih-Yu Chen, Zachery R. Jarrell, Kristal M. Maner-Smith, Eric A Ortlund

2064-A | LIVER BIOPSY VERSUS NON-INVASIVE TESTS (NITS) WITH LABORATORY AND DEMOGRAPHIC ANALYSIS ACROSS ALL FIBROSIS STAGES IN 460 US PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Keerthi Thallapureddy[1], David Twitchell[1], Kristen Ott[1], Lisa Pedicone[2], Jonathan Gelfond[1], Nagasri Shankar[1], Martin Goros[1], Anna Liles[2], Chioma Owo[1], Fatma Ozguc[1], Fatima Ochoa Nunez[2], Nina Kumar[1], Iqra Kazi[1], Harry Nguyen[1], Eric Lawitz[1,2], Eugenia Tsai[1,2], Fabian Rodas[1,2], Carmen E. Landaverde[1,2] and Fred

Poordad[1,2], (1)UT Health San Antonio, (2)Texas Liver Institute

Background: Liver biopsy remains the "gold" standard in quantifying steatosis and fibrosis in NAFLD. While NITs are often used in clinical practice, it remains unclear which modality is best to use, how they compare to each other and how various patient variables may impact degree of fibrosis. **Methods:** The dataset includes 460 patients seen in South Texas from 2017-2022. All patients had a liver biopsy, 457 had FIB-4 score, 455 had NAFLD Fibrosis Score (NFS) and 237 had FibroScan. Patient demographics, baseline characteristics, labs, biopsy, and NIT results were analyzed based on degree of fibrosis defined by liver biopsy (F0 vs F1/F2 vs F3/F4). Kruskal-Wallis rank sum test, Pearson's Chi-squared test or Fisher's exact test was used to calculate p-value. Wilcoxon rank sum test was used to compare tissue sample length vs specialist performing the biopsy (Radiology or Hepatology). Association between BMI and degree of steatosis was estimated with Spearman's rank correlation test ($\alpha = 0.05$). **Results:** Median age was 51, 66.4% were female, and 73.3% were Hispanic/Latino White. Patients in the F3/F4 subgroup were significantly older and had the highest proportion of diabetes (69.3%; $p < 0.001$) and/or hypertension (71.5%; $p = 0.008$) (Table 1). There were differences in AST ($p < 0.001$), GGT ($p = 0.005$), ALP ($p = 0.041$) and Tbili ($p = 0.005$) across all fibrosis stages with highest values in the F3/F4 group. AST/ALT ratio increased as the stage of fibrosis increased ($p < 0.001$). Median BMI was 35 kg/m^2 and there was no association with levels of fibrosis ($p = 0.2$). Spearman's rank correlation revealed no association between BMI and steatosis ($p = 0.076$). FibroScan, FIB-4 and NFS showed statistically significant associations to liver biopsy staging ($p < 0.001$) (Table 1). Further analyses of predictors and steatosis quantification will be presented. The median biopsy sample length was 2.2 cm (0.6-3.2 cm) with 12 portal tracts; samples were statistically shorter when performed by Radiology (1.6 cm) vs Hepatology (2.2 cm) ($p < 0.001$). **Conclusion:** The analyses demonstrate that in NAFLD patients, age, diabetes, and hypertension were statistically associated with fibrosis. Interestingly, BMI did not correlate with degree of steatosis or advanced fibrosis suggesting that weight loss alone may not be adequate as a therapy for all NAFLD/NASH patients. Accurate biopsy interpretation relies on adequate tissue samples. Radiology-acquired samples were smaller which increases risk for sampling errors. NITs can be reliable tools as they generally correlate with liver biopsy fibrosis staging. Multivariate analyses comparing NITs to liver biopsy for staging and steatosis grade in this large cohort of NAFLD patients will be presented.

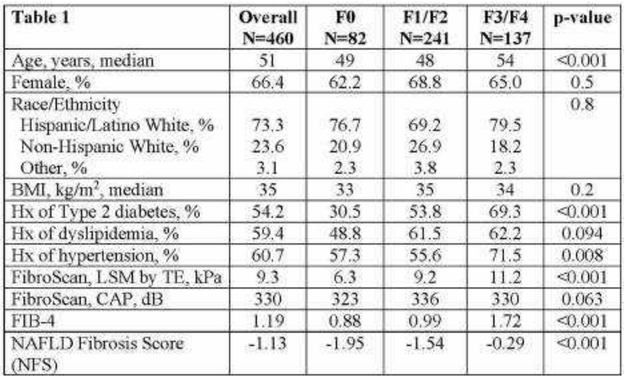

Table 1	Overall N=460	F0 N=82	F1/F2 N=241	F3/F4 N=137	p-value
Age, years, median	51	49	48	54	<0.001
Female, %	66.4	62.2	68.8	65.0	0.5
Race/Ethnicity					0.8
Hispanic/Latino White, %	73.3	76.7	69.2	79.5	
Non-Hispanic White, %	23.6	20.9	26.9	18.2	
Other, %	3.1	2.3	3.8	2.3	
BMI, kg/m^2, median	35	33	35	34	0.2
Hx of Type 2 diabetes, %	54.2	30.5	53.8	69.3	<0.001
Hx of dyslipidemia, %	59.4	48.8	61.5	62.2	0.094
Hx of hypertension, %	60.7	57.3	55.6	71.5	0.008
FibroScan, LSM by TE, kPa	9.3	6.3	9.2	11.2	<0.001
FibroScan, CAP, dB	330	323	336	330	0.063
FIB-4	1.19	0.88	0.99	1.72	<0.001
NAFLD Fibrosis Score (NFS)	-1.13	-1.95	-1.54	-0.29	<0.001

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f 2065-A | LIVER HISTOLOGY OVERESTIMATES STEATOSIS IN PRESENCE OF ADVANCED FIBROSIS: COMBINED DATA FROM MULTIPLE THERAPEUTIC TRIALS INCLUDING MORE THAN 6,000 PATIENTS (IN COLLABORATION WITH NAIL-NIT CONSORTIUM)

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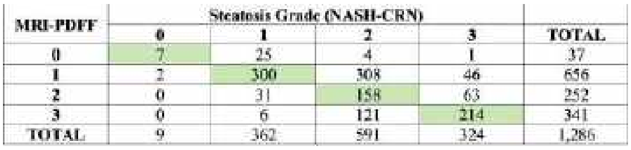
Background: Liver fat content (LFC) as measured by magnetic resonance imaging-proton density fraction (MRI-PDFF) is a validated and commonly used endpoint in nonalcoholic steatohepatitis (NASH) clinical trials. We aimed to describe the agreement between steatosis grade as defined by the NASH-CRN histologic scoring system and MRI-PDFF. **Methods:** We combined screening data from 7 NASH non-cirrhotic phase 2 trials. The previously validated thresholds were used to determine steatosis grades according to MRI-PDFF: grade 0 (LFC $<$ 6.4%), grade 1 (LFC: 6.4-17.4%), grade 2 (LFC: 17.4-22.1%), and grade 3 (LFC **e** 22.1%). Descriptive analyses were performed to describe the agreements between the 2 methods (histology versus imaging). **Results:** Out of the 6,558 patients, 1,286 with both MRI-PDFF and centrally read liver biopsy assessments were included. The mean age was 54.1 years (SD: 11.3). The majority of patients were female (61%), non-Hispanics (57%) and 41% had a glycated hemoglobin (HbA1c) **e** 6.5%. 48% of the patients met the criteria of “at-risk NASH" (NASH + NAS **e** 4 + Fibrosis Stages 2 or 3). The median NAS was 4 and the median steatosis grade was 2. The mean LFC was 18% (SD: 7.4). Agreement between histology and imaging steatosis grades was met in 52.8% of the cases whereas the histology grade was underestimated in 12.4% and overestimated in 34.8% of the cases compared to imaging grades (table). Among the “overestimated” group, 62% of patients met the “at-risk NASH” criteria according to histology. After reclassification of histology results based on imaging values, only 46% of the patients would have been considered “at-risk NASH”. The main differences between the “overestimated” and “agreement” groups were: fibrosis severity ($p < 0.001$; 51.6% of F2-F3 in the “agreement” group compared to 68% in the “overestimated” group) and presence of ballooning ($p < 0.001$; 63.3% in the “agreement” group versus 76.4% in the “overestimated” group). **Conclusion:** The likelihood of steatosis grade overestimation by liver histology is higher in patients with more advanced fibrosis and presence of ballooning. This overestimation might have an important impact on baseline assessment of patients within NASH clinical trials. Further analyses are warranted to gain a better understanding.



MRI-PDFF	Steatosis Grade (NASH-CRN)				
	0	1	2	3	TOTAL
0	7	25	4	1	37
1	2	300	308	46	656
2	0	31	158	63	252
3	0	6	121	214	341
TOTAL	9	362	591	324	1,286

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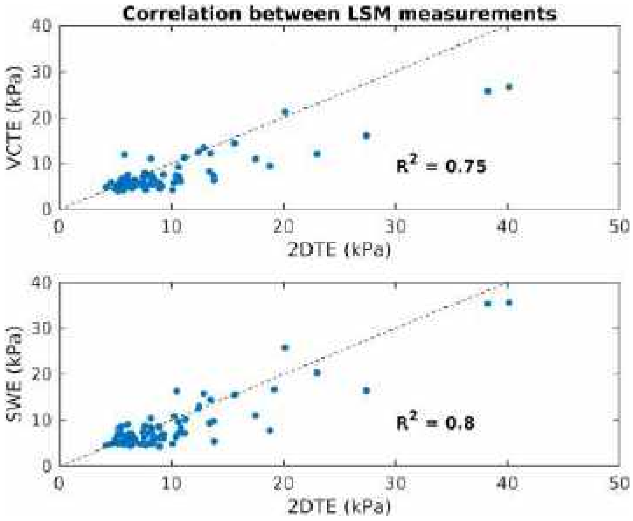
2066-A | LIVER STIFFNESS MEASUREMENTS WITH A NEW POINT-OF-CARE DEVICE, HEPATOSCOPE, USING TWO-DIMENSIONAL TRANSIENT ELASTOGRAPHY SHOWED GOOD CORRELATION TO OTHER NON-INVASIVE TESTS

Victor De Ledinghen[1], Dan Cohen-Dutartre[2], Adrien Besson[3], Francoise Manon[4], Joelle Abiven[4], Anne-Laure De Araujo[4], Rhizlane Houmadi[4], Julie Dupuy[4], Juliette Foucher[4], Joel Gay[3] and Claude Cohen-Bacrie[3], (1)University Hospital Bordeaux, (2)Inria, (3)E-Scopics, (4)CHU Bordeaux, Bordeaux, France

Background: Non-invasive tests (NITs) are recommended for the risk stratification of patients at risk of non-alcoholic steatohepatitis (NASH). Liver stiffness measurement (LSM) by ultrasound-based transient elastography (TE) is one of them, and Fibroscan® (FS) provides a 1D-measurement of shear wave speed (VCTE™) in hepatology practice. Large-scale screening of NAFLD-NASH could benefit from an available and affordable tool in primary care that would provide point-of-care reproducible and reliable LSM. We assessed the correlation between LSM obtained with TE using 2D-measurements of shear wave speed (2DTE) on a new ultrasound imaging point-of-care device, Hepatoscope™, and other NITs. **Methods:** 96 adult patients referred to routine hepatology consultation for chronic liver diseases were enrolled in this prospective single center study (NCT04782050). The following NITs for liver fibrosis were collected: LSM with VCTE, LSM with Aixplorer® ShearWave Elastography (SWE), FIB-4, APRI and NAFLD Fibrosis Score (NFS). LSM values as previously defined using 2DTE were collected with Hepatoscope within a region of interest positioned in the image. Data were analyzed with R to determine the correlation coefficient (r^2) between Hepatoscope LSM and other non-invasive tests. Patients of 70 years of age or older were excluded from correlation analyses with FIB-4. **Results:** All NITs used for liver fibrosis assessment were positively correlated with each other. LSM with VCTE, SWE and 2DTE were strongly correlated: $r^2 = 0.79$ (VCTE vs SWE), $r^2 = 0.75$ (VCTE vs 2DTE), and $r^2 = 0.80$ (2DTE vs SWE). Correlations between blood tests were weaker: $r^2 = 0.49$ (FIB-4 vs NFS), $r^2 = 0.31$ (FIB-4 vs APRI), and $r^2 = 0.10$ (APRI vs NFS).

2DTE correlated significantly better ($p < 0.001$) with APRI ($r^2 = 0.64$) than VCTE ($r^2 = 0.27$) and SWE ($r^2 = 0.33$). FIB-4 correlated moderately with 2DTE and SWE ($r^2 = 0.19$), and better than with VCTE ($r^2 = 0.12$; $p = 0.05$). NFS correlated weakly with 2DTE ($r^2 = 0.08$), and significantly better with VCTE ($r^2 = 0.16$) and SWE ($r^2 = 0.21$) ($p < 0.01$). **Conclusion:** LSM performed with the new point-of-care ultrasound imaging device Hepatoscope and 2DTE strongly correlated with other ultrasound-based LSM techniques (VCTE and SWE). Correlations between LSM by any technique and blood tests were found to be weak to good. These results suggest that Hepatoscope 2DTE may be used at the bedside in lieu of other LSM techniques for large scale screening purposes. Future comparative studies against liver biopsy are needed to validate existing LSM cutoffs for the triage of patients at risk of fibrotic NASH. Figure 1.

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



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

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

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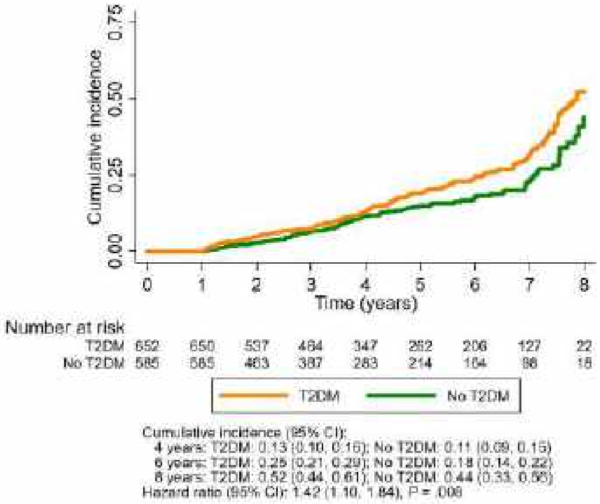
Background: There are limited data regarding whether liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) progresses faster in people with type 2 diabetes mellitus (T2DM) versus those without T2DM in biopsy-proven nonalcoholic fatty liver disease (NAFLD). Therefore,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

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

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



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Biopharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; NovoNordisk: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Sonic Incytes: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Terns Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; LipoNexus Inc.: Executive role , No, No;

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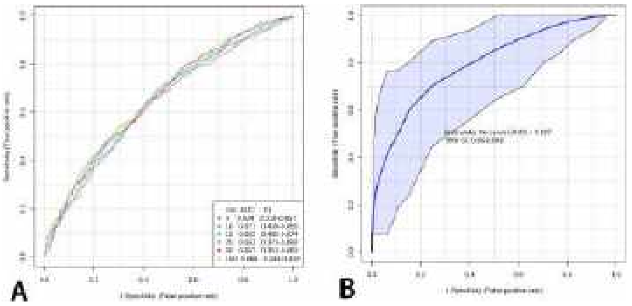
Disclosure information not available at the time of publication: Laura Wilson, Brent A. Tetri, James Tonascia

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

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

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



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Disclosure information not available at the time of publication: Brett Phineey

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

2069-A | MACHINE LEARNING ADVANCED FIBROSIS IN NASH (ALADDIN) WITH WEB-BASED CALCULATION FOR PROBABILITY PREDICTION

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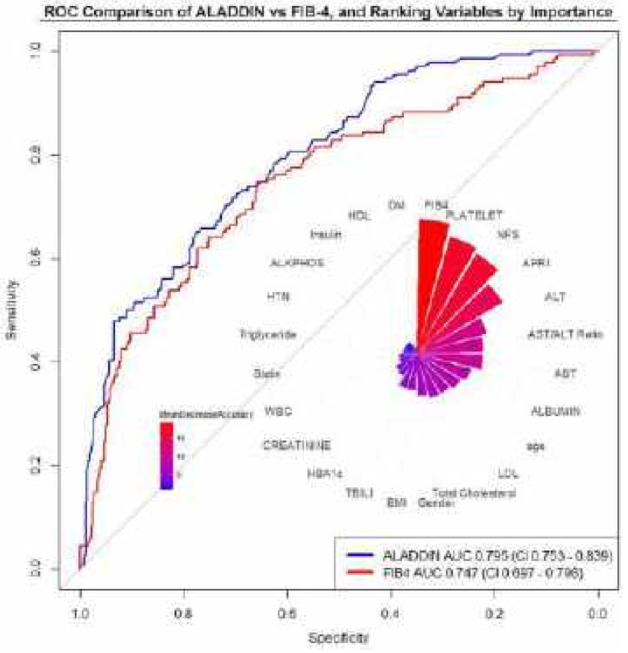
Background: Nonalcoholic Fatty Liver Disease (NAFLD) prevalence poses a significant challenge, with fibrosis stage acting as a crucial prognostic indicator. Advanced fibrosis/cirrhosis (F3-4) cases often face swift disease progression. Non-Invasive Tests (NITs) for hepatologist referral or biopsy have limited accuracy. We propose a machine learning (ML) model offering a probabilistic prediction adaptable for both community and referral centers, where prevalence varies from 3.7 – 50%. Preliminary two-center data from the multi-center consortium inform this model. **Methods:** We collected retrospective data on patients diagnosed with NAFLD, Nonalcoholic Steatohepatitis (NASH), or cryptogenic cirrhosis; patients with other liver diseases were excluded. The primary outcome was advanced fibrosis (F3) or cirrhosis (F4). Data was divided into derivation (training) and validation (testing) cohorts. We employed Random Forest for ML, considering other models such as ElasticNet and Grant Boosting Machines. **Results:** The study incorporated 986 patients, with 269 having advanced fibrosis or cirrhosis. The mean FIB-4 was 1.76 (SD 1.52). The proposed ALADDIN score presented a 1 - Out-of-Bag (OOB) error rate of 78.3%, suggesting a strong fit to the training data. In the validation cohort, ALADDIN score demonstrated an AUC of 0.794 (95% CI 0.750 – 0.837), surpassing FIB-4 0.747 (0.697 – 0.798), p = 0.0039. With a 65% probability threshold, ALADDIN showed a PPV and NPV of 79%, against FIB-4's 65% PPV and 80% NPV at a 2.66 threshold. The Net Reclassification Improvement (NRI) of 0.379 and Integrated Discrimination Improvement (IDI) of 0.068 accentuate ALADDIN Score's enhanced reclassification and discrimination capacities over FIB-4. Figure 1 displayed ROC comparison of ALADDIN and FIB-4, and the top 20 variables. **Conclusion:** Preliminary data underscores the ALADDIN score's potential in outperforming the conventional FIB-4 score in a tertiary referral center setting. Patients with an ALADDIN score > 65% might require liver biopsy, 15% - 65% may need additional noninvasive testing, and < 15% can be monitored in primary care. The ALADDIN score facilitates tailor-made care based on specific cirrhosis probability. With further data, the model can be calibrated for community settings. This is the first ML model with an online calculator for public use, enabling personalized care. The model is accessible at https://globalalchep.shinyapps.io/ALADDIN/.



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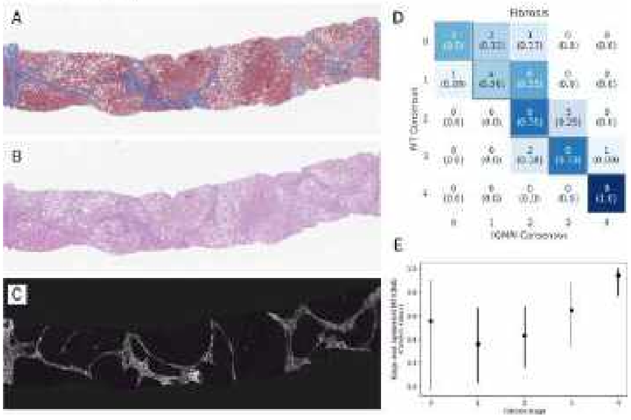
2070-A | MACHINE LEARNING-ASSISTED FIBROSIS STAGING IN H&E-STAINED TISSUE IS COMPARABLE TO STAGING WITH MASSON'S TRICHROME IN NON-ALCOHOLIC STEATOHEPATITIS

Yibo Zhang, Jun Zhang, Michael Griffin, Tan Nguyen, Filip Kos, Adam Stanford-Moore, Robert Egger, Yi Liu, Lara P. Murray, Julia A. Varao, James A. Allay, Chinmay R. Surve, Brea Johnson, Morgan Sweeney, Dana Lau-Corona, Michael G. Drage, Murray Resnick, Janani Iyer and Justin Lee, Pathai, Inc.

Background: In NASH clinical trials, fibrosis is staged via histologic examination of stained liver biopsies. However, stain quality is often highly variable, leading to inter-pathologist variability in staging. Here, we develop a machine learning (ML) method to infer the presence of fibrosis in hematoxylin and eosin (HE)-stained NASH biopsies, and test whether ML-based fibrosis augmentation in HE can be used for accurate NASH Clinical Research Network (CRN) fibrosis staging. **Methods:** Three expert NASH pathologists each staged fibrosis from Masson's Trichrome (MT)-stained WSIs (1A) in 50 cases of histologically-confirmed NASH. Separately, ML models were trained to detect fibrosis in HE-stained WSIs using inferred Quantitative Multimodal Anisotropy Imaging (iQMAI; previously described). iQMAI was deployed on 50 independent HE WSIs (1B), corresponding to the 50 NASH cases evaluated previously using MT. Three expert NASH pathologists were each asked to: (i) stage fibrosis in these 50 HE WSIs with iQMAI overlays (iQMAI+HE; 1C), and (ii) gauge feasibility of staging from iQMAI+HE. Median consensus fibrosis stage was computed for each WSI, and linearly-weighted Cohen's Kappa was computed to compare staging performed in iQMAI+HE versus MT WSIs. **Results:** Pathologist consensus was established on MT and iQMAI+HE for 49/50 cases and 50/50 cases, respectively. WSIs covered a representative distribution of fibrosis stages (1D). Overall concordance between fibrosis staging from iQMAI+HE versus MT was 0.75 (95% CI 0.63–0.85; 1D). Stage-level agreement between iQMAI+HE and MT was greatest for stages F4 and F3, while for lower stages iQMAI+HE staging exhibited a bias towards more sensitive fibrosis detection (1D, 1E). Pathologists reported that staging fibrosis in iQMAI+HE was easier than, similar to, and more difficult than MT in 4%, 78%, 0% of cases, respectively (three-way discordance rate = 18%). **Conclusion:** Here, we show that pathologists can stage fibrosis in HE-stained NASH biopsies when provided with ML-derived iQMAI fibrosis augmentation. Currently, HE sections are used to evaluate NAFLD Activity Score component features only – the ability to additionally stage fibrosis from HE without requiring direct scanning of physical slides or adjacent MT sections could reduce study timelines, associated costs, and the impact of MT stain variability on inter-rater agreement. Future work should assess whether iQMAI may be more sensitive to patterns of early-stage fibrosis than MT, and whether this may improve screening and detection of drug effect in clinical trials.

Figure 1. (A) Example MT WSI staged by three pathologists. (B) Paired HE WSI corresponding to MT WSI in A. (C) iQMAI+HE overlay corresponding to HE WSI in B was staged by three pathologists. (D) Confusion matrix showing concordance between iQMAI+HE and MT reads. (E) Stage-level concordance between MT and iQMAI+HE scoring.



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2071-A | MENOPAUSE MAY BE A GREATER RISK FACTOR FOR NONALCOHOLIC FATTY LIVER DISEASE IN LEAN WOMEN THAN OBESE WOMEN

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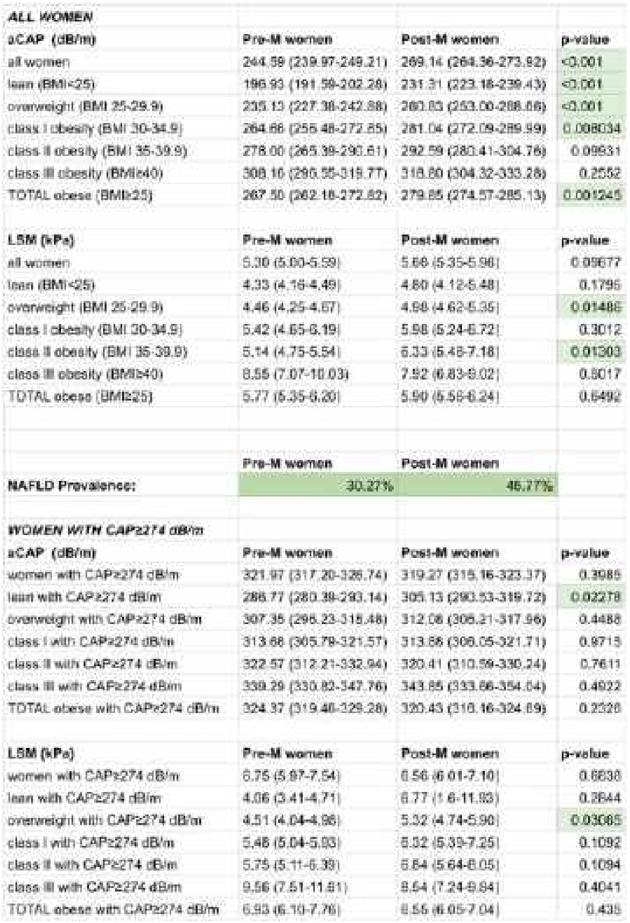
Background: Murine studies have shown that endogenous estrogen may be protective against nonalcoholic fatty liver disease (NAFLD). Epidemiologic studies suggest that postmenopausal (post-M) women are more likely to develop NAFLD and advanced liver fibrosis. In this study, we aimed to compare the severity and prevalence of NAFLD and liver stiffness in premenopausal (pre-M) and post-M women of different weight classes. **Methods:** Using the National Health and Nutrition Examination Surveys (NHANES) dataset from 2017-2020, we excluded all men, women < 18 years, women with excessive alcohol use (e 7 drinks per week), and women with viral hepatitis to arrive at a sample size of 3059 subjects. Out of these, only 1284 women (41.97%) had FibroScan® data and were included in this study. NAFLD was defined as a controlled attenuation parameter (CAP) score e 274 dB/m. Based on the BMI, the subjects were categorized into lean (BMI < 25 kg/m^2), overweight (BMI 25-29.9 kg/m^2), class I (BMI 30-34.9 kg/m^2), class II (BMI 35-39.9 kg/m^2), and class III obesity (BMI e 40 kg/m^2). Menopausal state was determined via a subject's response to the NHANES questionnaire. Average CAP score (aCAP) and liver stiffness measurement (LSM) were obtained via FibroScan®. **Results:** 740 women were pre-M and 544 women were post-M. The prevalence of NAFLD was 30.27% for the pre-M women, which is lower than the 45.77% for the post-M women. The aCAP for pre-M women was 244.59 dB/m vs 269.14 dB/m for post-M women ($p < 0.05$). Lean, overweight, and class I obese pre-M women had lower aCAP than post-M women ($p < 0.05$). Notably, the differences in aCAP are more pronounced the leaner the subjects are. This indicates that leaner women (BMI < 35) are more likely to develop worsening hepatic steatosis after menopause than obese women (BMI **e** 35). For women with NAFLD, only lean post-M women had higher steatosis compared to lean pre-M women, with aCAP of 305.13 dB/m vs 286.77 dB/m ($p < 0.05$), respectively. This highlights the influence of menopause on lean women with NAFLD. In terms of liver stiffness, only the overweight and class II post-M women had higher average LSMs than pre-M women in the respective weight classes ($p < 0.05$). **Conclusion:** Our data suggests that menopause, and by implication estrogen, may play a more crucial role in the development of steatosis in women with a lower BMI than those with a higher BMI.



ALL WOMEN			
aCAP (dB/m)	**Pre-M women**	**Post-M women**	**p-value**
all women	244.59 (239.97-249.21)	269.14 (264.36-273.92)	<0.001
lean (BMI<25)	196.93 (191.59-202.28)	231.31 (223.18-239.43)	<0.001
overweight (BMI 25-29.9)	235.13 (227.38-242.88)	260.83 (253.00-268.66)	<0.001
class I obesity (BMI 30-34.9)	264.66 (256.48-272.85)	281.04 (272.09-289.99)	0.008034
class II obesity (BMI 35-39.9)	278.00 (265.39-290.61)	292.59 (280.41-304.76)	0.09931
class III obesity (BMI≥40)	308.16 (296.55-319.77)	318.80 (304.32-333.28)	0.2552
TOTAL obese (BMI≥25)	267.50 (262.18-272.82)	279.85 (274.57-285.13)	0.001245
LSM (kPa)	**Pre-M women**	**Post-M women**	**p-value**
all women	5.30 (5.00-5.59)	5.66 (5.35-5.96)	0.09677
lean (BMI<25)	4.33 (4.16-4.49)	4.80 (4.12-5.48)	0.1796
overweight (BMI 25-29.9)	4.46 (4.25-4.67)	4.98 (4.62-5.35)	0.01486
class I obesity (BMI 30-34.9)	5.42 (4.65-6.19)	5.98 (5.24-6.72)	0.3012
class II obesity (BMI 35-39.9)	5.14 (4.75-5.54)	6.33 (5.48-7.18)	0.01303
class III obesity (BMI≥40)	8.55 (7.07-10.03)	7.92 (6.83-9.02)	0.5017
TOTAL obese (BMI≥25)	5.77 (5.35-6.20)	5.90 (5.56-6.24)	0.6492
	Pre-M women	**Post-M women**	
NAFLD Prevalence:	30.27%	45.77%	
WOMEN WITH CAP≥274 dB/m			
aCAP (dB/m)	**Pre-M women**	**Post-M women**	**p-value**
women with CAP≥274 dB/m	321.97 (317.20-326.74)	319.27 (315.16-323.37)	0.3985
lean with CAP≥274 dB/m	286.77 (280.39-293.14)	305.13 (290.53-319.72)	0.02278
overweight with CAP≥274 dB/m	307.35 (296.23-318.48)	312.08 (306.21-317.96)	0.4488
class I with CAP≥274 dB/m	313.68 (305.79-321.57)	313.88 (306.05-321.71)	0.9713
class II with CAP≥274 dB/m	322.57 (312.21-332.94)	320.41 (310.59-330.24)	0.7611
class III with CAP≥274 dB/m	339.29 (330.82-347.76)	343.85 (333.66-354.04)	0.4922
TOTAL obese with CAP≥274 dB/m	324.37 (319.46-329.28)	320.43 (316.16-324.69)	0.2328
LSM (kPa)	**Pre-M women**	**Post-M women**	**p-value**
women with CAP≥274 dB/m	6.75 (5.97-7.54)	6.56 (6.01-7.10)	0.6838
lean with CAP≥274 dB/m	4.06 (3.41-4.71)	6.77 (1.6-11.93)	0.2844
overweight with CAP≥274 dB/m	4.51 (4.04-4.98)	5.32 (4.74-5.90)	0.03085
class I with CAP≥274 dB/m	5.48 (5.04-5.93)	6.32 (5.39-7.25)	0.1092
class II with CAP≥274 dB/m	5.75 (5.11-6.39)	6.84 (5.64-8.05)	0.1094
class III with CAP≥274 dB/m	9.56 (7.51-11.61)	8.54 (7.24-9.84)	0.4041
TOTAL obese with CAP≥274 dB/m	6.93 (6.10-7.76)	6.55 (6.05-7.04)	0.435

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AbbVie/Allergan: Speaking and Teaching, No, No; Alexion: Speaking and Teaching, No, No; Echosens: Speaking and Teaching, No, No; Eisai: Speaking and Teaching, No, No; Exelixis: Speaking and Teaching, No, No; Gilead: Speaking and Teaching, No, No; Intercept: Speaking and Teaching, No, No; Perspectum: Speaking and Teaching, No, No; Salix: Speaking and Teaching, No, No; Theratechnologies: Speaking and Teaching, No, No;

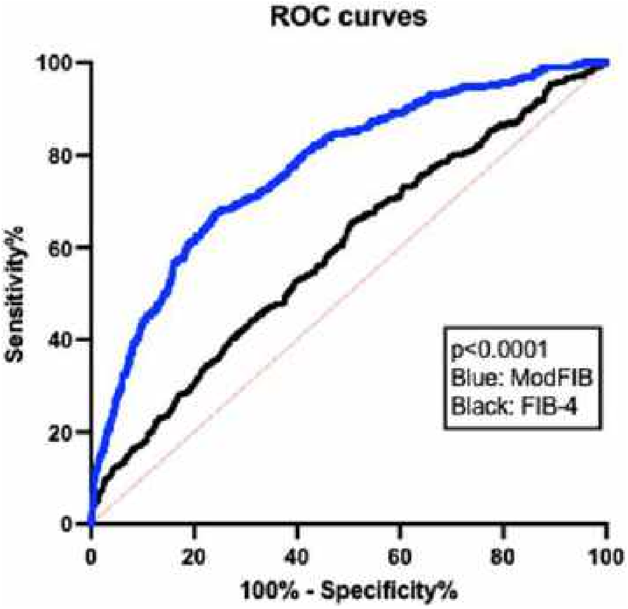
Mazen Noureddin – ChronWell: Stock – privately held company (individual stocks and stock options), No, No; Zydus: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Viking: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Terns: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Takeda: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Shire: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Novo Nordisk: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Novartis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; GSK: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Genfit: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Galectin: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Enanta: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Corcept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Conatus: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Bristol Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Allergan: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Akero: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Terns: Advisor, No, No; Takeda: Advisor, No, No; Siemens: Advisor, No, No; Roche diagnostic: Advisor, No, No; Perspectum: Advisor, No, No; Novo Nordisk: Advisor, No, No; Merck: Advisor, No, No; Madrigal: Advisor, No, No; GSK: Advisor, No, No; EchoSens: Advisor, No, No; Cytodyn: Advisor, No, No; Boehringer Ingelheim: Advisor, No, No; Altimmune: Advisor, No, No; 89bio: Advisor, No, No; CIMA: Stock – privately held company (individual stocks and stock options), No, No; Rivus Pharma: Stock – privately held company (individual stocks and stock options), No, No;

The following people have nothing to disclose: Madeleine Chang, Elizabeth W. Brombosz, Tamneet Basra, Sudha Kodali

2072-A | MODFIB: A SIMPLE IMPROVEMENT OVER FIB-4 TO OPTIMIZE REFERRAL OF NAFLD PATIENTS FROM PRIMARY CARE TO SPECIALTY CARE

Nehna Abdul Majeed, Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Allison Carroll, Northwestern University Feinberg School of Medicine, Harish Gopalakrishna, Clinical Research Section, Gaithesberg, MD and Yaron Rotman, National Institute of Diabetes and Digestive and Kidney Diseases, Nih

Background: Among patients with nonalcoholic fatty liver disease (NAFLD), only those with significant fibrosis require referral to specialty care. Since NAFLD is extremely common, proper selection is crucial to detect all those in need while not overloading hepatologists. AASLD guidelines recommend using FIB-4 in primary care and referring those with FIB-4 > 1.3 for vibration controlled transient elastography (VCTE) as second line. However, the initial FIB-4 cut-off has limited accuracy. We aimed to use readily-available clinical parameters to improve the accuracy of FIB-4 to determine referral of people with NAFLD from primary care to hepatology. **Methods:** Cross-sectional study utilizing National Health and Nutrition Examination Survey (NHANES) 2017-2020 data. We included all adults with complete anthropometric, laboratory, and VCTE data. The analysis was limited to subjects with NAFLD, defined as controlled attenuation parameter > 263dB/m. Subjects were randomly split 80:20 to derivation (n = 2292) and validation (n = 573) cohorts. The primary outcome was TE > = 8 kPa. Ethnicity, systolic blood pressure, body-mass index (BMI), total cholesterol, HbA1c, and FIB-4 were chosen *a priori* as potential predictors and tested using univariate and multivariate logistic regression. A predictive model was established using the regression coefficients, compared to FIB-4 in the derivation cohort, and cut-offs validated in the validation cohort. **Results:** In the derivation cohort, 381 (17%) of people with NAFLD had TE > = 8 kPa, suggestive of significant fibrosis. Of the tested clinical variables, BMI, HbA1c and FIB-4 were significantly associated with TE > = 8kPa on univariate and multivariate regression ($p < 0.0001$) and were used to derive the modified fibrosis score (ModFIB). ModFIB had higher area under receiver operating curve (AUROC) compared to FIB-4 (0.77 vs. 0.59, $p < 0.0001$) (Fig 1). Using the FIB-4 1.3 cut-off would have resulted in referral of 595 (26%) subjects to VCTE, with specificity of 76% but sensitivity of only 36%. For the same sensitivity, ModFIB would have 93% specificity with only 279 subjects needing referral. For the same number of referred subjects as FIB-4 (n = 595), ModFIB has sensitivity and specificity of 61% and 81%, respectively. The latter cutoff was examined in the validation cohort and had sensitivity and specificity of 68% and 92%, respectively. **Conclusion:** Fib-4 has reasonable specificity but poor sensitivity, with 64% of people with significant fibrosis missed. We provide a simple, non-invasive modification based on clinical parameters, that performs significantly better than FIB-4. The employment of ModFIB in primary care setting can markedly improve the selection of patients for VCTE and subsequent hepatology referral.



Disclosures: The following people have nothing to disclose: Nehna Abdul Majeed, Allison Carroll, Harish Gopalakrishna, Yaron Rotman

2073-A | MORPHOMETRIC AUTOMATED DIGITAL PATHOLOGY ANALYSIS REVEALS DIFFERENTIAL EFFECTS OF LANIFIBRANOR AND SEMAGLUTIDE IN THE BIOPSY-CONFIRMED GAN DIO-NASH MOUSE MODEL

Cindy Serdjebi[1], *Florine Chandes*[1], *Bastien Lepoivre*[1], *Susanne E. Pors*[2] *and Michael Feigh*[3], *(1)Biocellvia, (2) Gubra a/S, Copenhagen, Denmark, (3)Gubra Aps*

Background: Non-alcoholic steatohepatitis (NASH) predisposes to development of advanced fibrosis/cirrhosis. Currently, many clinical trials are ongoing to obtain either significant resolution of NASH without worsening of fibrosis or improvement of fibrosis without worsening of NASH. Semaglutide (glucagon-like-receptor (GLP)-1 agonist) and lanifibranor (pan-peroxisome proliferator activated receptor agonist) are currently in late-stage clinical testing. The present study aimed at investigating the effects of these two monotherapies in the Amylin NASH (GAN) diet-induced obese (DIO) and biopsy-confirmed mouse model with advanced fibrosis using morphometric digital pathology. **Methods:** GAN-DIO-NASH mice were treated with either vehicle, lanifibranor or semaglutide, and lean chow-fed animals served as control group. The pre- and post-treatment liver biopsies were stained with picrosirius red (PSR) and hematoxylin and eosin (H&E) and scanned at the magnification of X20. Histopathological NAFLD Activity Score (NAS) and fibrosis stage were evaluated by Gubra Histopathological Objective Scoring Technique (GHOST) AI-deep learning-based image analysis. In parallel, MorphoQuant, a fully automated and deterministic artificial intelligence to assess steatosis, fibrosis and collagen fiber dimensions (length and width). Effects of treatments were compared. **Results:** MorphoQuant analysis of pre-treatment biopsies showed no difference across the three GAN-DIO-NASH groups. Interestingly, a spontaneous regression of steatosis (-40.01%) and fibrosis (-11.68%) was observed in vehicle-treated animals. Using GHOST, semaglutide and lanifibranor promoted **e** 2-point significant improvement in NAS but none significantly improved fibrosis stage, albeit lanifibranor reduced levels of perisinusoidal and periportal fibrosis. MorphoQuant evidenced reduction of steatosis for semaglutide and lanifibranor (-63.93 and -78.26%, respectively). Fibrosis was greatly impacted by lanifibranor (-31.13%) whereas semaglutide showed a fibrosis reduction similar to vehicle-treated animals (-10.19%). Collagen fiber length was shortened for lanifibranor and semaglutide. Surprisingly, the width of collagen fiber tended to increase for semaglutide while no change was seen for lanifibranor. **Conclusion:** The GAN DIO-NASH mouse is highly applicable for profiling novel drug therapies targeting

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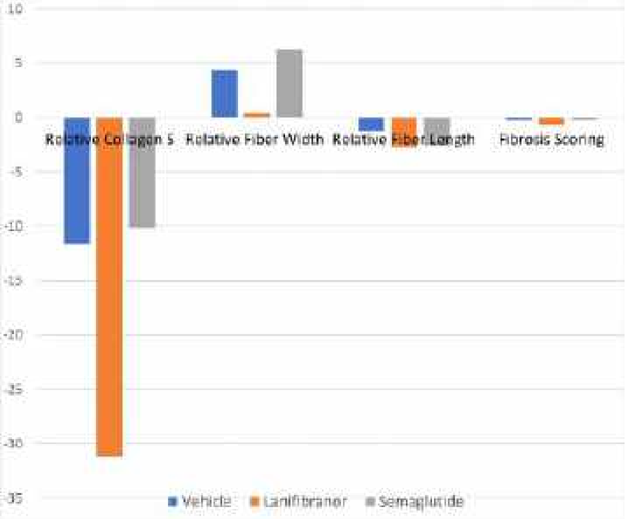
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

NASH with advanced fibrosis. Notably, morphometric AI-digital pathology showed superior anti-steatotic action for lanifibranor, compared to semaglutide. In addition, anti-fbrotic effect of lanifibranor, but not semaglutide, was demonstrated, in alignment with the Phase 2 clinical trial data. Importantly, evaluation of collagen fibers dimensions allows to provide a better understanding of drug effect on fibrosis regression.



Disclosures: Cindy Serdjebi – Biocellvia: Employee, Yes, No; Biocellvia: Stock – privately held company (individual stocks and stock options), Yes, No;
Florine Chandes – Biocellvia: Employee, Yes, No;
Bastien Lepoivre – Biocellvia: Employee, Yes, No; Biocellvia: Stock – privately held company (individual stocks and stock options), Yes, No;
Susanne E. Pors – Gubra: Employee, Yes, No;
Michael Feigh – Gubra: Employee, Yes, No; Gubra: Stock - publicly traded company (excluding mutual/ index funds or pension plans), Yes, No; Gubra: Executive role , Yes, No;

2074-A | MR ELASTOGRAPHY CAN RELIABLY PREDICT PORTO-SYSTEMIC COLLATERALS IN NON ALCOHOLIC FATTY LIVER DISEASE

Ameet Mandot[1], Tanvi Chipkar[1], Hiteshi Dhami- Shah[1], Gautham Pranesh[2], Rashmi Badhe[1] and Samir Ramnik Shah[1], (1)Global Hospitals, Mumbai, (2)Mitopower LLC

Background: MR Elastography(MRE) is a non-invasive gold-standard for evaluating liver fibrosis in Non-alcoholic Fatty Liver Disease (NAFLD). The sensitivity & specificity of other non-invasive studies like Fibro-Scan to detect clinically significant portal hypertension (CSPH) have traditionally been low due to technical factors related to obesity. Porto-systemic collaterals (PsC) signify presence of CSPH which is known to be associated with the risk of complications such as variceal hemorrhage, GI bleed, overt encephalopathy. The study aimed to establish a threshold level of liver stiffness(LS) using MRE for detection of PsC which would indicate CSPH in NAFLD. Additionally, the study explored combined use of FIB4 index & splenomegaly as indicators of PsC, offering potential applicability in community settings for NAFLD. **Methods:** A retrospective analysis was conducted on subjects with NAFLD who underwent MRE between January 2015 & December 2022. T2 weighted images were obtained during sequencing to assess spleen size & PsC. The spearman rank correlation test was used to determine the correlation between LS, FIB4 index & PsC. ROC analysis was performed to determine the threshold levels of MRE for predicting the presence of PsC. **Results:** A total of 392 subjects (Males:257; Females:135) with a mean age of 47 years ± 13 years & a median LS score of 2.7 kPa ± 2.8 kPa were included in the retrospective analysis. Of the 392 subjects, 104 subjects had advanced fibrosis (LS ≥ 5 kPa). The correlation coefficient of PsC was significant with MRE ($r = 0.543$, $p < 0.001$) & FIB4 index ($r = 0.478$, $p < 0.001$). The MRE threshold level of 6.15 kPa correlated with the presence of PsC, with a sensitivity of 76.9% & specificity of 77.1%, (AUC = 0.877). A regression model incorporating MRE, splenomegaly & platelet count showed an accuracy of 90.2% for predicting CSPH in the form of PsC, while a regression model including FIB4 index, splenomegaly & platelets demonstrated an accuracy of 87% predicting PsC. **Conclusion:** MR Elastography is a reliable non-invasive method for predicting the presence of PsC & hence CSPH in patients with NAFLD. The MRE threshold level of 6.15 kPa serves as a robust indicator. Additionally, FIB4 alone & a regression model combining FIB4 index, splenomegaly & platelet count shows similar accuracy and can be beneficial in community settings where MRI may not be available.

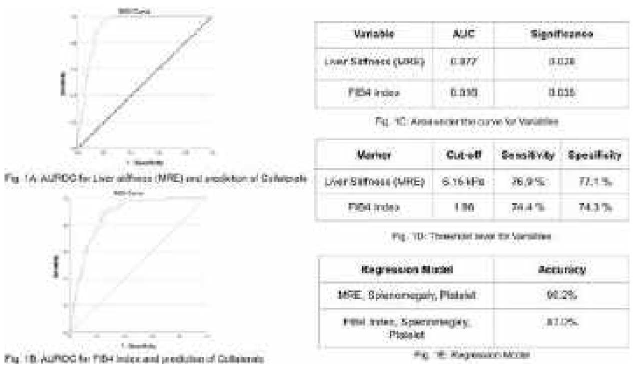


Fig. 1A: AUROC for Liver stiffness (MRE) and prediction of Collaterals

Fig. 1B: AUROC for FIB4 index and prediction of Collaterals

Variable	AUC	Significance
Liver Stiffness (MRE)	0.877	0.028
FIB4 index	0.830	0.035

Fig. 1C: Area under the curve for Variables

Marker	Cut-off	Sensitivity	Specificity
Liver Stiffness (MRE)	6.16 kPa	76.9%	77.1 %
FIB4 index	1.86	74.4 %	74.3 %

Fig. 1D: Threshold level for Variables

Regression Model	Accuracy
MRE, Splenomegaly, Platelet	90.2%
FIB4 index, Splenomegaly, Platelet	87.0%

Fig. 1E: Regression Model

Disclosures: The following people have nothing to disclose: Ameet Mandot, Tanvi Chipkar, Hiteshi Dhami-Shah, Gautham Pranesh, Rashmi Badhe, Samir Ramnik Shah

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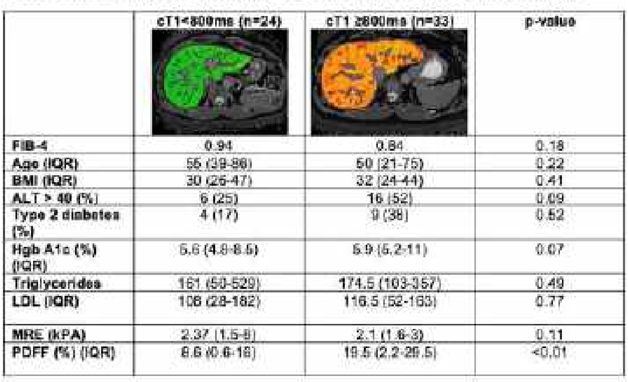
2075-A | MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING IMPROVES DETECTION OF PATIENTS WITH HIGH RISK NAFLD: REAL WORLD EXPERIENCE IN NAFLD CARE

Tatiana Hage[1], *Meaghan Phipps*[2], *Lauren Nicolosi*[2], *Andrea Dennis*[3], *Mazen Noureddin*[4] *and Julia J. Wattacheril*[5], *(1)Cedars-Sinai Medical Center, Los Angeles, CA, (2)Columbia University Medical Center, New York, NY, (3)Perspectum Ltd, (4)Houston Liver Institute, Houston, TX, (5)Columbia University, New York, NY*

Background: Early identification of patients with nonalcoholic fatty liver disease (NAFLD) at risk for advanced fibrosis (AF) is important in preventing disease progression to cirrhosis and decompensated liver disease. Non-invasive tests (NITs) including multi-parametric magnetic resonance (mpMR) imaging have emerged as clinically useful tools to stratify patients and identify those at risk for NASH and AF. Despite advancements in NITs, current clinical guidelines recommend using the Fibrosis-4 (FIB-4) score as the primary tool for risk stratification. We aimed to evaluate 1) the application of recent AASLD 2023 practice guidance recommendations for patients with suspected or established NAFLD and 2) the potential benefits of utilization of mpMR to improve detection of patients with NAFLD and AF. **Methods:** A prospective observational study was conducted on patients with NAFLD who received mpMR between 1/2019 and 12/2021 as part of standard clinical care. Patient demographics, medical comorbidities, and laboratory data were collected. We then applied the 2023 AASLD clinical practice guidance algorithm for patients with suspected or established NAFLD based on initial FIB-4 to our cohort. We compared this risk stratification with mpMR results, for which a cT1 value cutoff ≥ 800ms was considered an indicator of high risk for NASH or fibrosis. **Results:** Of 103 patients with NAFLD diagnosed by hepatologists at two large, academic medical centers, 64% (66/103) had a FIB-4 < 1.3. Of these patients at low risk for NASH or AF by initial stratification, 57 patients had cT1 data available; 58% (33/57) had cT1 ≥ 800ms on mpMR. Compared with patients with cT1 < 800ms on mpMR, there were trends for those with cT1 ≥ 800ms to be younger (55 v. 50, p = 0.22), more likely to be women (p < 0.01), have higher BMI (32 v. 30, p = 0.75), and more likely to have diabetes (27% v. 17%, p = 0.52). Despite higher rates of dyslipidemia among patients with cT1 < 800ms (63% v. 52%, p = 0.84), fewer patients were on treatment for dyslipidemia in this group compared with those with cT1 ≥ 800ms (40% v. 76%). cT1 was positively correlated with ALT (r = 0.26), AST (r = 0.26), liver fat from PDFF (r = 0.72), and fasting glucose levels (r = 0.23). **Conclusion:** In this real-world application of mpMR to aid in risk stratification of patients with NAFLD, *over half* of patients stratified as low risk by FIB-4 < 1.3 had cT1 ≥ 800ms on mpMR, suggestive of increased risk for developing NASH or AF. Incorporation of mpMR earlier in the algorithm for patients with suspected or established NAFLD may improve our detection of those with advanced disease and allow for earlier intervention to prevent disease progression and complications.

Table 1: Characteristics of patients with FIB-4≤1.3 stratified by cT1 values on mpMR



	cT1<800ms (n=24)	cT1 ≥800ms (n=33)	p-value
FIB-4	0.94	0.84	0.18
Age (IQR)	55 (39-86)	50 (21-75)	0.22
BMI (IQR)	30 (26-47)	32 (24-44)	0.41
ALT > 40 (%)	6 (25)	16 (52)	0.09
Type 2 diabetes (%)	4 (17)	9 (38)	0.52
Hgb A1c (%) (IQR)	5.6 (4.8-8.5)	5.9 (5.2-11)	0.07
Triglycerides	161 (50-529)	174.5 (103-357)	0.49
LDL (IQR)	108 (28-182)	116.5 (52-163)	0.77
MRE (kPA)	2.37 (1.5-8)	2.1 (1.6-3)	0.11
PDFF (%) (IQR)	8.6 (0.6-18)	19.5 (2.2-28.5)	<0.01

ALT (alanine aminotransferase), BMI (body mass index), LDL (low density lipoprotein), MRE (magnetic resonance elastography), PDFF (proton density fat fraction). Example of cT1 images of a participant with cT1 626ms (green) and 850ms (orange).

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Julia J. Wattacheril – AMRA Medical: Advisor, No, Yes; Intercept Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Galectin Therapeutics: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genfit: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; AlphaSights: Advisor, No, No;

The following people have nothing to disclose: Tatiana Hage, Meaghan Phipps

Disclosure information not available at the time of publication: Lauren Nicolosi, Andrea Dennis

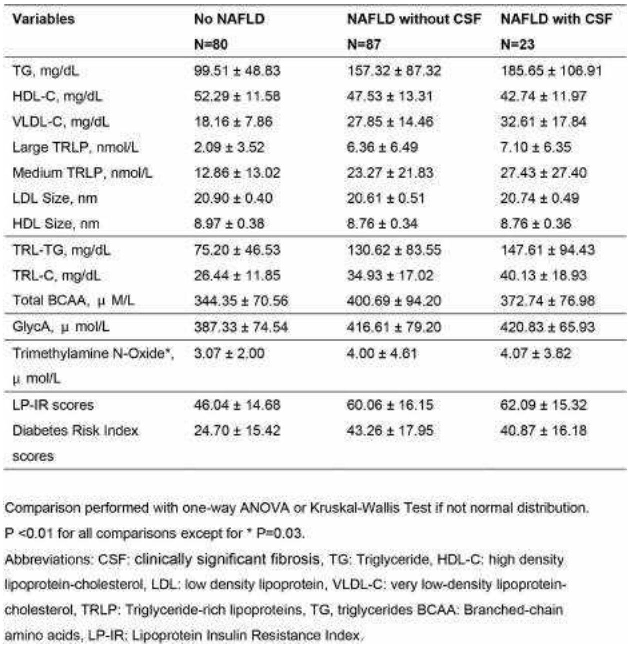
2076-A | NAFLD IS ASSOCIATED WITH HIGH RISK LIPIDOMIC AND METABOLOMIC PROFILE IN VIRALLY SUPPRESSED PERSONS WITH HIV

Kung-Hung Lin[1], Eduardo Vilar[1], Kathleen E. Corey[2], Margery Connelly[3], Samir K. Gupta[1], Jordan E. Lake[4], Naga P. Chalasani[1] and Samer Gawrieh[5], (1)Indiana University School of Medicine, (2)Massachusetts General Hospital, Somerville, MA, (3)University of Florida, (4)University of Texas - Houston, (5)Indiana University School of Medicine, Indianapolis, IN

Background: NAFLD affects nearly half of the US adult persons with HIV (PWH). Metabolic dysregulation in NAFLD is associated with atherogenic dyslipidemia and production of circulating metabolites that enhance systemic inflammation and risk of cardiovascular disease, diabetes, and mortality. We investigated whether NAFLD in PWH is associated with changes in lipidomic and metabolomic parameters linked to cardiometabolic outcomes (CMO), and whether NAFLD severity influenced these changes. **Methods:** Consenting, adult PWH without alcohol abuse or chronic liver disease underwent vibration-controlled transient elastography for controlled attenuation parameter (CAP) and liver stiffness measurement (LSM). Lipidomic and metabolomic profiling on fasting serum samples was performed with NMR spectroscopy. Hepatic steatosis was defined by CAP e 263 dB/m. LSM e 8 kPa indicated clinically significant fibrosis (CSF). Logistic regression models assessed associations between NAFLD, CSF and lipidomic and metabolic parameters. **Results:** 192 participants were included: 70% cisgender male, 96% on suppressive (HIV-1 RNA < 50 copies/

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

mL) antiretroviral therapy (ART) and median age 51 (IQR 38-58) years, BMI 29 (IQR 26-33) kg/m^2, and CD4$^+$ T cell count 700 (IQR 510-951) /mm^3. Prevalence of NAFLD and CSF were 58% and 12%, respectively. Compared to PWH without NAFLD (No-NAFLD), PWH with NAFLD (NAFLD) had high cardiometabolic risk factors including higher total triglyceride, VLDL-C, branched-chain amino acids, GlycA, trimethylamine N-oxide levels, Lipoprotein-Insulin Resistance and Diabetes Risk Index scores, and lower HDL-C levels (Table). Alterations in these indices worsened from No-NAFLD to NAFLD without CSF to NAFLD with CSF (Table), while CD4$^+$ T cell count, HIV-1 RNA and ART classes were similar across the 3 groups. In a multivariable regression model adjusting for age, sex, race/ethnicity, BMI, and diabetes, NAFLD was independently associated with all these alterations, except for GlycA. **Conclusion:** In virally suppressed PWH, NAFLD is independently associated with altered lipidomic and metabolomic profiles that portend higher risk for CMO. This profile worsens further with increasing severity of NAFLD. To reduce risk for CMO, PWH and NAFLD, and especially those with CSF, should be screened for and offered interventions to address these lipid-metabolic changes.



Variables	No NAFLD N=80	NAFLD without CSF N=87	NAFLD with CSF N=23
TG, mg/dL	99.51 ± 48.83	157.32 ± 87.32	185.65 ± 106.91
HDL-C, mg/dL	52.29 ± 11.58	47.53 ± 13.31	42.74 ± 11.97
VLDL-C, mg/dL	18.16 ± 7.86	27.85 ± 14.46	32.61 ± 17.84
Large TRLP, nmol/L	2.09 ± 3.52	6.36 ± 6.49	7.10 ± 6.35
Medium TRLP, nmol/L	12.86 ± 13.02	23.27 ± 21.83	27.43 ± 27.40
LDL Size, nm	20.90 ± 0.40	20.61 ± 0.51	20.74 ± 0.49
HDL Size, nm	8.97 ± 0.38	8.76 ± 0.34	8.76 ± 0.36
TRL-TG, mg/dL	75.20 ± 46.53	130.62 ± 83.55	147.61 ± 94.43
TRL-C, mg/dL	26.44 ± 11.85	34.93 ± 17.02	40.13 ± 18.93
Total BCAA, μ M/L	344.35 ± 70.56	400.69 ± 94.20	372.74 ± 76.98
GlycA, μ mol/L	387.33 ± 74.54	416.61 ± 79.20	420.83 ± 65.93
Trimethylamine N-Oxide*, μ mol/L	3.07 ± 2.00	4.00 ± 4.61	4.07 ± 3.82
LP-IR scores	46.04 ± 14.68	60.06 ± 16.15	62.09 ± 15.32
Diabetes Risk Index scores	24.70 ± 15.42	43.26 ± 17.95	40.87 ± 16.18

Comparison performed with one-way ANOVA or Kruskal-Wallis Test if not normal distribution.

P <0.01 for all comparisons except for * P=0.03.

Abbreviations: CSF: clinically significant fibrosis, TG: Triglyceride, HDL-C: high density lipoprotein-cholesterol, LDL: low density lipoprotein, VLDL-C: very low-density lipoprotein-cholesterol, TRLP: Triglyceride-rich lipoproteins, TG, triglycerides BCAA: Branched-chain amino acids, LP-IR: Lipoprotein Insulin Resistance Index.

Disclosures: Kathleen E. Corey – Intercept: Consultant, No, No; Theratechnologies: Consultant, No, Yes; Medscape: Speaking and Teaching, No, No;
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The following people have nothing to disclose: Kung-Hung Lin, Naga P. Chalasani
Disclosure information not available at the time of publication: Eduardo Vilar, Samir K. Gupta, Jordan E. Lake

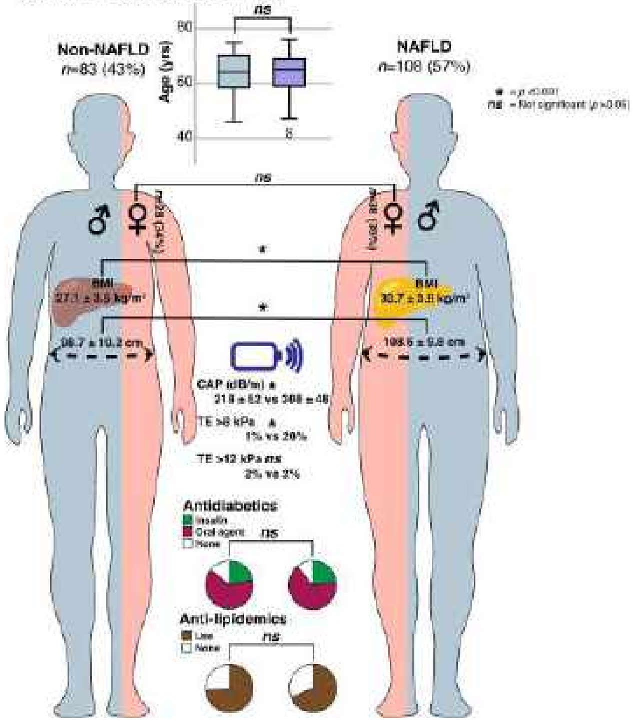
2077-A | NAFLD PREVALENCE AND PREDICTORS IN PATIENTS WITH T2D IN PRIMARY CARE – INTERIM RESULTS FROM THE EPSONIP STUDY

Wile Balkhed[1], Patrik Nasr[2], Mikael Fredrik Forsgren[3], Martin Bergram[4], Olof Dahlqvist Leinhard[3], Nils Dahlström[4], Carl-Johan Carlhäll[4], Peter Lundberg[4], Karin Rådholm[4], Fredrik Iredahl[4], Stergios Kechagias[2] and Mattias Ekstedt[2], (1)Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden, Solna, Sweden, (2)Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden, (3)Amra Medical, (4) Linköping University

Background: The number of people with NAFLD has increased in parallel with the obesity epidemic. Type 2 diabetes (T2D) is associated with progressive NAFLD. Therefore, many guidelines recommend screening for NAFLD in T2D patients. Most NAFLD studies have been conducted in specialist care, not necessarily representative for primary care. Therefore, we aimed to investigate the prevalence of NAFLD and advanced fibrosis in primary care patients with T2D utilizing magnetic resonance (MR) imaging and transient elastography (TE). In this study, we present interim results from the EPSONIP study (NCT03864510). **Methods:** Patients with T2D, without previous liver disease, were prospectively included from primary care. Study participants underwent laboratory investigation, TE with controlled attenuation parameter (CAP) and MR imaging with liver proton density fat fraction (PDFF). **Results:** Two-hundred and eighty-seven participants have been included with available PDFF data for 191 patients to date. Out of these, 108 (57%) had a PDFF **e** 5 % and were classified as NAFLD. The mean PDFF in participants with NAFLD was 13.1 ± 6.7%. There was no difference in sex (35% and 34% were women in the NAFLD and non-NAFLD groups, respectively), age

(63.8 ± 8.0 and 64.1 ± 7.2 y), nor in diabetes- or lipid lowering treatment between groups (Figure 1). However, participants with NAFLD had a greater mean BMI (30.7 ± 3.9 *vs.* 27.1 ± 3.5 kg/m^2, $p = < 0.001$), waist circumference (108.5 ± 9.8 *vs.* 98.7 ± 10.2 cm, $p = < 0.001$), and HbA1c (52.8 ± 11.1 *vs.* 49.5 ± 9.5 mmol/mol, $p = 0.049$) compared to those without NAFLD. TE > 8kPa was observed more frequently in NAFLD patients (19.6% *vs* 1.2%, $p = < 0.001$) while there was no difference for > 12kPa, 1.9% and 2.5% in NAFLD and non-NAFLD groups respectively, $p = 0.778$. CAP was higher in participants with NAFLD, with an AUROC of 0.866 for detecting PDFF **e** 5%. Applying a sensitivity of > 90% for the presence of PDFF **e** 5%, a cut-off for CAP of 248 dB/m had a specificity of 66%. Regression analysis of factors to predict NAFLD found BMI, elevated CAP (> 248 dB/m), and elevation of ALT, HbA1c and GT predictive of NAFLD, and this relationship was confirmed when adjusting for age, sex, and BMI. However, in analysis adjusting for all the factors together, only BMI and elevated CAP were independent predictors of NAFLD, where higher BMI increased likelihood of NAFLD by 15% for every kg/m^2, while elevated CAP was associated with an 11.2 times increased risk of NAFLD. **Conclusion:** In this cohort of highly phenotyped primary care patients with T2D, more than half had NAFLD (57%), of whom 21% had suspected advanced fibrosis. Patients with NAFLD had higher BMI, waist circumference and HbA1c, however the only independent predictors of NAFLD were elevated CAP and BMI.

Figure 1 Clinical, and liver specific imaging characteristics of included T2D patients (n=191) (Mean ± SD or n (%))



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2078-A | NASH

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Background: HTD1801 is a new molecular entity which has been shown to significantly reduce liver fat content (LFC) and corrected T1 (cT1) as determined by MRI in an 18-week, placebo-controlled Phase 2 study in patients with nonalcoholic steatohepatitis (NASH) and type 2 diabetes (T2DM) (NCT03656744). Achieving response criteria by LFC or cT1 have both been associated with improvements in liver histology (**e** 2-point improvement in the NAFLD activity score). The purpose of this post-hoc analysis was to assess the characteristics and on-treatment changes in patients who achieved an MRI response. **Methods:** One hundred patients were randomized and treated with HTD1801 1000 mg BID (n = 34), HTD1801 500 mg BID (n = 33), or placebo (n = 33) for 18 weeks. MRI data was collected prospectively for evaluation of the primary endpoint (LFC), and cT1 was evaluated after the completion of the study for patients who had been randomized to HTD1801 1000 mg BID or placebo. MRI response was defined as achieving either **e** 30% LFC reduction or **e** 80 ms cT1 reduction. As cT1 was not assessed in the 500 mg BID group, this analysis focuses on patients randomized to HTD1801 1000 mg BID and placebo. **Results:** MRI response criteria was achieved by 2-fold more patients treated with HTD1801 compared to placebo (52% vs 24%). 22% of all patients randomized to HTD1801 vs 12% randomized to placebo achieved both the LFC and cT1 criteria. At baseline, LFC was balanced between MRI responders and non-responders, but cT1 was elevated in MRI responders. For patients who had been randomized to HTD1801, the baseline biochemical characteristics of MRI responders were indicative of more severe disease compared to MRI non-responders (Table 1). In contrast, patients who had been randomized to placebo and were MRI responders had less severe disease by biochemistry. Within the subgroup of MRI responders, patients who had been randomized to HTD1801 had substantial improvements in ALT, FIB-4, FPG, HbA1c, LDL-C and weight. Furthermore, within the non-responders, modest improvements in ALT, FPG, HbA1c, LDL-C and weight were observed with HTD1801 compared to no change observed in placebo randomized patients. **Conclusion:** Twice as many patients achieved MRI response criteria with HTD1801 compared to placebo. Furthermore, improvements were observed with HTD1801 in liver biochemistry and key cardiometabolic parameters in both responders and non-responders. HTD1801 continues to be evaluated in a biopsy-based Phase 2b study (NCT05623189).

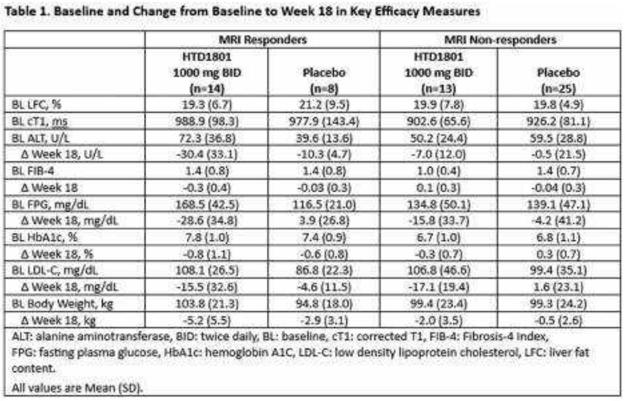

Table 1. Baseline and Change from Baseline to Week 18 in Key Efficacy Measures

	MRI Responders		MRI Non-responders	
	HTD1801 1000 mg BID (n=14)	Placebo (n=8)	HTD1801 1000 mg BID (n=13)	Placebo (n=25)
BL LFC, %	19.3 (6.7)	21.2 (9.5)	19.9 (7.8)	19.8 (4.9)
BL cT1, ms	988.9 (98.3)	977.9 (143.4)	902.6 (65.6)	926.2 (81.1)
BL ALT, U/L	72.3 (36.8)	39.6 (13.6)	50.2 (24.4)	59.5 (28.8)
Δ Week 18, U/L	-30.4 (33.1)	-10.3 (4.7)	-7.0 (12.0)	-0.5 (21.5)
BL FIB-4	1.4 (0.8)	1.4 (0.8)	1.0 (0.4)	1.4 (0.7)
Δ Week 18	-0.3 (0.4)	-0.03 (0.3)	0.1 (0.3)	-0.04 (0.3)
BL FPG, mg/dL	168.5 (42.5)	116.5 (21.0)	134.8 (50.1)	139.1 (47.1)
Δ Week 18, mg/dL	-28.6 (34.8)	3.9 (26.8)	-15.8 (33.7)	-4.2 (41.2)
BL HbA1c, %	7.8 (1.0)	7.4 (0.9)	6.7 (1.0)	6.8 (1.1)
Δ Week 18, %	-0.8 (1.1)	-0.6 (0.8)	-0.3 (0.7)	0.3 (0.7)
BL LDL-C, mg/dL	108.1 (26.5)	86.8 (22.3)	106.8 (46.6)	99.4 (35.1)
Δ Week 18, mg/dL	-15.5 (32.6)	-4.6 (11.5)	-17.1 (19.4)	1.6 (23.1)
BL Body Weight, kg	103.8 (21.3)	94.8 (18.0)	99.4 (23.4)	99.3 (24.2)
Δ Week 18, kg	-5.2 (5.5)	-2.9 (3.1)	-2.0 (3.5)	-0.5 (2.6)

ALT: alanine aminotransferase, BID: twice daily, BL: baseline, cT1: corrected T1, FIB-4: Fibrosis-4 Index, FPG: fasting plasma glucose, HbA1c: hemoglobin A1C, LDL-C: low density lipoprotein cholesterol, LFC: liver fat content.

All values are Mean (SD).

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Stephen A Harrison – Novo Nordisk: Speaking and Teaching, Yes, No;

Abigail Flyer – HighTide Therapeutics: Consultant, No, No;

Alexander Liberman – HighTide Therapeutics: Employee, No, No;
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Disclosure information not available at the time of publication: Guy W. Neff

2079-A | NASH CIRRHOSIS: DISTINCT PHENOTYPICAL DIFFERENCES, MORE SYSTEMIC INFLAMMATION, AND MORE FRAIL THAN VIRAL-RELATED CIRRHOSIS

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Background: NASH is replacing viral hepatitis as the fastest-growing etiology of liver cirrhosis globally with limited therapeutic options. The phenotypic, immunological and functional comparison between NASH and viral-related cirrhosis were limited. We aim to compare the phenotypical, immunological and functional differences between NASH and viral-related cirrhosis patients. **Methods:** This single-centre prospective cohort study recruited stable cirrhosis patients from May 2022 to January 2023. Baseline laboratory tests, liver stiffness measurement (LSM) and gender-specific functional tastings (handgrip, sit-to-stand (STS) and gait speed) were performed on the same day. Serum cytokines were measured using BioLegend LegendPlex Assay. Clinically significant portal hypertension (CSPH) was defined as either the presence of varices, collaterals, ascites, hepatic encephalopathy, or HVPG **e** 10mmHg. Controlled etiology was defined as normal ALT ($<$35Iu/ml), with either virological suppression ($<$20Iu/ml) in HBV, SVR12 in HCV, or non-obese (BMI $<$ 30kg/M^{2}) in NASH cirrhosis. Patients with signs of infection or immunosuppressants were excluded. **Results:** A total of 47 stable cirrhosis patients (NASH: 46.8%, Viral: 53.2% (HBV: 40.4%, HCV: 12.8%) were analyzed. Most patients had compensated cirrhosis (95.8% Child-Pugh Class A, 75% ALBI grade 1). The median (IQR) age was 63 years-old (56-71), BMI was 27.1kg/m^{2} (23.7-30.2). Metabolic risk factors were prevalent: 89.4% had at least 1 metabolic risk factor, and 70.2% fulfilled metabolic syndrome. At baseline, the median (IQR) white blood cell (WBC) was 6.4 (5.0-7.5), neutrophil/leukocyte ratio (NLR) was 1.8 (1.5-2.8), and ALT was 30 (22-46). Compared to viral-related cirrhosis, NASH cirrhosis patients were more likely to be female gender (*64% vs 38%, p = 0.02*), with diabetes (*77% vs 44%, p = 0.036*), hypertension (*91% vs 56%, p = 0.01*), and dyslipidemia (*96% vs 60%, p = 0.0005*). NASH cirrhosis was less likely to have controlled underlying etiology (*27% vs 64%, p = 0.019*). Both NASH and viral-related cirrhosis patients were comparable in CTP-score, ALBI score, baseline liver stiffness measurement, and the prevalence of CSPH. However, NASH cirrhosis had a significantly higher level of inflammatory cytokines than viral-related cirrhosis: TNF-α (*6.9 vs 0, p = 0.029*), IL-8 (*28.6 vs 3.9, p = 0.002*), IL-12p70 (*9.1 vs 3.9, p = 0.029*), and IL-17A (*1.9 vs 0, p = 0.029*). NASH cirrhosis patients also more likely to have a weaker handgrip (*59.1% vs 28.0%, p = 0.042*), prolonged STS (*64% vs 44%, p = 0.244*), and reduced gait speed (*43% vs 20%, p = 0.117*). **Conclusion:** NASH cirrhosis patients had distinct phenotypic differences compared to viral-related cirrhosis. NASH cirrhosis had more systemic inflammation, were frailer, and yet were less likely to have controlled etiology than viral-related cirrhosis. Our findings highlight the unmet therapeutic need in NASH cirrhosis patients.

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Rahul Kumar – Gilead: Speaking and Teaching, No, No; Abbvie: Speaking and Teaching, No, No; Intercept Pharma: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; Verve Therapeutics: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; Crisper Therapeutics: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; Madrigal Therapeutics: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; ETNB: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
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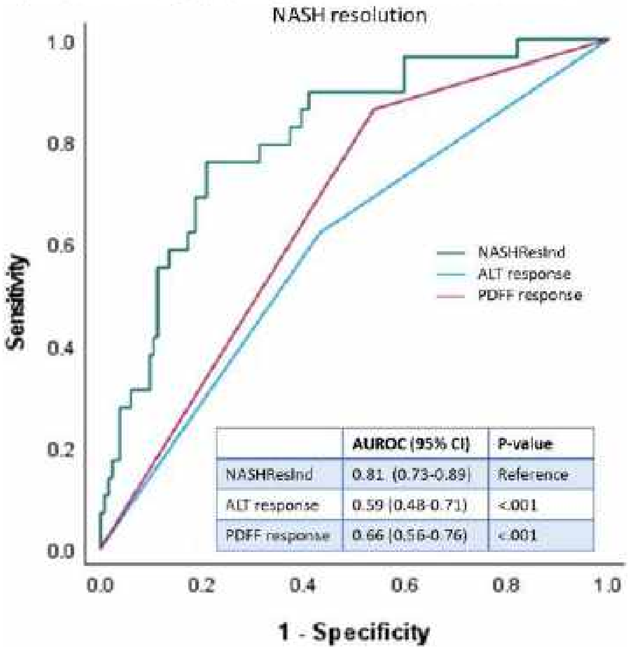
2080-A | NASH RESOLUTION INDEX: DEVELOPMENT AND EXTERNAL VALIDATION OF A NON-INVASIVE SCORE TO PREDICT HISTOLOGIC RESOLUTION OF NASH

Rohit Loomba[1], Maral Amangurbanova[2], Egbert Madamba[2], Harris Siddiqi[2], Claude B. Sirlin[2], Ricki Bettencourt[2], Lisa M. Richards[2] and Daniel Q Huang[3], (1)University of California, San Diego, San Diego, CA, (2)University of California, San Diego, (3)National University Health System (NUHS)

Background: The resolution of nonalcoholic steatohepatitis (NASH) is an accepted regulatory endpoint for subpart H approval of therapies developed for NASH stage 2 or 3 fibrosis but requires an invasive liver biopsy procedure for its assessment. There is a major unmet need to non-invasively determine the resolution of NASH in a precise and reproducible manner. Emerging data suggest that dynamic changes in non-invasive tests (NITs), such as changes in alanine aminotransferase (ALT) and magnetic resonance imaging proton-density-fat-fraction (MRI-PDFF) may help to predict NASH resolution, but a combination of NITs may be more accurate than either alone. We developed a novel non-invasive score, the NASH Resolution Index, to predict the histologic resolution of NASH. **Methods:** This study included 95 well-characterized patients (67% women) with biopsy-confirmed NASH who underwent paired contemporaneous MRI-PDFF and liver biopsy at two-time points as the derivation cohort. The primary objective was to determine a non-invasive score, comprising of a change in ALT, a change in MRI-PDFF, and a third clinical variable, to predict NASH resolution with no worsening of fibrosis. The score was then externally validated in a distinct cohort of 164 participants with biopsy confirmed NASH and a second liver biopsy after 24 weeks. **Results:** The median (IQR) age and BMI were 55 (22-75) years and 32.0 (21.0-47.0) kg/m^2, respectively, in the derivation cohort. The most predictive model (NASH Resolution Index) combined a change in MRI-PDFF, a change in ALT, and baseline AST, which was selected based on the highest area under the receiver operating curve (AUROC), and the lowest Akaike information criterion and Bayesian information criterion. The NASH Resolution index had an AUROC of 0.78 for predicting NASH resolution in the derivation cohort and calibrated well. The score calibrated well, performed robustly in an external validation cohort (AUROC 0.81), and outperformed MRI-PDFF (decline of ≥ 30%) and ALT response (decline of ≥ 17 U/L) (Figure 1), (all $P < 0.001$). **Conclusion:** The NASH Resolution index may be a useful score to non-invasively predict NASH resolution.

Figure 1: NASH Resolution Index versus ALT response (decline of 17 U/L or higher) and MRI-PDFF response (decline of 30% or higher) for predicting NASH resolution in the external validation cohort



	AUROC (95% CI)	P-value
NASHResInd	0.81 (0.73-0.89)	Reference
ALT response	0.59 (0.48-0.71)	<.001
PDFF response	0.66 (0.56-0.76)	<.001

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

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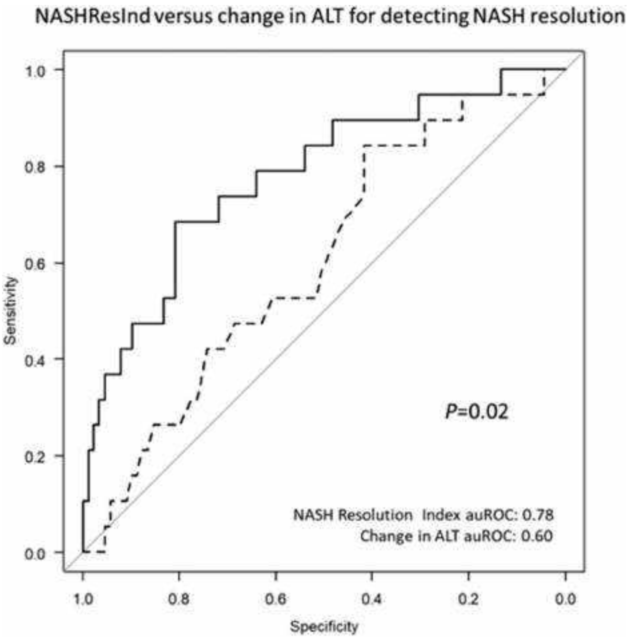
Disclosure information not available at the time of publication: Egbert Madamba, Claude B. Sirlin, Ricki Bettencourt, Lisa M. Richards

2081-A | NASH RESOLUTION INDEX: DEVELOPMENT OF A NON-INVASIVE SCORE TO PREDICT HISTOLOGIC RESOLUTION OF NASH

Rohit Loomba[1], Maral Amangurbanova[2], Egbert Madamba[2], Harris Siddiqi[3], Claude B. Sirlin[2], Ricki Bettencourt[2], Lisa M. Richards[2] and Daniel Q Huang[4], (1)University of California, San Diego, San Diego, CA, (2)University of California, San Diego, (3)University of California San Diego, (4)National University of Singapore

Background: The resolution of nonalcoholic steatohepatitis (NASH) is an accepted regulatory endpoint for subpart H approval of therapies developed for NASH stage 2 or 3 fibrosis but requires an invasive liver biopsy procedure for its assessment. There is a major unmet need to non-invasively determine the resolution of NASH in a precise and reproducible manner. Emerging data suggest that dynamic changes in non-invasive tests (NITs), such as changes in alanine aminotransferase (ALT) and magnetic resonance imaging proton-density-fat-fraction (MRI-PDFF) may help to predict NASH resolution, but a combination of NITs may be more accurate than either alone. We developed a novel non-invasive score, the NASH Resolution Index, to predict the histologic resolution of NASH. **Methods:** This study included 108 well-characterized patients (61% women) with biopsy-confirmed NAFLD who underwent paired contemporaneous MRI-PDFF and liver biopsy at two-time points. The primary objective was to determine a score, comprising of a change in ALT, a change in MRI-PDFF, and a third clinical variable, to predict NASH resolution with no worsening of fibrosis. **Results:** The median (IQR) age and BMI were 54 (43-61) years and 32.0 (29.0-37.0) kg/m^2, respectively. The most predictive model combined a change in MRI-PDFF, a change in ALT, and baseline AST, which was selected based on the highest area under the receiver operating curve (AUROC), and the lowest Akaike information criterion and Bayesian information criterion. The NASH Resolution index calibrated well, had an AUROC of 0.78 for predicting NASH resolution and outperformed change in ALT (AUROC 0.60), P = 0.02 (Figure 1). **Conclusion:** The NASH Resolution index may be a useful score to non-invasively predict NASH resolution.



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2082-A | NIS2-MICE, AN ADAPTATION OF THE CLINICAL NIS2+" DIAGNOSTIC TEST FOR THE DETECTION OF NAS e 4 & F e 2 IN GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF NASH WITH ADVANCED FIBROSIS

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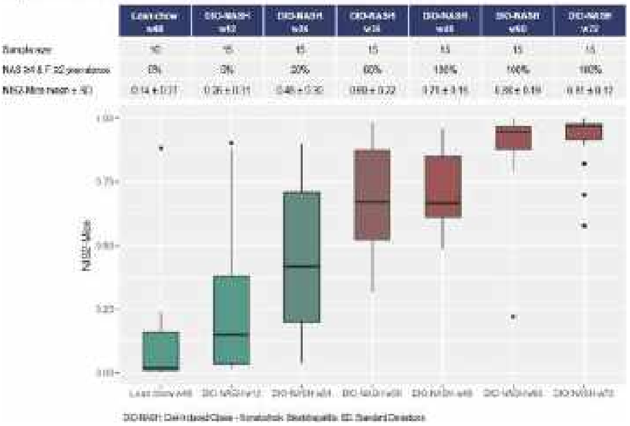
Background: The Gubra-Amylin NASH (GAN) diet-induced obese (DIO) and biopsy-confirmed mouse model of NASH with progression to advanced fibrosis (stage F3) represents a validated translational model used in preclinical research and drug discovery. NIS2+™ is a clinical blood-based dual biomarker (miR34-a, YKL-40) test that has been recently developed and validated for the detection of at-risk NASH (NAS **e** 4 & F **e** 2) in humans. We here aimed to develop NIS2-Mice, an adapted mouse version of the NIS2+™ test and assessed its performance in the GAN DIO-NASH mouse model. **Methods:** Disease progression was profiled in C57BL6/J mice fed the GAN diet (40% fat, 22% fructose, 2% cholesterol) for 12-72 weeks ($n = 15$ per timepoint). Chow-fed mice ($n = 10$) served as healthy lean controls. Blood samples were collected for measuring miR34-a and YKL-40 and compared to automated deep-learning-based histopathological scoring of non-alcoholic fatty liver disease activity score (NAS) and fibrosis stage. A logistic regression was trained using the data obtained in the present study, fitting for the binomial NAS **e** 4 & F **e** 2 condition. Training diagnosis performance of NIS2-Mice test validity and its composite markers were assessed (AUC, sensitivity, specificity, Positive and Negative Predicted Values [PPV, NPV]). **Results:** After **e** 48 weeks on GAN diet, all mice demonstrated histologically-confirmed NAS **e** 4 & F **e** 2. The mean of NIS2-Mice constantly increased with disease severity, from 0.14 in lean controls to 0.91 at week 72 in GAN DIO-NASH mice. When compared with a paired-Delong test, NIS2-Mice test attained a significantly larger AUC compared with miR34-a (0.897 vs 0.853, $p = 0.033$) and YKL-40 (0.897 vs 0.635, $p < 0.0001$) alone, confirming the added-value of dual biomarker assessment over single biomarker use. Using a derived Youden cutoff (0.5492), the diagnostic performance of NIS2-Mice reached a sensitivity of 90%, a specificity of 78%, a PPV of 86% and an NPV of 84%. **Conclusion:** As observed in human patients for the clinical blood-based dual biomarker test NIS2+™, the adapted NIS2-

Mice test accurately and non-invasively detects histologically-confirmed NAS e 4 & F e 2 in the GAN DIO-NASH mouse model, further supporting clinical translatability and utility of the model in preclinical drug discovery for NASH. Furthermore, the NIS2-Mice test introduces an approach directly related to animal reduction and refinement in regulatory 3Rs preclinical testing and animal experimentation.

Figure. NIS2-Mice evolution against NAS ≥4 & F ≥2 prevalence evolution



Disclosures: Yacine Hajji – Genfit S.A.: Employee, Yes, No;
Jérémy Magnanensi – GENFIT S.A.: Employee, Yes, No;
Susanne E. Pors – Gubra: Employee, Yes, No;
Michael Feigh – Gubra: Employee, Yes, No; Gubra: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No; Gubra: Executive role , Yes, No;
Disclosure information not available at the time of publication: Elodie Delecroix, Zouher Majd, Audrey Levy, Malte Hasle Nielsen, Christian Rosenquist

2083-A | NONINVASIVE DIAGNOSIS OF NONALCOHOLIC FATTY LIVER DISEASE BY ULTRASOUND-DERIVED FAT FRACTION: A MULTICENTER STUDY

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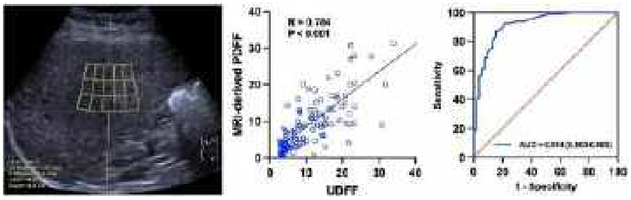
Background: To prospectively assess the role of ultrasound-derived fat fraction (UDFF) in the detection of hepatic steatosis using magnetic resonance imaging-derived proton density fat fraction (MRI-derived PDFF) as the reference standard. **Methods:** From January 2023 to April 2023, participants with or suspected of having nonalcoholic fatty liver disease (NAFLD) were prospectively recruited by multi-center. All participants underwent UDFF and MRI-derived PDFF measurements on the same day. Detailed medical history records were gathered. An MRI-derived PDFF cutoff of 5 % was used for the definition of NAFLD. The correlation between UDFF (%) and MRI-derived PDFF (%) was calculated using the Spearman correlation coefficient. The area under the receiver operating characteristic curve (AUC) was calculated to assess the accuracy of UDFF in the diagnosis of hepatic steatosis. **Results:** A total of 132 participants were included: 50.0 % (66/132) were male, median age was 41.0 years (interquartile ranges [IQR]: 32.3 - 54.0); 20.5 % (27/132) and 55.3 % (73/132) were categorized as over-weight (body mass index [BMI]: 23–25 kg/m^2) and obese (BMI$>$25 kg/m^2), respectively; 60.6 % (80/132) of participants had NAFLD, 28.8 % (38/132) had dyslipidemia, 22.7 % (30/132) had type 2 diabetes mellitus, and 16.7 % (22/132) had hypertension. The UDFF had significant correlations with BMI (**Á**=0.595, $P<0.001$), triglycerides (**Á**=0.506, $P<0.001$), gamma-glutamyl transferase (**Á**=0.452, $P<0.001$), alanine aminotransferase (**Á**=0.428, $P<0.001$), aspartate aminotransferase (**Á**=0.276, $P=0.001$), high-density lipoprotein cholesterol (**Á**=- 0.221, $P=0.011$), and total cholesterol (**Á**=0.213, $P=0.014$). The median UDFF and MRI-derived PDFF were 9.1 % (IQR: 4.4, 15.3) and 7.7 % (IQR: 3.4, 12.9), respectively. The Spearman correlation coefficient was 0.784 ($P<0.001$) for UDFF versus MRI-derived PDFF. Using MRI-derived PDFF **e** 5 % as a reference, UDFF had good accuracy for the diagnosis of NAFLD (AUC of 0.914 [95 % confidence intervals [CI]: 0.863, 0.965]), with a sensitivity of 87.5 % (95 % CI: 0.785, 0.931) and a specificity of 84.6 % (95 % CI: 0.725, 0.920). The interobserver agreement and intraobserver agreement of UDFF measurement were excellent (correlation coefficients 0.904-0.969, $P<0.001$). **Conclusion:** The UDFF was useful for assessing NAFLD when using MRI-derived PDFF as the reference standard.



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f 2084-A | NOVEL ARTIFICIAL INTELLIGENCE-ASSISTED DIGITAL PATHOLOGY QUANTITATIVE IMAGE ANALYSIS PREDICTS THE OCCURRENCE OF LIVER-RELATED CLINICAL EVENTS IN THE MULTICENTRIC, EUROPEAN, HEPATIC OUTCOMES AND SURVIVAL FATTY LIVER REGISTRY (HOTSURFR) STUDY

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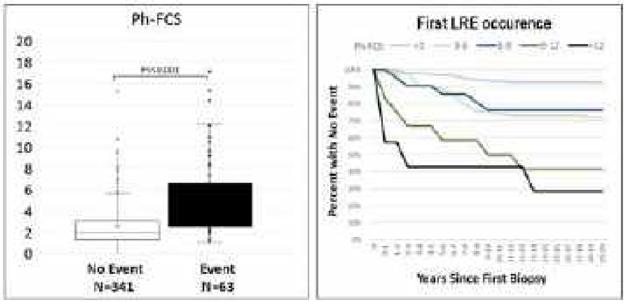
Background: Artificial intelligence-assisted digital pathology provides an automated, operator independent, sensitive and quantitative assessment of histological changes with the ability to identify patterns of fibrosis progression or regression. We previously showed that quantitative traits of collagen fiber parameters can be used to build a fibrosis score that is correlated with the semiquantitative histological NASH CRN stages. However, the value of the fibrosis severity continuous score for the prediction of clinical outcomes is unknown. Here, we aimed to determine if the same score established from baseline liver biopsies is correlated with incident liver-related events (LRE) in a large, multicentric, European cohort with long-term follow-up. **Methods:** 404 patients from 6 European centers with liver biopsy performed before 2011 for suspected NAFLD and clinical follow-up, were retrospectively analyzed. LRE were defined as occurrence of cirrhosis, cirrhosis decompensation events or hepatocellular carcinoma. Formalin-fixed, paraffin-embedded biopsies where stained with collagen stains (Masson Trichrome or Picro Sirius Red) and digitized at 40X. Histology was read centrally (NASH CRN classification). High resolution quantitative image analysis was used to generate a quantitative fibrosis severity score, Ph-FCS, previously optimized to model progression of fibrosis severity. **Results:** Mean age was 53.7 yrs, 58% were males, mean BMI 31.2 kg/m², 37% had diabetes and 60% arterial hypertension. The proportion of histological fibrosis stages were: stage 0: 53%, stage 1: 19%, stage 2: 8%, stage 3: 13% and stage 4: 7%. Median follow-up was 11.4 yrs (IQR 4.7). 63 pts (15.6%) had at least one LRE. Mean (median, sd) Ph-FCS was 5.19 (3.91, 3.74) in pts with LRE vs 2.60 (2.00, 2.22) in pts without LRE ($p < 0.001$) (Figure). At a cut-off value of 3, Ph-FCS had a sensitivity of 0.67 and specificity of 0.75 for the prediction of LRE. When the cut-off value was changed by +/-5% the sensitivity and specificity varied within a -0.048 to +0.028 range. A Ph-FCS score < 2 ruled-out (sensitivity 0.89) while a Ph-FCS score > 3.2 ruled-in (specificity 0.77) the occurrence of LRE. The risk of first LRE occurrence could be stratified using the baseline Ph-FCS score (Figure). **Conclusion:** Quantitative image analysis by digital pathology performed on stained liver slides provides continuous scores (Ph-FCS) that correlates with NASH CRN fibrosis stages and can predict the occurrence of liver-related events. Further validation for clinical outcomes on additional cases is ongoing with the objective to provide better histological surrogates for therapeutic trials.



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2085-A | NOVEL MATRICELLULAR SERUM MARKERS PREDICT LIVER FIBROSIS AND FIBROGENESIS IN PATIENTS WITH NAFLD UNDERGOING BARIATRIC SURGERY

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Background: Obesity is a risk factor for NAFLD and the prevalence of NAFLD in patients eligible for bariatric surgery (BS) can reach 75% to 100%. BS provides successful weight loss and metabolic normalization, and leads to liver histological improvement in some but not all patients. We established and assessed novel serum markers of fibrogenesis in follow-up of a well-defined cohort of patients with obesity and NAFLD undergoing bariatric surgery. **Methods:** Sandwich ELISAs measuring the matricellular fibrosis marker thrombospondin-2 (TSP2) and the metabolism/inflammation/fibrosis-related markers insulin-like growth factor binding protein-7 (IGFBP7), CD163 and a disintegrin and metalloprotease thrombospondin like-9 (ADAMTS9) were established using combinations of recombinant proteins, commercial and self-produced monoclonal and polyclonal antibodies. Sensitivity and specificity were optimized, with intra- and Inter assay variations for serum or plasma below 10% and 15%, resp. 132 severely obese patients with matched liver biopsies were included. 54 patients showed intermediate to advanced fibrosis (stage F2-4) and 74 fibrosis stage F0-1. The evolution of the serum fibrosis markers post-bariatric surgery was analyzed from a subset of 51 subjects with follow-up at 3 & 12 months after BS. **Results:** Patients with F2-4 fibrosis displayed significantly higher baseline levels of the three markers vs patients with fibrosis F0-1 at baseline for TSP2 (88.6 vs 53.9), IGFBP7 (208.8 vs 128), ADAMTS9 (83.3 vs 47.4; ng/ml). These differences were more pronounced comparing fibrosis F3-4 with F0-2. The AUROC values to distinguish fibrosis F2-4 or F3-4 from F0-1 or F0-2 were 0.74 and 0.84 for TSP2, 0.84 and 0.78 for IGFBP7, and 0.72 and 0.70 for ADAMTS9. The AUROC value to distinguish fibrosis F2-4 and F3-4 from F0-1 and F0-2 was significantly increased for the combination of TSP2, IGFBP7 & CD163, reaching the range of a perfect test in view of biopsy sampling error. Levels of TSP2 significantly decreased 3 months after BS in patients with baseline F2-4 fibrosis, supporting its prominent role in liver fibrogenesis, and of IGFBP7, CD163 and ADAMTS9 in fibrogenic inflammation. **Conclusion:** We identified and validated 4 novel noncollagen serum markers of liver fibrogenesis and metabolic inflammation in a unique cohort of patients undergoing BS. The markers TSP2 and IGFBP7 showed the currently highest predictive value for predicting F2-4 fibrosis and response to BS.

Disclosures: The following people have nothing to disclose: Rambabu Surabattula, Pierre Bel Lassen, Sudharani Myneni, Judith Aron-Wisnewsky, Laurent Genser, Jean-Daniel Zucker, Karine Clément, Detlef Schuppan

2086-A | ONLINE EDUCATION SIGNIFICANTLY IMPROVED GASTROENTEROLOGISTS' KNOWLEDGE OF THE IMPORTANCE AND USES OF NONINVASIVE TESTS FOR LIVER FIBROSIS IN PATIENTS WITH NAFLD

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Background: It is estimated that one in four adults world wide has non-alcoholic fatty liver disease

(NAFLD) which can develop into liver fibrosis. Historically, liver biopsy has been used to assess fibrosis but noninvasive tests have now been developed that can be used to assess fibrosis risk. We assessed whether online education could improve gastroenterologists' understanding of the role of noninvasive tests for liver fibrosis and improve their confidence and competence in using these tests in clinical practice. **Methods:** Gastroenterologists participated in 2 online activities: a video lecture and a round table discussion with synchronized slides. For each activity, responses to 3 multiple-choice, knowledge or competence questions and 1 self-efficacy, 5-point Likert scale confidence question were analyzed. Educational effect was assessed using a repeated-pair design, pre-/post-assessment. A paired samples t-test was conducted for significance testing on overall average number of correct responses and for confidence rating. A series of McNemar's tests were conducted at the question level (5% significance level, $P < 0.05$). Activity 1 launched 1 Dec. 2022, data collection 6th Feb. 2023. Activity 2 launched 20th Jan. 2023, data collection 16th Mar. 2023. **Results:** Activity 1 (n = 393 gastroenterologists)

- Significant improvement in knowledge of serum biomarkers used in the FIB-4 test (50% correct responses at baseline, 63% post-activity; $P < 0.001$) and the ELF test (25% correct responses at baseline, 51% post-activity; $P < 0.001$)
- 48% gained confidence in their ability to use risk stratification scores to assess liver fibrosis

Activity 2 (n = 304 gastroenterologists)

- Significant improvement in knowledge of the advantages of the FIB-4 score (53% correct responses at baseline, 64% post-activity; $P < 0.001$) and of fibrosis and its link to liver-related mortality (79% correct responses at baseline, 84% post-activity; $P < 0.01$)
- Significant improvement in competence in selecting the AACE-recommended fibrosis biomarker panel to use in a paient case (44% correct responses at baseline, 65% post-activity; $P < 0.001$)
- 42% gained confidence in their ability to use noninvasive tests to assess the risk of liver fibrosis

Conclusion: These online video activities significantly improved gastroenterologists' knowledge, competence and confidence in the use of noninvasive tests to assess the risk of liver fibrosis.

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The following people have nothing to disclose: Elaine Bell, Anne G Le

2087-A | OPTIMIZING SURVEILLANCE FREQUENCY USING TRANSIENT ELASTOGRAPHY IN LOW-RISK NONALCOHOLIC FATTY LIVER DISEASE

Harish Gopalakrishna, Clinical Research Section, Gaithesberg, MD, Gayatri Nair, Medstar Georgetown University Hospital, Roham Salman Roghani, Eisenhower Health, Natarajan Ravendhran, Johns Hopkins School of Medicine and Yaron Rotman, National Institute of Diabetes and Digestive and Kidney Diseases, Nih

Background: Most individual’s with nonalcoholic fatty liver disease (NAFLD) lack significant fibrosis and are considered “low risk”. The optimal frequency of monitoring these individual’s for progression is uncertain and guidance is based on expert opinion. We aimed to develop a prediction model to determine which low risk subjects can safely avoid re-screening with vibration controlled transient elastography (VCTE) within one year. **Methods:** We included two independent prospective cohorts (derivation and validation) of unselected subjects with NAFLD. All subjects had baseline liver stiffness measurement (LSM) using VCTE which was repeated after 6-12 months irrespective of baseline. Subjects with LSM < 8 kPa at baseline were defined as low risk. The primary endpoint was LSM **e** 8 kPa at follow up, suggesting possible progression. Models to predict the likelihood of possible progression were constructed using univariate and multivariate binary logistic regression. A sequential-testing algorithm was developed on the derivation cohort using the best performing model, maximizing negative predictive value (NPV) and accuracy, and its performance was tested on the independent validation cohort. **Results:** Out of 206 subjects in the derivation cohort, 96 were low risk. 24 (25%) low-risk subjects had a repeat LSM **e** 8 kPa after a median of 10 months. Potential progressors had higher baseline LSM (7 vs 5.6 kPa, $p < 0.01$), higher follow-up BMI ($p = 0.02$) and ALT ($p = 0.04$). A multivariate model combining baseline LSM ($p < 0.01$) and change in ALT from baseline to follow up visit ($p = 0.02$) performed best in identifying progressors with area under the ROC curve of 0.84 (95% CI: 0.74-0.94). Using this combination, a two-step decision algorithm was developed (figure). Baseline LSM thresholds determine which subjects require a follow-up VCTE in a year, while in subjects with intermediate baseline LSM, only those with ALT increase > 6 U/L require re-screening. This algorithm had a NPV of 92%, specificity of 78%, and accuracy of 78% in the derivation cohort. In the independent validation cohort ($n = 64$), it showed NPV of 91%, specificity of 72%, and accuracy of 71%. Applying the algorithm to both cohorts, would have decreased the number of repeat VCTE tests within 1 year by 75% with only 25% of possible progressors misclassified. **Conclusion:** For people with low-risk NAFLD based on baseline VCTE, a simple algorithm which can be applied in primary care setting can be used to avoid the need for a repeat VCTE in a year. Validation of the algorithm for longer monitoring intervals is ongoing.

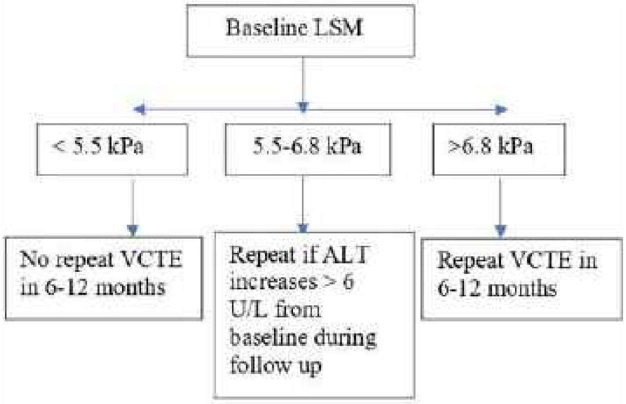

Baseline LSM
< 5.5 kPa
5.5-6.8 kPa
>6.8 kPa
No repeat VCTE in 6-12 months
Repeat if ALT increases > 6 U/L from baseline during follow up
Repeat VCTE in 6-12 months

Figure: Step-wise decision algorithm

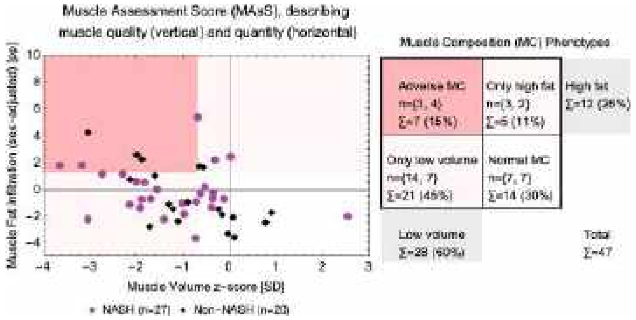
Disclosures: The following people have nothing to disclose: Harish Gopalakrishna, Gayatri Nair, Roham

Salman Roghani, Natarajan Ravendhran, Yaron Rotman

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

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

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



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The following people have nothing to disclose: Omar Jamil, Nirmal Desai, Jonathan Taylor

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

Sven Francque[1], Stephen A Harrison[2], Jorn Schattenberg[3], Bérénice Alard[4], Jérémy Magnanensi[4], Zouher Majd[4], Dean W Hum[4], Bart Staels[5], Quentin M. Anstee[6], Vlad Ratziu[7] and Arun Sanyal[8], (1)University of Antwerp, Edegem, Belgium, (2)Summit Clinical

Research; Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom, San Antonio, TX, (3)I. Department of Medicine, University Medical Centre Mainz, Germany, (4)Genfit S.a., Loos, France, (5) Université De Lille, Inserm, CHU Lille, Institut Pasteur De Lille, Lille, France, (6)Newcastle Nihr Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK, (7) Sorbonne Université, Institute for Cardiometabolism and Nutrition, Hôpital Pitié-Salpêtrière, Paris, France, (8)Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

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

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2090-A | PNPLA3, MBOAT7 AND TM6SF2 MODIFY MITOCHONDRIAL DYNAMICS IN NAFLD PATIENTS: DISSECTING THE ROLE OF CELL-FREE CIRCULATING mtDNA AND COPY NUMBER

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Background: Mitochondrial (mt) dysfunction is a hallmark of progressive NAFLD. MtDNA copy number (mtDNA-CN) and cell-free circulating mtDNA (ccf-mtDNA), which reflect mt-mass and mt-dysfunction, respectively, are gaining attention for NAFLD non-invasive assessment. We demonstrated that PNPLA3, MBOAT7 and TM6SF2 deficiency in HepG2 cells increased mt-mass, mtDNA-CN and ccf-mtDNA. Aims: To assess the genetic contribution on mt-dynamics, mtDNA-CN and ccf-mtDNA in 1) primary mouse hepatocytes silenced for PNPLA3/MBOAT7/TM6SF2 genes; 2) Discovery (n = 28) and Validation (n = 773) cohorts, including biopsied NAFLD patients, stratified according to number of risk variants (NRV = 3). **Methods:** Mt-morphology was assessed by TEM. mtDNA-CN was measured in the entire Validation cohort (n = 773), while ccf-mtDNA in a subgroup (n = 300) with available serum samples. mtDNA-CN and mt-related genes were evaluated in liver biopsies. **Results:** Primary mouse hepatocytes challenged with fat overload or PNPLA3/TM6SF2/MBOAT7 co-silencing lowered mt-fusion paralleled by higher mt-fission and ccf-mtDNA release, suggesting that lipid accumulation and genetics may independently unbalance mt-dynamics. In the Discovery cohort, NRV = 3 patients showed the highest mtDNA-CN compared to those with 1-2 or no variants. At TEM, NRV = 3 carriers increased mt-mass and presented an elevated pattern of mt-morphological alterations (swollen shapes, double membranes rupture). In the Validation cohort, mtDNA-CN associated with the NAFLD histological spectrum and NRV = 3 at multivariate analyses, supporting that both NAFLD severity and genetics may modulate mt-dynamics. In liver biopsies, mtDNA-CN was higher in NRV = 3 patients together with reduction of mt-fusion and activation of mt-fission, resembling what observed in hepatocytes. Ccf-mtDNA was augmented in NRV = 3 patients with low-moderate/severe NAFLD, thereby sustaining that this effect was amenable to the 3 at-risk polymorphisms. By stratifying the Validation cohort according to the clinical phenotype, we found that circulating mtDNA-CN progressively increased from steatosis to HCC and ROC curves showed that it significantly discriminated HCC cases ($p < 0.0001$; AUC: 0.86), resulting a good candidate for NAFLD monitoring. Serum ccf-mtDNA increased in HCC patients and it foretold HCC onset ($p < 0.0001$; AUC: 0.91). **Conclusion:** mtDNA-CN and ccf-mtDNA may have pathological and predictive significance in NAFLD patients at high-risk, especially in those genetically-predisposed.

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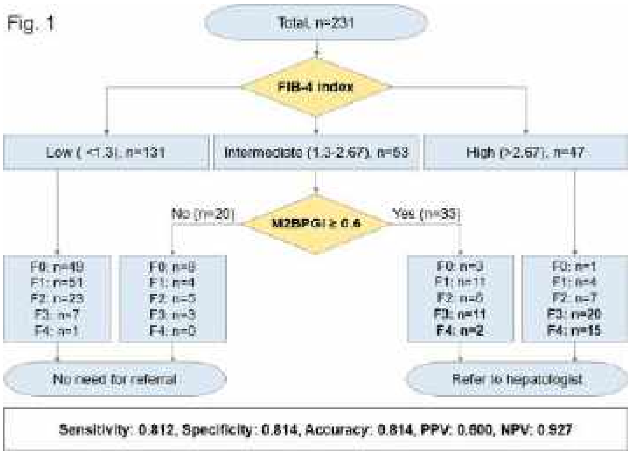
2091-A | PROPOSAL OF A NOVEL SEROLOGICAL ALGORITHM COMBINING A FIBROSIS INDEX BASED ON FOUR AND SERUM MAC-2 BINDING PROTEIN GLYCOSYLATION ISOMER FOR ADVANCED FIBROSIS IN NON-ALCOHOLIC FATTY LIVER DISEASE

Yeowool Kang[1], Yang Hyun Baek[2], Sang Yi Moon[2], Dae Won Jun[3], Se Young Jang[4], Ki Tae Yoon[5], Young Youn Cho[6] and Hoon Gil Jo[7], (1)Dong-a University, (2) Dong-a University College of Medicine, (3)Hanyang University College of Medicine, (4)School of Medicine, Kyungpook National University, (5)Pusan National University Hospital, Busan, Republic of Korea, (6) Chung-Ang University Hospital, (7)Wonkwang University College of Medicine and Hospital

Background: Noninvasive testing methods have become increasingly critical in the diagnosis of liver fibrosis in chronic liver diseases. Herein, we compared the diagnostic performance of serum Mac-2 binding protein glycosylation isomer (M2BPGi) and other serological panels for fibrosis in patients with non-alcoholic fatty liver disease (NAFLD) and proposed an improved two-step diagnostic algorithm for advanced fibrosis in NAFLD. **Methods:** From March 2015 to September 2022, we enrolled 231 patients diagnosed with NAFLD at Dong-A University Hospital and Kyungpook National University Hospital who underwent liver biopsy in this retrospective study. Liver fibrosis stage was assessed according to the system devised by the nonalcoholic steatohepatitis (NASH) clinical research network (CRN) scoring system. F3-F4 was defined as an advanced fibrosis. As a non-invasive method for assessing liver fibrosis, serum M2BPGi, fibrosis index based on four factors (FIB-4), aspartate aminotransferase-to-platelet ratio index (APRI), and nonalcoholic fatty liver disease fibrosis score (NFS) were evaluated. The accuracy of non-invasive markers in the diagnosis of liver fibrosis was calculated using area under the receiver–operator curve (AUROC) analysis. Statistical significance was considered at P-value < 0.05. **Results:** The average age of enrolled patients was 45.7 years. There were 124 (53.7%) males. Associated metabolic diseases were obesity (body mass index **e** 25 kg/m2) (n = 195, 84.4%) and diabetes (n = 75, 32.5%). The confirmed fibrosis grade in liver biopsy was F0 in 61 (26.4%) patients, F1 in 70 (30.3%), F2 in 41 (17.8%), F3 in 41 (17.8%), and F4 in 18 (7.8%). The areas under the receiver operating characteristic curves of serum M2BPGi, FIB-4, APRI, and NFS for advanced fibrosis (**e** F3) were 0.823, 0.858, 0.779, and 0.827, respectively. To reduce the performance of unnecessary liver biopsy, we propose a two-step algorithm using FIB-4 as an initial diagnostic tool and serum M2BPGi (**e** 0.6) as an additional diagnostic method for patients classified as intermediate (23%). Using the proposed algorithm, the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were 0.812, 0.814, 0.814, 0.600, and 0.927, respectively (Fig. 1). **Conclusion:** Serum M2BPGi is a simple and effective test for advanced fibrosis in patients with NAFLD. Application of the two-step algorithm based on FIB-4 and M2BPGi proposed here can improve diagnostic performance and reduce unnecessary tests, making diagnosis easily accessible, especially in primary medical centers

Fig. 1



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Disclosure information not available at the time of publication: Se Young Jang, Young Youn Cho

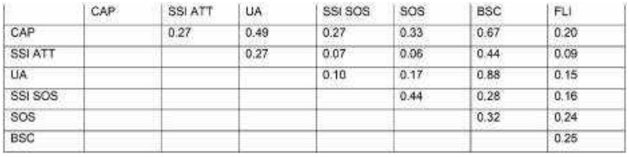
2092-A | QUANTITATIVE ULTRASOUND FOR LIVER STEATOSIS ASSESSMENT WITH A NEW POINT-OF-CARE DEVICE, HEPATOSCOPE, IS REPRODUCIBLE AND SHOWED GOOD CORRELATION TO OTHER NON-INVASIVE TESTS

Victor De Ledinghen[1], Dan Cohen-Dutartre[2], Baptiste Hériard-Dubreuil[3], Adrien Besson[3], Francoise Manon[4], Joelle Abiven[4], Anne-Laure De Araujo[4], Rhizlane Houmadi[4], Julie Dupuy[4], Juliette Foucher[4], Joel Gay[3] and Claude Cohen-Bacrie[3], (1)Centre D'investigation De La Fibrose Hépatique, Bordeaux University Hospital, Pessac, France; Inserm U1053, Bordeaux University, Bordeaux, France., (2)Inria, (3)E-Scopics, (4)CHU Bordeaux, Bordeaux, France

Background: Qualitative liver ultrasound (US) is the first line non-invasive modality to screen for steatosis. Quantitative imaging-derived parameters such as US attenuation (UA), backscatter coefficient (BSC) and speed of sound (SOS) are known to be related to steatosis and have been proposed to improve the qualitative assessment. We evaluated the repeatability (intra-operator) and reproducibility (inter-operator) of UA, BSC and SOS measurements performed by expert and novice operators with the Hepatoscope™, a new ultraportable point-of-care US device. We also assessed their correlation with other available routine non-invasive tests: Fatty Liver Index (FLI), Fibroscan Controlled Attenuation Parameter (CAP™), and Aixplorer® UA and SOS. **Methods:** 96 adult patients referred to routine hepatology consultation for chronic liver diseases were enrolled in this prospective single center study (NCT04782050). UA, BSC and SOS measurements were computed from prospective acquisitions of raw US data with Hepatoscope. Operators were blinded to any median value for each series of acquisitions. UA, BSC and SOS measurements were estimated using the median of an incremented number of consecutive valid values. Data were analyzed with R to determine repeatability and reproducibility intraclass correlation coefficients (ICC), and the r^2 correlation between non-invasive tests. **Results:** BSC and UA measurements were highly repeatable, regardless of the number of values used to compute a measurement: ICC **e** 0.87. Reproducibility of BSC and UA measurements obtained from 3 valid values were 0.86 and 0.84, respectively. Repeatability by experts and novices were similar: 0.91 (95%CI [0.86-0.94]) and 0.87 (95%CI [0.81-0.91]) for BSC, respectively; 0.89 (95%CI [0.85-0.93]) and 0.87 (95%CI [0.81-0.91]) for UA, respectively. Using 3 values to compute SOS measurements, their overall repeatability and reproducibility were moderate: 0.71 and 0.65, respectively.

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

As shown in Table 1, UA, SOS and BSC correlated moderately with CAP; BSC showed the highest correlations with CAP (0.67; 95%CI [0.51-0.79]) and UA (0.88; 95%CI [0.80-0.93]). US parameters correlated weakly with FLI. **Conclusion:** Three values of liver steatosis-related US parameters with the Hepatoscope were sufficient to ensure moderate to excellent repeatability and reproducibility. These measurements correlated well with Fibroscan CAP. Hepatoscope may be used at the bedside to assess liver steatosis efficiently, although future studies against liver biopsy and MRI PDFF should confirm its performance for the triage of patients at risk of NAFLD-NASH. Table 1. Correlation coefficients (r^2) between ultrasound parameters related to steatosis and FLI.



	CAP	SSI ATT	UA	SSI SOS	SOS	BSC	FLI
CAP		0.27	0.49	0.27	0.33	0.67	0.20
SSI ATT			0.27	0.07	0.06	0.44	0.09
UA				0.10	0.17	0.88	0.15
SSI SOS					0.44	0.28	0.16
SOS						0.32	0.24
BSC							0.25

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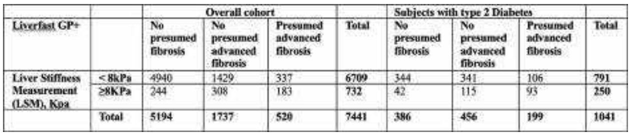
2093-A | RECOMMENDED CLINICAL CARE PATHWAYS (CCPS) WITH FIB-4 UNDERESTIMATES THE PREVALENCE OF ADVANCED FIBROSIS (AF) COMPARED TO SEQUENTIAL CCP WITH LIVERFAST GP+ (GP+) AND LIVER STIFFNESS MEASUREMENT (LSM) BY FIBROSCAN.

Naim Alkhouri, Arizona Liver Health, Phoenix, AZ, Ronald Quiambao, Fibronostics US Inc, USA and Mona Munteanu, Fibronostics

Background: CCPs have been developed to assist clinicians, including primary care medicine, in diagnosing NAFLD with AF based on noninvasive sequential testing with FIB-4 followed by liver stiffness measurement (LSM) by Fibroscan. (*Kanwal, Gastroenterology 2021; Rinella, Hepatology 2023*). Liverfast GP+ is a noninvasive blood-based AI-algorithm combining common biochemistry with anthropometrics that outperforms FIB-4 and has no limitations related to age or diabetes. (*deLédinghen, JHepatol 2023-A)* We recently validated GP+ that achieved 100% histological confirmation when concordant for AF with LSM. *(Alkhouri,JHepatol 2023-A).* The study aims to perform a comparative assessments of the prevalence of AF using recommended CCP (sequential FIB4 and LSM) and using newly released triage tool, GP +, downstream of LSM, on the 2017-March 2020 Pre-pandemic NHANES cohort. **Methods:** We performed a retrospective analysis of data collected from 15,560 US subjects from the nationally representative sample of NHANES 2017-March 2020 pre-pandemic cohort. Subjects were assigned to one of the four GP+ diagnostic categories; GP+ 4th category defines the presumed AF. Cut-offs of 2.68 and 1.3 have been used for FIB4 to assign AF and the indeterminate zone (IZ), respectively. All subjects aged 18 years or more without missing data for GP+, FIB-4 and LSM with IQR/median LSM $<$ 30% have been included. Clinically significant fibrosis was assigned as per LSM **e** 8.0KPa. The prevalence and the agreement to identify AF have been estimated using recommend CCP and newly released GP+ in sequential combination with LSM. **Results:** A total of 7441 subjects have been included [mean(se) age 49(0.2) years, BMI 29.6(0.1)kg/m2, ALT 22(0.2)U/L, AST 22(0.2)U/L, diabetes 14%, LSM 5.8(0.06)kPa, CAP 263(1)dB/m]. 227 (3.1%) subjects had FIB4 $>$ 2.67 and, among them, 86 (1.2%) have been presumed AF with LSM; among them, 57/86 have been presumed AF with GP+. In 1765 (23.7%) subjects FIB-4 ranged 1.30-2.67 (indeterminate); among them, 226 (3.0%) had presumed AF with LSM and 85/226 have been presumed AF with GP+. When GP+ have been used instead of FIB4, 520 (7.0%) subjects have been identified with AF and 183 (2.5%) have been confirmed with LSM. Among 1041 subjects whose doctor told them they had diabetes, 52 (5.0%) had FIB4 $>$ 2.67 and 28 (2.7%) had AF confirmed with LSM; 381 (36.6%) had FIB4 indeterminate and, among them, 94 had AF confirmed with LSM. 199 (19.1%) had GP+ presumed AF and, among them, 93 (8.9%) have been confirmed with LSM. **Conclusion:** Using the strength of concordance between GP+ and LSM, the prevalence of presumed AF in the NHANES pre-pandemic cohort was estimated as being twice higher than if presumed with FIB4 (2.5% vs. 1.2%, respectively). Among patients with diabetes, the prevalence of presumed AF was 8.9%. GP+ can be used as a triage tool, confirmed with LSM, to better identify subjects to be addressed to hepatologists.



Liverfast GP+		Overall cohort				Subjects with type 2 Diabetes			
		No presumed fibrosis	No presumed advanced fibrosis	Presumed advanced fibrosis	Total	No presumed fibrosis	No presumed advanced fibrosis	Presumed advanced fibrosis	Total
Liver Stiffness Measurement (LSM), Kpa	<8kPa	4940	1429	337	6709	344	341	106	791
	≥8KPa	244	308	183	732	42	115	93	250
	Total	5194	1737	520	7441	386	456	199	1041

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Inventiva: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Ionis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; NGM: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; 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Mona Munteanu – Fibronostics: Employee, No, No;

2094-A | REDUCING SCREEN FAILURE RATES FOR NASH CLINICAL TRIALS USING BALLOONING AND FIBROSIS ASSESSMENT WITH SECOND HARMONIC GENERATION/TWO-PHOTON EXCITATION MICROSCOPY AND ARTIFICIAL INTELLIGENCE ANALYSIS: RESULTS FROM THE TANDEM TRIAL

Kutbuddin Akbary[1], Ya-Yun Ren[1], Dean Tai[2], Naim Alkhouri[3], Dominique Brees[4] and Jossy Kochuparampil[4], (1)Histoindex Pte Ltd, (2)Histoindex Pte Ltd, Singapore, (3)Arizona Liver Health, Phoenix, AZ, (4)Novartis Pharma AG

Background: Liver biopsy evaluation in non-alcoholic steatohepatitis clinical research network classification (NASH-CRN) by pathologists' interpretation are used in clinical trials for inclusion criteria and treatment endpoints. Alternative methods maybe more sensitive and offer quantitative evaluation of liver histology. We describe second harmonic generation/two-photon excitation (SHG/TPE) microscopy with artificial intelligence (AI) analyses of liver biopsies for quantitative assessment of fibrosis and ballooning and its potential in reducing screening failure rates in NASH drug trials. **Methods:** Biopsy from 138 patients diagnosed with non-alcoholic fatty liver disease (NAFLD) excluded due to histologic criteria in a NASH phase 2 trial (NCT03517540), were evaluated for liver fibrosis and ballooning using SHG/TPE microscopy, providing measurements on a continuous scale (qFibrosis [qF] and qBallooning [qB]). Continuous values were changed to categorical scores (qF0–qF4/qB0-qB3) using previously established cut-offs. Patients excluded from the trial due to ballooning score (B0) or fibrosis score (F0, F1, F4) were evaluated. Comparative analysis was done to determine number of patients who failed screening, evaluated by central pathologist and SHG/TPE microscopy. **Results:** Based on central pathologist's readings, 56 patients were excluded for B = 0 score. Additionally, 64 patients who had B > 0 score were excluded due to fibrosis stage being either F0, F1 or F4 (F-screen) (Figure 1). Based on SHG/TPE microscopy and AI analysis, 45 patients with qB = 0 could potentially excluded from the trial. Additionally, 65 patients could be potentially excluded from the trial as their qF stage would be either qF0, qF1 or qF4 (qF-screen) (Figure 1). The difference between patients with B = 0 (n = 56) and qB = 0 (n = 45) is n = 11, with qB identifying more patients with non-zero ballooning grade compared to central pathologist. Using qB scores (qB = 0), it would have been possible to identify 11 patients that could have been included in the trial, if they had undergone a quantitative assessment of their ballooning grade using SHG/TPE. In other words, screen failure rate with B = 0 was 40.6% (56/138) whereas screen failure rate using qB = 0 was reduced to 32.6% (45/138) of patients. Exclusion of patients by central pathologist fibrosis stage and qF was almost identical (n = 64 and n = 65 respectively). **Conclusion:** Incorporating SHG/TPE with AI analyses for assessment along with central pathologist evaluations may be an effective means of improving screening failure rates in NASH trials, especially in assessing ballooning. This study suggests screen failure rates are high in pathologists assessments as they may underestimate grade of ballooning when compared to SHG/TPE imaging. Further research is needed to study clinical significance of such changes and identify appropriate parameters for assessing patient selection for clinical trials.

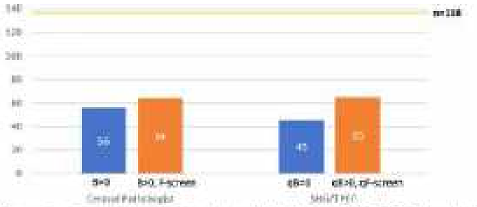

Figure 1. Comparison of Central pathologist and SHG/TPEF based fibrosis and ballooning scores in screen failure patients.

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

Disclosures: Naim Alkhouri – 89Bio: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AbbVie/Allergan: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Akero: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Better Therapeutics: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boehringer Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; 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Dominique Brees – Novartis Pharma AG: Employee, No, No; Novartis Pharma AG: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;

Jossy Kochuparampil – Novartis Pharma AG: Employee, No, No; Novartis Pharma AG: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;

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2095-A | RELEVANCE OF BODY COMPOSITION ASSESSMENT METHODS IN LEAN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Claudineia Almeida Almeida de Souza, Federal University of Bahia, Helma P Cotrim, Ufba; Federal University of Bahia- Brazil; Medicine School and Raquel Rocha; Luiza Vieira Valóis; Naiade Silveira; Urânia Oliveira; Rafael Peixoto; Carla Daltro

Background: The characteristics of NAFLD in lean patients (LEAN-P) have not been fully established. These patients have a predominance of visceral obesity or lipodystrophy, and the body mass index (BMI) may not be sufficiently to define LEAN-P with NAFLD. AIM: to assess the body composition of LEAN-P with NAFLD using anthropometric methods other than BMI. **Methods:** A cross-sectional study involved NAFLD patients, **e** 18 years old. NAFLD criteria: presence of steatosis by ultrasound; consumption **d** 140g of ethanol/week; absence of other liver diseases. The presence of liver fibrosis was assessed by FIB4 score. To evaluate body composition were used waist circumference (WC), neck circumference (NC), and tetrapolar bioimpedance (TBP). The sample was divided into two groups: LEAN-P ($BMI < 24.9$ kg/m²) and non-lean ($BMI > 25$ kg/m²). **Results:** Out of the 71 patients with NAFLD, 8.5% were classified as LEAN-P. Among these 83.3% had mild/moderate steatosis, 16.7% diabetes, 33.3% arterial hypertension. Fibrosis wasn't observed by FIB4 score. These characteristics were similar in non-lean. Excess fat mass was less common in lean patients (16.7% vs 90.5% $p < 0.001$), indicating a more balanced body composition in LEAN-P. Depletion of lean mass was less frequent in the LEAN-P compared to non-lean (16.7% vs 73.4%, $p = 0.010$). **Conclusion:** LEAN-P with NAFLD presented a more balanced body composition compared to non-lean. They also demonstrated a more favorable distribution of visceral obesity and low-fat mass. These results emphasize the relevance of considering body composition beyond BMI alone in the assessment of NAFLD in LEAN-P, leading to improve evaluation and clinic management of these cases.

Disclosures: The following people have nothing to disclose: Claudineia Almeida Almeida de Souza, Helma P Cotrim

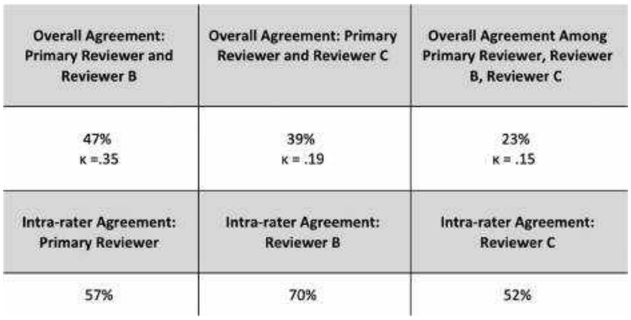
2096-A | RELIABILITY OF LIVER ULTRASONOGRAPHY IN THE ASSESSMENT OF STEATOSIS IN THE CONTEXT OF PREGNANCY

Theresa Worthington[1], Tatyana Kushner[2], Pamela Argiriadi[1], Deborah Feldman[1], Sonam Rosberger[1], Marcia Lange[1], Keith Sigel[1], Rhoda Sperling[1] and Scott L. Friedman[1], (1)Icahn School of Medicine at Mount Sinai, (2)Icahn School of Medicine at Mount Sinai, New York, NY

Background: Non-alcoholic fatty liver disease (NAFLD) currently affects around 15% of women of child-bearing age in the United States, and this number is expected to increase in the coming decade. Liver sonography is the initial diagnostic test for NAFLD with prior data showing intra-observer kappa of 0.4-0.6 and inter-observer kappa of 0.2. Given the rise of NAFLD in the pregnancy population and increased use of ultrasound for diagnosis, we sought to evaluate reliability of ultrasound assessment in pregnant individual's. **Methods:** As part of the prospective Fatty Liver in Pregnancy (FLIP) study, pregnant adults with a BMI **e** 25 and no significant history of alcohol use were eligible for the

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

study. Consented individual's underwent a liver ultrasound at the time of their routine obstetrics anatomy scan at 18-26 weeks gestation. Three obstetric sonography technicians were trained to perform liver sonography by a diagnostic radiologist with expertise in abdominal imaging. One of three ultrasound units with a 2- to 5 MHz convex transducer was used to capture images of the maternal liver. To assess inter-rater reliability, images were de-identified and sent to two additional radiologists blindly for review, who were asked to grade the images as "no steatosis", "grade 1, 2, or 3 steatosis", or "non-diagnostic due to poor image quality." To assess intra-rater reliability, the images were later sent to the radiologists for a second blind review. A survey was conducted to delineate reasons for sub-optimal agreeability. **Results:** Liver ultrasound images were reviewed from 100 patients recruited to participate in the FLIP study from October 2022 to May 2023. The median age of the cohort was 29 (IQR: 24-32) with a median BMI of 30.5 (IQR: 24.9-34.6). A majority (53%) of the cohort identified as being Hispanic or Latino, and 36% identified as Black or African American. Based on our primary reviewer, 60% had no steatosis, 15% had stage 1, 5% had stage 2, 0% had stage 3, and 20% were non-diagnostic. Agreeability between our primary reviewer and reviewer B was 47% ($\kappa = 0.35$). Agreeability between our primary reviewer and reviewer C was 39% ($\kappa = 0.19$). Amongst all 3 reviewers, agreeability was 23% ($\kappa = 0.15$). Intra-rater agreement was 57% for our primary reviewer, 70% for reviewer B, and 52% for reviewer C. **Conclusion:** Inter-rater reliability is fair in the context of pregnancy, which is in line with prior data in non-pregnant settings. To improve inter- and intra-rater reliability, obstetric ultrasound technicians should receive frequent reinforcement training to ensure adequate image quality. Implementation of a scoring system that accounts for image quality issues in the context of pregnancy in addition to disease state would also be beneficial.



Overall Agreement: Primary Reviewer and Reviewer B	Overall Agreement: Primary Reviewer and Reviewer C	Overall Agreement Among Primary Reviewer, Reviewer B, Reviewer C
47% κ =.35	39% κ = .19	23% κ = .15
Intra-rater Agreement: Primary Reviewer	**Intra-rater Agreement: Reviewer B**	**Intra-rater Agreement: Reviewer C**
57%	70%	52%

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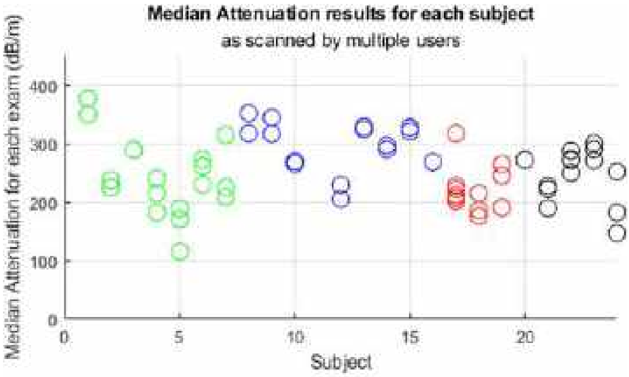
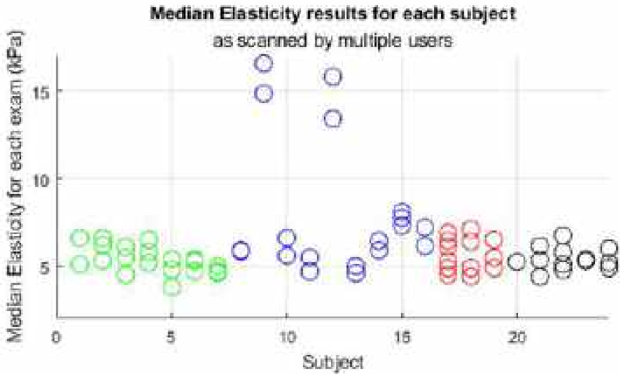
Disclosure information not available at the time of publication: Pamela Argiriadi, Deborah Feldman, Sonam Rosberger, Marcia Lange, Keith Sigel, Rhoda Sperling

2097-A | REPEATABILITY OF VELACUR MEASUREMENTS USING SAME-DAY DIFFERENT-SCANNERS MEASUREMENTS

Stephen A Harrison[1], Caitlin Marie Schneider[2], Kathryn Jean Lucas[3], Tarek Hassanein[4] and Madhavi Rudraraju[1], (1)Pinnacle Clinical Research Center, San Antonio, TX, (2)Sonic Incytes Medical Corp, (3) Diabetes & Endocrinology Consultants, PC, (4) Southern California Research Center

Background: As non-invasive biomarkers become more integrated into the standard of care for diagnosis and monitoring of patients with chronic liver disease, it is important to understand their reproducibility. Here we report the results of the 'same-day, different-scanner' measurements for Velacur elasticity and attenuation in volunteers and patients. **Methods:** Several individual's were trained to perform Velacur exams on the same volunteer on the same day. Velacur exams were collected at 4 different sites across the United States. Exams were performed on both healthy volunteers and patients. Each exam with a particular scanner was made up of 3 to 5 measurements of elasticity and attenuation. The median value of these measurements was used as the result of the exam for analysis. The primary objective was to estimate the Standard Error of Measurement for both elasticity and attenuation, on the same subject, on the same day, with multiple scanners. The Standard Error of Measurement is an absolute measure of reliability of a test score and represents the error attributable to the scanner. **Results:** A total of 14 scanners at four sites in the US participated in this study. 24 volunteers were scanned, with an average of 2.9 scans per volunteer, ranging from 2 to 7. Of these volunteers, nine were patients with various degrees of non-alcoholic fatty liver disease and 15 were volunteers with no history of liver disease. The elasticity scores for all subjects ranged from 3.8 to 16.5 kPa with a mean of 6.1 kPa, and the attenuation measurements ranged from 115 to 376 dB/m, with a mean of 254 dB/m. The Standard Error of Measurement for Elasticity was 0.71 kPa and the Standard Error of Measurement for attenuation was 28 dB/m. **Conclusion:** The Standard Error of Measurement between users is a representation of the difference one might expect if different scanners at the same clinic were to measure the same patient. This represents a 12.5% difference in elasticity measurements and a 11.7% difference in attenuation measurements. This is consistent with reported values from other modalities such as MRE. As all the scanners in the study were new to Velacur, these results are expected to improve as scanners gain experience. These results may help inform future use and understanding of Velacur-based assessments.





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Tarek Hassanein – AbbVie, Bristol-Myers Squibb, Gilead, Mallinckrodt, Merck, Organovo: Advisor, No, No; AbbVie, Bristol-Myers Squibb, Gilead, Mallinckrodt, Merck, Organovo: Consultant, No, No; AbbVie, Allergan, Amgen, Biolinq, Bristol- Myers Squibb, Cytodyn, Assembly, Astra Zeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, CARA, DURECT Corporation, Enanta, Escient, Fractyl, Galectin, Gilead, Grifols, HepQuant, Intercept, Janssen, Merck, Miru: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AbbVie, Bristol-Myers Squibb, Gilead: Speaking and Teaching, No, No;

Disclosure information not available at the time of publication: Kathryn Jean Lucas, Madhavi Rudraraju

2098-A | RISK STRATIFICATION MODEL WITH A HIGH SENSITIVITY IN IDENTIFYING “AT-RISK” FIBROTIC NASH IN A SCREENING STUDY

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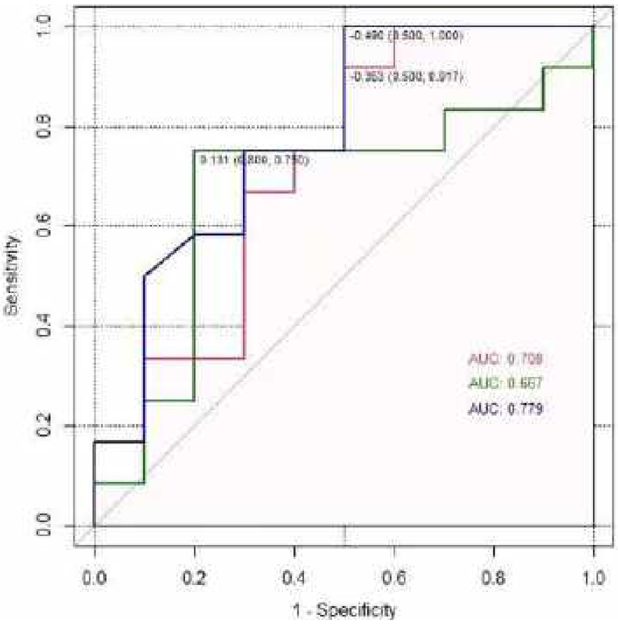
Background: Liver stiffness measurement (LSM) **e** 8kPa detected on FibroScan is highly indicative of at-risk fibrosis. However, many community or non-tertiary medical centers do not have LSM examinations due to lack of the devices. we developed a non-invasively accessible method using serological biomarkers to identify or screen those at-risk fibrotic NASH subjects so that they may be further stratified with FibroScan at tertiary medical centers after initial screening. **Methods:** Patients and laboratory data from 2015 to 2021 were retrospectively reviewed, and divided into “low-risk” and “at-risk” groups using LSM **e** 8kPa as a cut-off for fibrotic NASH. Major serological biomarkers were collected along with subsequent FibroScan reports, and patients confirmed later with NAS < 4 were excluded. The variables with $p < 0.2$ in univariate analysis were then selected for risk stratification modeling using logistic regression. A risk score was developed in the training data set (70% of all data) and validated in the test set (30% of all data). The area under the curve (AUC), sensitivity and specificity were assessed as model performance indicators and then compared to other serological scores (FIB-4 and Aspartate aminotransferase-to-Platelet Ratio Index). **Results:** A total of 73 subjects were included (low-risk: $n = 30$ vs at-risk: $n = 43$). The mean age was 39.2 ± 14.5 years and 45.1 ± 14.3 years in the low-risk and at-risk group, respectively. Among them 25% were female, 23% had type 2 diabetes, and 26% had hypertension. Univariate analysis showed that sex ($p = 0.025$), platelets (PLT) ($p = 0.085$), aspartate aminotransferase(AST) ($p = 0.045$), AST/ALT ratio ($p = 0.038$), and creatinine ($p = 0.014$) were associated with at-risk NASH. The risk stratification model integrated these selected variables and used stepwise regression with akaike information criterion (AIC), and then formulated in logistic scores. AST was an independent predictor of at-risk fibrotic NASH ($p < 0.05$), while AST/ALT ratio and creatinine showed a marginal significance ($p = 0.06$ and 0.054, respectively). The AUC, sensitivity, and specificity were 0.71, 0.92 and 0.5 in the test data, respectively. Delong’s test showed no significant difference between our model and FIB-4 ($AUC = 0.78$), and APRI score ($AUC = 0.67$) in the test set (Figure 1). **Conclusion:** Our risk stratification model integrated easily accessible clinical information and laboratory indicators, and was sensitive in detecting at-risk fibrotic NASH when LSM is unavailable in a screening setting.



Disclosures: The following people have nothing to disclose: Dong Tang, Hanyu LI, JUN Yang, Kehui Nie

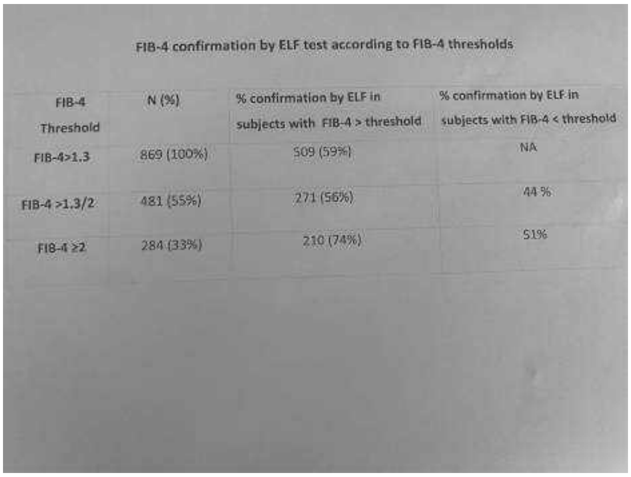
2099-A | SCREENING FOR HEPATIC FIBROSIS IN PRIMARY CARE BY FIB-4 SCORE, AUTOMATICALLY CALCULATED, FOLLOWED IN SECOND LINE BY THE ELF (ENHANCED LIVER FIBROSIS) TEST: WHAT ARE THE BEST FIB-4 THRESHOLDS

Denis Ouzan, Rhecca; Institut Arnault Tzanck, Guillaume Penaranda, Hopital Europeen, Malik Jlaiel, Bioesterel BIO Group and Jeremie Corneille, Bioesterel Biogroup

Background: Screening for liver fibrosis in the general population is a public health issue. We have shown in a previous study that FIB-4, can detect liver fibrosis in general practice and identify a possible cause of liver disease (1). The optimal FIB-4 threshold that allows this screening remains to be specified. FIB-4 thresholds usually used are: low risk if < 1.30, intermediate risk between 1.3 and 2.67, and high risk if **e** 2.67. Only one study has proposed an age-dependent FIB-4 threshold: FIB-4 **e** 1.3 for subjects younger than 65 years and **e** 2 for those older than 65 years (2). The objective of our work was to explore different FIB-4 thresholds and in particular the threshold of 2 for all patients (which is much simpler and independent of age), by performing a second-line ELF (Enhanced Liver Fibrosis) score, after screening for liver fibrosis by FIB-4 in general practice **Methods:** The FIB-4 score was performed prospectively from March to September 2022 in all consecutive patients seen by 15 general practitioners , outside the emergency. When the FIB-4 was **e** 1.3, it was defined

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

as positive, and a confirmatory ELF test was systematically performed. The positive FIB-4 test was confirmed when the second line ELF test was **e** 9.8 . **Results:** Among the 3427 patients seen in general practice, 869 (25%) had a positive FIB4 score,784 (22.5%) at intermediate (FIB-4:1.3-2.67) and 85 (2.5 %) at high risk of fibrosis (FIB-4 > 2.67). Among the 869 FIB-4 positive patients, 509 (59%) were confirmed by the ELF test. 35% of them were older than 65 years. Confirmation was significantly more frequent in subjects over 65 years of age compared to those under 65 years of age: 84 % vs 16 %, p < 0.0001 and in those with a FIB-4 in the high-risk zone, compared to the intermediate zone: 80% versus 56%, p < 0.0001. For an age-dependent FIB-4 threshold (> 1.3 (< 65 yrs.) / > 2 (> 65 yrs.) which concerned 55% of the FIB-4 positive subjects (n = 481), 56% were confirmed by the ELF test (n = 271). For the FIB-4 threshold of 2, regardless of age which concerned 33% of the FIB-4 positive subjects (n = 284), 74% of the FIB-4 **e** 2 subjects were confirmed by ELF testing versus 51% of those with a FIB-4 score < 2 (RR 1.88 (95% CI 1.52-2.32) p < 0 .001). The percentage of FIB-4 subjects in the intermediate fibrosis risk decreases from 22.5 % for a FIB-4 between 1.3 and 2.67, to 12 % for a FIB-4 between 1.3/2 and 2.67, and to 6 % for a FIB-4 between 2 and 2.67. **Conclusion:** ELF testing performed in the second line had significantly more confirmed advanced fibrosis in subjects with FIB-4 **e** 2. A threshold of 2 retains a high percentage of confirmation while reducing the size of the intermediate risk zone for fibrosis and may allow more effective screening for liver fibrosis in primary care. (1) Ouzan D et al. Prospective screening for significant liver fibrosis by FIB-4 in primary care patients. Eur J Gastroenterol Hepatol 2021;33:986-991. (2) McPherson S. et al. Age as a Confounding Factor for the Diagnosis NAFLD fibrosis Am J Gastroenterol 2017;112:740–51.



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

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

Disclosures: The following people have nothing to disclose: Denis Ouzan

Disclosure information not available at the time of publication: Guillaume Penaranda, Malik Jlaiel, Jeremie Corneille

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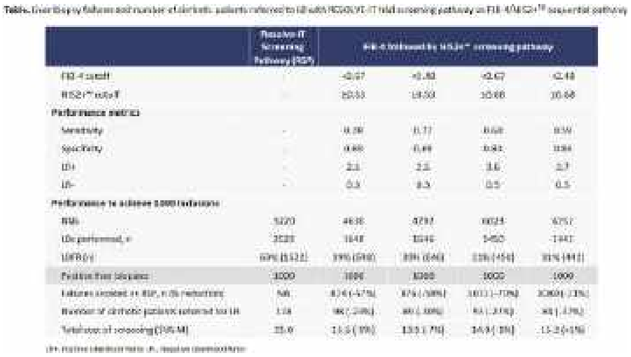
f 2100-A | SEQUENTIAL USE OF FIB-4 AND NIS2+" FOR AN ACCURATE DETECTION OF NON-CIRRHOTIC AT-RISK NASH PATIENTS FOR ENROLLMENT IN NASH CLINICAL TRIALS

Vlad Ratziu[1], Stephen A Harrison[2], Yacine Hajji[3], Jérémy Magnanensi[3], Stephanie Petit[3], Zouher Majd[3], Morgane Dehornois[3], Christian Rosenquist[4], Dean W Hum[3], Bart Staels[5], Quentin M. Anstee[6] and Arun Sanyal[7], (1)Sorbonne Université, Institute for Cardiometabolism and Nutrition, Hôpital Pitié-Salpêtrière, Paris, France, (2)Summit Clinical Research; Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom, San Antonio, TX, (3)Genfit S.a., Loos, France, (4)Novo Nordisk, Soborg, Denmark, (5)Université De Lille, Inserm, CHU Lille, Institut Pasteur De Lille, Lille, France, (6)Newcastle Nihr Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK, (7)Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

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

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



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

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

Huapeng Lin[1], Hye Won Lee[2], Terry Cheuk-Fung Yip[3], Emmanuel A. Tsochatzis[4], Salvatore Petta[5], Elisabetta Bugianesi[6], Masato Yoneda[7], Ming-Hua Zheng[8], Hannes Hagström[9], Jérôme Boursier[10], Jose Luis Calleja[11], George Boon-Bee Goh[12], Wah Kheong Chan[13], Manuel Romero-Gómez[14], Arun Sanyal[15], Victor De Ledinghen[16], Philip N. Newsome[17], Jian-Gao Fan[18], Laurent Castera[19], Michelle Lai[20], Stephen A Harrison[21], Celine D. Fournier-Poizat[22], Grace Lai-Hung Wong[1], Grazia Pennisi[23], Angelo Armandi[24], Atsushi Nakajima[7], Wen Yue Liu[8], Ying Shang[25], Marc De Saint Loup[26], Elba Llop[11], Kevin Kim Jun Teh[12], Carmen Lara Romero[27], Amon Asgharpour[28], Sara Mahgoub[17], Mandy Chan[22], Clemence Canivet[26], Racio Gallego-Durán[29], Seung Up Kim[30] and Vincent Wai-Sun Wong[31], (1)The Chinese University of Hong Kong, (2)Yonsei Liver Center, Severance Hospital, Seoul, South Korea, (3)The Chinese University of Hong Kong, Hong Kong, 91, China, (4)UCL Institute for Liver and Digestive Health, London, UK, (5)Sezione Di Gastroenterologia, Dipartimento Promozione Della Salute, Materno-Infantile, Di Medicina Interna e Specialistica Di Eccellenza "G. D'alessandro", Università Di Palermo, Palermo, Italy, (6)University of Turin, (7)Yokohama City University, (8)Wenzhou Medical University, (9)Unit of Hepatology, Department of Upper GI Diseases, Karolinska University Hospital, Stockholm, Sweden, (10)Service Hépato-Gastroentérologie Et Oncologie Digestive, Centre Hospitalier Universitaire, Angers, France; & Laboratoire Hifih, Sfr Icat 4208, Université D'angers, Angers, France, (11)Universidad Autonoma De Madrid, (12) Singapore General Hospital, (13)University of Malaya, KUALA LUMPUR, Malaysia, (14)Ucm Digestive Diseases, Virgen Del Rocio University Hospital, Instituto De Biomedicina De Sevilla, Ciberehd, University of Seville, Sevilla, Spain, (15)Virginia Commonwealth University, (16)Centre D'investigation De La Fibrose Hépatique, Bordeaux University Hospital, Pessac, France; Inserm U1053, Bordeaux University, Bordeaux, France., (17)University of Birmingham, Birmingham, United Kingdom, (18)Department of Gastroenterology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, (19)Department of Hepatology, Beaujon Hospital, AP-HP, Université Paris Cité, Inserm UMR1149, Clichy, France., (20)Beth Israel

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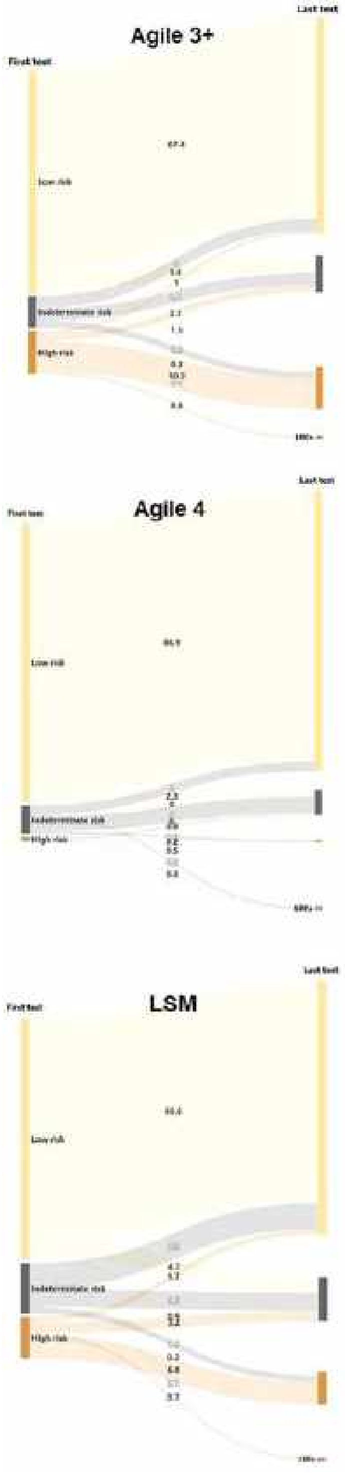
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Deaconess Medical Center, Harvard Medical School, Boston, MA, (21)Pinnacle Clinical Research Center, San Antonio, TX, (22)Echosens, (23)Section of Gastroenterology and Hepatology, Dipartimento Di Promozione Della Salute, Materno Infantile, Medicina Interna e Specialistica Di Eccellenza (PROMISE), (24) Department of Medical Sciences, University of Torino, (25)Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden, (26)Angers University Hospital, Angers, France, (27)Instituto De Biomedicina De Sevilla, Ibis/Hospital Universitario Virgen Del Rocío/ Csic/Universidad De Sevilla. Digestive Diseases Ucm and Ciberehd, (28)Virginia Commonwealth University Health System, (29)University of Seville, (30)Yonsei University College of Medicine, Seoul, Republic of Korea, (31)The Chinese University of Hong Kong, Hong Kong, China

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



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

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

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

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

cases with stage e 2 and NAS e 4. Additionally, repeated liver biopsies of 110 patients with NASLD (mean observation period of 4 (0.5–21) years) were compared based on serum CK18f levels and hepatic histological changes (stage, grade, steatosis, and NAS). **Results:** The levels of serum CK18f were associated with serum ALT and AST, as well as liver inflammation, ballooning, and NAS. Of the 419 patients with FIB-4 index <2.6, 206 (67.3%) demonstrated CK18f e 260 and possible NAS e 4, therefore, recommended for treatment. Conversely, 67% of cases with FIB-4 index <2.6 and CK18f <260 and 83% of cases with type IV collagen 7S <5 and CK18f <260 were diagnosed with stage <2 and NAS <4, excluding FDA criteria was possible.In the 110 repeated liver biopsy cases, inflammation, ballooning, and NASH changes were strongly correlated with CK18f changes. The Δ value of CK18f significantly decreased from 3.3 ± 2.8 to 1.4 ± 1.0 ($P < 0.0001$) in patients with 'no worsening fibrosis' and 'improved NAS', while significantly decreased from 3.1 ± 3.3 to 2.0 ± 1.6 ($P < 0.05$) in patients with 'improving fibrosis' and 'no worsening NAS'. **Conclusion:** CK18f levels are positively correlated with liver inflammation, ballooning, and NAS, reflecting changes in these factors and can predict NASLD progression and improvement. Moreover, CK18f is a useful non-invasive diagnostic marker for FDA criteria recommending treatment and can effectively replace liver biopsy.

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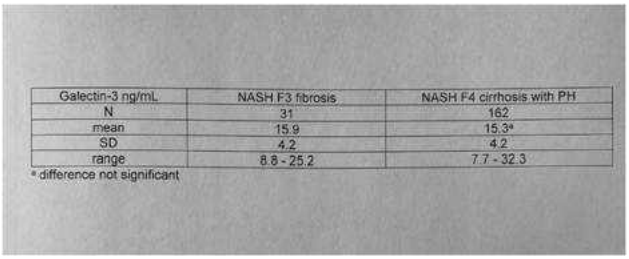
2103-A | SERUM GALECTIN-3 IN PORTAL HYPERTENSION DUE TO NONALCOHOLIC STEATOHEPATITIS (NASH)

Pol Boudes, Ezra Lowe, Michael Inkmann and Steven Schoenfeld, Galectin Therapeutics

Background: Galectin-3 is a major driver of tissue inflammation and fibrosis. It is mainly produced by activated liver macrophages[1] and secreted in the extracellular matrix where it polymerizes to interact with macromolecules and cells to form a lattice structure called the galectin-3 fibrosome. Most galectin-3 is either intra-cellular or in the extra-cellular matrix and it is of interest to understand if serum measurement reflects its intra-tissular content. We use data from two clinical trials, one in non-cirrhotic NASH patients with liver fibrosis and one in cirrhotic NASH patients with portal hypertension (PH) to evaluate serum galectin-3 at different stages of the disease. **Methods:** The first study enrolled 31 NASH patients with Brunt F3 fibrosis (NCT01899859), the second study enrolled 162 NASH patients with Brunt F4 cirrhosis, with portal hypertension hemodynamically determined by a hepatic venous pressure gradient (HVPG) >6 mm Hg but no decompensation (NCT02462967). Serum galectin-3 was measured at baseline with a commercial assay. Descriptive statistics, mean, standard deviation (SD), and ranges were provided and compared between F3 and F4 populations. For clinical relevance, serum galectin-3 was correlated with HVPG. **Results:** Serum galectin-3 appears normally distributed in both population and means (SD) were similar between F3 and F4 populations (Table), indicating that levels do not increase while disease progresses. In patients with PH, serum galectin-3 was not correlated with the measurement of HVPG ($R^2 = 0.0105$). **Conclusion:** Serum galectin-3 might not be a useful biomarker of disease activity in NASH, particularly in compensated cirrhosis with portal hypertension. As in the oncology setting, intra-tissular galectin-3 might be a more relevant biomarker of disease activity and a predictor of response to galectin-3 inhibitor treatment[2]. [1] Goodman, et al. Hepatic expression of galectin-3, a pro-fibrotic and pro-inflammatory marker. An immunohistochemical survey. Hepatology 2022;76(Suppl.1): S419-20 [2] Curti BD, et al. Enhancing clinical and immunological effects of anti-PD-1 with belapectin, a galectin-3 inhibitor. J Immunother Cancer 2021;9: e002371



Galectin-3 ng/mL	NASH F3 fibrosis	NASH F4 cirrhosis with PH
N	31	162
mean	15.9	15.3[a]
SD	4.2	4.2
range	8.8 - 25.2	7.7 - 32.3

[a] difference not significant

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2104-A | SKIN AUTOFLUORESCENCE IS ASSOCIATED WITH FIB-4, FORNS AND FATTY LIVER INDEX – THE MAASTRICHT STUDY

Leen Heyens[1,2,3], Hanna Kenjic[2], Pieter Dagnelie[2], Casper Schalkwijk[2], Coen Stehouwer[2], Steven Meex[2], Jeroen Kooman[2], Otto Bekers[2], Marleen Van Greevenbroek[2], Hans Savelberg[2], Bastiaan De Galan[2], Annemarie Koster[2], Martinus Van Dongen[2], Simone Eussen[2] and Ger H. Koek[2], (1)Hasselt University, (2) Maastricht University, (3)Ziekenhuis Oost-Limburg

Background: Non-Alcoholic Fatty Liver Disease (NAFLD) is the most frequent cause of chronic liver disease in the Western world. In people with type 2 diabetes mellitus (T2DM), NAFLD is reaching epidemic proportions. Among T2DM patients and in normoglycemic individual's with NAFLD, higher levels of advanced glycation endproducts (AGEs) were seen. AGEs can be measured via skin autofluorescence (SAF). As SAF can be easily and non-invasively measured with an AGE reader, it could be a new way to assess the risk for steatosis and fibrosis in T2DM patients. We aimed to examine the association between SAF and liver steatosis and fibrosis, using non-invasive tests in the well-characterized cohort, The Maastricht Study. **Methods:** Data from The Maastricht Study, a prospectively designed, population-based observational cohort study, were used. Participants were excluded when they had alcohol overconsumption and missing data. Multivariable linear regression analysis was used to investigate the association of SAF with the standardized fibrosis-4 index (FIB-4), the Forns index (FI), and the fatty liver index (FLI). Regression models were adjusted for the following key potential confounders; age, sex, and educational status. Other potential confounders additionally adjusted for were: blood pressure, total-HDL cholesterol ratio, smoking status, history of cardiovascular disease, waist circumference, treatment for hypertension, lipid disorders, and glucose lowering medication. For FIB4, age was left out of the model, for FI, this was age and total-HDL cholesterol ratio, and for the FLI this was waist circumference, as these variables are part of the non-invasive score calculations. An interaction analysis was performed to assess the influence of sex. AGEs were assessed with the AGE Reader (DiagnOptics Technologies BV, Groningen, the Netherlands), which uses the characteristic fluorescent properties of certain AGEs to quantify their accumulation in the skin as SAF. **Results:** Of the 3451 participants, 1955 (56.6%) were used for analysis, of whom 598 (30.6%) had T2DM, 264 (13.5%) prediabetes, and 1069 (54.7%) a normal glucose metabolism (NGM). Median age and BMI were 63 (±12) yr and 29.6 (±6.6) kg/m² for T2DM, 62 (±11) yr and 27.3 (±5.4) kg/m² for prediabetes and 58 (±13) yr and 25.3 (±4.4) kg/m² for NGM, respectively. After full adjustment, it was seen that SAF was associated with a higher FLI (Stβ 0.083 [0.036;0.129]), a higher FI (Stβ, 0.106[0.069;0.143]), and FIB-4 (Stβ, 0.087 [0.037;0.137]). Male gender significantly influenced the SAF and FIB4 association (Stβ, 0.125 [0.061;0.189]). **Conclusion:** This observational cohort study showed a positive link between the non-invasive scores FLI, FIB-4 and FI, and SAF. Suggesting that SAF could be a potential non-invasive biomarker to detect liver steatosis and fibrosis among people with T2DM in a non-invasive way. Further research is warranted to confirm these results.

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2105-A | SPATIAL DISTRIBUTION OF COLLAGEN IN NAFLD AFFECTS LEVELS OF N-TERMINAL PRO-PEPTIDE OF TYPE III COLLAGEN (PRO-C3)

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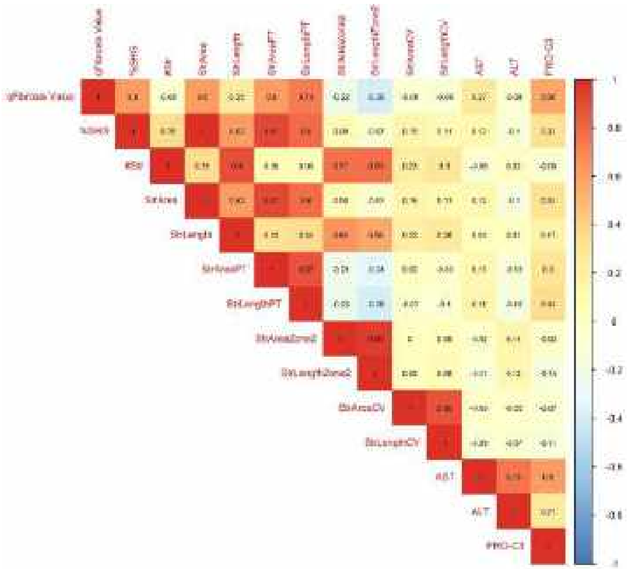
Background: In NAFLD hepatic fibrosis develops slowly over time. The NASH CRN scoring system uses a 5-tier semi-crude system to stage hepatic fibrosis. Little is known about the correlation of non-invasive tests in relation to the spatial distribution of collagen in the liver. **Methods:** In this retrospective analysis liver biopsies of 132 patients with NAFLD were explored. Second harmonic imaging was used to quantitate hepatic fibrosis by qFibrosis. qFibrosis is a composite index combining collagen strings (#StrNumber), length of collagen strings (StrLength) in the central vein (CV), portal tract (PT) and zone 2. Pro-C3 (ELISA), a type III collagen formation marker of fibrosis was measured and correlated to the spatial distribution of collagen. **Results:** The mean age of the cohort was 54 years [43-60], 52.7% male and a mean BMI of 32.2 [28.7-37.0]. Comorbidities included type 2 diabetes (41.2%), arterial hypertension (72.5%), hypertriglyceridemia (32.8%) and obesity (BMI > 30; 54.2%). Standard laboratory included ALT (U/l) 73.0 [50.0-115.7] and AST 50 [38-67]. The histological fibrosis stages were distributed, according to Kleiner, as follows F0 (3.1%), F1a-c (27.5%), F2 (35.1%), F3 (23.7%) and F4 (10.7%). The median (Q1, Q3) qFibrosis value was 1.70 (1.39, 2.38) with a range from 0.48 – 7.77. The median (Q1, Q2) PRO-C3 (ng/mL) was 11.5 (9.4-16.2) with a range from 6.1 – 57.7. The Spearman correlation between PRO-C3 and qFibrosis was high ($\rho = 0.56$, 95% CI [0.43, 0.67]). This was not seen for AST ($\rho = 0.27$, 95 % CI [0.10, 0.43]), nor for ALT ($\rho = -0.080$, 95% CI [-0.25, 0.10]). When exploring the absolute amount of collagen across all regions (% SHG) the correlation with PRO-C3 was $\rho = 0.33$, 95% CI [0.16, 0.48]. The spatial distribution of collagen correlated with PRO-C3 only in the portal tract (StrAreaPT $\rho = 0.3$, 95% CI [0.13, 0.46]; StrLengthPT $\rho = 0.35$, 95% CI [0.18, 0.50]), but not zone 2 (StrAreaZ2 $\rho = -0.02$, 95% CI [-0.20, 0.16]; StrLengthZ2 $\rho = -0.15$, 95% CI [-0.32, 0.03]) or the central vein area (StrAreaCV $\rho = -0.07$, 95% CI [-0.25, 0.11]; StrLengthCV $\rho = -0.11$, 95% CI [-0.28, 0.07]). This correlation was not seen for either AST or ALT (all $\rho < 0.2$). **Conclusion:** The current analysis highlights that the correlation of non-invasive collagen biomarkers with hepatic collagen is dependent on the spatial distribution of collagen. While the NASH-CRN system stresses changes of collagen in the peri-portal region, the current finding highlight that in the design of blood-based biomarkers such as ProC3 spatial fibrosis distribution is relevant.



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2106-A | SYSTEMIC SOLUBLE TREM2 AS POTENTIAL BIOMARKER FOR NAFLD RISK STRATIFICATION

Eva Messer[1], Janett Fischer[1], Albrecht Böhlig[1,2], Johannes Wiegand[1], Thomas Berg[3] and Toni Herta[1],

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

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Background: Non-alcoholic fatty liver disease (NAFLD) may progress to liver cirrhosis and hepatocellular carcinoma (HCC). Biomarkers to identify patients at risk for progression who potentially benefit from a closer surveillance are lacking. Serum levels of soluble triggering receptor expressed on myeloid cells 2 (TREM2), a decoy receptor with pro-inflammatory effects on monocyte activation in the liver, was recently proposed as biomarker in NAFLD to identify patients with florid hepatic inflammation and, therefore, risk of disease progression (J Hepatol 2022;77:1373 and Hepatology 2023;77:558). We report TREM2 serum levels in patients with NAFLD, NAFLD cirrhosis and healthy controls. **Methods:** Soluble TREM2 serum levels were determined by a soluble TREM2 ELISA (Abcam). Laboratory parameters, patient characteristics, and vibration controlled transient elastography results were recorded. NAFLD patients were genotyped for rs738409 in PNPLA3, rs58542926 in TM6SF2, rs641738C > T in MBOAT7, rs1260326 in GCKR, and rs72613567 in HSD17B13 to calculate the polygenic risk score for HCC risk stratification in NAFLD (J Hepatol 2021;74:775). **Results:** Soluble TREM2 serum levels were higher in 146 NAFLD patients (age 55 ± 12 y, 54% female, 51% with cirrhosis) compared to 50 healthy controls (age 54 ± 2 y, 50% female) (48.8 ± 26.6 ng/mL vs. 27.2 ± 10.7 ng/mL, $p = 5.35x10^{-9}$). Patients with NAFLD cirrhosis had higher soluble TREM2 serum levels than non-cirrhotic NAFLD patients (52.4 ± 25.3 ng/mL vs. 44.9 ± 27.5 mg/mL, $p = 0.032$). Soluble TREM2 serum levels correlated with serum aspartate transaminase ($p = 4.79x10^{-5}$), alanine transaminase ($p = 0.001$), total bilirubin ($p = 0.008$), body mass index ($p = 0.019$), FibroScan-AST (FAST) score ($p = 3.23x10^{-8}$), and controlled attenuation parameter ($p = 0.002$) as non-invasive marker for liver steatosis, but not with liver stiffness measurements. High TREM2 serum levels were associated with a high polygenic risk score for HCC ($p = 0.001$). **Conclusion:** NAFLD patients with high soluble TREM2 serum levels might be at increased risk of disease progression, and potentially benefit from a closer surveillance.

Disclosures: The following people have nothing to disclose: Eva Messer, Janett Fischer, Albrecht Böhlig, Johannes Wiegand, Thomas Berg, Toni Herta

2107-A | THE ALCOHOLIC LIVER DISEASE/NONALCOHOLIC FATTY LIVER DISEASE INDEX (ANI) IN CLASSIFICATION OF PATIENTS WITH METABOLIC DYSFUNCTION ASSOCIATED FATTY LIVER DISEASE (MAFLD)

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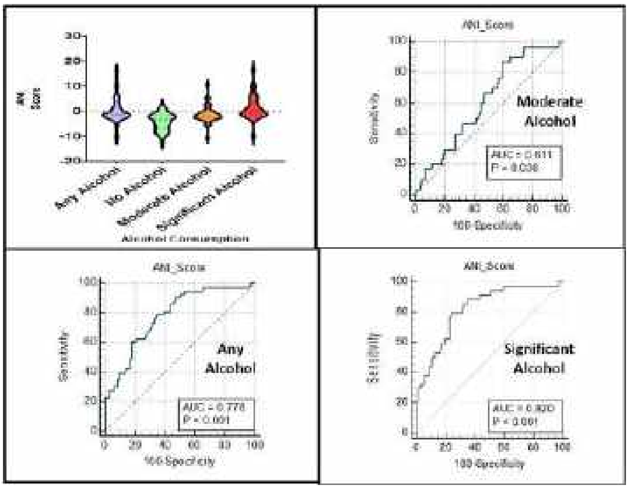
Background: Metabolic dysfunction associated fatty liver disease (MAFLD) does not preclude alcohol consumption (AC) as a prerequisite for diagnosis. AC to a variable extent is not uncommon in patients with MAFLD. The Alcoholic Liver Disease (ALD)/Non-alcoholic Fatty Liver Disease Index (ANI) has been proposed as a differentiating tool, with an ANI score < 0 incrementally favouring non-alcoholic fatty liver disease (NAFLD). **Methods:** Consecutive patients with evidence of fatty liver (defined by MRI-PDFF > 6.5%) who met the definition of MAFLD were included. Patients with alcoholic hepatitis, established cirrhosis, hepatocellular carcinoma, endstage renal disease, advanced heart failure, contraindications to undergo MR imaging and pregnancy were excluded. AC was classified as moderate or significant according to standard definitions.ANI was calculated with an available online calculator. **Results:** 159 patients satisfied the inclusion criteria (22.1% females, mean age 46.59 ± 11.5, mean body mass index 28.1 ± 3.81) with 11.9%, 79.8%, 42,1% being overweight, obese and diabetic respectively. Alcohol consumption was reported in 66 (41.5%) of the patients [32 (20.1%) moderate, 34(21.3%) significant]. ANI scores were significantly different between no alcohol -3.5(-4.80 to -2.72)], any alcohol -1.27(-1.66 to -0.35), moderate alcohol -2.09(-2.68 to-1.15) and significant alcohol -0.02 (-1.3 to 1.5) consumers ($p < 0.05$ for all). The area under curve for ANI for any alcohol use, moderate alcohol use and significant alcohol use were 0.77, 95%CI, 0.705-0.84, cut-off -2.5), 0.61 (95%CI 0.53-0.68, cut-off -3.5) 0.82(95%CI 0.75-0.87, cut-off -1.56). ANI misclassified 8(5.1%) lifetime abstainers as probable ALD and 17 (10.6%) significant alcohol consumers as probable NAFLD. Gamma-glutamyl transpeptidase showed a weak co-relation with ANI [r = 0.28(95% CI 0.13-0.42, $p = 0.03$). **Conclusion:** ANI scores differ across the spectrum of AC in MAFLD and identified significant AC in MAFLD. Different cut-offs instead of dichotomous splitting may better aid sub-stratification of AC in MAFLD.



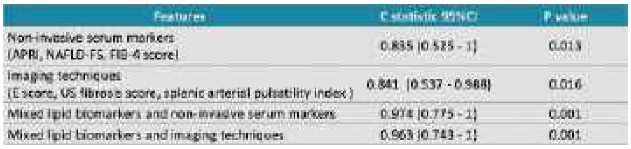
Disclosures: The following people have nothing to disclose: Akash Roy, Nipun Verma

Disclosure information not available at the time of publication: Usha Goenka, Surabhi Jajodia, Awanish Tewari, Mahesh Goenka

2108-A | THE APPLICATION OF LIPIDOMIC ANALYSIS ON NONALCOHOLIC FATTY LIVER DISEASE IN MORBIDLY OBESE PATIENTS

Yin-Ru Hsieh[1], Hua-Chien Wu[2], Weu Wang[3], Ching-Wen Chang[4], I-Wei Chang[5], Chi-Long Chen[5], Chun-Chao Chang[6], Wei-Yu Kao[6] and Shih-Yi Huang[1], (1) School of Nutrition and Health Sciences, Taipei Medical University, Taipei, Taiwan, (2)Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, (3)Division of Digestive Surgery, Department of Surgery, Taipei Medical University Hospital, Taipei, Taiwan, (4) Graduate Institute of Metabolism and Obesity Sciences, Taipei Medical University, Taipei, Taiwan, (5) Department of Pathology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, (6)Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan

Background: Nonalcoholic fatty liver disease (NAFLD) is a spectrum of liver disease including simple hepatic steatosis (NAFL) and nonalcoholic steatohepatitis (NASH) with or without fibrosis or cirrhosis. Approximately 25% global population has NAFLD. This study aims to use untargeted lipidomic analysis to investigate lipidomic profile features in liver and serum among with patients with NASH with mild fibrosis, NASH with significant liver fibrosis and healthy individual's. **Methods:** Lipidomics analysis was performed using ultra-high-performance liquid chromatography–tandem mass spectrometry on serum and liver samples from a prospective cohort study involving morbidly obese patients who underwent sleeve gastrectomy at Taipei Medical University Hospital between September 2016 and December 2020. Ultrasonography (US) and transient elastography (E score) were performed before surgery. Wedge liver biopsy was performed during surgery and significant liver fibrosis was defined as a fibrosis score > 2. Based on these criteria, We selected 10 patients without NAFLD, 20 patients with NASH in fibrosis stage 0-1 and 20 patients with NASH in fibrosis stage 2-4. **Results:** From the data of lipidome, significant changes were observed in sixty-eight lipid species in the liver and ninety lipid species in the serum. Lipids classification includes glycerolipids (GL), glycerophospholipids (GP), sphingolipids (SP), and sterol lipids (ST) that were identified and quantified with false discovery rate (FDR)-adjusted significant P values less than 0.05. Fourteen overlapping lipid species were found in the liver and serum. The heatmap shows that the relative abundance of lipid species in the liver and serum does not follow the same trend as the severity of liver fibrosis. The correlations of the lipid species in serum with clinical, metabolic features and with NAFLD parameters are presented. DG 32:0, TG 56:4, LPC 6:0, PC 40:8, PE 34:2, PE O-38:4, PE O-40:4,and CL 76:1 are positively correlated with the specific clinical characteristics; on the contrary, MG 18:1, DG 44:8, PA 28:3;O2, LPC 20:1 are negatively correlated with the specific clinical characteristics. Multiple predictive models were developed based on the top 3 high-variable importance plots-score metabolites and dimorphic data for detecting NASH with significant liver fibrosis detection. The AUROC (0.904, P = 0.005) was highest with the features of mixed lipid biomarkers and non-invasive serum markers (Figure 1). **Conclusion:** The concentrations of particular lipid species were associated with severity of fibrosis of the liver in NASH. Higher PE O-38:4, PE 34:2, and CL 76:1 in serum were associated with higher risk of significant liver fibrosis. The AUROC was highest with mixed lipid biomarkers and non-invasive serum markers.



Features	C-statistic (95%CI)	P value
Non-invasive serum markers (APRI, NAFLD-FS, FIB-4 score)	0.835 (0.525 - 1)	0.013
Imaging techniques (E score, US fibrosis score, splenic arterial pulsatility index)	0.841 (0.537 - 0.988)	0.016
Mixed lipid biomarkers and non-invasive serum markers	0.974 (0.775 - 1)	0.001
Mixed lipid biomarkers and imaging techniques	0.963 (0.743 - 1)	0.001

Disclosures: The following people have nothing to disclose: Yin-Ru Hsieh, Hua-Chien Wu, Weu Wang, Ching-Wen Chang, I-Wei Chang, Chi-Long Chen, Chun-Chao Chang, Wei-Yu Kao, Shih-Yi Huang

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

2109-A | THE DIAGNOSTIC ABILITY FOR THE DEGREE OF LIVER FIBROSIS USING FIB-3 INDEX, FIB-4 INDEX AND TRANSIENT ELASTOGRAPHY

Takashi Nishimura[1], Toshifumi Tada[2], Yukihisa Yuri[1], Ryota Nakano[1], Tomoyuki Takashima[1], Nobuhiro Aizawa[1], Naoto Ikeda[1], Shinya Fukunishi[1], Hideyuki Shiomi[1], Hirayuiki Enomoto[1], Seiichi HIrota[1], Hirohisa Yano[3] and Hiroko Iijima[4], (1)Hyogo Medical University, (2)Japanese Red Cross Himeji Hospital, (3)Kurume University School of Medicine, (4)Hyogo Medical University, Nishinomiya, Japan

Background: Fib-4 index and transient elastography (TE) is widely used as the non-invasive methods for diagnosing the degree of liver fibrosis in chronic liver disease. Otherwise, Fib-4 index can be influenced by age. Recently, new non-invasive biomarker based on AST, ALT and platelet without age, namely Fib-3 index, has been developed in NAFLD/NASH patients. The aim of this study was to compare the diagnostic ability for the degree of liver fibrosis among Fib-3 index, Fib-4 index and TE **Methods:** The 687 chronic viral hepatitis patients with 330 males(48%), 225 HBV(32.8%) from March 2021 to January 2022 were included in this study. The median age was 67 years old and the number of F0/F1/F2/F3/F4 were 32/ 280/ 138/ 163/ 74, respectively. IQR/median more than 0.3 in the liver stiffness values using TE were excluded. The histological liver fibrosis stage estimated by METAVIRE score was as reference standard. **Results:** Fib-3 index, Fib-4 index and TE increased significantly with the progression of F stage($p < 0.001$). AUROC and cut off values for advanced fibrosis(F3 **d**) were 0.757/ 2.916 in Fib-3 index, 0.772/ 1.944 in Fib-4 index, 0.861/ 7.8(kPa) in TE. AUROC and cut off values for liver cirrhosis were 0.806/ 3.072 in Fib-3 index, 0.804/ 3.919 in Fib-4 index and 0.936/10.1(kPa). The correlation coefficients(r) was 0.907 between Fib-3 index and Fib-4 index, 0.616 between Fib-3 index and TE, 0.590 between Fib-4 index and TE. Moreover, the sensitivity(Se)/ specificity(Sp)/ accuracy(AC) for advanced fibrosis(F3 **d**) using the aforementioned cut off value between the patients with more than 65 age and less than 65 age were examined. In patients with more than 65 age, Se/Sp/AC were 71.9/ 59.4/ 65.5 in Fib-3 index, 90.1/26.6/57.4 in Fib-4 index, 76.9/ 74.2/ 75.5 in TE. In patients with less than 65 age, Se/Sp/AC were 57.8/ 84.1/ 77.2 in Fib-3 index, 65.6/ 79.5/75.8 in Fib-4 index, 70.7/ 87.0/ 82.6 in TE. Se/Sp/AC in Fib-4 index between the twe groups were the largest difference. **Conclusion:** Fib-3 index was a useful non-invasive liver fibrosis diagnostic marker in patient with viral hepatitis.

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The following people have nothing to disclose: Takashi Nishimura, Toshifumi Tada, Yukihisa Yuri, Ryota Nakano, Tomoyuki Takashima, Nobuhiro Aizawa, Naoto Ikeda, Shinya Fukunishi, Hideyuki Shiomi, Hirayuiki Enomoto, Seiichi HIrota, Hirohisa Yano

2110-A | THE DIAGNOSTIC ACCURACY OF NON-INVASIVE TESTS OF FIBROSIS IN PATIENTS WITH METABOLIC ASSOCIATED FATTY LIVER DISEASE. A COMPARATIVE STUDY BETWEEN LIVER BIOPSY AND NON-INVASIVE SCORES OR FIBROSCAN.

Annalisa Cespiati[1,2], Rosa Lombardi[1,2], Daniel Smith[1,2], Cristina Bertelli[1], Felice Cinque[3] and Anna Ludovica Fracanzani[2], (1)SC Medicina Ad Indirizzo Metabolico, Fondazione Irccs Cà Granda Ospedale Maggiore Policlinico, Milan, Italy, (2)Università Degli Studi Di Milano, (3)Mcgill University Health Centre

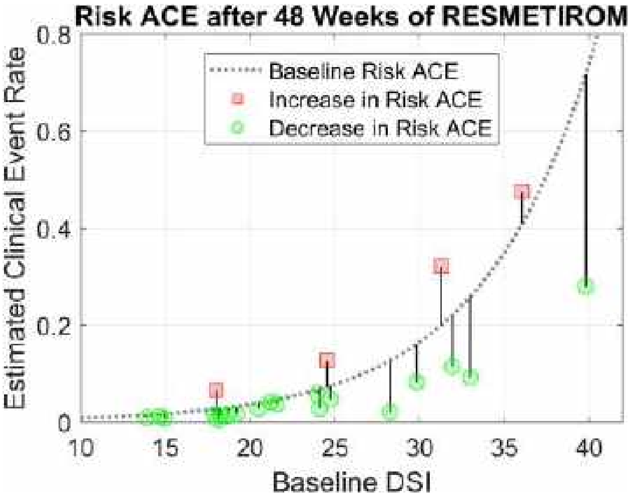
Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is characterized by liver steatosis and at least one metabolic comorbidity. Due to limitations of liver biopsy, non-invasive tests of fibrosis (NITs) (FIB4 and NFS) and liver stiffness measurement (LSM) by Fibroscan are used to diagnose fibrosis. Aims 1) to evaluate the diagnostic accuracy of NITs and LSM in MAFLD 2) to evaluate their performance specifically in diabetic and obese subjects 3) to identify new thresholds for scores NITs and LSM in MAFLD. **Methods:** We enrolled 164 biopsy-proven MAFLD (mean age 56 ± 12 ys, 62% males) in Milan. Clinical, laboratory and Fibroscan data were collected within 6 months from biopsy. FIB-4 < 1.3, NFS < -1.455 and LSM < 8 kPa ruled out advanced fibrosis ($\geq$F3), FIB-4 > 3.25, NFS > 0.675 and LSM **e** 8 kPa suggested advanced fibrosis. **Results:** Prevalence of fibrosis > F3 was 24% at histology. FIB4 and NFS ruled out advanced fibrosis in 49% and 44% of cases, diagnosed it in 7% and 8% and had indeterminate values in 43% and 49% of cases, respectively. LSM **e** 8 kPa in 62% of subjects. All NITs showed a lower accuracy for both identification (AUROCs FIB-4 0.62; NFS 0.57; LSM 0.72) and exclusion (AUROCs FIB-4 0.65; NFS 0.68; LSM 0.72) of advanced fibrosis at biopsy compared to those for non-alcoholic fatty liver disease (NAFLD). The 59% of the cohort was obese, 47% diabetic. For ruling-in advanced fibrosis, FIB-4 and LSM performed worst in diabetic vs non-diabetic (AUROCs FIB-4 0.58 vs 0.69 $p < 0.001$; LSM 0.66 vs 0.71 $p < 0.001$) and in obese vs non-obese MAFLD (AUROCs FIB-4 0.59 vs 0.65 $p<0.001$; LSM 0.68 vs 0.75 $p<0.001$). NFS accuracy did not significantly differ between diabetic and non-diabetic (AUROCs 0.58 vs 0.50 $p=0.06$), whereas it seemed to perform better in obese vs non-obese (AUROCs 0.58 vs 0.55 $p=0.01$). For the exclusion of fibrosis, all NITs performed worst in diabetic vs non-diabetic (AUROCs FIB-4 0.59 vs 0.67 $p=0.001$; NFS 0.58 vs 0.63 $p=0.003$; LSM 0.68 vs 0.69 $p=0.06$) and in obese vs non-obese (AUROCs FIB-4 0.66 vs 0.69 $p=0.002$; NFS 0.65 vs 0.70 $p=0.003$; LSM 0.68 vs 0.74 $p<0.001$). The Youden indexes of current cut-offs for FIB4 and NFS were <0.5 for both ruling in and ruling out advanced fibrosis, whereas new thresholds as FIB-4 > 1.63/NFS > -1.09 and FIB-4 < 1.22/NFS < -1.23 had the best Youden indexes. As for Fibroscan, LSM > 10.4 kPa seemed to better identify MAFLD patients with advanced fibrosis, whereas a cut-off of 8.4 kPa to exclude it. **Conclusion:** In MAFLD, both FIB4 and NFS and Fibroscan performed worse compared to NAFLD, with the latter having the higher accuracy. The presence of diabetes and obesity impairs the performance of score and LSM. In MAFLD lower cut-off of both FIB-4 and NFS are warranted, whereas no change seems to be needed for LSM. Nevertheless, more accurate NITs should be developed specifically for MAFLD.

Disclosures: The following people have nothing to disclose: Annalisa Cespiati, Rosa Lombardi, Daniel Smith, Cristina Bertelli, Felice Cinque, Anna Ludovica Fracanzani

2111-A | THE NEXT GENERATION HEPQUANT TESTS MEASURE REDUCTION IN RISK FOR CLINICAL EVENTS IN COMPENSATED NASH CIRRHOSIS SUBJECTS TREATED WITH RESMETIROM

Michael P. McRae[1], *Steve M. Helmke*[2], *Rebecca A. Taub*[3] *and Gregory T Everson*[2], *(1)Custom DX Solutions LLC, (2)Hepquant, (3)Madrigal Pharmaceuticals*

Background: HepQuant SHUNT test (V1.1) quantifies liver function and physiology from the portal and systemic clearances of stable isotopes of carbon-13-labeled cholate (13C-CA) intravenously (IV) and deuterium-labeled cholate (d4-CA) orally. Simplified versions of the Test (V2.0 and LDT 1.0), which require fewer blood samples and shorter testing time, have been proposed for clinical applications. The objective of this study was to determine whether these NEXT GENERATION (NGEN) HepQuant Tests, using Risk ACE as endpoint, could detect treatment effects in MAESTRO-NAFLD-1 (NCT04197479), an open label, single arm study of resmetirom, a thyroid hormone receptor-β agonist being studied for the treatment of NASH (Harrison et al., Lancet 2019, 394:2012-24). **Methods:** Thirty-four subjects with compensated NASH cirrhosis (eligibility required at least 3 metabolic risk factors, and NASH cirrhosis diagnosed on liver biopsy or according to accepted criteria) underwent baseline testing and subsequent retesting at 28 and 48 weeks. For each test, IV 13C-CA and oral d4-CA were administered. Blood was sampled at 0, 5, 20, 45, 60, and 90 minutes for serum cholate concentrations. Using a compartmental model (McRae et al., 2023), V2.0 was calculated from IV and oral data; LDT 1.0 from only oral data; both at 20 and 60 minutes. Previously, a Poisson model (Risk ACE) was developed to estimate an individual's annual clinical event rate based on 220 subjects with 52 clinical events from the HALT-C trial. Risk ACE was calculated for each subject from the baseline and week 48 disease severity index (DSI). Risk ACE results between methods were compared. **Results:** For LDT 1.0, Risk ACE decreased with resmetirom treatment in 21 of 23 subjects, with significant decrease in the mean (−0.0182 clinical events per person-year, $p=0.0407$). At 48 weeks, Risk ACE decreased in 19 of 23 subjects (−0.0355, $p=0.1222$) (Figure 1). V1.1 and V2.0 also showed similar reductions in Risk ACE at 28 weeks (V1.1: −0.0194, $p=0.1028$; V2.0: −0.0170, $p=0.1145$) and 48 weeks (V1.1: −0.0257, $p=0.1389$; V2.0: −0.0325, $p=0.1605$). **Conclusion:** This study demonstrated that NGEN Tests measured a reduction in estimated clinical event rate after 28 weeks of resmetirom. These results show potential for these Tests and Risk ACE to provide a sensitive and interpretable metric of risk for All Clinical Events in monitoring patients. Further evaluation and clinical validation of NGEN Tests and Risk ACE is warranted.



Disclosures: Michael P. McRae – HepQuant LLC: Consultant, Yes, No;

Disclosure information not available at the time of publication: Steve M. Helmke, Rebecca A. Taub, Gregory T Everson

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

2112-A | THE PREDICTIVE SCORE FOR SCREENING METABOLIC ASSOCIATED FATTY LIVER DISEASE WITH SIGNIFICANT FIBROSIS IN THE PRIMARY CARE SETTING: A MULTICENTER STUDY★

Kessarin Thanapirom[1,2,3], Kanokwan Sonsiri[1], Panarat Thaimai[1], Sirinporn Suksawatamnuay[1,2,3], Piyawat Komolmit[1,2,3] and Sombat Treeprasertsuk[4], (1)Division of Gastroenterology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand, (2)Center of Excellence in Liver Fibrosis and Cirrhosis, Chulalongkorn University, Bangkok, Thailand., (3) Excellence Center in Liver Diseases, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand, (4)Chulalongkorn University, Bangkok, Thailand

Background: Identification of patients with metabolic associated fatty liver disease (MAFLD) at high risk for significant fibrosis (SF) in resource-limited settings remains challenging due to the inaccessibility of liver biopsy or liver elastography. This study aimed to develop prediction models using clinical factors (CF) with or without simple laboratory tests to detect MAFLD with SF in primary care centers. Futhermore, we investigated the correlation between serum Mac-2 binding protein glycosylation isomer (M2BPGi), a novel liver fibrosis biomarker, and transient elastography (TE), as well as its role in the setting of unavailability of TE. **Methods:** We prospectively enrolled individual's without chronic Hepatitis B, C virus or excessive alcohol consumption from 6 primary hospitals in Thailand during 2021-2022. SF and liver steatosis were defined by TE using Fibroscan as cutoff **e** 7 kilopascal and controlled attenuated parameter (CAP) **e** 248 dB/m, respectively. Multivariate logistic regression was performed to develop models that predict MAFLD and SF using TE as the reference standard. A weight score was assigned for each predictor and the optimal cut-off of each model was determined. Excessive weight circumference (EWC) was defined as **e** 90 cm in male and **e** 80 cm in female. **Results:** In total, 613 of the 702 subjects were enrolled with a mean age of 54.9 ± 11.5 years. Of these, 29.4% (n = 180) were diagnosed with MAFLD and SF. Multivariate analysis found diabetes mellitus (DM), body mass index (BMI), EWC, ALT, AST to Platelet ratio index (APRI) and Fibrosis-4 (FIB-4) were potential predictors for detecting MAFLD with SF. Four predictive models were developed and assigned scores (Table 1). All models had a good ability to identify MAFLD with SF with an AUROC of 0.68 for CF, 0.75 for CF+ALT, 0.74 for CF+APRI and 0.74 for CF+FIB-4 ($p < 0.001$). The cutoff of CF **e** 2 demonstrated a 91.3% negative predictive value (NPV), 80.7% sensitivity, 48.2% specificity and the AUROC of 0.65 (95%CI: 0.60-0.69), indicating it was suitable to use for ruling-out MAFLD with SF patients in primary care settings. While employing the CF+ALT **e** 2.5 points had 75.6% sensitivity, 61.7% specificity and AUROC of 0.69 (95%CI: 0.64-0.74), which might be the most practical model for referral decisions. The levels of M2BPGi had a moderate positive correlation ($r = 0.67$, $p < 0.001$) with TE and related to the severity of liver fibrosis. Using M2BPGi **e** 0.87 cutoff index (Jang SY et al. Ann Lab Med 2021) to define SF, CF + ALT **e** 2.5 points had 42.5% sensitivity, 80.3% NPV and an AUROC of 0.58 (95%CI: 0.51-0.65, $p = 0.03$). **Conclusion:** In resource-limited setting, three simple clinical factors, including DM, EWC and BMI **e** 25 kg/m^2 could be used for ruling out MAFLD with SF. Moreover, combining serum ALT with these clinical factors may guide in the decision on referral to specialists for further investigation. If unavailable of TE, serum-based fibrosis marker e.g., M2BPGi might be used to evaluate SF.

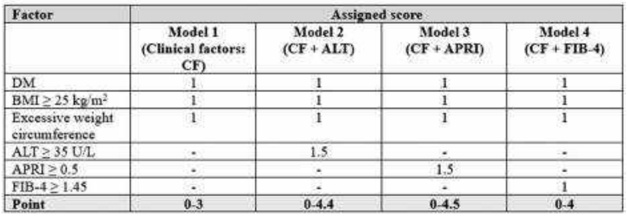

Table 1 Predictors and assigned score for MAFLD and significant fibrosis.

Factor	Assigned score			
	Model 1 (Clinical factors: CF)	Model 2 (CF + ALT)	Model 3 (CF + APRI)	Model 4 (CF + FIB-4)
DM	1	1	1	1
BMI ≥ 25 kg/m^2	1	1	1	1
Excessive weight circumference	1	1	1	1
ALT ≥ 35 U/L	-	1.5	-	-
APRI ≥ 0.5	-	-	1.5	-
FIB-4 ≥ 1.45	-	-	-	1
Point	**0-3**	**0-4.4**	**0-4.5**	**0-4**

Disclosures: The following people have nothing to disclose: Kessarin Thanapirom, Kanokwan Sonsiri, Panarat Thaimai, Sirinporn Suksawatamnuay, Piyawat Komolmit, Sombat Treeprasertsuk

2113-A | THE SILENT THREAT: NONINVASIVE ASSESSMENT AND PREDICTORS OF ADVANCED FIBROSIS IN PATIENTS WITH TYPE 2 DIABETES AND NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) IN A REAL-LIFE SETTING

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Background: Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes are common metabolic disorders whose prevalence rates are expected to rise worldwide due to aging and increasing obesity. Compared to the general population (around 25%), 50% to 70% of people with diabetes have NAFLD, and the severity of NAFLD (including fibrosis) tends to worsen with the presence of diabetes. Recent guidelines recommend screening for NAFLD and case findings of advanced disease with fibrosis in patients with type-2 diabetes. Therefore, we aimed to determine the role of non-invasive fibrosis tests in diagnosing advanced fibrosis in patients with type 2 diabetes and NAFLD in a real-life setting to facilitate their early identification and management. **Methods:** In this prospective cohort study, we recruited patients with type 2 diabetes attending the diabetes clinic at a tertiary university hospital and unaware of having NAFLD. Patients with secondary causes of hepatic steatosis were excluded. Clinical and demographical data collected were age, sex, nationality, body mass index, complete blood count, fasting blood sugar, hemoglobin A1c (HbA1c) level, liver enzymes, renal function, prothrombin time (PT), presence of comorbidities, dyslipidemia, and medications used. To estimate the prevalence of advanced fibrosis, we performed liver stiffness measurement (LSM) by transient elastography (Fibroscan, Echosens, France), and the NAFLD fibrosis score (NFS) and fibrosis-4 (FIB-4) index were calculated. Moreover, AST, ALT, and platelet counts were measured within one month of the Fibroscan evaluation. We used logistic regression to identify predictors of advanced fibrosis. **Results:** A total of 304 patients were included, and advanced fibrosis was seen in 56 (18.4%) patients with type 2 diabetes. The mean age was 53.0 ± 12.7 years; the majority were females (54.6%), Saudi nationals (86.5%), obese (65.5%), and with HbA1C **e** 7 (59.3%). The mean LSM was 8.4 ± 10.1 kPa, FIB-4 was 1.0 ± 0.9, and NFS was -0.6 ± 1.4. On multivariate analysis, the use of insulin, obesity, low platelets, low albumin, high transaminases, elevated HbA1c, and prolonged prothrombin time were frequently associated with advanced fibrosis. Obesity, the use of insulin, elevated ALT and GGT, and prolonged PT were independent predictors of advanced fibrosis. **Conclusion:** This study highlights the high prevalence of advanced fibrosis in patients with type 2 diabetes and NAFLD and identifies obesity, the use of insulin, elevated liver enzymes, and prolonged PT as significant risk factors. The use of noninvasive fibrosis tests such as LSM, FIB-4, and NFS can aid in the early identification and management of advanced fibrosis in these patients. Early detection and management of these conditions are crucial to prevent progression to cirrhosis and its sequala. Further research is needed to explore effective interventions for this high-risk population.

Disclosures: The following people have nothing to disclose: Mona H. Ismail

2114-A | THE UTILITY OF SEQUENTIAL SAFE SCORE AND FIBROSCAN IN PREDICTING CLINICALLY SIGNIFICANT FIBROSIS IN ASIAN NAFLD PATIENTS.

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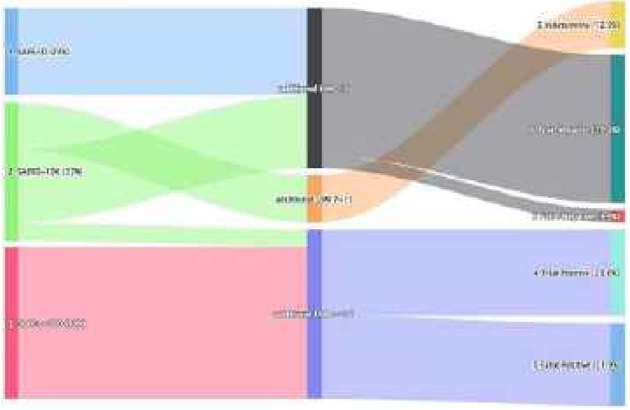
Background: Clinically significant fibrosis (fibrosis stage 2 or higher, SF) has been proven to be associated with an increased risk of both liver-related and overall mortality in patients with NAFLD. However, the currently available algorithms of noninvasive tests mainly focus on the detection of the later stage of fibrosis (F3-4). We aimed to validate the recently proposed score (Steatosis-Associated Fibrosis Estimator, SAFE) in comparison with FIB-4, NFS and vibration controlled transient elastography (VCTE) and determine the diagnostic accuracy of the 2-step approach for the detection of F ≥ 2 in Asian NAFLD patients. **Methods:** The data of biopsy-proven NAFLD patients from 6 centers in 3 Southeast Asian countries (Thailand, Malaysia, and Singapore) were collected (N = 889). Liver biopsy was used as the reference standard, liver fibrosis stage was graded using NASH CRN criteria. We included only patients with available liver stiffness data measured by VCTE. Those with incomplete data on variables used to calculate SAFE, FIB-4, and NFS were excluded, as well as those with AST or ALT > 200 IU/L. The performance of SAFE, FIB-4, NFS, and VTCE in the diagnosis of SF were evaluated using areas under the receiver operating characteristics curve (AUROC). The sequential combination approach was also assessed. **Results:** A total of 383 patients were eligible for the analysis, SF was presented in 115 patients (30%). The mean SAFE, FIB-4, NFS scores and liver stiffness were significantly different between those with and without SF. Among blood-based biomarkers, SAFE score yielded the highest AUROC of 0.773, followed by FIB-4 (AUROC 0.759, p = 0.39), and significantly better than NFS (AUROC 0.729, p = 0.024). While VCTE showed the non-significantly higher AUROC of 0.785 (p = 0.68 vs SAFE). At the given low cutoff of < 0, SAFE yielded 92.17%

sensitivity and NPV of 89.9%. To maximize the ability of ruling out patients with no/mild fibrosis, the sequential combination of SAFE ($<0;>100$) followed by VCTE ($<7;>11$ kPa) showed a promising result in excluding patients with SF as shown in the figure. The proportion of patients having false negative results using this 2-step approach is only 3.4%. **Conclusion:** SAFE consistently showed the highest AUROC among blood-based noninvasive biomarkers in the diagnosis of SF in NAFLD patients and demonstrated the comparable AUROC with that of VCTE with a sensitivity > 90% in the detection of SF. In primary care setting, SAFE might be a useful screening tool, and sequential SAFE followed by VCTE is effective in identifying patients who can be managed safely with primary care doctors.



Disclosures: Wah Kheong Chan – Novo Nordisk: Consultant, No, No; Echosens: Speaking and Teaching, No, Yes; Roche: Consultant, No, Yes; Hisky Medical: Speaking and Teaching, No, Yes; Viatris: Speaking and Teaching, No, Yes; Abbvie: Advisor, No, Yes; Boehringer Ingelheim: Consultant, No, Yes;

The following people have nothing to disclose: Pimsiri Sripongpun, Sombat Treeprasertsuk, Apichat Kaewdech, Naichaya Chamroonkul, Cheng Han Ng, Yock Young Dan, W. Ray Kim

Disclosure information not available at the time of publication: Phunchai Charatcharoenwitthaya, Mark Dhinesh Muthiah

2115-A | TYPE VII COLLAGEN DEGRADATION IDENTIFIES EARLY FIBROSIS, STEATOSIS AND DISEASE ACTIVITY IN NAFLD

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Background: Collagen turnover is a key feature in the progression of nonalcoholic fatty liver disease (NAFLD). The assessment of collagens can help to better understand the pathogenesis of NAFLD and to develop non-invasive tools for early diagnostic of disease. Type VII collagen is the main component of anchoring fibrils which connects the basement membrane to the interstitial matrix providing structural support to fibril forming collagens in the ECM. The anchoring fibrils differ significantly from the fibrillar collagens, type I, III and V, although they share the collagen domain structure. The role of type VII collagen in the pathogenesis of NAFLD and other liver diseases remains unestablished. The current study investigated type VII collagen turnover in health and NAFLD using the C7M neoepitope reflecting type VII collagen degradation. **Methods:** Serum concentrations of C7M and other non-invasive biomarkers associated with ECM remodeling including PRO-C3 (type III collagen formation), PRO-C4 (type IV collagen formation), were measured in 140 biopsy confirmed NAFLD patients and compared to 160 healthy individual's. **Results:** In the NAFLD group at the baseline, most participants were men (53%), 40% had type II diabetes, the mean age was 51 years and the distribution between fibrosis stages F0/F1/F2/F3/F4 was 3%/26%/36%/23%/11%. NAFLD patients exhibited significantly higher serum C7M levels in comparison to healthy individual's ($p = 1.5 \times 10^{-12}$). Serum concentrations of C7M were able to differentiate healthy individual's from NAFLD patients even in early disease stages (F0-F1; $p = 6.2 \times 10^{-12}$), hepatocyte ballooning (stage 0; $p = 0.04$), lobular inflammation (stage 0; $p = 9.8 \times 10^{-7}$), steatosis (stage 1; $p = 3.1 \times 10^{-12}$) and disease activity (NAS = 2; $p = 5.9 \times 10^{-5}$). PRO-C3 levels were able to discriminate different stages of fibrosis in NAFLD, however, did not distinguish early disease stages from healthy controls. The combination of C7M and PRO-C3 improved the distinguishing capability in NAFLD subgroups describing different stages of the disease (fibrosis; steatosis; ballooning; NAS) when compared to the isolated biomarkers. C7M was significantly different among individual's with healthy BMI, overweight and obese individual's. **Conclusion:** Type VII collagen degradation may provide an early indication of metabolic stress associated with enhanced activity of matrix metalloproteinases causing tissue remodeling driving tissue changes during the early stages of NAFLD.

Disclosures: Andressa de Zawadzki – Nordic Bioscience: Employee, No, No;

Morten Karsdal – Nordic Bioscience: Employee, No, No;

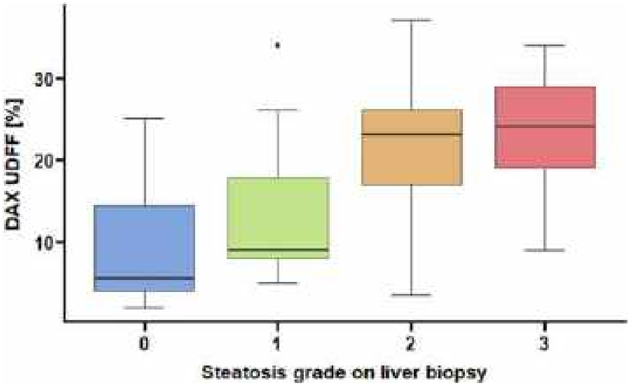
Jörn M. Schattenberg – AstraZeneca, Apollo Endosurgery, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Intercept Pharmaceuticals, Ipsen, Inventiva Pharma, Madrigal, MSD, Northsea Therapeutics, Novartis, Pfizer, Roche, Sanofi, Siemens Health: Consultant, No, No; Novo Nordisk: Consultant, Yes, No; Gilead Sciences, Boehringer Ingelheim, Siemens Healthcare GmbH: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AGED diagnostics, Hepta Bio: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; Boehringer Ingelheim, Echosens, MedPublico GmbH, Madrigal Pharmaceuticals, Histoindex, MedPublico GmbH.: Speaking and Teaching, No, No; Novo Nordisk: Speaking and Teaching, Yes, No;

Disclosure information not available at the time of publication: Diana Lemming, Peder Frederiksen

2116-A | ULTRASOUND-DERIVED FAT FRACTION (UDFF) AND AUTO-POINT SHEAR WAVE (AUTO-PSWE) ON THE DEEP ABDOMINAL TRANSDUCER (DAX) FOR LIVER FAT QUANTIFICATION AND LIVER FIBROSIS ASSESSMENT - A PROSPECTIVE BIOPSY-CONTROLLED STUDY

Georg Semmler[1], Larissa Nixdorf[2], Lukas Hartl[1], Michael Schwarz[3], Lorenz Balcar[1], Mathias Jachs[3], Paula Richwien[2], Magdalena Mairinger[2], Daniel M Felsenreich[4], Benedikt Simbrunner[5], Julia Jedamzik[2], Lisa Gensthaler[4], Felix B Langer[4], Mattias Mandorfer[5], Thomas Reiberger[6], Gerhard Prager[2] and David Josef Maria Bauer[3], (1)Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria, (2)Department of General Surgery, Division of Visceral Surgery, Medical University of Vienna, Vienna, Austria, (3)Medical University of Vienna, (4)Medical Univesity of Vienna, (5) Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, (6)Cemm Research Center for Molecular Medicine of the Austrian Academy of Sciences

Background: Ultrasound-derived fat fraction (UDFF) and auto-point shear wave (Auto-pSWE), have emerged as novel techniques for liver steatosis and fibrosis quantification. However, their diagnostic accuracy and cutoffs for steatosis and fibrosis staging have not been evaluated, yet. **Methods:** A prospective study, using liver biopsy as the gold standard, was conducted on obese participants with suspected or diagnosed non-alcoholic fatty liver disease (NAFLD) who were evaluated for bariatric surgery. Employing the Siemens Sequoia ultrasound VA30 system with the Deep Abdominal ultrasound transducer (DAX), the Auto-pSWE function triggers 15 pSWE measurements within a user-determined sectored region of interest. Participants underwent 5 Virtual Touch UDFF and Auto-pSWE measurements using the DAX, and 10 vibration-controlled transient elastography (VCTE) and CAP (CAP) measurements using the appropriate M- or XL-probe on the Fibroscan. VCTE was considered reliable when VCTE was **d** 7.1kPa or IQR/Median **d** 30%. The rule-in and rule-out cutoffs were chosen for approximately 90% specificity and sensitivity. **Results:** The study recruited 77 participants, 51 (66.2%) of which were female, with 61 (79.2%) biopsy-confirmed NAFLD. Participants' median age was 44 (IQR: 17.0) years, with a median BMI of 42.9 (IQR: 10.9) kg/m^2. Reliable VCTE was obtained in 65 (84.4%) participants. 61 (79.2%) displayed any steatosis (**e** S1), with 40 (51.9%) presenting at least moderate steatosis (**e** S2) on liver biopsy. UDFF detected any steatosis (**e** S1) with an ROC = 0.76 (rule-in cutoff: UDFF **e** 22% and rule-out cutoff: UDFF < 7%). For moderate steatosis (**e** S2), the ROC was 0.82 (rule-in cutoff: UDFF **e** 24% and rule-out cutoff: UDFF < 13%). While the UDFF and CAP ROC for diagnosing different grades of steatosis differed numerically, the differences were not statistically significant. 18 (23.4%) participants showed **e** F2, and only 5 (6.5%) showed **e** F3 on liver biopsy. Auto-pSWE diagnosed significant fibrosis (**e** F2) with an accuracy of ROC = 0.68 (rule-in cutoff: **e** 5.0kPa and rule-out cutoff < 2.4kPa). DeLong test revealed no significant difference in ROCs of reliable VCTE and Auto-pSWE for diagnosing significant fibrosis. **Conclusion:** UDFF and Auto-pSWE on the DAX probe are accurate non-invasive methods to rapidly assess steatosis and fibrosis in obese individual's. Hepatic steatosis (**e** S1) can be excluded with UDFF < 7% and confirmed with UDFF **e** 22%. Advanced liver fibrosis (**e** F2) can be confirmed with Auto-pSWE **e** 5.0kPa and excluded with Auto-pSWE < 2.4kPa.



Disclosures: Thomas Reiberger – AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, Yes; Boehringer Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; MSD: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Myr Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, Yes; Philips Healthcare: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Siemens: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; AbbVie: Consultant, Yes, Yes; Boehringer Ingelheim: Consultant, Yes, No; Gilead: Consultant, Yes, Yes;

The following people have nothing to disclose: Georg Semmler, Larissa Nixdorf, Lukas Hartl, Michael Schwarz, Lorenz Balcar, Mathias Jachs, Paula Richwien, Magdalena Mairinger, Daniel M Felsenreich, Benedikt Simbrunner, Julia Jedamzik, Lisa Gensthaler, Felix B Langer, Mattias Mandorfer, Gerhard Prager, David Josef Maria Bauer

2117-A | UNDER-IDENTIFICATION OF PATIENTS WITH METABOLIC RISK FACTORS AT HIGH RISK OF NON-ALCOHOLIC FATTY LIVER DISEASE CIRRHOSIS IN THE PRIMARY CARE CLINICS: A SINGLE CENTER RETROSPECTIVE STUDY

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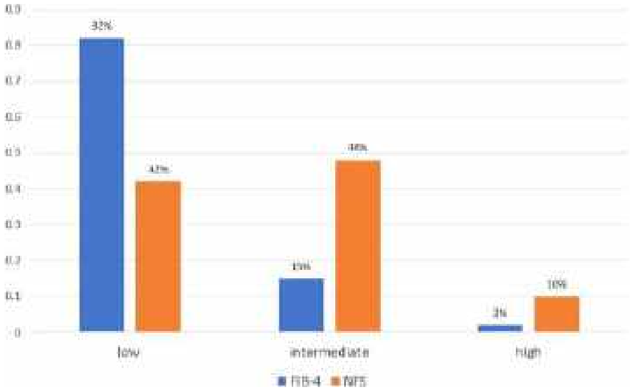
Background: The incidence of NASH cirrhosis is on the rise mostly fueled by increasing prevalence of metabolic risk factors/obesity. The current AASLD guideline recommends the screening of high-risk patients for NASH cirrhosis. The well-validated and cost-effective non-invasive tests (NITs) such as the FIB-4 and NFS are useful in stratifying patients in the primary care setting and ensuring early identification of patients at high risk of NASH Cirrhosis. This study explores the utility of NITs and tests the hypothesis – that patients with metabolic risk factors in primary care clinics at risk of NASH cirrhosis are under-identified. **Methods:** This is a single center contemporary retrospective analysis of outpatients who have been seen at the primary care clinic at our institution from October 2021 to January 2022. Patients included had to be aged 35-65 years which is the age range for the scoring criteria for NAFLD in addition to diabetes mellitus or impaired glucose tolerance, or 2 or more other identified metabolic risk factors such as obesity or overweight, hypertension, PCOS and dyslipidemia. Primary outcome is proportion of patients screened at risk for NASH cirrhosis using NITs. **Results:** After screening and excluding 39% of patients with no lab data and not fulfilling inclusion criteria, a final number of 471 patients were analyzed. Majority of patients were African American (64%), mean age was 53.7 ± 8.1 and 55% were females. About two-thirds (313) have diabetes mellitus or impaired fasting glucose, while a significant number had hypertension (84%) and dyslipidemia (83%). More than half (68%) were classified as obese with a mean BMI of 33.4 ± 9.0 for the whole sample. Using the FIB-4 score to assess risk, 15% (72) were within intermediate risk while only 2% (11) were labeled as high risk. Meanwhile, using NFS score, 58% (272) and 10% (45) of patients were labeled intermediate and high risk respectively. Using the NFS, among those at high risk of NASH cirrhosis, 96% of them had 3 metabolic risk factors, there was statistically significant association between number of metabolic risk factors and risk by NFS score $p < 0.001$. Results obtained using FIB-4 also showed a high proportion of patients in the intermediate and high-risk category having 3 metabolic risk factors or DM, but the association was not statistically significant. Only 28% (131) of all patients had some form of imaging, and among these patients, 39% (51) had findings of steatosis. There were more FIB-4 intermediate risk scores among those with steatosis on imaging 29% vs 16% in those without steatosis, but this did not reach statistical significance $p = 0.07$. **Conclusion:** There is a significant proportion of patients with multiple metabolic risk factors who present to a general medicine practice who are at risk for NASH fibrosis, who are not appropriately recognized. The use of yearly routine work-up and validated non-invasive scores may improve recognition of these patients.



Disclosures: The following people have nothing to disclose: Oluwanifemi Balogun, Blanche Echikunwoke, Prutha Shah, Abiodun Idowu, Isaac Ogunmola, Smarajita Ghosh, Jessica Genkil, Mikaela Nikkola Jara-Tantoco, Nandakumar Mohan, Matthew Behme, Kevin B Lo, Maria Lagarde Mussa

2118-A | URINARY METABOLITE BIOMARKERS CHANGES IN OBESITY-INDUCED NAFLD AND OBESITY-INDUCED NAFLD PLUS XX.

Helena Yong[1], Ka Lung Andrew Chan[2], Gerald Larrouy-Maumus[3], Joseph Okor[1], Michael Munday[1], Andrew Rennie Hall[4], Alberto Quaglia[4] and Jude A. Oben[2,5], (1) University College London, (2)King's College University, (3)Imperial College University, (4)Royal Free Hospital, (5)Guy's and St Thomas' Hospital

Background: Obesity-induced Non-alcoholic fatty liver disease (NAFLD) is the leading causes of chronic liver disease, affecting 25% globally. It starts as hepatic steatosis, progresses to steatohepatitis, fibrosis, cirrhosis and possible hepatocellular cancer. NAFLD is often associated with obesity plus insulin resistance or type 2 diabetes. Liver function blood tests and non-invasive radiological imaging are clinically used to detect NAFLD. Whilst, liver biopsy remains the "gold standard" for detection and staging, the procedure is invasive and can be unreliable especially in obese patients.[1-3] There is a need for specific, non-invasive biomarkers for the detection and staging of NAFLD. Our aim was to assay urine metabolite changes in mice with obesity-induced NAFLD and obesity-induced NAFLD plus agent XX. **Methods:** C57BL/6 mice ($n = 78$) were fed a diet comprising high fat(54%), high cholesterol(1.4%) with high sucrose(55%) and fructose(45%) in drinking water, to simulate the diet typically consumed by obese patients with NAFLD. The urine of mice fed the obesogenic diet(OD) and OD plus XX (OD-XX), with their parallel controls fed normal chow (NC) for ~40 weeks, were assayed with metabolomic techniques. These techniques were Fourier-transform infrared(FT-IR), ^{1}HNuclear magnetic resonance(NMR), 2D ^{1}H–^{1}H total correlation heteronuclear single quantum coherence(TOCSY) and electrospray liquid chromatography-mass spectrometry(ESI-LC-MS/MS) with multivariate analysis. Body, liver, liver/body weights, liver biochemistry and liver histology were evaluated. **Results:** Sera AST(IU/L) were elevated in OD and OD-XX cohorts compared to NC and decreased in OD-XX group vs OD (367.00 ± 46 vs 544.00 ± 22 vs 335.70 ± 35.05; NC vs OD vs OD-XX; $p < 0.01$). Sera ALT(IU/L) levels were also increased in OD and OD-XX cohorts and reduced in OD-Tx group vs OD (101.70 ± 15.79 vs 401.40 ± 10.57 vs 319.40 ± 43.79, NC vs OD vs OD-XX; $p < 0.01$). The NASH clinical research network scores increased for OD and OD-XX livers vs NC (1.0 ± 0.2 vs 5.10 ± 0.28 vs 5.92 ± 0.28; NC vs OD and NC vs OD-XX, $p < 0.04$; OD vs OD-XX - not significant). Principal component analysis score (PCA) plot (Fig.1) urine NMR spectra displayed differences between OD and OD-Tx groups, indicating that XX induced metabolite changes. **Conclusion:** We have identified specific urinary metabolites with ^{1}HNMR, 2D ^{1}H–^{1}H TOCSY and ESI-LC-MS/MS. The results demonstrate that metabolomic approaches may be useful in detecting novel biomarkers in human NAFLD.

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

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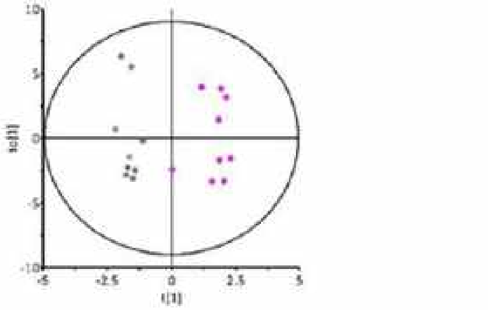

Fig.1:PCA of the urine samples acquired by NMR spectra showing separation of the OD (n=9, grey circles) & OD-XX (n=9, pink circles) cohort (R²X=0.857, Q²=0.747).

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Disclosure information not available at the time of publication: Ka Lung Andrew Chan, Gerald Larrouy-Maumus, Joseph Okor, Michael Munday, Andrew Rennie Hall, Alberto Quaglia, Jude A. Oben

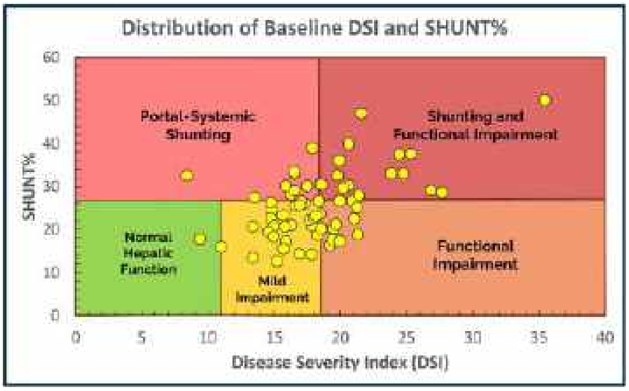
2119-A | USE OF AGILE 3+ AS A SCREENING TOOL SUCCESSFULLY TARGETS NON-ALCOHOLIC STEATOHEPATITIS (NASH) SUBJECTS WITH IMPAIRED HEPATIC FUNCTION AND PORTAL-SYSTEMIC SHUNTING EVALUATED BY HEPQUANT SHUNT TEST: LESSONS LEARNED FROM THE HEPION ALTITUDE-NASH (e F3) TRIAL

Stephen A Harrison[1], Patrick Mayo[2], Todd Hobbs[2], Caroline Zhao[2], Carlos Canizares[2], Robert Foster[2] and Gregory T Everson[3], (1)Summit Clinical Research; Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom, San Antonio, TX, (2)Hepion Pharmaceuticals Inc., (3)Hepquant

Background: The progression of hepatic fibrosis in NASH has been linked to increased mortality and morbidity. Rencofilstat, a non-immunosuppressive pan-cyclophilin inhibitor, has demonstrated pleotropic effects well-suited for the treatment of NASH with advanced fibrosis. In this Phase 2 study, subjects were identified using the AGILE 3+ screening criteria, a predictor of **e** F3 fibrosis, and had baseline liver function and portal-systemic shunting measured by the HepQuant SHUNT test. The SHUNT test's Disease Severity Index (DSI) of 18.3 and systemically shunted portal flow (SHUNT%) of 27% have been linked to transition from F3 to compensated cirrhosis, portal hypertension, varices, and risk for adverse clinical outcomes. The baseline characteristics from the ALTITUDE-NASH trial are reported herein. **Methods:** In this multi-center, open-label study, 70 F3 NASH subjects with AGILE 3+ score > 0.53 were enrolled in a screening period of 2.4 months and randomized to receive rencofilstat once daily at 75, 150, or 225 mg for 120 days. Hepatic function was assessed using the SHUNT test, in which ^{13}C-cholate was administered intravenously and d4-cholate was taken orally, with blood sampled to determine cholate clearances. SHUNT% and DSI were calculated from the clearances and compared to other baseline tests. Additional objectives were to evaluate safety, tolerability, and PK. **Results:** Baseline mean (± SD) measurements were:

- Agile 3+ score 0.73 (0.15)
- FibroScan® kPa 15.0 (7.5)
- AST 27.2 (2.4)
- ALT 29.7 (2.7)
- ELF 9.6 (0.2)
- Fib-4 1.1 (0.1)
- Pro-C3 38.4 (2.4) ng/mL

Nearly half of subjects with baseline AGILE 3+ score **e** 0.53 had significant hepatic functional impairment as assessed by HepQuant Shunt DSI > 18.3, including a quarter with both significant functional impairment and increased portal-systemic shunting (SHUNT% > 27%) (Figure 1). This group demonstrated mean Pro-C3 levels of 38.4 (20.0) ng/mL with ELF scores of 9.7 (0.93). Average age was 60 years with an average BMI of 38; 51% were female and 71% with diabetes. Demographics were similar across the 3 treatment groups. **Conclusion:** Use of AGILE 3+ as a screening tool for identifying subjects was successful in allowing a timely recruitment of F3 NASH subjects. In addition, the sequential use of AGILE 3+ coupled with the HepQuant SHUNT test may identify subjects at high risk for clinical complications from an otherwise well-compensated advanced NASH population.



Disclosures: Stephen A Harrison – Terns: Consultant, No, No; Viking: Consultant, No, No; Pinnacle Clinical

Research: Executive role , No, No; Northsea: Consultant, No, No; Novartis: Consultant, No, No; Novo Nordisk: Consultant, No, No; Perspectum: Consultant, No, No; Poxel: Consultant, No, No; Sagimet: Consultant, No, No; Sonic Incytes: Consultant, No, No; Hepta Bio: Consultant, No, No; Hightide: Consultant, No, No; HistoIndex: Consultant, No, No; Intercept: Consultant, No, No; Madrigal: Consultant, No, No; Medpace: Consultant, No, No; NGM Bio: Consultant, No, No; Altimmune: Consultant, No, No; AstraZeneca: Consultant, No, No; Axcella: Consultant, No, No; Chronic Liver Disease Foundation: Consultant, No, No; Echosens: Consultant, No, No; Genfit: Consultant, No, No; Gilead: Consultant, No, No; GSK: Consultant, No, No; Hepion: Consultant, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; 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Kowa Research: Consultant, No, Yes; Merck: Consultant, No, Yes; MGGM: Consultant, No, No; Microba: Consultant, No, Yes; Neurobo: Consultant, No, No; Nutrasource: Consultant, No, Yes; Pathai: Advisor, No, Yes; Pfizer: Consultant, No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Piper Sandler: Consultant, No, Yes; Prometic (now Liminal): Consultant, No, Yes; Ridgeline: Consultant, No, Yes; Second Genome: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Silverback: Consultant, No, Yes; Zahgen: Consultant, No, Yes;

Patrick Mayo – Hepion Pharmaceuticals Inc.: Employee, Yes, No;
Todd Hobbs – Hepion Pharmaceuticals Inc: Employee, Yes, No;
Caroline Zhao – Hepion Pharmaceuticals: Employee, Yes, No;
Carlos Canizares – Hepion Pharmaceuticals, Inc.: Employee, Yes, No;
Gregory T Everson – HepQuant LLC: Employee, Yes, No;
Disclosure information not available at the time of publication: Robert Foster

2120-A | USE OF MULTI-PARAMETRIC MEASURES TO DIFFERENTIATE AND BETTER ASSESS FIBROSIS PATTERNS BETWEEN BASELINE AND END-OF-TREATMENT (EOT) PATIENTS IN NASH CLINICAL TRIALS: RESULTS FROM THE FALCON-1 AND 2 CLINICAL TRIALS

Kutbuddin Akbary[1], Dean Tai[2], Ya-Yun Ren[1], Anne Minnich[3] and Edgar D. Charles[3], (1)Histoindex Pte Ltd, (2)Histoindex Pte Ltd, Singapore, (3)Bristol Myers Squibb

Background: Clinical trials for NASH conducted recently target specific pathological pathways in development of fibrosis, steatosis, inflammation. Effects on steatosis and inflammation impact fibrosis indirectly, compared to drugs that targets fibrosis directly. In the past, quantitative fibrosis assessment was done as a single measure, either biomarkers like ProC3, or histology-based measurements like collagen proportionate area (CPA). Performances of these tests showed significant differences in drug trials, between baseline and EOT (End-Of-Treatment) respectively. This study investigates the possibility to overcome this limitation using multi-parametric measurements like Somalogic (a biomarker) and qFibrosis (AI histology). **Methods:** Biopsy slides were obtained from FALCON-1 (NCT03486899) and FALCON-2 (NCT03486912) clinical trials. SHG/TPE (Single Harmonic Generation/Two-Photon Excitation) microscopy and AI (Artificial-Intelligence) analysis were used to estimate NASH-CRN based fibrosis parameters as continuous variables for 301 biopsy slide pairs. Biomarker data used are serum AST and ALT; additional biomarkers like ProC3, PC3X, ELF, Somalogic; SHG/TPE digital pathology measures like qFibrosis continuous values, qFibrosis stages, % SHG-CPA (percentage area of SHG). Biomarker data in Falcon-1 was at 24 weeks and Falcon-2 at 48 weeks. These data were correlated with histopathological assessment by pathologists using NASH-CRN fibrosis staging (used as a benchmark). Statistical analysis was done using Spearman correlation (r-values for each pair). **Results:** Correlation results of data against NASH-CRN staging scores is summarised in Figure 1. Overall, amongst biomarkers, Somalogic showed best correlation ($r = 0.61$) with NASH-CRN, followed by PC3X ($r = 0.52$). Among SHG/TPE data, %SHG-CPA showed best correlation ($r = 0.53$) followed by qFibrosis values ($r = 0.42$). Comparing differences in these correlation values between baseline and EOT data, there is hardly any difference for single parameter measures like PC3X ($r = 0.54$ to $r = 0.5$) and %SHG-CPA ($r = 0.54$ to $r = 0.53$). But for multi-parameter measures like Somalogic ($r = 0.54$ to $r = 0.66$) and qFibrosis values ($r = 0.51$ to $r = 0.32$), differences between baseline and EOT appear more marked. **Conclusion:** With promising drugs for NASH in the pipeline, it is essential to identify biomarkers to better assess fibrosis changes post-treatment. Drug effects on SHG parameters suggest fibrosis regression and progression patterns differ qualitatively, and can be taken into consideration in evaluating biomarkers. Multi-parametric components within biomarkers take into consideration changes between baseline and EOT patients, to better assess heterogeneity of fibrosis progression and regression. Furthermore, we can evaluate the parameter level correlation between SHG/TPE imaging and multi-parametric biomarkers to better understand fibrosis regressions.

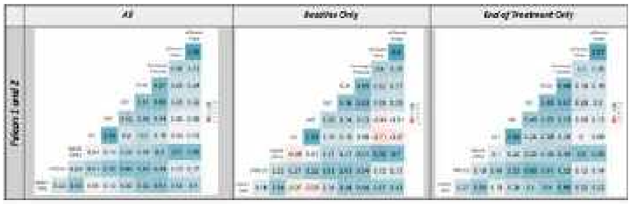
All
Baseline Only
End of Treatment Only
Falcon 1 and 2

Figure 1: Correlation of various NIT measures and SHG/TPE based digital pathology measurements bench marking with NASH-CRN staging results on fibrosis assessment. On the left, all patients were included in the assessment; and on the right, patients from baseline and end-of-treatment are assessed separately.

Disclosures: Anne Minnich – Bristol Myers Squibb: Consultant, No, No;

Edgar D. Charles – Bristol Myers Squibb: Employee, Yes, No; Bristol Myers Squibb: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

The following people have nothing to disclose: Kutbuddin Akbary, Dean Tai, Ya-Yun Ren

2121-A | USE OF NIS4 IN PRIMARY CARE AND ENDOCRINOLOGY CLINICS IDENTIFIES PEOPLE WITH TYPE 2 DIABETES AT A HIGHER RISK OF SEVERE NONALCOHOLIC STEATOHEPATITIS

Srilaxmi Kalavalapalli[1], Eddison GodinezLeiva[1], Romina Lomonaco[1], Stephen Marangi[1], Enrique ValdezSaenz[1], Andrea Ortiz Rocha[1], Yasmine Mohseni[1], Margery Connelly[1], Toni Prezant[2], Kelly Chun[2], Maria Lupi[1], Juan Munoz Pena,[1], Juan Perdomo Rodriguez[1], Jeffrey Budd[1], Anu Sharma[1], Diana Barb[1] and Kenneth Cusi[1], (1)University of Florida, (2)Labcorp

Background: The noninvasive diagnosis of non-alcoholic steatohepatitis (NASH) remains challenging. Liver biopsy still remains the gold standard to diagnose NASH but it is usually not feasible. The novel diagnostic biomarker NIS4 is a blood-based test that measures four independent NASH-associated biomarkers (A1c, miR-34a-5p, A2M and YKL-40) and produces a score. The aim of this study was to assess the prevalence of high-risk NASH (NASH with significant fibrosis [≥F2]) as estimated by NIS4 or elastography in a university-based outpatient clinic setting. **Methods:** To this end, we recruited from primary care and endocrine clinics a total 600 participants attending routine clinic appointments (age: 56 ± 11 y; BMI: 31.4 ± 6.6 kg/m^2; T2DM: 40%; obese without T2DM [OB]: 30%), unaware of having NAFLD. Participants were screened by: a) Transient elastography (Fibroscan®) for steatosis (CAP ≥274 dB/m) and for fibrosis (LSM ≥7.0 kPa); and b) NIS4 for high-risk NASH (defined as a NIS4 ≥0.63; low-risk: < 0.36). **Results:** Among patients with T2DM or OB, 70% had steatosis compared to 29% without obesity or T2DM (CON) ($p < 0.01$), while fibrosis (LSM ≥7.0 kPa) was present in 17% of patients with T2DM and 8% in those with OB (CON = 1%; $p < 0.01$). High-risk NASH by NIS4 occurred frequently among patients with T2DM, whether they had (30%) or not (20%) obesity, but less frequent in OB (6%) and was rare in those without T2DM or obesity (1%). NIS-4 correlated with steatosis (CAP) ($r = 0.39$; $p < 0.001$) and fibrosis (LSM) ($r = 0.35$; $p < 0.001$). The strongest correlation was for patients having LSM ≥8.0 kPa (≥F2; $r = 0.49$, $p < 0.01$; r = 0.42-45 for ≥F3-4, $p < 0.05$). Patients with high-risk NASH (NIS4 ≥0.63) compared to those with low-risk NASH (NIS4 < 0.36) more often had fibrosis (26% vs 4%), AST ≥30 IU/L (40% vs. 8%) and ALT ≥30 IU/L (38% vs. 13%), hepatic- and adipose tissue-insulin resistance (HOMA-IR: 63% vs. 29% and adipo-IR: 72% vs 56%, respectively; all $p < 0.01$). NIS4 correlated with having metabolic syndrome ($r = 0.41$; $p < 0.01$) and high-risk NASH was more common in people from endocrinology vs. primary care clinics (28% vs. 10%; $p < 0.05$). **Conclusion:** Presence of NASH with clinically significant fibrosis is common in T2DM, and increases significantly ($> 50\%$) if obesity is present. An elevated NIS4 can help identify people with more severe NASH and an unfavorable cardiometabolic profile in need of intensive multidisciplinary care.

Disclosures: Margery Connelly – Labcorp: Employee, No, No;

Toni Prezant – Labcorp: Employee, No, No;

Kelly Chun – Labcorp: Employee, No, No;

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The following people have nothing to disclose: Srilaxmi Kalavalapalli, Eddison GodinezLeiva, Romina Lomonaco, Stephen Marangi, Enrique ValdezSaenz, Andrea Ortiz Rocha, Yasmine Mohseni, Maria Lupi, Juan Munoz Pena, Juan Perdomo Rodriguez, Jeffrey Budd, Anu Sharma, Diana Barb

2122-A | USE OF NONINVASIVE FIBROSIS CALCULATORS IN AN URBAN DIABETES CENTER SUGGESTS LARGE BURDEN OF UNDETECTED ADVANCED LIVER DISEASE

Valeria Martinez Lebron[1], Seta Degann[1], Ahmed Ebeid[2], Cyrus Adams-Mardi[3], Andrea Fry[4], Ameer Abutaleb[5], Diala El-Maouche[6], Zahid Masood Vahora[5], Stephen Gray[5] and Lynt B. Johnson[5], (1)Department of Medicine, George Washington University Hospital, Washington, DC, (2)Alexandria University Faculty of Medicine, Alexandria, Egypt, (3)The George Washington University School of Medicine and Health Sciences, (4)George Washington University Medical Faculty Associates, (5)Department of Surgery, George Washington University Medical Faculty Associates, (6) Department of Endocrinology, George Washington University Medical Faculty Associates

Background: Nonalcoholic fatty liver disease (NAFLD) is prevalent in up to 60% of patients with type 2 diabetes mellitus (T2DM). T2DM accelerates the risk of hepatic fibrosis and hepatocellular carcinoma in patients with NAFLD. Our goal in this study was to identify patients with suspected NAFLD and hepatic fibrosis in a large T2DM clinic by using noninvasive fibrosis scoring systems. **Methods:** We conducted a retrospective study of patients with T2DM seen by an endocrinologist at the Medical Faculty Associates (MFA) Diabetes Center in Washington, DC, from November 1, 2021, until November 1, 2022. We included all subjects who were over 18 years old with a hemoglobin A1c (HbA1c) of 6.5 or higher. Patients with a history of significant alcohol consumption, decompensated cirrhosis, previous bariatric surgery, or prior chronic liver disease were excluded from the study. We identified patients at risk for hepatic fibrosis by using the Fibrosis-4 (FIB-4) Index, NAFLD Fibrosis Score (NFS) and AST to Platelet Ratio Index (APRI) when lab values were available. **Results:** A total of 1,411 were evaluated for T2DM by an endocrinology provider during the one-year period. 336 patients met one or more of the exclusion criteria, leaving a total of 1075 patients included in the analysis. The majority were African American (n = 582, 54%), 261 were Caucasian (24.3%), and 85 were Hispanic (7.9%). Most patients were females (n = 675, 62.7%). The mean HbA1c was 8.1 ± 2.3. 643 patients (59.8%) were insulin dependent. Based on FIB-4 scores, we found that 21 (2%) patients had a score of > 3.25 associated with advanced fibrosis and 205 (19%) patients with scores of 1.45-3.25 had moderate fibrosis. Using the NFS calculator, there were 280 (26%) patients with values of > 0.675 consistent with F3-F4 disease. 247 (23%) had F0-F2 fibrosis. The rest of the cohort (n = 469, 44%) had indeterminate fibrosis scores. 79 patients had missing data (7%). A total of 6 (< 1%) patients met criteria for advanced fibrosis by APRI scoring. **Conclusion:** In our urban Diabetes Center, utilizing the NFS calculator may detect many patients with an advanced liver disease. Further research is needed to correlate these findings with transient elastography and other imaging evidence of fatty liver disease.

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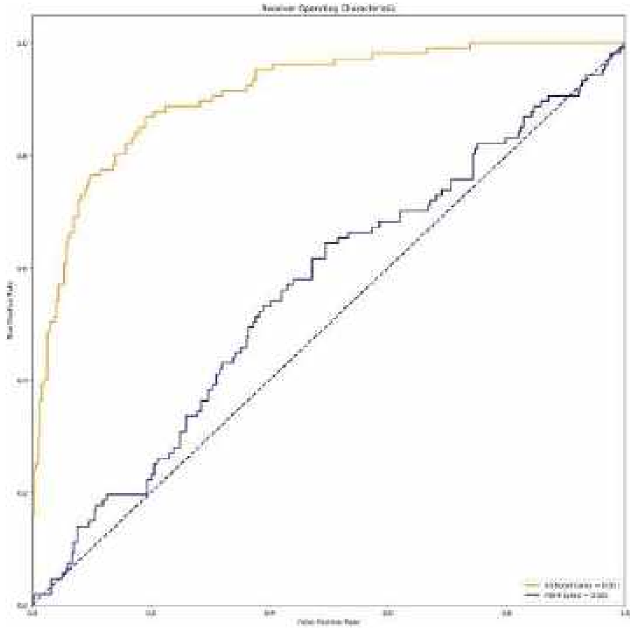
Disclosure information not available at the time of publication: Seta Degann, Ahmed Ebeid, Cyrus Adams-Mardi, Andrea Fry, Ameer Abutaleb, Diala El-Maouche, Zahid Masood Vahora, Stephen Gray, Lynt B. Johnson

2123-A | UTILIZING MACHINE LEARNING TO IDENTIFY AT-RISK PATIENTS FOR TRANSIENT ELASTOGRAPHY IN NAFLD AND NASH

Donald J. Lazas[1,2], Josh O'Rourke[1], Christian Bonnell[1], Senthil K. Raghavan[3], Landon D. Humphrey[4], Broderick G. Eaton[5], Elizabeth L. Reinhard[4], Kiran V. Rao[6], Saeid S. Goshtasbi[7], Matthew K. Mukherjee[7], Erik G. Kerekes[7], Charles A. Dasher Jr.[8], David T. Steele[8], Carrie Rothermel[8], Mary K. Veazey[8], Bradley W. Anderson[9] and Michael D. Williams[9], (1) Objectivehealth, (2)Digestive Health Research, (3) Arcare Center for Clinical Research - Little Rock, (4) Arcare Center for Clinical Research - Conway, (5) *Arcare Center for Clinical Research - Jonesboro, (6) Premier Health Research, LLC, (7)Digestive Health Research of Southern California, LLC, (8)Birmingham Digestive Health Research, LLC, (9)GI Associates Research, LLC*

Background: Transient elastography (TE) is a non-invasive procedure for identifying patients with suspected NAFLD, NASH, or Cirrhosis. However, existing screening methods like the FIB-4 index have limited utility in identifying which patients should undergo this procedure. Although FIB-4 can identify patients with advanced fibrosis, it lacks precision in detecting mild or moderate fibrosis and neglects common NAFLD and NASH risk factors like BMI and Type 2 Diabetes. Our aim was to utilize machine learning to better predict abnormal TE results. **Methods:** A cohort of 4062 patients who underwent TE was selected from the 2017-2020 NHANES dataset (78%, n = 3206) and combined with patients from primary care and specialty practices (22%, n = 856). Those with viral hepatitis, HIV, or excessive alcohol use were excluded. Patients were divided into control (LSM < 7.5 and CAP < 260, n = 1579) and treatment (LSM > = 7.5 and CAP > = 260, n = 534) groups. These groups were then combined into training (80%, n = 1690) and test sets (20%, n = 423) using a stratified shuffle split. Using XGBoost, multiple models were trained with seven features - Age, Sex, BMI, AST, ALT, Platelet Count (PLT), and Hemoglobin A1c (HbA1c) - expanding upon those used by FIB-4. Models were validated using Stratified K-Fold Cross Validation and performance was evaluated across several metrics, with F1 Score used to select the final model. For FIB-4, a cutoff of 1.45 was used to differentiate between control and treatment groups. **Results:** The final model demonstrated robust performance, surpassing FIB-4 across all metrics. PPV was 0.72 ± 0.05, NPV was 0.93 ± 0.02, Sensitivity was 0.79 ± 0.08, Specificity was 0.90 ± 0.03, F1 Score was 0.75 ± 0.05, AUROC was 0.92 ± 0.02, and Matthew's Correlation Coefficient (MCC) was 0.67 ± 0.07. Feature importance was also assessed using the gain metric with BMI (0.26 ± 0.02) and HbA1c (0.21 ± 0.03) ranking as top features. Conversely, FIB-4 scored significantly lower, with PPV = 0.28, NPV = 0.76, Sensitivity = 0.27, Specificity = 0.76, F1 = 0.27, AUROC = 0.56, and MCC = 0.03. **Conclusion:** The final model, expanding on FIB-4 features by including NAFLD and NASH risk factors, offers robust performance in identifying patients suitable for TE. These results validate the use of machine learning as a viable option for identifying at-risk patients in electronic health record systems, improving patient detection, and accelerating recruitment for NAFLD and NASH studies.



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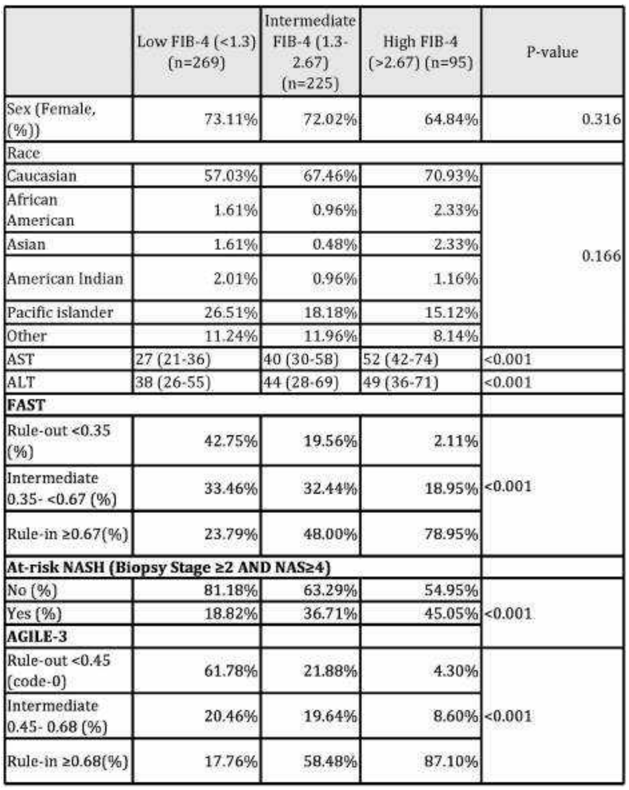
Bradley W. Anderson – Abbvie: Speaking and Teaching, No, No; Exact Sciences: Speaking and Teaching, No, No;
The following people have nothing to disclose: Donald J. Lazas, Josh O'Rourke, Christian Bonnell, Senthil K. Raghavan, Landon D. Humphrey, Elizabeth L. Reinhard, Kiran V. Rao, Saeid S. Goshtasbi, Matthew K. Mukherjee, Erik G. Kerekes, Charles A. Dasher, David T. Steele, Carrie Rothermel, Mary K. Veazey, Michael D. Williams

2124-A | VALIDATION OF A CLINICAL CARE PATHWAY TO RISK STRATIFY PATIENTS WITH NAFLD AND COMPARING FIB4 SCORING WITH OTHER NON-INVASIVE TESTING

Ria Ghose Kundu[1], Pooja Rangan[2], Claire Faulkner[3], Majd Aboona[3], Dylan Grade[1], Rahul Sharma[1], Vir Dolasa-Sahani[1], Naina Shaik[1], Rayna Shaik[1], Rida Nadeem[1], Karn Wijarnpreecha[2] and Naim Alkhouri[1], (1) Arizona Liver Health, Phoenix, AZ, (2)University of Arizona College of Medicine Phoenix, Phoenix, AZ, (3) University of Arizona College of Medicine, Phoenix, AZ

Background: FIB4 index was originally developed to diagnose advanced fibrosis, it has been incorporated recently into algorithms by the AGA,AACE,AASLD as the initial screening test to identify patients with at-risk

NASH that need referral to specialty clinics.FIB4 < 1.3 are low risk and will remain in primary care setting.This approach is reasonable in low-prevalence populations, the impact of using this approach in specialty clinic is not well-understood.This study was to assess the performance of low FIB4 in specialty clinic. We aim to determine validity of FIB4 index in identifying at risk NASH population and compare FIB4 index against other non invasive tests–FAST score, AGILE3 and AGILE 4 scores. **Methods:** Patients with biopsy-proven NAFLD and Fibroscan/ laboratory tests sufficient to calculate the FIB4 and other Fibroscan-based scores were included in this analysis. The histologic assessment was done based on the NASH CRN criteria and at-risk NASH was defined as NAS > / = 4 and fibrosis stage 2-4. The FAST score was calculated based on Fibroscan measured liver stiffness (LSM) and controlled attenuation parameter (CAP) + AST as a non-invasive test to diagnose at-risk NASH. The AGILE3+ was calculated based on LSM, AST, ALT, platelet count, diabetes, age and gender as a non-invasive test for advanced fibrosis.We conducted a single center retrospective cohort study on NAFLD patients in a tertiary care clinic in Phoenix, AZ. Patients with significant or advanced fibrosis on liver biopsy examination and fibroscans were included in the study. FAST score, AGILE 3+ score AGILE 4 score are all designed to identify advance fibrosis /cirrhosis in suspected NAFLD patients. Baseline characteristics, laboratory test, NITs, and at-risk NASH were compared across FIB-4 categories (low, intermediate, high). **Results:** A total of 589 NAFLD patients were included in this study. The mean age was 65 in high FIB4 group and 52 in the low FIB4 group. Female population were 73.11% and 64.84% respectively in low FIB4 and high FIB4 group. The prevalence of at-risk NASH is 45.05% in high FIB4 group and 18.82% in low FIB4 group. 46% of the population had FIB4 < 1.3 and would have stayed within primary care without being further evaluated. In patients with FIB < 1.3, 23.8% of patients had a FAST score in the rule-in zone e 0.67 indicating the possibility of having at-risk NASH. Furthermore, on liver biopsy, 18.8% of patients had histology confirmed at risk NASH. Moreover, 17.8% of patients had AGILE3+ in the rule-in zone for advanced fibrosis (e 0.67). **Conclusion:** Approximately 20% of patients with NAFLD and low FIB4 index who are seen in specialty care may have at-risk NASH and 17% may have advanced fibrosis. These results validate the recommendation by AASLD that sequential testing starting by FIB4 index should only be used in low-prevalence populations by PCPs and not in high-prevalence populations seen in specialty clinics.



	Low FIB-4 (<1.3) (n=269)	Intermediate FIB-4 (1.3-2.67) (n=225)	High FIB-4 (>2.67) (n=95)	P-value
Sex (Female, (%))	73.11%	72.02%	64.84%	0.316
Race				
Caucasian	57.03%	67.46%	70.93%	0.166
African American	1.61%	0.96%	2.33%	
Asian	1.61%	0.48%	2.33%	
American Indian	2.01%	0.96%	1.16%	
Pacific islander	26.51%	18.18%	15.12%	
Other	11.24%	11.96%	8.14%	
AST	27 (21-36)	40 (30-58)	52 (42-74)	<0.001
ALT	38 (26-55)	44 (28-69)	49 (36-71)	<0.001
FAST				
Rule-out <0.35 (%)	42.75%	19.56%	2.11%	<0.001
Intermediate 0.35- <0.67 (%)	33.46%	32.44%	18.95%	
Rule-in ≥0.67(%)	23.79%	48.00%	78.95%	
At-risk NASH (Biopsy Stage ≥2 AND NAS≥4)				
No (%)	81.18%	63.29%	54.95%	<0.001
Yes (%)	18.82%	36.71%	45.05%	
AGILE-3				
Rule-out <0.45 (code-0)	61.78%	21.88%	4.30%	<0.001
Intermediate 0.45- 0.68 (%)	20.46%	19.64%	8.60%	
Rule-in ≥0.68(%)	17.76%	58.48%	87.10%	

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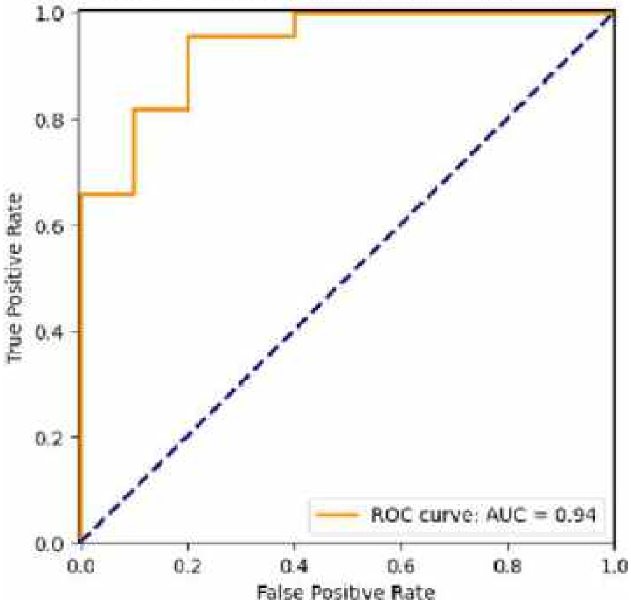
Disclosure information not available at the time of publication: Pooja Rangan, Claire Faulkner, Majd Aboona, Dylan Grade, Rahul Sharma, Vir Dolasa-Sahani, Naina Shaik, Rayna Shaik

2125-A | VALIDATION OF A PLASMA SCREENING PANEL FOR PEDIATRIC NONALCOHOLIC FATTY LIVER DISEASE USING METABOLOMICS

Helaina E. Huneault[1], *Alasdair E. Gent*[2], *Catherine C. Cohen*[3], *Zhulin He*[4], *Zachery R. Jarrell*[5], *Rishikesan Kamaleswaran*[2] *and Miriam B. Vos*[6], *(1)Nutrition & Health Sciences Doctoral Program, Laney Graduate School, Emory University, Atlanta, GA, USA, (2) Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA, USA, (3) Section of Nutrition, Department of Pediatrics, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA, (4)Pediatric Biostatistics Core, Department of Pediatrics, School of Medicine, Emory University, Atlanta, GA, USA, (5)Division of Pulmonary, Allergy and Critical Care Medicine, Emory University, Atlanta, GA, USA, (6)Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics and Nutrition and Health Sciences Graduate Program, Emory University*

Background: Nonalcoholic fatty liver disease (NAFLD), the most common liver disease in children, is a leading cause of liver-related morbidity and mortality. Histological evaluation of liver biopsy remains the gold standard for diagnosis, although more efficient screening methods are needed. We previously developed a novel NAFLD screening panel in youth using machine learning applied to high-resolution metabolomics (HRM) and clinical phenotype data. Our objective was to validate this panel in a separate cohort. **Methods:** Clinical data were collected from a combined cross-sectional sample of children from three previously conducted studies. HRM was performed on fasting plasma samples. NAFLD was assessed by magnetic resonance imaging proton density fat fraction (MRI-PDFF), magnetic resonance spectroscopy (MRS), or evaluation of liver biopsy. Given available data, we used a modified version of our previous panel, which included waist circumference (WC), fasting insulin, glucose, and triglycerides. Metabolite features included three amino acids, two phospholipids, and dihydrothymine. To validate the panel, our data was split into training (67%) and test (33%) sets. Due to recruitment restrictions, oversampling was used to balance the training set. Support vector machine and random forest classifiers were tested. Model-specific hyperparameters were selected from a grid search (5-fold cross-validation) with an area under the receiver operating characteristic (AUROC) used for scoring. **Results:** A total of 161 patients with stored frozen samples were analyzed (75% male; 12.8 ± 2.6 years of age; BMI 31.0 ± 7.0 kg/m^2; 81% with NAFLD, 58% Hispanic race/ethnicity). Fasting insulin, triglycerides, HOMA-IR, total cholesterol, ALT, AST, and WC were significantly higher in children with NAFLD than non-NAFLD controls (all $p < 0.05$). Previously, our screening panel detected NAFLD with an AUROC of 0.94, sensitivity of 73%, and specificity of 97%, using a random forest classification model. Our present random forest model achieved an AUROC of 0.94, 95% sensitivity, and 80% specificity for detecting NAFLD in the test set (Figure 1). **Conclusion:** We were able to validate a modified version of our previous screening panel of metabolites and clinical phenotype variables for detecting pediatric NAFLD. Therefore, this panel has promising potential for use as a screening tool for NAFLD in youth. Further investigation to understand the biological significance of the included metabolic features is warranted.

Figure 1. ROC curve produced from the random forest classifier.



Disclosures: The following people have nothing to disclose: Helaina E. Huneault, Miriam B. Vos
Disclosure information not available at the time of publication: Alasdair E. Gent, Catherine C. Cohen, Zhulin He, Zachery R. Jarrell, Rishikesan Kamaleswaran

2126-A | VALIDATION OF FIB-4 FOR DETECTION OF NAFLD STAGE F4

Heather Kosick[1,2], *Chinmay Bera*[1,2], *Mohamed Shengir*[3], *Oyedele A. Adeyi*[4], *Giada Sebastiani*[5,6] *and*

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Background: Non-invasive methods to detect advanced fibrosis (F3-4) and cirrhosis (F4) are increasingly utilized to risk-stratify patients with non-alcoholic fatty liver disease (NAFLD). These include simple serum-based tests such as FIB-4 score. The recent AASLD guidance suggests use of 'rule-in' and 'rule-out' cut-offs, FIB4 **e** 3.48 and < 1.67, respectively, to detect F4. 'Rule-in' cut-off was based on a recent individual patient meta-analysis with 90% specificity for detection of cirrhosis. Our aim was to validate and assess performance of FIB-4 cut-offs in our cohort of patients with biopsy-proven NAFLD from two Canadian tertiary care centres. **Methods:** Patients were **e** 18 years at time of study onset, with biopsy-proven NAFLD, with biopsy completed between 2010 – 2021 at one of two tertiary care centres (University Health Network, Toronto, ON; McGill University Health Centre, Montreal, QC), with available FIB-4 scores from within ± 6 months of biopsy. Alternate causes of liver disease were excluded based on clinical review. were applied. Diagnostic test performance for FIB4 < 1.67 and **e** 3.48 to predict F4 was assessed using area under the receiver operating curve (AUROC). **Results:** 390 patients were included with mean age 48.7 ± 12.9 years, 54.6% were male, and 30.8% had diabetes. Prevalence of F4 was 22% (n = 87), with 21% F3 (n = 83), and 56.4% (n = 220) F0-2. Overall mean FIB-4 score was 1.81 ± 1.75, and 3.24 ± 2.16 for F4. FIB-4 had AUROC 0.79 at proposed thresholds, with 32% indeterminate or misclassified (Table 1) . Of patients with F4, 57.8% (n = 50) had a FIB-4 score < 3.48, and 23.0% (n = 20) had a FIB-4 score < 1.67. **Conclusion:** In our cohort of biopsy-proven NAFLD patients, FIB-4 with cut-offs **e** 3.48 and < 1.67 to 'rule in' and 'rule out' F4, respectively, performed with high specificity but limited sensitivity. However, nearly 60% of patients with cirrhosis would have been missed using an upper FIB-4 cut-off of 3.48. As such, the proposed FIB-4 thresholds for F4 are not yet optimized for use in tertiary clinical practice.

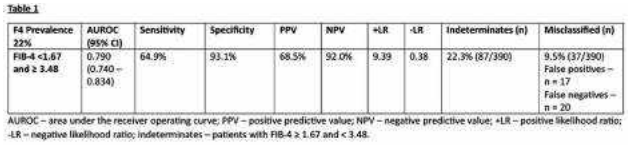

Table 1

F4 Prevalence 22%	AUROC (95% CI)	Sensitivity	Specificity	PPV	NPV	+LR	-LR	Indeterminates (n)	Misclassified (n)
FIB-4 <1.67 and ≥ 3.48	0.790 (0.740 – 0.834)	64.9%	93.1%	68.5%	92.0%	9.39	0.38	22.3% (87/390)	9.5% (37/390) False positives – n = 17 False negatives – n = 20

AUROC – area under the receiver operating curve; PPV – positive predictive value; NPV – negative predictive value; +LR – positive likelihood ratio; -LR – negative likelihood ratio; indeterminates – patients with FIB-4 ≥ 1.67 and < 3.48.

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2127-A | VALIDATION OF LIVERFAST-GP+ (GP+) AS A NON-INVASIVE TEST FOR RISK STRATIFICATION FOR PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD): SINGLE-CENTRE STUDY USING LIVER BIOPSY AS REFERENCE STANDARD★

Yong Wen Leow[1], Lee Lee Lai[1], Nik Raihan Nik Mustapha[2], Sanjiv Mahadeva[1], Ronald Quiambao[3], Mona Munteanu[3] and Wah Kheong Chan[1], (1) University of Malaya, (2)Hospital Sultanah Bahiyah, (3) Fibronostics US Inc, USA

Background: LIVERFASt-GP+ (GP+) is an AI-based non-invasive test, devised to screen for and provide risk stratification for non-alcoholic fatty liver disease (NAFLD), by using simple blood biomarkers and anthropometric measurements. A study has found it to be superior to Fibrosis-4 score (FIB4), with no grey zone and no drawbacks related to age. Previous studies on GP+ have been carried out in US-based population and there are few validation studies elsewhere. We aimed to validate GP+ in our local population and to explore its role in combination with other non-invasive tests. **Methods:** We performed a retrospective analysis of data from NAFLD patients who underwent a liver biopsy at the University of Malaya Medical Centre in two previous studies. In addition, patients with diabetes who underwent transient elastography in a separate study and had controlled attenuation parameter < 248 dB/m and liver stiffness measurement (LSM) < 5 kPa were considered as not having steatosis and fibrosis. Patients were assigned to one of the four GP+ diagnostic categories, which included "No steatosis and fibrosis", "Steatosis only, no fibrosis", "Mild or moderate fibrosis, any steatosis", and "Advanced fibrosis, any steatosis", based on a proprietary algorithm. **Results:** The data for 350 patients were analyzed (median age 55 y, 45% male, advanced fibrosis 22%).

The Cohen's weighted kappa value for the agreement between GP+ diagnostic category and histological diagnosis was 0.179 (95% confidence interval 0.126 - 0.233; p-value = < 0.001), indicating a poor agreement. The sensitivity, specificity, positive predictive value, negative predictive value, misclassification rate and indeterminate results from assessments using GP+ alone, GP+ in combination with LSM, FIB4 alone and FIB4 in combination with LSM to diagnose advanced fibrosis are shown in Table 1. GP+ had a higher negative predictive value for advanced fibrosis compared with FIB4 and a lower misclassification rate when used as a two-step approach in combination with LSM for the diagnosis of advanced fibrosis compared to FIB4 in combination with LSM. **Conclusion:** GP+ may have a role in identifying NAFLD patients who require further evaluation with LSM and in risk stratification when used as a two-step approach in combination with LSM.

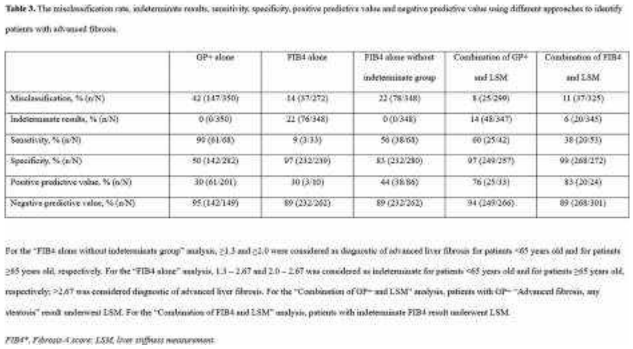

Table 3. The misclassification rate, indeterminate results, sensitivity, specificity, positive predictive value and negative predictive value using different approaches to identify patients with advanced fibrosis.

	GP+ alone	FIB4 alone	FIB4 alone without indeterminate group	Combination of GP+ and LSM	Combination of FIB4 and LSM
Misclassification, % (n/N)	42 (147/350)	14 (37/272)	22 (78/348)	8 (25/299)	11 (37/325)
Indeterminate results, % (n/N)	0 (0/350)	22 (76/348)	0 (0/348)	14 (48/347)	6 (20/345)
Sensitivity, % (n/N)	90 (61/68)	9 (3/33)	56 (38/68)	60 (25/42)	38 (20/53)
Specificity, % (n/N)	50 (142/282)	97 (232/239)	83 (232/280)	97 (249/257)	99 (268/272)
Positive predictive value, % (n/N)	30 (61/201)	30 (3/10)	44 (38/86)	76 (25/33)	83 (20/24)
Negative predictive value, % (n/N)	95 (142/149)	89 (232/262)	89 (232/262)	94 (249/266)	89 (268/301)

For the "FIB4 alone without indeterminate group" analysis, ≥1.3 and ≥2.0 were considered as diagnostic of advanced liver fibrosis for patients <65 years old and for patients ≥65 years old, respectively. For the "FIB4 alone" analysis, 1.3 – 2.67 and 2.0 – 2.67 was considered as indeterminate for patients <65 years old and for patients ≥65 years old, respectively; >2.67 was considered diagnostic of advanced liver fibrosis. For the "Combination of GP+ and LSM" analysis, patients with GP+ "Advanced fibrosis, any steatosis" result underwent LSM. For the "Combination of FIB4 and LSM" analysis, patients with indeterminate FIB4 result underwent LSM.

FIB4, Fibrosis-4 score; LSM, liver stiffness measurement.*

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The following people have nothing to disclose: Yong Wen Leow
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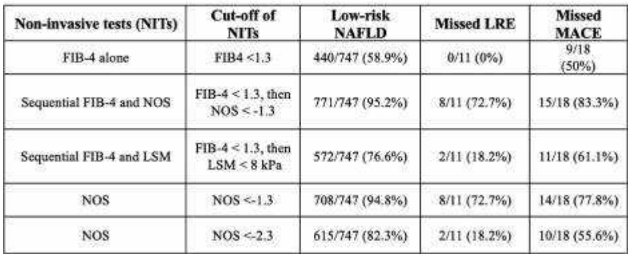
2128-A | VALIDATION OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) OUTCOME SCORE (NOS) TO PREDICT LIVER-RELATED EVENTS IN NAFLD: AN INTERNATIONAL MULTICENTER STUDY

Wei Xuan Tay[1]*, Yiong Huak Chan*[2]*, Majd Aboona*[3]*, Michael W Song*[4]*, Claire Faulkner*[3]*, Nicole Xinrong Han*[5]*, Jessica Cristiu*[6]*, Karn Wijarnpreecha*[7]*, Vincent Chen*[8] *and Yu JUN Wong*[1]*, (1)Department of Gastroenterology & Hepatology, Changi General Hospital, Singapore, (2)Yong Loo Lin School of Medicine, National University of Singapore, Singapore, (3)University of Arizona College of Medicine, Phoenix, AZ, (4)University of Michigan, Ann Arbor, (5)Changi General Hospital, (6)University of Michigan, Ann Arbor, Michigan, USA, (7)University of Arizona College of Medicine Phoenix, Phoenix, AZ, (8)University of Michigan Medical Center*

Background: Current AASLD and AGA guidelines recommend the sequential use of FIB-4 and liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) to risk stratify Non-alcoholic fatty liver disease (NAFLD) patients, but availability of VCTE may limits the scalability of this approach. The NAFLD Outcome score (NOS), derived from six routine parameters (albumin, platelet, age, bilirubin, diabetes and INR) was introduced to identify at-risk NAFLD patients requiring surveillance for liver-related events (LRE). However, the comparative performance between NOS and liver-stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE), with or without FIB-4, as recommended by current guidelines, remained unclear. Aim: To compare NOS against LSM, with or without FIB-4 to predict the occurrence of the first LRE or major adverse cardiac events (MACE). **Methods:** We conducted an international multicenter retrospective cohort study including consecutive NAFLD patients who underwent VCTE from three centers in USA and Singapore. We exclude patients with prior LRE or MACE, concomitant liver disease, significant alcohol intake, unreliable LSM, missing value for NOS and those with follow-up less than 6 months. LRE was defined as liver decompensation, hepatocellular carcinoma and liver transplantation. MACE was defined as composite endpoints of either myocardial infarction, coronary revascularization, heart failure requiring hospitalization or stroke. **Results:** A total of 747 NAFLD patients with a diverse ethnic background were included (57.3% Asian, 13.5% Hispanic, 20.1% White, 3.5% black). The mean (± standard deviation) age was 55 (± 14), 50% was male, 58% were obese, 49% were diabetic. Median FIB-4 was 1.1, median LSM was 6.7kPa, with 18% having advanced fibrosis and 21.6% having cirrhosis. Over a median follow-up of 34.5 months, the cumulative incidence of LRE and MACE was 6.2 (95%CI: 3.6-12.8) and 10.7 (95%CI: 10.6-10.9) per 1,000 person-years, respectively. While NOS had a comparable accuracy to predict LRE at 5 years than VCTE and FIB-4 (tAUC 0.93 vs 0.82 vs 0.92), NOS is more accurate than FIB-4 to predict MACE at 5-years (tAUC: 0.79 vs 0.62, DeLong's test: $p = 0.003$). To identify low-risk NAFLD patients who can be discharge to primary care, sequential FIB-4 and LSM identify more "low-risk NAFLD patients" at the expense of missing 18.2% of LRE than Fib-4 alone (0%)

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

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



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

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Disclosure information not available at the time of publication: Yiong Huak Chan, Majd Aboona, Michael W Song, Claire Faulkner, Nicole Xinrong Han, Jessica Cristiu

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

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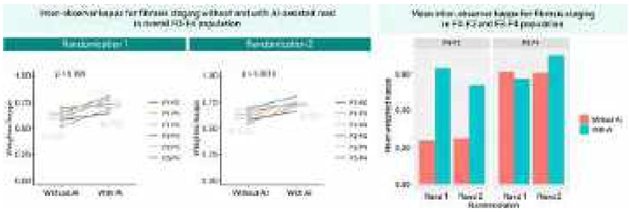
Background: Intra- and inter-observer variability in histological staging of fibrosis in NASH clinical trials lead to suboptimal selection of patients and confound assessment of fibrosis response. Aim: To prospectively evaluate the utility of the HistoIndex artificial intelligence (AI) digital pathology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

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



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

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Background: International regulatory agencies recommend testing drug therapy for patients with compensated nonalcoholic fatty liver disease (NAFLD)-related cirrhosis or with noncirrhotic fibrotic nonalcoholic steatohepatitis (NASH) because they are at risk of developing liver-related events (LRE). We aimed to compare the risk of LRE in NAFLD patients stratified for F2-F4 fibrosis and NASH. The secondary aim was to compare the accuracy of histologically defined fibrotic NASH with liver stiffness measurement (LSM) and AGILE 3+ score for prediction of LRE. **Methods:** 1938 consecutive patients with biopsy-proven NAFLD (Kleiner scoring system) were enrolled. Fibrotic NASH was defined as NASH with F2-F4 fibrosis. LSM was measured by transient elastography (FibroScan device). LRE were recorded during follow-up. Cox multivariate models were used to assess the association between fibrotic NASH or F2-F4 fibrosis without NASH, of LSM (e 8 or e 10 Kpa) and of AGILE 3+ with LRE. The diagnostic performance for the prediction of LRE was assessed using the area under the receiver operating characteristic (AUROC) curves. **Results:** The observed 5-year actuarial rate of LRE was 0.4%, 0.2%, 5.1% and 6.6% in patients with F0-F1 fibrosis without NASH, F0-F1 fibrosis with NASH, F2-F4 fibrosis without NASH, and fibrotic NASH, respectively. At multivariate Cox regression analysis using F0-F1 fibrosis without NASH as reference, both F2-F4 fibrosis without NASH (adjusted hazard ratio [aHR] 9.96, 95% C.I. 3.35 - 29.62, $p < 0.001$) and fibrotic NASH (aHR 10.14, 95% C.I. 3.51 - 29.25, $p < 0.001$) were associated with LRE occurrence. In the 1074 patients with available LSM, LSM **e** 10 KPa (aHR 6.31, 95% C.I. 2.46 - 16.2, $p < 0.001$) or AGILE 3+ > 0.67 (aHR 27.45, 95% C.I. 5.72 – 131.74, $p < 0.001$) independently predicted the development of LRE and had similarly acceptable 5-year AUROC to fibrotic NASH and F2-F4 fibrosis (0.772, 0.818, 0.739, and 0.780, respectively). **Conclusion:** The risk of developing LRE is similar in patients with fibrotic NASH and with F2-F4 fibrosis without NASH. The use of LSM **e** 10 KPa or AGILE 3+ > 0.67 could be an accurate option to identify NAFLD patients worthy to be included in clinical trials testing new pharmacological agents.

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2131-A | A CROSS-SECTIONAL ONLINE SURVEY TO UNDERSTAND EXISTING NAFLD/NASH CURRICULUM GAPS IN US PRIMARY CARE PROVIDER AND SPECIALTY TRAINING PROGRAMS

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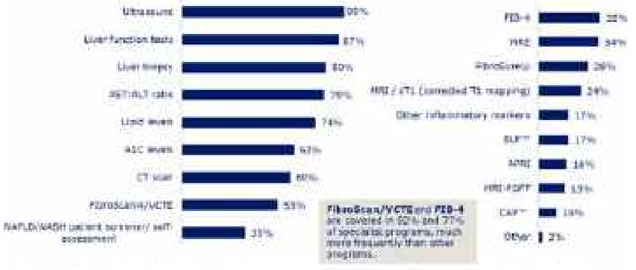
Background: NAFLD affects approximately 30% of the US population and up to 25% of patients with NAFLD progress to NASH. Unrecognized and unaddressed, NASH can lead to significant hepatic and extrahepatic – especially cardiovascular – morbidity and mortality. Inclusion of NAFLD in the Graduate Medical Education curricula is critical to ensure proficiency in the identification and care of patients with NAFLD. This study aimed to identify gaps, uncover barriers to implementation and opportunities to improve NAFLD education in current US training programs for specialists and primary care providers (PCPs), who care for most patients with NAFLD. **Methods:** A nationwide, cross-sectional, quantitative online survey of residency / fellowship program leaders in hepatology, gastroenterology, endocrinology and primary care (internal medicine and family practice) and of NP/PA program leaders was conducted from 2/2023-5/2023. An IRB exemption was issued. **Results:** 181 respondents completed the survey; 93 (51%) represented PCP programs, 40 (22%) represented specialist programs and 48 (27%) represented NP/PA programs. NAFLD was included in the core curriculum of 97% of all programs and NASH was included in 92%, mostly via seminars, lectures or conferences; however, NASH education during inpatient rotations was included in 72%. The inclusion of NASH education was considered to be very appropriate (85%) and very important (73%) by majority of specialist programs, followed by PCP programs (72%, 56%) and NP/PA programs (63%, 50%). PCP curricula directors believe their trainees are more responsible than specialists for identifying and screening patients at risk for NASH. Among NASH core competencies, most PCP, specialty and NP/PA programs were likely to include education on risk factors/comorbidities, long-term complications, NASH clinical characteristics, NASH screening and diagnosis, and lifestyle management, but less likely to include education on pharmacologic intervention, clinical trials, and genetic risk. Of 18 NASH diagnostic test options surveyed within a program's core curriculum, only eight were included by at least 50% of programs (Fig. 1). FIB-4, a cornerstone screening tool, was covered in only a third of primary care programs but was covered in more than three quarters of specialty-based programs. The main barriers to integrating NASH education were lack of space in the curriculum, access to expert faculty and available treatments. Only 29% of respondents expressed plans to expand their NASH curricula. **Conclusion:** Despite inclusion in most PCP and specialist program curricula, results from this survey suggest significant gaps in NASH education, particularly in screening and diagnostic tools. However, directed training program enhancements may serve to elevate provider proficiency in the care of patients with NASH.



FibroScan/VCTE and FIB-4 are covered in 92% and 77% of specialist programs, much more frequently than other programs.

Figure 1: NASH Tools, Clinical Tests and Diagnostic Methods Covered in Core Program Curriculum

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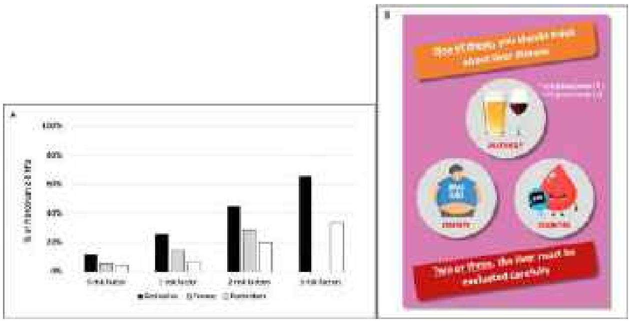
2132-A | A PICTURE OF THE PATIENT WHO SHOULD BE SCREENED FOR LIVER FIBROSIS

Clemence Canivet[1], Willem Pieter Brouwer[2], Thierry Thévenot[3], Marine Roux[4], Clemence Moreau[5], Severine Dubois[4], Sophie Vendeville[3], Frederic Gagnadoux[4], Sarwa Darwish Murad[6], Rob J. De Knegt[7], Dominique M Roulot[8] and Jérôme Boursier[9], (1)CHU of Angers, (2)Erasmus MC, University Medical Center, Rotterdam, Netherlands, (3)Jean Minjoz Hospital, (4)Angers University Hospital, Angers, France, (5)Laboratoire Hifih, Upres EA3859, Sfr 4208, Angers University, (6)Erasmus University Medical Center, (7)Erasmus MC, University Medical Center, (8) Avicenne Hospital, Assistance Publique- Hopitaux De Paris, (9)Service Hépato-Gastroentérologie Et Oncologie Digestive, Centre Hospitalier Universitaire, *Angers, France; & Laboratoire Hifih, Sfr Icat 4208, Université D'angers, Angers, France*

Background: EASL and AASLD both recommend screening of liver fibrosis in at-risk individual's. However, the criteria defining "at-risk individual's" are not clearly established. The aim of this study was to define the picture of the patient at risk of elevated liver stiffness who needs evaluation with non-invasive tests for liver fibrosis. **Methods:** Four cohorts of patients from tertiary care (included in diabetology, pneumology and cardiology) or primary care were included in the derivation set. Two cohorts from the general population (Rotterdam and France) were included in the validation set. All patients were older than 40 and had a LS measurement (LSM) with FibroScan. The primary endpoint was the presence of LSM > 8 kPa. **Results:** In the derivation cohort (1,483 patients): median age was 60 years, 68.6% were male, median BMI was 29.1 kg/m^2 (IQR 26.0-32.0), 32.8% had type 2 diabetes mellitus (T2DM), 60.1% were on antihypertensive therapy, 41.0% used lipid-lowering drugs. Median alcohol consumption was 20 g/week. Median LSM was 5.9 (IQR: 4.5-8.1) kPa, 25.7% of patients had a LSM > 8 kPa. In multivariate analysis adjusted for age and sex, three risk factors were significantly associated with LSM > 8 kPa: T2DM, BMI > 30 kg/m^2 and alcohol consumption more than WHO thresholds ($p < 0.001$). The rate of LSM > 8 kPa increased with the number of risk factors, from 10% (no risk factor) to 65% (3 risk factors; Figure 1A). In the validation cohorts from France and the Netherlands (Rotterdam study) respectively, 1,190 and 4,377 patients were included. Median age was 57 and 67 years, median BMI was 26.3 (IQR 23.5-28.7) and 26.8 (IQR 24.4-29.4) kg/m^2, and 7.6 and 8.2% had T2DM. Median LSM was 5.3 (IQR 4.4-6.5) and 4.8 (IQR 3.9-6.0) kPa; 7.7 and 6.0% of individual's had a LSM > 8 kPa. In the French cohort, the rate of LSM > 8 kPa increased, from 5.5% in patients without risk factors to 28.6% in case of 2 risk factors (no patient had 3 risk factors; Figure 1A). In the Dutch (Rotterdam) cohort, 4.2% without risk factors had LSM > 8 kPa and this rate reached to 33.3% in case of 3 risk factors (figure 1A). **Conclusion:** We propose that the definition of being at-risk for liver fibrosis in those individual's older than 40 years should be based on three clinical conditions: presence of T2DM, BMI > 30 kg/m^2 and alcohol consumption more than WHO thresholds. In case of one risk factor, a simple screening test should be prescribed. In case of 2 or 3 risk factors, the liver should be evaluated more carefully (Figure 1B).



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Dominique M Roulot – Gilead Sciences, Inc.: Speaking and Teaching, No, No;

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2133-A | A RAPID RISE IN THE GLOBAL PREVALENCE OF NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND NON-ALCOHOLIC STEATOHEPATITIS (NASH) AMONG PATIENTS WITH TYPE 2 DIABETES (T2D)

Zobair M. Younossi[1,2,3,4], Pegah Golabi[1,2,3,4], Jillian K. Price[1,2,3], Soroor Owrangi[1], Nagashree Gundu-Rao[5], Romona Satchi[5] and James M. Paik[1,2,3,4], (1)Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, (2)Center for Liver Disease, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, VA, (3)Inova Medicine, Inova Health System, Falls Church, VA, (4)The Global Nash Council, Washington, DC, (5)Division of Endocrinology, Inova Health System, Falls Church, VA

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease and closely associated with type 2 diabetes. (T2D). Our aim was to estimate the global prevalence of NAFLD, non-alcoholic steatohepatitis (NASH), and advanced fibrosis among patients with T2D. **Methods:** We systematically searched PubMed and Ovid MEDLINE for terms including NAFLD, NASH, and T2D and collected data from the (1990-2019) survey year (last published December 2022) according to PRISMA. Two reviewers independently assessed study eligibility, extracted data, and assessed studies for bias. The meta-analysis was conducted using a random-effects model. Assessment of bias risk used the Joanna Briggs Institute. **Results:** The search identified 3134 studies from 33 countries. Of these, data were extracted from 122 eligible studies that included 2,224,144 patients with T2D to determine the prevalence of NAFLD. Another 12 studies with 2,733 T2D patients with liver biopsy data were eligible for determination of the prevalence of NASH, significant fibrosis (SF, **e** F2) and advanced fibrosis (AF, **e** F3). Across the entire study period (1990-2021), the global pooled prevalence of NAFLD (based on transient elastography CAP) among patients with T2D was 62.25% (47.12-77.38%). In patients with T2D, the global NAFLD prevalence has increased by +50.09% [45.52% (25.01-67.57) in 1990-2004 to 68.32% (63.20-73.04)] in 2016-2021 ($p = 0.008$). The highest NAFLD prevalence among T2D patients was observed in Eastern Europe ($n = 11$ studies, 78.95%, 73.90-83.25%), followed by Middle East ($n = 15$, 69.83%, 60.67-77.86%), Western Europe ($n = 19$, 68.52%, 63.75-72.92%), USA & Australia ($n = 14$, 63.82%, 50.75-75.12%), South Asia ($n = 24$, 62.61%, 55.09-69.58%), East Asia ($n = 17$, 60.89%, 56.26-65.33%), Asia Pacific ($n = 10$, 51.56%, 38.83-64.08), Latin America ($n = 6$, 51.35, 38.83-64.08%), and Africa ($n = 6$, 43.05%, 20.82-68.49%). Among NAFLD patients withT2D who had available liver biopsy, the global pooled prevalence of NASH, significant fibrosis (**e** F2) and advanced fibrosis (**e** F3) were 59.69% (44.35-73.34%), 46.30% (29.35-64.16%), and 25.38% (15.95-37.87%), respectively. **Conclusion:** The prevalence of NAFLD among T2D is very high and growing. The majority of NAFLD patients with T2D have NASH with a significant proportion having Advanced Fibrosis. Patients with NAFLD and T2D should be prioritized for risk stratification using recently developed algorithms.

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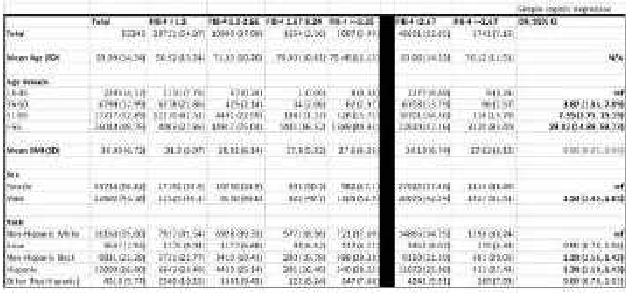
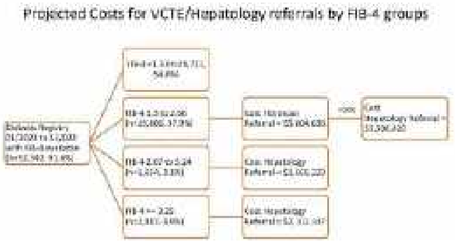
2134-A | AASLD/AGA NAFLD PRACTICE GUIDANCE FOR SCREENING DIABETICS: FACTORS ASSOCIATED WITH ADVANCED FIBROSIS, IMPLICATIONS FOR CARE DELIVERY, AND COST-REDUCTION USING AGE-ADJUSTED FIB-4 CUT-OFFS

Rohit R Nathani[1], Anna Mageras[2], Carolina Villarroel[3], Silpa Yarra[3], Nina Priven[1], Heather Viola[1], Stephanie Wang[1], Theresa Mack[1], Martin Arron[1], Fernando Carnavali[1], Xiaotao Zhang[2] and Meena B. Bansal[2], (1) Mount Sinai Morningside and West Hospital, (2)Icahn School of Medicine at Mount Sinai, (3)Mount Sinai Beth Israel Hospital

Background: Patients with NAFLD and advanced fibrosis have the highest risk of liver-related mortality. AASLD/AGA recommends a sequential algorithm of FIB-4 score followed by VCTE to identify diabetic patients with advanced fibrosis requiring hepatology evaluation. This study aimed to characterize a diverse urban DM population, calculate FIB-4 scores, identify factors associated with FIB-4 **e** 2.67, and determine cost implications of algorithm adherence. **Methods:** Using the Mount Sinai Health System's DM registry, we identified patients aged 18+ who received primary care in 2022. Labs to calculate FIB-4 scores and baseline demographic and referral data were extracted from the EMR. FIB-4 scores were stratified as low (< 1.30), indeterminate (1.3-2.66), high risk for advanced fibrosis (2.67-3.24), and cirrhosis (**e** 3.25). Chi square and Anova tests were used to compare demographics and BMI across FIB4 groups. Logistic regression was used to determine factors associated with FIB4 **e** 2.67. Total referral costs for VCTE/hepatology were calculated using insurance-specific rates (cohort: 49% Medicare, 36% commercial, 15% Medicaid), and sub-analyses were conducted to evaluate different age-specific cut-offs. **Results:** Among 57,151 adult diabetic patients, FIB-4 scores could be calculated for 91.6% (n = 52,342). Table 1 presents the distribution of age, BMI, sex, and racial/ethnic categories across FIB-4 categories. Male (1.53, 95% CI: 1.43, 1.65), Hispanic (1.30; 95% CI: 1.19, 1.43), and non-Hispanic Black (1.29, 95% CI: 1.16, 1.42) patients had increased odds of FIB4 **e** 2.67 compared to women and non-Hispanic white patients, respectively. BMI was inversely associated with FIB-4 **e** 2.67 (0.95, 95% CI: 0.95, 0.96). Only a small percentage of patients with FIB-4 1.3-2.66 (4%) were referred to VCTE or hepatology, while 14% with FIB-4 **e** 2.67 were referred to hepatology. Adjusting the indeterminate zone cut-off for patients over 65 to FIB-4 **e** 2 reduced the number of patients in the indeterminate zone from 57% to 17%, leading to potential cost savings of approximately $2 million. For patients aged 18-35, using a lower cut-off of FIB-4 **e** 1 increased potential costs by $24K as more patients would require further evaluation. **Conclusion:** FIB-4 scores can be easily calculated for most diabetic patients based on routinely ordered labs. Male sex, Hispanic and Black race/ethnicity were significantly associated with higher FIB-4 scores. The low referral rates to hepatology suggest a lack of awareness regarding FIB-4 use for risk stratification and adherence to AASLD/AGA guidance. Age-adjusted cut-offs can help reduce costs and unnecessary referrals. Implementing an EMR-based FIB-4 calculator, provider usage and patient outcome reports, and robust educational programs may improve adherence to the AASLD/AGA guidance pathway. The efficacy of these interventions is currently under evaluation.





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2135-A | ADHERENCE TO DIETARY APPROACHES TO STOP HYPERTENSION DIET AND NON-ALCOHOLIC FATTY LIVER DISEASE IN A NATIONALLY REPRESENTATIVE SAMPLE OF U.S. CHILDREN AND YOUTH

Vanessa Garcia-Larsen[1], Hani Tamim[2], Kirstie Ducharme-Smith[1], Faisal M Sanai[3] and Saleh A Alqahtani[4,5], (1)Johns Hopkins University, (2)Alfaisal University, (3)King Abdulaziz Medical City-Jeddah, (4) Johns Hopkins University School of Medicine, (5)King Faisal Specialist Hospital and Research Center

Background: Non-alcoholic fatty liver disease (NAFLD) has become increasingly prevalent among children and youth. Lifestyle-related factors, including diet, modulate the risk of NAFLD, but evidence on the role of diet quality in NAFLD in young people is scant. We aimed to investigate the association of adherence to the Dietary Approaches to Stop Hypertension (DASH) diet and NAFLD amongst U.S. youth. **Methods:** Children and youth aged 12-29 years of age participating in the National Health and Nutrition Examination Survey (NHANES) cycles between 2005-2016 were included in this study. NAFLD was assessed using the improved U.S. fatty liver index (iFLI) for the multiethnic U.S. population, which predicts the presence of NAFLD based on age, ethnicity, waist circumference, gamma-glutamyltransferase activity, fasting insulin, and fasting glucose. Diet quality was assessed using the DASH diet score (higher scores = better adherence). Survey-weighted logistic regression models were used to investigate the association of DASH score (quartiles) and NAFLD (iFLI **e** 30 used in this study), adjusting for age, sex, race/ethnicity, body mass index (BMI), total energy intake, household income, education, and NHANES cycle. **Results:** A total of 5,586 participants (mean age 19.1 ± 5.1 y) with complete data were included; 15.1% of all subjects, including 12.3% of children (< 18 y of age), and 17.9% of those aged 18+ had an iFLI **e** 30. The mean DASH pattern score of subjects was 22.3 (SD ± 5.0), indicative of 46% adherence to the DASH-style diet pattern. Compared with those with lowest adherence (quartile 1), those with highest adherence (quartile 4) to the DASH pattern had lower odds of having NAFLD (adjusted odds ratio 0.68; 95% confidence interval 0.48, 0.95). **Conclusion:** Amongst U.S. children and youth, adherence to the DASH diet was negatively associated with NAFLD, independently of other important risk factors, including BMI. Improving diet quality in this age group may contribute to preventing NAFLD.

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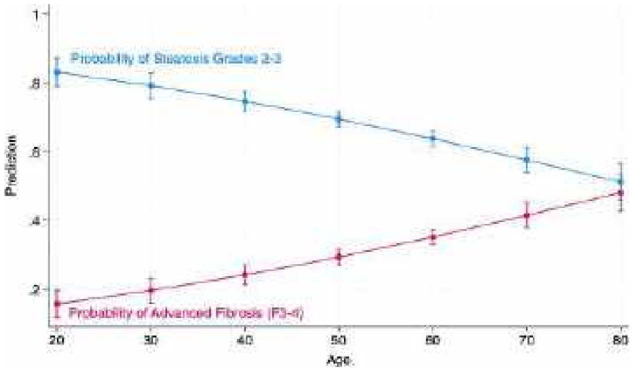
2136-A | AGE HAS INDEPENDENT POSITIVE AND NEGATIVE ASSOCIATIONS WITH ADVANCED FIBROSIS AND STEATOSIS: COMBINED DATA FROM MULTIPLE THERAPEUTIC TRIALS INCLUDING MORE THAN 6,000 PATIENTS (IN COLLABORATION WITH NAIL-NIT CONSORTIUM)

Stephen A Harrison[1], Julie Dubourg[2], Sophie Jeannin[2], Naim Alkhouri[3], Jörn M. Schattenberg[4] and Mazen Noureddin[5], (1)Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom, (2) Summit Clinical Research, San Antonio, TX, (3)Arizona Liver Health, Phoenix, AZ, (4)I. Department of Medicine, University Medical Centre Mainz, Johannes Gutenberg University, Mainz, Germany, Mainz, Germany, (5) Houston Research Institute, Houston, TX

Background: Age has been previously identified as an independent risk factor for fibrosis severity in nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). We aimed to assess the relationship between age and NAFLD/NASH components. **Methods:** We combined screening data from 7 NASH non-cirrhotic phase 2 trials. We performed univariate and multivariate logistic regression analyses to predict advanced fibrosis (as defined by fibrosis stages F3-F4) and to predict higher grades of steatosis (as defined by steatosis grades 2 or 3). **Results:** Out of 6,558 patients, 2,271 with centrally assessed liver biopsies were included in this analysis. The mean age was 54.2 years (y) (SD: 11.7). The presence of advanced fibrosis increased with age ranging from 12.5% in age < 25y, to 22.8% in age 25-45y, to 33.4% in age 45-65y and to 39.9% in age > 65y. Inversely, the presence of grade 3 steatosis decreased with age ranging from 40% in age < 25y, to 32.3% in age 25-45y, to 23.2% in age 45-65y and to 16.2% in age > 65y. In multivariate analysis, after adjustment on gender, ethnicity, AST, glycated hemoglobin (HbA1c) and liver stiffness measurement (as measured by FibroScan®), age remained significantly associated with the severity of fibrosis (p < 0.001, Figure). After adjustment on gender, ethnicity, ALT, HbA1c and controlled attenuation parameter (as measured by FibroScan®), age remained negatively associated with the severity of steatosis (p = 0.001, Figure). **Conclusion:** This analysis provides compelling evidence supporting the natural course of NAFLD as a disease with slow progression. As individual's age, we observed a decrease in steatosis accompanied by a worsening of fibrosis. These findings underscore the dynamic nature of NAFLD and highlight the importance of longitudinal studies to better understand its trajectory over time.



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

Eduardo Vilar-Gomez II[1], Samer Gawrieh[1], Jordan E. Lake[2], Tinsay A. Woreta[3], Montreca Releford[1], Mark S. Sulkowski[4], Rohit Loomba[5], Jennifer C. Price[6], Kathleen E. Corey[7], Susanna Naggie[8], Sonya Heath[9], Laura Wilson[10], Richard K. Sterling[11] and Naga P. Chalasani[1], (1)Indiana University School of Medicine, (2)University of Texas - Houston, (3)Johns Hopkins Medicine, Baltimore, MD, (4)Johns Hopkins Medicine, (5)University of California, San Diego, San Diego, CA, (6)University of California, San Francisco, (7)Harvard University, (8)Duke Clinical Research Institute, Durham, NC, (9)University of Alabama at Birmingham, (10)Johns Hopkins School of Public Health, (11)Virginia Commonwealth University Health System

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

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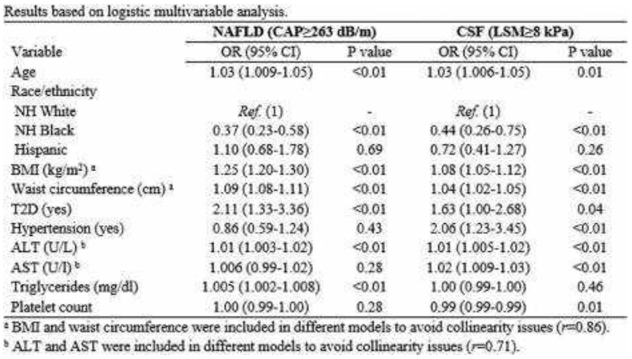
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

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



Results based on logistic multivariable analysis.

	NAFLD (CAP≥263 dB/m)		CSF (LSM≥8 kPa)	
Variable	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.03 (1.009-1.05)	<0.01	1.03 (1.006-1.05)	0.01
Race/ethnicity				
NH White	*Ref.* (1)	-	*Ref.* (1)	-
NH Black	0.37 (0.23-0.58)	<0.01	0.44 (0.26-0.75)	<0.01
Hispanic	1.10 (0.68-1.78)	0.69	0.72 (0.41-1.27)	0.26
BMI (kg/m^2) [a]	1.25 (1.20-1.30)	<0.01	1.08 (1.05-1.12)	<0.01
Waist circumference (cm) [a]	1.09 (1.08-1.11)	<0.01	1.04 (1.02-1.05)	<0.01
T2D (yes)	2.11 (1.33-3.36)	<0.01	1.63 (1.00-2.68)	0.04
Hypertension (yes)	0.86 (0.59-1.24)	0.43	2.06 (1.23-3.45)	<0.01
ALT (U/L) [b]	1.01 (1.003-1.02)	<0.01	1.01 (1.005-1.02)	<0.01
AST (U/l) [b]	1.006 (0.99-1.02)	0.28	1.02 (1.009-1.03)	<0.01
Triglycerides (mg/dl)	1.005 (1.002-1.008)	<0.01	1.00 (0.99-1.00)	0.46
Platelet count	1.00 (0.99-1.00)	0.28	0.99 (0.99-0.99)	0.01

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

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

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2138-A | ASSESSING NAFLD AWARENESS AND EDUCATIONAL NEEDS IN PATIENTS WITH TYPE 2 DIABETES

Alexander Kusnik, Hassan Liaqat, Javeria Nasir, Roshan Subedi, Rutwik Pradeep Sharma, Andrew Jung, Nicole Hunter, Rafia Zafar, Ari Chodos, Richard Alweis and Krishnakumar Rajamani, Rochester Regional Health

Background: Inadequate awareness of non-alcoholic fatty liver disease (NAFLD) is assumed among individual's with type 2 diabetes mellitus (T2DM), necessitating a better understanding of their existing awareness levels and educational requirements. This understanding is crucial for developing effective interventions and programs aimed at early detection and management of NAFLD. **Methods:** This prospective study utilized a 36-item survey administered through tablet computers in an endocrinologist's office, using the REDCap platform. A total of 179 patients participated in the study, providing information about their education, marital status, income, awareness of liver disease, knowledge of diabetes complications, and educational needs regarding NAFLD. These responses were also correlated with relevant blood work and medical imaging suggesting liver disease. **Results:** Out of 179 respondents, 59.00% were female (106) and 40.80% were male (73). The mean age for females was 61 years, and for males, it was 63 years. The majority identified as White (86.00%), followed by African-American (10.10%), Hispanic (2.20%), and Asian (1.7%). In terms of marital status, 59.9% were married, 19.8% were single, 10.70% were divorced, and 9% were widowed. Regarding educational status, the majority of patients were high school graduates (30.7%) or had completed professional/vocational/technical training (23.5%). Approximately 30% had a bachelor's degree or higher. The mean body mass index (BMI) was 61 for females and 62.6 for males. Respondents' income distribution: Less than $30,000 - 23.60%, $30,000-$50,000 - 24.10%, $50,000-$100,000 - 33.90%, $100,000 or above - approximately 18%.The mean duration of T2DM was 15.95 years for males and 22.58 years for females. More than 92% of respondents reported either having no preexisting liver disease or being uncertain about their own liver disease. Awareness of NAFLD was limited, with 72.9% having only slight awareness or being completely unaware. Summarizing the degree of agreement based on a 7-point Likert scale, the preferred learning methods regarding NAFLD were doctor-led education (93.2%), access to pamphlets in the doctor's office (82.4%), and educational videos during wait times (81.5%). Patients agreed that there is a need for more information about NAFLD from healthcare personnel (88.2%) and increased availability of NAFLD resources on the internet, television, or social media (81.3%). **Conclusion:** Our study reveals an interest among patients with T2DM to learn about NAFLD. The data collected in the endocrinology outpatient setting indicates that patients favor doctor-led education, pamphlets, and videos as their preferred learning methods for NAFLD, particularly during wait times. Supplying educational materials like pamphlets and videos on NAFLD could boost awareness in this high-risk population and potentially facilitate doctor-led education.

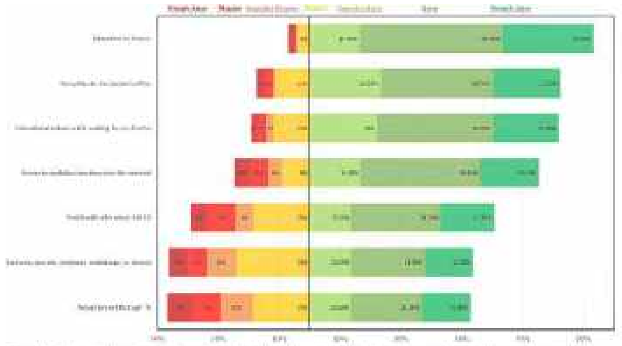


Figure 1 [illegible]

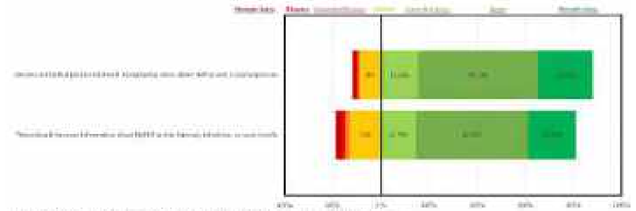


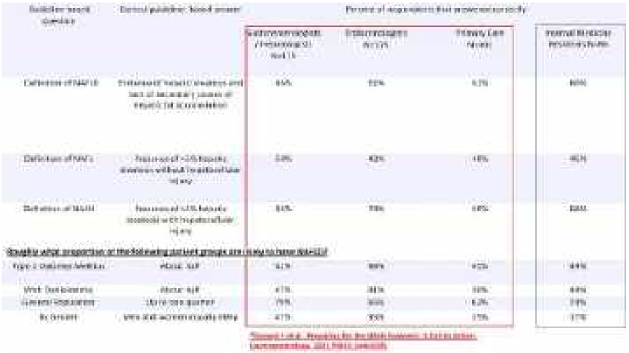
Figure 2 [illegible]

Disclosures: The following people have nothing to disclose: Alexander Kusnik, Hassan Liaqat, Javeria Nasir, Roshan Subedi, Rutwik Pradeep Sharma, Andrew Jung, Nicole Hunter, Rafia Zafar, Ari Chodos, Richard Alweis, Krishnakumar Rajamani

2139-A | ASSESSMENT OF NAFLD AWARENESS AND DIAGNOSTIC TOOL UTILIZATION AMONG INTERNAL MEDICINE RESIDENTS IN THE UNITED STATES

Alexander Kusnik[1], Richard Alweis[1], Andrew Brown[2], Ari Chodos[1], Seshavadhani Kumar[3] and Krishnakumar Rajamani[1], (1)Rochester Regional Health, (2)University of Rochester, (3)Rochester Institute of Technology

Background: NAFLD, often linked to obesity and metabolic syndrome, is commonly underdiagnosed, and the level of NAFLD knowledge among Internal Medicine Residents is largely unexplored. Considering their crucial role in patient care across diverse settings, it is imperative to identify and address knowledge gaps to improve patient outcomes. **Methods:** To assess NAFLD knowledge among Internal Medicine residents, an anonymous Research Electronic Data Capture (REDCap) survey was distributed via professional email addresses to residents from six community and university hospitals. The survey included questions adapted from the NASH Needs Assessment Survey, allowing for comparisons with existing data from gastroenterologists, endocrinologists, and Primary Care Physicians (PCPs). Additionally, the survey inquired about the utilization of recommended diagnostic tools, such as the FIB-4 score and elastography, to accurately diagnose NAFLD. **Results:** The study involved 86 Internal Medicine residents, whose responses regarding NAFLD prevalence and definitions are depicted in Figure 1. Comparing these findings with data from the NASH Needs Assessment Survey, including gastroenterologists, endocrinologists, and PCPs, strong evidence (p-value 0.001, at a significance level of 5%) suggests that the proportion of residents aware of the definition of non-alcoholic fatty liver (NAFL) is at least 9% smaller than that of Gastroenterologists/Hepatologists (G/H). Moreover, a statistically significant difference (p-value **H** 0) in awareness levels emerges among residents concerning the prevalence of NAFLD between men and women compared to primary care physicians. The upper bound of the 95% confidence interval is -0.096, indicating that the proportion of residents aware of the extent of NAFLD prevalence between men and women is at least 9.6% smaller than that of primary care physicians and at least 20% smaller than that of gastroenterologists. Despite the relative awareness of NAFLD, 75% of surveyed Internal Medicine residents reported not screening for NAFLD/NASH in clinical practice. Additionally, most respondents (88% and 82%) indicated that they had never or rarely utilized the recommended FIB-4 screening tool or liver stiffness measurement, respectively. Nearly all residents (98%) expressed the need for increased attention to NAFLD and its complications during their residency training. **Conclusion:** This study compares NAFLD awareness levels between Internal Medicine residents and other healthcare professionals. Despite some level of awareness, a notable proportion of surveyed residents exhibited limited familiarity with diagnostic tools and expressed a need for additional education on NAFLD/NASH during their residency training. This highlights the importance of implementing structural interventions within Internal Medicine residency programs to enhance NAFLD diagnostic strategies.



Disclosures: The following people have nothing to disclose: Alexander Kusnik, Richard Alweis, Andrew Brown, Ari Chodos, Seshavadhani Kumar, Krishnakumar Rajamani

2140-A | ASSOCIATION BETWEEN BARIATRIC SURGERY AND MACROVASCULAR DISEASE AND MORTALITY OUTCOMES IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE, TYPE 2 DIABETES, AND OBESITY

Arunkumar Krishnan, Atrium Health Levine Cancer Institute, Tinsay A. Woreta, Johns Hopkins Medicine, Baltimore, MD, Dipatsree Mukherjee, Apex Institute of Medical Sciences, William R. Hutson, West Virginia University School of Medicine and Saleh A Alqahtani, Johns Hopkins University School of Medicine; King Faisal Specialist Hospital and Research Center

Background: The prevalence of non-alcoholic fatty liver disease (NAFLD), one of the most common liver diseases, is rising. Patients with NAFLD have relevant metabolic comorbidities, including obesity and Type 2 Diabetes Mellitus (T2DM). Cardiovascular disease (CVD) is one of the major causes of death in this patient population. The role of bariatric surgery (BS) in reducing macrovascular complications, especially in patients with NAFLD, type 2 diabetes mellitus (T2DM), and obesity, has not been well characterized. We aimed to determine the association between BS and the development of major adverse cardiovascular events (MACE) among patients with NAFLD, T2DM, and obesity at a population level. **Methods:** This large population-based, retrospective cohort study was conducted using the TriNetX dataset. All adult patients (> 18 y) diagnosed with NAFLD and who had previous ischemic heart disease or heart failure (HF) were identified after excluding other chronic liver disease etiologies. We performed a 1:1 propensity score matching (PSM) for demographics, body mass index (BMI), and comorbid conditions to similar controls as patients without a surgical history. BS procedures included Roux-en-Y gastric bypass and sleeve gastrectomy. The primary outcomes were the incidence of macrovascular diseases defined as the composite indicator of the first occurrence of HF, MACE, or cerebrovascular disease. The secondary outcome was the incidence of all-cause mortality. We conducted sensitivity analyses to assess the robustness of our findings. The hazard ratio (HR) was calculated to compare the association of the BS with the outcomes. **Results:** Of the 53204 eligible adults, 2463 patients underwent BS, and 50741 patients did not undergo BS; following PSM, both cohorts are well matched with 2449 patients. Among the BS cohort, most participants were female, younger, white, and had a smoking history. BS patients had a higher mean BMI than the non-BS cohort. In the adjusted analysis (Table 1), the risks of MACE (HR, 0.37), HF (HR, 0.65), and a composite cerebrovascular disease (HR, 0.43) were significantly lower for BS than for non-BS patients. BS was also associated with a lower incidence of the secondary outcome all-cause mortality (HR, 0.40) and a composite outcome of major CVD. These outcomes were consistent at follow-up duration of 1, 3, 5, and 7 years. The results of the sensitivity analysis were consistent, and all statistically significant associations remained unchanged. **Conclusion:** Compared with nonsurgical care, bariatric surgery had a significantly lower risk of macrovascular complications and all-cause mortality in patients with NAFLD, T2DM, and obesity.

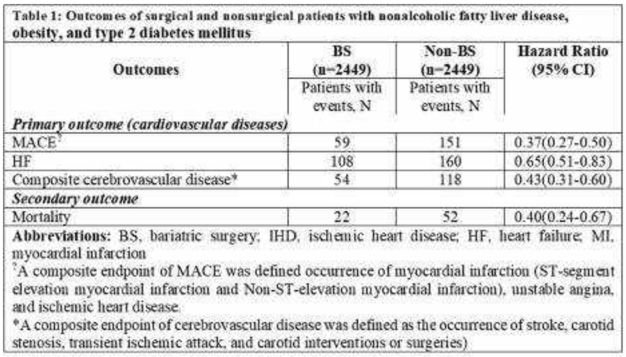


Table 1: Outcomes of surgical and nonsurgical patients with nonalcoholic fatty liver disease, obesity, and type 2 diabetes mellitus

Outcomes	BS (n=2449)	Non-BS (n=2449)	Hazard Ratio (95% CI)
	Patients with events, N	Patients with events, N	
Primary outcome (cardiovascular diseases)			
MACE[†]	59	151	0.37(0.27-0.50)
HF	108	160	0.65(0.51-0.83)
Composite cerebrovascular disease*	54	118	0.43(0.31-0.60)
Secondary outcome			
Mortality	22	52	0.40(0.24-0.67)

Abbreviations: BS, bariatric surgery; IHD, ischemic heart disease; HF, heart failure; MI, myocardial infarction

[†] A composite endpoint of MACE was defined occurrence of myocardial infarction (ST-segment elevation myocardial infarction and Non-ST-elevation myocardial infarction), unstable angina, and ischemic heart disease

*A composite endpoint of cerebrovascular disease was defined as the occurrence of stroke, carotid stenosis, transient ischemic attack, and carotid interventions or surgeries)

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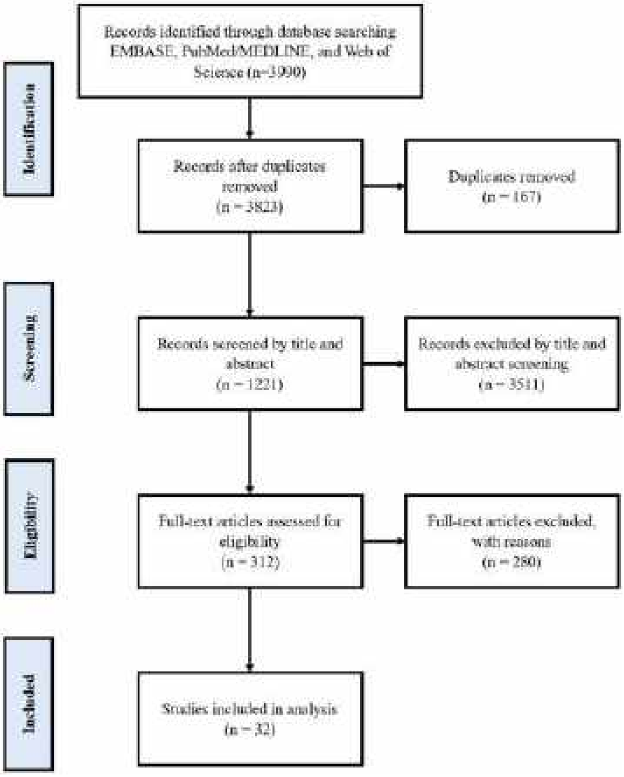
Disclosure information not available at the time of publication: William R. Hutson

2141-A | ASSOCIATION BETWEEN NON-ALCOHOLIC FATTY LIVER DISEASE AND CORONARY ARTERY DISEASE OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Hazem Abosheaishaa[1], Islam Mohamed[2], Muhammad Ghallab[1], Ahmed Alzamzamy[3], Natalie Balassiano[1], Jawad Khan[1], Moataz Yousry Soliman[4], Moaz Elshair[5], Mai Hussein[6], Md Ripon Ahammed[1], Muhammad Almas Baig[1], Amr Ali[7], Mohammed Abdelwahed[7], Ahmed Omran[8] and Mahmoud Nassar[1], (1)Icahn School of Medicine at Mount Sinai, (2)University of Missouri- Kansas City, (3)Department of Gastroenterology and Hepatology, Maadi Armed Forces Medical Complex, Military Medical Academy, Cairo, Egypt, (4)Faculty of Medicine, Al-Azhar University, (5) Faculty of Medicine , Al-Azhar University, (6)Clinical Research Administration/ Ministry of Health and Population, Egypt, (7)Department of Pathology, Donald and Barbara Zucker School of Medicine at Hofstra/ Northwell, Uniondale, New York., (8)Trmc/Rwjbh , Rutgers Njms

Background: To evaluate the association between non-alcoholic fatty liver disease (NAFLD) and cardiovascular outcomes, including angina, coronary artery disease (CAD), coronary artery calcification (CAC), myocardial infarction (MI), and calcified coronary plaques. **Methods:** A comprehensive search of databases, including PubMed, EMBASE, and Cochrane Library, was conducted up to January 2023. Studies were included investigating the relationship between NAFLD and cardiovascular outcomes in adult populations. Exclusion criteria were studies on animals, pediatric populations, and those not published in English. The risk of bias in the included studies was assessed using the Cochrane Collaboration's tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using random-effects models. **Results:** The meta-analysis included 32 studies with a total of 5610990 participants. Significant associations were found between NAFLD and increased risks of angina (RR: 1.45, 95% CI: 1.17, 1.79), CAD (RR: 1.21, 95% CI: 1.07, 1.38), and CAC > 0 (RR: 1.39, 95% CI: 1.15, 1.69). Additionally, a significant association was observed between NAFLD and calcified coronary plaques (RR: 1.55, 95% CI: 1.05, 2.27). However, no significant association was found between NAFLD and CAC > 100 (RR: 1.16, 95% CI: 0.97, 1.38) or MI (RR:

1.70, 95% CI: 0.16, 18.32). **Conclusion:** The meta-analysis demonstrated a significant association between NAFLD and cardiovascular outcomes independent of conventional CVD risk factors. These findings emphasize the importance of prevention, early detection, and proper management of NAFLD. PROSPERO reference number: CRD42023394727.


Identification
Records identified through database searching EMBASE, PubMed/MEDLINE, and Web of Science (n=3990)
Records after duplicates removed (n = 3823)
Duplicates removed (n = 167)
Screening
Records screened by title and abstract (n = 1221)
Records excluded by title and abstract screening (n = 3511)
Eligibility
Full-text articles assessed for eligibility (n = 312)
Full-text articles excluded, with reasons (n = 280)
Included
Studies included in analysis (n = 32)

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2142-A | ASSOCIATION BETWEEN SARCOPENIA AND CORONARY ATHEROSCLEROSIS IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

Yeonjung Ha, Young Eun Chon, Joo Ho Lee and Kwan Sik Lee, CHA Bundang Medical Center, CHA University

Background: The aim of this study was to examine the impact of sarcopenia on coronary atherosclerosis in patients with metabolic dysfunction-associated fatty liver disease (MAFLD). **Methods:** This retrospective study included 1,872 patients who were diagnosed with MAFLD between 2012 and 2016 at health check-ups and underwent coronary calcium scan or computed tomography angiography during follow-up. The primary outcome was the incidence of coronary atherosclerosis (calcium score > 100 or stenosis degree > 50%). Sarcopenia was defined if the sarcopenia index was < 0.789 in men and < 0.512 in women, respectively, on bioelectrical impedance analysis. Multivariate Cox proportional hazards regression was performed to assess associations between sarcopenia and outcomes. Propensity score matching was used to control baseline differences in cardiovascular risk or fibrosis burden. **Results:** Overall, 1,723 (92.0%) and 149 (8.0%) patients were non-sarcopenic and sarcopenic, respectively. Compared to the non-sarcopenic group, the sarcopenic group was older (56.9 vs. 46.8 y), had a higher body mass index, and more frequently had comorbidities such as hypertension or diabetes (Ps < 0.05). The incidence of coronary atherosclerosis was significantly higher in the sarcopenic group than in the non-sarcopenic group (P < 0.001) during a median follow-up of 67.3 months. Multivariable analysis demonstrated an independent association between sarcopenia and coronary atherosclerosis (hazard ratio, 1.73; 95% confidence interval, 1.28–2.34; P < 0.001). The results were confirmed in the propensity score stratification analysis. **Conclusion:** Sarcopenia was an independent predictor of coronary atherosclerosis after adjusting for baseline cardiovascular risk and fibrosis burden.

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Disclosure information not available at the time of publication: Joo Ho Lee, Kwan Sik Lee

2143-A | ASSOCIATIONS BETWEEN CIRCULATING microRNA LEVELS AND NONALCOHOLIC FATTY LIVER DISEASE IN ADOLESCENTS WITH SEVERE OBESITY

Yijie Li[1], Brittney O. Baumert[2], Nikos Stratakis[3], Jesse Goodrich[2], Haotian Wu[4], Jingxuan He[1], Yinqi Zhao[2], Max Aung[1], Hongxu Wang[2], Sandrah P. Eckel[2], Douglas I. Walker[5], Damaskini Valvi[6], Michele La Merrill[7], Justin Ryder[8,9], Thomas Inge[8,9], Todd Jenkins[10], Stephanie Sisley[11], Rohit Kohli[12], Stavra Xanthakos[13,14], Andrea Baccarelli[4], Rob McConnell[2], David V. Conti[2] and Lida Chatzi[2], (1)Keck School of Medicine, University of Southern California, (2) Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, (3)Instituto De Salud Global Barcelona, (4) *Columbia University Mailman School of Public Health, New York, NY, (5)Gangarosa Department of Environmental Health, Rollins School of Public Health, Emory University, (6)Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, (7)Department of Environmental Toxicology, University of California, Davis, (8) Northwestern University Feinberg School of Medicine, (9)Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, (10)Division of Biostatistics & Epidemiology, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati, (11)Children's Nutrition Research Center USDA/ARS, Baylor College of Medicine, (12)Children's Hospital Los Angeles, (13)Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, (14)University of Cincinnati College of Medicine*

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in pediatrics. NAFLD ranges in severity from isolated hepatic steatosis (nonalcoholic fatty liver [NAFL]) to non-alcoholic steatohepatitis (NASH) wherein hepatocellular inflammation, and/or fibrosis coexist with steatosis. Circulating microRNA (miRNA) levels are known to change in NAFLD but the extent to which microRNAs serve as predictive biomarkers of NAFLD remains unknown. This study aimed to investigate the relationship between plasma miRNA levels with histological features of NAFLD among adolescents from the multi-center perspective Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study. **Methods:** This nested case-cohort study included 81 adolescents diagnosed with NAFLD at the time of surgery and 54 controls. 843 plasma miRNA were profiled using the established HTG EdgeSeq platform. Intra-operative core liver biopsies were collected from cases and controls and liver tissues were analyzed by histology using validated criteria. We examined associations of miRNA and disease status using multivariate logistic regression after adjusting for age, sex, race, BMI, parental income and geographic clinical site of surgery. Ingenuity Pathways Analysis (IPA) was used to identify putative biological functions of NAFLD-associated miRNA ($p < 0.05$). **Results:** There were 15 significantly upregulated and 23 significantly downregulated plasma miRNA in NAFLD cases compared to controls ($p < 0.05$). Additionally, 17 miRNA were associated with 4 or more NASH-related stages, including NASH, NASH with fibrosis, lobular inflammation, ballooning or higher steatosis grade. Notably, miR-6741-5p was significantly up-regulated in all NASH related stages ($p < 0.05$). Moreover, miR-193b-5p and miR-122-5p were upregulated in NASH and NASH with fibrosis, lobular inflammation and higher steatosis grade ($p < 0.05$). Pathway analysis showed that 12 miRNA, including miR-100-5p, miR-122-5p, miR-143-3p, miR-146-5p, miR-182-5p, miR-193a-3p, miR-199a-5p, miR-22-3p, miR-221-3p, miR-2355-5p, miR-34a-5p and miR-378-3p were involved in hepatotoxicity (e.g., fibrosis, cirrhosis and hepatocellular carcinoma). **Conclusion:** Findings demonstrated that multiple, specific plasma miRNA were associated with advanced pediatric NAFLD. Larger studies with more heterogeneity of NAFLD phenotypes are needed to determine the ability of miRNA to accurately predict NAFLD stages in pediatrics.

Disclosures: Rohit Kohli – Epigen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Sanofi: Consultant, No, No; Intercept: Consultant, Yes, Yes; Mirum: Consultant, No, No; Albireo: Consultant, No, No;

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Disclosure information not available at the time of publication: Haotian Wu, Jingxuan He, Max Aung, Andrea Baccarelli

2144-A | AWARENESS AND KNOWLEDGE OF NON-ALCOHOLIC FATTY LIVER DISEASE AMONG NURSES IN BEIJING, CHINA

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Background: Prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing in China; however, awareness and knowledge of NAFLD is lacking among the Chinese public. We have conducted a survey on adult patients in Beijing in our previous studies and found less than 50% participants had awareness of NAFLD. **Methods:** We conducted a survey on nurses in the Peking University People's Hospital in Beijing, China. Subjects provided demographic and medical history data. NAFLD-related knowledge and diet and physical activity patterns were assessed. **Results:** 518 participants (5.2% with a diagnosis of NAFLD and 9.5% with a family history of NAFLD) completed the surveys.

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

Response rate was 98.9% (518/524). Median age was 32, 7.7% (40/518) were men, 65% participants had some college education, 72.8% were lean (normal BMI) but 39.2% were truncal obesity, 9.7% with a diagnosis of dyslipidemia, 44.4% had a history of high blood pressure, and 53.3% had at least twice night shifts in every week. More than 60% reported minimal physical activity and often eating dessert. 53.2% had awareness of NAFLD and about 90% reported that they had some knowledge of NAFLD. Median baseline knowledge score (of a total of 25) was 17 and detailed description was showed in Figure 1. Multivariate logistic regression analyses found higher knowledge score (> 17) was associated with higher BMI and family history of NAFLD or diabetes. **Conclusion:** Nurses in Beijing had not enough knowledge about NAFLD, and most were not physically active. Programs to increase public awareness of NAFLD and promote physical activity are critical to curb this growing epidemic.

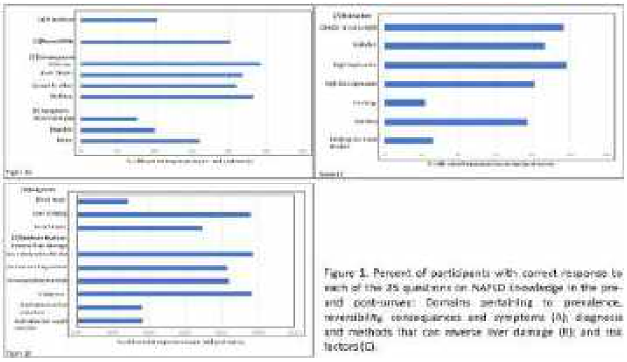
Figure 1. Percent of participants with correct response to each of the 25 questions on NAFLD knowledge in the pre- and post-survey. Domains pertaining to prevalence, reversibility, consequences and symptoms (A), diagnosis and methods that can reverse liver damage (B), and risk factors (C).

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Disclosure information not available at the time of publication: Danli Ma

f 2145-A | BARIATRIC SURGERY AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE, OBESITY, AND CARDIOVASCULAR DISEASE: A POPULATION-BASED RETROSPECTIVE COHORT STUDY★

Arunkumar Krishnan, Atrium Health Levine Cancer Institute, Dipatsree Mukherjee, Apex Institute of Medical Sciences, William R. Hutson, West Virginia University School of Medicine, Tinsay A. Woreta, Johns Hopkins Medicine, Baltimore, MD and Saleh A Alqahtani, Johns Hopkins University School of Medicine; King Faisal Specialist Hospital and Research Center

Background: The role of bariatric surgery (BS) in reducing major adverse cardiovascular events (MACE), especially in patients with nonalcoholic fatty liver disease (NAFLD) with preexisting cardiovascular disease (CVD), has not been well characterized. We aimed to determine the association between BS and the development of MACE among patients with NAFLD, CVD, and obesity at a population level. **Methods:** This large population-based, retrospective cohort study was conducted using the TriNetX dataset. All adult patients (> 18 y) diagnosed with NAFLD, who had previous ischemic heart disease or heart failure, were identified after excluding other chronic liver disease etiologies. We performed a 1:1 propensity score matching (PSM) for demographics, body mass index (BMI), and comorbid conditions to similar controls as patients without a surgical history. The primary outcome was the incidence of extended MACE, a composite endpoint of coronary artery interventions, and composite cerebrovascular events. Secondary outcomes included a 2-component composite outcome of major CVD and all-cause mortality. We conducted sensitivity analyses to assess the robustness of our findings. The hazard ratio (HR) was calculated to compare the association of the BS with the outcomes. **Results:** A total of 91946 patients were identified. Among these, 2827 patients had a history of BS, and 88119 did not, with a median follow-up time of 4.9 years. After PSM, BS and nonsurgical (NS) groups (3822 each) were well matched. Among the BS cohort, most participants were female, younger, white, and had a smoking history. BS patients had a higher mean BMI than the NS cohort. In the unadjusted cause-specific models, the BS cohort had a significantly reduced risk of major CVD compared with the NS group. In the adjusted analysis (Table 1), the risks of MACE (HR, 0.60), composite cerebrovascular diseases (HR, 0.67), and a composite outcome of coronary artery interventions or and surgeries (HR, 0.59) were significantly lower for BS than NS patients. BS was also associated with a lower incidence of the secondary outcome all-cause mortality (HR, 0.63) and a composite outcome of major CVD (HR, 0.82). These outcomes were consistent at follow-up duration of 1, 3, 5, and 7 years. The sensitivity analysis results were consistent, and all statistically significant associations remained unchanged. **Conclusion:** Compared with NS care, BS was associated with a significantly lower risk of MACE and all-cause mortality in patients with NAFLD, obesity, and CVD.

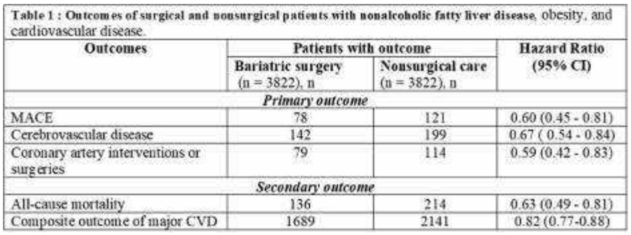
Table 1 : Outcomes of surgical and nonsurgical patients with nonalcoholic fatty liver disease, obesity, and cardiovascular disease.

Outcomes	**Patients with outcome**		**Hazard Ratio (95% CI)**
	Bariatric surgery (n = 3822), n	**Nonsurgical care** (n = 3822), n	
	Primary outcome		
MACE	78	121	0.60 (0.45 - 0.81)
Cerebrovascular disease	142	199	0.67 (0.54 - 0.84)
Coronary artery interventions or surgeries	79	114	0.59 (0.42 - 0.83)
	Secondary outcome		
All-cause mortality	136	214	0.63 (0.49 - 0.81)
Composite outcome of major CVD	1689	2141	0.82 (0.77-0.88)

Disclosures: The following people have nothing to disclose: Arunkumar Krishnan, Dipatsree Mukherjee, Tinsay A. Woreta, Saleh A Alqahtani

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

Disclosure information not available at the time of publication: William R. Hutson

2146-A | BURDEN OF NON-ALCOHOLIC FATTY LIVER DISEASE AND ASSOCIATION BETWEEN ADVANCED LIVER FIBROSIS AND CARDIOVASCULAR RISK IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: INTERIM ANALYSIS OF AN ITALIAN PROSPECTIVE MULTICENTRE STUDY

Gian Paolo Caviglia[1], Angelo Armandi[1], Roberta D'Ambrosio[2], Pietro Lampertico[3,4], Cristiana Bianco[5], Luca Valenti[5], Carlo Ciccioli[6], Grazia Pennisi[6], Salvatore Petta[7], Lucia Brodosi[8,9], Maria Letizia Petroni[8,9], Francesca Marchignoli[8,9], Loris Pironi[8,9], Alessandra Sgripanti[10], Maria Eva Argenziano[10], Gianluca Svegliati-Baroni[10] and Elisabetta Bugianesi[11], (1)Department of Medical Sciences, University of Torino, (2)Division of Gastroenterology and Hepatology, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, (3)CRC "a. M. and a. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, (4)Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, (5)Department of Transfusion Medicine and Haematology, Fondazione Irccs Ca' Granda Ospedale Maggiore Policlinico, (6)Section of Gastroenterology and Hepatology, Dipartimento Di Promozione Della Salute, Materno Infantile, Medicina Interna e Specialistica Di Eccellenza (PROMISE), (7)Sezione Di Gastroenterologia, Dipartimento Promozione Della Salute, Materno-Infantile, Di Medicina Interna e Specialistica Di Eccellenza "G. D'alessandro", Università Di Palermo, Palermo, Italy, (8)Department of Medical and Surgical Sciences, University of Bologna, (9)Irccs Aoubo - Bologna, (10)Liver Disease and Transplant Unit, Polytechnic University of Marche, (11) University of Turin

Background: Non-alcoholic fatty liver disease (NAFLD) is closely associated with type 2 diabetes mellitus (T2DM). Both these conditions are associated with an increased risk of cardiovascular disease (CVD), but the relation between the long-term risk of CVD and the severity of liver fibrosis in diabetic NAFLD patients is partially unknown. In a cohort of diabetic patients consecutively referred by Diabetes Units, we aimed to assess a) the prevalence of NAFLD and the prevalence of advanced liver fibrosis, and b) to explore the association between the risk of CVD and liver fibrosis in patients with T2DM. **Methods:** From April 2021 to April 2023, a total of 675 consecutive patients with T2DM attending 6 different diabetes referral centers were prospectively enrolled. Liver stiffness (LS) was assessed by vibration controlled transient elastography (VCTE) and liver steatosis by controlled attenuation parameter (CAP). Liver steatosis was defined according to CAP values ≥ 275 dB/m. A VTCE cut-off ≥ 8.0 kPa was used to identify patients at risk of advanced liver fibrosis. Framingham risk score (FRS) was used to estimate the 10-year CVD risk; FRS ≥ 21.6% for male and 21.5% for female identified patients at high CVD risk. **Results:** Overall 576 out of 675 patients underwent VCTE + CAP. Patients' median age was 59 (53–64) years and 334 (58.0%) of them were males; 51.3% of patients were obese (BMI ≥ 30 kg/m^2) and 66.1% had arterial hypertension. Elevated liver enzymes (ALT and/or AST and/or γGT) were found in 21.6% of patients. Liver steatosis by CAP was detected in 338 (58.7%) patients, among them 77 (22.8%) had a LS ≥ 8 kPa. Data for the estimation of FRS were available in 289/338 (85.5%) patients; 131/289 (45.3%) showed high CVD risk. The distribution of high CVD varied significantly according to LS (≥ 8 kPa, 56.1% vs. < 8 kPa, 42.2%; p = 0.047). At multivariate analysis corrected for BMI and transaminases, high CVD risk resulted significantly and independently associated to advanced liver fibrosis (OR = 1.87, 95%CI 1.14–3.07; p = 0.013). **Conclusion:** In patients with T2DM and NAFLD, the prevalence of advanced liver fibrosis by VTCE is approximately 23%. In these patients, the association between CVD risk and advanced liver fibrosis supports a careful integrated multidisciplinary follow-up. *This research was supported by Gilead Sciences, Inc (study ID: IN-IT-989-5790).*

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The following people have nothing to disclose: Angelo Armandi, Roberta D'Ambrosio, Luca Valenti, Salvatore Petta

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2147-A | CHANGES IN LIVER STIFFNESS AND CONTROLLED ATTENUATION PARAMETERS OF TRANSIENT ELASTOGRAPHY ACCORDING TO WEIGHT CHANGE IN NON-ALCOHOLIC FATTY LIVER PATIENTS

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Background: It is not clear how much controlled attenuation parameter (CAP) and liver stiffness (LS) of transient elastography (TE) decrease with weight loss. We investigated whether there were significant chnages in CAP and LS according to the degree of weight loss in patients with nonalcoholic fatty liver disease (NAFLD). **Methods:** From 2017 to 2022, the patients with NAFLD at Jeju National University Hospital in Korea who had TE tests more than once while losing body weight were analyzed. CAP and LS were compared between the time of the first test and the time of the weight was most lost during the follow-up. **Results:** A total of 410 patients were analyzed retrospectively and 74.6% of patients lost body weight during the follow-up period. The mean BMI was 28.71 ± 4.21 kg, and the average number of TE tests per patient was 2.90 ± 1.04, and up to 6 were performed. The interval between the first TE and follow-up TE tests was 597.9 ± 338.9 days. Patients who lost weight were divided into 5 groups according to the degree of weight loss (WL), and all groups showed significant CAP change (-25.62 in the 0 to 3% WL group, -21.52 in the 3 to 5% WL group, -41.92 in the 5 to 7% WL group, -32.79 in the 7 to 10% WL group, -74.16 in the more than 10% WL group, all p-values < 0.05). The mean LS change by group was +0.75 in the 0 to 3% WL group, -0.30 in the 3 to 5% WL group, +0.40 in the 5 to 7% WL group, -0.40 in the 7 to 10% WL group, –1.31 in the more than 10% WL group, and was significant only in the more than 10% WL group ($p = 0.002$). There was a significant correlation between WL and CAP in the 3 to 5% WL group (Pearson's $r = 0.300$, $p = 0.006$) and in the 5 to 7% WL group (Pearson's $r = 0.330$, $p = 0.025$), and a significant correlation between WL and LS in the more than 10% WL group (Pearson's $r = 0.413$, $p = 0.010$). **Conclusion:** In patients with NAFLD, there was a significant correlation between weight loss and CAP. LS decreases significantly when weight loss is greater than 10% of baseline body weight.

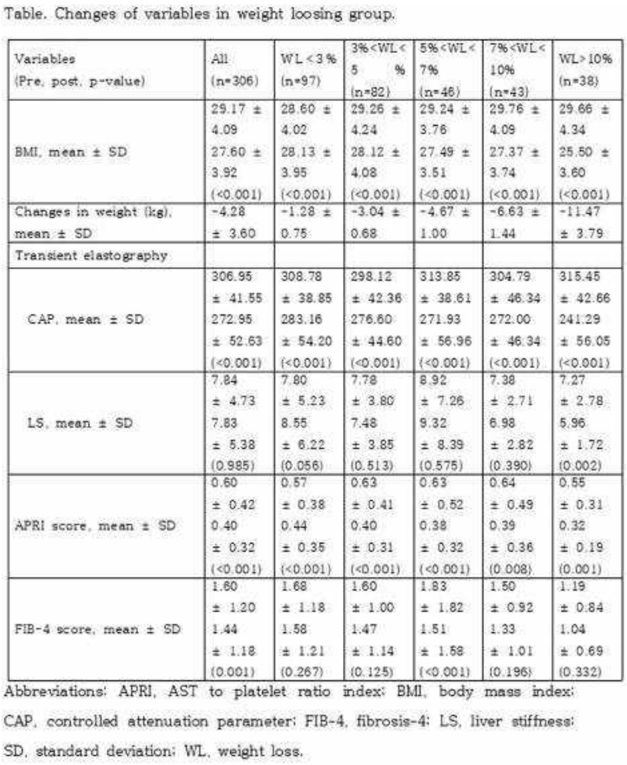

Table. Changes of variables in weight loosing group.

Variables (Pre, post, p-value)	All (n=306)	WL<3% (n=97)	3%<WL<5 % (n=82)	5%<WL<7% (n=46)	7%<WL<10% (n=43)	WL>10% (n=38)
BMI, mean ± SD	29.17 ± 4.09 27.60 ± 3.92 (<0.001)	28.60 ± 4.02 28.13 ± 3.95 (<0.001)	29.26 ± 4.24 28.12 ± 4.08 (<0.001)	29.24 ± 3.76 27.49 ± 3.51 (<0.001)	29.76 ± 4.09 27.37 ± 3.74 (<0.001)	29.66 ± 4.34 25.50 ± 3.60 (<0.001)
Changes in weight (kg), mean ± SD	-4.28 ± 3.60	-1.28 ± 0.75	-3.04 ± 0.68	-4.67 ± 1.00	-6.63 ± 1.44	-11.47 ± 3.79
Transient elastography						
CAP, mean ± SD	306.95 ± 41.55 272.95 ± 52.63 (<0.001)	308.78 ± 38.85 283.16 ± 54.20 (<0.001)	298.12 ± 42.36 276.60 ± 44.60 (<0.001)	313.85 ± 38.61 271.93 ± 56.96 (<0.001)	304.79 ± 46.34 272.00 ± 46.34 (<0.001)	315.45 ± 42.66 241.29 ± 56.05 (<0.001)
LS, mean ± SD	7.84 ± 4.73 7.83 ± 5.38 (0.985)	7.80 ± 5.23 8.55 ± 6.22 (0.056)	7.78 ± 3.80 7.48 ± 3.85 (0.513)	8.92 ± 7.26 9.32 ± 8.39 (0.575)	7.38 ± 2.71 6.98 ± 2.82 (0.390)	7.27 ± 2.78 5.96 ± 1.72 (0.002)
APRI score, mean ± SD	0.60 ± 0.42 0.40 ± 0.32 (<0.001)	0.57 ± 0.38 0.44 ± 0.35 (<0.001)	0.63 ± 0.41 0.40 ± 0.31 (<0.001)	0.63 ± 0.52 0.38 ± 0.32 (<0.001)	0.64 ± 0.49 0.39 ± 0.36 (0.008)	0.55 ± 0.31 0.32 ± 0.19 (0.001)
FIB-4 score, mean ± SD	1.60 ± 1.20 1.44 ± 1.18 (0.001)	1.68 ± 1.18 1.58 ± 1.21 (0.267)	1.60 ± 1.00 1.47 ± 1.14 (0.125)	1.83 ± 1.82 1.51 ± 1.58 (<0.001)	1.50 ± 0.92 1.33 ± 1.01 (0.196)	1.19 ± 0.84 1.04 ± 0.69 (0.332)

Abbreviations: APRI, AST to platelet ratio index; BMI, body mass index; CAP, controlled attenuation parameter; FIB-4, fibrosis-4; LS, liver stiffness; SD, standard deviation; WL, weight loss.

Disclosures: The following people have nothing to disclose: Seong Kyun Na

2148-A | CHARACTERISTICS AND ASSOCIATION OF OBESITY WITH NASH IN THE MANAGEMENT OF LIVER FIBROSIS

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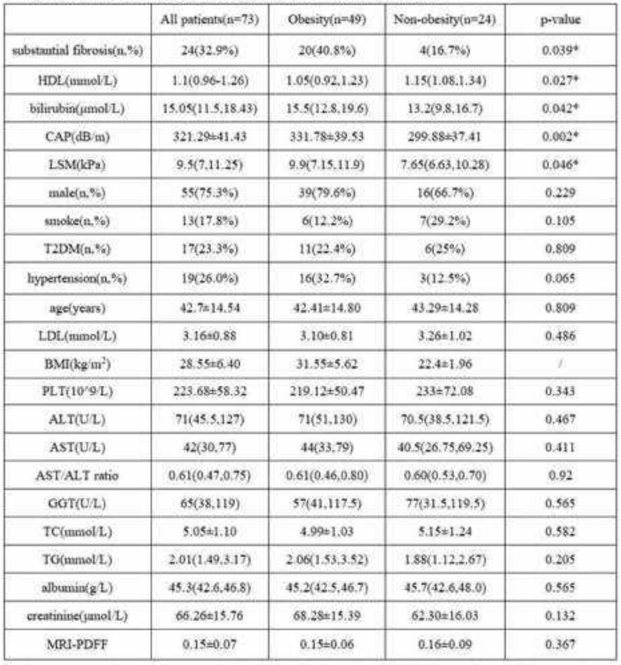
Background: Targeted management of NASH population with high-risk metabolic comorbidity is crucial for early interventions. This study investigated the relation of characteristics of obese patients with NASH fibrosis. Major laboratory indicators, imaging biomarkers and pathological results were reviewed and analyzed. **Methods:** This was a secondary analysis from the NASH study in 2015-2021 at our institution. All patients were histologically confirmed with NASH fibrosis and those with concomitant or preexisting severe liver diseases were excluded. Patients with a BMI **e** 25 kg/m^2 were sub-grouped as obese NASH and the rest were non-obese NASH. Liver fibrosis stages of F2-F4 defined substantial fibrosis. Demographics, serological variables, MRI biomarker, elastography stiffness and fibrosis stages between obese and non-obese NASH group were compared. Confounding factors were adjusted, and risk analyses of statistically significant variables were done using logistic regression. The primary outcome was the liver fibrosis. We also analyzed contribution of type 2 diabetes mellitus (T2DM) to NASH fibrosis in obese and non-obese subjects. **Results:** The study included 73 biopsy-confirmed NASH patients. Obese NASH patients had a significantly higher proportion of substantial fibrosis (40.8%) than non-obese NASH (16.7%, p = 0.039). Among the obese patients (n = 49), three had a fibrosis grade of F4, while no F4 patients were seen in the non-obese NASH. High density lipoprotein (HDL, p = 0.027), bilirubin (p = 0.042), controlled attenuation parameter (CAP, p = 0.002), and liver stiffness measurement (LSM, p = 0.046) were significantly different between obese and non-obese group. Moreover, obese patients had a significantly higher risk of substantial fibrosis (OR, 3.448; 95% CI, 1.023-11.625; p = 0.039) than non-obese group. After adjustment of sex, age, HDL, and bilirubin, obesity was an independent risk factor of substantial fibrosis (adjusted OR, 4.53; 95%CI, 1.084-18.937; p = 0.038). There was no significant difference in the proportion of patients with T2DM between obese (22.4%) and non-obese (25%) NASH, and no interaction between T2DM and obesity on the substantial fibrosis. **Conclusion:** Obesity added greater risk to liver fibrosis in the NASH patients. Serum indicators and imaging biomarkers were significantly different between obese and non-obese NASH group. Cross-interaction of T2DM with obesity on fibrosis needs to be investigated in a larger sample size.

Table 1. Characteristics of obese and non-obese patients and substantial fibrosis.



	All patients(n=73)	Obesity(n=49)	Non-obesity(n=24)	p-value
substantial fibrosis(n,%)	24(32.9%)	20(40.8%)	4(16.7%)	0.039*
HDL(mmol/L)	1.1(0.96-1.26)	1.05(0.92,1.23)	1.15(1.08,1.34)	0.027*
bilirubin(μmol/L)	15.05(11.5,18.43)	15.5(12.8,19.6)	13.2(9.8,16.7)	0.042*
CAP(dB/m)	321.29±41.43	331.78±39.53	299.88±37.41	0.002*
LSM(kPa)	9.5(7,11.25)	9.9(7.15,11.9)	7.65(6.63,10.28)	0.046*
male(n,%)	55(75.3%)	39(79.6%)	16(66.7%)	0.229
smoke(n,%)	13(17.8%)	6(12.2%)	7(29.2%)	0.105
T2DM(n,%)	17(23.3%)	11(22.4%)	6(25%)	0.809
hypertension(n,%)	19(26.0%)	16(32.7%)	3(12.5%)	0.065
age(years)	42.7±14.54	42.41±14.80	43.29±14.28	0.809
LDL(mmol/L)	3.16±0.88	3.10±0.81	3.26±1.02	0.486
BMI(kg/m^2)	28.55±6.40	31.55±5.62	22.4±1.96	/
PLT(10^9/L)	223.68±58.32	219.12±50.47	233±72.08	0.343
ALT(U/L)	71(45.5,127)	71(51,130)	70.5(38.5,121.5)	0.467
AST(U/L)	42(30,77)	44(33,79)	40.5(26.75,69.25)	0.411
AST/ALT ratio	0.61(0.47,0.75)	0.61(0.46,0.80)	0.60(0.53,0.70)	0.92
GGT(U/L)	65(38,119)	57(41,117.5)	77(31.5,119.5)	0.565
TC(mmol/L)	5.05±1.10	4.99±1.03	5.15±1.24	0.582
TG(mmol/L)	2.01(1.49,3.17)	2.06(1.53,3.52)	1.88(1.12,2.67)	0.205
albumin(g/L)	45.3(42.6,46.8)	45.2(42.5,46.7)	45.7(42.6,48.0)	0.565
creatinine(μmol/L)	66.26±15.76	68.28±15.39	62.30±16.03	0.132
MRI-PDFF	0.15±0.07	0.15±0.06	0.16±0.09	0.367

Note. LDL, low density lipoprotein; HDL, high density lipoprotein; BMI, body mass index; PLT, platelet; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, γ -Glutamyl Transferase;TC, total cholesterol;TG, triglyceride; CAP, controlled attenuation paremeter; LSM, liver stiffness measurement; PDFF, magnetic resonance imaging proton density fat fraction. * was represented for variables with $p<0.05$.

Disclosures: The following people have nothing to disclose: Dong Tang, Hanyu LI, JUN Yang, Kehui Nie

2149-A | CHARACTERIZING THE MANAGEMENT OF PATIENTS WITH NASH (WITH VERSUS WITHOUT CIRRHOSIS) IN REAL-WORLD CLINICAL PRACTICE: RARE ASSESSMENT BY HEPATOLOGISTS AND LOW FREQUENCY OF IMAGING

Christina Qian[1], Michael R. Charlton[2], Shelagh M Szabo[1], Rosie Sun[1], Hannah Rochon[1] and Jesse Fishman[3], (1)Broadstreet Heor, (2)University of Chicago, (3)Madrigal Pharmaceuticals

Background: Nonalcoholic steatohepatitis (NASH) affects 3-6% of US adults. Guidelines recommend patients with NASH undergo regular assessment and follow-up by specialists, specifically gastroenterologists/hepatologists to ensure adequate care and monitor for complications. However, intervals for follow-up vary depending on disease severity. Patients with cirrhosis should be assessed annually whereas those without every 2-3 years. While there is increased use of noninvasive tests (NITs), liver biopsy remains the gold standard for grading/staging NASH. This analysis aimed to characterize the management of patients with NASH (with vs without cirrhosis) in real-world clinical practice. **Methods:** Optum's de-identified Clinformatics® Data Mart Database (01Oct2015-31Dec2022) was used for this analysis. Adults with e 1 inpatient claim for NASH (ICD-10-CM K75.81) as the primary or secondary diagnosis or e 2 outpatient claims for NASH were included. Patients with other causes of liver disease, HIV, or exposure to heavy metals were excluded. Baseline cirrhosis status was classified by e 1 code for cirrhosis, decompensated cirrhosis, liver transplant, or hepatic cell carcinoma (HCC) in the 6 months before or 1 month after first NASH diagnosis. Patients were followed until death, loss of follow-up, or study end. Demographics, comorbidities, specialist visits, and imaging procedures were estimated for patients with vs without cirrhosis. Statistical analyses were performed within the Optum de-identified data workspace using Jupyter Notebook. **Results:** While almost all patients had e 1 specialist visit, only 67.3% with and 50.6% without cirrhosis visited a gastroenterologist and < 1% visited a hepatologist (Table). Average annual visits were less than half among patients without cirrhosis. Liver biopsy was rarely performed, even among patients with cirrhosis. Among imaging NITs, the most frequently used were abdominal ultrasound and CT. **Conclusion:** The results of this analysis suggest patients with NASH are not seen by a gastroenterologist and < 1% are seen by a hepatologist, even when diagnosed with cirrhosis. Liver biopsy is rarely performed, reflecting increased reliance on NITs. While additional stratification by comorbidities and disease severity may help better elucidate clinical

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

practice in the real world, the low frequency of abdominal imaging among patients with cirrhosis implies screening/surveillance for HCC only occur at ~50% the recommended frequency. Our results suggest clinical practice is only partially aligned with clinical guidelines.

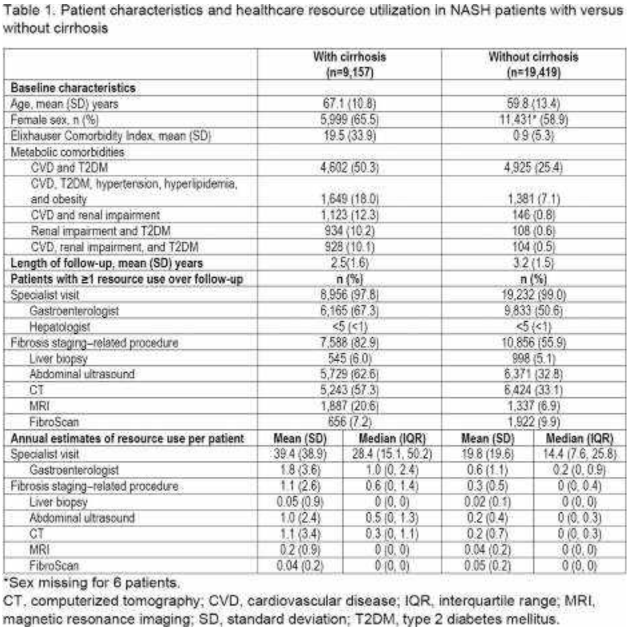


Table 1. Patient characteristics and healthcare resource utilization in NASH patients with versus without cirrhosis

	With cirrhosis (n=9,157)		Without cirrhosis (n=19,419)	
Baseline characteristics				
Age, mean (SD) years	67.1 (10.8)		59.8 (13.4)	
Female sex, n (%)	5,999 (65.5)		11,431* (58.9)	
Elixhauser Comorbidity Index, mean (SD)	19.5 (33.9)		0.9 (5.3)	
Metabolic comorbidities				
CVD and T2DM	4,602 (50.3)		4,925 (25.4)	
CVD, T2DM, hypertension, hyperlipidemia, and obesity	1,649 (18.0)		1,381 (7.1)	
CVD and renal impairment	1,123 (12.3)		146 (0.8)	
Renal impairment and T2DM	934 (10.2)		108 (0.6)	
CVD, renal impairment, and T2DM	928 (10.1)		104 (0.5)	
Length of follow-up, mean (SD) years	2.5(1.6)		3.2 (1.5)	
Patients with ≥1 resource use over follow-up	n (%)		n (%)	
Specialist visit	8,956 (97.8)		19,232 (99.0)	
Gastroenterologist	6,165 (67.3)		9,833 (50.6)	
Hepatologist	<5 (<1)		<5 (<1)	
Fibrosis staging–related procedure	7,588 (82.9)		10,856 (55.9)	
Liver biopsy	545 (6.0)		998 (5.1)	
Abdominal ultrasound	5,729 (62.6)		6,371 (32.8)	
CT	5,243 (57.3)		6,424 (33.1)	
MRI	1,887 (20.6)		1,337 (6.9)	
FibroScan	656 (7.2)		1,922 (9.9)	
Annual estimates of resource use per patient	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**
Specialist visit	39.4 (38.9)	28.4 (15.1, 50.2)	19.8 (19.6)	14.4 (7.6, 25.8)
Gastroenterologist	1.8 (3.6)	1.0 (0, 2.4)	0.6 (1.1)	0.2 (0, 0.9)
Fibrosis staging–related procedure	1.1 (2.6)	0.6 (0, 1.4)	0.3 (0.5)	0 (0, 0.4)
Liver biopsy	0.05 (0.9)	0 (0, 0)	0.02 (0.1)	0 (0, 0)
Abdominal ultrasound	1.0 (2.4)	0.5 (0, 1.3)	0.2 (0.4)	0 (0, 0.3)
CT	1.1 (3.4)	0.3 (0, 1.1)	0.2 (0.7)	0 (0, 0.3)
MRI	0.2 (0.9)	0 (0, 0)	0.04 (0.2)	0 (0, 0)
FibroScan	0.04 (0.2)	0 (0, 0)	0.05 (0.2)	0 (0, 0)

*Sex missing for 6 patients.

CT, computerized tomography; CVD, cardiovascular disease; IQR, interquartile range; MRI, magnetic resonance imaging; SD, standard deviation; T2DM, type 2 diabetes mellitus.

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Jesse Fishman – Madrigal Pharmaceuticals: Employee, Yes, No;

The following people have nothing to disclose: Christina Qian, Shelagh M Szabo, Rosie Sun, Hannah Rochon

2150-A | CLASSIFICATION ACCORDING TO SEQUENTIALLY COMBINED NON-INVASIVE TESTS CARRIES PROGNOSTIC VALUE IN PATIENTS WITH NAFLD

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Background: Combination of FIB4 and liver stiffness measured by vibration controlled transient elastography (LSM-VCTE) is supported by cross sectional studies of diagnostic accuracy. Here we aim to study the prognostic value of FIB-4 followed by LSM-VCTE. **Methods:** This was an individual participant data meta-analysis of people with NAFLD and baseline biopsy, LSM-VCTE, and FIB-4 measured within 6 months. The outcome was a composite endpoint of all-cause mortality, cirrhosis decompensation (ascites, variceal haemorrhage, hepatic encephalopathy), hepatocellular carcinoma, liver transplantation or progression to model of end stage liver disease score **e** 15. Study-specific cumulative hazard functions and derived aggregated survival curves were built for: G1 (FIB-4 < 1.3), G2 (1.3 **d** FIB-4 < 2.67; LSM-VCTE < 10 kPa), G3 (1.3 **d** FIB-4 < 2.67; 10kPa **d** LSM-VCTE < 20 kPa), G4 (1.3 **d** FIB-4 < 2.67; LSM-VCTE **e** 20kPa) and G5 (FIB-4 **e** 2.67). G3 was further stratified according to fibrosis (F0-2, F3, F4), and LSM-VCTE one (15 kPa) or two cut-offs (13.5 kPa, 17 kPa). G5 was similarly subclassified according to fibrosis and LSM-VCTE. Unreliable LSM-VCTE (LSM **e** 7.1 kPa and IQR/median > 0.3) readings were excluded. **Results:** Data from 2383 (51% males, median age 54 (IQR 19) years, 42% with type II diabetes mellitus) were available, after exclusion of unreliable LSM-VCTE. Median follow-up was 56 months and the primary outcome was reached in 5.3% (n = 127). There were significant differences in the prognostic information carried by all groups (study-stratified log-rank tests; p < 0.0001; Fig. 1a). Within G3, patients with cirrhosis (G3_F4) showed the poorest prognosis, and similar survival probabilities were seen between patients in G3_F0-2 and G3_F3 (p = 0.02; Fig. 1b). LSM-VCTE did not further separate G3 (Fig. 1c-d). Within G5, LSM-VCTE (p < 0.001, Fig. 1e), and histology (p = 0.004, Fig. 1f) provided further prognostic granularity. **Conclusion:** Sequential application of FIB-4 and LSM-VCTE classifies patients into 5 groups with differing risk of future adverse events, further supporting the continued use of this approach in clinical practice. In those with FIB4 **e** 2.67, LSM-VCTE and biopsy can provide further prognostic granularity. Biopsy can also separate out risk subgroups in those with 1.3 **d** FIB4 < 2.67. Our analysis is limited by relatively small numbers in groups G3 and G5. Repeated NIT measurements over time or other approaches may provide additional prognostic insight but these were beyond the remit of our study.

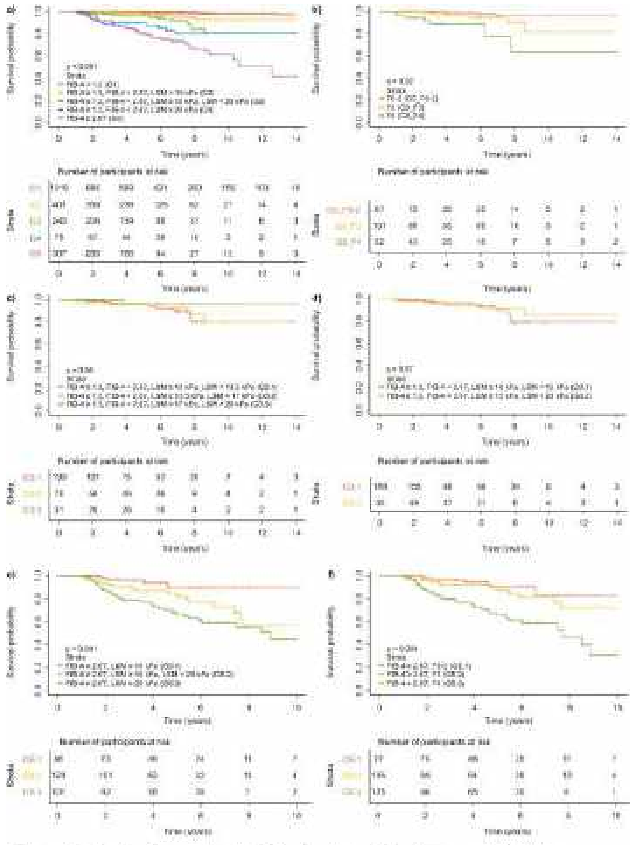

Figure 1 Estimates of survival probabilities for (a) participant groups stratified by sequential test cut-offs (FIB-4 followed by LSM-VCTE), (b) participants from group G3 stratified by histologically assessed fibrosis; (c) G3 participants further stratified by LSM-VCTE with two cut-off: 13.5 and 17 kPa, and (d) a single cut-off: 15 kPa. P-values were calculated using stratified log-rank tests.

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2151-A | COMPARISON OF CHARACTERISTICS AND OUTCOMES IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE WHO DID OR DIDN'T RECEIVE LIVER BIOPSY

Xinrong Zhang[1], Leslie Yeeman Kam[1], Scott D. Barnett[1], Linda Henry[1], Ramsey Cheung[1,2] and Mindie H. Nguyen[1], (1)Stanford University Medical Center, Palo Alto, CA, (2)Veterans Affairs Palo Alto Health Care System

Background: Liver fibrosis is an independent predictor for liver-related outcomes and mortality in nonalcoholic fatty liver disease (NAFLD). Although liver biopsy remains the reference standard to assess liver fibrosis, few patients undergo liver biopsy except in the setting of clinical trials. Thus, biopsy patients likely represent a highly selected group in clinical practice. However, data examining the outcomes of NAFLD patients who underwent liver biopsy versus those who did not are sparse. Therefore, this study aimed to compare clinical characteristics and outcomes in real-world adult NAFLD patients with and without liver biopsy using a large nation-wide insurance database in United States (US). **Methods:** We conducted a retrospective cohort study of adult patients with diagnosed NAFLD using the Truven Health MarketScan Research Database between January 2007 and December 2021. Patients were categorized into two groups: those with or without liver biopsy at any time during follow-up. We used Kaplan Meier methods to estimate the rates of developing hepatocellular carcinoma (HCC), cirrhosis and hepatic decompensation in NAFLD patients with or without liver biopsy after propensity score (PS) matching and factors associated with such outcomes. **Results:** We identified a total of 586,720 eligible NAFLD patients: 35,600 with biopsy and 551,120 without biopsy. There were significant differences in several baseline characteristics such as age, comorbidities, percent of patients with baseline cirrhosis and HCC. After 1:5 PS matching on age, sex, comorbidities, use of metformin and statins, a total of 35,600 NAFLD patients with liver biopsy and 178,000 matched NAFLD patients without liver biopsy who had similar distribution in age, sex, comorbidities and use of metabolic drugs were included in our study analysis. Compared to non-biopsy patients, matched biopsy patients had higher crude incidence per 1,000 person-years for HCC (1.15 vs. 0.08), cirrhosis (64.53 vs. 23.22) and hepatic decompensation (22.36 vs. 14.93), respectively (all $P < 0.001$; Table). In multivariable analysis, patients with liver biopsy had more than 14 times higher risk of developing HCC, close to 3 times higher risk of cirrhosis, and 51% higher risk of hepatic decompensation. In subgroup analysis, the association remained consistent and significant for all 3 outcomes when stratified by age (18-49, 50-59 and **e** 60 y), sex, diabetes, hypertension, hyperlipidemia and obesity (body mass index **e** 30 kg/m^2 vs. non-obese). **Conclusion:** In this large nation-wide cohort from US, discrepancies in clinical characteristics and liver-related outcomes exist between patients with and without liver biopsy. Patients with liver biopsy had a significantly higher risk of developing HCC, cirrhosis and hepatic decompensation than those without, and may represent a highly selected group of patients whose data may not be representative of the general population of NAFLD patients.

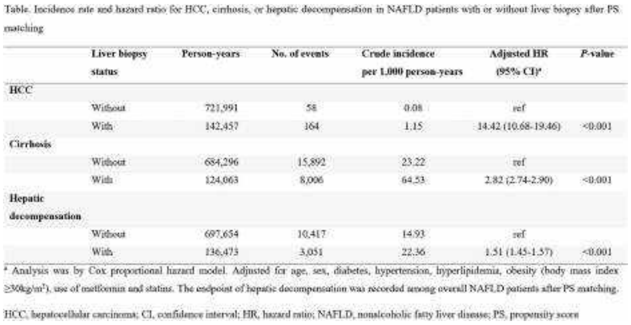

Table. Incidence rate and hazard ratio for HCC, cirrhosis, or hepatic decompensation in NAFLD patients with or without liver biopsy after PS matching

	Liver biopsy status	Person-years	No. of events	Crude incidence per 1,000 person-years	Adjusted HR (95% CI)*	P-value
HCC						
	Without	721,991	58	0.08	ref	
	With	142,457	164	1.15	14.42 (10.68-19.46)	<0.001
Cirrhosis						
	Without	684,296	15,892	23.22	ref	
	With	124,063	8,006	64.53	2.82 (2.74-2.90)	<0.001
Hepatic decompensation						
	Without	697,654	10,417	14.93	ref	
	With	136,473	3,051	22.36	1.51 (1.45-1.57)	<0.001

* Analysis was by Cox proportional hazard model. Adjusted for age, sex, diabetes, hypertension, hyperlipidemia, obesity (body mass index ≥30kg/m^2), use of metformin and statins. The endpoint of hepatic decompensation was recorded among overall NAFLD patients after PS matching.

HCC, hepatocellular carcinoma; CI, confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; PS, propensity score

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2152-A | COMPOSITE SCORES THAT INCLUDE LIVER STIFFNESS MEASUREMENT CAN PREDICT OUTCOMES IN PATIENTS WITH NAFLD

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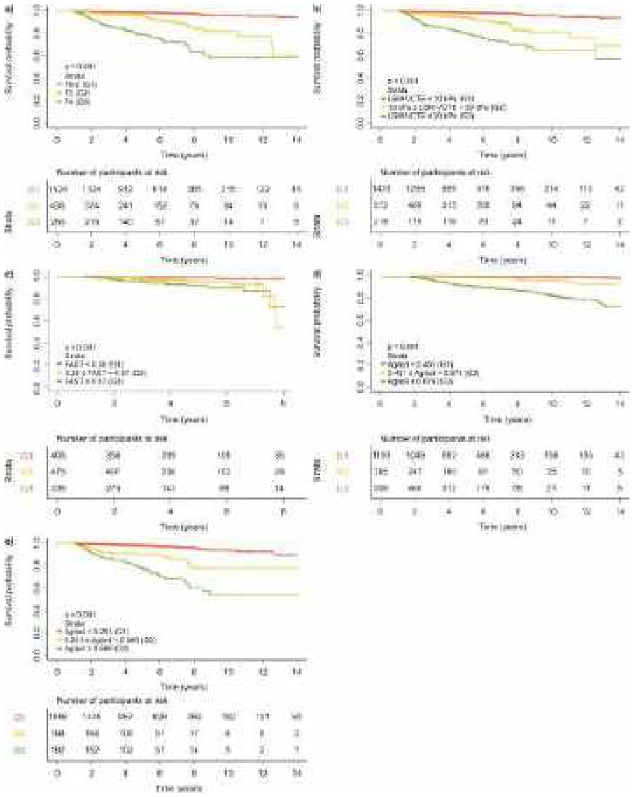
Background: Non-invasive tests (NITs) have good prognostic performance in patients with non-alcoholic fatty liver disease (NAFLD), but direct comparisons with the prognostic performance of histology are lacking. We conducted an individual patient data meta-analysis examining the prognostic performance of histologically assessed fibrosis, liver stiffness measurements by vibration controlled transient elastography (LSM-VCTE), Agile 3+, Agile 4 and FibroScan-AST (FAST) scores in patients with NAFLD. **Methods:** Patients with NAFLD were eligible for inclusion if they had baseline biopsy, LSM-VCTE readings and blood parameters measured within 6 months. The primary outcome was a

composite endpoint of all-cause mortality, decompensation of cirrhosis (ascites, variceal haemorrhage, hepatic encephalopathy), hepatocellular cancer, liver transplantation or progression to model of end stage liver disease score **e** 15. Study-specific cumulative hazard functions, derived aggregated survival curves, and study-stratified Cox regression models were built for the following groups: fibrosis stage F0-2, F3, F4 for histology; LSM < 10 kPa, 10 kPa **d** LSM < 20 kPa, and LSM **e** 20 kPa; Agile 3 + < 0.451 , 0.451 **d** Agile3+ < 0.679 , Agile3+ **e** 0.679 ; Agile 4 < 0.251 , 0.251 **d** Agile 4 < 0.565, Agile 4 **e** 0.565 ; FAST < 0.35 , 0.35 **d** FAST < 0.67, FAST **e** 0.67. **Results:** Data from 2518 patients were available and 2383 (51% males, median age 54 (IQR 19) years, 42% with type II diabetes mellitus) were included in the analysis, after exclusion of participants with unreliable LSM-VCTE. The primary outcome was reached in 5.3% (n = 127) after a median follow-up of 56 months. There were significant differences in the prognostic information carried by all trichotomised index tests (p < 0.0001; Figure 1). On Cox regression, fibrosis stage F3 (HR 3.8), and F4 (HR 16.8), 10 kPa **d** LSM < 20 kPa (HR 3.7), LSM **e** 20 kPa (HR 12.2), 0.451 **d** Agile3+ < 0.679 (HR 2.2), Agile3+ **e** 0.679 (HR 12.4), 0.251 **d** Agile4 < 0.565 (HR 4.4), Agile 4 **e** 0.565 (HR 12.8), 0.35 **d** FAST < 0.67 (HR 3.0) and FAST **e** 0.67 (HR 8.0) were independent predictors of outcomes after adjusting for confounders. **Conclusion:** LSM-VCTE based composite scores, like histologically assessed fibrosis are independent predictors of outcome in NAFLD after correcting for potential confounding factors.



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2153-A | CONCURRENT HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN PATIENTS WITH METABOLIC DYSFUNCTION ASSOCIATED FATTY LIVER DISEASE IS ASSOCIATED WITH SIGNIFICANTLY GREATER RISKS OF CIRRHOSIS AND HEPATOCELLULAR CARCINOMA

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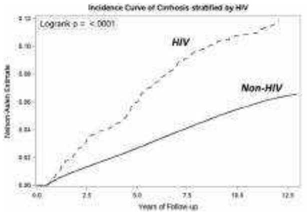
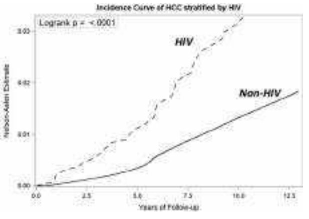
Background: Metabolic dysfunction associated fatty liver disease (MAFLD) is highly prevalent among U.S. adults, and particularly among U.S. Veterans. While human immunodeficiency virus (HIV) infection increases the risk of hepatic steatosis, it is not clear if concurrent HIV among patients with MAFLD is associated with increased risk of liver disease progression.

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

We aim to evaluate the association between HIV infection status and risk of incident cirrhosis, hepatocellular carcinoma (HCC), and hepatic decompensation among a national cohort of adult Veterans with MAFLD. **Methods:** Adults with MAFLD with and without concurrent HIV infection were identified using the national Veterans Affairs database from 1/1/2010 to 12/31/2017 with follow-up through 12/31/2022. Among patients without cirrhosis or HCC at baseline, the overall incidence of cirrhosis, HCC, and hepatic decompensation (ascites, hepatic encephalopathy, variceal bleeding, or hepatorenal syndrome) per 1000 person-years was evaluated using Nelson-Aalen methods for estimating cumulative hazards rates. Comparisons of incidence rates between MAFLD patients with vs. without concurrent HIV were performed using log-rank testing and the z-statistic. **Results:** Among 1,243,766 Veterans with MAFLD, 1,686 had concurrent HIV and 1,242,080 did not have concurrent HIV. Compared to MAFLD patients without HIV, those with concurrent HIV were more likely to be African American (48.5% vs. 19.4%, $p < 0.01$), were younger (55.6 vs. 61.9 y, $p < 0.01$), and had lower proportion with hypertension (56.1% vs. 58.4%, $p < 0.05$), diabetes (38.1% vs. 44.0%, $p < 0.01$), and dyslipidemia (62.5% vs. 67.9%, $p < 0.01$). Compared to MAFLD patients without HIV, those with concurrent HIV were significantly more likely to develop cirrhosis (13.0% vs. 6.1%, $p < 0.01$), HCC (2.9% vs. 1.2%, $p < 0.01$), and hepatic decompensation (12.4% vs. 7.2%, $p < 0.01$) on follow-up. On cumulative hazards assessment, the incidence of cirrhosis, HCC, and hepatic decompensation was 10.52 vs. 5.29 per 1000 person-years ($p < 0.01$), 2.70 vs. 1.27 per 1000 person-years ($p < 0.01$), and 12.72 vs. 7.31 per 1000 person-years ($p < 0.01$) among MAFLD patients with vs. without concurrent HIV, respectively. **Conclusion:** Among a national cohort of U.S. Veterans with MAFLD, patients with concurrent HIV had significantly greater risks of cirrhosis, HCC, and hepatic decompensation. Better understanding the drivers of this increased risk of liver disease progression associated with HIV infection in patients with MAFLD will help guide closer monitoring and targeted interventions improve long-term management and outcomes among this group of patients.





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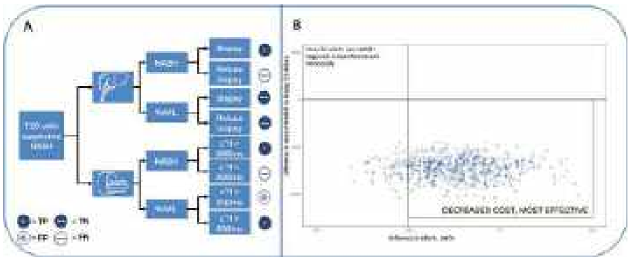
2154-A | COST-EFFECTIVENESS OF MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING COMPARED TO LIVER BIOPSY FOR THE DETECTION OF NON-ALCOHOLIC STEATOHEPATITIS AMONG PATIENTS WITH TYPE 2 DIABETES TREATED WITH SEMAGLUTIDE

Mohsen Rezaeihemami[1], Anneli Andersson[1], Prashant K. Pandya[2], Marika French[3], Kenneth Cusi[4] and Helena. Thomaides-Brears[1], (1)Perspectum Ltd, (2) Perspectum Inc, (3)Perspectum, (4)Division of Endocrinology, Diabetes and Metabolism, University of Florida, Gainesville, FL, USA

Background: Semaglutide is recommended for treating patients with type 2 diabetes (T2D) and non-alcoholic steatohepatitis (NASH) in American Association of Clinical Endocrinology guidelines. Multiparametric magnetic resonance imaging (mpMRI) is a non-invasive, quantitative alternative to biopsy for assessment of liver characteristics, including steatosis and disease activity. We aimed to evaluate the life-time cost-effectiveness of prescribing semaglutide in US people with T2D based on 1)diagnosis of NASH by liver mpMRI or biopsy and 2) suspicion of NASH only. **Methods:** We developed a multi-state Markov model for NAFLD progression in T2D comparing mpMRI to liver biopsy for the diagnosis of NASH (figure 1A). We considered 3 effects for semaglutide: slowing fibrosis progression, the regression of fibrosis and reducing mortality from cardiovascular and liver related causes. NAFLD stage and history, transition probabilities, costs, and quality of life scores were defined from literature. Relative risk of fibrosis progression/regression following semaglutide (costing $9500 over 52 weeks) was calculated from published NN9931-4296 study data. We assumed a hypothetical cohort of 1000 people with T2D aged 50 years suspected of having NASH in the US following initial triage by FIB4 and transient elastography (TE) who could be referred for semaglutide treatment. The outcomes were costs (in US dollars, year 2021 values) and quality adjusted life-years (QALYs), discounted at 3% annually over a lifetime horizon. **Results:** In this hypothetical cohort of 1000 T2D patients with suspected NASH, identifying patients for treatment with semaglutide using mpMRI would avoid 215 unnecessary biopsies in comparison to the biopsy-based diagnosis and 112 unnecessary treatments compared to the treat-all strategy. MpMRI results in direct cost savings of $3250 per patient compared with biopsy, and a gain of 0.162 QALYs over the patient lifetime (figure 1B). Using mpMRI also results in direct cost savings of $1787 per patient compared with treating all 1000 patients with semaglutide, and a gain of 0.018 QALYs over the patient lifetime. These findings were robust across deterministic and probabilistic sensitivity analyses. **Conclusion:** The implementation of mpMRI for detection of NASH among patients with T2D ahead of semaglutide prescription can lead to cost savings and improved lifelong patient quality of life. Such improvements would be seen if implemented instead of diagnosis by biopsy and instead of prescribing semaglutide to all patients without further confirmation of NASH beyond triage with FIB4 and TE.



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2155-A | CROSS-SECTIONAL STUDY IN GENERAL POPULATION FOR THE PREVALENCE OF NONALCOHOLIC FATTY LIVER DISEASE, DISTRIBUTION OF FIBROSIS STAGE USING VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY, AND DETERMINING THE BEST CUT OFF VALUE OF FIB-4 INDEX

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Background: Increase the prevalence of obesity, diabetes, and metabolic syndrome continues to grow the prevalence of nonalcoholic fatty liver disease (NAFLD). Non-invasive tests, such as Fibrosis-4 index (FIB-4), liver stiffness measurement (LSM), and serum markers are useful for identifying patients with advanced fibrosis. Since the prevalence of advanced fibrosis is different between in general population and in specialist clinics in tertiary centers, a general population-based study is important for the efforts to understand this epidemic and to mitigate the disease burden. We aimed to investigate the prevalence of NAFLD, the

distribution of fibrosis stage, and determining the best cut off value of FIB-4 index in general population. **Methods:** A cross-sectional study was conducted among 6540 subjects who received health check-up exams from 2018 to 2021 in 12 centers in Japan. All subjects were performed ultrasonography and the all subjects with fatty liver were performed vibration-controlled transient elastography (VCTE) with M probe. Reliable LSM was defined as LSM < 7 kPa or LSM **e** 7.1 kPa with interquartile range (IQR) < 30% in subjects with BMI < 30. **Results:** Mean age of the study subjects was 54.0 ± 61.0 years (range 47-61 y). The overall prevalence of NAFLD was 32.4%. Patients in each stage of liver fibrosis using VCTE were 89.6% (fibrosis stage 0), 7.6% (fibrosis stage 1), 1.5% (fibrosis stage 2), 0.8% (fibrosis stage 3), 0.5% (fibrosis stage 4). FIB-4 showed significantly steady stepwise increase in each stage of liver fibrosis. For the diagnosis of advanced fibrosis (fibrosis stage 3 or 4), we used FIB-4 index **e** 1.3, **e** 1.3+2.0 (**e** 1.3 for age < 65 and **e** 2.0 for age **e** 65). and **e** 1.45. The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of FIB-4 **e** 1.3/ **e** 1.3+2.0/ **e** 1.45 was 78.2/73.9%/78.2%, 75.5/82.6/ 84.0%, 99.6/99.5/99.6%, and 3.9/5.2/5.9%, respectively. When FIB-4 Index **e** 1.3/ **e** 1.3+2.0/ **e** 1.45 was used as an indicator for referral of advanced fibrosis to a hepatology clinic, the referral rate was 25.1/18.0/ 16.7%, respectively. **Conclusion:** A selection bias may exist in hepatology clinics in tertiary centers, then we conducted this general population-based (unbiased population-based) prospective study. As it is impossible to perform liver biopsy in the general population, we performed VCTE for all NAFLD patients and investigated the distribution of fibrosis stage. Our study showed that the accurate prevalence of NAFLD and the distribution of liver fibrosis stage using VCTE. FIB-4 showed high NPV but low PPV. The FIB-4 Index cut-off value of 1.45 suggested the possibility of reduction in the number of patients requiring hepatology assessment compared to FIB-4 **e** 1.3 or **e** 1.3+2.0. UMIN Clinical Trials Registry No. UMIN000035188

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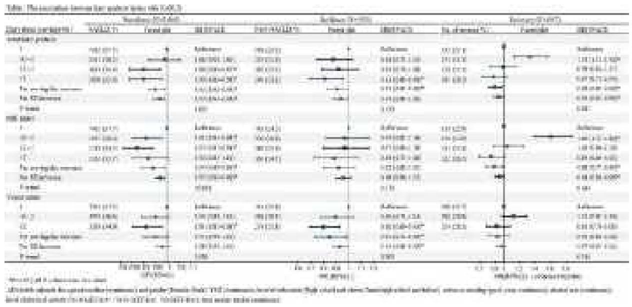
2156-A | DAIRY PRODUCTS INTAKE AND THE PREVALENCE, INCIDENCE, AND RECOVERY OF NON-ALCOHOLIC FATTY LIVER DISEASE IN EASTERN CHINESE POPULATION

Yurou Xu[1], *Youyi Wang*[1], *Qi Zhao*[1], *Bo Chen*[1], *Na Wang*[1], *Tiejun Zhang*[1], *Yonggen Jiang*[2], *Yilin Wu*[2], *Na He*[1], *Genming Zhao*[1] *and Xing Liu*[1], *(1)The Key Laboratory of Public Health Safety of Ministry of Education, Department of Epidemiology, School of Public Health, Fudan University, Shanghai 200032, China, (2)Songjiang District Center for Disease Control and Prevention, Shanghai 201600, China*

Background: Non-alcoholic fatty liver disease (NAFLD) is a growing public health concern. Modifiable factors such as diet and lifestyles are of research interest in preventing or reversing the disease. To date, the relationship between dairy products and NAFLD remains unclear. **Methods:** Based on the Shanghai Suburban Adult Cohort and Biobank study (SSACB), participants aged from 20 to 74 in Songjiang district were enrolled from 2016 to 2017, and a random sample was followed up from 2019 to 2020. Dietary intake and demographic characteristics were collected by questionnaire and physical examination at baseline. NAFLD was defined as having fatty liver diagnosed by ultrasonography in non-excessive alcohol drinkers (<30g/day for males and<20g/day for females). Multivariate logistic regression models were used to analyze the association between baseline prevalence and intake of dairy products, and Cox hazard proportion regression models were used to analyze the association between incidence and recovery with dairy products in the follow-up population. Stratified analysis and sensitivity analysis was also conducted in this study. **Results:** A total of 34040 participants were included in the baseline analyses. After adjusted for age, gender, BMI, education, smoking, alcohol intake, physical activity level and total energy intake, logistic regression model showed that higher dairy product intake was negatively correlated with the prevalence of NAFLD in Songjiang baseline population ($OR_{>2\sim7\ \text{vs}\ 0\ \text{servings/week}} = 0.90$, 95% CI: 0.84-0.97 and $OR_{>7\ \text{vs}\ 0\ \text{servings/week}} = 0.90$, 95% CI: 0.84-0.98). Out of 12,305 patients in the random sample, 9640 were eligible for inclusion criteria. Among those 5583 participants without NAFLD at baseline, 1306 developed NAFLD after a median follow-up time of 3.0 years. The incidence of NAFLD was also inversely associated with dairy intake ($HR_{>7\ \text{vs}\ 0\ \text{servings/week}} = 0.81$, 95% CI: 0.69-0.96). Among those 4057 participants with NAFLD at baseline, 1091 recovered after a 3-year follow-up. The recovery was positively associated with total dairy intake of >0-2 servings/week (HR = 1.45, 95%CI: 1.20-1.65), while the association of higher intake with reversal was not significant ($HR_{>7\ \text{vs}\ 0\ \text{servings/week}} = 0.87$, 95%CI: 0.72-1.04). **Conclusion:** In this study, we found that higher dairy product intake was associated with lower prevalence and incidence of NAFLD. Moderate intake was protective to NAFLD, whereas there was a trend towards poorer NAFLD reversal among those with higher intake.

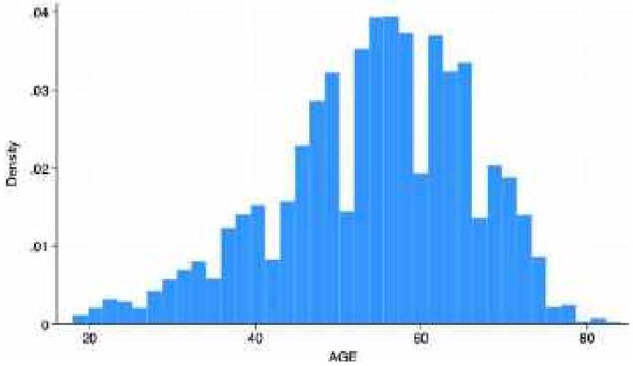


Disclosures: The following people have nothing to disclose: Yurou Xu, Youyi Wang, Qi Zhao, Bo Chen, Na Wang, Tiejun Zhang, Yonggen Jiang, Yilin Wu, Na He, Genming Zhao, Xing Liu

2157-A | DESCRIPTION OF DIVERSITY IN NONALCOHOLIC STEATOHEPATITIS (NASH) CLINICAL TRIALS: COMBINED DATA FROM MULTIPLE THERAPEUTIC TRIALS INCLUDING MORE THAN 6,000 PATIENTS (IN COLLABORATION WITH NAIL-NIT CONSORTIUM)

Naim Alkhouri[1], *Sophie Jeannin*[2], *Julie Dubourg*[2], *Jörn M. Schattenberg*[3], *Nicole E. Rich*[4], *Stephen A Harrison*[5] *and Mazen Noureddin*[6], *(1)Arizona Liver Health, Phoenix, AZ, (2)Summit Clinical Research, San Antonio, TX, (3)I. Department of Medicine, University Medical Centre Mainz, Johannes Gutenberg University, Mainz, Germany, Mainz, Germany, (4)University of Texas Southwestern Medical Center, (5)Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom, (6)Houston Research Institute, Houston, TX*

Background: Nonalchoholic fatty liver disease (NAFLD) and its severe form, nonalcoholic steatohepatitis (NASH), are associated with obesity, type 2 diabetes, and metabolic syndrome. NASH prevalence is estimated at 6% globally and up to 14% in middle-aged Americans, with a higher prevalence in Hispanics. There are significant disparities in clinical trial enrollment in the U.S. for most diseases, with Hispanic patients being significantly underrepresented, raising concerns about generalizing drug efficacy to this population. Our study aims to assess the representation of sex, age, and ethnicity in relation to disease severity across multiple US NASH clinical trials. **Methods:** We combined screening data from 8 NAFLD/NASH non-cirrhotic phase 2 trials. Descriptive analyses were performed. **Results:** We identified 6,623 patients with available demographic data; 57.4% were females and 49.3% self-identified as Hispanic. The mean age of the entire cohort was 54.3 years (SD 11.8). The distribution of patients across different age groups screened into the studies is illustrated in the figure. Among the 2,217 patients who underwent a liver biopsy, 63% of females were diagnosed with NASH, compared to 55% of males ($p < 0.001$). Furthermore, NASH with significant fibrosis (Fibrosis stage 2, 3, or 4) was observed in 51% of females and 42% of males ($p < 0.001$). In terms of ethnicity, 57% of Hispanics were diagnosed with NASH, while the proportion was slightly higher at 62% for non-Hispanics ($p = 0.039$). Similarly, the percentage of non-Hispanics with significant fibrosis (49%) was slightly higher than that of Hispanics (44%) ($p = 0.011$). **Conclusion:** Clinical trials focusing on NASH predominantly recruit middle-aged adults, with a noticeable underrepresentation of young adults and more importantly, elderly patients, who tend to present with more severe forms of the condition. Contrary to prior assumptions, our study findings indicate that Hispanics are adequately represented in NASH clinical trials conducted in the United States. This could be attributed to the presence of a broader network of trial sites in regions with significant Hispanic populations.



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

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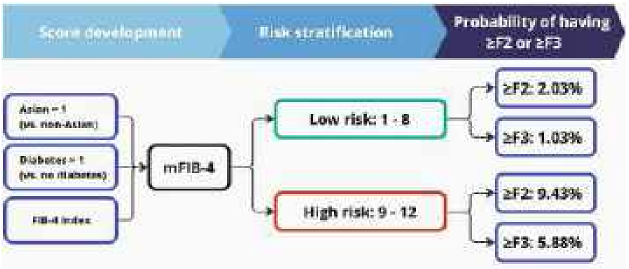
2158-A | DEVELOPMENT AND VALIDATION OF A RISK SCORE FOR FIBROSIS STAGE 2 OR HIGHER: A REAL-NAFLD STUDY OF 1902 REAL-WORLD PATIENTS WITH BIOPSY

Vy H. Nguyen[1,2], Takanori Ito[3], Hansen Dang[4], Pei-Chien Tsai[5], Miwa Kawanaka[6], Masanori Atsukawa[7], Taeang Arai[7], Korenobu Hayama[8], Ming-Lun Yeh[9], Mayumi Maeda[2], Scott D. Barnett[10], Wan Long Chuang[11], Chung-Feng Huang[5], Chia-Yen Dai[9], Jee-Fu Huang[12], Ramsey Cheung[10], Ming-Lung Yu[5], Shinichi Aishima[13], Hidenori Toyoda[14] and Mindie H. Nguyen[10], (1)Harvard Medical School, (2)Stanford University Medical Center, (3)Nagoya University Graduate School of Medicine, (4)Stanford University, (5)Hepatobiliary Section, Department of Internal Medicine, and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, (6)Kawasaki Medical School, (7) Nippon Medical School Hospital, (8)Nippon Medical School, (9)Kaohsiung Medical University, (10)Stanford University Medical Center, Palo Alto, CA, (11) Kaohsiung Medical University Hospital, Kaohsiung Medical University, (12)Hepatobiliary Section, Department of Internal Medicine, and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, Kaohsiung, Taiwan, (13)Saga University, (14) Ogaki Municipal Hospital

Background: Patients with nonalcoholic fatty liver disease (NAFLD) who develop fibrosis stage 2 or higher are at increased risk of both liver-related and non-liver-related morbidity and mortality. We aimed to develop and validate a simple-to-use and accurate fibrosis risk score using readily available clinical information from real-world patients with NAFLD. **Methods:** This study included 1902 patients with NAFLD with liver biopsy recruited in the REAL-NAFLD registry, an observational chart review registry at 5 centers (1 United States, 1 Taiwan, and 3 Japan). We randomly divided the patients into a training (N = 1268) and validation (N = 634) cohort on a 2:1 ratio. We used logistic regression with stepwise selection to identify statistically significant variables to assemble a modified fibrosis-4 index (mFIB-4) score. **Results:** The mFIB-4 score includes the original FIB-4 index, Asian race, and diabetes. This 12-point risk score yielded an area under receiver operating characteristic curves (AUC) of 0.67, 0.76, and 0.83 in distinguishing **e** F1, **e** F2, and **e** F3, respectively, in the validation cohort. Compared to the FIB-4 index, the mFIB-4 performs better at distinguishing **e** F1 and **e** F2 in the validation cohort (0.67 vs. 0.56, $p < 0.0001$, and 0.76 vs. 0.70, $p < 0.0001$, respectively). There was no significant difference between mFIB-4 and FIB-4 at distinguishing **e** F3 (0.82 vs. 0.81, $p = 0.11$, respectively). Using Youden's index and optimizing the sensitivity and specificity at each score, the mFIB-4 score was further categorized as follows: 1-8 low risk and 9-12 high risk. Patients in the high-risk categories are associated with nearly a 10% probability of having **e** F2, nearly 5 times higher than those in the low-risk group (Figure). Similarly, the probability of having **e** F3 is about 1% in the low-risk group but close to 6% in the high-risk group. **Conclusion:** The mFIB-4 score provides two distinct risk categories with no indeterminate group to stratify the risk of developing significant fibrosis in patients with NAFLD. Additional validation analyses are needed to validate the use of mFIB-4 in other subgroups to identify patients at increased risk of developing fibrosis.



Disclosures: Takanori Ito – Chugai Pharmaceutical Co., Ltd: Speaking and Teaching, No, No; Chugai Pharmaceutical Co., Ltd: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AstraZeneca: Speaking and Teaching, No, No;

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The following people have nothing to disclose: Vy H. Nguyen, Hansen Dang, Pei-Chien Tsai, Masanori Atsukawa, Taeang Arai, Ming-Lun Yeh, Mayumi Maeda, Scott D. Barnett, Wan Long Chuang, Chung-Feng Huang, Ramsey Cheung, Ming-Lung Yu, Shinichi Aishima, Hidenori Toyoda

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

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

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

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

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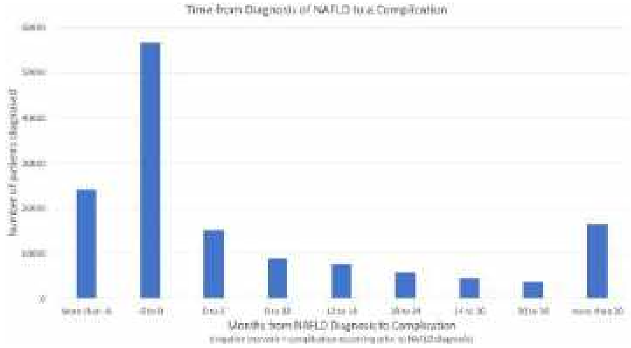
Background: Nonalcoholic fatty liver disease (NAFLD) is a condition in which screening guidelines remain controversial as the characteristics that predispose to the development of complications remain unclear. An earlier diagnosis of NAFLD may allow adequate time for intervention and help prevent complications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



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2161-A | DIET QUALITY, LIVER STEATOSIS, AND FIBROSIS IN U.S. YOUTH

Vanessa Garcia-Larsen[1], Hani Tamim[2], Noara Alhusseini[2], Saad A Alghamdi[3], Mohammad Shagrani[3], Faisal Abaalkhail[4], Waleed K Al-Hamoudi[4], Faisal M Sanai[5] and Saleh A Alqahtani[1,3], (1)Johns Hopkins University, (2)Alfaisal University, (3)King Faisal Specialist Hospital and Research Center, (4)King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, (5)King Abdulaziz Medical City-Jeddah

Background: Nonalcoholic fatty liver disease (NAFLD) is the fastest-growing lifestyle-related non-communicable disease in the world. Current evidence suggests metabolic disruptions associated with obesity and type II diabetes mellitus (T2DM) as main drivers of the disease in adults. Childhood diet and NAFLD have been less examined. We aimed to investigate the association between diet quality and objectively measured NAFLD in adolescents and youth from a population-based study. **Methods:** As part of the U.S. National Health and Nutrition Examination Survey (NHANES) Program, we analyzed data in individual's aged **e** $12 < 21$ years old participating in the 2017-2018 cycle, with valid FibroScan® measurements. Liver steatosis (NAFLD; controlled attenuation parameter [CAP] score of **e** 248 dB/m) and advanced fibrosis (liver stiffness measurement of **e** 9.4 kPa [F3-F4]) were measured through vibration-controlled transient elastography with CAP. Two diet quality indices widely used in the U.S. population were derived, namely the Dietary Approaches to Stop Hypertension (DASH; 8 = lowest adherence, 40 = highest adherence) and the Alternative Healthy Eating Index (AHEI; 0 = low adherence, 110 = highest adherence). The associations between diet quality indices (per standard deviation [SD] increase in score) and NAFLD-related outcomes were examined with survey-weighted logistic regressions adjusting for potential confounders. **Results:** Among 972 youth aged 15.7 ± 2.4 (male 51.0%) with complete data, the prevalence of liver steatosis was 28.3%, while 3.2% had advanced fibrosis. The mean DASH score was 21.8 (SD ± 4.7), indicative of 43.0% adherence to the DASH-style diet pattern, and the mean AHEI score was 53.7 (SD ± 7.9). A per-SD increase in DASH score was associated with lower odds of having liver steatosis (odds ratio [OR] 0.78.9; 95% confidence interval [95% CI] 0.65, 0.95; p-value 0.016), but not with advanced fibrosis (OR 1.44; 95% CI 0.79, 2.61). AHEI score was associated with lower odds of both outcomes, but these did not reach statistical significance. **Conclusion:** The high prevalence of NAFLD observed in youth represents a major public health challenge. A greater adherence to a DASH pattern was associated with liver steatosis but not fibrosis. Highlighting the importance of diet quality to prevent NAFLD and to promote higher adherence to a DASH pattern in adolescents may support public health strategies for its prevention.

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2162-A | DIETARY AND CALORIC INTAKE IN PATIENTS WITH NAFLD COMPARED TO THE GENERAL US POPULATION: INSIGHTS FROM THE NHANES STUDY

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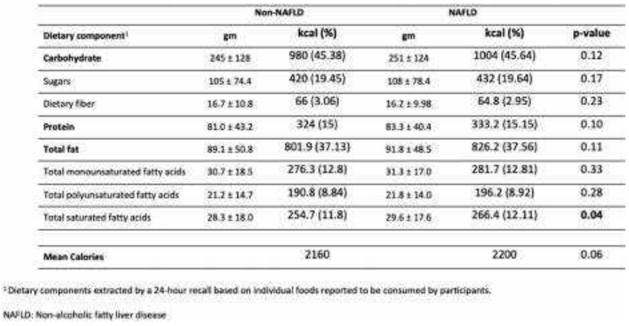
Background: Non-alcoholic fatty liver disease (NAFLD) is a complex, multisystemic condition associated with poor dietary habits, particularly high fat and high fructose intake, which develops in genetically predisposed individual's. The management of NAFLD typically involves reducing caloric intake and improving dietary quality. This study aims to examine the dietary composition and caloric intake of patients with NAFLD and compare them to patients without NAFLD. **Methods:** We conducted an analysis of data from the National Health and Nutrition Examination Survey (NHANES) spanning the years 2017 to 2020 to assess populations with and without NAFLD. NHANES encompasses self-reported demographic, socioeconomic, health, and dietary information. One in-person dietary recall was used. NAFLD was defined as having a controlled attenuation parameter (CAP) score equal or higher than 285 dB/m on vibration-controlled Transient Elastography (VCTE), with no other potential etiologies for liver steatosis. The NHANES study population consisted of 15,560 participants, with 3,598 individual's categorized as either NAFLD or non-NAFLD. **Results:** Among the included participants, 1,336 met the criteria for NAFLD, while 2,262 did not. Analysis of 24-hour recall data revealed no statistically significant difference in total caloric intake between the two groups (2200 kcal in NAFLD vs. 2160 kcal in non-NAFLD; p = 0.06). The macronutrient composition of the diets in both groups was generally similar, except for a higher intake of total saturated fatty acids observed in the NAFLD population (29.6 gm vs. 28.3 gm; p = 0.04). **Conclusion:** Patients with NAFLD exhibited comparable total caloric intake and macronutrient dietary composition, as reported in 24-hour recall data, compared to patients without NAFLD. However, there was a higher intake of total saturated fatty acids among individual's with NAFLD. These findings suggest that additional factors, including genetic polymorphisms, may play a larger role in the development of NAFLD compared to dietary composition alone.



	Non-NAFLD		NAFLD		
Dietary component[1]	gm	kcal (%)	gm	kcal (%)	p-value
Carbohydrate	245 ± 128	980 (45.38)	251 ± 124	1004 (45.64)	0.12
Sugars	105 ± 74.4	420 (19.45)	108 ± 78.4	432 (19.64)	0.17
Dietary fiber	16.7 ± 10.8	66 (3.06)	16.2 ± 9.98	64.8 (2.95)	0.23
Protein	81.0 ± 43.2	324 (15)	83.3 ± 40.4	333.2 (15.15)	0.10
Total fat	89.1 ± 50.8	801.9 (37.13)	91.8 ± 48.5	826.2 (37.56)	0.11
Total monounsaturated fatty acids	30.7 ± 18.5	276.3 (12.8)	31.3 ± 17.0	281.7 (12.81)	0.33
Total polyunsaturated fatty acids	21.2 ± 14.7	190.8 (8.84)	21.8 ± 14.0	196.2 (8.92)	0.28
Total saturated fatty acids	28.3 ± 18.0	254.7 (11.8)	29.6 ± 17.6	266.4 (12.11)	**0.04**
Mean Calories		2160		2200	0.06

[1] Dietary components extracted by a 24-hour recall based on individual foods reported to be consumed by participants.

NAFLD: Non-alcoholic fatty liver disease

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Walid S. Ayoub – Intercept: Speaking and Teaching, No, No; GIlead: Speaking and Teaching, No, No; Mirum: Independent contractor (including contracted research), No, No; Madrigal: Independent contractor (including contracted research), No, No; GSK: Independent contractor (including contracted research), No, No; Ipsen: Independent contractor (including contracted research), No, No; Genfit: Independent contractor (including contracted research), No, No; Zydus: Independent contractor (including contracted research), No, No; Cymabay: Independent contractor (including contracted research), No, No; Genkyotex: Independent contractor (including contracted research), No, No; perspectum: Speaking and Teaching, No, No; Intercept: Independent contractor (including contracted research), No, No; Gilead: Independent contractor (including contracted research), No, No;

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Disclosure information not available at the time of publication: Jiada Zhan

2163-A | DIFFERENCES BETWEEN BIOPSY-PROVEN NASH PATIENTS WITH AND WITHOUT DIABETES MELLITUS

Hansen Dang[1,2], Vy H. Nguyen[3,4], Pei-Chien Tsai[5], Takanori Ito[6], Miwa Kawanaka[7], Masanori Atsukawa[8], Taeang Arai[9], Korenobu Hayama[10], Ming-Lun Yeh[11], Mayumi Maeda[4], Wan Long Chuang[12], Chung-Feng Huang[5], Chia-Yen Dai[5], Jee-Fu Huang[13], Ramsey Cheung[14], Shinichi Aishima[15], Hidenori Toyoda[16], Ming-Lung Yu[17] and Mindie H. Nguyen[14], (1)Stanford University, (2)University of Iowa, Carver College of Medicine, (3)Harvard Medical School, (4)Stanford University Medical Center, (5)Hepatobiliary Section, Department of Internal Medicine, and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, (6)Nagoya University Graduate School of Medicine, (7)Kawasaki Medical School, (8)Nippon Medical School Hospital, Tokyo, Japan, (9)Nippon Medical School Hospital, (10)Nippon Medical School, (11)Kaohsiung Medical University, (12)Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, (13)Kaohsiung Medical University Hospital, (14)Stanford University Medical Center, Palo Alto, CA, (15)Saga University, (16)Ogaki Municipal Hospital, (17) Kaohsiung Chang Gung Memorial Hospital,

Background: Diabetes mellitus is strongly associated with the development of NAFLD and NASH. However, studies characterizing the effects of diabetes on the severity of NASH remain sparse. To address this, we aimed to examine the characteristics of patients with and without diabetes in a multinational cohort of biopsy-confirmed NASH patients. **Methods:** Data were obtained from REAL-NAFLD registry which includes 1902 patients with NAFLD with liver biopsy at five medical centers, one in the U.S. and four in Asia (Japan and Taiwan). Patients with biopsy-confirmed NASH were eligible for the study and were divided into those with diabetes (n = 407) and those without diabetes (n = 636). Logistic regression was performed to estimate odds ratios associated with worse fibrosis stage on pathology and NAS score **e** 5. **Results:** Analyses of baseline characteristics between the two groups revealed significant differences in demographics, comorbidities, and liver function. NASH patients with diabetes were older (55.34 vs 48.32, $p < 0.001$) and more likely to have hypertension (67.74% vs 40.63%, $p < 0.001$), hyperlipidemia (66.09% vs 45.42%, $p < 0.001$), and cirrhosis (31.96% vs 21.96%, $p < 0.001$) compared to those without diabetes. Additionally, they had lower ALT levels (68 U/L vs 75 U/L), higher FIB-4 index (1.85 vs 1.48), and were more likely to have advanced liver fibrosis on pathology (all $p < 0.05$). On multivariable logistic regression, adjusting for age, sex, ethnicity, BMI, diabetes, platelets, albumin, we found that diabetes was independently associated with increased odds of having liver fibrosis stage **e** F2 on biopsy (aOR = 1.92, 95% CI: 1.49-2.47, $p < 0.001$). When assessing for advanced fibrosis and higher (**e** F3), diabetes was again found to have a significant association (aOR = 2.10, 95% CI: 1.57-2.82, $p < 0.001$). Additionally, in a different multivariable logistic model, diabetes was found to be independently associated with a NAS score **e** 5 (aOR = 1.36, 95% CI: 1.06-1.75, $p < 0.001$). **Conclusion:** In our multinational study of biopsy-proven NASH patients, diabetes mellitus was found to be significantly associated with higher odds of worse fibrosis stage on biopsy and NAS score at the time of NASH diagnosis. More surveillance and interventions are needed for NASH patients with diabetes, as worse fibrosis stage increases the risk of cirrhosis and liver-related mortality.

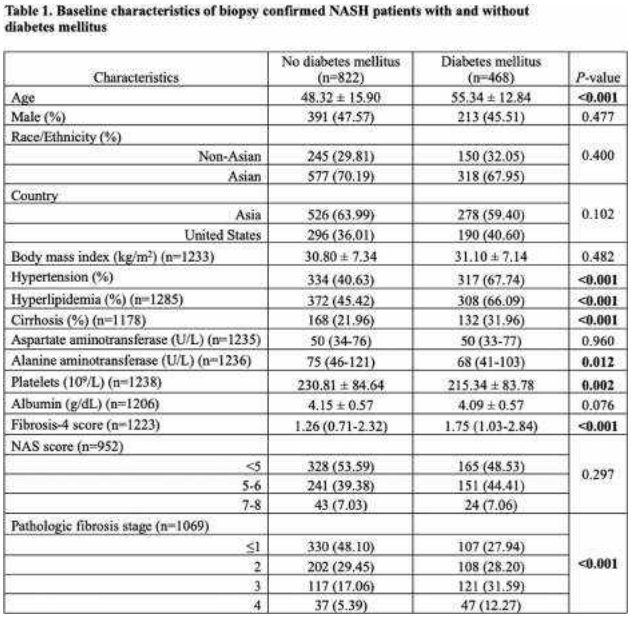

Table 1. Baseline characteristics of biopsy confirmed NASH patients with and without diabetes mellitus

Characteristics	No diabetes mellitus (n=822)	Diabetes mellitus (n=468)	*P*-value
Age	48.32 ± 15.90	55.34 ± 12.84	**<0.001**
Male (%)	391 (47.57)	213 (45.51)	0.477
Race/Ethnicity (%)			0.400
Non-Asian	245 (29.81)	150 (32.05)	
Asian	577 (70.19)	318 (67.95)	
Country			0.102
Asia	526 (63.99)	278 (59.40)	
United States	296 (36.01)	190 (40.60)	
Body mass index (kg/m²) (n=1233)	30.80 ± 7.34	31.10 ± 7.14	0.482
Hypertension (%)	334 (40.63)	317 (67.74)	**<0.001**
Hyperlipidemia (%) (n=1285)	372 (45.42)	308 (66.09)	**<0.001**
Cirrhosis (%) (n=1178)	168 (21.96)	132 (31.96)	**<0.001**
Aspartate aminotransferase (U/L) (n=1235)	50 (34-76)	50 (33-77)	0.960
Alanine aminotransferase (U/L) (n=1236)	75 (46-121)	68 (41-103)	**0.012**
Platelets (10⁹/L) (n=1238)	230.81 ± 84.64	215.34 ± 83.78	**0.002**
Albumin (g/dL) (n=1206)	4.15 ± 0.57	4.09 ± 0.57	0.076
Fibrosis-4 score (n=1223)	1.26 (0.71-2.32)	1.75 (1.03-2.84)	**<0.001**
NAS score (n=952)			0.297
<5	328 (53.59)	165 (48.53)	
5-6	241 (39.38)	151 (44.41)	
7-8	43 (7.03)	24 (7.06)	
Pathologic fibrosis stage (n=1069)			**<0.001**
≤1	330 (48.10)	107 (27.94)	
2	202 (29.45)	108 (28.20)	
3	117 (17.06)	121 (31.59)	
4	37 (5.39)	47 (12.27)	

Disclosures: Takanori Ito – Chugai Pharmaceutical Co., Ltd: Speaking and Teaching, No, No; Chugai Pharmaceutical Co., Ltd: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AstraZeneca: Speaking and Teaching, No, No;

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The following people have nothing to disclose: Hansen Dang, Vy H. Nguyen, Pei-Chien Tsai, Masanori Atsukawa, Taeang Arai, Ming-Lun Yeh, Mayumi Maeda, Wan Long Chuang, Chung-Feng Huang, Chia-Yen Dai, Ramsey Cheung, Shinichi Aishima, Hidenori Toyoda, Ming-Lung Yu, Mindie H. Nguyen

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2164-A | DIFFERENCES IN BODY COMPOSITION OF MAFLD PATIENTS ACCORDING TO BODY MASS INDEX AND METABOLIC PROFILE

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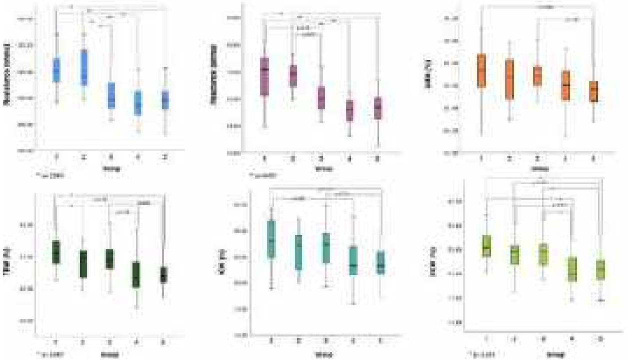
Background: Body composition (BC) has been linked to liver steatosis; however, there are not evidence about alterations in BC in MAFLD patients, therefore, the aim of this study is to describe differences in BC, in these patients **Methods:** It is a cross sectional study with patients whom attended at check-up unit. Liver steatosis was evaluated by controlled attenuation parameter (CAP) and patients were classified according to definition of MAFLD for overweight/obese and lean patients. Patients were classified according to body mass index (BMI), in five groups: G1: < 25kg/m^2-non-MAFLD; G2: < 25 kg/m^2-MAFLD; G3: 25-30 kg/m^2-MAFLD; G4: > 30 kg/m^2-MAFLD and metabolically healthy (< 3 metabolic abnormalities) (MH) and G5: > 30 kg/m^2-MAFLD and metabolically unhealthy (MU). BC was assessed by bioelectrical impedance (RJL Quantum IV) obtaining measurements of resistance; reactance; phase angle; percentages of fat; total body water (TBW%); intracellular and extracellular water (ICW% and ECW%) and skeletal muscle mass (SMM%). Differences in BC was analyzed by Kruskall-Wallis test. Continuous data showed as median and interquartile range. **Results:** A total of 140 patients were included (G1 n = 30; G2 n = 24; G3 n = 30; G4 n = 26; G5 n = 30). 56.4% (n = 79) were male with median of age of 49 [41-55] years. Overweight/obese MAFLD patients showed significant lower resistance and reactance levels (p **d** 0.05). Fat % was higher in MAFLD obesity groups (G4: 41[24-45] %; G5: 40.4 [36.5-43.2] %) than G1 (31[26.9-34.5]) (p **d** 0.001); according to vectorial analysis, chaquexia was observed in 18.4% (n = 7) of patients in G4 and 15.8%

(n = 6) in G5 patients. Fat% was also higher in patients of G5 (MU) than G2 (34.3[29.8-40.4], p = 0.02) and G3 (35[31.1-38.3], p = 0.01) patients. Obese MAFLD patients showed lower %TBW, ICW% and ECW% (p **d** 0.001). (Figure). According to SMM%, it was lower in MU obese MAFLD patients (29.1[26.3-31.1]) compared to healthy controls (33.4[29.3-36.8], p = 0.006) and overweight MAFLD patients (32[29.7-34.4], p = 0.02). Phase angle did not show significant differences. **Conclusion:** Overweight/obese MAFLD patients shows BC abnormalities in comparison with healthy controls and lean MAFLD patients. BC parameters of resistance, reactance, body water and skeletal muscle mass are significant lower in obese patients, metabolically healthy and unhealthy. These changes could be explained for the sarcopenia and fat-muscle interchange and no necessary for the presence of metabolic abnormalities.



Disclosures: The following people have nothing to disclose: Eva Juárez-Hernández, Iván López-Méndez, Karen D Bernal-Contreras, Alain Velázquez-Alemán, Andrea Maldonado-Rojas, Graciela Elia Castro-Narro, Martha Helena Ramos-Ostos, Misael Uribe

2165-A | DIFFERENCES IN INCIDENCE OF ADVERSE CLINICAL EVENTS AMONG NAFLD PARTICIPANTS WITH LIVER BIOPSY PROVEN NAFLD STRATIFIED BY NASH: A SYSTEMATIC REVIEW AND META-ANALYSIS

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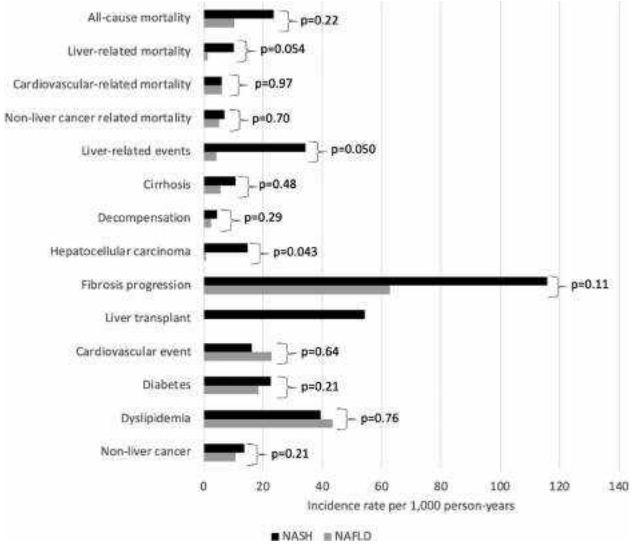
Background: Nonalcoholic fatty liver disease (NAFLD) exists as a spectrum, with nonalcoholic steatohepatitis (NASH) representing the more severe subtype of NAFLD. Both NAFLD and NASH are associated with increased risks of morbidity and mortality. We aimed to determine and compare the incidence rates of adverse clinical events associated with biopsy confirmed NAFLD and NASH. **Methods:** We performed a systematic review and meta-analysis of cohort studies of adults with NAFLD at baseline using 3 databases (Cochrane library, EMBASE, PubMed) to evaluate the pooled incidence of adverse clinical events associated with biopsy-confirmed NAFLD and NASH. Random-effects models were used to estimate the pooled incidence of adverse clinical events. **Results:** A total of 13 studies of biopsy confirmed NAFLD patients (n = 14570) and 16 studies of biopsy confirmed NASH patients (n = 9297) were identified and included in meta-analysis. Median study year for NAFLD was 2004 with median follow-up of 3612.5 person-years. Median study year for NASH was 2004 with median follow-up of 1722 person-years. All analyses showed significant heterogeneity (I^2 **e** 50%) and no asymmetry on funnel plot or significance on egger's test ($p > 0.05$). Data are reported as incidence rate per 1000 person-years. No significant differences in incidence were observed for all-cause (10.3 vs 23.5), cardiovascular-related (6.2 vs 6.1), and non-liver cancer related mortality (5.2 vs. 7.0) between those with NAFLD and NASH. Those with NASH had higher incidence of liver-related mortality compared to NAFLD (10.2 vs 1.4), however this did not reach statistical significance. Additionally, there were no significant differences in the development of non-liver cancer between NAFLD and NASH (10.8 vs 13.8). Compared to patients with NAFLD alone, significantly higher incidence of liver-related events was observed among patients with NASH (4.2 vs 34.2). Incidence for hepatocellular carcinoma was significantly higher among NASH patients (0.8 vs 14.8), however no significant differences were noted for fibrosis progression (62.8 vs 115.7), cirrhosis (5.7 vs 10.8), and decompensation (2.4 vs 4.6). No patients with NAFLD received a liver transplant, with 57/273 NASH patients undergoing liver transplant. Additionally, no significant differences were observed in the incidence rate per 1000 person-years of diabetes (18.4 vs 22.7), dyslipidemia (43.5 vs 39.4), and cardiovascular disease (22.9 vs 16.2) between those with NAFLD and NASH (figure). **Conclusion:** Compared to those with NAFLD alone, those with NASH had significantly higher incidence of liver-related events and hepatocellular carcinoma with a trend for higher incidence of liver-related mortality, though this did not achieve statistical significance. Identification and early intervention for patients with

NAFLD is vital towards preventing disease progression and the development of adverse clinical events.



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The following people have nothing to disclose: David M Le, Thomas Baez, Michael H Le, Hansen Dang, Vy H. Nguyen, Yee Hui Yeo, Fanpu Ji, Ramsey Cheung
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2166-A | DISEASE PROGRESSION IN TAIWANESE NON-ALCOHOLIC STEATOHEPATITIS PATIENTS: SUBGROUP ANALYSIS OF THE PLACEBO PATIENTS IN A DOUBLE-BLIND RANDOMIZED TRIAL

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Background: Disease progression remains elusive in Asian non-alcoholic steatohepatitis (NASH) patients. We aimed to investigate the paired histopathological features of the Taiwanese NASH patients randomized into placebo group in a double-blind randomized trial. **Methods:** All the placebo group patients received a 6-month strict multi-disciplinary program of lifestyle modifications led by physician, dietician, and nursing staff. The histopathological and clinical features obtained from paired biopsies 24 weeks apart were assessed. The endpoints were normalization of transaminase levels, metabolic parameters, decrease of NAFLD Activity Score (NAS) e 1, and fibrosis stage decrease e 1 stage. We also aimed to elucidate the predictors associated with disease progression. **Results:** A total of 37 biopsy-proven NASH patients were enrolled. The normalization of transaminase level increased from 0% to 13.5%. There were also significantly increased proportions of patients with normal total cholesterol, triglyceride, and hemoglobin A1c levels. Fifteen (40.5%) patients had increased NAS e 1, whereas 10 (27.0%) patients had NAS regression, respectively. Twelve (32.4%) patients had increased fibrosis e 1 stage. Only 2 (5.4%) patients had fibrosis regression. A high fasting plasma glucose (FPG) level was associated with NAS progression. Older age, higher transaminase and FPG levels were factors associated with fibrosis progression. There were 7 (18.9%) patients achieving body weight reduction > 3%, and 4 (57.1%) of them had NAS regression. No significant effect of weight reduction in the progression of fibrosis was observed. **Conclusion:** Taiwanese NASH patients had a significant disease progression with a short-term lifestyle modification program. A more precise or intensive program may be needed for disease control.

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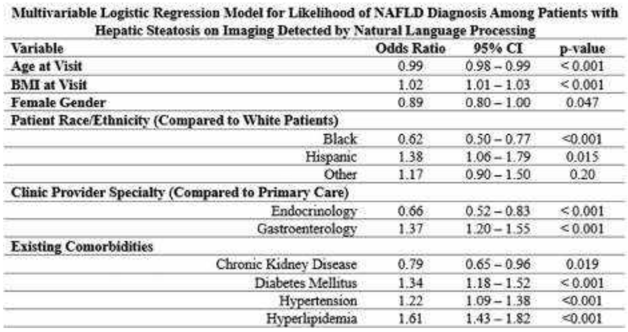
Disclosures: Jee-Fu Huang – Roche: Consultant, No, Yes; Bristol-Myer-Squibb: Consultant, No, Yes; Gilead: Consultant, No, Yes; Sysmex: Consultant, No, Yes; Aligos: Consultant, No, Yes; Abbvie: Speaking and Teaching, No, Yes; Gilead: Speaking and Teaching, No, Yes; Bristol-Myer-Squibb: Speaking and Teaching, No, Yes;

The following people have nothing to disclose: Ming-Lun Yeh, Chung-Feng Huang, Chia-Yen Dai, Ming-Lung Yu, Wan Long Chuang

2167-A | DISPARITIES AND DISCORDANCE IN PROBLEM LIST DOCUMENTATION OF FATTY LIVER DISEASE AMONG PATIENTS WITH RADIOGRAPHIC FINDINGS OF HEPATIC STEATOSIS IN OUTPATIENT SETTINGS

Ashley Spann, Dario Giuse and Manhal Izzy, Vanderbilt University Medical Center

Background: The prevalence of nonalcoholic fatty liver disease (NAFLD) is rapidly rising in the United States. Despite this, patients and providers are often unaware of the disease. Natural language processing (NLP) has previously been shown to accurately detect hepatic steatosis. By leveraging an electronic health record (EHR) embedded natural language processing (NLP) tool applied to radiology reports, we aimed to assess the concordance between NLP and existing chart documentation in identifying patients with NAFLD. **Methods:** This retrospective, single, large academic center study included patients who were seen in either outpatient office or telemedicine visits by gastroenterology/hepatology, primary care, or endocrinology providers during a 1-year period (1/1/2021 – 12/31/2021). Liver transplant recipients and those patients without an internally interpreted abdominal imaging study within the 3 years prior to their visit were excluded. An EHR-embedded NLP tool that maps unstructured contextual data within the electronic health record to Unified Medical Language System (UMLS) concept codes was applied to abdominal radiology reports obtained within the 3 years prior to the office visit. Multivariable logistic regression was used to assess for associations of NLP concordance with problem list documentation. **Results:** A total of 28,829 patients meeting inclusion criteria were seen in telemedicine or in office encounters during the observation period with available historical abdominal imaging. The NLP tool detected hepatic steatosis on imaging within the prior 3 years for 8,177 patients (28.4% of total patient population), however only 1,999 patients (24.4% of those positive for HS by NLP) had concordant problem list documentation of fatty liver disease at the time of their office visit. Among NLP-positive patients, patients had significantly greater odds of having concomitant problem list documentation of NAFLD if Hispanic, seen by a gastroenterology provider or had documented components of metabolic syndrome (Figure). Black patients, women, older patients and those seen in endocrinology clinics had significantly lower odds of having documentation of a NAFLD diagnosis (Figure). **Conclusion:** This study highlights that less than 1/4th of patients with HS on imaging as detected by NLP have discrete documentation of HS or NAFLD within their medical records. Additionally, black patients, women and those seen by endocrinology providers were less likely to have documented diagnoses of NAFLD within their medical records even in the presence of hepatic steatosis on imaging. Natural language processing techniques offer a solution to detect patients with hepatic steatosis on imaging from radiology reports and can augment accurate and equitable capture of these patients to potentially facilitate EHR-embedded decision support tools to provide directed care for these patients.



Multivariable Logistic Regression Model for Likelihood of NAFLD Diagnosis Among Patients with Hepatic Steatosis on Imaging Detected by Natural Language Processing

Variable	Odds Ratio	95% CI	p-value
Age at Visit	0.99	0.98 – 0.99	< 0.001
BMI at Visit	1.02	1.01 – 1.03	< 0.001
Female Gender	0.89	0.80 – 1.00	0.047
Patient Race/Ethnicity (Compared to White Patients)			
Black	0.62	0.50 – 0.77	<0.001
Hispanic	1.38	1.06 – 1.79	0.015
Other	1.17	0.90 – 1.50	0.20
Clinic Provider Specialty (Compared to Primary Care)			
Endocrinology	0.66	0.52 – 0.83	< 0.001
Gastroenterology	1.37	1.20 – 1.55	< 0.001
Existing Comorbidities			
Chronic Kidney Disease	0.79	0.65 – 0.96	0.019
Diabetes Mellitus	1.34	1.18 – 1.52	< 0.001
Hypertension	1.22	1.09 – 1.38	<0.001
Hyperlipidemia	1.61	1.43 – 1.82	<0.001

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2168-A | DOES STEATOSIS PREDICT OUTCOMES IN LIVER DISEASE? TRANSIENT ELASTOGRAPHY CAP SCORE IS ASSOCIATED WITH CIRRHOSIS, DECOMPENSATION, HCC AND DEATH AMONG U.S. VETERANS WITH LIVER DISEASE

Nicole J. Kim[1], Philip Vutien[1], Joleen A Borgerding[2], Lauren A. Beste[1,3] and George Ioannou[1,2], (1) University of Washington, (2)Veterans Affairs Puget Sound Healthcare System, (3)VA Puget Sound Healthcare System

Background: Liver steatosis is common in patients with chronic liver disease (CLD), but whether the degree and etiology of steatosis predicts disease progression or mortality remains unknown. **Methods:** We identified 13,008 U.S. Veterans with CLD and at least one FibroScan® done after 1/1/2015. We excluded patients with decompensation (ascites, variceal bleed, or hepatic encephalopathy) or hepatocellular carcinoma (HCC) prior to FibroScan® date. We categorized liver steatosis by FibroScan® Controlled Attenuated Parameter (CAP) scores, as stage 0 (<274 dB/m), 1 (274-289), 2 (290-301), and 3 (**e** 302). We assessed for development of cirrhosis, decompensation, HCC, and death until 1/1/2022. Multivariable Cox-proportional hazards regression (adjusting for age, sex, race/ethnicity, BMI, diabetes, history of alcohol use disorder, CLD etiology, and FibroScan® liver stiffness score) was used to assess for associations between CAP scores (by stage and stage **e** 1 vs. 0) and these outcomes, overall and by CLD etiology. **Results:** The cohort was 95% male, 52% White, 32% Black, 7.3% Hispanic, and 2.9% Asian, with a median age of 65.4 years (IQR 10.6). Fifty-seven percent (n = 7,433) had cirrhosis and CLD etiologies included active hepatitis C (HCV; 28%), cured HCV (21%), non-alcoholic fatty liver disease (NAFLD; 28%), alcohol-associated liver disease (ALD; 13%), and chronic hepatitis B (10%). Of the cohort, 46%, 8.1%, 5.7%, and 40% of patients had a CAP score of stage 0, 1, 2, and 3, respectively. On overall multivariable analysis, CAP score stage **e** 1 (vs. 0) was associated with an increased risk of cirrhosis (adjusted HR [aHR] 1.18 [95% CI: 1.01-1.37]), and a decreased risk of decompensation (aHR 0.77 [0.63-0.93]), HCC (aHR 0.80 [0.65-0.99]) and death (aHR 0.66 [0.59-0.75]). CAP score stage 3 (vs. 0) was associated with an increased risk of cirrhosis in active HCV (aHR 1.37 [1.07-1.75]) and NAFLD (aHR 1.37 [1.01-1.85]), decreased risk of decompensation in active HCV (aHR 0.58 [0.37-0.89]) and NAFLD (aHR 0.54 [0.36-0.79]), and decreased risk of death in cured HCV (aHR 0.64 [0.47-0.88]), ALD (aHR 0.45 [0.32-0.63]), and NAFLD (aHR 0.47 [0.36-0.62]). There was no association between CAP score and risk of HCC by CLD etiology. **Conclusion:** In patients with CLD who had a FibroScan®, CAP score **e** 274 dB/m is associated with an increased risk of cirrhosis and decreased risk of decompensation, HCC, and death. The associations between CAP score and liver disease outcomes vary by CLD etiology.

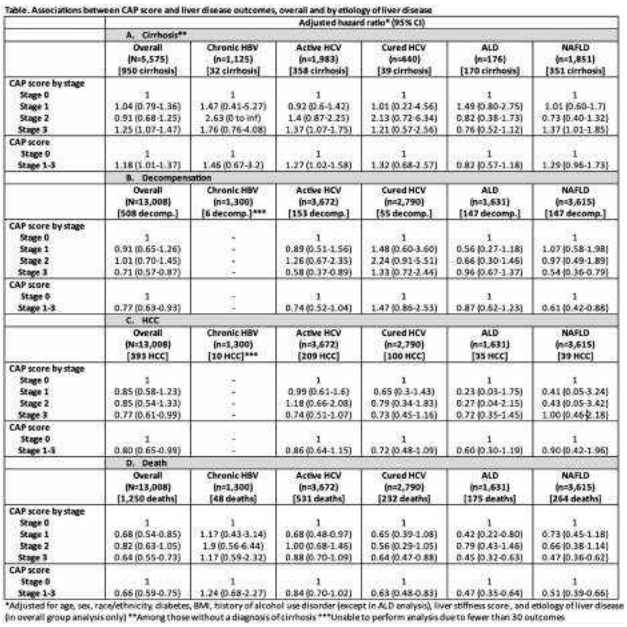

Table. Associations between CAP score and liver disease outcomes, overall and by etiology of liver disease

	Adjusted hazard ratio* (95% CI)					
	A. Cirrhosis**					
	Overall (N=5,575) [950 cirrhosis]	Chronic HBV (n=1,125) [32 cirrhosis]	Active HCV (n=1,983) [358 cirrhosis]	Cured HCV (n=440) [39 cirrhosis]	ALD (n=176) [170 cirrhosis]	NAFLD (n=1,851) [351 cirrhosis]
CAP score by stage						
Stage 0	1	1	1	1	1	1
Stage 1	1.04 (0.79-1.36)	1.47 (0.41-5.27)	0.92 (0.6-1.42)	1.01 (0.22-4.56)	1.49 (0.80-2.75)	1.01 (0.60-1.7)
Stage 2	0.91 (0.68-1.25)	2.63 (0 to inf)	1.4 (0.87-2.25)	2.13 (0.72-6.34)	0.82 (0.38-1.73)	0.73 (0.40-1.32)
Stage 3	1.25 (1.07-1.47)	1.76 (0.76-4.08)	1.37 (1.07-1.75)	1.21 (0.57-2.56)	0.76 (0.52-1.12)	1.37 (1.01-1.85)
CAP score						
Stage 0	1	1	1	1	1	1
Stage 1-3	1.18 (1.01-1.37)	1.46 (0.67-3.2)	1.27 (1.02-1.58)	1.32 (0.68-2.57)	0.82 (0.57-1.18)	1.29 (0.96-1.73)
	B. Decompensation					
	Overall (N=13,008) [508 decomp.]	Chronic HBV (n=1,300) [6 decomp.]***	Active HCV (n=3,672) [153 decomp.]	Cured HCV (n=2,790) [55 decomp.]	ALD (n=1,631) [147 decomp.]	NAFLD (n=3,615) [147 decomp.]
CAP score by stage						
Stage 0	1	-	1	1	1	1
Stage 1	0.91 (0.65-1.26)	-	0.89 (0.51-1.56)	1.48 (0.60-3.60)	0.56 (0.27-1.18)	1.07 (0.58-1.98)
Stage 2	1.01 (0.70-1.45)	-	1.26 (0.67-2.35)	2.24 (0.91-5.51)	0.66 (0.30-1.46)	0.97 (0.49-1.89)
Stage 3	0.71 (0.57-0.87)	-	0.58 (0.37-0.89)	1.33 (0.72-2.44)	0.96 (0.67-1.37)	0.54 (0.36-0.79)
CAP score						
Stage 0	1	-	1	1	1	1
Stage 1-3	0.77 (0.63-0.93)	-	0.74 (0.52-1.04)	1.47 (0.86-2.53)	0.87 (0.62-1.23)	0.61 (0.42-0.88)
	C. HCC					
	Overall (N=13,008) [393 HCC]	Chronic HBV (n=1,300) [10 HCC]***	Active HCV (n=3,672) [209 HCC]	Cured HCV (n=2,790) [100 HCC]	ALD (n=1,631) [35 HCC]	NAFLD (n=3,615) [39 HCC]
CAP score by stage						
Stage 0	1	-	1	1	1	1
Stage 1	0.85 (0.58-1.23)	-	0.99 (0.61-1.6)	0.65 (0.3-1.43)	0.23 (0.03-1.75)	0.41 (0.05-3.24)
Stage 2	0.85 (0.54-1.33)	-	1.18 (0.66-2.08)	0.79 (0.34-1.83)	0.27 (0.04-2.15)	0.43 (0.05-3.42)
Stage 3	0.77 (0.61-0.99)	-	0.74 (0.51-1.07)	0.73 (0.45-1.16)	0.72 (0.35-1.45)	1.00 (0.46-2.18)
CAP score						
Stage 0	1	-	1	1	1	1
Stage 1-3	0.80 (0.65-0.99)	-	0.86 (0.64-1.15)	0.72 (0.48-1.09)	0.60 (0.30-1.19)	0.90 (0.42-1.96)
	D. Death					
	Overall (N=13,008) [1,250 deaths]	Chronic HBV (n=1,300) [48 deaths]	Active HCV (n=3,672) [531 deaths]	Cured HCV (n=2,790) [232 deaths]	ALD (n=1,631) [175 deaths]	NAFLD (n=3,615) [264 deaths]
CAP score by stage						
Stage 0	1	1	1	1	1	1
Stage 1	0.68 (0.54-0.85)	1.17 (0.43-3.14)	0.68 (0.48-0.97)	0.65 (0.39-1.08)	0.42 (0.22-0.80)	0.73 (0.45-1.18)
Stage 2	0.82 (0.63-1.05)	1.9 (0.56-6.44)	1.00 (0.68-1.46)	0.56 (0.29-1.05)	0.79 (0.43-1.46)	0.66 (0.38-1.14)
Stage 3	0.64 (0.55-0.73)	1.17 (0.59-2.32)	0.88 (0.70-1.09)	0.64 (0.47-0.88)	0.45 (0.32-0.63)	0.47 (0.36-0.62)
CAP score						
Stage 0	1	1	1	1	1	1
Stage 1-3	0.66 (0.59-0.75)	1.24 (0.68-2.27)	0.84 (0.70-1.02)	0.63 (0.48-0.83)	0.47 (0.35-0.64)	0.51 (0.39-0.66)

*Adjusted for age, sex, race/ethnicity, diabetes, BMI, history of alcohol use disorder (except in ALD analysis), liver stiffness score, and etiology of liver disease (in overall group analysis only) **Among those without a diagnosis of cirrhosis ***Unable to perform analysis due to fewer than 30 outcomes

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Disclosure information not available at the time of publication: Philip Vutien, Joleen A Borgerding, Lauren A. Beste

2169-A | ELEVATED PREVALENCE OF UNDIAGNOSED ADVANCED LIVER DISEASE IN A HISPANIC COMMUNITY

Isela De La Cerda, Miryoung Lee, Joseph B. McCormick and Susan P. Fisher-Hoch, Uthealth Houston School of Public Health Brownsville Campus

Background: Assessment and prevention of non-alcoholic fatty liver disease (NAFLD) is absent at the community level. Noninvasive scoring algorithms (NSAs) incorporating hepatic biomarkers with FibroScan imaging identify stages of advanced liver disease (ALD). FibroScan® is a non-invasive measure of hepatic fibrosis measured in kiloPascals (kPa) and liver fat by the Controlled Attenuation Parameter (CAP). The FibroScan-AST score (FAST) identifies nonalcoholic steatohepatitis (NASH) the inflammatory subtype of NAFLD, Agile3+ identifies advanced liver fibrosis and Agile4 cirrhosis. We used these 3 NSAs to estimate the community-level prevalence of ALD in a large Hispanic cohort on the US/Mexico border where the population has elevated rates of cirrhosis and hepatocellular carcinoma. Since this cohort has high rates of metabolic syndrome, we assessed the association of this with ALD. **Methods:** This cross-sectional study included participants with a FibroScan between 2015-2023 from the Cameron County Hispanic Cohort (CCHC). The CCHC is an extensively phenotyped, randomly recruited community cohort. We identified NAFLD in those with $>5\%$ hepatic steatosis (CAP >233) and no history of alcohol abuse or hepatitis. Established cut offs for the NSAs are: FAST **e** 0.67 for NASH, Agile3+ **e** 0.68 for advanced fibrosis, and Agile4 **e** 0.57 for cirrhosis. We grouped NASH, advanced fibrosis, or cirrhosis into ALD, and metabolic syndrome as defined by the American Heart Association. We conducted bivariate analysis to compare those with ALD and those without. We conducted logistic regressions to estimate the prevalence odds ratio of metabolic syndrome and its components among those with ALD. **Results:** We detected NAFLD in 658 of 1,202 participants (55%). Using NSAs we then identified 43/658 (6.53%) with ALD. The prevalence odds ratio for presence of metabolic syndrome among the 43 was highly significant (POR: 2.06; 95% CI: 1.10 – 3.94). Further logistic regression models of the 5 components of metabolic syndrome showed that participants with hypertension had twice the odds (POR: 2.31; 95% CI: 1.18 – 4.51) of having ALD, and those with high fasting blood glucose levels 3 times (POR: 3.04; 95% CI: 1.53 – 6.33) compared to those who did not have signs of ALD. **Conclusion:** Liver disease NSAs are useful for screening of populations for ALD in the NAFLD spectrum. Using this approach, we were able to show high rates of undiagnosed but significant disease and identify those most at risk.

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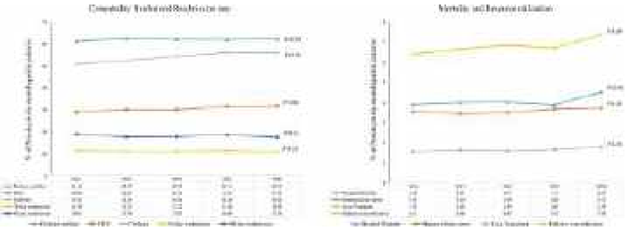
Disclosure information not available at the time of publication: Joseph B. McCormick, Susan P. Fisher-Hoch

2170-A | EPIDEMIOLOGIC TRENDS IN COMORBIDITY BURDEN AND HEALTHCARE RESOURCE UTILIZATION IN NONALCOHOLIC STEATOHEPATITIS (NASH): A LONGITUDINAL STUDY

Umer Farooq[1], Zahid Tarar[2], Abdallah El Alayli[1], Chengu Niu[3], Ammad Javaid Chaudhary[4] and Kamran Qureshi[1], (1)Saint Louis University, (2)University of Missouri, (3)Rochester General Hospital, (4)Henry Ford Hospital

Background: Nonalcoholic steatohepatitis (NASH) is on the rise globally, including the United States (US), and is linked to comorbidities, including diabetes mellitus (DM), cardiovascular disease (CVD), and chronic kidney disease (CKD). This has significant implications for healthcare resources including hospitalizations and undermines the quality of life. Despite extensive effort there is no FDA-approved treatment for NASH available as yet. In view of rising burden, we performed a longitudinal analysis to investigate trends of NASH related to hospitalizations and the impact of comorbidities on in-hospital mortality and on associated resources utilization. **Methods:** We used the National Readmission Database (2016-2020) which includes discharges for patients with and without repeat hospital visits in a year and those who have died in the hospital. We employed International Classification of Diseases (ICD)-10 codes to identify adult NASH patients. The linear trend of NASH diagnosis, hospitalizations, comorbidities, and mortality was tested using the Mantel-Haenszel linear trend test. The variables adjusted for in the regression models while computing adjusted hospitalization and readmission rates were: gender, age, Charlson Comorbidity Index score, median household income for patients' zip codes, hospital location/ bedside, and teaching status. We used Stata, version 14.2, to perform analyses considering 2-sided $P<0.05$ as statistically significant. **Results:** The analysis included 530,908 patients (mean age 62.15 y, females 61%). Incidence of NASH among hospitalized patients was noted to have increased from 27.82 to 43.44 per 10,000 patients from 2016 to 2020 ($P<0.01$). Comorbidities such as CKD (29.09% to 31.95%, $P<0.01$), liver cirrhosis (51.05% to 56.02%, $P<0.01$) showed increasing trends (Figure. 1). All-cause inpatient mortality in NASH adults increased from 3.92% to 4.53% ($P<0.01$), as well as palliative care utilization in this population (6.41% to 7.38%, P: 0.03). Liver transplantation rates did not significantly change (1.55% to 1.79%, P: 0.51). No decline was observed in 30 and 90-day readmission rates. Hepatic failure and cirrhosis (30.71%), infections (8.67%), NASH (5.84%), and non-variceal upper gastrointestinal bleeding (4.33%) were the leading causes of readmission. Mean hospitalization costs rose from $19,004 to $21,600 ($P<0.01$). Notably, comorbidities of DM and hepatocellular carcinoma in NASH did not exhibit an increase over the study period. **Conclusion:** Rising trend in hospitalizations noted in adult NASH population is concerning. The parallel rise in comorbidity burden, resource utilization, and mortality in hospitalized NASH patients is seen in the recent years while readmission trends exhibited a lack of decline. National strategies for effective management are needed to decrease the economic burden of NASH on the healthcare system.



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2171-A | EVALUATION OF PERFORMANCE CHARACTERISTICS OF NON-INVASIVE FIBROSIS SCORES AND MACHINE LEARNING MODELS IN PATIENTS WITH METABOLIC-ASSOCIATED FATTY LIVER DISEASE

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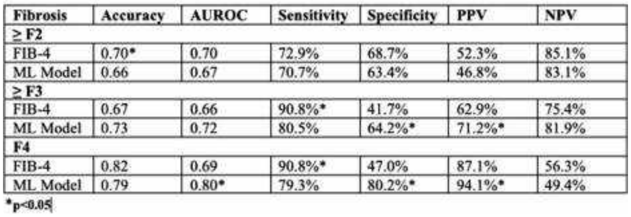
Background: Non-invasive fibrosis scores (NIFS) have excellent sensitivity (Sn) and negative predictive value (NPV) for evaluation of significant (SF) and advanced fibrosis (AF) in patients with non-alcoholic fatty liver disease (NAFLD). Machine learning models (MLM) have been shown to be superior to NIFS in patients with NAFLD. However, the performance characteristics of these tests have not been well defined in patients with type 2 diabetes mellitus (T2DM) and NAFLD (also called metabolic-associated fatty liver disease, MAFLD). We aimed to define the performance characteristics of NIFS and novel MLMs in patients with MAFLD. **Methods:** We analyzed data from the NIDDK NAFLD Adult database for 1073 patients with liver biopsy results available. Patients were divided into the NAFLD group (NAFLD +/- T2DM) & the MAFLD group (NAFLD with T2DM). We calculated FIB-4, APRI, BARD, and NAFLD Fibrosis scores (NFS) in all patients. We also created an MLM for each group of patients using an XGBoost model with 30 parameters. Cut-off values for SF (≥F2) were FIB-4 > 1.3, APRI > 0.7, BARD score > 2, and NFS of > -1.455. AF (≥F3) was assessed with FIB-4 > 2.67, APRI > 1, NFS > 0.675, and Cirrhosis (F4) with a FIB-4 > 3.48 or APRI > 1.5. Statistically significant values ($p < 0.05$) are annotated with an asterisk (*). **Results:** Among 1073 patients, 317 (29.5%) had T2DM, 298 (94%) of all patients had BMI > 27, 262 (82.6%) had a BMI > 30. Among NIFS, in the MAFLD group, FIB-4 had the best AUROC of 0.67*, specificity (Sp) (67.5%)*, and positive predictive value, PPV (47.9%)* for prediction of ≥ F2. However, APRI at a cut-off value of > 0.7 had better Sn (79.9%)* and NPV (82.7%)*. The Sn of FIB-4 did not improve by decreasing the cutoff value to < 1.3 or < 1. For ≥ F3, FIB-4 had the best AUROC (0.63)*, Sp (34.6%)*, PPV (58.8%)*, and NPV (78.3%)*. The Sn of FIB-4 was inferior to NFS (90.7% vs 92%) *. For patients with Cirrhosis, FIB-4 had better AUROC (0.64) *, Sp (36.9%)*, PPV (84.9%) *, & NPV (52.9%)*. APRI had superior Sn (95.5%* vs. 91.5%) than FIB-4. A comparison of performance characteristics of FIB-4 and MLM is shown in Table 1. MLM & FIB-4 perform similarly when predicting ≥ F2. However, for > F3 and F4, MLM has better AUROC, Sp, and PPV, while FIB-4 has better Sn but similar NPV. In the NAFLD group, for ≥ F2, FIB-4 had best AUROC and NPV, APRI > 0.7 had the best Sn (82.6%)* & BARD score had the highest Sp and PPV. For ≥ F3, AUROC of NFS was better* than FIB-4 but Sn* of FIB-4 was superior to NFS. For F4, FIB-4 significantly* outperforms others in all parameters. **Conclusion:** Performance of current NIFS in MAFLD is variable. FIB-4 & MLMs have better AUROC than other NIFS. MLMs have better AUROC, Sp, and PPV compared to FIB-4, whereas FIB-4 has better Sn & NPV. An approach using FIB-4 with cutoff of > 1.3 followed by MLM prediction may be superior and cost-effective for screening at a population level in patients with T2DM. The efficacy of MLMs needs to be further studied and compared to other blood & imaging-based tests in patients with MAFLD.

Table 1. Comparison of FIB-4 and Machine Learning Models in patients with MAFLD



Fibrosis	Accuracy	AUROC	Sensitivity	Specificity	PPV	NPV
≥ F2						
FIB-4	0.70*	0.70	72.9%	68.7%	52.3%	85.1%
ML Model	0.66	0.67	70.7%	63.4%	46.8%	83.1%
≥ F3						
FIB-4	0.67	0.66	90.8%*	41.7%	62.9%	75.4%
ML Model	0.73	0.72	80.5%	64.2%*	71.2%*	81.9%
F4						
FIB-4	0.82	0.69	90.8%*	47.0%	87.1%	56.3%
ML Model	0.79	0.80*	79.3%	80.2%*	94.1%*	49.4%

*p<0.05

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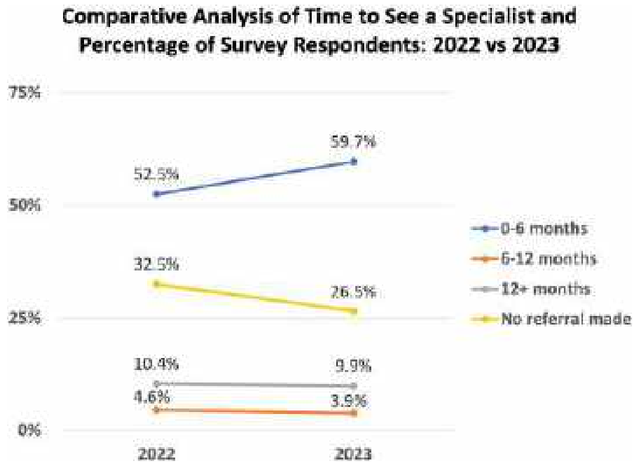
2172-A | EVOLVING TRENDS IN NAFLD/NASH PATIENT EXPERIENCES: COMPARATIVE ANALYSIS FROM “THE STATE OF NAFLD/NASH CARE IN AMERICA” 2022-2023 SURVEYS

Neeraj Mistry, Wayne Eskridge, Henry E Chang, Tiffany Mensah and Diana Evans, Fatty Liver Foundation

Background: The aim of this study was to understand the evolving social and medical experiences of NAFLD/NASH patients in the United States through the comparison of findings from "The State of NAFLD/ NASH Care in AmericaTM", an annual online patient survey, between 2022 and 2023. An understanding of the experiences of these patients is crucial in identifying needs and gaps in care that impact their health outcomes. Through an aggregated analysis, we aim to inform the development of effective interventions and policies addressing the unmet needs of this population. **Methods:** Survey items were developed with the patient community and FLF's Medical Advisory Group. The survey was available in English and Spanish and addressed four key domains of the patient experience: diagnosis and staging, medical management and physical impact, psychosocial and environmental impact, and current health. Social media, email, and partnerships with local community based organizations were used to distribute the survey. We conducted a comparative analysis of the 2022 and 2023 survey data. **Results:** Across both years, primary care physicians (PCPs) remain the most common entry point for NAFLD/NASH diagnosis. Consistent with the previous year, most respondents reported receiving none or not enough information at diagnosis. Compared to 2022, more respondents in 2023 reported visiting a specialist (hepatologist or gastroenterologist) within six months of diagnosis. Fewer received no referral to a specialist. There was an increase in respondents who felt they understood their condition somewhat or better than before after visiting a specialist. In 2023, we observed a shift in living arrangements, with fewer respondents living alone and a greater number residing with a spouse or long-term partner. Concurrently, respondents increasingly perceived their spouses or partners as crucial sources of support compared to 2022. The frequency of a psychologist or psychiatrist in respondents' care teams decreased from 2022 to 2023. Emotional health trends also shifted, with less reported depression and anger, yet an increase in feelings of fear and anxiety from 2022 to 2023. **Conclusion:** Targeted Continuing Medical Education (CME) for PCPs frequently in contact with NAFLD/NASH patients should be sustained at minimum and strengthened where resources allow. Resources on home-based care, care navigation, and other topics for spousal caretakers are needed given their prominent role within patients' lives. Implementing interventions to combat stigma, bolster mental health, and improve accessibility to mental health services is an urgent requirement for improving NAFLD/NASH patient care.



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The following people have nothing to disclose: Neeraj Mistry, Tiffany Mensah, Diana Evans

2173-A | EXAMINATION OF THE ROLE OF DIET QUALITY ON NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AMONG HISPANICS IN THE RIO GRANDE VALLEY: A CROSS-SECTIONAL STUDY

Maria Lisette Flores, Uthealth Science Center School of Public Health, Miryoung Lee, Uthealth Houston School of Public Health Brownsville Campus and Marcia C Otto, Uthealth Houston School of Public Health Houston Campus

Background: The prevalence of non-alcoholic fatty liver disease (NAFLD) has increased to epidemic proportions in the U.S. and disproportionately affects Hispanics. Literature suggested that diet quality and specific food items were associated with NAFLD. A dietary recall survey can help determine potential relationships between diet and NAFLD risk. In this cross-sectional study, we examined how overall diet quality and specific diet items were associated with NAFLD risk in Hispanics from the Cameron County Hispanic Cohort (CCHC), a population-based cohort in southernmost Texas. **Methods:** The study sample comprised 993 adults (Females 68%). Liver stiffness measurement (LSM) and steatosis using a controlled attenuation parameter (CAP) were obtained using FibroScan®. Interviews were conducted to obtain the demographics and medical history. To determine NAFLD risk, four outcomes were considered: LSMs (kPa), steatosis (CAP), significant fibrosis (LSM **e** 7.0 kPa), and steatosis status (CAP > 288 dB/m). Consumption frequency of twenty-eight food item groups was acquired through a 24-hr dietary recall survey. A modified dietary scoring system, Healthy Eating Index (HEI, range 0-55), was utilized to quantify overall diet quality. The independent relationships of food items with NAFLD outcomes were examined using multiple linear and logistic regression models. **Results:** Median (interquartile range) CAP and LSM scores were 286 (241-327) and 4.6(3.7-6.0). 49% of participants had steatosis, and 15% had significant fibrosis. The modified HEI's mean (SD) score was 6.2(3.3). Modified HEI seems negatively associated with fibrosis status (OR = 0.94, 95%CI: 0.89-0.99) in the age and gender-adjusted model, but the relationship was attenuated in the model adjusted for sociodemographic factors and comorbidity. Consumption of certain food groups was significantly related to increased NAFLD risk, including lower consumption of baked fish or wheat bread items. Compared to participants reporting no consumption of wheat bread items, including tortillas, participants who reported consuming them at least once had 0.5(95%CI 0.3-0.8) times the odds of having steatosis or 0.7(0.4-1.5) times the odds of having fibrosis. Similarly, participants with twice or more consumption had 0.9 (0.6-1.2) times the odds of steatosis or 0.6(0.4-1.0) times the odds of fibrosis. **Conclusion:** Our findings suggest that the consumption frequency of certain food items could potentially impact NAFLD risk in Hispanics.
Disclosures: The following people have nothing to disclose: Maria Lisette Flores, Miryoung Lee
Disclosure information not available at the time of publication: Marcia C Otto

2174-A | EXPERIENCES AND UNMET NEEDS IN NON-ALCOHOLIC STEATOHEPATITIS (NASH): INSIGHTS FROM PATIENTS AND PATIENT CAREGIVERS

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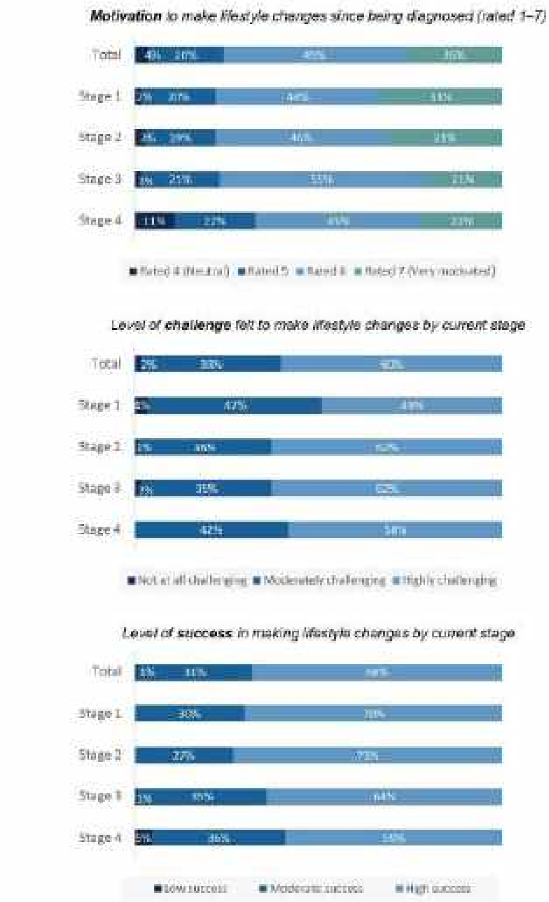
Background: Non-alcoholic steatohepatitis (NASH) is known to have a substantial impact on patients' health-related quality of life; however, a gap remains in quantifying patients' experiences and emotions throughout disease progression. This survey assessed primary experiences, emotions, and unmet needs of patients with NASH and caregivers of those with NASH. **Methods:** A 30-minute, web-based quantitative survey was conducted as part of a global research study; this was sent to patients with NASH and caregivers of those with NASH identified by quantitative fieldwork specialist organisations in the USA, UK, Canada, Germany, Japan and China. Respondents were aged 18–70 years, and they (or the person they cared for) had been diagnosed with NASH by a medical test, had a healthcare professional currently treating them and knew which stage of NASH they were originally diagnosed with and currently in. **Results:** 391 individual's were included in the final sample (n = 252 patients, n = 139 caregivers; 63%

male; mean age 43.0 y). Respondents often reported that nuanced symptoms (fatigue 47%, loss of appetite 42%, nausea 40%) prompted them to seek diagnosis. The most common form of diagnosis reported was CT scan (62%), elevated liver enzymes (50%) or liver biopsy (47%), with fibrosis assessments to monitor progression (55%). Most reported understanding the disease severity at diagnosis (97% reported diagnosis as moderately/very serious), but less than half fully understood their diagnosis. Almost all (99%) reported conducting their own research, but many were overwhelmed by the amount of information (66%). Respondents stated they were highly motivated to make lifestyle changes at diagnosis; 60% viewed such changes as highly challenging, but 68% felt very successful in implementing them (Figure). NASH substantially impacted respondents' lives in areas such as pain, weight perception, time with friends/family, and financial expenses of maintaining lifestyle changes (each ranked 'very impactful' by ~15%). Respondents were initially concerned and uncertain, but were more hopeful and confident after initial diagnosis. **Conclusion:** Patients received their NASH diagnosis via a variety of media, and a majority showed willingness to implement lifestyle changes. Patients feel overwhelmed by the available information when conducting research. The survey findings highlight the large unmet need for further disease education using clear, reliable information sources, and the need for improvements in disease management.

Figure. Patient views towards lifestyle changes by current stage of NASH



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ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Siemens Healthcare GmbH: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; AGED Diagnostics: Stock privately held company (individual stocks and stock options), Yes, No; Hepta Bio.: Stock privately held company (individual stocks and stock options), Yes, No; Boehringer Ingelheim: Speaking and Teaching, Yes, Yes; Echosens: Speaking and Teaching, Yes, Yes; MedPublico GmbH: Speaking and Teaching, Yes, Yes; Novo Nordisk: Speaking and Teaching, Yes, Yes; Madrigal: Speaking and Teaching, Yes, Yes; Histoindex: Speaking and Teaching, Yes, Yes;

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2175-A | FACTORS ASSOCIATED WITH ADVANCED LIVER FIBROSIS IN A POPULATION WITH TYPE 2 DIABETES: A 5-YEARS RETROSPECTIVE COHORT STUDY IN MEXICO CITY★

Zeltzin Soto Montes[1], Maria Juliana Corredor-Nassar[1], Froylan David Martinez-Sanchez[2], David Medina-Julio[1], Carolina Martinez-Perez[1], Gibran Gonzalez-Alvarez[1], Victor Manuel Paz-Zarza[1], Sandra Milena Feria-Agudelo[1], Alejandra Diaz-Jarquin[1], Omhariany Medina-Garza[1], Erika Karina Tenorio-Aguirre[2] and Jacqueline Cordova Gallardo[3], (1)Hospital General Manuel Gea Gonzalez, (2)Hospital General Manuel Gea González, (3)Hospital General Manuel Gea Gonz

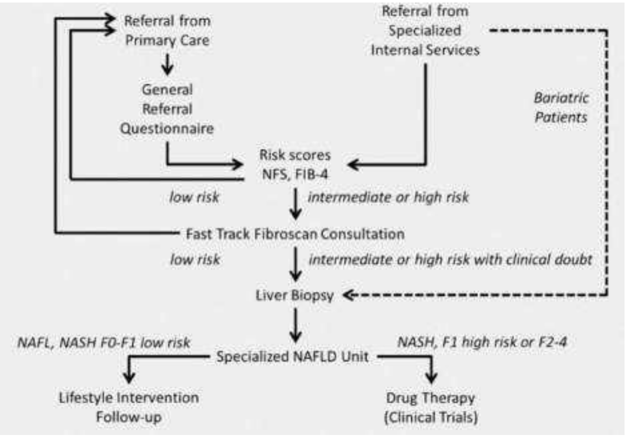
Background: Metabolic-associated fatty liver disease (MAFLD) is a major cause of liver related morbidity and mortality worldwide. Identifying people at high risk of experiencing complications is important to prevent disease progression. Some patients have metabolic risk factors associated with MAFLD such as Type 2 Diabetes. However, current practice guidelines do not recommend systematic screening, due to uncertainties surrounding the prevalence of advanced fibrosis in patients with diabetes. **Methods:** Retrospective cohort study that included clinical and biochemical data of 1,035 patients with diagnosis of diabetes. We defined advanced liver fibrosis as fibrosis-4 index (FIB-4 index) more than 4. Logistic regression analysis was used to estimate the Odds Ratios for advanced liver fibrosis in patients with diabetes. **Results:** The mean age of the patients was 59 ± 14 years, 68.7% were women, the mean body mass index (BMI) was 28.5 ± 6.0 kg/m^2, median serum creatinine was 0.87 (0.71-1.03) mg/dL, median fasting glucose was 122 (99-161) mg/dL and mean hemoglobin A1c was 7.63 ± 2.09 %. Overall, 15.1% had advanced fibrosis and 54.9 % had hypertension. Likewise, the frequency of evolution of diabetes was 60.2% in 0-4 years, 16.1% in 5-9 years and 23.7% in > 10 years. Fasting glucose levels (OR = 1.005 [1.003-1.008]), hemoglobin A1c (OR = 0.869 [0.769-0.982]), and diabetes evolution > 10 years (OR = 2.051 [1.329-3.167]) were independently associated with advanced liver fibrosis. **Conclusion:** Although lower hemoglobin A1c was associated with lower odds, uncontrolled fasting glucose and disease duration were independently associated with advanced liver fibrosis. These data could partially support that implementing systematic screening for liver fibrosis in patients with diabetes could reduce the burden of liver fibrosis by MAFLD.

Disclosures: The following people have nothing to disclose: Zeltzin Soto Montes, Maria Juliana Corredor-Nassar, Froylan David Martinez-Sanchez, David Medina-Julio, Carolina Martinez-Perez, Gibran Gonzalez-Alvarez, Victor Manuel Paz-Zarza, Sandra Milena Feria-Agudelo, Alejandra Diaz-Jarquin, Omhariany Medina-Garza, Erika Karina Tenorio-Aguirre, Jacqueline Cordova Gallardo

2176-A | FAST-TRACK ELASTOMETRY SERVICE FOR NONALCOHOLIC FATTY LIVER (NAFLD) PATIENTS

Mohamed Alsenbesy[1,2], Monika Rau[3], Johannes Weiss[3], Oliver Goetze[3] and Andreas Geier[4], (1)Arabian Gulf University (AGU), (2)South Valley University (SVU) Hospital, (3)Uniklinikum Wuerzburg, (4)Department of Hepatology, University of Würzburg, Würzburg, Germany

Background: Nonalcoholic fatty liver disease (NAFLD) is increasing globally with an estimated prevalence of approximately 25%. Nonalcoholic steatohepatitis as the progressive disease entity often leads to fibrosis and end-stage disease. The magnitude of NAFLD patients are not diagnosed and have no access to further clinical assessment. Diagnostic pathways for individual risk evaluation fitting with available resources are of utmost importance in real-world clinical practice. **Methods**: Retrospective analysis of 1346 anonymized outpa- tient datasets at Würzburg University Hospital, Germany. Transient elastography (TE) with controlled attenuation parameter and laboratory-based risk scores (NFS, FIB-4) were the main diagnostic workup tools for risk stratification **Results:** After preselection based on questionnaire information NAFLD still accounts for one-fifth of patients in the liver outpatient service. More than 80% of NAFLD patients receive their first-time diagnosis in our unit. Laboratory-based risk scores and TE are valuable tools for second-step risk assessment as shown in our clinical data analysis. Moreover, 65% of NAFLD patients use inpatient services for at least 1 day. The policy to perform liver biopsy in high-risk patients above the recommended threshold of 9.6 kPa if any clinical doubt exists regarding the diagnosis of cirrhosis leads to a histological down staging in almost 80%. **Conclusion:** Questionnaire-based referral from primary care followed by broadly available fast-track TE and eventually liver biopsy for selected patients is the standard practice in our unit. This approach represents a feasible model to handle the large gap between availability and clinical need for TE facilities.


Referral from Primary Care
Referral from Specialized Internal Services
General Referral Questionnaire
Bariatric Patients
Risk scores NFS, FIB-4
low risk
intermediate or high risk
Fast Track Fibroscan Consultation
low risk
intermediate or high risk with clinical doubt
Liver Biopsy
NAFL, NASH F0-F1 low risk
Specialized NAFLD Unit
NASH, F1 high risk or F2-4
Lifestyle Intervention Follow-up
Drug Therapy (Clinical Trials)

Disclosures: The following people have nothing to disclose: Mohamed Alsenbesy

Disclosure information not available at the time of publication: Monika Rau, Johannes Weiss, Oliver Goetze, Andreas Geier

2177-A | FATTY ACID DESATURASE 2 rs174583 GENETIC VARIANT IS INVOLVED IN ADVANCED FIBROSIS IN FATTY LIVER DISEASE

Shunsuke Ikejima, Kazuyoshi Kon, Kumiko Arai, Akira Uchiyama, Hiroo Fukada, Kyoko Fukuhara, Reiko Yaginuma, Toshifumi Sato, Maki Morinaga, Masahiro Tada, Hisafumi Yamagata, Hironao Okubo and Kenichi Ikejima, Juntendo University School of Medicine

Background: Genetic factors are deeply involved in the pathological progression of nonalcoholic fatty liver disease (NAFLD) and alcohol-associated liver disease (ALD); however, details remain unclear. In recent years, it has been demonstrated that the progression of fatty liver disease is closely associated with the risk of cardiovascular diseases. Genetic variants of fatty acid desaturase (FADS) are associated with fatty acid metabolism, and several studies have reported that minor allele homozygotes of FADS2 gene rs174583 are associated with essential fatty acid composition, serum insulin levels and cardiovascular risk factors. In this study, therefore, we investigated the impact of FADS single nucleotide polymorphism (SNP) on progression of fatty liver disease. **Methods:** A total of 34 patients with biopsy-proven fatty liver disease (10 with ALD, 24 with NAFLD) were evaluated. A control group consisted of 26 patients with non-fatty liver disease other than primary biliary cholangitis. Genotypes were established using Taqman assays targeting PNPLA3 rs738409, FADS1 rs174556, and FADS2 rs174583. Allele frequencies in each group were evaluated by Chi-square test. Patients with fatty liver disease were classified to non-advanced fibrosis (fibrosis stage 0-2) and advanced fibrosis (stage 3-4). Multiple linear regression analysis was performed to determine independent risk factors. **Results:** The GG allele carrier of PNPLA3 was significantly frequent in 44% of the fatty liver group compared to 8% of the control group. The frequency of TT minor allele of FADS1 and FADS2 was 15% and 19% in the control group, and 18% and 38% in the fatty liver group, showing no significant difference between the groups. In contrast, the TT allele of FADS2 was significantly higher at 64% in advanced fibrosis group compared to 20% in non-advanced fibrosis in fatty liver disease. In a multivariate analysis including PNPLA3 GG allele, FADS1 TT allele, FADS2 TT allele, etiology, age, and sex, only the TT allele of FADS2 was an independent risk factor for advanced fibrosis ($P = 0.011$). **Conclusion:** These findings clearly demonstrated that the TT allele of FADS2 is associated with the development of advanced fibrosis, whereas the GG allele of PNPLA3 is closely related to the development of fatty liver disease. It is postulated that the TT allele of FADS2 rs174583 is a critical bridge between progression of fatty liver and increased cardiovascular events.

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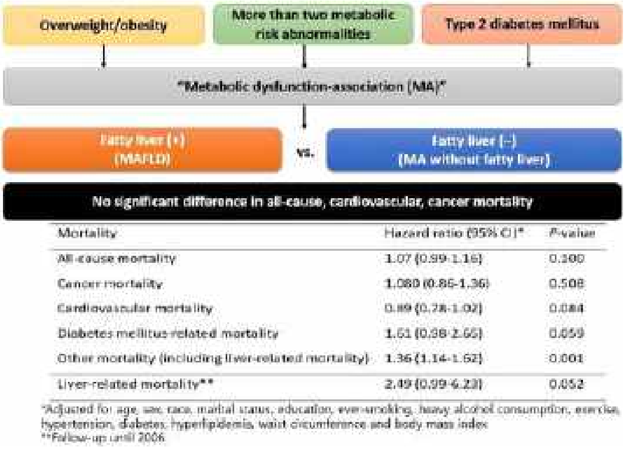
2178-A | FATTY LIVER ITSELF IN MAFLD DOES NOT INCREASE ALL-CAUSE MORTALITY IN INDIVIDUALS WITH METABOLIC DYSFUNCTION

Min-Sun Kwak[1], Hyunseok Kim[2], Z. Gordon Gordon Jiang[3], Mazen Noureddin[4] and Ju Dong Yang[2], (1) *Seoul National University Hospital Gangnam Center, (2) Cedars-Sinai Medical Center, Los Angeles, CA, (3)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (4)Houston Research Institute, Houston, TX*

Background: A novel term, metabolic dysfunction-associated fatty liver disease (MAFLD), was proposed by a group of experts. However, it remains unclear whether hepatic steatosis *per se* in MAFLD contributes to an elevated risk of mortality in individual's with overweight/obesity, metabolic dysregulation, or type 2 diabetes mellitus (DM) (referred to as the metabolic dysfunction-association (MA) group), which are known significant risk factors for increased mortality. This study aimed to compare all-cause and cause-specific mortality between the 'MAFLD' group and the 'MA without fatty liver' group. **Methods:** A total of 10,052 participants from NHANES III were included. Fatty liver was diagnosed using ultrasound, and MAFLD was defined based on the criteria proposed by an international panel of experts. Mortality risks were compared between the 'MAFLD' group and the 'MA without fatty liver' group using the Cox proportional hazards model with complex survey design weights, adjusted for demographic and anthropometry factors (age, sex, race, body mass index and waist circumference), social history (education, marriage status, smoking and alcohol history and exercise) and comorbidity variables (hypertension, DM and hyperlipidemia). Linked mortality data, including all-cause, cancer, cardiovascular, and other causes-related mortality, were examined from 1988 through 2019. For liver-related mortality, data were evaluated from 1988 through 2006. **Results:** Over an average follow-up period of 23.0 years, the 'MAFLD' group did not exhibit a significant increase in all-cause mortality (adjusted hazard ratio [95% confidence interval], 1.07 [0.99-1.16], $P = 0.100$), cancer mortality (1.08 [0.86-1.36], $P = 0.508$), or cardiovascular mortality (0.89 [0.78-1.02], $P = 0.084$) compared to the 'MA without fatty liver' group. However, other causes-related mortality, which included liver-related mortality, was higher in the MAFLD group (1.36 [1.14-1.62], $P = 0.001$). This trend persisted in sensitivity analyses conducted on participants without viral hepatitis or heavy alcohol consumption. No significant effect modification was observed according to subgroups. Liver-related mortality, assessed over a 13.8-year follow-up period, showed a marginal increase in the 'MAFLD' group (2.49 [0.99-6.23], P = 0.052) compared to the 'MA without fatty liver' group. **Conclusion:** The 'MAFLD' group did not demonstrate an elevated risk of all-cause, cardiovascular, or cancer mortality when compared to the 'MA without fatty liver' group. However, there was a trend toward an increased risk of liver-related mortality in the MAFLD group.


Overweight/obesity
More than two metabolic risk abnormalities
Type 2 diabetes mellitus
"Metabolic dysfunction-association (MA)"
Fatty liver (+) (MAFLD)
vs.
Fatty liver (−) (MA without fatty liver)
No significant difference in all-cause, cardiovascular, cancer mortality

Mortality	Hazard ratio (95% CI)*	P-value
All-cause mortality	1.07 (0.99-1.16)	0.100
Cancer mortality	1.080 (0.86-1.36)	0.508
Cardiovascular mortality	0.89 (0.78-1.02)	0.084
Diabetes mellitus-related mortality	1.61 (0.98-2.65)	0.059
Other mortality (including liver-related mortality)	1.36 (1.14-1.62)	0.001
Liver-related mortality**	2.49 (0.99-6.23)	0.052

*Adjusted for age, sex, race, marital status, education, ever-smoking, heavy alcohol consumption, exercise, hypertension, diabetes, hyperlipidemia, waist circumference and body mass index
**Follow-up until 2006

Disclosures: Z. Gordon Gordon Jiang – Olix: Advisor, No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
Ju Dong Yang – AstraZeneca: Consultant, No, No; Eisai: Consultant, No, No; Exact Sciences: Consultant, No, No; Exelixis: Consultant, No, No; Fujifilm Medical Sciences: Consultant, No, No; Merck: Consultant, No, No;
The following people have nothing to disclose: Min-Sun Kwak, Hyunseok Kim, Mazen Noureddin

2179-A | FIRST RESULTS OF THE EVOLUTION AND THE INFLUENCE OF STATIN TREATMENT ON NAFLD IN A PRIMARY CARE COHORT OVER A 2-YEAR PERIOD

Leen Heyens[1,2,3], Wouter Robaeys[2], Liesbet Vernijns[4], Anneleen Robaeys[5], Sven Francque[6] and Geert Robaeys[2], (1)Ziekenhuis Oost-Limburg, (2)Hasselt University, (3)Maastricht University, (4)Huisartsenbox, (5)Huisartsenpraktijk Termolen, (6)University of Antwerp, Edegem, Belgium

Background: Non-alcoholic fatty liver disease (NAFLD) has become the most frequent cause of chronic liver disease. Non-alcoholic fatty liver can evolve into non-alcoholic steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. Data concerning the evolution of NAFLD in a primary care continuum remain scarce. As a therapeutic option, besides lifestyle changes, statins might influence the evolution of steatosis or fibrosis.

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

Disclosures: Sven Francque – Inventiva: Consultant, No, No; Eisai: Consultant, No, Yes; Siemens Healthcare: Speaking and Teaching, No, Yes; Novo Nordisk: Speaking and Teaching, No, Yes;

The following people have nothing to disclose: Leen Heyens, Wouter Robaeys, Liesbet Vernijns, Anneleen Robaeys, Geert Robaeys

2180-A | FOOD INSECURITY IS ASSOCIATED WITH LOWER NAFLD PREVALENCE BUT GREATER LIVER FIBROSIS IN PEOPLE WITH HIV

Ani Kardashian, University of Southern California, Los Angeles, CA, Audrey Lloyd, University of Alabama at Birmingham Heersink School of Medicine, Eduardo Vilar-Gomez II, Indiana University School of Medicine, Susanna Naggie, Duke Clinical Research Institute, Durham, NC, Mark S Sulkowski, Johns Hopkins University School of Medicine, Division of Infectious Diseases, Tinsay A. Woreta, Johns Hopkins Medicine, Baltimore, MD, Jordan E. Lake, University of Texas - Houston, Holly Crandall, Indiana University, Rohit Loomba, University of California, San Diego, San Diego, CA, Laura Wilson, Johns Hopkins School of Public Health, Richard K. Sterling, Virginia Commonwealth University Health System, Sonya Heath, University of Alabama at Birmingham, Naga P. Chalasani, Indiana University Medical Center, Indianapolis, IN and Jennifer C. Price, University of California, San Francisco

Background: Food insecurity, defined as the economic or social condition of limited or uncertain access to nutritionally adequate foods, is a growing public health problem in the US. In recent years, it has emerged as a risk factor for nonalcoholic fatty liver disease (NAFLD) and advanced liver fibrosis in the general population. However, little is known about the impact of food insecurity on liver disease in people with HIV (PWH). We aimed to examine associations between food insecurity and NAFLD and liver fibrosis prevalence in a diverse multicenter cohort of PWH. **Methods:** PWH aged 20 years on suppressive antiretroviral therapy, HIV RNA < 200 copies/mL, and without chronic viral hepatitis or other known cause of liver disease were screened for NAFLD and fibrosis by vibration controlled transient elastography at 8 US centers. NAFLD was defined as CAP ≥ 263 decibels/m in the absence of self-reported heavy alcohol use and advanced fibrosis was defined as liver stiffness measurement (LSM) ≥ 10 kPa. Food security was measured using the validated Six-Item Short Form US Household Food Security Survey Module, and participants were categorized as being food secure or food insecure. We used multivariable logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) of NAFLD and advanced fibrosis by food security status. **Results:** Among 570 PWH, mean age was 54 years, 410 (72%) were male, 26% White, 49% Black, 21% Hispanic, 267 (47%) had BMI ≥ 30 kg/m^2, and 171 (30%) were diabetic. NAFLD was present in 306 (54%) and advanced fibrosis in 45 (8%) of participants. Food insecurity was present in 175 (31%) of the entire cohort, 84 (27%) of those with NAFLD, and 21 (47%) of those with advanced fibrosis. Among the entire cohort, participants who were food insecure were less likely to have type 2 diabetes (25% vs 32%) and undetectable HIV-1 RNA (76% vs 85%) compared to those who were food secure ($P < 0.05$ for all) but there were no differences in age, body mass index (BMI), or race and ethnicity. In a fully covariate-adjusted analysis, food insecurity was associated with a lower risk of NAFLD (OR = 0.51 [95% CI: 0.31-0.83], $P < 0.01$) (Table). By contrast, food insecurity was associated with a higher risk of advanced fibrosis among the entire cohort (OR = 2.32 [95% CI: 1.15-4.67], $P = 0.02$) after adjustment for age, sex, race and ethnicity, BMI, physical activity, and education level (Table). **Conclusion:** Food insecurity is highly prevalent among adult PWH and is associated with a lower risk of NAFLD but a greater risk of advanced fibrosis. Our findings suggest that food insecurity in PWH may contribute to hepatic fibrosis through mechanisms other than hepatic steatosis. Further studies are needed to confirm our observations and to better understand their mechanisms and implications.

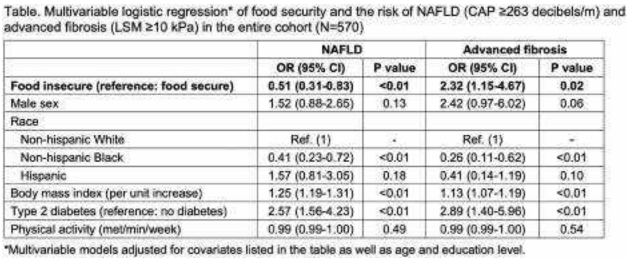


Table. Multivariable logistic regression* of food security and the risk of NAFLD (CAP ≥263 decibels/m) and advanced fibrosis (LSM ≥10 kPa) in the entire cohort (N=570)

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

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

Disclosures: Rohit Loomba – Aardvark Therapeutics: Consultant, No, No; Altimmune: Consultant, No, No; Anylam/Regeneron: Consultant, No, No; Amgen: Consultant, No, No; Arrowhead Pharmaceuticals: Consultant, No, No; AstraZeneca: Consultant, No, No; Bristol-Myer Squibb: Consultant, No, No; CohBar: Consultant, No, No; Eli Lilly: Consultant, No, No; Galmed Pharmaceuticals: Consultant, No, No; Gilead: Consultant, No, No; Glympse Bio: Consultant, No, No; Hightide: Consultant, No, No; Inipharma: Consultant, No, No; Intercept: Consultant, No, No; Inventiva: Consultant, No, No; Ionis: Consultant, No, No; Janssen Inc.: Consultant, No, No; Madrigal Pharmaceuticals: Consultant, No, No; Metacrine, Inc.: Consultant, No, No; NGM Biopharmaceuticals: Consultant, No, No; Novartis: Consultant, No, No; NovoNordisk: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Sagimet Biosciences: Consultant, No, No; Theratechnologies: Consultant, No, No; 89 bio: Consultant, No, No; Terns Pharmaceuticals: Consultant, No, No; 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Terns Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; LipoNexus Inc.: Executive role , No, No; Jennifer C. Price – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), Yes, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Abbvie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), Yes, No; Genentech: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, Yes; Zydus: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; VIR: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No;

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

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

Tamoor Afzaal, David Hudson, Mohammad Qasim Khan, Karim Mohammed Qumosani and Anouar Teriaky, Western University

Background: It is estimated 1.5 billion people worldwide have some element of chronic liver disease (CLD) or cirrhosis.[1] Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of CLD, affecting up to 30% of the world population.[1,2] It is well known cirrhosis is the strongest risk factor for the development of hepatocellular carcinoma. However, several studies have shown the association of NAFLD and the development of extra hepatic malignancies, specifically an increased risk of gastrointestinal malignancies.[2-5] The aim of this study was to determine the incidence of gastrointestinal malignancies (esophagus, gastric, colorectal, pancreatic) for patients with NAFLD compared to controls without NAFLD using an adult inpatient population. **Methods:** Using a population based retrospective study design, we analysed data from the United States Nationwide Inpatient Sample (NIS) database for 2013. Using validated International Classification of Diseases, Ninth Revision (ICD-9) codes we identified inpatients 18 years or older with NAFLD and a diagnosis of a gastrointestinal malignancy (esophagus, gastric, colorectal, pancreatic). We then compared that cohort to adult inpatients without NAFLD. We adjusted for multiple confounders (age, payer type, location, hypertension, dyslipidemia, obesity, type 2 diabetes mellitus, chronic kidney disease, smoking, alcohol and cirrhosis) and performed a multivariable logistic regression analysis to evaluate the impact of NAFLD on gastrointestinal related malignancies. **Results:** Utilizing the NIS database we were able to identify 36,597,790 potential patients to include in the study. 235,035 patients had NAFLD and a gastrointestinal malignancy while 36,362,755 patients were in the control group. The average age of the NAFLD group was 54.91 and non-NAFLD was 57.37. The NAFLD group had 56.9% females while the non-NAFLD group had 59.1%. Majority of patients in both groups were white, 70.9% in the NAFLD group and 68.6% in the control group. Patients with NAFLD had a higher incidence of gastric cancer (odds ratio [OR]: 1.25, 95% confidence interval [CI]: 1.01-1.55), colon cancer (OR: 1.14, 95% CI: 1.05-1.25), and pancreatic cancer (OR: 1.51, 95% CI: 1.30-1.77). There was no significant difference between the two groups for rectal cancer (OR: 0.94, 95% CI: 0.78-1.12), esophageal cancer (OR: 0.91, 95% CI: 0.69-1.18) and hepatic cancer (OR: 1.11, 95% CI: 0.97-1.27). **Conclusion:** Using a large database, when compared to controls, patients with non-alcoholic fatty liver disease had an increased incidence of gastric, colonic and pancreatic malignancies but no difference in rectal, esophageal and hepatic malignancies.

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2182-A | GLYCEMIC CONTROL TARGET ASSOCIATED WITH A LOWER RISK OF LIVER-RELATED AND CARDIOVASCULAR EVENTS IN NONALCOHOLIC FATTY LIVER DISEASE

Nobuharu Tamaki[1], Shunichi Wakabayashi[2], Takefumi Kimura[2], Yutaka Yasui[1], Kaoru Tsuchiya[1], Hiroyuki Nakanishi[1], Daniel Q Huang[3], Takeji Umemura[2], Masayuki Kurosaki[1] and Namiki Izumi[1], (1)Musashino Red Cross Hospital, (2)Shinshu University Hospital, Matsumoto, Japan, (3)National University Health System (NUHS)

Background: Optimizing glycemic control in diabetes mellitus may prevent liver-related events and major adverse cardiovascular events (MACE) in patients with nonalcoholic fatty liver disease (NAFLD). However, the hemoglobin A1c (HbA1c) threshold associated with a lower complication rate is unknown. In this nationwide population-based cohort study, we investigated the association between HbA1c levels and these complications. **Methods:** We investigated a nationwide large claim database from 2016 to 2021 and identified 633,295 patients with NAFLD with mean 4.2 years follow-up. HbA1c levels were measured annually with mean 4.26 times and the mean HbA1c value was used for analyses. The *primary endpoint* was the incidence of liver-related events and MACE, and the optimal HbA1c level associated with a lower incidence of complications was determined. **Results:** The 5-year incidence of liver-related events in patients with the mean HbA1c of < 6.0%, 6.0-6.9%, 7.0-7.9%, 8.0-8.9%, and **e** 9.0% were 0.04%, 0.07%, 0.17%, 0.16%, and 0.15%, respectively, and those of MACE were 0.38%, 0.73%, 1.0%, 1.3%, and 2.2%, respectively. Multivariable analyses demonstrated that adjusted hazard ratios (HR, 95% confidence interval [CI]) of HbA1c (per 1%) for liver-related events and MACE were 1.26 (1.12-1.42) and 1.36 (1.32-1.41), respectively. When compared to patients with < 6.0%, adjusted HRs (95% CI) in patient with HbA1c levels of 6.0-6.9%, 7.0-7.9%, 8.0-8.9%, and **e** 9.0% were 1.28 (0.9-1.7), 2.34 (1.7-3.5), 2.79 (1.6-5.0), and 3.52 (1.8-7.0) for liver-related events, and were 1.25 (1.1-1.4), 1.68 (1.5-1.9), 2.33 (1.9-2.8), and 4.11 (3.4-5.0) for MACE. The risk of liver-related events and MACE increased in a dose-dependent fashion with an increase in HbA1c. A HbA1c level of 7% was selected as the optimal threshold for predicting liver-related events and MACE. Adjusted HRs (95% CI) of HbA1c **e** 7.0% compared to < 7.0% for liver-related events and MACE were 2.40 (1.79-3.22) and 1.98 (1.78-2.19), respectively. **Conclusion:** HbA1c of 7% was the optimal threshold associated with a lower incidence of complications and be utilized as a target for glycemic control in patients with NAFLD.

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2183-A | HEALTH CARE RESOURCE UTILIZATION AND COST BURDEN OF HIGH DISEASE SEVERITY IN US ADULTS WITH NONALCOHOLIC STEATOHEPATITIS: A RETROSPECTIVE COHORT STUDY

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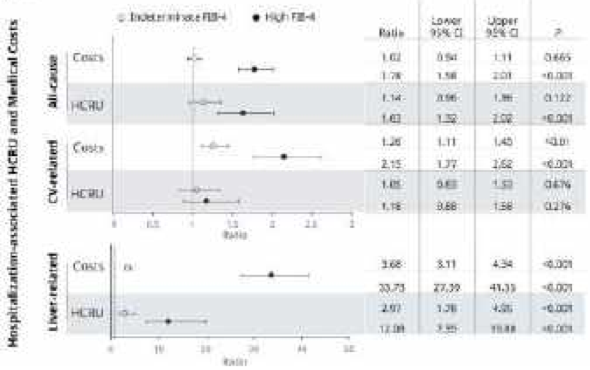
Background: Nonalcoholic steatohepatitis (NASH) is the progressive, inflammatory form of non-alcoholic fatty liver disease. Recent professional society guidance recommends noninvasive initial screening for more severe disease with fibrosis-4 index (FIB-4) scores; thus, it is important to understand whether health care resource utilization (HCRU) varies with FIB-

4 score. This study aimed to assess and compare the economic and HCRU burdens of NASH in adults aged **e** 18 years, stratified by disease severity based on FIB-4. **Methods:** This observational, retrospective study utilized the Healthcare Integrated Research Database (HIRD®), which contains health care claims data for commercially insured and Medicare Advantage health plan members from 14 geographically diverse plans across the United States. Primary outcomes were all-cause, cardiovascular (CV)-related, and liver-related medical costs and HCRU associated with hospitalization stratified by FIB-4 score in patients with **e** 2 diagnoses of NASH during the patient identification period (October 1, 2016, to May 31, 2022). Generalized linear regression with negative binomial and gamma distribution models were used to compare HCRU and costs, respectively, by disease severity while controlling for confounders. **Results:** The cohort included a total of 5104 patients with NASH and was composed of 3162, 1343, and 599 patients with low, indeterminate, and high FIB-4 scores, respectively. After adjustment, the rate of all-cause HCRU was significantly higher in the high FIB-4 group when compared with the low FIB-4 group reference (rate ratio, 1.63; 95% CI, 1.32-2.02; $P < 0.001$). No significant differences in the rate of CV-related HCRU were observed; however, the CV-related cost ratio was 1.26 (95% CI, 1.11-1.45; $P < 0.01$) in the indeterminate group and 2.15 (95% CI, 1.77-2.62; $P < 0.001$) in the high FIB-4 group. Patients with indeterminate and high FIB-4 scores were 2.97 (95% CI 1.78-4.95) and 12.08 (95% CI 7.35-19.88) times more likely to utilize liver-related health care resources and 3.68 (95% CI 3.11-4.34) and 33.73 (95% CI 27.39-41.55) times more likely to incur liver-related costs, respectively ($P < 0.001$ for all). **Conclusion:** Compared with patients with NASH with low FIB-4 scores, those with indeterminate and high FIB-4 scores were more likely to utilize liver-related healthcare resources and incur higher CV- and liver-related costs after controlling for confounders.

HCRU and medical costs associated with hospitalization for patients with indeterminate and high FIB-4 scores vs patients with low FIB-4 scores. Incidence rate ratios (IRR) of HCRU and costs ratios after adjustment are shown. The low FIB-4 reference is represented by a vertical dashed line. Error bars represent the 95% CI values. Open circles represent indeterminate FIB-4 IRR and costs ratios, and filled circles represent high FIB-4 IRR and costs ratios.



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2184-A | HIERARCHICAL CONTRIBUTION OF COMPONENTS OF METABOLIC SYNDROME TO THE PROGRESSION OF NONALCOHOLIC FATTY LIVER DISEASE

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Background: Metabolic syndrome (MetS) is characterized by the presence of three or more of the following five cardiometabolic risk factors: large waist, impaired fasting glucose/diabetes, low high-density lipoprotein, hypertriglyceridemia, and hypertension. Patients with MetS have greater risk of developing the more severe forms of nonalcoholic fatty liver disease (NAFLD), such as advanced fibrosis, nonalcoholic steatohepatitis (NASH), and hepatocellular carcinoma. In this study, we evaluated the effect of MetS and its components, as well as baseline histology, on the progression and regression of NAFLD. **Methods:** We conducted a multi-center prospective cohort study using the NASH Clinical

Research Network (NASH CRN)'s noninterventional registry (2002-2022). We included patients **e** 18 years with biopsy-proven NAFLD who had paired biopsies **e** 1 year apart and no missing data on MetS. Outcomes included histological progression or regression defined by NAFLD activity score (NAS), NASH or fibrosis using predefined criteria. Crude incidence rate (IR) was compared among groups with versus without MetS or individual components using Kaplan-Meier curves and the log-rank test. Cox proportional hazard models were used to estimate the effect of MetS on fibrosis progression/regression, adjusted for patient demographics and baseline histology. **Results:** Of the 452 patients followed for 4.3 (range: 1-15.6) years, mean age was 51 years, one-third were male, and 85% were White. At baseline, patients with MetS, large waist circumference or impaired glucose/diabetes had worse ballooning and fibrosis scores and were more likely to have definite NASH than those without, while patients with hypertension had a higher prevalence of advanced fibrosis (F **e** F2) than those without. MetS was not associated with any outcomes in either adjusted or unadjusted models. In adjusted model, impaired glucose/diabetes was associated with a higher risk for fibrosis progression (aHR = 1.61; 95% CI: 1.11-2.34) while hypertension was associated with a lower risk (aHR = 0.64; 95% CI: 0.43-0.96). No other components were associated with the outcomes. **Conclusion:** In this NASH CRN patient cohort, MetS was not a risk factor for fibrosis progression or regression, but impaired glucose/diabetes was associated with increased progression and hypertension with decreased progression. Further studies are needed to understand the mechanism underlying the impact of hypertension on fibrosis progression in NAFLD patients.

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Disclosure information not available at the time of publication: Moosa Tatar, Michael Rothberg, Laura Wilson, Daniela Allende, Brent Neuschwander-Tetri, James Tonascia

2185-A | HIGHER ULTRA-PROCESSED FOOD INTAKE WAS POSITIVELY ASSOCIATED WITH ODDS OF NAFLD IN BOTH US ADOLESCENTS AND ADULTS: A NATIONAL SURVEY

Longgang Zhao[1], Xinyuan Zhang[1], Euridice Martinez Steele[2], Chun-Han Lo[3], Fang Fang Zhang[4] and Xuehong Zhang[1,5], (1)Brigham and Women's Hospital, Harvard Medical School, (2)University of São Paulo, (3) University of Nevada, (4)Tufts University, (5)Harvard T.H. Chan School of Public Health

Background: The influence of consumption of ultra-processed foods (UPF) on non-alcoholic fatty liver diseases (NAFLD) remains poorly understood. Related evidence for adult NAFLD is limited and no study has yet evaluated adolescent NAFLD. **Methods:** We conducted a study among 806 adolescents and 2,734 adults who participated in the National Health and Nutrition Examination Survey (2017-2018). UPF intake was estimated using the dietary data collected by two 24-hour dietary recalls. NAFLD was defined by transient elastography. Logistic regression was used to estimate the multivariable odds ratio (OR) and 95% confidence intervals (CI) for associations between UPF consumption and NAFLD with survey weight adjustments. **Results:** The mean consumption of UPF was 812 grams/day for adolescents and 823 grams/day for adults. A total of 12.4% among adolescents and 35.6% of the participants among adults had NAFLD. Higher UPF intake was associated with higher odds of NAFLD in both adolescents ($OR_{\text{Quintile 5 vs Quartile 1}}=2.34$, 95% CI = 1.01-5.41, $P_{\text{trend}}=0.15$) and adults ($OR_{\text{Quintile 5 vs Quintile 1}}=1.78$, 95% CI = 1.04-3.03, $P_{\text{trend}}=0.002$). In adults, about 68% and 71% of the association between UPF intake and NAFLD was mediated by body mass index and waist circumference (all P values < 0.001), respectively. We also found higher UPF intake was positively associated with serum levels of albumin and C-reactive protein in adults. Results were similar for adolescents though not statistically significant. **Conclusion:** Higher UPF intake was associated with higher odds of having NAFLD among both adolescents and adults. These associations are largely mediated by elevated body fatness. Further prospective studies are needed to confirm our findings. If confirmed, reducing UPF intake might help prevent NAFLD in both adolescents and adults.
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2186-A | HISTOLOGICAL CLASSIFICATIONS AND PREDICTION OF LIVER-RELATED EVENTS : RESULTS FROM THE MULTICENTRIC, EUROPEAN, HEPATIC OUTCOMES AND SURVIVAL FATTY LIVER REGISTRY (HOTSURFR) STUDY

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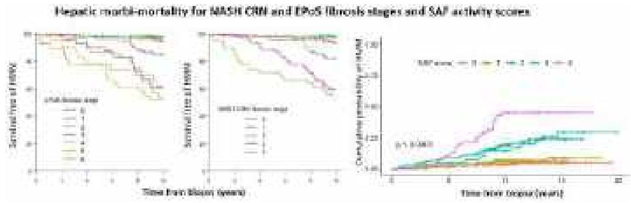
Background: NASH trials assume that histological classifications predict hepatic events. We evaluated the diagnostic performance of the new European EPoS staging and SAF grading systems. **Methods:** Patients from 7 European centers biopsied for suspected NAFLD before 2011 and with long-term follow-up were scored by the NASHCRN and the EPoS 7 tier (1 minimal fibrosis, 2: portal/periportal fibrosis, 3:early bridging, 4: advanced bridging, 5 early cirrhosis, 6 advanced cirrhosis) staging systems by a central pathologist. Activity was scored by NAS and SAF grading. Hepatic morbimortality (HMM) was a composite of liver-related death, occurrence of cirrhosis, cirrhosis decompensation events. Overall mortality, primary liver cancer (PLC), cardiovascular events (CVE) and extra-hepatic malignancies (EHM) were recorded. Median follow-up was calculated by reverse Kaplan-Meier. Incidence rates were compared using log-rank test and univariate and multivariate Cox proportional hazard models were used to estimate hazard ratios (HR) for each outcome. **Results:** 711 patients were included: 63% males, mean age 52 yrs, BMI 30.1 kg/m², diabetes 36%, arterial hypertension 59%, dyslipidemia 54%, daily alcohol 0-5 g: 84%, 5-20/30 g: 13%, moderate (20/30-50 g): 3%, active smokers 19%. Prevalence of fibrosis stages was: NASH CRN, F0:45%, F1:24%, F2:11%, F3:14%, F4:6% and EPoS, F0:48%, F1:20%, F2:11.5%, F3:6.5%, F4:4%, F5:6%, F6:4%. Median follow-up was 11.12 yrs (0.1-20). 84 pts died (11.8%), 92 pts developed HMM (12.9%), 32 PLC (4.5%), 72 CVE (10.1%) and 80 EHM (11.3%). The 5 and 10 yr incidence of HMM was 4.8% (3.2-6.4) and 12.7% (10-15), and that of all-cause death 2.9%(1.6-4.1) and 9.3% (7-11.5). In multivariable analysis, age, diabetes, arterial hypertension and moderate alcohol consumption were associated with an increased risk of HMM. After adjustment for clinical variables and NAS, fibrosis stage was associated with HMM: HRs *vs stage 0 were,* for NASH CRN: F1: 3.06; F2: 11.04; F3: 21.1; F4: 21.2, for EPoS: F1: 2.3; F2: 8.3; F3: 19.8; F4: 18.1; F5+6: 21.7. Both staging systems had similar calibration and discrimination Harrell's C index (0.84). AUROCs for cumulative incidence of HMM at 5 yrs was 0.83 and at 10 yrs 0.86. Both were significantly associated with overall survival, PLC, CVE and EHM. SAF histological activity was associated with HMM starting grade 2 ($p < 0.001$). Steatohepatitis stage 2-4 (but not 0-1) by EPOS and cirrhosis (5-6 by EPOS) were significantly associated with HMM. Only cirrhosis was associated with CVE. Baseline FIB4 risk strata were significantly associated with HMM, overall survival, PLC, cardiovascular events but not EHM. **Conclusion:** This large multicentric cohort demonstrated the prognostic value of the EPoS classification. Fibrosis starting stage 1 (NASH CRN) or stage 2 (EPoS) and activity grade predicted hepatic events.



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

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f 2187-A | HISTOLOGICALLY ASSESSED FIBROSIS IS THE MAIN DETERMINANT OF PROGNOSIS IN PATIENTS IN NAFLD

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Background: Previous studies showed that fibrosis stage predicts all-cause and disease specific mortality in patients with NAFLD. Here we aim to study whether the presence non-alcoholic steatohepatitis (NASH) adds prognostic information to different fibrosis stage groups. **Methods:** We conducted an individual participant data meta-analysis of patients with NAFLD who had baseline biopsy. NASH was defined as NAFLD activity score e 4 with score of at least 1 for steatosis, lobular inflammation, and ballooning. The primary

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

outcome was a composite endpoint of all-cause mortality, cirrhosis decompensation (ascites, variceal haemorrhage, hepatic encephalopathy), hepatocellular carcinoma, liver transplantation or progression to a model of end stage liver disease score **e** 15. Study-specific cumulative hazard functions and derived aggregated survival curves were built for F0-1, F2-4 without and with NASH. We further stratified the histologically assessed fibrosis groupings to: F0-1, F2-3 without and with NASH, F4 without and with NASH. **Results:** Data from 29 studies and 2,518 participants with biopsy proven NAFLD were included in the analysis (45% females, median age 54 (IQR 19) years, 46% with type II diabetes mellitus) 48% with NASH. The primary outcome was reached in 5.8% (n = 145) after a median follow-up of 58 months. The presence of NASH did not add prognostic information to the group of patients with F2-4 fibrosis, but those with F2-4 fibrosis had worse outcomes that those with fibrosis F0-1 (study-stratified log-rank tests, p < 0.001; Figure 1a), however, similar probabilities of reaching the composite endpoint were observed within patient groups with F2-4 irrespective of the presence of NASH. When histologically assessed fibrosis was further stratified to F0-1, F2-3 and F4, the presence of NASH did not add prognostic information to those with F2-3 fibrosis, and seemed to have a protective effect on those with cirrhosis (Figure 1b). **Conclusion:** The presence of NASH remains important for diagnostic purposes, however does not appear to add prognostic information to fibrosis stage. In the context of cirrhosis, absence of NASH indicates more advanced disease with worse prognosis.

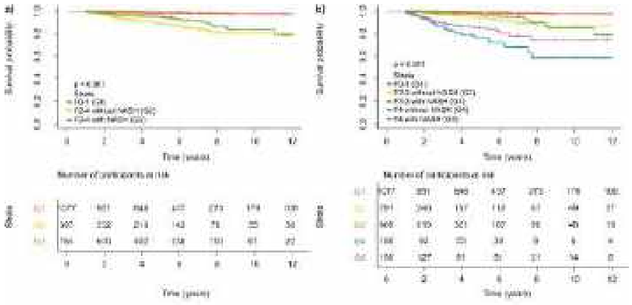

Figure 1 Estimates of survival probabilities for participant groups stratified by histologically assessed fibrosis: (a) F0-1 vs F2-4 with or without NASH and (b) F0-1 vs F2-3 with and without NASH vs F4 with and without NASH. P-values correspond to the outcome of the study-stratified log-rank test.

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2188-A | HOSPITALIZATION OUTCOMES AND READMISSION RATES IN NASH CIRRHOSIS WITH TYPE II DIABETES MELLITUS: A POPULATION-BASED STUDY

Adnan Malik, Midwestern University, Waseem Amjad, Harvard University Medical School, Syed Hammad Rahman, Methodist Houston, Manpreet Bains, Saint Joseph Medical Center and Shailendra Singh, West Virginia University School of Medicine

Background: Non-Alcoholic Steatohepatitis (NASH) has a bidirectional relationship with diabetes mellitus. NASH-related cirrhosis is the one of the leading cause of liver transplantation. Our study aims to investigate hospital resource utilization in hospitalized patients with NASH cirrhosis and type 2 Diabetes Mellitus (DMII). **Methods:** We identified adult patients with NASH cirrhosis through the ICD-9 and ICD-10 CM diagnosis codes for the primary discharge diagnosis in the national readmission database (NRD) for 2010-2017. The inclusion criteria for index admissions include adult patients(age $>$ 18 y), non-elective admissions, NASH, and cirrhosis. We excluded the patients who were admitted in December or other causes of cirrhosis (Alcohol liver disease, Hepatitis B virus, Hepatitis C virus, Autoimmune Hepatitis, Hemochromatosis, Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, and Wilson's disease) and Type I Diabetes Mellitus. Outcomes of NASH cirrhosis in relationship with DMII was computed in a multivariate model adjusted for age, gender, comorbid conditions and hepatic decompensatory events. **Results:** 1,960,205 hospitalizations for NASH cirrhosis were identified from 2010 to 2017. Out of these, a total of 958,838 (48.9%) patients had a DMII, while 1,001,368 (51.08%) did not have DMII. Diabetes prevalence in the NASH cirrhotic population has been slowly trending up from 48% to 52% from 2010 to 2017. DMII were elder (66.1 ± 11.4 vs 63.6 ± 14.3, $p < 0.001$) and had more presentation of female (52.8% vs. 46.8%. $p < 0.001$) than non-diabetes. Prevalence of obesity, heart disease and chronic kidney disease was higher in DMII.DMII in NASH cirrhosis was

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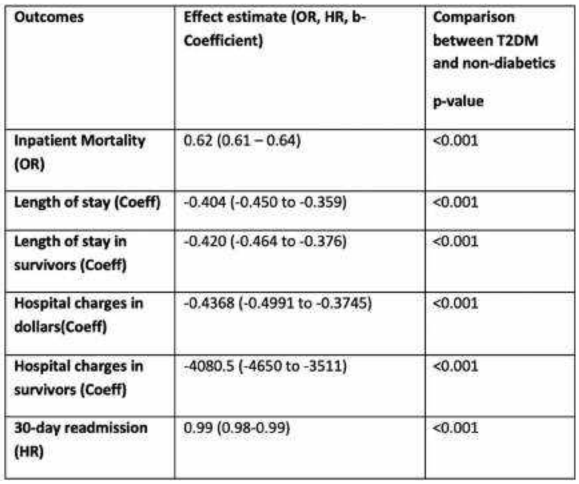
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

associated with lower 30-day readmission (Hazard Ratio (HR) 0.99 (Confidence Interval 0.98-0.99), $P < 0.001$) and in hospital mortality (Odds ratio [OR]: 0.62, 95% CI: (0.61 – 0.64), $p < 0.001$). The first three common causes of re-admission in the DMII group were Cirrhosis related complications, Sepsis, and Acute Kidney Injury (AKI).The length of hospital stay (β: -0.404 (-0.450 to -0.359), $p < 0.001$) for the DMII group was statistically significantly shorter. The median cost of hospitalization (β:33,797 (18,479 – 64,872)], $p < 0.001$) for the DMII group was significantly lower than the non-DMII group. **Conclusion:** DMII prevalence is increasing in NASH cirrhosis and these patients have high comorbidity index. These patients have a lower risk of 30-day readmission and lower mortality compared to patients without diabetes. The median cost of hospitalization and length of stay was also statistically significantly lower. The most common cause for readmission, second to cirrhosis-related complications was sepsis. Also, we think the clinical outcomes are better in the diabetic NASH cirrhotic population due to improved outpatient care and follow-ups.

Table 2: Primary outcomes and association with type 2 diabetes mellitus in NASH cirrhosis (Multivariate)



Outcomes	Effect estimate (OR, HR, b-Coefficient)	Comparison between T2DM and non-diabetics p-value
Inpatient Mortality (OR)	0.62 (0.61 – 0.64)	<0.001
Length of stay (Coeff)	-0.404 (-0.450 to -0.359)	<0.001
Length of stay in survivors (Coeff)	-0.420 (-0.464 to -0.376)	<0.001
Hospital charges in dollars(Coeff)	-0.4368 (-0.4991 to -0.3745)	<0.001
Hospital charges in survivors (Coeff)	-4080.5 (-4650 to -3511)	<0.001
30-day readmission (HR)	0.99 (0.98-0.99)	<0.001

Disclosures: The following people have nothing to disclose: Adnan Malik, Waseem Amjad
Disclosure information not available at the time of publication: Syed Hammad Rahman, Manpreet Bains, Shailendra Singh

2189-A | HYPERFERRITINEMIA PREDICTS NON-ALCOHOLIC FATTY LIVER DISEASE AND SIGNIFICANT FIBROSIS IN PATIENTS WITH TYPE 2 DIABETES

Maral Amangurbanova[1], Daniel Q Huang[1], Kaleb Tesfai[1], Ricki Bettencourt[1], Harris Siddiqi[1] and Rohit Loomba[2], (1)University of California, San Diego, (2) University of California, San Diego, San Diego, CA

Background: Elevated levels of serum ferritin, a marker of hepatic iron overload and inflammation, may be associated with non-alcoholic fatty liver disease (NAFLD) and insulin resistance. However, this relationship remains unclear in patients with type 2 diabetes mellitus (T2DM) and hyperferritinemia. Therefore, we aimed to determine the prevalence of NAFLD and significant hepatic fibrosis among patients with T2DM and hyperferritinemia. **Methods:** This is a cross-sectional analysis of a prospective cohort of 523 adults (64% female) aged 50–80 years old with T2DM and without a diagnosis of hemochromatosis. NAFLD and significant fibrosis were defined as magnetic resonance imaging-proton density fat fraction (MRI-PDFF) **e** 5% and magnetic resonance elastography (MRE) **e** 3.0 kPa, respectively. Hyperferritinemia was defined as serum ferritin **e** 200 µg/L in females or **e** 300 µg/L in males. The prevalence of NAFLD and significant fibrosis were compared between patients with and without hyperferritinemia. A logistic regression analysis was used to assess the association between serum ferritin and NAFLD. **Results:** The mean age and body mass index (BMI) were 64.1 (±8.1) years and 31.5 (±5.9) kg/m^{2,} respectively. The overall prevalence of hyperferritinemia was 20.5% (N = 107). Patients with hyperferritinemia were more likely to be younger, Asian, and have a longer duration of T2DM, compared to those without hyperferritinemia. Hyperferritinemia was associated with higher aspartate transaminase (AST), alanine aminotransferase (ALT), bilirubin, albumin, hemoglobin, and low-density lipoprotein cholesterol (LDL-C) levels.The median (IQR) MRI-R2* (60.90 [51.67, 72.01] s^{-1} Hz vs 46.22 [41.23, 51.41] s^{-1} Hz, $P < 0.001$), MRI-PDFF (11.23% [5.75, 18.32] vs 7.21% [3.33, 13.06], $P < 0.001$), MRE (2.48 [2.12, 3.31] kPa vs 2.32 [2.02, 2.83] kPa, $P = 0.043$) and vibration-controlled transient elastography (VCTE) (6.70 [4.70, 9.50] kPa vs 5.60 [4.40, 7.90], $P = 0.003$) were higher in participants with hyperferritinemia, compared to those without hyperferritinemia. The prevalence of NAFLD (78.5% vs 62.1%, $P = 0.001$) and significant fibrosis (35.5% vs 22.1%, $P = 0.002$) were higher in patients with hyperferritinemia compared to those without hyperferritinemia (Figure 1). Hyperferritinemia remained an independent predictor of NAFLD (OR 2.01, 95% CI 1.19-3.39, $P = 0.009$) and significant fibrosis (OR 2.33, CI 1.43-3.77, $P = 0.001$), even after adjustment for age, sex, obesity, and insulin use. **Conclusion:** The presence of hyperferritinemia is associated with a substantially higher risk of NAFLD and significant fibrosis. Hyperferritinemia may be a useful biomarker for NAFLD and significant fibrosis in people with T2DM.

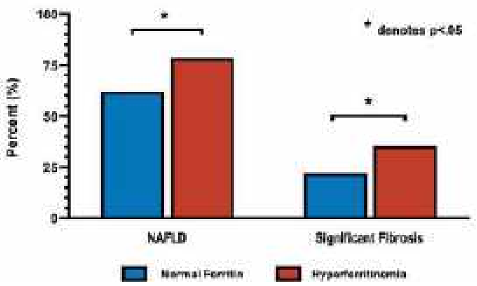


Figure 1: Prevalence of NAFLD and significant fibrosis, stratified by the presence of hyperferritinemia

Disclosures: Rohit Loomba – Sagimet Biosciences: Consultant, No, No; Pfizer: Consultant, No, No; Merck: Consultant, No, No; NovoNordisk: Consultant, No, No; Novartis: Consultant, No, No; NGM Biopharmaceuticals: Consultant, No, No; Metacrine, Inc.: Consultant, No, No; 89 bio: Stock – privately held company (individual stocks and stock options), No, No; Ionis: Consultant, No, No; Inventiva: Consultant, No, No; Intercept: Consultant, No, No; Inipharma: Consultant, No, No; Hightide: Consultant, No, No; Glympse Bio: Consultant, No, No; Galmed Pharmaceuticals: Consultant, No, No; Eli Lilly: Consultant, No, No; CohBar: Consultant, No, No; Bristol-Myer Squibb: Consultant, No, No; AstraZeneca: Consultant, No, No; Arrowhead Pharmaceuticals: Consultant, No, No; Sagimet Biosciences: Stock – privately held company (individual stocks and stock options), No, No; Altimmune: Consultant, No, No; Aardvark Therapeutics: Consultant, No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; 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89 bio: Consultant, No, No; Terns Pharmaceuticals: Consultant, No, No; Viking Therapeutics: Consultant, No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Hanmi: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Inventiva: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Ionis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Janssen Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Madrigal Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Amgen: Consultant, No, No; Anylam/Regeneron: Consultant, No, No; Madrigal Pharmaceuticals: Consultant, No, No; Janssen Inc.: Consultant, No, No; Theratechnologies: Consultant, No, No; Gilead: Consultant, No, No; Sonic Incytes: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Galmed Pharmaceuticals: Grant/Research Support

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

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The following people have nothing to disclose: Maral Amangurbanova, Daniel Q Huang, Kaleb Tesfai, Ricki Bettencourt, Harris Siddiqi

2190-A | IMPACT OF ANTHROPOMETRIC PARAMETERS ON OUTCOMES IN ASIANS WITH METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

Yeonjung Ha, Young Eun Chon, Joo Ho Lee and Kwan Sik Lee, CHA Bundang Medical Center, CHA University

Background: We examined the incidence and predictors of clinical outcomes in metabolic dysfunction-associated fatty liver disease (MAFLD), focusing on anthropometric parameters. **Methods:** Adult patients with MAFLD were identified in nationwide databases and a hospital cohort. Primary endpoints were atherosclerotic cardiovascular disease (ASCVD) and advanced fibrosis. Logistic and Cox regression analyses were used to analyze the association between anthropometric parameters and endpoints. **Results:** In total, 4,407 of 15,256 (28.9%) and 6,274 of 25,784 subjects (24.3%) had MAFLD in the nationwide database; of these, 403 (9.2%) and 437 (7.0%) subjects were of lean/normal weight, respectively. Compared to the overweight/obese group, the lean/normal weight group had a significantly lower muscle mass (15.0 kg vs. 18.9 kg) and hand grip strength (31.9 kg vs. 35.1 kg), and had a higher ASCVD risk (9.0% vs. 6.3% and 15.9% vs. 8.5%; Ps < 0.001). Sarcopenia (odds ratio [OR], 6.66; 95% confidence interval [CI], 1.79−24.80) and hand grip strength (OR, 0.92; 95% CI, 0.86−0.97; Ps = 0.005) were associated with the ASCVD risk in the lean/normal weight group. In a hospital cohort (n = 1,363), the ASCVD risk was significantly higher in the lean/normal weight group than in the overweight/obese group (median follow-up, 39.1 mo). Muscle mass was inversely correlated with the ASCVD risk (hazard ratio [HR], 0.72; 95% CI, 0.56−0.94); while visceral adiposity was associated advanced fibrosis (HR, 1.36; 95% CI, 1.10−1.69; Ps < 0.05). **Conclusion:** Muscle mass/strength was significantly associated with the ASCVD risk in patients with MAFLD. Visceral adiposity was an independent predictor of advanced fibrosis.
Disclosures: The following people have nothing to disclose: Yeonjung Ha, Young Eun Chon
Disclosure information not available at the time of publication: Joo Ho Lee, Kwan Sik Lee

2191-A | IMPACT OF HELICOBACTER PYLORI ERADICATION ON CLINICAL AND LABORATORY PARAMETERS IN NON-ALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE RANDOMIZED CONTROLLED TRIALS

Fouad Jaber[1], Saqr Alsakarneh[2], Azizullah Beran[3], Tala Alsharaeh[4], Abdelrahman Abdelshafi[5], Mohamed Jaber[6], Mohamed Ahmed[1], Yazan Abood[7], Kimberly Sanders[1], Adel Muhanna[2], Mir Mirzulqarnain[8], Mohammad Almeqdadi[9], Hassan Ghoz[1], Wendell K. Clarkston[2] and John H. Helzberg[10], (1)University of Missouri- Kansas City, (2)University of Missouri-Kansas City, (3)Indiana University School of Medicine, Department of Gastroenterology and Hepatology, Indianapolis, IN, (4)University of Jordan, Department of Medical Education - Faculty of Medicine, Amman, Jordan, (5)Department of Medical Education, Faculty of Medicine-Assiut University, Assiut, Egypt, (6) Department of Medical Education, Al-Azhar University-Faculty of Medicine, Gaza, Palestine, (7)Department of Internal Medicine, Rutgers New Jersey Medical School, Newark, NJ, USA., (8)University of Missouri Kansas City, Department of Gastroenterology and Hepatology, Kansas City, MO, (9)Tufts Medical Center, (10) University of Missouri Kansas City, Department of Gastroenterology and Hepatology - Saint Luke's Hospital, Department of Gastroenterology and Hepatology, Kansas City, MO

Background: Helicobacter pylori (HP) infection is associated with non-alcoholic fatty liver disease (NAFLD) and insulin resistance; however, the correlation between HP eradication and NAFLD remains controversial. This systematic review and meta-analysis examined the effect of HP treatment on clinical and laboratory parameters in NAFLD patients. **Methods:** We conducted a literature search of PubMed, Embase, Scopus, and Web of Science databases through October 2022 for randomized controlled trials (RCTs) examining the effect of HP treatment in NAFLD patients versus lifestyle changes alone. The primary outcome was the change in steatosis parameters. Secondary endpoints were changes in anthropometric parameters, inflammatory markers (TNF-a), and metabolic parameters (fasting blood glucose (FSG), homeostasis model assessment of insulin resistance (HOMA-IR), AST/ALT, and lipid profile). The random effects model was used to calculate the standardized mean difference (SMD) with associated 95% confidence intervals (CI) for our desired outcome. **Results:** Four RCTs met our inclusion criteria. 453 patients were included (mean age 42.8 years, 58.5% males), with 228 (50.3%) in the HP eradication group and 225 (49.7%) in the lifestyle modification group. HP eradication had a significant effect on reducing liver steatosis and TNF-α levels compared to lifestyle modification alone (SMD: -0.9; 95% CI: -14.67, -3.82, I2 = 0% and SMD: -6.3; 95% CI: -9.04, -3.56, I2 = 0%, respectively) (Figure. 1). No significant effect between the two groups was noticed in regards to BMI (SMD: -0.21; 95% CI: -0.9, 0.49, I2 = 0%), ALT (SMD: -3.2; 95% CI: -8.36, 1.96, I2 = 11%) or AST levels (SMD: -0.96; 95% CI: -4.61, 2.69, I2 = 0%), HOMA-IR measurements (SMD: -0.21; 95% CI: -0.57, 0.14, I2 = 0%) as well as in serum FBG levels (SMD: -0, 06, 95% CI: -0.29, 0.16, I2 = 0%), or lipid profile (Table. 1). **Conclusion:** This meta-analysis revealed that HP eradication significantly reduced liver steatosis and inflammatory marker (TNF) levels in patients with NAFLD. However, HP eradication appears to have similar effects on NAFLD outcomes compared to lifestyle changes in other metabolic aspects such as liver enzymes, FSG, lipid profile, HOM-IR, and anthropometric measurements. The variability in interventions, confounding variables, and diagnostic limitations of the included studies emphasize the need for further studies to validate our results.

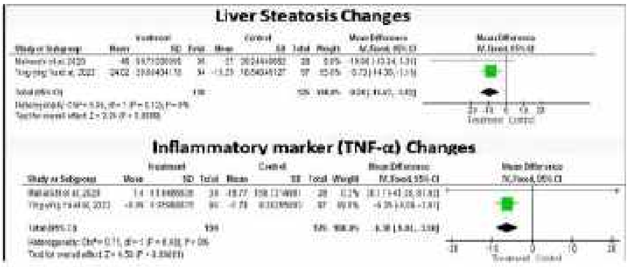
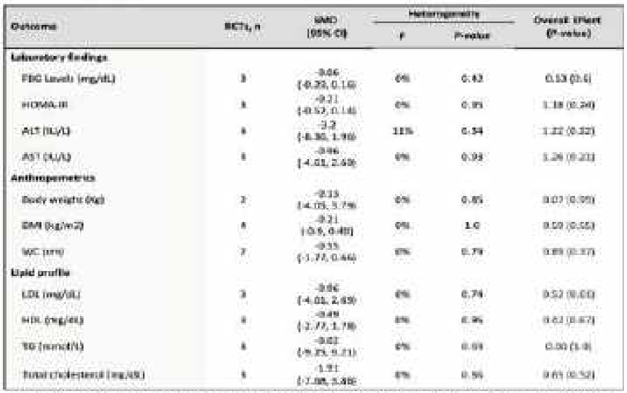


Figure 1: Forest plot of total change difference in (A) Controlled Attenuation parameter (CAP) measurement and (B) Tumor Necrosis Factor-a (TNF-a) between the intervention and control groups with their 95% confidence interval.



Outcome	RCTs, n	SMD (95% CI)	Heterogeneity I²	Heterogeneity P-value	Overall Effect (P-value)
Laboratory findings					
FBG Levels (mg/dL)	3	-0.06 (-0.29, 0.16)	0%	0.42	0.53 (0.6)
HOMA-IR	4	-0.21 (-0.57, 0.14)	0%	0.95	1.18 (0.24)
ALT (IU/L)	6	-3.2 (-8.36, 1.96)	11%	0.34	1.22 (0.22)
AST (IU/L)	6	-0.96 (-4.61, 2.69)	0%	0.93	1.26 (0.21)
Anthropometrics					
Body weight (Kg)	2	-0.13 (-4.05, 3.79)	0%	0.85	0.07 (0.95)
BMI (kg/m2)	4	-0.21 (-0.9, 0.49)	0%	1.0	0.59 (0.55)
WC (cm)	7	-0.55 (-1.77, 0.66)	0%	0.79	0.89 (0.37)
Lipid profile					
LDL (mg/dL)	3	-0.96 (-4.61, 2.69)	0%	0.74	0.52 (0.60)
HDL (mg/dL)	6	-0.49 (-2.77, 1.78)	0%	0.96	0.42 (0.67)
TG (mmol/L)	6	-0.02 (-9.25, 9.21)	0%	0.99	0.00 (1.0)
Total cholesterol (mg/dL)	5	-1.51 (-7.08, 5.48)	0%	0.56	0.65 (0.52)

Table 1. Results of meta-analyses comparing laboratory, anthrometric and lipid profiles between the two groups.

Abbreviations: ALT; alanine aminotransferase, AST; aspartate aminotransferase, BMI; body mass index, CI; confidence interval, FBG; fasting blood glucose, HDL; high density lipoprotein, HOMA-IR; Homeostatic Model Assessment-Insulin Resistance index, LDL; low density lipoprotein, RCT; randomized controlled trial, SMD; standardized mean differences, TG; triglycerides, WC; waist circumference.

Disclosures: The following people have nothing to disclose: Fouad Jaber, Saqr Alsakarneh, Azizullah Beran, Tala Alsharaeh, Abdelrahman Abdelshafi, Mohamed Jaber, Mohamed Ahmed, Yazan Abood, Kimberly Sanders, Mohammad Almeqdadi, Hassan Ghoz

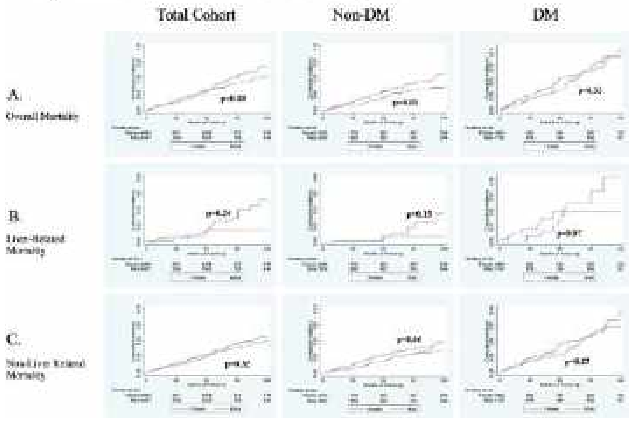
Disclosure information not available at the time of publication: Adel Muhanna, Mir Mirzulqarnain, Wendell K. Clarkston, John H. Helzberg

2192-A | IMPACT OF SEX AND DIABETES ON LONG-TERM OUTCOMES OF PATIENTS WITH NAFLD

Catherine Hand[1,2], Vy H. Nguyen[2,3], Leslie Yeeman Kam[4], Jung Eun Park[2], Richard Hx Le[2,5], Nicholas Ajit Rouillard[2], Ashley Fong[2], Surya Gudapati[2,6], Audrey Ha[2], Mayumi Maeda[2], Scott D. Barnett[4], Linda Henry[4], Ramsey Cheung[4,7] and Mindie H. Nguyen[2,4], (1)Long School of Medicine Uthscsa, (2)Stanford University Medical Center, (3)Harvard Medical School, (4)Stanford University Medical Center, Palo Alto, CA, (5)William Carey University College of Osteopathic Medicine, (6) Washington University, (7)Veterans Affairs Palo Alto Health Care System

Background: Nonalcoholic fatty liver disease (NAFLD) is one of the leading causes of cirrhosis and liver cancer in the United States (U.S). Male sex and diabetes mellitus (DM) are both known to associate with the risk of NAFLD. However, there are limited data on the impact of sex and DM on the long-term mortality outcomes of patients with NAFLD. As such, we aimed to characterize the mortality outcomes among NAFLD patients stratified by sex and DM. **Methods:** In this retrospective study, NAFLD were identified using liver imaging and/or histology at a U.S. medical center from 1995-2021. Patients with other concurrent liver diseases were excluded. We used Kaplan-Meier curves to evaluate mortality outcomes of patients with NAFLD stratified by sex and DM. We used Cox proportional hazard regression to evaluate the association between DM on mortality among DM and non-DM, and among subgroups of male and female patients. **Results:** Our study included 10,207 eligible NAFLD patients (43% male). Compared to females, males were younger (48.1 ± 15.2) with less comorbidities at baseline (obesity: 49.1% vs. 57.6%; DM: 24.9% vs. 32.1%; non-liver cancer:16.2% vs. 18.6%, all $P < 0.001$). Similar findings were observed in subgroup analysis of NAFLD patients without DM. However, in NAFLD patients with DM, we observed opposite findings with males more likely to have comorbidities at baseline. DM NAFLD males were also noted to have higher percentage of cirrhosis as compared to females (35.0% vs. 29.9%, P = 0.004). Mortality rates (per 1000 person-years) were lower in males compared to females in the total cohort for all-cause (0.06 [0.04-0.07] vs. 0.07 [0.06-0.08], P = 0.18), liver-related (0.004 [0.002-0.008] vs. 0.01[0.01-0.02], P = 0.24), and non-liver related (0.05 [0.04-0.07] vs. 0.06 [0.05-0.07], P = 0.32) mortality, but these differences were not statistically significant (Figure 1A-C, left panels). In NAFLD patients without DM, males had a significantly lower incidence of all-cause mortality compared to females (0.04 [0.03-0.05] vs. 0.06 [0.04-0.03], P = 0.02) but not in analysis of cause-specific mortalities (Figure 1A-C, middle panels). Meanwhile, overall and cause-specific mortalities among DM NAFLD patients were similar between males and females (Figure 1A-C, right panels). In multivariable Cox's regression analysis adjusted for age, sex, ethnicity, BMI, FIB-4 index, baseline cirrhosis or HCC, and Charlson Comorbidity index, male sex was independently associated with lower mortality compared to females though this association did not reach conventional level of statistical significance (aHR 0.66 95%CI 0.42-1.02, P = 0.06). **Conclusion:** Non-DM male patients with NAFLD had lower mortality than female patients, while there was no significant difference in mortality between DM male and female patients. Further studies are needed to examine the interaction between sex and metabolic comorbidities to inform individualized therapies for patients with NAFLD.

Figure 1. Mortality Outcomes of NAFLD Patients by Sex



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Disclosure information not available at the time of publication: Jung Eun Park, Richard Hx Le, Ashley Fong, Surya Gudapati, Audrey Ha

2193-A | IMPACT OF SEX AND TYPE 2 DIABETES MELLITUS ON QUALITY OF LIFE AMONG NON-ALCOHOLIC FATTY LIVER DISEASE PATIENTS: A LARGE CANADIAN COHORT STUDY

Elizabeth Baguley[1], Madelyn Knaub[1], Wendy Schaufert[2], Mark Gordon Swain[1] and Abdel-Aziz Shaheen[3], (1)University of Calgary, (2)Alberta Health Services, (3)Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

Background: Non-alcoholic fatty liver disease (NAFLD) is a growing epidemic worldwide. A NAFLD diagnosis can significantly impact quality of life (QoL). We described QoL among NAFLD patients at risk of advanced liver fibrosis. We evaluated associations between sex and type 2 diabetes mellitus (T2DM) status on QoL domains. **Methods:** In this prospective study, the Patient-Reported Outcomes Measurement Instrument Survey (PROMIS-29), a 29-item validated survey with seven health domains (pain interference, depression, physical function, ability to participate in social roles/activities, fatigue, anxiety and sleep disturbance, and a single pain intensity item) was administered to patients identified in primary care through the Calgary NAFLD pathway with either an inconclusive or elevated (**e** 8kPa) shearwave elastography (n = 812) between March 2017 and March 2023. Patients completed the PROMIS-29 survey before assessments with transient elastography (Fibroscan®) and hepatologist discussion. PROMIS-29 scores were compared between our NAFLD cohort and a reference 2000 General US Census population. PROMIS-29 scores of our cohort were compared based on sex (female vs. male) and T2DM status (yes vs. no). A T2DM diagnosis was confirmed in patients with hemoglobin A1c **e** 6.5%, or a previous T2DM diagnosis and treatment with T2DM medications. **Results:** Participants had a median age of 58 yrs (IQR:48.3-66.0). Over half of the participants were female (57.4%), and 41.0% had T2DM. Compared to the reference population, our cohort scored worse in the physical function, sleep disturbance, anxiety, and pain interference domains (p < 0.001); however, our cohort showed a better score for participation in social roles and activities (p = 0.001). Females experienced worse (p < 0.001) QoL compared to men across all PROMIS-29 domains (Table 1). Participants with T2DM experienced greater issues with physical functioning (p < 0.001), more fatigue (p = 0.004), increased depression (p = 0.044), more sleep disturbances (p < 0.001), reduced ability to participate in social roles and activities (p = 0.003), higher pain interference (p < 0.001), and increased overall pain intensity (p < 0.001), when compared to participants without T2DM (Table 1). **Conclusion:** Among NAFLD patients identified in primary care at risk for significant liver fibrosis, females and patients with T2DM had reduced QoL. Further, NAFLD patients have reduced QoL across many health domains compared to the general population.

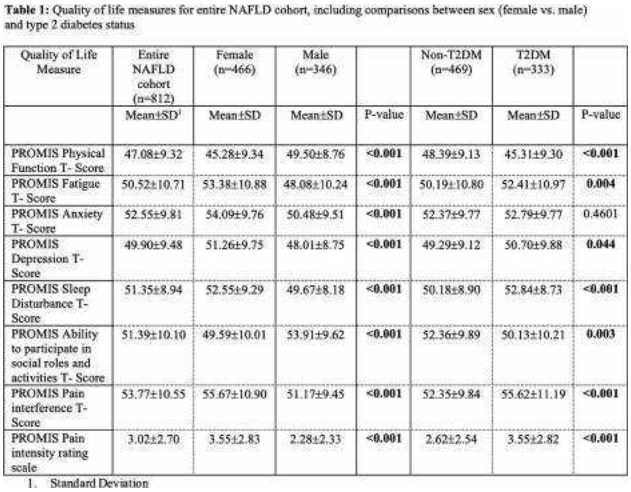
Table 1: Quality of life measures for entire NAFLD cohort, including comparisons between sex (female vs. male) and type 2 diabetes status

Quality of Life Measure	Entire NAFLD cohort (n=812)	Female (n=466)	Male (n=346)		Non-T2DM (n=469)	T2DM (n=333)	
	Mean±SD[1]	Mean±SD	Mean±SD	P-value	Mean±SD	Mean±SD	P-value
PROMIS Physical Function T- Score	47.08±9.32	45.28±9.34	49.50±8.76	**<0.001**	48.39±9.13	45.31±9.30	**<0.001**
PROMIS Fatigue T- Score	50.52±10.71	53.38±10.88	48.08±10.24	**<0.001**	50.19±10.80	52.41±10.97	**0.004**
PROMIS Anxiety T- Score	52.55±9.81	54.09±9.76	50.48±9.51	**<0.001**	52.37±9.77	52.79±9.77	0.4601
PROMIS Depression T-Score	49.90±9.48	51.26±9.75	48.01±8.75	**<0.001**	49.29±9.12	50.70±9.88	**0.044**
PROMIS Sleep Disturbance T-Score	51.35±8.94	52.55±9.29	49.67±8.18	**<0.001**	50.18±8.90	52.84±8.73	**<0.001**
PROMIS Ability to participate in social roles and activities T- Score	51.39±10.10	49.59±10.01	53.91±9.62	**<0.001**	52.36±9.89	50.13±10.21	**0.003**
PROMIS Pain interference T-Score	53.77±10.55	55.67±10.90	51.17±9.45	**<0.001**	52.35±9.84	55.62±11.19	**<0.001**
PROMIS Pain intensity rating scale	3.02±2.70	3.55±2.83	2.28±2.33	**<0.001**	2.62±2.54	3.55±2.82	**<0.001**

1. Standard Deviation

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2194-A | IMPACT OF USE OF SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS ON DEVELOPMENT OF LIVER-RELATED COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES: A TERRITORY-WIDE COHORT STUDY

Guanlin Li[1,2,3], Yin Leung[4], Tsz-Fai Yam[1,2,3], Grace Lai-Hung C Wong[1,2,3], Vincent Wai-Sun Wong[1,2,3] and Terry Cheuk-Fung Yip[1,2,3], (1)Department of Medicine and Therapeutics, the Chinese University of Hong Kong, (2)Medical Data Analytics Centre (MDAC), the Chinese University of Hong Kong, (3)Institute of Digestive Disease, the Chinese University of Hong Kong, (4)Faculty of Medicine, the Chinese University of Hong Kong

Background: Emerging data show that sodium-glucose cotransporter 2 inhibitors (SGLT2i) can improve liver function and ameliorate hepatic steatosis in patients with type 2 diabetes (T2D). However, some studies reported conflicting results on the long-term effect of SGLT2i on liver-related complications. We aimed to study the impact of the use of SGLT2i on the development of liver-related complications in patients with T2D. **Methods:** Adult T2D patients in 2007-2021 were identified using a territory-wide electronic database in Hong Kong. T2D was defined by any use of non-insulin antidiabetic agents, continuous use of insulin for e 28 days, hemoglobin A_{1c} e 6.5%, fasting glucose e 7mmol/L, and/or diagnosis codes. The primary outcome was liver-related events (LRE), which included hepatocellular carcinoma, ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, liver transplantation, and liver-related death. Patients with LRE before or within 6 months after T2D diagnosis, type 1 diabetes, or a history of cancer were excluded. A time-dependent cause-specific hazard model was used to examine the impact of the use of SGLT2i and other antidiabetic drugs over time and the risk of LRE, with non-liver-related death as a competing event. **Results:** Of 624,067 T2D patients (mean age 61.7 ± 13.2 y, 53.4% males), 2.3% had cirrhosis at T2D diagnosis; 6.8% and 0.5% had hepatitis B virus (HBV) and hepatitis C virus (HCV) infection respectively. At a median (25th-75th percentile) follow-up of 6.2 (3.0-9.9) years, 35,664 (5.7%) patients received SGLT2i and 9,026/624,067 (1.4%) patients developed LRE. In multivariable analysis, older age, male gender, presence of cirrhosis, HBV infection, and HCV infection were associated with a higher rate of LRE. The use of SGLT2i was not associated with a lower rate of developing LRE (adjusted cause-specific hazard ratio [aCSHR] 0.89, 95% confidence interval [CI] 0.76-1.05, p = 0.156). The use of statin (aCSHR 0.74 [95% CI 0.71-0.78]), metformin (0.90 [0.86-0.95]), and alpha-glucosidase inhibitors (0.67 [0.50-0.90]) were associated with a lower rate of developing LRE, while the use of insulin (3.15 [3.00-3.30]), sulfonylureas (1.26 [1.20-1.32]), and dipeptidyl peptidase 4 inhibitors (1.16 [1.08-1.25]) were associated with a higher rate of developing LRE. The use of SGLT2i was associated with a lower rate of non-liver-related death (aCSHR 0.76, 95% CI 0.70-0.82, p < 0.001) (Table). **Conclusion:** The use of statin, metformin, and alpha-glucosidase inhibitors but not SGLT2i was associated with reduced development of liver-related complications in a large territory-wide cohort of patients with T2D.

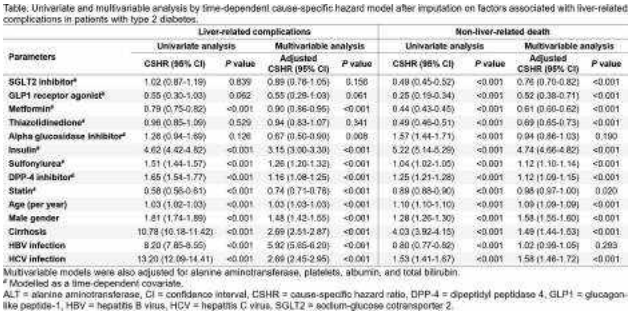

Table: Univariate and multivariable analysis by time-dependent cause-specific hazard model after imputation on factors associated with liver-related complications in patients with type 2 diabetes.

Parameters	Liver-related complications				Non-liver-related death			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
	CSHR (95% CI)	P value	Adjusted CSHR (95% CI)	P value	CSHR (95% CI)	P value	Adjusted CSHR (95% CI)	P value
SGLT2 inhibitor[#]	1.02 (0.87-1.19)	0.839	0.89 (0.76-1.05)	0.156	0.48 (0.45-0.52)	<0.001	0.76 (0.70-0.82)	<0.001
GLP1 receptor agonist[#]	0.55 (0.30-1.03)	0.062	0.55 (0.29-1.03)	0.061	0.25 (0.19-0.34)	<0.001	0.52 (0.38-0.71)	<0.001
Metformin[#]	0.79 (0.75-0.82)	<0.001	0.90 (0.86-0.95)	<0.001	0.44 (0.43-0.45)	<0.001	0.61 (0.60-0.62)	<0.001
Thiazolidinedione[#]	0.96 (0.85-1.09)	0.529	0.94 (0.83-1.07)	0.341	0.49 (0.46-0.51)	<0.001	0.69 (0.65-0.73)	<0.001
Alpha glucosidase inhibitor[#]	1.28 (0.94-1.69)	0.126	0.67 (0.50-0.90)	0.008	1.57 (1.44-1.71)	<0.001	0.94 (0.86-1.03)	0.190
Insulin[#]	4.62 (4.42-4.82)	<0.001	3.15 (3.00-3.30)	<0.001	5.22 (5.14-5.29)	<0.001	4.74 (4.66-4.82)	<0.001
Sulfonylurea[#]	1.51 (1.44-1.57)	<0.001	1.26 (1.20-1.32)	<0.001	1.04 (1.02-1.05)	<0.001	1.12 (1.10-1.14)	<0.001
DPP-4 inhibitor[#]	1.65 (1.54-1.77)	<0.001	1.16 (1.08-1.25)	<0.001	1.25 (1.21-1.28)	<0.001	1.12 (1.09-1.15)	<0.001
Statin[#]	0.58 (0.56-0.61)	<0.001	0.74 (0.71-0.78)	<0.001	0.89 (0.88-0.90)	<0.001	0.98 (0.97-1.00)	0.020
Age (per year)	1.03 (1.02-1.03)	<0.001	1.03 (1.03-1.03)	<0.001	1.10 (1.10-1.10)	<0.001	1.09 (1.09-1.09)	<0.001
Male gender	1.81 (1.74-1.89)	<0.001	1.48 (1.42-1.55)	<0.001	1.28 (1.26-1.30)	<0.001	1.58 (1.55-1.60)	<0.001
Cirrhosis	10.78 (10.18-11.42)	<0.001	2.69 (2.51-2.87)	<0.001	4.03 (3.92-4.15)	<0.001	1.49 (1.44-1.53)	<0.001
HBV infection	8.20 (7.85-8.55)	<0.001	5.92 (5.65-6.20)	<0.001	0.80 (0.77-0.82)	<0.001	1.02 (0.99-1.05)	0.293
HCV infection	13.20 (12.09-14.41)	<0.001	2.69 (2.45-2.95)	<0.001	1.53 (1.41-1.67)	<0.001	1.58 (1.46-1.72)	<0.001

Multivariable models were also adjusted for alanine aminotransferase, platelets, albumin, and total bilirubin.

[#] Modelled as a time-dependent covariate.

ALT = alanine aminotransferase, CI = confidence interval, CSHR = cause-specific hazard ratio, DPP-4 = dipeptidyl peptidase 4, GLP1 = glucagon-like peptide-1, HBV = hepatitis B virus, HCV = hepatitis C virus, SGLT2 = sodium–glucose cotransporter 2.

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Vincent Wai-Sun Wong – Sagimet: Consultant, No, Yes; Pfizer: Consultant, No, Yes; Novo Nordisk: Speaking and Teaching, Yes, Yes; Novo Nordisk: Consultant, Yes, Yes; Inventiva: Consultant, No, Yes; Intercept: Consultant, No, Yes; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences: Speaking and Teaching, No, No; Gilead Sciences: Consultant, No, Yes; Echosens: Consultant, Yes, Yes; Boehringer Ingelheim: Consultant, No, Yes; AbbVie: Speaking and Teaching, No, Yes; AbbVie: Consultant, No, Yes; Abbott: Speaking and Teaching, No, Yes; TARGET PharmaSolutions:

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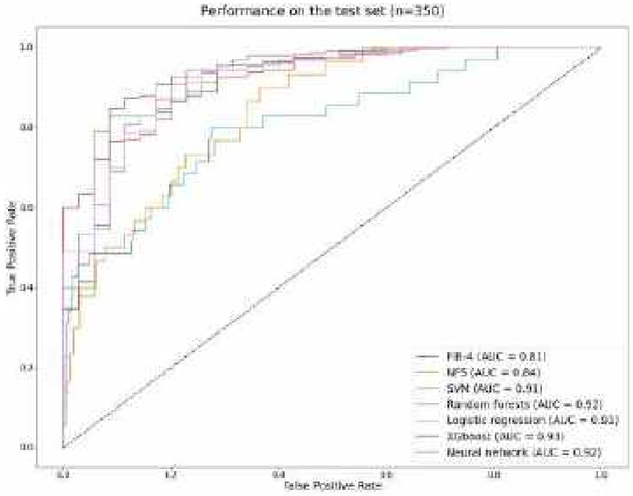
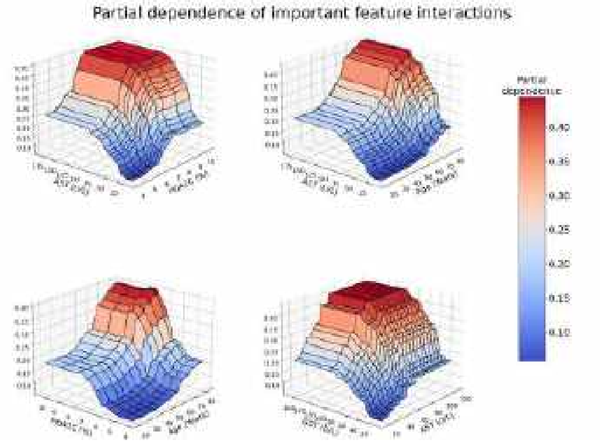
The following people have nothing to disclose: Guanlin Li, Yin Leung, Tsz-Fai Yam

2195-A | IMPLEMENTATION OF MACHINE LEARNING ALGORITHMS FOR THE SCREENING OF ADVANCED LIVER FIBROSIS AMONG NON-ALCOHOLIC FATTY LIVER DISEASE PATIENTS: AN IN-DEPTH EXPLANATORY MODELING★

Shoham Dabbah[1,2], Itamar Mishani[3], Yana Davidov[2], Mariya Likhter[2], Monika-Inda Kaufmann[2] and Ziv Ben-Ari[1,2], (1)Tel Aviv University, (2)Sheba Medical Center, (3)Carnegie-Mellon University

Background: The increasing prevalence of non-alcoholic fatty liver disease (NAFLD) has created an urgent need to improve the screening for advanced liver fibrosis among NAFLD patients, with the goal of reducing its associated morbidity and mortality. Machine learning algorithms (MLAs) have the potential to predict advanced fibrosis in NAFLD patients, however it is essential to justify and speculate on the predictions made by these MLAs to ensure responsible and safe use by clinicians in the future. We aim to train and validate MLAs for predicting advanced fibrosis in NAFLD patients and to provide sound reasoning for these predictions. **Methods:** In this study we collected laboratory, demographic, and clinical features of NAFLD patients managed at a large, single-tertiary center between January 2013 and January 2022 ($n = 618$). MLAs were trained to identify advanced fibrosis, defined as **e** F3 based on liver biopsy ($n = 123$) or as **e** 9.3 kPa according to 2-dimensions shear wave elastography ($n = 495$), based on routine features documented within 6-month of fibrosis assessment. Area under ROC curves of MLAs were compared against NAFLD fibrosis score (NFS) and Fibrosis-4 index (FIB-4) on a test dataset collected independently during 2022 ($n = 350$). The sensitivity and specificity of NFS **e** -1.445 and FIB-4 **e** 1.3 on the test dataset were compared to that of each MLA's threshold which was tuned to achieve 95% sensitivity. Feature importance was derived using extreme gradient boosting (XGBoost) and partial dependence plots were used to assess the relationship with the probability of advanced fibrosis. Probabilities were calibrated to allow customized decisions in different clinical scenarios. **Results:** Artificial neural network, random forest and XGBoost algorithms outperformed both FIB-4 and NFS in advanced fibrosis prediction while logistic regression and support vector machine (SVM) outperformed only FIB-4 ($p < 0.05$ all). XGBoost's threshold achieved sensitivity equal to NFS **e** -1.445 (94% vs. 97%, $p = 0.3$) but higher compared to FIB-4 **e** 1.3 (94% vs. 83%,$p < 0.05$) with significantly higher specificity (76%) compared to both NFS (50%) and FIB-4 (58%) (both $p < 0.01$). The most important features for prediction were hemoglobin A1c (HbA1c), aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT), platelet count and age, while the least important were gender and serum triglycerides. Age showed interactions with AST and HbA1c, while HbA1c strongly interacted with AST and with GGT. **Conclusion:** This study demonstrated the potential of MLAs to improve the screening for advanced fibrosis among NAFLD patients. Utilizing interpretable MLAs, clinicians could gain a deeper understanding of the features contributing to the probability of advanced fibrosis and to tailor further liver fibrosis stage assessment to the patient's circumstances. Overall, our findings highlight the promise of MLAs in improving clinical decision-making for NAFLD patients.



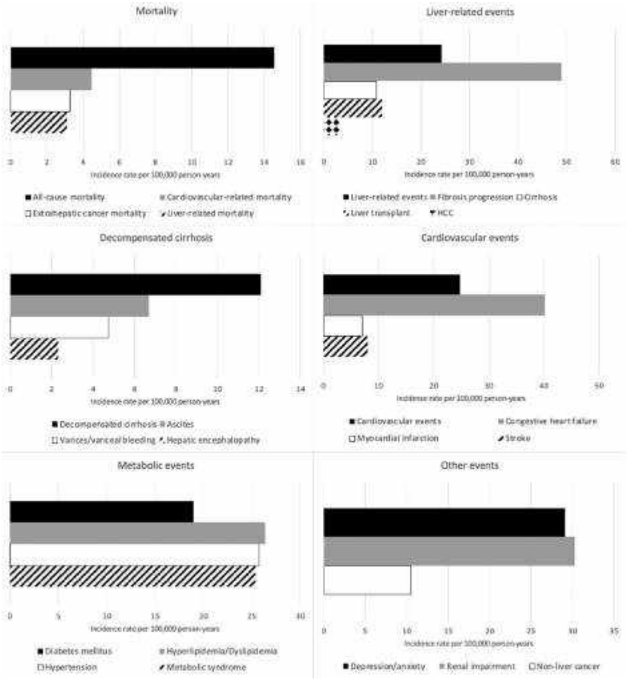


Disclosures: The following people have nothing to disclose: Shoham Dabbah, Itamar Mishani, Yana Davidov, Mariya Likhter, Monika-Inda Kaufmann, Ziv Ben-Ari

2196-A | INCIDENCE OF ADVERSE CLINICAL EVENTS IN PERSONS WITH NAFLD: A SYSTEMATIC REVIEW AND META-ANALYSIS

David M Le[1], *Thomas Baez*[1], *Michael H Le*[2], *Hansen Dang*[3,4], *Vy H. Nguyen*[5], *KeeSeok Lee*[3], *Takanori Ito*[6], *Yuankai Wu*[5], *Yee Hui Yeo*[7], *Fanpu Ji*[8], *Ramsey Cheung*[9] *and Mindie H. Nguyen*[9], *(1)Burrell College of Osteopathic Medicine, (2)Larner College of Medicine at the University of Vermont, San Jose, CA, (3)Stanford University, (4)University of Iowa, Carver College of Medicine, (5)Stanford University Medical Center, (6) Nagoya University Graduate School of Medicine, Japan, (7)Cedars-Sinai Medical Center, Culver City, CA, (8)The Second Affiliated Hospital of Xi'an Jiaotong University, (9)Stanford University Medical Center, Palo Alto, CA*

Background: Nonalcoholic fatty liver disease (NAFLD) is associated with a multitude of adverse outcomes. We aimed to estimate the pooled incidence rate of adverse events associated with NAFLD. **Methods:** We performed a systematic review and meta-analysis of cohort studies of adults with NAFLD at baseline using 3 databases (Cochrane library, EMBASE, PubMed) to evaluate the pooled incidence of adverse events. Random-effects models were used to estimate the pooled incidence of adverse clinical events. **Results:** A total of 79 eligible studies (1,377,466 persons) were analyzed. Diagnostic modality included ultrasound (n = 31), biopsy (n = 29), ICD-code (n = 13), and other imaging (n = 6). 74% of studies were good quality with a median study year ranging from 1987 to 2017. Baseline characteristics (mean/proportion (95% confidence interval)) of NAFLD patients were as follows: mean age 51.5 years (50.0-52.9), BMI 28.9 kg/m^2 (28.0-29.8), fasting glucose 105.7 mg/dL (102.3-109.1), total cholesterol 205.3 mg/dL (200.6-210), triglycerides 162.3mg/dL (153.2-171.4), ALT 56.0 U/L (49.4-62.6), AST 40.7 U/L (36.4-44.9), diabetes 28.7% (24.5-33.0), hypertension 42.6% (37.5-47.9), dyslipidemia 42.4% (32.8-52.3), metabolic syndrome 41.7% (26.6-57.7), smoking 31.1% (26.9-35.4), fibrosis 54.5% (40.8-68.0), cirrhosis 22.0% (12.5-33.2), NASH 58.9% (47.2-70.0). All analyses revealed significant heterogeneity (all I^2 **e** 50%) with no asymmetry on funnel plot and no significant differences on egger's test for all outcomes ($p > 0.05$). Using a modified Newcastle-Ottawa scale, the majority (74%) of studies were of good quality with a median score of 8 out of total 9. Incidence rate per 1000 person-years varied by cause of death: all-cause mortality (14.6) cardiovascular related (4.53), non-liver cancer related (3.27), and liver-related mortality (3.10). Incidence rate per 1000 person-years for liver-related events was 24.3. Further subgroup analysis identified fibrosis progression (49.0), cirrhosis (10.9), liver transplant (12.0), and hepatocellular carcinoma (3.39). Incidence of cirrhotic decompensation was (12.1) with decompensation-specific events inclusive of ascites (6.7), varices (4.7), and hepatic encephalopathy (2.31). Incidence rate per 1000 person-years of metabolic events included metabolic syndrome (25.4), hypertension (25.8), hyperlipidemia/dyslipidemia (26.4), and diabetes mellitus (19.0). Overall incidence of cardiovascular events was 24.77, inclusive of coronary artery disease/congestive heart failure (40.1), myocardial infarction (7.1), and stroke (8.1). Other non-liver events included renal impairment (30.3), depression/anxiety (29.1), and non-liver cancer (10.5) (Figure). **Conclusion:** The estimated incidence rates for adverse events among those with NAFLD is high. Early identification and treatment are necessary to prevent disease progression and its associated morbidity and mortality.



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The following people have nothing to disclose: David M Le, Thomas Baez, Michael H Le, Hansen Dang, Vy H. Nguyen, Yee Hui Yeo, Fanpu Ji, Ramsey Cheung

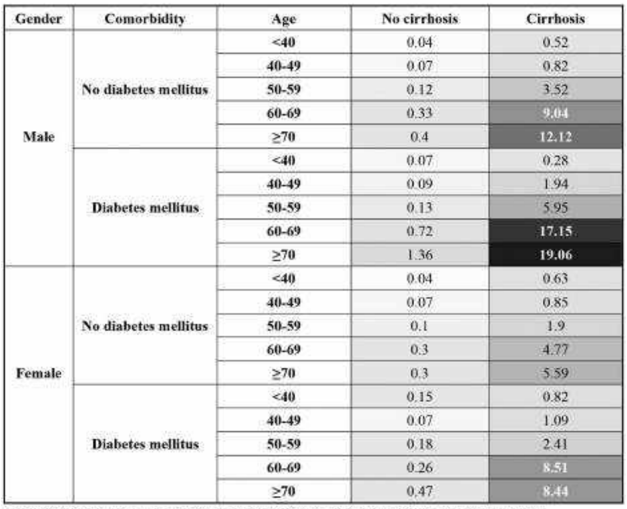
Disclosure information not available at the time of publication: KeeSeok Lee, Yuankai Wu, Mindie H. Nguyen

2197-A | INCIDENCE OF NAFLD-RELATED HEPATOCELLULAR CARCINOMA WITH DETAILED STRATIFICATION BY RISK FACTORS: A NATIONWIDE UNITED STATES COHORT STUDY

Rongtao Lai[1], Scott D. Barnett[2], Leslie Yeeman Kam[2] and Mindie H. Nguyen[2], (1)Shanghai Ruijin Hospital, (2) Stanford University Medical Center, Palo Alto, CA

Background: Prior studies have suggested that patients with non-alcoholic fatty liver disease (NAFLD) are at higher risk for hepatocellular carcinoma (HCC) development regardless of cirrhosis status. HCC risk varies by several factors including sex, age, and the presence of cirrhosis and/or diabetes mellitus (DM). To date, data on HCC incidence stratified by a combination of relevant background risks are limited. Therefore, our goal was to estimate HCC incidence in a stratified manner using a large nationwide U.S. cohort of NAFLD patients. These granular data can help inform HCC surveillance strategies and to inform future economic modeling and public health planning studies. **Methods:** We performed a retrospective cohort study utilizing the Truven Health MarketScan® Databases (January 2007-December 2021) to identify patients with NAFLD as defined by ICD-9/10 codes. We excluded patients with other concurrent liver disease etiologies, HCC at baseline, and those with follow-up < 1 year. We used Kaplan-Meier methods to estimate HCC incidence and multivariable Cox's regression analysis to identify factors associated with HCC. HCC incidence estimates were stratified by sex, age, cirrhosis status, and the presence of DM. **Results:** We identified 741,816 NAFLD patients who met our study criteria. The cohort mean age was 51.5 ± 12.8 years, with 46% male, and 49% with cirrhosis. The HCC incidence (per 1000 person-years [PY]) was 0.72 overall (95% confidence interval [CI], 0.68-0.75), 0.95 (95%CI, 0.89-1.01) for male *vs* 0.52 (95%CI, 0.48-0.56) for female, 4.29 (95% CI, 4.06-4.51) for cirrhosis *vs* 0.14 (95%CI, 0.13-0.16) for non-cirrhosis, and 1.19 (95%CI, 1.12-1.26) for DM *vs* 0.41 (95%CI, 0.38-0.44) for non-DM. An age trend was evident, especially for the **e** 60 years group as compared to the younger group (2.72, 95%CI 2.55-2.88 *vs* 0.35, 95%CI, 0.33-0.38) (all *P* = 0.0001). As shown in heatmap Table, NAFLD incidence was as low as 0.04 for both males and females (95%CI, 0.01-0.07 males, 0.01-0.08 females) among patients younger than 40 years without cirrhosis or DM and as high as 19.06 (95%CI, 16.10-22.01) in males and 8.44 (95%CI, 6.78-10.10) in females among patients aged **e** 70 years with cirrhosis and diabetes. On multivariable analysis adjusted for age, sex, cirrhosis status, and DM, the strongest significant risk for HCC was cirrhosis (adjusted hazard ratio [aHR], 17.01), while there was almost 50% higher HCC risk with DM (aHR, 1.41) and with each yearly increase in age (aHR, 1.03) (all *P* < 0.001). **Conclusion:** In this large nationwide cohort of real-world NAFLD patients, we have utilized heat map to provide detailed, stratified HCC incidence rates across various combinations of risk factors. We identified subsets of the population with low to high HCC risk, thus providing essential information to inform HCC surveillance, prevention, public health efforts, and future modeling studies.

Table. Heat map of incidence rate per 1000 person-year of HCC in 741,816 patients with NAFLD using four background risks for stratified analysis



Gender	Comorbidity	Age	No cirrhosis	Cirrhosis
Male	No diabetes mellitus	<40	0.04	0.52
		40-49	0.07	0.82
		50-59	0.12	3.52
		60-69	0.33	9.04
		≥70	0.4	12.12
	Diabetes mellitus	<40	0.07	0.28
		40-49	0.09	1.94
		50-59	0.13	5.95
		60-69	0.72	17.15
		≥70	1.36	19.06
Female	No diabetes mellitus	<40	0.04	0.63
		40-49	0.07	0.85
		50-59	0.1	1.9
		60-69	0.3	4.77
		≥70	0.3	5.59
	Diabetes mellitus	<40	0.15	0.82
		40-49	0.07	1.09
		50-59	0.18	2.41
		60-69	0.26	8.51
		≥70	0.47	8.44

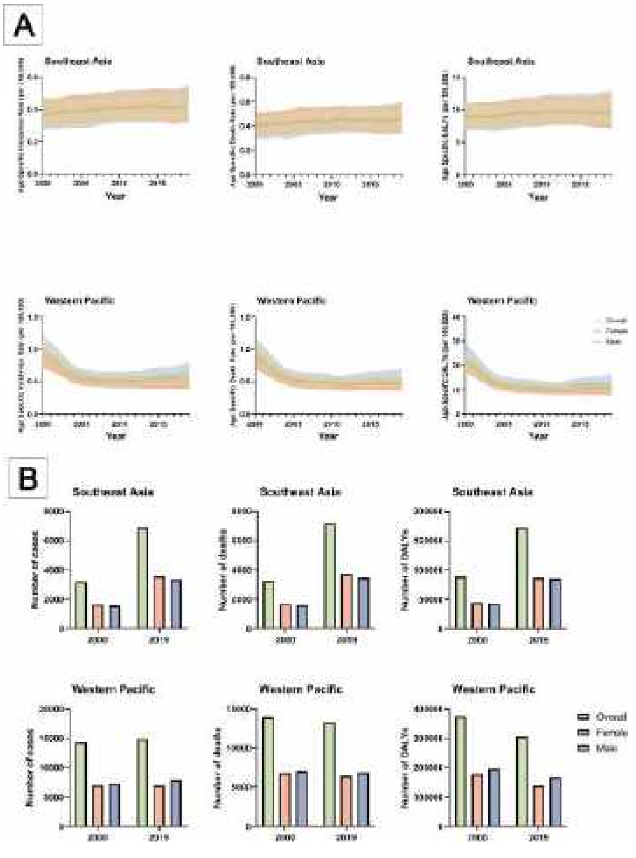
Abbreviations: HCC, Hepatocellular carcinoma; NAFLD, Non-alcoholic fatty liver disease

Disclosures: The following people have nothing to disclose: Rongtao Lai, Scott D. Barnett, Leslie Yeeman Kam, Mindie H. Nguyen

2198-A | INCIDENCE, DISABILITY-ADJUSTED LIFE YEAR, AND MORTALITY OF NON-ALCOHOLIC STEATOHEPATITIS-RELATED LIVER CANCER IN SOUTHEAST ASIA AND WESTERN PACIFIC REGIONS FROM 2000 TO 2019

Aunchalee Jaroenlapnopparat, Mount Auburn Hospital/Harvard Medical School, Pojsakorn Danpanichkul, Chiang Mai University, Natchaya Polpichai, Weiss Memorial Hospital, Panisara Fangsaard, Bassett Medical Center and Karn Wijarnpreecha, University of Arizona College of Medicine Phoenix, Phoenix, AZ

Background: The etiologies of liver cancer in Asia has shifted from viral to non-viral. Given varieties of socio-economic factors and advancement of healthcare in Asia, we aimed to study the epidemiology trend of non-alcoholic steatohepatitis (NASH)-related liver cancer in South East Asia (SEA) and West Pacific (WP) from 2000 to 2019. **Methods:** This study analyzed the incidence, disability-adjusted life years (DALYs), and mortality for NASH-related liver cancer in the SEA and WP regions between 2000 and 2019 from the Global Burden Disease (GBD) Study 2019. Raw numbers of cases, age-standardized rate, and genders were extracted from the study. Joinpoint program was used to analyze the annual percentage change (APC). **Results:** Between 2000 and 2019, the incidence of NASH-related liver cancer had decreased in WP, with a greater decrease in females (APC -3.06 in females vs -2.4 in males). On the contrary, NASH-related liver cancer incidence had increased in SEA, with a greater increase in males than females (APC 0.84 in males vs 0.57 in females). Similarly to the decrease in incidence, mortality and DALYs due to NASH-related liver cancer had decreased in WP, especially in females. As the increased incidence of NASH-related liver cancer in SEA, mortality and DALYs had increased. In SEA, males had a higher increase in mortality, and DALYs than females. **Conclusion:** Over the past decade, the incidence, mortality, and DALYs of NASH-related liver cancer had decreased in WP but increased in SEA. This may reflect an improvement of prevention and management of NASH-related liver cancer in the WP region. Males in both regions had a higher burden of NASH-related liver cancer when compared to females. Further studies are warranted to elaborate underlying sexual disparity in the burden of NASH-related liver cancer.



Disclosures: The following people have nothing to disclose: Aunchalee Jaroenlapnopparat, Pojsakorn Danpanichkul, Natchaya Polpichai, Panisara Fangsaard, Karn Wijarnpreecha

2199-A | INCIDENTAL FINDING OF HEPATIC STEATOSIS ON ABDOMINAL ULTRASOUND: INCIDENCE AND MANAGEMENT

Chad Spencer[1], Alvin Green[1], Hajira Malik[1], Cesar Moreno[1], Michael Tran[1], Ian Tfirn[2] and Rajab Idriss[1], (1) University of South Alabama, (2)Independent Researcher

Background: Due to the high prevalence of obesity/metabolic syndrome, fatty liver disease is increasingly detected as an incidental finding on imaging and maybe dismissed without further evaluation. The goals of our study are 1) to determine the incidence of hepatic steatosis on outpatient ultrasounds obtained for non-liver related causes and 2) to assess if patients were referred for specialist care and fibrosis assessment. **Methods:** We conducted a retrospective study of all adult patients who underwent outpatient abdominal ultrasound for non-liver related reasons at our institution between January, 2018 - December, 2018. A total of 459 patients were included in the initial assessment; of these, 227 patients were excluded from the study for either of the following: known history of liver disease, heavy alcohol use and/or already seeing a gastroenterologist or hepatologist. The following data was collected: demographic information, medical comorbidities, body mass index (BMI), lab results, referral to gastroenterology/hepatology, and fibrosis assessment. Chi-square test and independent samples t-test was performed to evaluate for differences between patients based on the presence or absence of hepatic steatosis on ultrasound. Patients in the hepatic steatosis subgroup were further analyzed to determine if any factors predicted referral to gastroenterology/hepatology. **Results:** The cohort was predominantly female (78.45%), Caucasian (56%) with mean age of 42.3 years old. Of the 232 patients included in the study, 74 (31.9%) were found to have hepatic steatosis on ultrasound. Those with hepatic steatosis were more likely to have hypertension ($p = 0.024$), hyperlipidemia ($p = 0.021$), obese BMI (mean BMI 33.33 kg/m² vs. 28.32 kg/m²; $p = 0.001$), and elevated ALT (27.69 IU/L vs. 20.88 IU/L; $p = 0.027$). Of the 74 patients with hepatic steatosis on ultrasound, 29 (39.1%) were referred to a gastroenterologist or hepatologist, but only 14 underwent fibrosis assessment with elastography and/or liver biopsy. Patients with hepatic steatosis who were referred to gastroenterology/hepatology were more likely to be Caucasian (72.41% vs. 51.1%; $p = 0.163$), older (mean age 47 vs. 44.6; $p = 0.568$) and have elevated ALT (31 IU/L vs. 25.62 IU/L; $p = 0.228$). **Conclusion:** In this cohort of patients without known liver disease, many were incidentally found to have hepatic steatosis on ultrasound, with an incidence of 31.9%. Those with hepatic steatosis were more likely to have hypertension, hyperlipidemia, obesity, and elevated ALT. Patients with higher ALT, older and Caucasian were more likely to be referred for further work up.

Disclosures: The following people have nothing to disclose: Chad Spencer, Alvin Green, Hajira Malik, Cesar Moreno, Michael Tran, Ian Tfirn, Rajab Idriss

2200-A | INCREASED MORTALITY AND LIVER-RELATED COMPLICATIONS IN LEAN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE COMPARED TO NON-LEAN

Claire Faulkner[1], *Majd Aboona*[2], *Pooja Rangan*[2,3], *Vincent Chen*[4], *Cheng Han Ng*[5], *Daniel Q Huang*[6], *Mark Dhinesh Muthiah*[6], *Donghee Kim*[7], *Moises Ilan Nevah Rubin*[3,8], *Ma Ai Thanda Han*[3,8], *Michael Fallon*[3,8] and *Karn Wijarnpreecha*[3,8], *(1)University of Arizona College of Medicine - Phoenix, Phoenix, AZ, (2)University of Arizona College of Medicine-Phoenix, Phoenix, AZ, (3) Banner University Medical Center, (4)University of Michigan Medical Center, (5)Yong Loo Lin School of Medicine, National University of Singapore, (6)National University Health System (NUHS), (7)Stanford University Medical Center, (8)University of Arizona College of Medicine Phoenix, Phoenix, AZ*

Background: Nonalcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease worldwide. About 20% of patients with NAFLD are not overweight or obese (lean NAFLD). The natural history and racial disparities of lean NAFLD versus non-lean NAFLD are not well understood. **Methods:** In this multi-state health system study, we included patients with NAFLD with follow-up duration of over 365 days at the Banner Health System between 2012 and 2022 based on ICD codes. We excluded those with underweight BMI, missing data on race, body mass index (BMI), or lab values, other etiologies of liver disease, baseline decompensated cirrhosis, baseline cancer diagnosis, or bariatric surgery. Primary outcomes were mortality and incident outcomes (cardiovascular disease, liver-related events (LRE), cirrhosis, cancer, and type 2 diabetes (DM)) amongst lean vs. non-lean subjects with NAFLD. **Results:** A total of 37,027 NAFLD subjects were included, 8.76% of which were classified as lean, 22.96% overweight, 29.29% obesity class I, and 38.99% obesity class II or III. Our cohort was predominantly female (60.76%) and White (63.83%). Median follow-up duration was 1,398 days. Compared to lean subjects, overweight (HR 0.48, 95% CI 0.38-0.61), obese class 1 (HR 0.48 95% CI 0.38-0.60), and obese class 2-3 (HR 0.55, 95% CI 0.44-0.70) individual's had significantly lower mortality, after adjusting for confounders. Furthermore, the incidence of LRE was also significantly lower in overweight (HR 0.59, 95% CI 0.45-0.78), obese class 1 (HR 0.58, 95% CI 0.45-0.76), and obese class 2-3 (HR 0.56, 95% CI 0.43-0.73) subjects. Among the lean NAFLD group, Native American/Alaska Native (NA/AN) subjects had a significantly higher incidence of LRE as compared to White subjects (HR 3.50, 95% CI 1.00-12.21). Within the non-lean group, Black and NA/AN subjects had significantly higher mortality, LRE, and DM compared to White subjects. **Conclusion:** This study highlights varied mortality and incident outcomes amongst lean and non-lean subjects with NAFLD, showing that lean NAFLD may portend a poorer prognosis with higher incidence of death and LRE, despite similar incidences of cirrhosis and CVD. We also found racial disparities in lean NAFLD, showing NA/AN individual's have a significantly higher incidence of LRE compared to White individual's. Further research is needed to elucidate the underlying disparities in NAFLD.

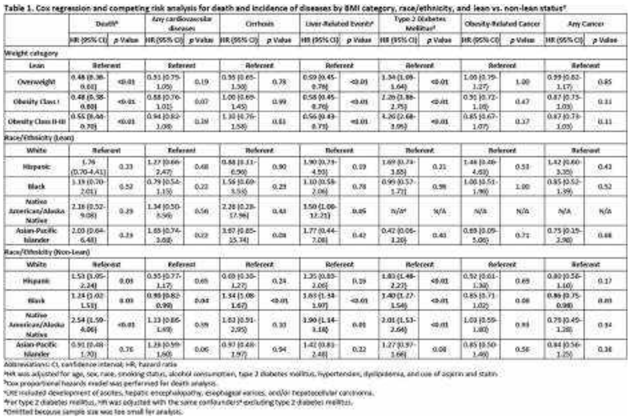


Table 1. Cox regression and competing risk analysis for death and incidence of diseases by BMI category, race/ethnicity, and lean vs. non-lean status^a

	Death^b		Any cardiovascular diseases		Cirrhosis		Liver-Related Events^c		Type 2 Diabetes Mellitus^d		Obesity-Related Cancer		Any Cancer	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Weight category														
Lean	Referent		Referent		Referent		Referent		Referent		Referent		Referent	
Overweight	0.48 (0.38-0.61)	<0.01	0.91 (0.79-1.05)	0.19	0.95 (0.69-1.30)	0.78	0.59 (0.45-0.78)	<0.01	1.34 (1.09-1.64)	<0.01	1.00 (0.79-1.27)	1.00	0.99 (0.82-1.17)	0.85
Obesity Class I	0.48 (0.38-0.60)	<0.01	0.88 (0.76-1.01)	0.07	1.00 (0.69-1.45)	0.99	0.58 (0.45-0.76)	<0.01	2.28 (1.88-2.75)	<0.01	0.91 (0.72-1.16)	0.47	0.87 (0.73-1.03)	0.11
Obesity Class II-III	0.55 (0.44-0.70)	<0.01	0.94 (0.82-1.08)	0.39	1.10 (0.76-1.58)	0.61	0.56 (0.43-0.73)	<0.01	3.26 (2.68-3.95)	<0.01	0.85 (0.67-1.07)	0.17	0.87 (0.73-1.03)	0.11
Race/Ethnicity (Lean)														
White	Referent		Referent		Referent		Referent		Referent		Referent		Referent	
Hispanic	1.76 (0.70-4.41)	0.23	1.27 (0.66-2.47)	0.48	0.88 (0.11-6.96)	0.90	1.90 (0.79-4.53)	0.19	1.69 (0.73-3.85)	0.21	1.46 (0.46-4.63)	0.53	1.42 (0.60-3.35)	0.42
Black	1.19 (0.70-2.01)	0.52	0.79 (0.54-1.15)	0.22	1.56 (0.69-3.55)	0.29	1.10 (0.58-2.08)	0.78	0.99 (0.57-1.71)	0.98	1.00 (0.51-1.96)	1.00	0.85 (0.52-1.39)	0.52
Native American/Alaska Native	2.18 (0.52-9.08)	0.29	1.34 (0.50-3.56)	0.56	2.28 (0.28-17.96)	0.43	3.50 (1.00-12.21)	0.05	N/A^e	N/A	N/A	N/A	N/A	N/A
Asian-Pacific Islander	2.03 (0.64-6.48)	0.23	1.65 (0.74-3.68)	0.22	3.67 (0.85-15.74)	0.08	1.77 (0.44-7.08)	0.42	0.42 (0.06-3.20)	0.41	0.69 (0.09-5.06)	0.71	0.75 (0.19-2.90)	0.68
Race/Ethnicity (Non-Lean)														
White	Referent		Referent		Referent		Referent		Referent		Referent		Referent	
Hispanic	1.53 (1.05-2.24)	0.03	0.95 (0.77-1.17)	0.65	0.63 (0.30-1.27)	0.24	1.35 (0.89-2.06)	0.19	1.83 (1.48-2.27)	<0.01	0.92 (0.61-1.38)	0.69	0.80 (0.58-1.10)	0.17
Black	1.24 (1.02-1.51)	0.03	0.90 (0.82-0.99)	0.04	1.34 (1.08-1.67)	<0.01	1.63 (1.34-1.97)	<0.01	1.40 (1.27-1.54)	<0.01	0.85 (0.71-1.02)	0.08	0.86 (0.75-0.98)	0.03
Native American/Alaska Native	2.54 (1.59-4.06)	<0.01	1.13 (0.86-1.49)	0.39	1.63 (0.91-2.95)	0.10	1.90 (1.14-3.18)	0.01	2.01 (1.53-2.64)	<0.01	1.03 (0.59-1.80)	0.93	0.79 (0.49-1.28)	0.34
Asian-Pacific Islander	0.91 (0.48-1.70)	0.76	1.26 (0.99-1.60)	0.06	0.97 (0.48-1.97)	0.94	1.42 (0.81-2.48)	0.22	1.27 (0.97-1.66)	0.08	0.85 (0.50-1.46)	0.56	0.84 (0.56-1.25)	0.38

Abbreviations: CI, confidence interval; HR, hazard ratio

^a HR was adjusted for age, sex, race, smoking status, alcohol consumption, type 2 diabetes mellitus, hypertension, dyslipidemia, and use of aspirin and statin.

^b Cox proportional hazards model was performed for death analysis.

^c LRE included development of ascites, hepatic encephalopathy, esophageal varices, and/or hepatocellular carcinoma.

^d For type 2 diabetes mellitus, HR was adjusted with the same confounders^a excluding type 2 diabetes mellitus.

^e Omitted because sample size was too small for analysis.

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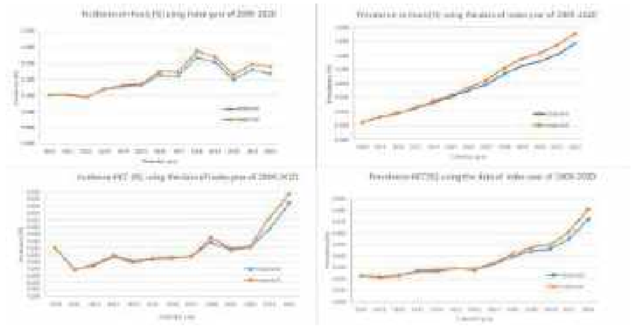
2201-A | INCREASING INCIDENCE AND PREVALENCE OF HCC AND CIRRHOSIS IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Ronald Samuel[1], Basim Ali[1], Jennifer Kramer[2], Yumei Cao[2], George Cholankeril[1], Ruben Hernaez[3], Tzu-Hao (Howard) Lee[3], Hashem B. El-Serag[1] and Fasiha Kanwal[4], (1)Baylor College of Medicine, (2)Micheal E Debakey, (3)Baylor College of Medicine, Houston, TX, (4)Michael E. Debakey VA Medical Center

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



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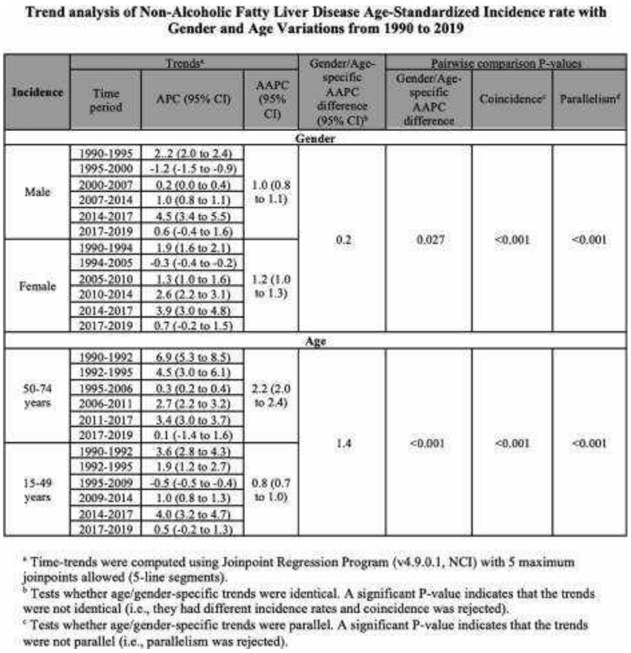
Disclosure information not available at the time of publication: Basim Ali, Jennifer Kramer, Yumei Cao, Ruben Hernaez, Hashem B. El-Serag

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

Saqr Alsakarneh[1], Saeed Abughazaleh[2], Fouad Jaber[1], Mohammad Aldiabat[3], Yassine Kilani[4], Mohamed Ahmed[5], Wael T Mohamed[1], Mohamad Khaled Almujarkesh[6], Nikki Duong[7], Mohammad Almeqdadi[8] and Hassan Ghoz[5], (1)University of Missouri-Kansas City, (2)Tufts University, (3)New York University, (4)Lincoln Medical Center, (5)University of Missouri- Kansas City, (6)Wayne State University, (7) Virginia Commonwealth University Health System, Oakland, CA, United States, (8)Lahey Clinic Medical Center

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

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



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

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

[a] Time-trends were computed using Joinpoint Regression Program (v4.9.0.1, NCI) with 5 maximum joinpoints allowed (5-line segments).

[b] Tests whether age/gender-specific trends were identical. A significant P-value indicates that the trends were not identical (i.e., they had different incidence rates and coincidence was rejected).

[c] Tests whether age/gender-specific trends were parallel. A significant P-value indicates that the trends were not parallel (i.e., parallelism was rejected).

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

Arunkumar Krishnan[1], Dipatsree Mukherjee[2], William R. Hutson[3], Shailendra Singh[3], Shyam Thakkar[3], Tinsay A. Woreta[4] and Saleh A Alqahtani[5,6], (1)Atrium Health Levine Cancer Institute, (2)Apex Institute of Medical Sciences, (3)West Virginia University School of Medicine, (4)Johns Hopkins Medicine, Baltimore, MD, (5)Johns Hopkins University School of Medicine, (6) King Faisal Specialist Hospital and Research Center

Background: Nonalcoholic fatty liver disease (NAFLD) is highly prevalent among patients with type 2 diabetes mellitus (T2DM). There has been a growing interest in the effects of second-line antidiabetic drugs, such as glucagon-like peptide 1 receptor agonists (GLP-1 RA) and sodium–glucose cotransporter-2 inhibitors (SGLT-2i), on reducing hepatic fat content beyond their glucose-lowering effects. The association between these drugs and the risks of NAFLD and hepatocellular carcinoma (HCC) has not been explored in the US population. Thus, we aimed to determine whether GLP-1 RA and SGLT-2i are associated with a decreased risk of new onset of NAFLD and HCC compared with dipeptidyl peptidase-4 inhibitors (DPP-4i) among patients with T2DM. **Methods:** We conducted a population-based, retrospective cohort study with consecutive adult patients diagnosed with T2DM using TriNeTx dataset. Cohort entry was defined as the date of the first-ever prescription for one of the drugs of interest (GLP-1 RA or SGLT-2i, compared to DPP4i) during the study period. We used a lag of 6 months for all exposures to minimize protopathic bias. We performed a 1:1 propensity score matching (PSM) to reduce confounding effects. The primary outcomes were defined as the first incidence of NAFLD and HCC. We conducted a secondary and sensitivity analysis to assess the robustness of our findings. The outcomes were estimated using a Cox proportional hazards model with hazard ratios (HR) and 95% confidence intervals (CI). **Results:** In this cohort, 425641 patients received GLP-1A treatment, 353887 patients received SGLT-2i, and 352098 patients received DPP-4i were included. After PSM matching (341015 patients), 1687 patients developed new-onset NAFLD after GLP1-RA, whereas 2087 patients after SGLT-2i (HR 0.19; 95% CI: 0.18-0.30) (Table 1). Similarly, the new incidence of HCC was also lower among new users of GLP1-RA (HR 0.51). SGLT2i (353051 patients after PSM), was also associated with lower risks of new-onset NAFLD (HR: 0.49) and HCC (HR: 0.25). The results from the secondary analysis by increasing lag exposure of drugs and in a sensitivity analysis by excluding the previous events remained consistent with the one generated in the primary analyses. **Conclusion:** New users of GLP1-RA and SGLT-2i were associated with lower risks of new-onset NAFLD and HCC compared with DPP4i, and both drugs seemed to be safe and efficacious in lowering the risk of new incidences of NAFLD and HCC in patients with T2DM.

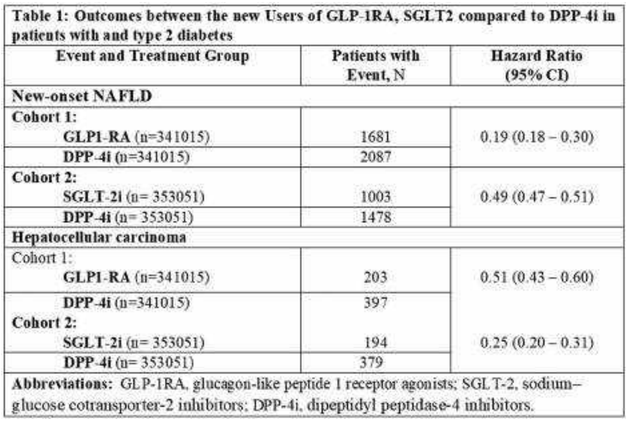

Table 1: Outcomes between the new Users of GLP-1RA, SGLT2 compared to DPP-4i in patients with and type 2 diabetes

Event and Treatment Group	Patients with Event, N	Hazard Ratio (95% CI)
New-onset NAFLD		
Cohort 1:		
GLP1-RA (n=341015)	1681	0.19 (0.18 – 0.30)
DPP-4i (n=341015)	2087	
Cohort 2:		
SGLT-2i (n= 353051)	1003	0.49 (0.47 – 0.51)
DPP-4i (n= 353051)	1478	
Hepatocellular carcinoma		
Cohort 1:		
GLP1-RA (n=341015)	203	0.51 (0.43 – 0.60)
DPP-4i (n=341015)	397	
Cohort 2:		
SGLT-2i (n= 353051)	194	0.25 (0.20 – 0.31)
DPP-4i (n= 353051)	379	

Abbreviations: GLP-1RA, glucagon-like peptide 1 receptor agonists; SGLT-2, sodium–glucose cotransporter-2 inhibitors; DPP-4i, dipeptidyl peptidase-4 inhibitors.

Disclosures: The following people have nothing to disclose: Arunkumar Krishnan, Dipatsree Mukherjee, Tinsay A. Woreta, Saleh A Alqahtani

Disclosure information not available at the time of publication: William R. Hutson, Shailendra Singh, Shyam Thakkar

2204-A | INDIVIDUALS WITH ADVANCED FIBROSIS HAVE WORSE FINE MOTOR PERFORMANCE

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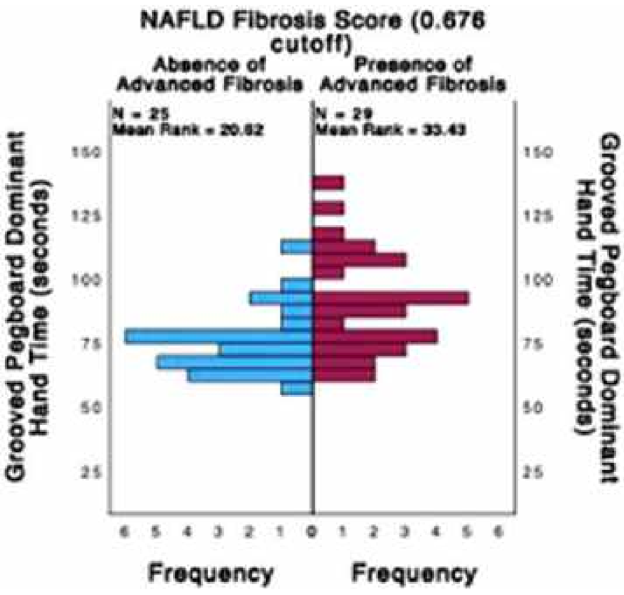
Background: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide. With the growing prevalence of NAFLD, there is an increased interest in the potential relationship between NAFLD and cognitive function. However, NAFLD is a broad term that comprises a wide range of liver pathologies, ranging from simple steatosis to non-alcoholic steatohepatitis. Therefore, fibrosis, a marker of severity, may be a better way to investigate this potential relationship. Fine motor performance (FMP) may serve as an early warning sign for cognitive deficits and issues with mental health. Our aim was to determine if there was a difference in FMP comparing those with advanced fibrosis to those without. **Methods:** Individual's aged 25-69 were enrolled in a cross-sectional study. Those with excess alcohol consumption or viral liver disease were excluded. Each participant performed the Grooved Pegboard Test (GPT), a well-established measure of FMP. The GPT is a manual dexterity test consisting of a pegboard with 25 slots where examinees are asked to match the groove of each peg with the groove of the board before they can be inserted. The NAFLD Fibrosis Score (NFS) was calculated for each individual. Those with scores higher than 0.676 were considered to have advanced fibrosis. **Results:** A total of 54 participants (54% advanced fibrosis, 44% female, age: 58.7 ± 8.4 years, body-mass index (BMI): 33.9 ± 6.0 kg/m^2) completed the assessments. GPT times were statistically significantly slower (see Figure) in those with advanced fibrosis (90.1 ± 19.3 seconds) compared to those without (75 ± 12.8 seconds; $p < 0.05$). Individual's with advanced fibrosis were statistically significantly older and had higher BMI's than those without (p's < 0.05). Statistically significant differences on GPT remained present after controlling for age and BMI (p's < 0.05). **Conclusion:** Presence of advanced fibrosis is associated with reduced FMP compared to the absence of advanced fibrosis. Since FMP may be an early warning sign for cognitive deficits, there is a need for prospective trials investigating potential explanatory mechanisms that can elucidate the relationship between liver fibrosis and FMP.



Disclosures: Zobair M. Younossi – Bristol Myers Squibb: Consultant, No, No; Gilead: Consultant, No, No; Intercept: Consultant, No, No; Novo Nordisk: Consultant, No, No; Terns: Consultant, No, No; Merck: Consultant, No, No; Quest: Consultant, No, No; Siemens: Consultant, No, No; Madrigal: Consultant, No, No;

The following people have nothing to disclose: Pegah Golabi, Lynn Gerber

Disclosure information not available at the time of publication: Ali A. Weinstein, Leyla De Avila, Jillian K. Price, Carey Escheik

2205-A | INFLAMMATORY GENE EXPRESSIONS IN SUBCUTANEOUS AND VISCERAL ADIPOSE TISSUES AND LIVER HISTOLOGY IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

Zhengyi Wang[1], *Harsha Chandraratna*[2], *Jeremy Tan*[3], *Bastiaan De Boer*[4], *Jeffrey M Hamdorf*[1], *Gary P. Jeffrey*[1], *George Garas*[1] *and Leon A. Adams*[5], *(1)The University of Western Australia, (2)Murdoch Hospital, (3)Singapore General Hospital, (4)Pathwest, (5)University of Western Australia*

Background: Non-alcoholic fatty liver disease (NAFLD) is a common metabolic disorder however the underlying pathogenic mechanisms remain unclear. One potential pathway is through the systemic inflammation regulated by adipose tissue which promotes hepatic steatosis and fibrosis in patients with obesity. This study aimed to investigate the association between immune/inflammatory gene expression in adipose tissue in patients with and without NASH/NAFLD. **Methods:** Clinical data, liver, subcutaneous and visceral adipose tissue samples (SAT; VAT) were prospectively collected from 75 adult patients aged 20 to 65 years during bariatric surgery. Patients were categorized as normal liver (n = 30), simple steatosis (n = 29), and non-alcoholic steatohepatitis (NASH; n = 16). mRNA expression was assessed by RT^2 profiler array with gene expression calculated as fold changes standardised to two housekeeping genes. **Results:** Macrophage markers *TREM2, CD68*, and *MSR1* had increased gene expression in NASH subjects compared to those with normal liver in both SAT and VAT (*TREM2* fold change SAT 2.8 ± 2.0 vs. 2.1 ± 2.9, P = 0.002; VAT 2.8 ± 1.8 vs. 1.5 ± 1.2; P = 0.01; *CD68* SAT 1.5 ± 0.5 vs. 1.2 ± 0.8; P = 0.022; *MSR1* SAT 1.7 ± 1.2 vs. 1.1 ± .5 P = 0.022). *NLRP3* expression increased in both simple steatosis and NASH compared to the normal liver group in VAT (simple steatosis 1.6 ± 1.4 vs.1.0 ± 0.3, P = 0.003; NASH 2.0 ± 2.0, P = 0.001). These genes were also more expressed in SAT compared to VAT in all three groups (all P < 0.05). In contrast, gene expression of inflammatory and immune modulating cytokines and chemokines (including *IL2, 6, 10, 18, 33* and *CXCL2, 8, 10)* were not different between groups. *TREM2* expression in both tissues were positively associated with serum ALT (SAT: r_s 0.384, P = 0.001; VAT 0.333, P = 0.004), glucose (SAT: 0.348, P = 0.002; VAT: 0.424, P < 0.001), insulin (SAT: 0.373, P = 0.002; VAT: 0.393, P = 0.001), and triglycerides (SAT: 0.303, P = 0.009; VAT: 0.339, P = 0.003) in the whole cohort. *MSR1* expression levels were also correlated with higher fasting glucose (SAT: 0.387, P = 0.001; VAT: 0.301, P = 0.009) and insulin (SAT: 0.416, P < 0.001; VAT: 0.414, P < 0.001) in both tissues whereas in SAT it was also correlated with increased ALT (0.390, P = 0.001) and AST (0.327, P = 0.006). **Conclusion:** Macrophage markers rather than inflammatory cytokines, are upregulated in adipose tissue in patients with NASH compared to those with normal liver histology, and correlate with markers of metabolic dysfunction.

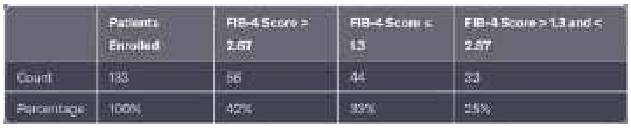
Disclosures: The following people have nothing to disclose: Zhengyi Wang, Leon A. Adams

Disclosure information not available at the time of publication: Harsha Chandraratna, Jeremy Tan, Bastiaan De Boer, Jeffrey M Hamdorf, Gary P. Jeffrey, George Garas

2206-A | INTEGRATING FIB-4 SCORE INTO ANNUAL VISIT SCREENING FOR OPTIMAL NON-ALCOHOLIC FATTY LIVER DISEASE EVALUATION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AT A COMMUNITY INTERNAL MEDICINE RESIDENCY CLINIC

Adalberto Guzman[1], Evelyn Calderon Martinez[1], Wern Lynn Ng[1], Anas Atrash[1], Fernanda Ibarra[2] and Douglas M. Levin[3], (1)UPMC, (2)Woodhull Medical and Mental Health Center, (3)Ohio State University, Columbus, OH, United States

Background: Non-Alcoholic Fatty Liver Disease (NAFLD) is a prevalent condition in patients with type 2 diabetes mellitus (T2DM). Identifying patients at higher risk of advanced liver disease is crucial for appropriate management. This study aimed to assess the utility of integrating the FIB-4 score into annual visit screening for optimal NAFLD evaluation in patients with T2DM at a community clinic. **Methods:** A total of 133 patients with T2DM were enrolled in this study. During their annual visits, FIB-4 scores were calculated based on readily available clinical parameters, including age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count. Patients with a FIB-4 score above 2.67 were referred to GI/Hepatology care for further evaluation. Patients with a FIB-4 score less than or equal to 1.3 were advised to continue regular follow-ups in 1 year. Patients with a FIB-4 score above 1.3 but less than 2.67 underwent a secondary risk assessment. **Results:** In our study, a total of 133 patients were enrolled to assess their liver fibrosis using the FIB-4 scoring system. Among these patients, 56 individual's (42%) exhibited a FIB-4 score above the threshold of 2.67, indicating a higher risk of liver disease progression. As a result, these patients were promptly referred to GI/Hepatology care for comprehensive evaluation and further management. Conversely, 44 patients (33%) demonstrated a FIB-4 score equal to or below 1.3, indicating a lower risk of advanced liver disease. For this group, it was recommended that they continue with regular follow-ups over the course of the next year to monitor any potential changes in their liver health. Interestingly, an additional 33 patients (25%) fell into an intermediate range of FIB-4 scores, above 1.3 but below 2.67. This range raises concern for potential underlying liver disease and warrants a more in-depth assessment to identify any secondary risk factors. As a result, these patients were identified for further investigation through a secondary risk assessment, ensuring a comprehensive evaluation of their liver health status. **Conclusion:** Integrating the FIB-4 score into annual visit screening in patients with T2DM at a community clinic showed promising results for optimizing NAFLD evaluation. A significant proportion of patients with T2DM had FIB-4 scores above 2.67, indicating a higher risk of advanced liver disease and necessitating further evaluation by Hepatology specialists. Patients with scores less than or equal to 1.3 were deemed at lower risk and advised to continue regular follow-ups. Patients with scores above 1.3 but less than 2.67 underwent a secondary risk assessment to guide appropriate management strategies. By accurately categorizing patients into different risk groups, healthcare professionalscan make informed decisions regarding appropriate referrals, follow-up plans, and additional risk assessments.



	Patients Enrolled	FIB-4 Score > 2.67	FIB-4 Score ≤ 1.3	FIB-4 Score > 1.3 and < 2.67
Count	133	56	44	33
Percentage	100%	42%	33%	25%

Disclosures: The following people have nothing to disclose: Adalberto Guzman, Evelyn Calderon Martinez, Wern Lynn Ng, Anas Atrash, Fernanda Ibarra, Douglas M. Levin

2207-A | INTERPLAY OF METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE AND VIRAL HEPATITIS ON LIVER DISEASE SEVERITY: A LARGE COMMUNITY-BASED STUDY IN A VIRAL ENDEMIC AREA

Chung-Feng Huang, Kaohsiung Medical University Hospital

Background: The features of metabolic dysfunction-associated fatty liver disease (MAFLD) and the interplays with viral hepatitis on liver disease severity in a community setting is elusive. **Methods:** We conducted a mass liver surveillance program in a hepatitis B virus (HBV) and hepatitis C virus (HCV) hyper-endemic area. The program aimed to identify MAFLD and non-MAFLD subjects with potentially advanced fibrosis, defined as one of the following: fibrosis-4 index (FIB-4) > 2.67, transient elastography > 8 kPa or NAFLD fibrosis score > 0.675. **Results:** A total of 5,378 subjects were consecutively enrolled in the current study. The prevalence of anti-HCV and HBsAg seropositivity were 19.3% and 9.7%, respectively. A total of 2,242 (41.7%) subjects had MAFLD, and 375 (7.0%) had advanced fibrosis. MAFLD subjects had a significantly higher proportion of advanced fibrosis than non-MAFLD counterparts (8.7% vs. 5.7%, P < 0.001). The proportions of advanced fibrosis in subjects with non-HBV and non-HCV infection (NBNC), mono-HBV infection (mono-B) and mono-HCV infection (mono-C) were 2.8%, 5.7% and 23.4%, respectively. Factors associated with advanced fibrosis in the entire population included age > 65 years (odds ratio [OR]/95% confidence interval [CI]: 4.8/3.7-6.0, P < 0.001), male (OR/CI: 1.3/1.0-1.7, P = 0.019), anti-HCV seropositivity (OR/CI: 5.9/4.6-7.5, P = 0.019), MAFLD-lean metabolic dysregulation (MS) (OR/CI: 2.6/1.3-5.2, P = 0.005; compared to the non-MAFLD group) and MAFLD-diabetes (OR/CI: 1.5/1.1-2.1, P = 0.008; compared to the non-MAFLD group). MAFLD did not aggravate liver disease severity in HBV- or HCV-infected patients. However, among NBNC subjects, factors associated with advanced liver disease included age > 65 years (OR/CI: 10.6/7.1-15.8, P < 0.001), male (OR/CI: 1.3/1.0-1.6, P = 0.041), MAFLD-lean MS group (OR/CI: 9.1/2.4-34.6, P = 0.001; compared to non-MAFLD group) and MAFLD-DM group (OR/CI: 2.0/1.2-3.2, P = 0.004; compared to non-MAFLD group). **Conclusion:** MAFLD patients with diabetes and metabolic dysregulation had a higher risk of advanced liver disease in the community. The effect was enhanced only in nonviral hepatitis subjects.

Disclosures: The following people have nothing to disclose: Chung-Feng Huang

2208-A | LIFESTYLE AND DIETARY BEHAVIORS OF PEOPLE WITH DIAGNOSED AND UNDIAGNOSED NON-ALCOHOLIC FATTY LIVER DISEASE - A NATIONALLY REPRESENTATIVE SAMPLE OF THE UNITED STATES

Madeline Novack[1], Wei-Ting Lin[2], Po-Hung (Victor) Chen[3], Chiung-kuei Huang[1], Hui-Yi Lin[4], Tung-Sung Tseng[4] and Peng-Sheng Ting[1], (1)Tulane University School of Medicine, New Orleans, LA, (2)Tulane University School of Public Health, (3)Johns Hopkins University School of Medicine, (4)Louisiana State University Health Sciences Center

Background: Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of liver disease in the United States, affecting an estimated 25% of adults. NAFLD is closely associated with metabolic syndrome and health behaviors. As such, reporting awareness of disease, and consequent lifestyle behavior changes, play an important role in NAFLD progression. In this study, we aim to compare the lifestyle and dietary behaviors of US adults with NAFLD who report being diagnosed with NAFLD to those who do not report diagnosis of NAFLD, to help clinicians identify high yield topics for behavioral counseling to reduce disease progression. **Methods:** National Health and Nutrition Examination Survey (NHANES) participants e 20 years-old with completed data including controlled attenuation parameter (CAP), liver stiffness measurement (LSM), alcohol intake, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and body mass index from the 2017-2020 NHANES cycle were selected in this study. Undiagnosed NAFLD was defined as no self-reported liver disease, CAP > 302, and non or light alcohol drinkers (d 14 and d 7 standard drinks per week in men and women, respectively). Diagnosed NAFLD was based on self-report. Chi-square test and simple linear regression model were performed for categorical and continuous variables. All analyses were conducted under survey module with appropriate sampling weights. **Results:** Among US adults with NAFLD, 92.5% and 7.5% are undiagnosed NAFLD and diagnosed NAFLD, respectively. Participants with undiagnosed NAFLD were more likely to be non-Hispanic whites and college graduates or above (p's d 0.024). 84.4% of population with diagnosed NAFLD had low physical activity (p = 0.019), but other reported health behaviors were similar to those with undiagnosed NAFLD, such as any alcohol use, cigarette smoking, and daily caloric/sugar intake. Individual's with diagnosed NAFLD had higher AST and ALT (p's d 0.013). **Conclusion:** In this study, participants with diagnosed NAFLD were less physically active, but otherwise shared many similar habits to those with undiagnosed NAFLD. It appears the awareness of NAFLD alone did little to alter health behaviors. In addition, the relatively large proportion of participants who meet NAFLD by clinical criteria, but are not aware of NAFLD, supports the need for increased disease awareness. Our observation that there are more non-Hispanic Whites in the undiagnosed NAFLD group suggest there are disparities in the diagnosis of NAFLD that deserve further investigation.

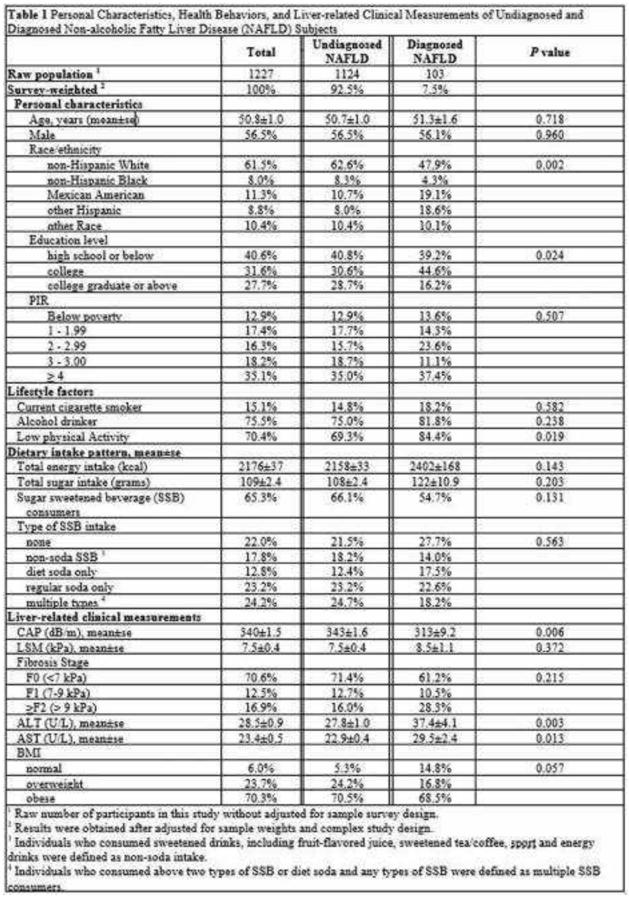


Table 1 Personal Characteristics, Health Behaviors, and Liver-related Clinical Measurements of Undiagnosed and Diagnosed Non-alcoholic Fatty Liver Disease (NAFLD) Subjects

	Total	Undiagnosed NAFLD	Diagnosed NAFLD	*P* value
Raw population [1]	1227	1124	103	
Survey-weighted [2]	100%	92.5%	7.5%	
Personal characteristics				
Age, years (mean±se)	50.8±1.0	50.7±1.0	51.3±1.6	0.718
Male	56.5%	56.5%	56.1%	0.960
Race/ethnicity				
non-Hispanic White	61.5%	62.6%	47.9%	0.002
non-Hispanic Black	8.0%	8.3%	4.3%	
Mexican American	11.3%	10.7%	19.1%	
other Hispanic	8.8%	8.0%	18.6%	
other Race	10.4%	10.4%	10.1%	
Education level				
high school or below	40.6%	40.8%	39.2%	0.024
college	31.6%	30.6%	44.6%	
college graduate or above	27.7%	28.7%	16.2%	
PIR				
Below poverty	12.9%	12.9%	13.6%	0.507
1 - 1.99	17.4%	17.7%	14.3%	
2 - 2.99	16.3%	15.7%	23.6%	
3 - 3.00	18.2%	18.7%	11.1%	
≥ 4	35.1%	35.0%	37.4%	
Lifestyle factors				
Current cigarette smoker	15.1%	14.8%	18.2%	0.582
Alcohol drinker	75.5%	75.0%	81.8%	0.238
Low physical Activity	70.4%	69.3%	84.4%	0.019
Dietary intake pattern, mean±se				
Total energy intake (kcal)	2176±37	2158±33	2402±168	0.143
Total sugar intake (grams)	109±2.4	108±2.4	122±10.9	0.203
Sugar sweetened beverage (SSB) consumers	65.3%	66.1%	54.7%	0.131
Type of SSB intake				
none	22.0%	21.5%	27.7%	0.563
non-soda SSB [3]	17.8%	18.2%	14.0%	
diet soda only	12.8%	12.4%	17.5%	
regular soda only	23.2%	23.2%	22.6%	
multiple types [4]	24.2%	24.7%	18.2%	
Liver-related clinical measurements				
CAP (dB/m), mean±se	340±1.5	343±1.6	313±9.2	0.006
LSM (kPa), mean±se	7.5±0.4	7.5±0.4	8.5±1.1	0.372
Fibrosis Stage				
F0 (<7 kPa)	70.6%	71.4%	61.2%	0.215
F1 (7-9 kPa)	12.5%	12.7%	10.5%	
≥F2 (> 9 kPa)	16.9%	16.0%	28.3%	
ALT (U/L), mean±se	28.5±0.9	27.8±1.0	37.4±4.1	0.003
AST (U/L), mean±se	23.4±0.5	22.9±0.4	29.5±2.4	0.013
BMI				
normal	6.0%	5.3%	14.8%	0.057
overweight	23.7%	24.2%	16.8%	
obese	70.3%	70.5%	68.5%	

[1] Raw number of participants in this study without adjusted for sample survey design.

[2] Results were obtained after adjusted for sample weights and complex study design.

[3] Individuals who consumed sweetened drinks, including fruit-flavored juice, sweetened tea/coffee, sport and energy drinks were defined as non-soda intake.

[4] Individuals who consumed above two types of SSB or diet soda and any types of SSB were defined as multiple SSB consumers.

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2209-A | LIFESTYLE FACTORS AFFECTING NEW ONSET NONALCOHOLIC FATTY LIVER DISEASE

Yosuke Takahata[1], Atsushi Takahashi[2], Yukio Anzai[3], Naoto Abe[1], Tatsuro Sugaya[1], Masashi Fujita[1], Manabu Hayashi[1], Kazumichi Abe[4] and Hiromasa Ohira[1], (1) Department of Gastroenterology,Fukushima Medical University School of Medicine, (2)Fukuoka University, (3)Department of Gastroenterology,Watari Hospital, (4) Fukushima Medical University School of Medicine, Fukushima, Japan

Background: Evidence for the influence of lifestyle factors on nonalcoholic fatty liver disease (NAFLD) onset is limited because the association between lifestyle and NAFLD has been reported mostly based on cross-sectional studies. Our purpose was to elucidate which lifestyle factors are associate with NAFLD onset by a longitudinal study. **Methods:** This was a longitudinal study of 1,713 Japanese men and women who underwent multiple health checkups from June 2013 to the end of March 2018 at Watari Hospital in Fukushima, Japan, and they were not diagnosed with NAFLD at the first health checkup; the mean follow-up was 41 months. Baseline characteristics, including lifestyle factors, were compared among participants with and without NAFLD onset. We then conducted Cox regression analyses to identify the association between lifestyle factors and NAFLD onset. **Results:** Among 1,713 participants, 420 (24.5%) developed NAFLD. There were significant differences in body mass index, hepatobiliary enzymes, lipids, glucose, smoking and fast eating between participants with and without NAFLD onset. A multivariable logistic regression analysis adjusted for sex, age and lifestyle factors showed that fast eating (hazard ratio (HR): 1.51, 95% confidence interval (CI): 1.24-1.83, $p < 0.01$) and skipping breakfast (HR: 1.49, 95% CI: 1.05-2.10, $p = 0.03$) were risk factors for NAFLD onset. Moreover, fast walking was a preventive factor against NAFLD onset (HR: 0.78, 95% CI: 0.64-0.95, $p = 0.01$). **Conclusion:** These findings could help to identify and prevent future NAFLD onset.

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Disclosure information not available at the time of publication: Atsushi Takahashi, Yukio Anzai, Naoto Abe, Tatsuro Sugaya, Masashi Fujita, Manabu Hayashi, Kazumichi Abe, Hiromasa Ohira

2210-A | LIVER CHEMISTRIES TRENDS IN PREGNANT PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

Zoe Finer[1], Christine R Lopez[2], Suzanne R. Sharpton[2], Rolanda Lister[2], Jennifer Thompson[2], Yue Gao[2], Christopher Lindsell[2] and Manhal Izzy[2], (1)Vanderbilt University School of Medicine, (2)Vanderbilt University Medical Center

Background: The pathophysiology of non-alcoholic fatty liver disease (NAFLD) is linked with insulin resistance and oxidative stress, both of which can be heightened in pregnancy. However, the effects of pregnancy on NAFLD are not well-defined. This study aimed to evaluate the possibility of worsening liver inflammation, as reflected by liver chemistries, during pregnancy in NAFLD patients. **Methods:** This is a retrospective study of all adult pregnant patients at a Tertiary North American Center between 2000-2021.

Diagnostic codes and keywords from radiology reports identified patients with NAFLD prior to pregnancy compared to age-matched controls without liver disease. Patients without documented aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet values within 2 years prior to conception were excluded. For pre-pregnancy AST/ALT values, the value closest to the date of pregnancy was used. For during-pregnancy AST/ALT values, the highest value during pregnancy was used. Multivariate linear regression was used for during pregnancy AST/ALT and logistic regression was used for categorical outcomes. **Results:** 285 patients were included with 117 NAFLD cases and 168 controls. Patients with NAFLD had significantly higher pre-pregnancy transaminases compared to controls. However, transaminases were comparable between the two groups during pregnancy, and so were the mean differences during pregnancy compared to pre-pregnancy (Table 1). In multivariate analysis, NAFLD ($p = 0.39$), pre-pregnancy AST ($p = 0.65$), and the interaction between NAFLD and pre-pregnancy AST ($p = 0.60$) were not associated with AST level during pregnancy. Furthermore, NAFLD ($p = 0.31$), pre-pregnancy ALT ($p = 0.70$), and the interaction between NAFLD and pre-pregnancy ALT ($p = 0.75$) were not associated with ALT level during pregnancy. In a subgroup analysis of patients with NAFLD, being at risk for advanced fibrosis (defined by having intermediate or high FIB4 or NAFLD and metabolic syndrome) was not associated with during pregnancy AST or ALT (AST $p = 0.71$, ALT $p = 0.50$). Of note, neither NAFLD ($p = 0.18$) nor its interaction with baseline transaminases predicated gestational diabetes ($p = 0.11$). **Conclusion:** Neither NAFLD nor its severity influenced the trends of transaminases during pregnancy. Changes in liver enzymes during pregnancy should not be attributed to NAFLD despite the pregnancy-related metabolic changes. Multi-center prospective studies are needed to validate our findings.

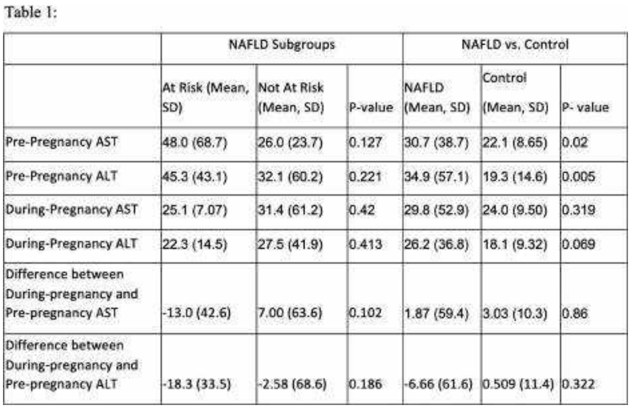

Table 1:

	NAFLD Subgroups			NAFLD vs. Control		
	At Risk (Mean, SD)	Not At Risk (Mean, SD)	P-value	NAFLD (Mean, SD)	Control (Mean, SD)	P- value
Pre-Pregnancy AST	48.0 (68.7)	26.0 (23.7)	0.127	30.7 (38.7)	22.1 (8.65)	0.02
Pre-Pregnancy ALT	45.3 (43.1)	32.1 (60.2)	0.221	34.9 (57.1)	19.3 (14.6)	0.005
During-Pregnancy AST	25.1 (7.07)	31.4 (61.2)	0.42	29.8 (52.9)	24.0 (9.50)	0.319
During-Pregnancy ALT	22.3 (14.5)	27.5 (41.9)	0.413	26.2 (36.8)	18.1 (9.32)	0.069
Difference between During-pregnancy and Pre-pregnancy AST	-13.0 (42.6)	7.00 (63.6)	0.102	1.87 (59.4)	3.03 (10.3)	0.86
Difference between During-pregnancy and Pre-pregnancy ALT	-18.3 (33.5)	-2.58 (68.6)	0.186	-6.66 (61.6)	0.509 (11.4)	0.322

Disclosures: The following people have nothing to disclose: Zoe Finer, Suzanne R. Sharpton, Manhal Izzy

Disclosure information not available at the time of publication: Christine R Lopez, Rolanda Lister, Jennifer Thompson, Yue Gao, Christopher Lindsell

2211-A | LIVER INDEXES AS A PREDICTOR OF ATRIAL FIBRILLATION AND STROKE IN TYPE 2 DIABETES MELLITUS: A POPULATION-BASED COHORT STUDY

Helen Huang, Royal College of Surgeons in Ireland, Oscar Hou In Chou, The University of Hong Kong, Jiandong Zhou, University of Oxford, Gary Tse, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University; Kent and Medway Medical School, University of Kent and Canterbury Christ Church University; Hong Kong Metropolitan University and Cardiovascular Analytics Group (CVAG)

Background: The fibrosis-4 (FIB-4) index and the AST to platelet ratio index (APRI) were proposed to be non-invasive liver fibrosis indicator for screening and risk stratification of metabolic dysfunction associated fatty liver disease (MAFLD) amongst Type-2 diabetes mellitus (T2DM) patients. However, the predictive value of liver indexes on the development of atrial fibrillation and stroke in T2DM has not yet been addressed. **Methods:** The retrospective observational study in Hong Kong analyzed T2DM patients recruited from 1st January 2000 to 31st December 2003 and followed up until 31st December 2019. The primary outcome were new-onset atrial fibrillation (AF) and stroke, and mortlaity as secondary outcomes. We used univariate Cox proportional hazard models with Kaplan-Meier curves, as well as multivariate models adjusted demographics, past co-morbidities and medication. The optimal cut-offs were found with maximally selected rank statistics. **Results:** This cohort included 6,354 patient patients (male: 2,676, 41.0%; baseline age median: 67.16 [56.38 - 74.44] years; follow-up median: 16.67 [IQR: 10.63-18.05] years) with complete laboratory results. Univariate Cox regressions revealed significant associations of FIB-4 quartiles with all outcomes except for hemorrhagic stroke, while APRI quartiles were associated with all except for atrial fibrillation and transient ischemic stroke (Figure 1). Multivariable analyses identified quartile 3 for FIB-4 to be significantly associated with atrial fibrillation, ischemic and hemorrhagic stroke (all outcomes $HR < 1.0$, 95%CI: [< 1.0], $p < 0.05$). Quartile 3 for APRI were associated with ischemic stroke only (HR: 1.17, 95%CI: [1.02-1.37], $p = 0.02$). FIB-4 and APRI indexes at quartile 4 to be associated with an increased risk of all-cause mortality (FIB4 hazard ratio [HR]: 1.02, 95% confidence interval [CI]: [1.02 – 1.16], $p = 0.007$; APRI HR: 1.17, 95%

CI: [1.09 – 1.25], $p < 0.0001$). The results remained consistent in the sensitivity analysis. **Conclusion:** Liver fibrosis biomarkers FIB-4 and APRI predicted an increased risk of ischemic stroke and all-cause mortality amongst T2DM patients during a 16-year period, while FIB-4 independently predicted an increased risk in atrial fibrillation.

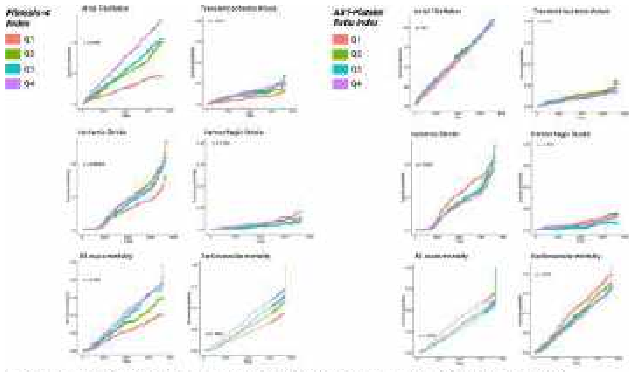

Figure 1. Univariate Kaplan Meier Curves demonstrated associations of quartiles with primary and secondary outcomes. Significance is achieved if the p-value is less than 0.05.

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f 2212-A | LIVER STIFFNESS MEASUREMENT BASED COMPOSITE SCORES HAVE COMPARABLE PROGNOSTIC PERFORMANCE TO HISTOLOGICALLY ASSESSED FIBROSIS STAGE

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

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Background: Histologically assessed fibrosis in patients with non-alcoholic fatty liver disease (NAFLD) carries prognostic information. Here we aim to compare prognostic accuracy of histologically assessed fibrosis with liver stiffness measured by vibration-controlled transient elastography (LSM-VCTE), Agile 3+, Agile 4 and Fibroscan-AST (FAST) scores. **Methods:** This was an individual patient data meta-analysis of patients with NAFLD who had baseline biopsy, LSM-VCTE and blood parameters measured within 6 months. The primary outcome was a composite endpoint of all-cause mortality, decompensation of cirrhosis (ascites, variceal haemorrhage, hepatic encephalopathy), hepatocellular cancer, liver transplantation or progression to model of end stage liver disease score e 15. Prognostic accuracy for each non-invasive test (NIT) was compared to histology using time-dependent area under the curve (tAUC) analysis. Cumulative sensitivity and dynamic specificity are reported for a time horizon of 5 years for previously published thresholds for all index tests. **Results:** Data were available for 2,518 patients with biopsy proven NAFLD, of whom 135 (5.4%) were excluded due to unreliable LSM-VCTE values leaving 2383 in the final analysis (49% females, median age 54 (IQR 19) years, 42% with type II diabetes mellitus). The composite endpoint was seen in 5.3% (n = 127) after a median follow-up of 56 months. LSM based composite scores other than FAST showed a good and comparable tAUC to histology (Figure 1) and head-to-head pairwise comparison of LSM, Agile3 + and Agile4 against histology in all time frames show no statistically significant differences in predicting composite endpoints. For a time horizon of 5 years, the cumulative sensitivity (cSe) and dynamic specificity (dSp) were respectively 58% and 71%, and 44% and 90% for F3 and F4; 61% and 67%, and 36% and 91% for LSM-VCTE 10 kPa d LSM < 20 kPa, and LSM e 20 kP; 80% and 62%, and 71% and 73% for 0.451 d Agile3 + < 0.679, Agile3+ e 0.679; 55% and 83%, and 37% and 91% for 0.251 d Agile 4 < 0.565, Agile 4 e 0.565; and 91% and 37%, and 51% and 74% for 0.35 d FAST < 0.67, FAST e 0.67. **Conclusion:** Composite scores that include liver stiffness measurements (Agile 3 and Agile 4) have comparable prognostic accuracy to that of histologically assessed fibrosis and could be used for risk stratification in clinical practice. Assessing how change in composite scores over time impacts prognosis should be the focus of future studies.

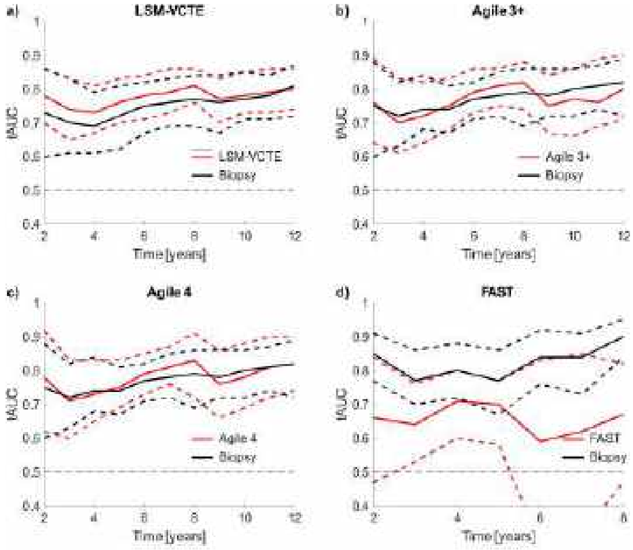

Figure 1 Time-dependent AUCs for LSM-VCTE (a), Agile 3+ (b), Agile 4 (c), and FAST (d) in head-to-head comparison with liver histology (in black). Dashed lines represent the 95% confidence intervals for all AUC estimates. Horizontal dashed lines represent an AUC of 0.5.

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f 2213-A | LONGITUDINAL STUDY OF NAFLD PROGRESSION USING PAIRED BIOPSIES IN A WELL-CHARACTERISED EUROPEAN COHORT

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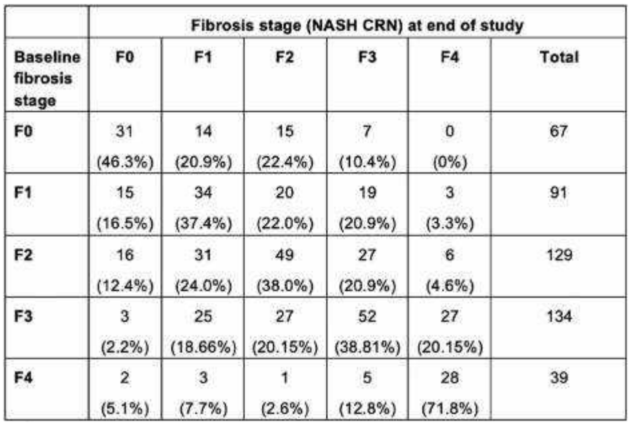
Background: There remains uncertainty about the natural history and prognosis of non-alcoholic fatty liver disease (NAFLD). We evaluated the transition between fibrosis stages in NAFLD patients with serial biopsies and related them to clinically relevant outcomes including hepatocellular carcinoma (HCC) and death. **Methods:** The study included patients enrolled in the European NAFLD Registry with e 2 biopsies taken > 240 days apart. Biopsies were scored by expert liver pathologists using the NASH CRN scoring system. Fibrosis progression rate was computed as the change in fibrosis stage over the time interval between the paired biopsies. The Kaplan-Meier method was employed to evaluate time to death and HCC diagnosis. The log-rank test was then used to compare the distributions. **Results:** We included 460 participants (59.3% male) that had undergone at least 2 liver biopsies of sufficient quality for evaluation. At baseline, age (mean ± SD) 51.9 ± 11.9; BMI 32.6 ± 5.3 kg/m^2. 51.5% had type 2 diabetes. 134 (29.1%) had NAFL and 326 (70.9%) NASH. The distribution of fibrosis stages was F0 67 (14.6%), F1 91 (19.8%), F2 129 (28.0%), F3 134 (29.1%), F4 39 (8.5%). The median interval between the paired biopsies was 4.75 years (range 0.7-23.8). Cases were followed for 0.7 to 29.8 years (mean/median of 8.3/6.3 yrs) from baseline and for up to 20 years from the second biopsy (mean/median of 3.6/1.8 yrs), providing > 3,819 person-years of follow-up for clinical outcomes. Fibrosis progressed in 138 patients (30%), mean interval 4.7 yrs/stage (ie 0.2 stages/yr); regressed in 128 (27.8%) patients, 2.4 yrs/stage (ie 0.4 stages/yr); and remained stable in 194 (42.2%) patients. Time to progress from F2 to F3: 6.7 ± 3.8 yrs, and from F3 to F4: 3.8 ± 2.0 yrs, suggesting fibrosis progression may accelerate as disease advances. Inter-stage change is summarised in Table 1. A total of 28 (6%) patients are known to have died at the time of the analysis. Seven (1.5% of cases, 25% of deaths) were liver-related. Ten (2.2%) patients had developed HCC during follow-up. Subsequent development of HCC was strongly associated with advanced fibrosis stages F3/4 at baseline (p-value < 0.0001). Survival probability was also lower in advanced fibrosis at baseline (p-value $= 0.00049$). **Conclusion:** Serial biopsy data from a European NAFLD cohort shows that 30% of patients exhibit fibrosis progression, whilst 27% exhibit regression over a mean interval of 4.8 years. Rates of change suggest that fibrogenesis progression may accelerate as disease becomes more advanced. As previously reported, cases with more advanced fibrosis exhibit worse survival. Further studies in larger cohorts with protocolised biopsies are warranted.



	Fibrosis stage (NASH CRN) at end of study					
Baseline fibrosis stage	F0	F1	F2	F3	F4	Total
F0	31 (46.3%)	14 (20.9%)	15 (22.4%)	7 (10.4%)	0 (0%)	67
F1	15 (16.5%)	34 (37.4%)	20 (22.0%)	19 (20.9%)	3 (3.3%)	91
F2	16 (12.4%)	31 (24.0%)	49 (38.0%)	27 (20.9%)	6 (4.6%)	129
F3	3 (2.2%)	25 (18.66%)	27 (20.15%)	52 (38.81%)	27 (20.15%)	134
F4	2 (5.1%)	3 (7.7%)	1 (2.6%)	5 (12.8%)	28 (71.8%)	39

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f 2214-A | LONG-TERM HEALTH CONSEQUENCES OF PEDIATRIC NONALCOHOLIC FATTY LIVER DISEASE

Jeffrey Schwimmer[1,2], Cynthia A. Behling[3], Sheila L Noon[1], Nhat Thai[1], Lauren F Chun[1], Rhys David[2], Nidhi P. Goyal[4], Warren L Shapiro[1,5], Andrew Wang[1], Elizabeth L. Yu[1] and Kimberly P Newton[1,2], (1)UC San Diego, (2)Rady Children's Hospital San Diego, (3) Pacific Rim Pathology, (4)University of California, San Diego, (5)Kaiser Permanente

Background: The incidence of nonalcoholic fatty liver disease (NAFLD) is on the rise in children, but the natural history and associated outcomes of this disease remain poorly understood. To fill this gap, we conducted a longitudinal cohort study investigating the progression of NAFLD and its potential implications for health outcomes, including mortality and incident comorbidity. **Methods:** Our study included patients who were diagnosed with NAFLD as children between the ages of 2-18 years, from 2000 to 2017. We extracted data from electronic medical records, including laboratory tests, liver imaging, and liver histology reports. The diagnosis of NAFLD was based on imaging or liver biopsy showing hepatic steatosis in the absence of other causes of liver disease. Medical records were reviewed from the time of diagnosis of NAFLD to the most recent clinical encounter. Mortality was determined by examining the National Death Index. Surviving participants were invited to partake in a clinical research visit to evaluate their present health status and development of comorbid diagnoses. **Results:** We analyzed a cohort of 1605 children with NAFLD. The mean age at diagnosis was 12.7 ± 3.0 years, and 65.4% of participants were male. The mean duration of follow-up was 7.3 ± 4.2 years, accounting for a cumulative 11,717 person-years. Over this period, 3.8% (60/1605) of children with NAFLD died, with a mortality rate of 512 per 100,000 person-years (95% CI 394 - 655). The age and sex-adjusted standardized mortality ratio relative to the U.S. general population was 48.8 (95% CI 37.6-62.4). We found that older age at diagnosis (adjusted Hazard Ratio (aHR): 1.17, 95% CI: 1.04-1.31), male sex (aHR: 5.08, 95% CI: 1.85-13.91), and higher baseline gamma-glutamyl transferase (GGT) levels (aHR: 1.05, 95% CI: 1.02-1.08) were associated with increased mortality risk. Moreover, among those who died, 47% had liver-related mortality. At baseline, the prevalence of type 2 diabetes, hypertension, dyslipidemia, and obstructive sleep apnea were 4.9%, 8.5%, 21.8%, and 6.9%, respectively, with incidence rates of 879, 1878, 3949, and 1179 new cases per 100,000 person-years at risk. **Conclusion:** Our findings shed light on the natural history of pediatric NAFLD, revealing significant morbidity and mortality risks associated with the disease. The results underscore the need for increased awareness, early detection, and management of NAFLD in children to prevent the development of severe hepatic and extrahepatic comorbidities.

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The following people have nothing to disclose: Cynthia A. Behling, Nidhi P. Goyal, Kimberly P Newton

Disclosure information not available at the time of publication: Sheila L Noon, Nhat Thai, Lauren F Chun, Rhys David, Warren L Shapiro, Andrew Wang, Elizabeth L. Yu

2215-A | MAFLD DIAGNOSTIC CRITERIA CAN EASILY IDENTIFY INDIVIDUALS WITH FATTY LIVER IN LEAN AND OVERWEIGHT INDIVIDUALS AMONG THE INDIAN POPULATION, EVEN WITHOUT HS-CRP

Anand V. Kulkarni[1], Sowmya T R[1], Pravalika Amike[1], Sathwika P[1], Hajera Fathima[2], Santhosh Cp Reddy[1], Shantan Venishetty[1], Manasa Alla[1], Mithun Sharma[3], Nageshwar D Reddy[1] and Padaki Nagaraja Rao[1], (1) Aig Hospitals, Hyderabad, India, (2)Joginpally B R Pharmacy College, (3)Asian Institute of Gastroenterology, Hyderabad, Telangana, India

Background: Metabolic (dysfunction)-associated fatty liver disease (MAFLD) criteria requires at least two metabolic risk abnormalities to be present in patients with lean individual's (Body mass index [BMI] < 25 kg/m^2 in Caucasians and < 23 kg/m^2 in Asians). These criteria also include high-sensitivity C-reactive protein (HS-CRP) and homeostatic model assessment for insulin resistance (HOMA-IR), which are not universally available. There is a paucity of data on the validity of this MAFLD criterion in the Indian population with a BMI < 25 kg/m^2, which we aimed to assess. **Methods:** Consecutive patients diagnosed with NAFLD based on ultrasonography and/or transient elastography attending the outpatient department over a period of 6 months were included prospectively. The primary objective was to assess the prevalence of non-obese NAFLD, and the secondary was to assess the proportion of patients satisfying at least two criteria of MAFLD among lean (Gr. A: BMI < 23 kg/m^2) and overweight individual's (Gr. B. BMI < 25 kg/m^2) for which data from previous studies were included from our centre. **Results:** Of the 301 patients diagnosed with NAFLD, 13.62% (41/301: 95%CI, 9.7-18.5%) were lean, and 17% (51/301; 95% CI, 12.6-22.3) were overweight individual's. Including data from other retrospective studies of non-obese patients, the total number of lean individual's was 95 (Gr. A), and overweight individual's were 63 (Gr. B). The mean age (44.6 vs. 43.9 y) and sex distribution (females: 18% vs. 19%) were similar among the two groups. The mean BMI was higher in Gr. B (23.91 ± 0.58 kg/m^2) than in Gr. A (21.58 ± 1.72 kg/

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

m^2; $P < 0.001$). Similarly, the mean waist circumference was higher in Gr. B (93.4 ± 4.5 cms) than in Gr. A (89.7 ± 6.72 cms; $P < 0.001$). The controlled attenuation parameter score (CAP) was lower in Gr. A (268 ± 45.24 dB/m) than Gr. B (295.37 ± 40.46 dB/m; $P < 0.001$). The liver stiffness measurement, FIB-4 and APRI score were similar among both groups. Similarly, the HDL, triglycerides, HbA1C and fasting blood sugar levels were similar among the two groups. None of the patients had HS-CRP reports available, and only 58 patients (40 among Gr. A and 18 among Gr. B) had HOMA-IR values. The proportion of patients satisfying at least two criteria of MAFLD was lower in Gr. A (87.4%) than in Gr. B (96.8%; $P = 0.04$) despite the absence of complete data. The proportion of patients satisfying three criteria (48.4% and 54%; $P = 0.51$), four criteria (21.1% vs. 23.8%; $P = 0.7$), five criteria (8.4% vs. 3.2%; $P = 0.31$) and six criteria (2.1% vs. 1.6%;$P = 1$) of MAFLD were similar among both groups. **Conclusion:** MAFLD diagnostic criteria can easily identify individual's with fatty liver in lean and overweight individual's among the Indian population, even without HS-CRP.

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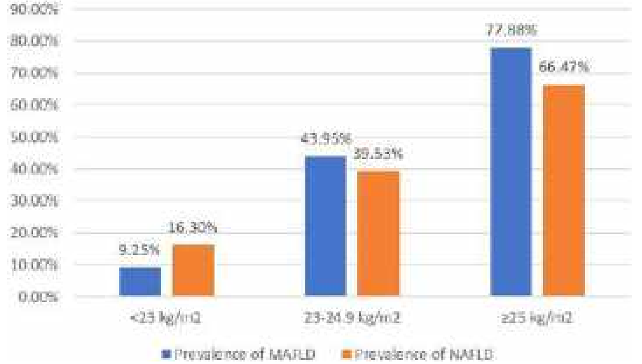
2216-A | MAFLD EXCLUDES LEAN FATTY LIVER DISEASE PATIENTS WITH SIMILAR METABOLIC PROFILES AND HEPATIC FIBROSIS COMPARED TO LEAN HEALTHY SUBJECTS

Ming Yang[1], Huixin Liu[2], Shunmin Guo[3], Pingqiu Shen[3], Ying Qiao[3], Wurong Chen[3], Yanqiu Gu[3], Rao Teng[3], Guiping Li[3], Jianzeng Qin[3], Xiaoran Yang[3], Zhi Qi[3], Yi Feng[3], Mengqi He[3], Zhe Liu[3], Wenyao He[3] and Lai Wei[1], (1)Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, (2)Department of Clinical Epidemiology and Biostatistics, Peking University People's Hospital, (3)Meinian Onehealth Healthcare Holding Co., Ltd

Background: The prevalence and clinical characteristics data of lean metabolic dysfunction-associated fatty liver disease (MAFLD) are sparse. We aimed to investigate the clinical characteristics of lean MAFLD and the impact of new definition on the prevalence of fatty liver disease in the lean population. **Methods:** We consecutively enrolled 2,019 Chinese adults in 31 health check-up centers from 11 cities in 2022. A detailed questionnaire and the results of blood biochemical examinations and transient elastography were collected. **Results:** The prevalence of Lean MAFLD in the overall and MAFLD population was 3.3% (67 of 2,019) and 7.2% (67 of 925), respectively. Compared with non-lean MAFLD subjects, Lean MAFLD subjects were elder, more likely to be women, and to have lower proportion of metabolic syndrome, waist circumference, diastolic blood pressure, liver enzymes, HOMA-IR, AST-to-platelet ratio index, NAFLD fibrosis score, liver stiffness measurement, controlled attenuation parameter (CAP) but higher high-density lipoprotein cholesterol. The prevalence of MAFLD was lower than that of nonalcoholic fatty liver disease (NAFLD) in the lean population (9.25% vs. 16.30%, $P < 0.05$). Among 128 lean subjects with fatty liver, 59 fulfilled the diagnostic criteria for both lean MAFLD and lean NAFLD (lean MAFLD+NAFLD+), 59 lean MAFLD-NAFLD+, and 8 lean MAFLD+NAFLD-. The metabolic dysfunction and hepatic fibrosis in lean MAFLD-NAFLD+ subjects were comparable to those in lean healthy subjects. **Conclusion:** The new definition of MAFLD may reduce the prevalence of fatty liver disease in lean population but can exclude patients who have comparable metabolic profiles and hepatic fibrosis with lean healthy subjects.



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2217-A | MAJOR ADVERSE CARDIOVASCULAR AND MORTALITY OUTCOMES WITH GLP-1 RECEPTOR AGONISTS COMPARED TO OTHER GLUCOSE-LOWERING DRUGS IN NONALCOHOLIC FATTY LIVER DISEASE WITH TYPE 2 DIABETES: A REAL EVIDENCE

Arunkumar Krishnan, Atrium Health Levine Cancer Institute, Carolin Victoria Schneider, University Hospital

Rwth Aachen, Dipatsree Mukherjee, Apex Institute of Medical Sciences, William R. Hutson, West Virginia University School of Medicine and Saleh A Alqahtani, Johns Hopkins University School of Medicine; King Faisal Specialist Hospital and Research Center

Background: Nonalcoholic fatty liver disease (NAFLD) is a serious health problem due to its consequences. Clinical trials showed that GLP-1 receptor agonists (GLP-1RA) protect the heart in an array of patients with type 2 diabetes (T2D). However, the extent of these benefits in patients with NAFLD and T2D needs further investigation. Thus, we investigated the major adverse cardiovascular events (MACE) and mortality for patients with NAFLD and T2D taking GLP-1RA compared to other glucose-lowering drugs. **Methods:** This was a propensity score-matched, population-based cohort study with consecutive patients diagnosed with NAFLD and T2DM using the TriNeTx dataset. Cohort entry was defined as the date of the first-ever prescription for one of the drugs of interest (GLP-1 RA, sodium–glucose cotransporter-2 inhibitors [SGLT-2i] or other second/third-line drugs) during the study period. We used a lag of 6 months for all exposures to minimize protopathic bias. We performed a 1:1 propensity score matching (PSM) to reduce confounding effects. The primary outcomes were defined as the first incidence of new-onset heart failure (HF), composite MACE, and a composite of cerebrovascular disease, and the secondary outcome was mortality. We conducted a secondary analysis and sensitivity analysis to assess the robustness of our findings. The outcomes were estimated using a Cox proportional hazards model with hazard ratios (HR) and 95% confidence intervals (CI). **Results:** A total of 53249 new users of GLP-1RA were identified, and 39795 patients who received SGLT-2i were included in the control. For the secondary analysis, 2638687 were in second-or third line anti-diabetic treatment. The GLP-1RA group was non-inferior to the SGLT-2i group in terms of CV outcomes: the incidences of MACE (hazard ratio [HR], 1.06), HF (HR, 10.9), cerebrovascular diseases (HR, 0.99) were similar to SGLT-2i group (Table 1). Moreover, the mortality rates between the GLP-1RA were non-inferior to the SGLT-2i group (HR, 1.06). When compared to patients taking second-or third-line glucose-lowering drugs also, a significantly lower risk of MACE, HF, and mortality was observed (HRs 0.90). Sensitivity analysis showed a similar magnitude to the one generated in the primary and secondary analyses. **Conclusion:** In patients with NAFLD and T2D, initiators receiving GLP1-RA showed a significantly lower incidence of MACE and all-cause mortality rates. However, GLP1-RA was not inferior to SGLT-2i. These findings further suggest that GLP1-RA and SGLT-2i may provide additional protective effects against MACE.

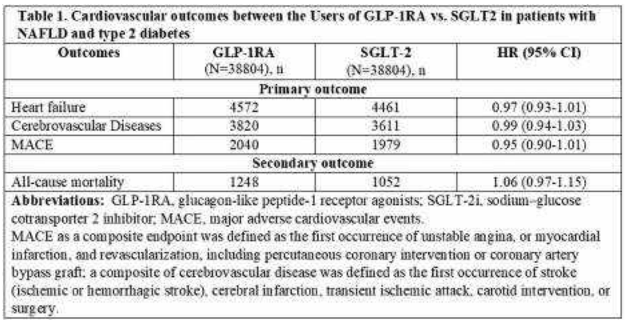

Table 1. Cardiovascular outcomes between the Users of GLP-1RA vs. SGLT2 in patients with NAFLD and type 2 diabetes

Outcomes	GLP-1RA (N=38804), n	SGLT-2 (N=38804), n	HR (95% CI)
Primary outcome			
Heart failure	4572	4461	0.97 (0.93-1.01)
Cerebrovascular Diseases	3820	3611	0.99 (0.94-1.03)
MACE	2040	1979	0.95 (0.90-1.01)
Secondary outcome			
All-cause mortality	1248	1052	1.06 (0.97-1.15)

Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT-2i, sodium–glucose cotransporter 2 inhibitor; MACE, major adverse cardiovascular events.
MACE as a composite endpoint was defined as the first occurrence of unstable angina, or myocardial infarction, and revascularization, including percutaneous coronary intervention or coronary artery bypass graft; a composite of cerebrovascular disease was defined as the first occurrence of stroke (ischemic or hemorrhagic stroke), cerebral infarction, transient ischemic attack, carotid intervention, or surgery.

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2218-A | MANAGEMENT OF NONALCOHOLIC FATTY LIVER DISEASE IN A PRIMARY CARE SETTING

Julia R Gips[1], Lisa Yanek[1], Jiajun Wu[1], Tinsay A. Woreta[2], James P. Hamilton[2] and Jeanne M Clark[1], (1) Johns Hopkins University School of Medicine, (2)Johns Hopkins Medicine, Baltimore, MD

Background: The prevalence of nonalcoholic fatty liver disease (NAFLD) has grown exponentially in recent years. In many cases, primary care physicians (PCPs) are the first to suspect or diagnose NAFLD, often based on steatosis seen on abdominal imaging or elevated liver enzymes. While guidelines have been published detailing NAFLD management in the primary care setting, it is unclear what PCPs are doing in practice. **Methods:** For this retrospective cohort study, we used electronic health record (EHR) data from over 650,000 patients who had completed at least one PCP visit within a large Maryland medical network between July 2016 and March of 2023. Using ICD-10 codes, we extracted information including demographics, comorbidities, laboratory results, prescriptions, imaging orders, and referrals, on all patients who had a billed diagnosis of NAFLD or NASH during this time period. We then performed descriptive analyses within RStudio. **Results:** We identified 19,143 patients who had a diagnosis code of NAFLD (88.6%) and/or NASH (13.2%) at their PCP visit. Just over half (54.3%) were female, mean age was 55.2 years, and mean BMI was 31.1 kg/m^2. More than 50% of patients had hypertension and hyperlipidemia, and 35% had diabetes. Prior to diagnosis, 64% had an abdominal ultrasound, 41% an abdominal CT, and 12% an abdominal MRI. At the same visit as

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the diagnosis, about 7% had ultrasound elastography ordered, 6% a liver biopsy, and less than 1% magnetic resonance elastography. During a mean follow-up time ranging from 0 to 7 years (mean 1.3 ± 1.8), patients had a mean of 11 visits (for any reason), during which 26% were identified as having fibrosis or cirrhosis. Only 19% overall were referred to a nutritionist and 11% had an appointment; 2.2% were referred to hepatology and 6% had an appointment. Less than 35% of patients had abdominal imaging ordered at any time after their first NAFLD visit. While nearly 80% of patients had overweight or obesity based on BMI, less than 15% were prescribed weight loss medication. **Conclusion:** Despite published recommendations on NAFLD management, PCPs are not following guidelines for risk stratification, referral to specialists, monitoring for fibrosis, or prescribing weight loss medication. As a result, care of patients with NAFLD, including a substantial minority with fibrosis or cirrhosis, may be suboptimal. Patients might benefit from targeted education of PCPs on the topic of NAFLD and improved support for its management in the primary care setting including better access to non-invasive fibrosis screening.

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Disclosure information not available at the time of publication: Lisa Yanek, Jiajun Wu, James P. Hamilton, Jeanne M Clark

2219-A | MEASURES OF CARDIOMETABOLIC RISK AND ADVANCED FIBROSIS IN PRIMARY CARE PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Andrew Schreiner, Medicine University of South Carolina

Background: Advanced fibrosis is the best predictor of future severe liver disease outcomes in patients with NAFLD. Though emerging evidence suggests significant roles for weight loss and diabetes avoidance may play roles in preventing advanced fibrosis, less is known about the relationship of other cardiometabolic risk factors with NAFLD progression to advanced fibrosis. In this study, we aimed to compare measures of cardiometabolic risk by progression to high-risk for advanced fibrosis in primary care patients with NAFLD. **Methods:** We performed a retrospective cohort study of primary care patients with NAFLD in a between 2012 and 2021. We evaluated patients with NAFLD and Fibrosis-4 Index (FIB-4) scores $<$ 2.67 within 6 months of NAFLD ascertainment. Patients with preceding diagnoses of cirrhosis were excluded. Patients were followed from index FIB-4 until the outcome of a FIB-4 $\geq$ 2.67 or the end of the study period. Variables of interest were body mass index (BMI), systolic blood pressure (SBP), hemoglobin A1c (HgbA1c), triglycerides, low-density lipoprotein (LDL), thyroid stimulating hormone (TSH), estimated glomerular filtration rate (eGFR), and smoking status. Variables were treated as continuous variables and categorized by the threshold for primary care therapy intensification. Analyses were performed for the whole cohort and by the occurrence of a high-risk FIB-4 score. Chi square tests were used to compare categorical variables and two sample t-tests were used for continuous variables. **Results:** The cohort included 1,347 patients with a mean follow-up of 2.6 years (SD 2.5). Patients had a median of 9 (IQR 2-22) BMI and SBP values, 2 (IQR 1-4) HgbA1c values, and 4 (IQR 2-9) eGFR values. Of the cohort, 258 (19%) had a subsequent FIB-4 $\geq$ 2.67. A higher proportion of patients with a high-risk FIB-4 outcome had an eGFR $<$ 59 ml/min (54% vs. 24%, $p < 0.001$), a TSH $>$ 4.94 mIU/L (9% vs. 5%, $p = 0.043$), and were smokers (19% vs. 12%, $p = 0.005$), compared to patients without a FIB-4 $>$ 2.67. A lower proportion of patients with FIB-4 $\geq$ 2.67 had a BMI $>$ 30kg/m^2 (61% vs. 70%, $p = 0.002$) compared to patients without a high-risk FIB-4. SBP, HgbA1c, and triglyceride values did not differ between patients by FIB-4 outcome. **Conclusion:** Nearly 1 in 5 primary care patients with NAFLD transitioned to a high-risk FIB-4 score during 2.6 years of follow-up, and reduced kidney function, thyroid dysfunction, and smoking were associated with a future high-risk for advanced fibrosis by FIB-4. Measures of cardiometabolic risk may offer primary care targets for NAFLD management to prevent future advanced fibrosis.

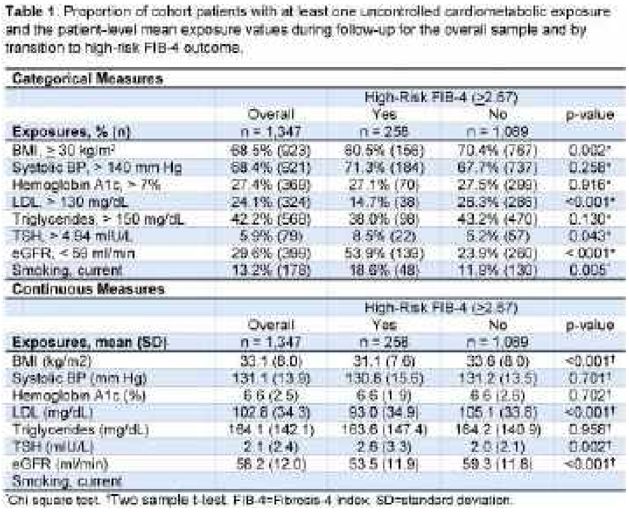

Table 1. Proportion of cohort patients with at least one uncontrolled cardiometabolic exposure and the patient-level mean exposure values during follow-up for the overall sample and by transition to high-risk FIB-4 outcome.

Categorical Measures

		High-Risk FIB-4 ($\geq$2.67)		
	Overall	Yes	No	p-value
Exposures, % (n)	n = 1,347	n = 258	n = 1,089	
BMI, ≥ 30 kg/m^2	68.5% (923)	60.5% (156)	70.4% (767)	0.002*
Systolic BP, > 140 mm Hg	68.4% (921)	71.3% (184)	67.7% (737)	0.258*
Hemoglobin A1c, > 7%	27.4% (369)	27.1% (70)	27.5% (299)	0.916*
LDL, > 130 mg/dL	24.1% (324)	14.7% (38)	26.3% (286)	<0.001*
Triglycerides, > 150 mg/dL	42.2% (568)	38.0% (98)	43.2% (470)	0.130*
TSH, > 4.94 mIU/L	5.9% (79)	8.5% (22)	5.2% (57)	0.043*
eGFR, < 59 ml/min	29.6% (399)	53.9% (139)	23.9% (260)	< 0.001*
Smoking, current	13.2% (178)	18.6% (48)	11.9% (130)	0.005*

Continuous Measures

		High-Risk FIB-4 ($\geq$2.67)		
	Overall	Yes	No	p-value
Exposures, mean (SD)	n = 1,347	n = 258	n = 1,089	
BMI (kg/m2)	33.1 (8.0)	31.1 (7.6)	33.6 (8.0)	<0.001†
Systolic BP (mm Hg)	131.1 (13.9)	130.6 (15.6)	131.2 (13.5)	0.701†
Hemoglobin A1c (%)	6.6 (2.5)	6.6 (1.9)	6.6 (2.5)	0.702†
LDL (mg/dL)	102.6 (34.3)	93.0 (34.9)	105.1 (33.6)	<0.001†
Triglycerides (mg/dL)	164.1 (142.1)	163.6 (147.4)	164.2 (140.9)	0.958†
TSH (mIU/L)	2.1 (2.4)	2.6 (3.3)	2.0 (2.1)	0.002†
eGFR (ml/min)	58.2 (12.0)	53.5 (11.9)	59.3 (11.8)	<0.001†
Smoking, current				

*Chi square test. †Two sample t-test. FIB-4=Fibrosis-4 index; SD=standard deviation.

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

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

Figure 1. Prescribing patterns for weight loss medications

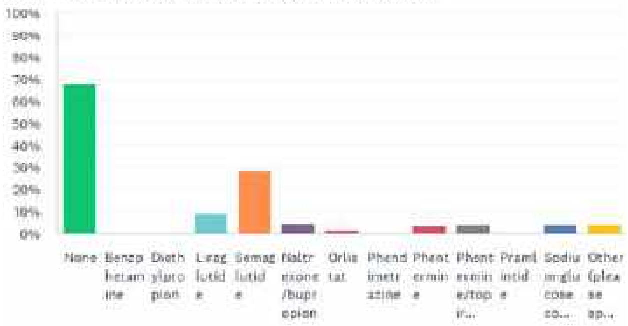
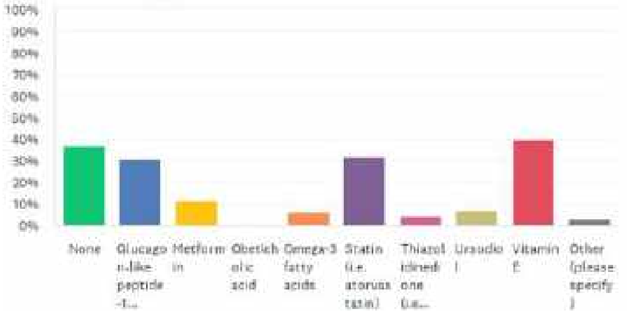


Figure 2. Prescribing patterns for NASH medications



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

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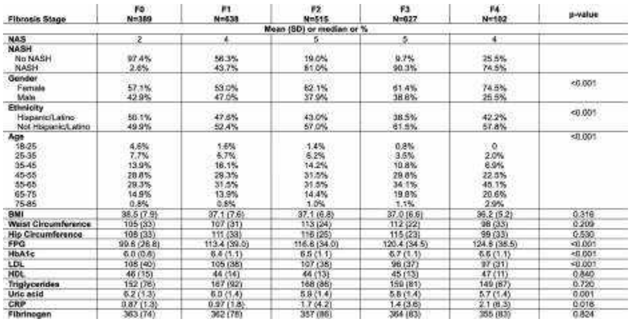
Background: Metabolic comorbidities are well-established risk factors for nonalcoholic steatohepatitis (NASH) and liver fibrosis. Metabolic derangement has been hypothesized to independently contribute to the severity of NASH fibrosis stages. We aimed to describe patients' characteristics and liver histology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



Fibrosis Stage	F0 N=389	F1 N=638	F2 N=515	F3 N=627	F4 N=102	p-value
	Mean (SD) or median or %					
NAS	2	4	5	5	4	
NASH						
No NASH	97.4%	56.3%	19.0%	9.7%	25.5%	
NASH	2.6%	43.7%	81.0%	90.3%	74.5%	
Gender						<0.001
Female	57.1%	53.0%	62.1%	61.4%	74.5%	
Male	42.9%	47.0%	37.9%	38.6%	25.5%	
Ethnicity						<0.001
Hispanic/Latino	50.1%	47.6%	43.0%	38.5%	42.2%	
Not Hispanic/Latino	49.9%	52.4%	57.0%	61.5%	57.8%	
Age						<0.001
18-25	4.6%	1.6%	1.4%	0.8%	0	
25-35	7.7%	6.7%	6.2%	3.5%	2.0%	
35-45	13.9%	16.1%	14.2%	10.8%	6.9%	
45-55	28.8%	28.3%	31.5%	29.8%	22.5%	
55-65	28.3%	31.5%	31.5%	34.1%	45.1%	
65-75	14.9%	13.9%	14.4%	19.8%	20.6%	
75-85	0.8%	0.8%	1.0%	1.1%	2.9%	
BMI	38.5 (7.9)	37.1 (7.6)	37.1 (6.8)	37.0 (6.6)	36.2 (5.2)	0.316
Waist Circumference	105 (33)	107 (31)	113 (24)	112 (22)	98 (33)	0.209
Hip Circumference	108 (33)	111 (38)	116 (25)	115 (23)	99 (33)	0.530
FPG	99.6 (26.8)	113.4 (39.0)	116.8 (34.0)	120.4 (34.5)	124.8 (38.5)	<0.001
HbA1c	6.0 (0.6)	6.4 (1.1)	6.5 (1.1)	6.7 (1.1)	6.6 (1.1)	<0.001
LDL	108 (40)	105 (38)	107 (38)	98 (37)	97 (31)	<0.001
HDL	46 (15)	44 (14)	44 (13)	45 (13)	47 (11)	0.840
Triglycerides	152 (76)	167 (92)	168 (86)	159 (81)	149 (87)	0.720
Uric acid	6.2 (1.3)	6.0 (1.4)	5.9 (1.4)	5.8 (1.4)	5.7 (1.4)	0.001
CRP	0.87 (1.3)	0.97 (1.8)	1.7 (4.2)	1.4 (3.6)	2.1 (6.3)	0.016
Fibrinogen	363 (74)	362 (78)	357 (86)	364 (83)	355 (83)	0.824

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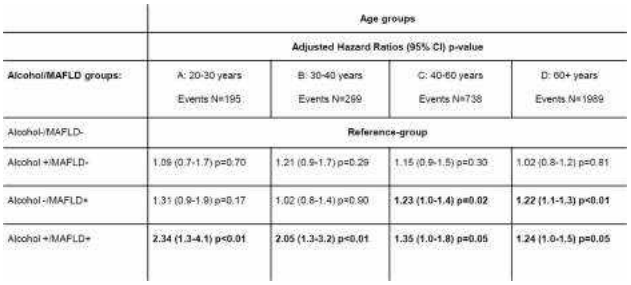
2222-A | METABOLIC DYSFUNCTION ASSOCIATED FATTY LIVER DISEASE AND ALCOHOL USE HAVE A SYNERGISTIC IMPACT ON SURVIVAL AMONG YOUNGER POPULATIONS

Jesse Pustjens[1], Laurens A. Van Kleef[1], Milan J. Sonneveld[2], Harry L. A. Janssen[3], Rob J. De Knegt[4] and Willem Pieter Brouwer[1], (1)Erasmus MC University Medical Center Rotterdam, (2)Erasmus University Medical Center, (3)Erasmus MC, University Medical Center Rotterdam, (4)Erasmus MC, University Medical Center

Background: It is currently unknown whether metabolic dysfunction associated fatty liver disease (MAFLD) with or without the use of alcohol equally impacts on survival across all ages. **Methods:** We studied the association between MAFLD, alcohol use, and the combination with all-cause mortality within the NHANES III cohort. Participants with missing values for classification of MAFLD, alcohol use and/or outcome were excluded. MAFLD was defined according to clinical practice guidelines. Alcohol use was defined as >10 gram or >20 gram daily for women and men, respectively. A total of 12.277 included participants were divided into equally sized age-groups: A) 20-29 ($n=3120$), B) 30-39 ($n=3034$), C) 40-59 ($n=3095$) and D) e 60 ($n=3028$) years. The association between MAFLD ± alcohol use with all-cause mortality was explored across the age groups through multivariable Cox regression analysis adjusted for sex, age, age^2, race, marital status, household income, and smoking. **Results:** Of 12.277 participants, 5.729 (47%) were male, MAFLD was detected in 3.816 (31%) and alcohol use in 1873 (13%). During a median follow-up of 23 years, 3.750 (31%) deaths occurred. Follow-up time was evenly distributed across age-groups, except for the oldest group. Combined presence of MAFLD and alcohol use showed an important synergistic detrimental effect in the younger population, which attenuated by increasing age category: for age-group A/B/C/D: adjusted Hazard Ratio (aHR) 2.34 (1.3-4.1), $p=0.003$, aHR 2.05 (1.3-3.2) $p=0.001$, aHR 1.35 (1.0-1.8) $p=0.049$ and aHR 1.24 (0.9-1.6) $p=0.053$, respectively (Table). In contrast to groups A/D, presence of MAFLD without alcohol was a significant factor impacting on survival for groups C/D (aHR 1.23 $p=0.015$ and aHR 1.22 $p<0.001$, respectively, Table). In groups C/D, alcohol use on top of MAFLD showed a clear additive effect. **Conclusion:** MAFLD and alcohol use show a synergistic detrimental effect on survival in younger populations, while this

synergistic effect attenuated into an additive effect with increasing age. These results further guide screening for at-risk liver disease in the younger, general population, and further support current practices advocating alcohol abstinence among patients with MAFLD.



	Age groups			
	Adjusted Hazard Ratios (95% CI) p-value			
Alcohol/MAFLD groups:	A: 20-30 years Events N=195	B: 30-40 years Events N=299	C: 40-60 years Events N=738	D: 60+ years Events N=1989
Alcohol-/MAFLD-	**Reference-group**			
Alcohol +/MAFLD-	1.09 (0.7-1.7) p=0.70	1.21 (0.9-1.7) p=0.29	1.15 (0.9-1.5) p=0.30	1.02 (0.8-1.2) p=0.81
Alcohol -/MAFLD+	1.31 (0.9-1.9) p=0.17	1.02 (0.8-1.4) p=0.90	**1.23 (1.0-1.4) p=0.02**	**1.22 (1.1-1.3) p<0.01**
Alcohol +/MAFLD+	**2.34 (1.3-4.1) p<0.01**	**2.05 (1.3-3.2) p<0.01**	**1.35 (1.0-1.8) p=0.05**	**1.24 (1.0-1.5) p=0.05**

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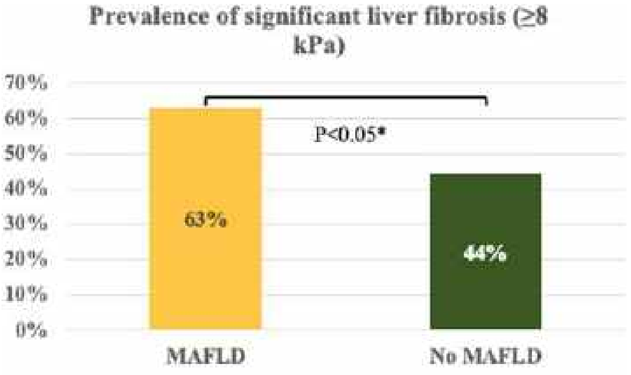
Rob J. De Knegt – Abbvie: Advisor, No, No; GSK: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Echosens: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences: Advisor, No, No; Inventiva: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

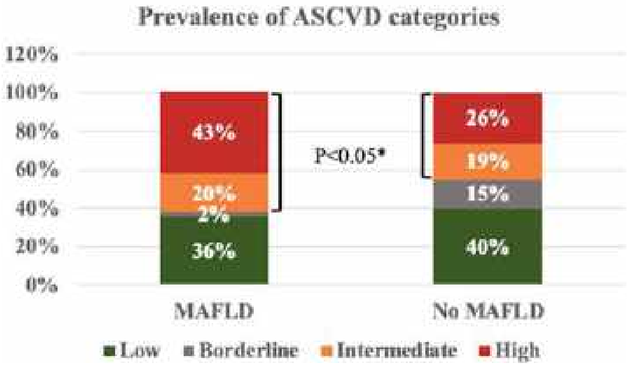
The following people have nothing to disclose: Jesse Pustjens, Laurens A. Van Kleef, Willem Pieter Brouwer

2223-A | METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE AND ITS EFFECT ON CARDIOVASCULAR DISEASE RISK IN PATIENTS WITH HCV

Wesal Elgretli[1], *Mohamed Shengir*[1], *Solomon Sasson*[2], *Luz Ramos Ballesteros*[2], *Philip Wong*[3], *Tianyan Chen*[3], *Marc Deschenes*[2] *and Giada Sebastiani*[1,2], *(1)Mcgill University, (2)Mcgill University Health Centre, (3) Department of Medicine, McGill University Health Centre, Montreal, QC, Canada*

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a new definition of fatty liver disease that does not require the exclusion of secondary causes of hepatic steatosis (HS), such as viral hepatitis. The hepatitis C virus (HCV) is associated with HS and metabolic and cardiovascular dysregulation. Thus, the aim of our study was to determine the prevalence of MAFLD and significant liver fibrosis in HCV mono-infected patients and the frequency of cardiovascular disease (CVD) risk categories. **Methods:** This was a retrospective single-center study of HCV patients in the direct-acting antiviral era, in which HCV patients were evaluated for HS and liver fibrosis with liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) by transient elastography. MAFLD was diagnosed based on the presence of HS, defined as CAP 248 dB/m, plus one of the following metabolic conditions: overweight/obesity (BMI e 30 kg/m^2), type 2 diabetes, or evidence of metabolic dysregulation in lean individual's. According to these criteria, MAFLD was subclassified into three phenotypes.Significant liver fibrosis was defined as LSM e 8 kPa. Factors associated with MAFLD were identified via a multivariate logistic regression model. CVD risk was assessed using the 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimator, and the prevalence of intermediate- and high-risk categories were estimated since both are associated with more cardiovascular events. **Results:** We included 137 HCV mono-infected patients (mean age 59 years, 51% male, 27% with sustained virological response, SVR). The overall prevalence of MAFLD was 34%. Overweight/obesity was the predominant MAFLD phenotype, with a prevalence of 41%, followed by the diabetes phenotype at 31%. Significant liver fibrosis was more prevalent in those with MAFLD than in those without (see Figure, p = 0.036). The multivariate model adjusted for age, sex, infection with HCV genotype 3 revealed that those with SVR had an almost 90% lower risk of MAFLD than those without (adjusted odds ratio 0.11, 95% CI 0.02–0.65). Intermediate-high-risk ASCVD categories were more prevalent in the MAFLD group than in the no MAFLD group (see figure, 63 vs. 45%, p = 0.047). **Conclusion:** MAFLD is frequent among patients with hepatitis C. Nonetheless, achieving SVR significantly reduces its likelihood. MAFLD is associated with a higher prevalence of significant liver fibrosis and an intermediate-to-high CVD risk.





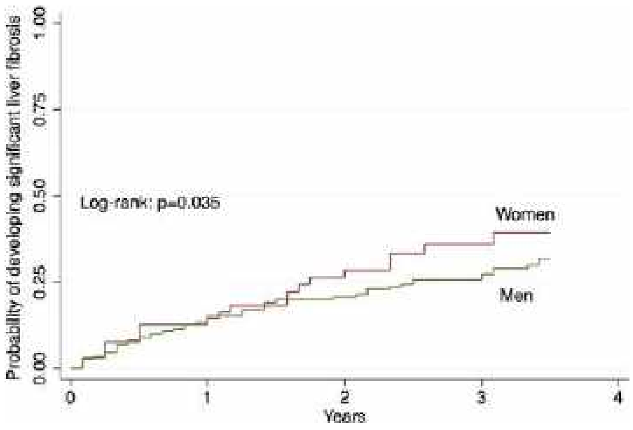
Disclosures: Giada Sebastiani – Merk: Speaking and Teaching, No, No; Gilead: Speaking and Teaching, No, No; Abbvie: Speaking and Teaching, No, No; Novonordisk: Speaking and Teaching, No, No; Pfizer: Speaking and Teaching, No, No; Pfizer: Advisor, No, No; Merk: Advisor, No, No; Novonordisk: Advisor, No, No; Gilead: Advisor, No, No; Theratec: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Wesal Elgretli, Mohamed Shengir, Solomon Sasson, Luz Ramos Ballesteros, Philip Wong, Tianyan Chen, Marc Deschenes

2224-A | METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE IS A SEXUAL DIMORPHIC DISEASE IN PEOPLE WITH HIV

Dana Kablawi[1], Thierry Fotsing Tadjo[1], Jovana Milic[2], Wesal Elgretli[3], Claudia Gioe[4], Bertrand Lebouché[1], Felice Cinque[1], Luz Ramos Ballesteros[1], Antonio Cascio[4], Giovanni Guaraldi[5], Giovanni Mazzola[6] and Giada Sebastiani[7], (1)Mcgill University Health Centre, (2) University of Modena and Reggio Emilia, Modena, Italy, (3)Mcgill University, Montreal, Canada, (4)University of Palermo, (5)Policlinico of Modena, Modena, Italy, (6) Sant'Elia Hospital, Caltanissetta, (7)Department of Medicine, McGill University Health Centre, Westmount, QC, Canada

Background: People with HIV (PWH) are at high risk for metabolic dysfunction-associated fatty liver disease (MAFLD). In the general population, sex differences exist in frequency and severity of MAFLD, with higher prevalence of MAFLD in men, but higher incidence of liver fibrosis in women. Less is known about sex differences in MAFLD and liver fibrosis in the setting of HIV infection. **Methods:** This was a multicenter cohort study of consecutive PWH who underwent screening for MAFLD and liver fibrosis by liver stiffness measurement (LSM) with associated controlled attenuation parameter (CAP). MAFLD was diagnosed as hepatic steatosis with a CAP ≥ 270 dB/m, plus any among type 2 diabetes, overweight (BMI > 25 Kg/m^2) or two other metabolic abnormalities. Significant liver fibrosis was diagnosed as LSM ≥ 8 kPa. Incidence of MAFLD and significant liver fibrosis was assessed through survival analysis. **Results:** 1359 PWH (25% females, 70% HIV mono-infected) were included. Prevalence of MAFLD at baseline was lower in women than men with HIV (17.7% vs. 24.3%, p = 0.013). Conversely, there was no difference in prevalence of liver fibrosis (10.7% vs. 13.4%) between women and men, but this was higher in women after menopause, at 28.5%. Women with MAFLD were more frequently of black ethnicity (48% vs. 14%, p < 0.001), had lower ALT (26.4 ±20.4 vs. 33.4±22.5; p = 0.035), higher HDL cholesterol (1.46±0.57 vs. 1.11±0.33; p < 0.001), lower triglycerides (1.69±0.96 vs. 2.47±2.63; p = 0.035). 485 of these PWH were followed for a median of 3.5 years. Incidence of MAFLD was similar between women and men with HIV. However, incidence of liver fibrosis was higher in women (7.0 per 100 person-years [PY] vs. 5.9 per 100 PY; p = 0.035) (Figure 1). Sex hormones analysis demonstrated higher FSH (41.5 vs 33.8 mIU/mL) and LH (21.4 vs 17.5 IU/L) in women with HIV and liver fibrosis than those without fibrosis. They were also more likely to have prior Tamoxifen exposure (3% vs 0.7%). On multivariable Cox regression, MAFLD (adjusted hazard ratio [aHR] 3.3, 95% CI 2.0-5.6) and female sex (aHR 2.2, 95% CI 1.3-3.5) were independent predictors of developing significant liver fibrosis. **Conclusion:** MAFLD presents with sex differences in PWH. Despite lower rates of MAFLD, women with HIV have higher incidence of significant liver fibrosis than men, especially after the age of 50 and after menopause. Future studies should target adequate consideration of sex differences in the clinical investigation of MAFLD to implement precision medicine for PWH.



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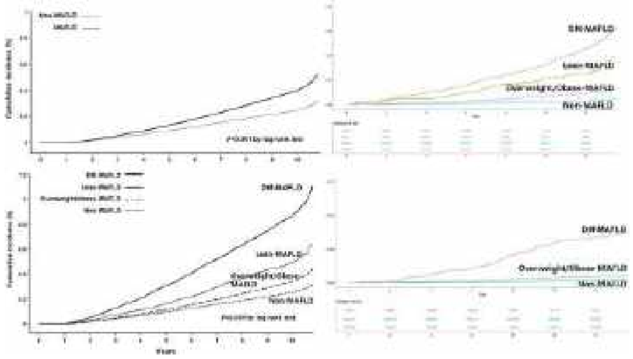
Giada Sebastiani – Merk: Speaking and Teaching, No, No; Gilead: Speaking and Teaching, No, No; Abbvie: Speaking and Teaching, No, No; Novonordisk: Speaking and Teaching, No, No; Pfizer: Speaking and Teaching, No, No; Pfizer: Advisor, No, No; Merk: Advisor, No, No; Novonordisk: Advisor, No, No; Gilead: Advisor, No, No; Theratec: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Dana Kablawi, Thierry Fotsing Tadjo, Jovana Milic, Wesal Elgretli, Claudia Gioe, Bertrand Lebouché, Felice Cinque, Luz Ramos Ballesteros, Antonio Cascio, Giovanni Mazzola

2225-A | METABOLIC DYSFUNCTION–ASSOCIATED FATTY LIVER DISEASE IS ASSOCIATED WITH INCREASED RISK OF LIVER-RELATED COMPLICATIONS: A NATIONWIDE COHORT STUDY

Hyunjae Shin[1], Min Kyung Park[2], Hye-Sung Moon[3], Sung Won Chung[4], Yunmi Ko[2], Youngsu Park[2], Jeayeon Park[2], Moon Haeng Hur[1], Yun Bin Lee[1], Eun Ju Cho[2], Jeong-Hoon Lee[5], Su Jong Yu[2], Jung-Hwan Yoon[2] and Yoon Jun Kim[6], (1)Seoul National University Hospital, (2)Seoul National University College of Medicine, (3)Rexsoft, (4)Asan Medical Center, Seoul, Korea, Republic of (South), (5)Seoul National University College of Medicine, Seoul, South Korea, (6) Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, South Korea

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD), a new definition encompassing the fatty liver disease associated with metabolic disorders, has been recently proposed. We aimed to analyze the long-term outcome of MAFLD, by focusing on liver-related outcomes. **Methods:** We conducted an analysis using data from the National Health Insurance Service of South Korea, which included 7,454,412 participants who took part in the 2009 health screening program. MAFLD was defined by an international expert consensus statement previously proposed. Based on this definition, participants were categorized into four groups: non-MAFLD, DM-MAFLD, overweight/obese-MAFLD, and lean-MAFLD. The primary outcome was the development of liver-related complications, including hepatocellular carcinoma, liver transplantation, decompensated liver cirrhosis, and liver-related mortality. We also examined cirrhosis and hepatocellular carcinoma risks in various MAFLD subgroups using the UK Biobank (UKB) dataset as a validation cohort. The UKB dataset included 466,162 individual's of Caucasian ethnicity. **Results:** Of the study subjects, 2,500,080 (33.5%) had MAFLD. During the median follow-up of 10.3 years, 20,843 patients (0.28%) developed liver-related complications. The MAFLD group had a higher overall risk of liver-related complications than the non-MAFLD group (adjusted cause-specific hazard ratio [aCHR] = 1.24; 95% confidence interval [CI] = 1.21–1.28; P < 0.001). The DM-MAFLD group showed a significantly higher risk of liver-related complications compared to the non-MAFLD group (aCHR = 1.82; 95% CI = 1.74–1.91; P < 0.001), followed by the lean-MAFLD group (aCHR = 1.22; 95% CI = 1.12–1.33; P < 0.001), and the overweight/obese-MAFLD group (aCHR = 1.13; 95% CI = 1.09–1.33; P < 0.001). Subgroup analysis and sensitivity analyses using Fine-Gray models and various definitions of MAFLD showed similar trends of the primary result of our study. In the UKB cohort, the DM-MAFLD group also had a higher risk of developing cirrhosis (aHR = 4.21; 95% CI = 3.43–5.16; P < 0.001) and hepatocellular carcinoma (aHR = 5.52; 95% CI = 3.40–8.95; P < 0.001) than the non-MAFLD group. **Conclusion:** Our study demonstrated a consistent association between MAFLD and the development of liver-related complications, in both our nationwide cohort analysis and among individual's of Caucasian ethnicity. Different subgroups of MAFLD had varying risks of complications, with the DM-MAFLD group showing the highest risk. Stratifying MAFLD patients based on specific criteria representing metabolic disorders may aid in identifying those at a higher risk of liver-related complications. This approach could prove beneficial for screening and surveillance, facilitating early intervention and improved management for patients at an increased risk of liver-related complications.



Disclosures: The following people have nothing to disclose: Min Kyung Park, Sung Won Chung, Yunmi Ko, Youngsu Park, Jeayeon Park, Moon Haeng Hur, Yun Bin Lee, Eun Ju Cho, Jeong-Hoon Lee, Su Jong Yu, Jung-Hwan Yoon, Yoon Jun Kim

Disclosure information not available at the time of publication: Hyunjae Shin, Hye-Sung Moon

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

Daniela Allende[1], Oscar Cummings[2], Alice L Sternberg[3], Cynthia A. Behling[4], Danielle Carpenter[5], Ryan Gill[6], Cynthia D. Guy[7], Matthew M. Yeh[8], Naga P. Chalasani[9], Richard K. Sterling[10], Susanna Naggie[11], Rohit Loomba[12], Jennifer C. Price[13], Mary McLaughlin[14], Colleen Hadigan[14], Holly Crandall[2], Patricia Belt[15], Laura Wilson[15] and David E Kleiner[16], (1)Cleveland Clinic, (2)Indiana University, (3)Johns Hopkins University, (4)Pacific Rim Pathology, (5)Saint Louis University, (6)University of California San Francisco, (7)Duke University, (8)University of Washington, (9)Indiana University Medical Center, Indianapolis, IN, (10)Virginia Commonwealth University Health System, (11)Duke Clinical Research Institute, Durham, NC, (12)University of California, San Diego, San Diego, CA, (13)University of California, San Francisco, (14)National Institute of Allergy and Infectious Disease (NIAID), (15)Johns Hopkins School of Public Health, (16)Laboratory of Pathology, National Cancer Institute, Bethesda, MD

Background: People with HIV (PWH) are at risk for acute and chronic liver injury including alcohol and metabolic disorders. The morphologic spectrum of non-alcoholic fatty liver disease (NAFLD) and utility of NAFLD activity score (NAS) in predicting fibrosis in PWH remains unknown. In this study, we compared liver histological features of NAFLD in individual's with and without HIV. **Methods:** Two ongoing NIDDK funded observational studies had 123 liver biopsies from PWH with NAFLD (NAFLD-PWH) and 3244 liver biopsies from individual's with NAFLD without HIV. From these datasets, we selected 107 NAFLD-PWH biopsies with 107 age, sex, race/ethnicity, BMI and ALT matched controls (i.e. individual's with NAFLD without HIV). Case and control liver biopsies were centrally read using the NASH CRN histological scoring system. **Results:** NAFLD-PWH were comparable to the control group on age (49 vs 47 y), sex (79% male), race (White 65% vs 61% and African American 13%), ethnicity (Hispanic/Latino 26%), diagnosis of type 2 diabetes (24%), and mean BMI (31 kg/m^2). Compared to the control group, NAFLD-PWH had lower steatosis grade (grades 1 or 2 in 63% cases vs 47% controls, p = 0.01), lower inflammation grade (grades 1 or 2 in 70% cases vs 60% controls, p = 0.03), less hepatocyte ballooning (cases: 61% had none, 15% had many versus controls: 45% had none and 27% had many, p = 0.03) and less portal inflammation (8% had more than mild versus 21% of controls). As a result, NAS was lower in NAFLD-PWH (3.17 ± 1.6 vs 3.97 ± 1.59 controls, $p < 0.001$). There was a trend towards lower steatohepatitis in NALFD -PWH (61%) vs controls (71%, p = 0.09). Conditional multiple logistic regression (Table 1) demonstrated that steatosis (p = 0.02), portal inflammation (p = 0.001) and ballooning (p = 0.01) are less associated with NAFLD-PWH than controls while fibrosis was more associated with NAFLD-PWH than controls (p = 0.03). **Conclusion:** The NAS and histologic drivers of fibrosis (e.g., inflammation and hepatocyte ballooning) are less pronounced in NAFLD-PWH and yet fibrosis stage was generally higher when compared to matched controls with NAFLD but no HIV. This may suggest HIV-specific factors beyond hepatic necroinflammation may contribute to fibrosis in NAFLD-PWH.

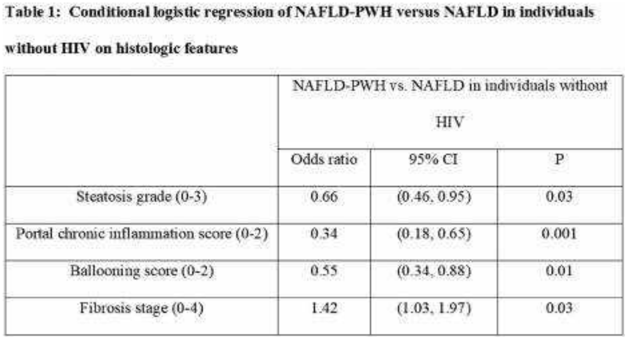


Table 1: Conditional logistic regression of NAFLD-PWH versus NAFLD in individuals without HIV on histologic features

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

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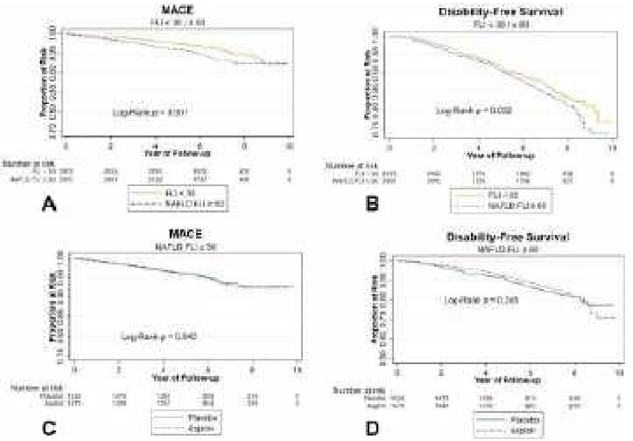
Disclosure information not available at the time of publication: Oscar Cummings, Alice L Sternberg, Danielle Carpenter, Ryan Gill, Matthew M. Yeh, Susanna Naggie, Mary McLaughlin, Colleen Hadigan, Holly Crandall, Patricia Belt, Laura Wilson

2227-A | NAFLD INCREASES THE RISK OF MACE AND REDUCES DISABILITY-FREE SURVIVAL IN OLDER AUSTRALIANS BUT IS NOT AMELIORATED BY ASPIRIN: DATA FROM THE ASPIRIN IN REDUCING EVENTS IN THE ELDERLY (ASPREE) RANDOMISED TRIAL

Daniel Clayton-Chubb[1,2,3], Stuart Keith Roberts[1], Cammie Tran[2], Ammar Majeed[1], Robyn L Woods[2], John Lubel[1], Alexander D. Hodge[3], Hans Schneider[1], John J McNeil[2] and William W. Kemp[1], (1)Alfred Health, (2)Monash University, (3)Eastern Health

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

metabolic comorbidities (including the metabolic syndrome [70.9% vs 12.5%, $p < 0.001$], diabetes [17.8% vs 4.5%, $p < 0.001$], hypertension [82.6% vs 69.6%, $p < 0.001$], and chronic kidney disease [30.3% vs 22.3%, $p < 0.001$]). When adjusting for age, gender, and baseline diabetes, NAFLD had an increased hazard of MACE (HR 1.39, $p = 0.01$) (Figure 1A) and reduced disability-free survival (HR 1.19, $p = 0.02$) (Figure 1B). When stratifying the NAFLD cohort by aspirin vs placebo (with no significant baseline differences between NAFLD-aspirin and NAFLD-placebo), there was no benefit of aspirin in reducing these risks in NAFLD subjects (Figure 1C-D) (both $p > 0.05$). **Conclusion:** Our data indicate that the presence of NAFLD is associated with an increased risk of MACE and reduced disability-free survival in older Australian adults, but this risk is not ameliorated by aspirin. This has implications for risk stratification and clinical relevance for the futility of aspirin as a primary prevention strategy in this population.



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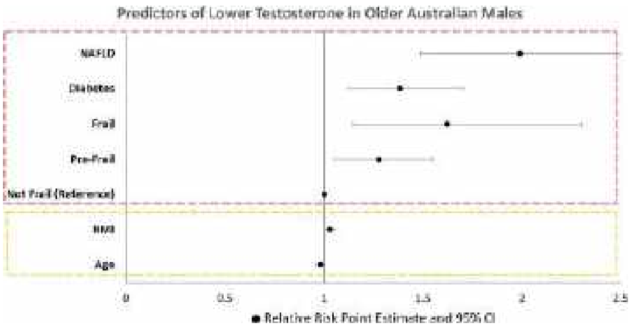
Disclosure information not available at the time of publication: Stuart Keith Roberts, Cammie Tran, Ammar Majeed, Robyn L Woods, John Lubel, Alexander D. Hodge, Hans Schneider, John J McNeil, William W. Kemp

2228-A | NAFLD IS INDEPENDENTLY ASSOCIATED WITH LOWER SERUM TESTOSTERONE IN OLDER AUSTRALIAN MALES: DATA FROM THE ASPIRIN IN REDUCING EVENTS IN THE ELDERLY (ASPREE) RANDOMIZED TRIAL

Daniel Clayton-Chubb[1,2,3], *Cammie Tran*[3], *Bu B Yeap*[4], *Robyn L Woods*[3], *William W. Kemp*[1], *John Lubel*[1], *Ammar Majeed*[1], *Hans Schneider*[1], *Alexander D. Hodge*[2], *John J McNeil*[3] *and Stuart Keith Roberts*[1], *(1) Alfred Health, (2)Eastern Health, (3)Monash University, (4)University of Western Australia*

Background: Lower serum total testosterone (TT) concentrations are associated with increased risks of frailty, stroke, and all-cause mortality in older males, as well as poorer quality of life. Conversely, exogenous testosterone replacement in men with androgen deficiency due to pituitary or testicular disease improves body composition, bone density, and sexual function. Central adiposity is associated with both non-alcoholic fatty liver disease (NAFLD) and lower TT, raising the question of whether NAFLD and lower TT are directly or bidirectionally related. We aimed to assess the associations of lower TT with NAFLD and other health outcomes in a large cohort of community-dwelling older Australian males. **Methods:** We included participants from the ASPREE trial that enrolled 7524 male Australian participants aged e 70 years without independence-limiting physical disability, dementia, or cardiovascular disease. Anthropometry, biochemical, and questionnaire data were collected at baseline. NAFLD was defined as a Fatty Liver Index (FLI) e 60 without excess alcohol intake (> 21 units/week) or steatogenic medications. FLI of < 30 was used to define a no-NAFLD comparator group. Lower TT was defined as the lowest quartile of the ASPREE population (< 12.3 nmol/L) (Q1TT). We excluded those on hormonal modulators or a prostate cancer history. Associations were assessed using Poisson regression with robust variance. **Results:** 4713 participants (mean testosterone 16.6 ± 6.5 nmol/L, age 75.0 ± 4.2 y) were evaluated, with 2090 classified as NAFLD (1300, 62.2%) vs no-NAFLD (790, 37.8%). Comparing those with Q1TT to those without (TT 9.6 ± 2.3 vs 19.0 ± 5.6 nmol/L), those with Q1TT had higher rates of NAFLD (82.7% vs 54.7%, $p < 0.001$) and diabetes (20.8% vs 10.7%, $p < 0.001$), were heavier (BMI 29.4 ± 4.1 vs 27.4 ± 3.6 kg/m^2, $p < 0.001$), and were more likely to be pre-frail/frail (52.1% vs 36.3%, $p < 0.001$). The Q1TT group was slightly younger (74.8 ± 4.2 vs 75.1 ± 4.2 y, $p = 0.029$). Men with Q1TT were more likely to have NAFLD (Relative Risk [RR] 1.99, $p < 0.001$), diabetes (RR 1.38, $p = 0.002$), pre-frailty (RR 1.28, $p = 0.013$), and frailty (RR 1.62, $p = 0.007$) (Figure). BMI was weakly associated with Q1TT (RR 1.03, $p = 0.035$) but age was not ($p > 0.05$). **Conclusion:** In older Australian men, lower TT is associated with a greater risk of having NAFLD, diabetes, and frailty. Whether these associations are causal, and the scope for intervention to improve health of older men with NAFLD, merit further evaluation.



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2229-A | NAFLD, BODY AND MUSCLE COMPOSITION PROFILE IN PATIENTS WITH T2D IN PRIMARY CARE – INTERIM RESULTS FROM THE EPSONIP STUDY

Wile Balkhed[1], Mikael Fredrik Forsgren[2], Patrik Nasr[3], Martin Bergram[3], Fredrik Iredahl[3], Karin Rådholm[3], Carl-Johan Carlhäll[3], Nils Dahlström[3], Peter Lundberg[3], Stergios Kechagias[4], Olof Dahlqvist Leinhard[2] and Mattias Ekstedt[4], (1)Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden, Solna, Sweden, (2)Amra Medical, (3) Linköping University, (4)Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

Background: Sarcopenia is common in patients with advanced liver disease but associations between sarcopenia and early-stage liver disease have not been established. Most NAFLD studies include selected patients from specialist care. We aimed to investigate the prevalence of NAFLD and sarcopenia as well as myosteatosis in primary care patients with type 2 diabetes (T2D) utilizing magnetic resonance imaging (MRI). **Methods:** Patients with T2D, without previous liver disease, were prospectively included from primary care. All participants underwent transient elastography (TE), neck-to-knee MRI, including liver proton density fat fraction (PDFF), quantification of visceral and abdominal subcutaneous adipose tissue (VAT and ASAT) and muscle composition (MC) assessment (thigh muscle fat infiltration [MFI] and fat-free muscle volume z-score [MVZ]) using AMRA® Researcher. MC phenotypes were defined as either only high MFI (myosteatosis), only low MVZ (low muscle volume), adverse MC ([AMC] *i.e.,* high MFI and low MVZ combined), or normal MC. **Results:** The first 151 participants with complete data were studied. Comparing participants with normal MC to those with only high MFI or only low MVZ, there was no difference in age (62 ± 7.9, 65 ± 6.4 and 65 ± 7.3 yrs respectively). There were 37%, 43% and 14% women respectively and women less frequently had only low MVZ compared to men, $p=0.048$. Participants with only high MFI compared to only low MVZ had a greater mean BMI (30.3 ± 3.4 *vs* 26.8 ± 4.5 kg/m^2, $p=0.002$), waist circumference (106.6 ± 7.6 *vs* 98.6 ± 10.6 cm,$p=0.006$), higher VAT (6.83 ± 2.53 *vs* 5.08 ± 2.12 L, $p=0.029$) and ASAT (8.78 ± 2.99 *vs* 7.20 ± 3.92 L, $p=0.036$) (Figure 1). Comparing participants with AMC to all other participants, there was no sex difference (15% *vs* 34% women, $p=0.083$). However, those with AMC were older (69.4 ± 4.3 *vs* 63.3 ± 7.5 yrs, $p=<0.001$), had a greater waist circumference (111.1 ± 12.1 *vs* 103.6 ± 10.5 cm, $p=0.004$), higher VAT (7.96 ± 2.37 *vs* 5.99 ± 2.44 L, $p=0.002$), HbA1c (57.8 ± 12.1 *vs* 51.2 ± 10.5 mmol/mol, $p=0.009$), as well as a higher frequency of FIB-4 $>$ 1.35 (75% *vs* 52%, $p=0.046$). TE $>$ 8 kPa was observed in 11% of participants with no difference in MC phenotypes. Of participants, 90 (60%) had NAFLD (*i.e.,* PDFF e 5 %). There were no differences in prevalence of MC phenotypes between NAFLD and non-NAFLD participants ($p=0.284$). In those with NAFLD, only high MFI, only low MVZ and AMC was observed in 18 (20%), 10 (11%) and 15 (17%), respectively. In non-NAFLD participants, only high MFI, only low MVZ and AMC was observed in 12 (13%), 12 (13%) and 5 (8%), respectively. **Conclusion:** In this cohort of primary care patients with T2D, AMC was more common with concurrent NAFLD, but there were overall no significant differences observed in MC between groups. Participants with low MVZ alone were leaner than those with high MFI alone, while participants with AMC were the most metabolically burdened. Patients with AMC had a higher frequency of elevated FIB-4.

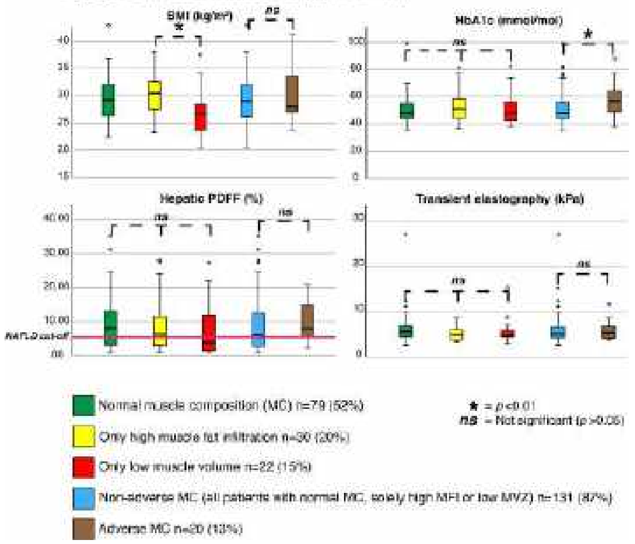

Figure 1 Box-plot series for clinical, biochemical, body composition and liver specific imaging characteristics of included T2D patients (n=151)

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2230-A | NASH SEVERITY ASSESSED BY THE NAFLD ACTIVITY SCORE (NAS) DOES NOT ADD PROGNOSTIC INFORMATION TO FIBROSIS STAGE IN PATIENTS WITH NAFLD

Ferenc Emil Mozes[1], Senamjit Kaur[1], Yasaman Vali[2], Osama Alzoubi[3], Vincent Wai-Sun Wong[4], Guanlin Li[4], Grace Lai-Hung C Wong[5], Katharina Staufer[6], Michael Trauner[7], Rafael Paternostro[8], Rudolf E. Stauber[9], Elisabetta Bugianesi[10], Silvia Gaia[11], Angelo Armandi[10], Monica Lupsor-Platon[12], Giada Sebastiani[13], Sanjiv Mahadeva[14], Ruveena Rajaram[15], Ming-Hua Zheng[16], Jacob George[17], Mohammed M. Eslam[18], Grazia Pennisi[19], Guruprasad P. Aithal[20], Naaventhan Palaniyappan[21], Daeho Lee[22], Patrik Nasr[23], Christophe Cassinotto[24], Victor De Ledinghen[25], Annalisa Berzigotti[26], Yuly Paulin Mendoza[27], Mazen Noureddin[28], Emily Truong[29], Jérôme Boursier[30], Marc De Saint Loup[31], Masashi Hirooka[32], Toshihide Shima[33], Dr Shalimar[34], Hannes Hagström[35], Mattias Ekstedt[23], Camilla Akbari[36], Wah Kheong Chan[14], Emmanuel A. Tsochatzis[37], Antonio Liguori[38], Salvatore Petta[39], Mauro Vigano[40], Sofia Ridolfo[41], Masato Yoneda[42], Atsushi Nakajima[42], Adriaan G. Holleboom[43], Anne-Marieke Van Dijk[2], Anne Linde Mak[44], Jeremy F L Cobbold[1], Thomas Karlas[45], Johannes Wiegand[46], Celine Fournier[47], Miljen Martic[48], Theresa Tuthill[49], Carla Yunis[50], Quentin M. Anstee[51], Stephen Harrison[52], Patrick Bossuyt[2] and Michael Pavlides[53], (1)University of Oxford, (2)University of Amsterdam, (3)The University of Jordan, (4)Institute of Digestive Disease, the Chinese University of Hong Kong, (5) Medical Data Analytics Centre (MDAC), the Chinese University of Hong Kong, (6)Versantis AG, (7)Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, (8) Medical University of Vienna, (9)Medical University of Graz, (10)Department of Medical Sciences, University of Torino, (11)University of Turin, (12)Octavian Fodor Regional Institute of Gastroenterology and Hepatology, 400162 Cluj-Napoca, Romania, (13) Department of Medicine, McGill University Health Centre, Westmount, QC, Canada, (14)University of Malaya, (15)University of Malaysia, Kuala Lumpur, Malaysia, (16)Wenzhou Medical University, (17)Storr Liver Centre, Westmead Hospital, Westmead Millennium Institute for Medical Research and University of Sydney, Westmead, New South Wales, Australia, (18)The University of Sydney, (19)Section of Gastroenterology and Hepatology, Dipartimento Di Promozione Della Salute, Materno Infantile, Medicina Interna e Specialistica Di Eccellenza (PROMISE), (20) Nottingham University Hospital NHS Trust and University of Nottingham, Nottingham, UK, (21) University of Nottingham, (22)Gachon University Gil Medical Center, (23)Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden, (24)University Hospital of Montpellier, (25) University Hospital Bordeaux, (26)Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, (27)Bern University Hospital, University of Bern, (28)Houston Research Institute, Houston, TX, (29)Cedars-Sinai Medical Center, Los Angeles, CA, (30)Service Hépato-Gastroentérologie Et Oncologie Digestive, Centre Hospitalier Universitaire, Angers, France; & Laboratoire Hifih, Sfr Icat 4208, Université D'angers, Angers, France, (31)Angers University Hospital, Angers, France, (32)Ehime University Graduate School of Medicine, (33)Saiseikai Suita Hospital, Suita, Osaka, Japan, (34)All India Institute of Medical Sciences, New Delhi, (35)Unit of Hepatology, Department of Upper GI Diseases, Karolinska University Hospital, Stockholm, Sweden, (36) Karolinska Institutet, (37)UCL Institute for Liver and Digestive Health, Royal Free Hospital, University College of London (UCL), London, UK, (38)Università Cattolica Di Roma, (39)Sezione Di Gastroenterologia, Dipartimento Promozione Della

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

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Background: Previous studies have shown that the presence of non-alcoholic steatohepatitis (NASH) and fibrosis stage carry prognostic information in patients with NAFLD. Here we aimed to assess whether grading with the NAFLD activity score (NAS) had any additional prognostic value to fibrosis stage. **Methods:** We conducted an individual participant data meta-analysis of patients with NAFLD who had baseline biopsy. NASH is defined as NAFLD activity score e 4 with score of at least 1 for steatosis, lobular inflammation, and ballooning. The primary outcome was a composite endpoint of all-cause mortality, decompensation of cirrhosis (ascites, variceal haemorrhage, hepatic encephalopathy), hepatocellular carcinoma, liver transplantation or progression to a model of end stage liver disease score e 15. Study-specific cumulative hazard functions and derived aggregated survival curves were built for F0-1, F2-3 and F4. Within each grouping we further divided cases into those without NASH, and those with NASH and NAS < 6 or NAS e 6. Survival curves were compared using a study-stratified log-rank test. **Results:** Data from 29 studies and 2,518 patients with biopsy proven NAFLD were included in the analysis (45% females, median age 54 (IQR 19) years, 46% with type II diabetes mellitus) 48% participants had NASH. The primary outcome was reached in 5.8% (n = 145) after a median follow-up of 58 months. In patients without cirrhosis, the presence and severity of NASH did not have any impact on developing the composite end point during follow-up of NASH (p = 0.43 for F0-1, Figure 1a; p = 0.95 for F2-3, Figure 1b). In patients with cirrhosis the survival curves appeared to diverge, but the differences between NAS categories did not reach significance probably due to small numbers (p = 0.054, Figure 1c). **Conclusion:** The NAS score remains useful for the diagnosis of NASH but based on our data carries no prognostic information in non-cirrhotic NAFLD. In NAFLD cirrhosis, conclusions are limited by relatively small numbers.

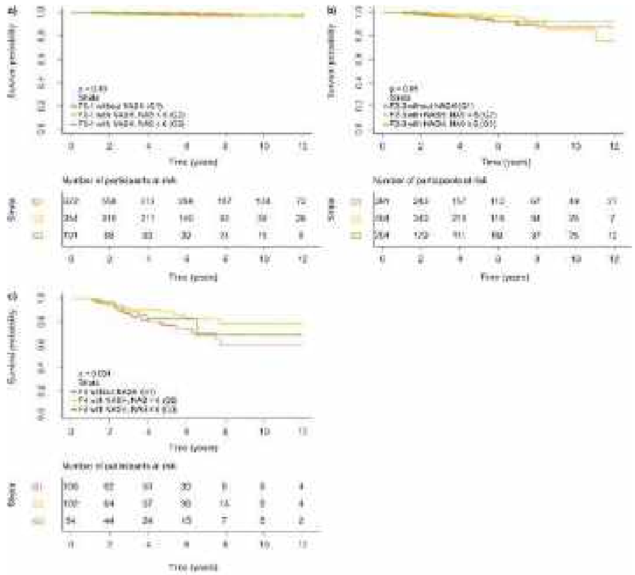

Figure 1 Estimates of survival probability in patients without NASH and with NASH stratified by their NAFLD activity score. P-value corresponds to the outcome of the study-stratified log-rank test.

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Celine Fournier – Echosens: Employee, Yes, No;
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2231-A | NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND HEPATITIS B VIRUS (HBV) INTERPLAY: THEIR ROLE IN LIVER DISEASE DEVELOPMENT

Ploutarchos Pastras, Stavros Kanaloupitis, Ioanna Aggeletopoulou, Aspasia Antonopoulou, Efthymios Tsounis, Maria Kalafateli, Vasileios Issaris, Anna Boulouta, Konstantinos Papantoniou, Dimosthenis Drakopoulos, Evangelos Zazas, Eleni-Eirini-Konstantina Kottaridou, Georgia Diamantopoulou, Aggeliki Tsintoni, Konstantinos Thomopoulos and Christos Triantos, University Hospital of Patras

Background: Hepatitis B virus (HBV) infection is associated with lower risk of non-alcoholic fatty liver disease (NAFLD) in the absence of concurrent metabolic disorder. The aim of this retrospective case-control study is to evaluate the HBV infection impact on NAFLD patients, the clinical/laboratory characteristics of NAFLD-HBV patients and the NAFLD-HBV coexistence relation with the liver disease development. **Methods:** The medical charts of 575 NAFLD patients referred to outpatients' clinic due to abnormal liver biochemistry and/or presence of fatty liver were thoroughly reviewed. Fifty-seven patients were excluded because of other chronic liver diseases. Finally, 518 patients were included; 402 NAFLD and 116 NAFLD-HBV patients. Categorical data were compared using Pearson's chi-squared test or two-sided Fisher's exact test, when applicable. Mann-Whitney U test was used to compare differences between two independent groups. Binary logistic regression was performed to assess the risk factors associated with liver disease progression. **Results:** NAFLD-HBV patients had significantly lower levels of γ-GT ($p<0.001$), and platelets ($p=0.041$), and higher levels of ALP ($p=0.023$) and INR ($p=0.028$) compared to NAFLD patients. Moreover, a significantly lower percentage of NAFLD-HBV patients were overweight or obese compared to pure NAFLD patients ($p=0.007$). Patients with NAFLD-HBV admitted to hospital more often than NAFLD patients ($p=0.004$), but no difference was documented in mortality rates between the examined groups ($p=0.999$). Multivariate analysis was used to explore the factors associated with liver disease development; HBV coexistence (aOR = 3.509, 95%CI: 1.201-10.254, $p=0.022$), diabetes mellitus (aOR = 3.375, 95%CI: 1.176-9.683, $p=0.024$), platelet count (aOR = 0.976, 95%CI: 0.965-0.987, $p<0.001$) and total bilirubin (aOR = 1.785, 95% CI: 1.145-2.781, $p=0.01$) were demonstrated as independent prognostic factors. **Conclusion:** NAFLD-HBV comorbidity was associated with reduced body weight, increased risk of hospital admissions and end-stage liver disease development. NAFLD-HBV coexistence constituted an independent risk factor for liver disease development. Active treatment for both disorders should be recommended.

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2232-A | NONALCOHOLIC FATTY LIVER DISEASE (NAFLD): PREVALENCE, LIFESTYLE FACTORS, AND HEALTHCARE UTILIZATION AMONG HISPANIC AND NON-HISPANIC WHITE RESIDENTS IN US

Pankil Shah, Uthealth San Antonio, Mazen Noureddin, Houston Research Institute, Houston, TX, Naim Alkhouri, Arizona Liver Health, Phoenix, AZ and Naim et al.

Background: Nonalcoholic fatty liver disease (NAFLD) is a silent epidemic in U.S. with a disproportionately higher burden and worse outcomes in Hispanic population. Large-scale population-based analyses of association between *demographic, socioeconomic, and lifestyle factors* with NAFLD, stratified by Hispanic ethnicity, are lacking. **Methods:** This cross-sectional study used vibration controlled transient elastography (VCTE) data from the National Health and Nutrition Examination Survey (NHANES) 2017-2018 to examine the prevalence and disease severity of NAFLD in Hispanic and Non-Hispanic white (NHW) residents of U.S. Adjusted odds ratios and 95% confidence intervals for demographic, socioeconomic, comorbidity, and lifestyle factors associated with NAFLD were estimated from a multivariable logistic regression model. We also examined education, awareness, and healthcare utilization by Hispanic and NHW individual's with NAFLD. **Results:** A total of 2229 Hispanic and NHW participants met the inclusion criteria. The weighted analytic subset represented a population that was 79% for NHW and 21% for Hispanic, with a mean (standard error [se]) age of 48.9 (0.9) years and 51.9% women. The prevalence of NAFLD was significantly higher in Hispanic individual's (64.1% and 32.3%) compared to the NHW individual's (55.3% and 27.0%) based on the controlled attenuation parameter cutoff of 248 dB/m and 302 dB/m, respectively. After adjusting for other covariates, odds of NAFLD were significantly higher for Hispanic individual's compared to NHW (adjusted odds ratio [aOR]: 1.55, 95% CI: 1.15 – 2.10). Older age (aOR, 95% CI for every 10-year age interval: 1.30, 1.21 – 1.39), male sex (1.55, 1.14 - 2.11), less than college education (1.54, 1.05 - 2.26), shorter duration of sleep per hour (1.12, 1.01 - 1.24), intake higher than estimated energy requirement per 100 kcals/day (1.02, 1.002 - 1.03), prediabetes (2.70, 1.77 - 4.13) and diabetes (6.31, 3.28 - 12.1) were significantly associated with NAFLD. Despite this high prevalence, only 5.1% of Hispanic and 2.5% of NHW patients with NAFLD reported being informed about having a fatty liver disease and majority patients reported having good or excellent health status. Half of the patients with NAFLD reported not having visited their healthcare provider in more than two years (Hispanic: 54.7% vs. NHW: 46,7%). **Conclusion:** A large proportion of U.S. adults have NAFLD, with significantly higher prevalence in Hispanic individual's than in NHW individual's. Individual and societal interventions to change an interconnected grid of modifiable factors (e.g., higher education, better work schedule, longer and better sleep, healthy diet, healthcare access, physician/patient ratio and communication, education/awareness campaigns and weight loss programs) are urgently needed to reduce the burden of NAFLD and its downstream consequences in U.S. residents, especially in vulnerable minority groups.

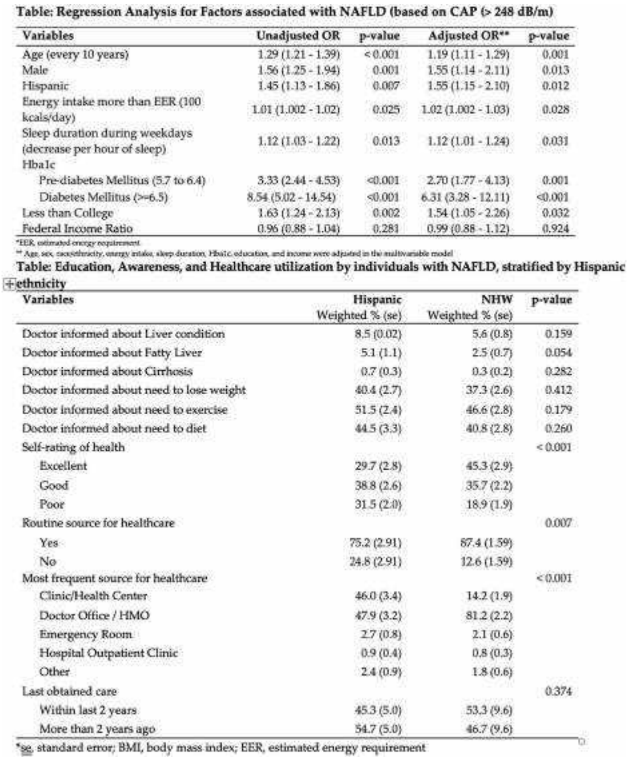

Table: Regression Analysis for Factors associated with NAFLD (based on CAP (> 248 dB/m)

Variables	Unadjusted OR	p-value	Adjusted OR**	p-value
Age (every 10 years)	1.29 (1.21 - 1.39)	< 0.001	1.19 (1.11 - 1.29)	0.001
Male	1.56 (1.25 - 1.94)	0.001	1.55 (1.14 - 2.11)	0.013
Hispanic	1.45 (1.13 - 1.86)	0.007	1.55 (1.15 - 2.10)	0.012
Energy intake more than EER (100 kcals/day)	1.01 (1.002 - 1.02)	0.025	1.02 (1.002 - 1.03)	0.028
Sleep duration during weekdays (decrease per hour of sleep)	1.12 (1.03 - 1.22)	0.013	1.12 (1.01 - 1.24)	0.031
Hba1c				
Pre-diabetes Mellitus (5.7 to 6.4)	3.33 (2.44 - 4.53)	<0.001	2.70 (1.77 - 4.13)	0.001
Diabetes Mellitus (>=6.5)	8.54 (5.02 - 14.54)	<0.001	6.31 (3.28 - 12.11)	<0.001
Less than College	1.63 (1.24 - 2.13)	0.002	1.54 (1.05 - 2.26)	0.032
Federal Income Ratio	0.96 (0.88 - 1.04)	0.281	0.99 (0.88 - 1.12)	0.924

*EER, estimated energy requirement

** Age, sex, race/ethnicity, energy intake, sleep duration, Hba1c, education, and income were adjusted in the multivariable model

Table: Education, Awareness, and Healthcare utilization by individuals with NAFLD, stratified by Hispanic ethnicity

Variables	Hispanic Weighted % (se)	NHW Weighted % (se)	p-value
Doctor informed about Liver condition	8.5 (0.02)	5.6 (0.8)	0.159
Doctor informed about Fatty Liver	5.1 (1.1)	2.5 (0.7)	0.054
Doctor informed about Cirrhosis	0.7 (0.3)	0.3 (0.2)	0.282
Doctor informed about need to lose weight	40.4 (2.7)	37.3 (2.6)	0.412
Doctor informed about need to exercise	51.5 (2.4)	46.6 (2.8)	0.179
Doctor informed about need to diet	44.5 (3.3)	40.8 (2.8)	0.260
Self-rating of health			< 0.001
Excellent	29.7 (2.8)	45.3 (2.9)	
Good	38.8 (2.6)	35.7 (2.2)	
Poor	31.5 (2.0)	18.9 (1.9)	
Routine source for healthcare			0.007
Yes	75.2 (2.91)	87.4 (1.59)	
No	24.8 (2.91)	12.6 (1.59)	
Most frequent source for healthcare			< 0.001
Clinic/Health Center	46.0 (3.4)	14.2 (1.9)	
Doctor Office / HMO	47.9 (3.2)	81.2 (2.2)	
Emergency Room	2.7 (0.8)	2.1 (0.6)	
Hospital Outpatient Clinic	0.9 (0.4)	0.8 (0.3)	
Other	2.4 (0.9)	1.8 (0.6)	
Last obtained care			0.374
Within last 2 years	45.3 (5.0)	53.3 (9.6)	
More than 2 years ago	54.7 (5.0)	46.7 (9.6)	

*se, standard error; BMI, body mass index; EER, estimated energy requirement

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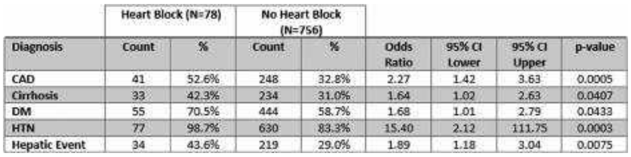
2233-A | NONALCOHOLIC FATTY LIVER DISEASE IS ASSOCIATED WITH AN INCREASED RISK OF HEART BLOCK AND HEPATIC EVENTS

Marie-Lise Chrysostome[1], Sameer Prakash[2,3], Antonio J. J. Sanchez[2] and Patrick Ten Eyck[4], (1)Drexel University College of Medicine, Pittsburgh, PA, (2) University of Iowa Hospitals and Clinics, (3)Memorial Hermann, (4)University of Iowa

Background: Non-alcoholic fatty liver disease (NAFLD) has been associated with an increased risk of cardiovascular disease. Few studies have examined the association between NAFLD and the risk of cardiac conduction defects. We aimed to elucidate the relationship between heart block (HB) in NAFLD patients and development of hepatic decompensation events. **Methods:** We used the TriNetX platform to perform a retrospective cohort study of inpatient admissions at a large tertiary referral center, the University of Iowa Hospitals and Clinics, between January 2010 and December 2020. We identified patients with ICD-10 codes for NAFLD and at least one of the following: bradycardia, fascicular block, complete atrioventricular block, or other conduction disorder. Hepatic decompensation events were identified as ascites, hepatic encephalopathy, esophageal variceal bleeding, or hepatocellular carcinoma. We examined associated comorbidities including hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), and hyperlipidemia (HLD

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

and the incidence of pacemaker placement. All diagnoses were summarized as counts and percentages. Two-way comparisons between measures were investigated by calculating odds ratio point and interval estimates along with p-values. **Results:** 834 patients with NAFLD were identified. 426 (51.08%) were male. 753 (90.29%) were white and 81 (9.72%) were not white. 78 (9.4%) patients also had a diagnosis of HB. 253 (30.34%) NAFLD patients experienced hepatic events. Table 1 shows subgroup characteristics of patients with/without HB 219 (29%) of the NAFLD patients without HB experienced hepatic events, while 34 (43.6%) of the NAFLD patients with HB experienced hepatic events (OR [95% CI], 1.89 [1.18-3.04]) ($p = 0.0095$). DM, HTN, and CAD were significantly associated with HB. Cirrhosis was significantly associated with HB (OR [95% CI],1.64 [1.02-2.63]) ($p = 0.0407$). **Conclusion**: To our knowledge, this is the first study to suggest that the presence of HB increases the odds of developing hepatic decompensation events in patients with NAFLD and cirrhosis. Our results are consistent with the fact that advanced NAFLD is strongly associated with cardiovascular complications, confirming a novel association with cardiac conduction defects which may increase the risk of disease progression and hepatic decompensation. Future studies are required to elucidate the biological mechanisms responsible for this association.



	Heart Block (N=78)		No Heart Block (N=756)					
Diagnosis	Count	%	Count	%	Odds Ratio	95% CI Lower	95% CI Upper	p-value
CAD	41	52.6%	248	32.8%	2.27	1.42	3.63	0.0005
Cirrhosis	33	42.3%	234	31.0%	1.64	1.02	2.63	0.0407
DM	55	70.5%	444	58.7%	1.68	1.01	2.79	0.0433
HTN	77	98.7%	630	83.3%	15.40	2.12	111.75	0.0003
Hepatic Event	34	43.6%	219	29.0%	1.89	1.18	3.04	0.0075

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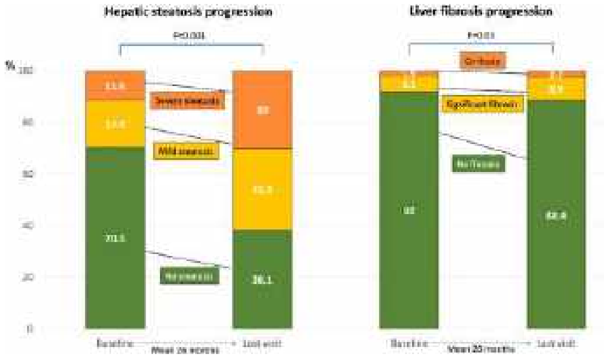
The following people have nothing to disclose: Marie-Lise Chrysostome, Sameer Prakash, Patrick Ten Eyck

2234-A | NONALCOHOLIC FATTY LIVER DISEASE IS ASSOCIATED WITH MULTI-ORGAN COMORBIDITIES AND FIBROSIS PROGRESSION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Dana Kablawi[1], Solomon Sasson[1], Faisal Aljohani[1], Chiara Saroli Palumbo[2], Alain Bitton[1], Waqqas Afif[1], Peter Lakatos[1], Gary Wild[1], Talat Bessissow[1] and Giada Sebastiani[3], (1)Mcgill University Health Centre, (2)Yale University, New Haven, CT, (3)Department of Medicine, McGill University Health Centre, Westmount, QC, Canada

Background: Patients with inflammatory bowel disease (IBD) are at risk for nonalcoholic fatty liver disease (NAFLD) due to chronic inflammation, hepatotoxic drugs, alteration of gut microbiota. NAFLD carries higher risk of both liver fibrosis progression and extensive extra-hepatic involvement, including cardiovascular disease, extra-hepatic cancer, hypothyroidism, chronic kidney disease. Data on the association of NAFLD with liver fibrosis progression and its association with multi-organ disease are lacking in this population. **Methods:** We prospectively included consecutive IBD patients who underwent liver stiffness measurement (LSM) with associated controlled attenuation parameter (CAP) by Fibroscan as a part of a routine screening program at a single centre. NAFLD was diagnosed as any grade hepatic steatosis (HS) in absence of alcohol abuse and viral hepatitis co-infection. HS progression was defined as development of any grade HS (CAP $>$ 270 dB/m), or transition to severe HS (CAP $>$ 330 dB/m) for those with CAP $>$ 270 but $<$ 330 dB/m at baseline. Fibrosis progression was defined as development of significant liver fibrosis (LSM $\geq$ 8 kPa), or transition to cirrhosis (LSM $\geq$ 13 kPa) for those with LSM $>$ 8 but $<$ 13 kPa at baseline. We estimated incidence rates of HS and fibrosis progression by dividing the number of participants developing the outcome by number of person-years (PY) of follow-up. Covariate adjustments for HS progression were evaluated by multivariable time-dependent Cox regression models. Predictors of extra-hepatic conditions were investigated by multivariable logistic regression analysis. **Results:** 430 patients were included (mean age 43 y, BMI 25 Kg/m^2, disease duration 14 years, c-reactive protein 5.2, ALT 22; females 45%, ulcerative colitis 31.8%, diabetes mellitus 4.7%). Patients with NAFLD had higher proportion of cardiovascular events (12% vs. 6%), chronic kidney disease (8% vs. 3%) and hypothyroidism (12% vs. 6%) compared to those without NAFLD. After adjusting for age, male sex, diabetes (aOR 3.53, 95% CI 1.68-7.42; $p = 0.001$) and Crohn's disease IBD subtype, NAFLD remained an independent predictor of extra-hepatic comorbidities (aOR 1.79, 95% CI 1.15–2.78; $p = 0.01$). Patients were followed for a mean of 26 months (standard deviation 16.4). The rate of HS progression was 16.2 per 100 PY (95% CI, 11.5-22.8), respectively. The rate of liver fibrosis progression was 6.12 per 100 PY (95% CI 3.48-10.44) (see Figure). In multivariable analysis and after adjusting for duration of IBD and BMI, ulcerative colitis was associated with faster progression of hepatic steatosis (adjusted hazard ratio 2.21, 95% CI 1.02-4.91). **Conclusion:** NAFLD is associated with extra-hepatic co-morbidities in patients with IBD and can progress to liver fibrosis and cirrhosis.



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The following people have nothing to disclose: Dana Kablawi, Solomon Sasson, Faisal Aljohani, Chiara Saroli Palumbo, Alain Bitton, Waqqas Afif, Peter Lakatos, Gary Wild, Talat Bessissow

2235-A | NONALCOHOLIC STEATOHEPATITIS (NASH) REAL-WORLD EVIDENCE: ADVANCED APPROACHES TO ACHIEVE HIGH VALIDITY

Erin Murray, Mahder Teka, Paddu Vedam and Daniel Riskin, Verantos, Inc.

Background: Regulatory, market access, and prescribing decisions are increasingly based on insights from routine care, also known as real-world evidence (RWE). As RWE increasingly influences the standard of care, data quality has come under scrutiny. The data quality standard of accuracy, completeness, and traceability have been distilled to measurable values. To enable RWE in NASH, data quality must be understood in NASH. **Methods:** Accuracy was tested in two study arms for 19 pre-selected NASH-related concepts. The traditional RWE approach study arm was limited to structured data (open claims and electronic health record problem list). The advanced RWE approach study arm utilized structured data plus narrative data (primary care and specialist physician notes) processed using NASH-optimized technology, including natural language processing (NLP) and artificial intelligence (AI)-based inference. Data were extracted from 6087 encounters, each with paired structured and narrative data. A manual reference standard was created via chart abstraction with two annotators reviewing each record with a minimum required 80% inter-rater reliability measured as Cohen's kappa score. F1-score, a weighted average of recall (sensitivity) and precision (positive predictive value) was used to measure accuracy, with 80% considered the threshold for high reliability. A two-sided p-value of 0.05 and a Chi-squared test were used to compare the study arms. **Results:** The average recall, precision, and F1-score in the traditional study arm were 37.2%, 98.9%, and 54.1%, respectively. The average recall, precision, and F1-score in the advanced (NLP plus AI-based inference) study arm were 96.0%, 97.4%, and 96.7%, respectively. There was a 42.6% absolute increase and a 78.7% relative increase in F1-score between traditional and advanced approaches. A statistically significant difference between the two arms was indicated ($p < 0.001$) for all data elements where data were available. Cohen's kappa score indicated 88% inter-rater reliability, reflecting a highly credible reference standard. Applying AI-based inference following NLP improved concept extraction accuracy in situations where doctors used highly variable language. In particular, for liver fibrosis and alcohol use, F1-scores were 80.1% and 75.3% using NLP alone versus 94.7% and 91.2% using NLP plus inference. This represented an average relative increase of 19.7% by applying inference over NLP alone. **Conclusion:** Advanced data

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

and technology can enable high-validity RWE in NASH. Given substantial variability in data and technology, accuracy should be measured if the study protocol requires high-validity evidence. NLP alone may be insufficient technology to enable high accuracy, as seen in clinically important NASH concepts such as liver fibrosis and alcohol use.

Disclosures: The following people have nothing to disclose: Daniel Riskin

Disclosure information not available at the time of publication: Erin Murray, Mahder Teka, Paddu Vedam

f 2236-A | PFHPA ALTERS LIPID METABOLISM AND INCREASE ODDS OF NAFLD IN YOUTH

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Background: Accumulating evidence suggests that poly- and perfluoroalkyl substances (PFAS), a class of persistent organic pollutants, cause changes in hepatic lipid, amino acid, and glucose metabolism. Glucose homeostasis changes significantly during puberty, increasing the risk of developing metabolic syndromes. We performed a multi-layered study to determine the association of PFAS exposure with non-alcoholic fatty liver disease (NAFLD) in teenagers and to identify the molecular mechanisms whereby PFAS alters liver metabolism. **Methods:** Adolescents undergoing bariatric surgery were enrolled in the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS, 2007-2012). We measured plasma-PFAS by LC-MS/MS and plasma untargeted metabolomics by LC-HR/MS. Targeted proteomics was determined via Proximity Extension Assay technology (Olink®). Logistic regression controlling for confounders was used to investigate the association between PFAS and NAFLD. Metabolome and proteome datasets integration used latent unknown clustering integrating multi-omics data (LUCID) to identify multi-omic profiles of adolescents at higher risk of NAFLD. 3D InSight^{TM} human liver spheroids (InSphero) were exposed to 20μM PFHpA for 7 days and analyzed by 10x genomics scRNAseq (kit 3' v3.1). **Results:** Among adolescents in the Teen-LABS study, we observed 68% higher odds of NAFLD per doubling of perfluoroheptanoic acid (PFHpA). We identified two distinct multi-omic risk profiles associated with high PFHpA exposure and higher odds of NAFLD. The first omic risk profile showed an association between high PFHpA levels and altered proteins, including low levels of C-C motif chemokine ligand 28 (CCL28), and high levels of several metabolic proteins, such as Carboxylesterase 1 and Aminoacylase 1. NAFLD was 6 times more likely in this PFHpA-protein risk profile. The second risk profile showed an association between high PFHpA and altered levels of amino acids and lipids metabolites. NASH was 4 times more likely in the PFHpA-metabolite risk profile, independent of the proteomic risk profile. In liver spheroids, PFHpA upregulated pathways involved in lipid and cholesterol metabolism, especially in hepatocytes, corroborating the second omic risk profile. **Conclusion:** This is the first study showing that high PFHpA exposure during childhood was associated with NAFLD. PFHpA primarily affected the lipid metabolism of hepatocytes in liver spheroids, supporting the omic risk profiles generated by metabolomics and proteomics dataset integration.

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2237-A | POLYCYSTIC OVARIAN SYNDROME IS AN INDEPENDENT RISK ASSOCIATION FOR NAFLD AFTER CONTROLLING FOR METABOLIC AND GENETIC RISK FACTORS

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Background: Polycystic ovarian syndrome (PCOS) affects up to 15% of reproductive-aged women. Nonalcoholic fatty liver disease (NAFLD) is frequently observed in women with PCOS, often attributed to comorbid insulin resistance, obesity, diabetes, and dyslipidemia. Susceptibility to NAFLD is influenced by genetic variants in *PNPLA3*, *TM6SF2*, and *HSD17B13*; however, the interactions between genetic and metabolic risk factors among women with PCOS are unclear. We sought to characterize the links between PCOS and NAFLD. **Methods:** We extracted clinical, laboratory, and whole exome sequencing data for European ancestry (EA) and African ancestry (AA) women from the Penn Medicine BioBank (PMBB v.2.2). PCOS was defined by ICD9/ICD10 codes, excluding disorders with similar clinical presentations. NAFLD was diagnosed as any of the following: 1) chronic elevation of alanine aminotransferase, 2) hepatic steatosis on CT imaging, or 3) ICD9/ICD10 codes for NAFLD, NASH, or cirrhosis. Subjects with liver diseases other than NAFLD were excluded. The association of PCOS with NAFLD and log-transformed median hepatic enzymes was tested using logistic and linear regression analyses. Meta-analysis of odds ratios was computed using the inverse variance method. Analyses were adjusted for allelic status at *PNPLA3*-p.I148M, *TM6SF2*-p.E167K, and *HSD17B13* (sum of variants in rs72613567, rs80182459 and rs62305723), in addition to age, age-squared, BMI, hypertension, DM2, dyslipidemia, and 10 principal components of genetic ancestry. **Results:** Among EA women, we identified 407 cases of PCOS (17.0% with NAFLD), and 11,630 non-PCOS cases (13.1% with NAFLD). There were 247 AA women with PCOS (13.8% with NAFLD) and 5,494 AA women without PCOS (13.1% with NAFLD). PCOS was associated with 1.68 higher odds of NAFLD (95% CI: 1.24, 2.28, $p = 0.0008$) among EA women; the association was not significant among AA women (OR 1.49, 95% CI: 0.98, 2.25). Meta-analysis of EA and AA cohorts found that PCOS was associated with 1.61 higher odds of NAFLD (95% CI: 1.26, 2.06, $p = 0.0001$). In both cohorts, PCOS was associated with increased AST (EA, $p = 0.01$; AA, $p = 0.001$) and more robustly associated with higher ALT levels (EA, $p = 0.0007$; AA, $p = 0.00001$). A synergistic interaction was observed between PCOS and p.I148M genotype among EA women only ($p = 0.03$ for AST, $p = 0.0005$ for ALT). Analyses were conducted in R (v.4.1.0). **Conclusion:** PCOS was associated with higher levels of AST and ALT among European and African ancestry women. Among European women, the impact of PCOS on hepatic enzymes was amplified by the presence of the *PNPLA3* p.I148M polymorphism. Trans-ancestral meta-analysis found that PCOS conferred 1.61 higher odds of NAFLD, after adjusting for common metabolic and genetic risk factors. This suggests that factors other than metabolic syndrome and genetic risk may predispose to NAFLD among women with PCOS.

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2238-A | POST LIVER TRANSPLANT SURVIVAL AMONG HISPANIC AND NON-HISPANIC WHITE PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS (NASH): AN ORGAN PROCUREMENT AND TRANSPLANTATION NETWORK (OPTN) ANALYSIS

Pankil Shah, Uthealth San Antonio, Mazen Noureddin, Houston Research Institute, Houston, TX and Naim Alkhouri, Arizona Liver Health, Phoenix, AZ

Background: End-stage liver disease (ESLD) is the last stage in the spectrum of nonalcoholic fatty liver disease (NAFLD)/NASH pathology, with liver transplant being the only definite treatment option. Compared to Non-Hispanic White patients, Hispanics have a higher prevalence of NAFLD/NASH and 30% higher mortality rates due to ESLD. We aimed to assess 5-year survival rate in patients receiving transplantation for NASH and examine disparity associated with Hispanic ethnicity. **Methods:** We assessed the survival in adult liver transplant recipients who had their transplant surgery between 2008 and 2018, using the limited dataset from OPTN. All-cause mortality was the primary outcome, re-transplantation was treated as a competing event, and ethnicity was the primary predictor using the Fine-Gray regression model. A bivariable model, a multivariable model with *a priori* clinical confounders, and a LASSO penalized feature selected model were built to examine racial/ethnic disparity in post-transplant survival. The confounding variables examined were age, sex, education, insurance, employment, citizenship, functional status, BMI, Model for End-stage liver disease (MELD), waitlist time, transplant type, region, comorbidity, hospitalization, life-supportive treatment, and Share-35 policy. **Results:** A total of 10,043 recipients, including 8445 (84%) Non-Hispanic White (NHW) and 1598 (16%) Hispanic, were identified and included. The overall probability of death was 20% in NHW and 18% in Hispanic patients at five years. The unadjusted subdistribution hazard ratio (SHR) (95% confidence interval [CI]) was 0.84 (0.72 – 0.98), adjusted SHR [CI] was 0.70 (0.60 – 0.83), and SHR [CI] of the penalized model was 0.71 (0.61 – 0.83) for Hispanic recipients compared to NHW recipients. Better survival for Hispanics was observed for one year, 10-year follow-up, after exclusion of non-US nationals, and stratification by pre- and post-Share-35 policy era. **Conclusion:** The better survival outcome was observed in Hispanic than NHW patients, which, despite clinical and socioeconomic risk profile being unfavorable in that group, perhaps points to cultural exposure or genetic traits of Hispanic patients that might drive such differences. With still a 5-year mortality rate of around 20%, there is a substantial need for continued research and advancement in the treatment and care of liver transplant recipients to prolong their survival.

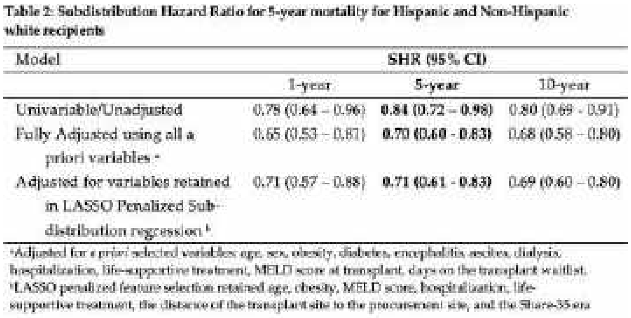
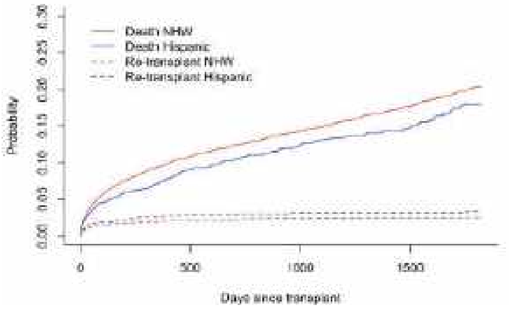


Table 2: Subdistribution Hazard Ratio for 5-year mortality for Hispanic and Non-Hispanic white recipients

Model	SHR (95% CI)		
	1-year	5-year	10-year
Univariable/Unadjusted	0.78 (0.64 – 0.96)	**0.84 (0.72 – 0.98)**	0.80 (0.69 - 0.91)
Fully Adjusted using all a priori variables [a]	0.65 (0.53 – 0.81)	**0.70 (0.60 - 0.83)**	0.68 (0.58 – 0.80)
Adjusted for variables retained in LASSO Penalized Sub-distribution regression [b]	0.71 (0.57 – 0.88)	**0.71 (0.61 - 0.83)**	0.69 (0.60 – 0.80)

[a] Adjusted for a priori selected variables: age, sex, obesity, diabetes, encephalitis, ascites, dialysis, hospitalization, life-supportive treatment, MELD score at transplant, days on the transplant waitlist.
[b] LASSO penalized feature selection retained age, obesity, MELD score, hospitalization, life-supportive treatment, the distance of the transplant site to the procurement site, and the Share-35 era

Figure 1b. Cumulative Incidence Function, stratified by Ethnicity: A 5-year competing risk regression of the study population indicating the relative probability of death and re-transplantation following the first liver transplant in the Non-Hispanic White and Hispanic study population.



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2239-A | PREDICTORS OF LIVER FIBROSIS AND ITS PROGRESSION IN THE GENERAL POPULATION

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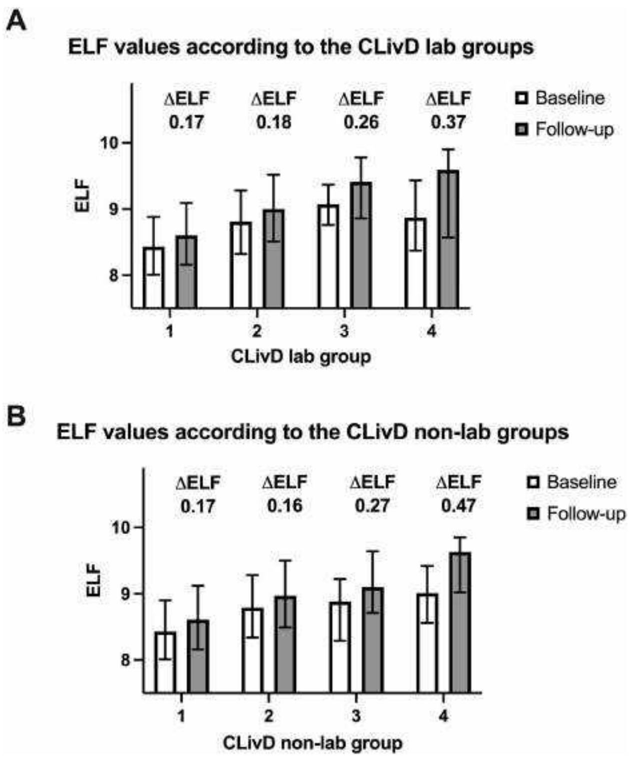
Background: Liver fibrosis stage is the key prognostic factor for liver-related outcomes in many liver diseases. There are only a few studies on the prevalence and progression of fibrosis and associated risk factors on the population level. The Enhanced Liver Fibrosis (ELF) test is a composite score based on three serum markers of matrix turnover. We evaluated factors associated with advanced fibrosis based on the ELF test and fibrosis progression over a 10-year follow-up. **Methods:** ELF was measured from frozen blood samples from the Health 2000 study, a population-based epidemiologic survey conducted in Finland in 2000-2001 (study baseline) and its follow-up study, Health 2011 (follow-up). Advanced fibrosis was defined as ELF e 9.8 and clinically significant fibrosis progression as an ELF-change > 0.6 over the follow-up. Chronic Liver Disease (CLivD) risk score, a recently published risk score for severe liver-related outcomes based on phenotypic data, clinical measurements and with ($CLivD_{lab}$) or without ($CLivD_{nonlab}$) laboratory test gamma-glutaminase was calculated at baseline (Åberg et al., J Hepatology 2022). **Results:** The baseline sample (Health 2000) comprised 6084 individual's, and the follow-up sample (Health 2011) 2937 individual's. Percentages of men in the baseline and follow-up samples were, respectively, 46% and 45%, mean age 52.7 and 48.5 years, mean BMI 26.9 kg/m2 and 26.5kg/m2, and prevalences of diabetes 10% and 6.2%. The age-adjusted prevalence of advanced fibrosis among men and women was 8.3% (95% CI 7.0 – 9.6) and 5.9% (95% CI 4.9-7.0), respectively. The most significant risk factors for advanced fibrosis in both sexes were obesity (BMI), abdominal obesity (waist circumference and waist-hip ratio), insulin resistance (HOMA-IR), and elevated transaminases ($p < 0.001$). Most individual's with advanced fibrosis had normal liver enzymes. The risk factors for a clinically significant fibrosis progression were obesity and especially abdominal obesity ($p < 0.05$) among women, and abdominal obesity and AST > 40 IU ($p < 0.05$) among men. The CLivD score was associated with a consistent elevation of ELF values at baseline (Figure 1). Also, the CLivD score predicted the magnitude of ELF increases over follow-up, independently of baseline ELF ($p < 0.001$). **Conclusion:** The majority of individual's with advanced fibrosis, estimated by the ELF test, present with normal liver enzymes. The CLivD score predicted both baseline ELF and its change over the follow-up.



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2240-A | PREVALENCE AND PROGNOSIS OF PATIENTS WITH MAFLD-RELATED CIRRHOSIS AFTER ICU HOSPITALIZATION IN FRANCE: A MONOCENTRIC PROSPECTIVE STUDY

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Background: Metabolic-associated fatty liver disease (MAFLD) has been recently defined. No data are available on decompensated MAFLD-related cirrhosis. We aimed to estimate the burden of MAFLD in patients (pts) with cirrhosis hospitalized in intensive care unit (ICU) for decompensation, and to compare prognosis of MAFLD-related cirrhosis to that of cirrhosis related to other cause, such as alcohol. **Methods:** All consecutive pts hospitalized in our ICU were prospectively included between Feb19 and Sept21. The diagnosis of MALFD was based on past exposure to diabetes or obesity/overweight, or on the combination of at least 2 minor metabolic risk factors metabolic abnormalities. We distinguished 3 groups of pts: MAFLD alone, alcohol-related cirrhosis ($>$30g/day), and mixed MAFLD (MAFLD and alcohol-related cirrhosis). One-year transplant-free survival (TFS), further decompensation (ascites, hepatic encephalopathy (HE), or acute variceal bleeding (AVB)), hepatocellular carcinoma (HCC), readmission, and liver transplantation (LT) were compared one year after hospitalization in ICU. **Results:** 410 pts were hospitalized in our ICU, and 335 pts were analyzed: 44 in the MAFLD, 188 in the alcohol, and 103 in the mixed MAFLD groups, respectively. Overall, the MALFD etiology (MALFD or mixed MAFLD) accounted for 147/335 (35.8%) pts. 38% of pts were admitted for AVB, 9.3% for HE, 24% for liver failure, 11% for sepsis, 8.1% for renal failure, 8.7% for TIPS placement, and 0.9 % for other causes, without any difference between the 3 groups. At baseline, pts in the MAFLD group were significantly older than pts in the alcohol and mixed groups (65 vs 57 and 60 years, respectively, $p < 0.001$), had lower Child-Pugh (8 vs 11 vs 10, $p < 0.001$) and MELD scores (16 vs 22 vs 20, $p < 0.001$), and a more severe portal hypertension (large esophageal varices in 91 vs 71 and 76%, $p = 0.03$). The one-year TFS was not statistically different in the MAFLD group: 56.8% in the MAFLD group vs 45.2% in the alcohol group and 49.5% in the mixed group ($p = 0.2$). There was no difference regarding the development of further decompensation, HCC or readmission. Cardiovascular mortality was not higher in the MAFLD group and was responsible for less than 5% of mortality all groups. **Conclusion:** MAFLD, either alone or associated with alcohol, accounted for $> 1/3$ of the causes of cirrhosis in our cohort. MAFLD-related cirrhosis is as severe as alcohol-related cirrhosis, and mortality is liver and not cardiovascular-driven. LT should be rapidly discussed in those pts because of older age and comorbidities.

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2241-A | PREVALENCE OF HEPATIC STEATOSIS IN A MEXICAN THIRD LEVEL HOSPITAL AND RISK FACTORS FOR DEVELOPMENT OF CIRRHOSIS

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Background: Non-alcoholic fatty liver disease (NAFLD) has become a growing concern worldwide, with hepatic steatosis being a key component of its pathogenesis. Understanding the prevalence of hepatic steatosis and identifying associated risk factors for hepatic fibrosis is crucial for early detection and intervention. Aim: to determine the prevalence of hepatic steatosis in asymptomatic patients admitted for suspected or diagnosis of atypical pneumonia. **Methods:** Clinical, laboratory, and imaging data were collected from electronic medical records. A total of 2353 patients were included and their demographic characteristics, prevalence of hepatic steatosis, and associated risk factors were analyzed. We used computerized tomography for the diagnosis of steatosis taking the Hounsfield units ($<$40 HU) as cutoff value evaluated on the III and VI hepatic lobes. **Results:** Out of the initial sample of 2353 patients, 17 were excluded, resulting in a final study population of 2336 patients. The average age of the participants was 56 years, ranging from 18 to 96. Of the total population, 871 (37%) were females and 1482 (63%) males. Among the study participants, a total of 931 (39.8%) patients were classified as overweight, while

1012 (43.3%) were classified as obese. In terms of specific conditions, 701 (29%) had diabetes mellitus and 796 (34.1%) met the diagnostic criteria for hepatic steatosis. Among the patients with hepatic steatosis, 245 (30.8%) also had diabetes mellitus. In terms of weight status, from the patients that were classified as overweight, 221 (23.7%) had hepatic steatosis, and from the patients that were classified as obese, 464 (45.8%) had hepatic steatosis. In terms of liver fibrosis scores, according to the APRI score, 151 patients met the criteria for fibrosis and 76 (50%) were classified as having significant fibrosis. Out of these 76 patients with significant fibrosis, 59 also had hepatic steatosis. The remaining 76 patients were diagnosed with advanced fibrosis and cirrhosis, of which 27 had coexisting steatosis. Using the FIB-4 index, 627 patients were identified as having fibrosis. Among them, 520 patients had fibrosis grades 2-3. Out of these 520 patients, 159 had concurrent hepatic steatosis. Additionally, 107 patients were classified as having advanced fibrosis, and 28 of them had steatosis. Furthermore, 164 patients had an FIB-4 index indicating advanced fibrosis and 40 had coexisting steatosis. According to the NAFLD fibrosis score, 225 patients were found to have advanced fibrosis, and 67 had hepatic steatosis. **Conclusion:** this study aimed to determine the prevalence and incidence of hepatic steatosis in asymptomatic patients. The findings revealed a significant burden of hepatic steatosis among the study population. Prioritizing the importance of early detection and intervention for hepatic steatosis, particularly in patients with associated risk factors such as diabetes, overweight, and obesity.

Prevalence of hepatic steatosis in patients with Diabetes Mellitus

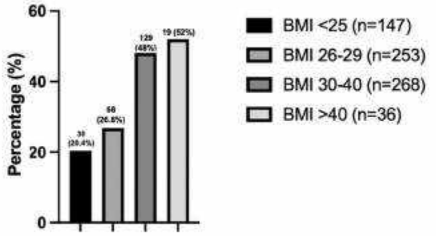

Figure A

Prevalence of hepatic steatosis in patients without Diabetes Mellitus

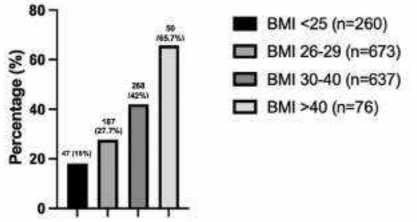

Figure B

Disclosures: The following people have nothing to disclose: José Alonso Ávila Rojo, Esmeralda Avila Rojo, David Aguirre-Villarreal, Ernesto Elizondo Zepeda, Ignacio García Juárez

2242-A | PREVALENCE OF NAFLD AND ACCURACY OF NITS IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

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Background: Patients with Polycystic Ovary Syndrome (PCOS) might be at increased risk for NAFLD. Only one study (PMID: 22837189) assessed the presence of NAFLD in adult PCOS using the gold standard for non-invasive detection of liver steatosis being MRI-PDFF. The results of previous studies regarding the prevalence of steatosis in PCOS measured by other tests (*e.g.*, controlled attenuation parameter CAP™, blood derived scores) were discordant, did not include the gold standard and studied multiple different patient groups.

The aim of the current prospective study is to investigate the prevalence of NAFLD in PCOS based on MRI and to assess the accuracy of CAP™ and non-invasive blood-derived tests in a well-defined patient population with and without PCOS. **Methods:** In this ongoing, prospective, monocentric, Belgian study NAFLD is detected in patients with PCOS diagnosed according to the Rotterdam consensus (2003) compared to apparently healthy women by means of hepatic MRI, CAP™ and blood based non-invasive tests (*a.o.*, Hepatic Steatosis Index (HSI)).

Using CAP™ NAFLD has been defined as CAP™ > 215 dB/m while moderate to severe NAFLD has been defined as CAP™ > 275 dB/m.

By means of hepatic MRI PDFF NAFLD has classically been defined as a value > 5% but recently a threshold of 3.71% was proposed. **Results:** The demographics of the 42 PCOS patients and 29 healthy controls were: age 32 ± 5 vs. 35 ± 7 years (p = 0.046), BMI 26.9 [25.6-29.2] vs. 23.7

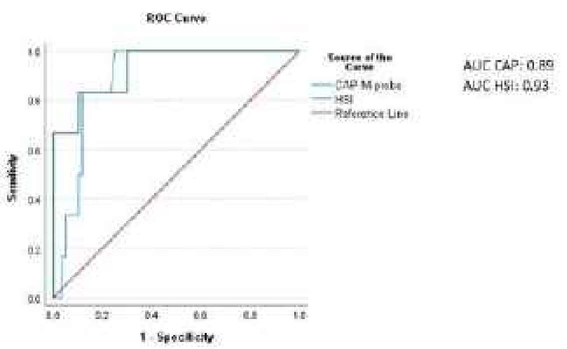
[23.5-27.0] kg/m^2 ($p > 0.05$), waist circumference 82 ± 80 cm vs. 77.4 ± 10.3 cm ($p > 0.05$), number of menstrual cycles 4.5 [4.3-6.6]] vs. 12.0 [10.3-12.1] ($p < 0.001$). Based on MRI NAFLD was detected using a threshold of 3.71% and of 5% in resp. 7 (21%) and 4 (10%) women with PCOS vs. 0 ($p = 0.02$) and 0 ($p = 0.09$) in controls.

Using CAP™ (cut-offs 215 dB/m and 275 dB/m) resp. 28 (67%) and 8 (19%) of the PCOS patients vs. 14 (48%) and 6 (21%) in controls were diagnosed with NAFLD ($p = 0.12$ and $p = 0.86$). HSI was increased in 16 (38%) patients with PCOS vs. 5 (17%) in controls ($p = 0.06$).

Diagnostic accuracy for NAFLD (MRI PDFF > 3.71%) was also high (AUC: resp. 0.89 and 0.93) (Figure 1). **Conclusion:** The MRI threshold significantly impacts on the observed prevalence of NAFLD in PCOS, with 5% substantially underestimating the prevalence, when studying this risk group. CAP™ and HSI have high accuracy to detect NAFLD as defined by MRI PDFF > 3.71%.

NAFLD is more prevalent in PCOS compared to controls. Further studies using a fully matched cohort and evaluating the reason for false positivity regarding CAP and HSI are in progress.

Figure 1: The accuracy of CAP™ and HSI compared to MRI-PDFF with a threshold of 3.71%



Disclosures: Sven Francque – Inventiva: Consultant, No, No; Eisai: Consultant, No, Yes; Siemens Healthcare: Speaking and Teaching, No, Yes; Novo Nordisk: Speaking and Teaching, No, Yes;

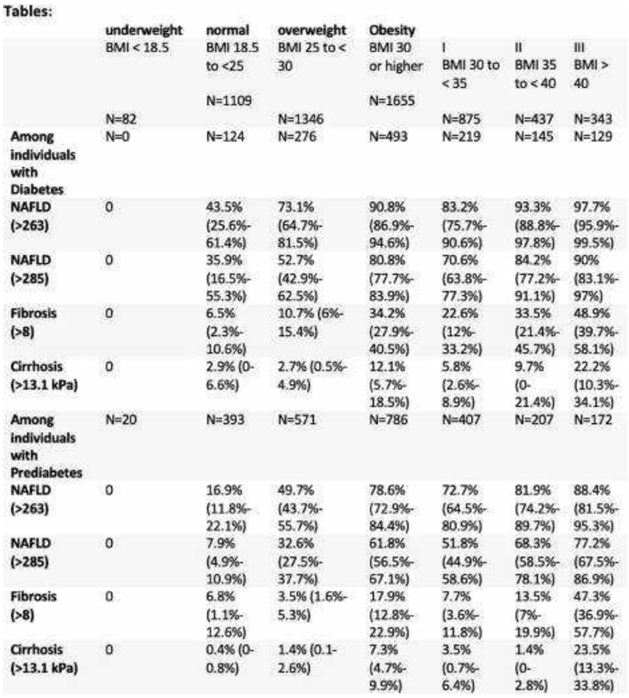
The following people have nothing to disclose: Wouter Robaeys, Leen Heyens, Ger H. Koek, Geert Robaeys

Disclosure information not available at the time of publication: Nathalie Dhont, Geert Verswijvel, Struyve Mathieu, Penders Joris

2243-A | PREVALENCE OF NONALCOHOLIC FATTY LIVER DISEASE AND FIBROSIS IN PATIENTS WITH PREDIABETES/ DIABETES BASED ON BODY MASS INDEX

Omar Alshuwaykh, California Pacific Medical Center, Aijaz Ahmed, Stanford University School of Medicine, George Cholankeril, Baylor College of Medicine and Donghee Kim, Stanford University Medical Center

Background: NAFLD is now the most common liver disease and may soon become the leading indication for liver transplantation **Methods:** We used data from the 2017-2018 NHANES. Excluding individual's with significant alcohol use and viral hepatitis, 4192 adult individual's had transient elastography. 893 individual's had diabetes and 1770 patients had prediabetes. We then categorized into three subgroups based on their BMI of normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), obesity (e 30 kg/m^2). Diabetes was defined as having hemoglobin A1c (A1c) e 6.5%, fasting blood glucose e 126 mg/dL, and/or treatment with oral hypoglycemic agent or insulin. Prediabetes was defined as fasting glucose of 100-125 mg/dL and A1c 5.7-6.4. CAP scores of e 263 dB/m were defined as NAFLD. A transient elastography e 8 kPa (e F2) and e 13.1 kPa (e F4) were defined as suspected fibrosis and cirrhosis **Results:** Population mean age was 49 years, 48% of the individual's were men. NAFLD prevalence was 81.2% (95% CI: 77.6-84.8) in patients with diabetes, and 55.9% (95% CI:52.9-59) in patients with prediabetes. Among patients with diabetes, prevalence of NAFLD was substantially higher in obesity (90.8%, 95% CI: 86.9-94.6), followed by overweight (73.1%, 95% CI: 64.7-81.5), and normal BMI (43.5%, 95% CI: 25.6-61.4). Among obese individual's, increasing obesity class was associated with increased NAFLD prevalence ($P < 0.001$). Prevalence of fibrosis (e F2) was highest among individual's with obesity (34.2%, 95% CI: 27.9-40.5). Likewise, prevalence of cirrhosis was highest (12.1%, 95% CI: 5.7-18.5) among individual's with diabetes. Among patients with pre-diabetes, prevalence of NAFLD was substantially higher in obesity (78.6%, 95% CI: 72.9-84.4), followed by overweight (49.7%, 95% CI: 43.7-55.7), and normal BMI (16.9%, 95% CI: 11.8-22.1). Among obese individual's, increasing obesity class was associated with increased prevalence of NAFLD ($P < 0.001$). Prevalence of fibrosis (e F2) was highest among individual's with obesity (17.9%, 95% CI: 12.8-22.9). Likewise, prevalence of cirrhosis was highest (7.3%, 95% CI: 4.7-9.9) among individual's with diabetes. Among obese individual's, increasing obesity class was linearly associated with increased prevalence of fibrosis and cirrhosis in those with diabetes and prediabetes ($P < 0.001$) **Conclusion:** Our findings highlight that patients with DM and obesity are more likely to have NAFLD and advanced fibrosis and should purse definitive diagnostic studies to receive the recommended interventions and follow up



Tables:

	underweight BMI < 18.5 N=82	normal BMI 18.5 to <25 N=1109	overweight BMI 25 to < 30 N=1346	Obesity BMI 30 or higher N=1655	I BMI 30 to < 35 N=875	II BMI 35 to < 40 N=437	III BMI > 40 N=343
Among individuals with Diabetes	N=0	N=124	N=276	N=493	N=219	N=145	N=129
NAFLD (>263)	0	43.5% (25.6%-61.4%)	73.1% (64.7%-81.5%)	90.8% (86.9%-94.6%)	83.2% (75.7%-90.6%)	93.3% (88.8%-97.8%)	97.7% (95.9%-99.5%)
NAFLD (>285)	0	35.9% (16.5%-55.3%)	52.7% (42.9%-62.5%)	80.8% (77.7%-83.9%)	70.6% (63.8%-77.3%)	84.2% (77.2%-91.1%)	90% (83.1%-97%)
Fibrosis (>8)	0	6.5% (2.3%-10.6%)	10.7% (6%-15.4%)	34.2% (27.9%-40.5%)	22.6% (12%-33.2%)	33.5% (21.4%-45.7%)	48.9% (39.7%-58.1%)
Cirrhosis (>13.1 kPa)	0	2.9% (0-6.6%)	2.7% (0.5%-4.9%)	12.1% (5.7%-18.5%)	5.8% (2.6%-8.9%)	9.7% (0-21.4%)	22.2% (10.3%-34.1%)
Among individuals with Prediabetes	N=20	N=393	N=571	N=786	N=407	N=207	N=172
NAFLD (>263)	0	16.9% (11.8%-22.1%)	49.7% (43.7%-55.7%)	78.6% (72.9%-84.4%)	72.7% (64.5%-80.9%)	81.9% (74.2%-89.7%)	88.4% (81.5%-95.3%)
NAFLD (>285)	0	7.9% (4.9%-10.9%)	32.6% (27.5%-37.7%)	61.8% (56.5%-67.1%)	51.8% (44.9%-58.6%)	68.3% (58.5%-78.1%)	77.2% (67.5%-86.9%)
Fibrosis (>8)	0	6.8% (1.1%-12.6%)	3.5% (1.6%-5.3%)	17.9% (12.8%-22.9%)	7.7% (3.6%-11.8%)	13.5% (7%-19.9%)	47.3% (36.9%-57.7%)
Cirrhosis (>13.1 kPa)	0	0.4% (0-0.8%)	1.4% (0.1-2.6%)	7.3% (4.7%-9.9%)	3.5% (0.7%-6.4%)	1.4% (0-2.8%)	23.5% (13.3%-33.8%)

Disclosures: The following people have nothing to disclose: Omar Alshuwaykh, Aijaz Ahmed, George Cholankeril, Donghee Kim

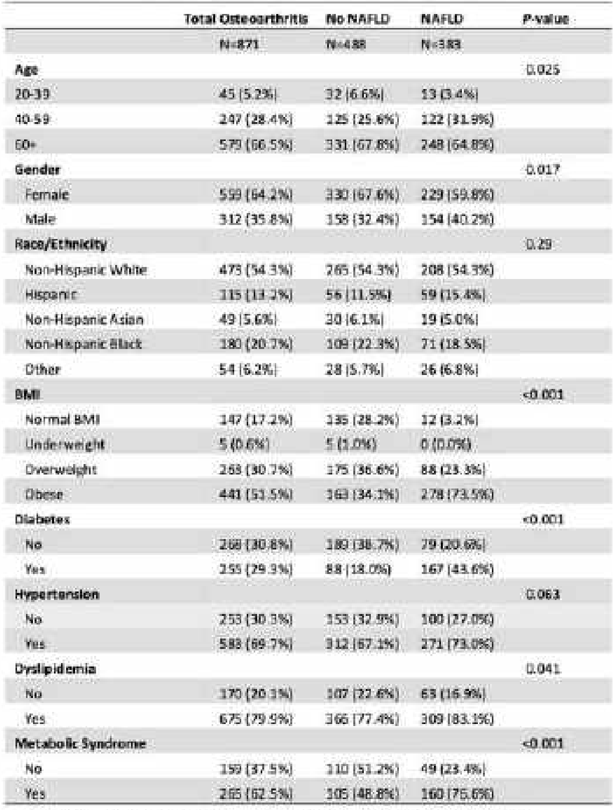
2244-A | PREVALENCE OF NON-ALCOHOLIC FATTY LIVER DISEASE, HIGH-RISK NON-ALCOHOLIC STEATOHEPATITIS, AND LIVER FIBROSIS IN PATIENTS WITH OSTEOARTHRITIS

Markos Kalligeros[1], Athanasios Vassilopoulos[1], Stephanos Vassilopoulos[1], Jack R. Wands[2] and Kittichai Promrat[3], (1)Brown University, (2)Warren Alpert Medical School of Brown University, Providence, RI, (3)Brown University School of Medicine

Background: Non-alcoholic fatty liver disease (NAFLD) and osteoarthritis (OA) are two major health issues with an increasing global prevalence. This study sought to determine the prevalence of NAFLD, high-risk non-alcoholic steatohepatitis (NASH), and liver fibrosis among patients with OA. **Methods:** Utilizing data from the U.S. National Health and Nutrition Examination Survey (NHANES) 2017-2020 cycle, we calculated the age-adjusted prevalence of NAFLD (CAP e 285 dB/m), high-risk NASH (FAST score), and liver fibrosis (LSM) in OA patients. Sample weights were applied to ensure representative estimates. Independent risk factors for these conditions among OA patients were identified through multivariable logistic regression analysis. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) are presented. **Results:** Among the 871 patients with OA, the majority were aged 60 and above (66.5%), were female (64.2%), and of non-Hispanic white ethnicity (54.3%). The NAFLD was more prevalent in higher age groups, males, individual's with obesity (BMI e 30), diabetes, dyslipidemia, and metabolic syndrome, with all showing statistically significant differences ($p\text{-value} < 0.05$) (Figure 1a). The racial/ethnic distribution and presence of hypertension did not demonstrate a statistically significant difference between the NAFLD and non-NAFLD groups. The age-adjusted prevalence of NAFLD among U.S. adults with OA was estimated at 39.81% (95% CI: 29.55-51.04%). The prevalence of high-risk NASH, with FAST scores exceeding 0.35 and 0.67, was found to be 9.08% (95% CI: 3.63-20.95%) and 5.26% (95% CI: 1.35-18.39%), respectively. Furthermore, the age-adjusted prevalence of clinically significant fibrosis (LSM e 8 kPa) and advanced fibrosis (LSM e 13.1 kPa) was 12.71% (95% CI:5.76-25.73%) and 5.78% (95% CI: 20.48-15.27%), respectively (Figure 1b). Notably, OA patients with NAFLD demonstrated a higher likelihood of having diabetes (aOR 3.14; 95% CI: 1.33-7.41) and a $BMI > 30$ kg/m^2 (aOR 10.87; 95% CI: 2.81-42.13). **Conclusion:** Our findings suggest a higher prevalence of NAFLD, high-risk NASH, and liver fibrosis among OA patients compared to the general population, implicating obesity as a potential common denominator for these conditions. The coexistence of OA and NAFLD, particularly among patients with obesity, can pose substantial challenges to the implementation of lifestyle interventions due to physical limitations induced by OA. This predicament necessitates the need for clinicians to consider additional, tailored interventions that are feasible and effective for this patient group. Furthermore, an integrated approach for early screening and management of NAFLD in OA patients is crucial to mitigate potential adverse health outcomes. Future research should focus on alternative strategies that accommodate the physical constraints of this population, paving the way for comprehensive and effective patient care.

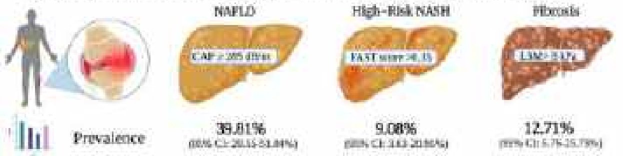
Figure 1: Characteristics and prevalence of NAFLD in Patients with Osteoarthritis

(a) Patient Baseline characteristics



	Total Osteoarthritis	No NAFLD	NAFLD	P-value
	N=871	N=488	N=383	
Age				0.025
20-39	45 (5.2%)	32 (6.6%)	13 (3.4%)	
40-59	247 (28.4%)	125 (25.6%)	122 (31.9%)	
60+	579 (66.5%)	331 (67.8%)	248 (64.8%)	
Gender				0.017
Female	559 (64.2%)	330 (67.6%)	229 (59.8%)	
Male	312 (35.8%)	158 (32.4%)	154 (40.2%)	
Race/Ethnicity				0.29
Non-Hispanic White	473 (54.3%)	265 (54.3%)	208 (54.3%)	
Hispanic	115 (13.2%)	56 (11.5%)	59 (15.4%)	
Non-Hispanic Asian	49 (5.6%)	30 (6.1%)	19 (5.0%)	
Non-Hispanic Black	180 (20.7%)	109 (22.3%)	71 (18.5%)	
Other	54 (6.2%)	28 (5.7%)	26 (6.8%)	
BMI				<0.001
Normal BMI	147 (17.2%)	135 (28.2%)	12 (3.2%)	
Underweight	5 (0.6%)	5 (1.0%)	0 (0.0%)	
Overweight	263 (30.7%)	175 (36.6%)	88 (23.3%)	
Obese	441 (51.5%)	163 (34.1%)	278 (73.5%)	
Diabetes				<0.001
No	268 (30.8%)	189 (38.7%)	79 (20.6%)	
Yes	255 (29.3%)	88 (18.0%)	167 (43.6%)	
Hypertension				0.063
No	253 (30.3%)	153 (32.9%)	100 (27.0%)	
Yes	583 (69.7%)	312 (67.1%)	271 (73.0%)	
Dyslipidemia				0.041
No	170 (20.1%)	107 (22.6%)	63 (16.9%)	
Yes	675 (79.9%)	366 (77.4%)	309 (83.1%)	
Metabolic Syndrome				<0.001
No	159 (37.5%)	110 (51.2%)	49 (23.4%)	
Yes	265 (62.5%)	105 (48.8%)	160 (75.6%)	

(b) Age adjusted prevalence of NAFLD, high risk NASH and clinically significant fibrosis



Disclosures: The following people have nothing to disclose: Markos Kalligeros, Athanasios Vassilopoulos, Stephanos Vassilopoulos, Jack R. Wands, Kittichai Promrat

2245-A | PROJECTION OF THE CLINICAL BURDEN OF NAFLD IN US ADULTS FROM 2020-2050: A MODELING STUDY

Phuc Le[1], Moosa Tatar[1], Srinivasan Dasarathy[2], Naim Alkhouri[3], William Herman[4], Abhishek Deshpande[1], Glen Taksler[1], Wen Ye[5] and Michael Rothberg[1], (1) Cleveland Clinic, (2)Cleveland Clinic Foundation, (3) Arizona Liver Health, Phoenix, AZ, (4)University of Michigan Medical School, (5)University of Michigan

Background: Following the alarming rise in prevalence of obesity and diabetes, nonalcoholic fatty liver disease (NAFLD) is projected to become the leading indication for liver transplant (LT) in the United States in the next decade. A better understanding of the clinical burden associated with NAFLD will enable health systems to prepare to meet this imminent demand from patients. Our objective was to project the burden of NAFLD in US adults from 2020-2050 using a population-based natural history model. **Methods:** We developed an agent-based state transition model that consisted of two components, with a yearly cycle. The first component simulated the US population starting from the year 2000, incorporating new births and immigrants annually based on Census data. The second component tracked the natural history of NAFLD progression in adults, encompassing 14 distinct health states including no steatosis, simple steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), LT, and liver-related or other causes of death. Model inputs were derived from the literature; unknown inputs were calibrated and validated against published estimates. **Results:** Validation of our model demonstrated a close match between predicted outcomes from 2000 to 2018 and published data on US population, trends in NAFLD prevalence, NASH proportion, incidence of HCC and LT, and overall survival rates among NAFLD patients. Our model predicts a steady increase in the prevalence of NAFLD among US adults from 27.8% in 2020 to 34.3% by 2050. Among NAFLD cases, the proportion of NASH is expected to increase from 20.0% to 21.8%. Prevalence should remain relatively stable for people aged 18-29 years but increase significantly for all other age groups. The proportion of NAFLD cases who develop cirrhosis is projected to increase from 1.9% in 2020 to 3.1% in 2050, and liver-related deaths should increase from 0.4% of all deaths to 1%. By 2050, NAFLD should cause 19,300 new cases of HCC and 4,200 new cases of LT per year, a substantial increase from 10,400 and 1,700 cases in 2020, respectively. **Conclusion:** Our model forecasts a substantial clinical burden of NAFLD over the next three decades. In the absence of effective treatments, health systems should plan for large increases in the number of HCC cases and the need for LT.

Disclosures: Naim Alkhouri – 89Bio: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AbbVie/Allergan: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Akero: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Better Therapeutics: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boehringer Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol-Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Corcept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; DSM: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Galectin: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genentech: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; 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AbbVie/Allergan: Speaking and Teaching, No, No; Alexion: Speaking and Teaching, No, No; Echosens: Speaking and Teaching, No, No; Eisai: Speaking and Teaching, No, No; Exelixis: Speaking and Teaching, No, No; Gilead: Speaking and Teaching, No, No; Intercept: Speaking and Teaching, No, No; Perspectum: Speaking and Teaching, No, No; Salix: Speaking and Teaching, No, No; Theratechnologies: Speaking and Teaching, No, No;

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Disclosure information not available at the time of publication: Moosa Tatar, William Herman, Abhishek Deshpande, Glen Taksler, Wen Ye, Michael Rothberg

2246-A | PSD3 RS 71519934 LACKED SIGNIFICANT EFFECT ON THE RISK FOR HEPATIC STEATOSIS AND CLINICALLY SIGNIFICANT FIBROSIS IN US ADULTS

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Background: Nonalcoholic fatty liver disease (NAFLD) has a strong heritable component. A recent study (PMID: 35102341) identified a multiple nucleotide variation (rs71519934, GT/AG) at the Pleckstrin and Sec7 domain-containing 3 (*PSD3*) gene which reduces susceptibility to the entire spectrum of NAFLD in individual's at risk. However, strengths of associations varied among different cohorts in that study. We examined the association between *PSD3* rs71519934 and the prevalence of hepatic steatosis and clinically significant fibrosis in two separate cohorts of US adults. **Methods:** *PSD3*-rs71519934 variant was genotyped using TaqMan SNP assay in patients from 2 cohorts, including 686 persons with NAFLD and 621 persons with HIV (PWH). Both cohorts had controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) measured via vibration controlled transient elastography. Both CAP and LSM were tested as a continuous trait and as dichotomously categorized. NAFLD was defined as CAP e 263 dB/m in the absence of heavy alcohol consumption or other liver diseases. Clinically significant fibrosis was defined as LSM e 8 kPa. Associations between *PSD3* rs71519934 and CAP and LSM were examined separately in two cohorts. Linear and logistic regression analyses were adjusted for age, sex, and race/ethnicity. *PSD3* rs71519934 was additively coded for the minor (GT) allele. A meta-analysis was conducted by combining the results from the two cohorts. **Results:** Table 1 summarizes selected demographics, clinical characteristics, CAP and LSM values, and rs71519934 allele and genotype frequencies. For CAP, we did not observe statistically significant association between rs71519934 and either continuous or dichotomized CAP, in either PWH, NAFLD cohort, or meta-analysis. However, in the PWH cohort GT allele showed a trend for higher CAP value (increase of 9.1 dB/m per GT allele, p = 0.07). For LSM, either as a continuous or a categorical variable, there was no statistically significant association with rs71519934 in either PWH, NAFLD cohort, or meta-analysis. However, GT allele showed a trend for decreasing LSM measures (decrease of 0.33 kPa per GT allele, p = 0.33). **Conclusion:** The *PSD3* GT allele was not significantly associated with CAP and LSM in our study, but we observed a numerical trend towards lower liver stiffness but higher hepatic steatosis.

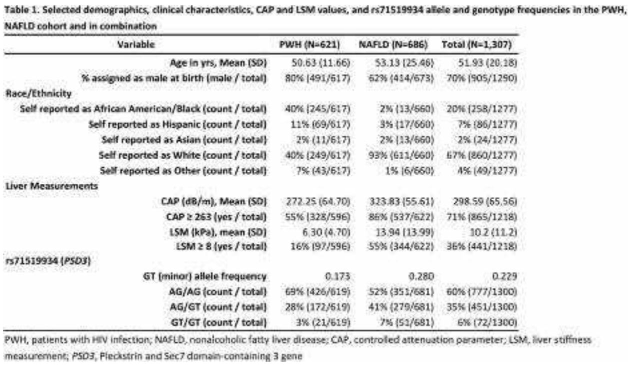

Table 1. Selected demographics, clinical characteristics, CAP and LSM values, and rs71519934 allele and genotype frequencies in the PWH, NAFLD cohort and in combination

Variable	PWH (N=621)	NAFLD (N=686)	Total (N=1,307)
Age in yrs, Mean (SD)	50.63 (11.66)	53.13 (25.46)	51.93 (20.18)
% assigned as male at birth (male / total)	80% (491/617)	62% (414/673)	70% (905/1290)
Race/Ethnicity			
Self reported as African American/Black (count / total)	40% (245/617)	2% (13/660)	20% (258/1277)
Self reported as Hispanic (count / total)	11% (69/617)	3% (17/660)	7% (86/1277)
Self reported as Asian (count / total)	2% (11/617)	2% (13/660)	2% (24/1277)
Self reported as White (count / total)	40% (249/617)	93% (611/660)	67% (860/1277)
Self reported as Other (count / total)	7% (43/617)	1% (6/660)	4% (49/1277)
Liver Measurements			
CAP (dB/m), Mean (SD)	272.25 (64.70)	323.83 (55.61)	298.59 (65.56)
CAP ≥ 263 (yes / total)	55% (328/596)	86% (537/622)	71% (865/1218)
LSM (kPa), mean (SD)	6.30 (4.70)	13.94 (13.99)	10.2 (11.2)
LSM ≥ 8 (yes / total)	16% (97/596)	55% (344/622)	36% (441/1218)
rs71519934 (*PSD3*)			
GT (minor) allele frequency	0.173	0.280	0.229
AG/AG (count / total)	69% (426/619)	52% (351/681)	60% (777/1300)
AG/GT (count / total)	28% (172/619)	41% (279/681)	35% (451/1300)
GT/GT (count / total)	3% (21/619)	7% (51/681)	6% (72/1300)

PWH, patients with HIV infection; NAFLD, nonalcoholic fatty liver disease; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; *PSD3*, Pleckstrin and Sec7 domain-containing 3 gene

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

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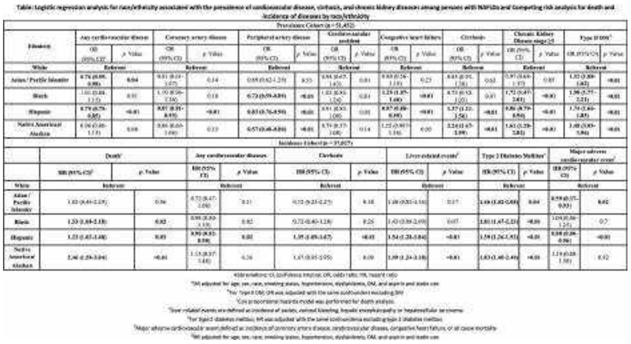
Background: Nonalcoholic fatty liver disease (NAFLD) has increased in prevalence in recent years. Data on NAFLD in Native Americans are limited. We conducted a study to estimate the prevalence and incidence of NAFLD and its complications in an ethnically diverse population. **Methods:** We conducted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



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

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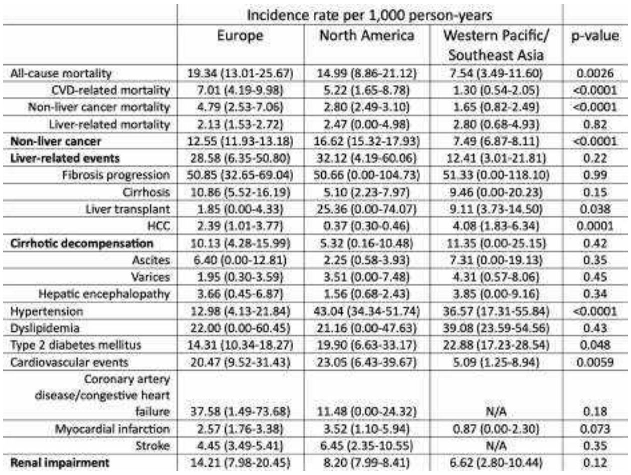
Background: Nonalcoholic fatty liver disease (NAFLD) incidence and prevalence varies by region. We aimed to determine the regional incidence rates of adverse clinical events associated with NAFLD. **Methods:** We performed a systematic review and meta-analysis of cohort studies of adults with NAFLD at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



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

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

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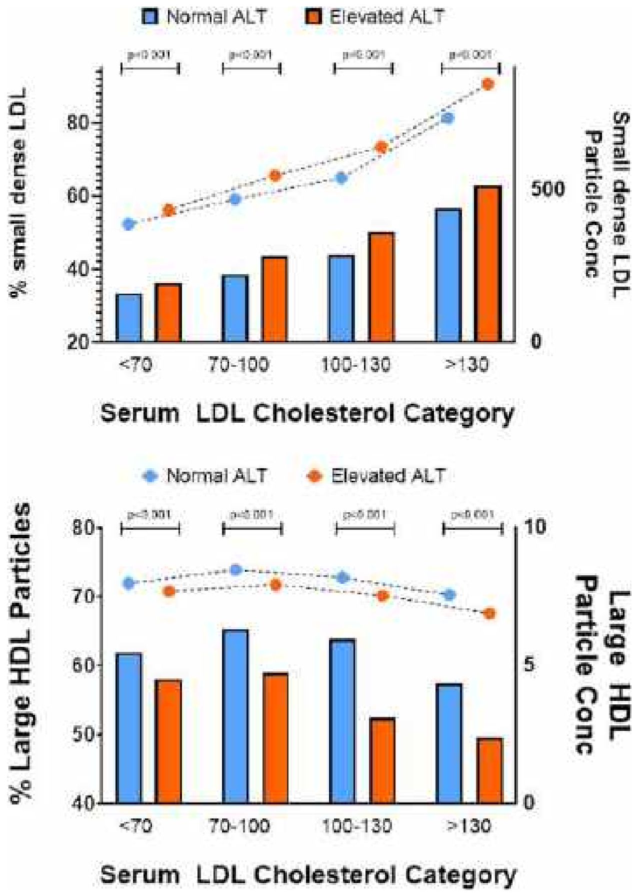
Background: Liver plays a central role in lipoprotein metabolism and is a key driver of atherogenesis. This relationship is best described in patients with nonalcoholic fatty liver disease (NAFLD) where cardiovascular disease is the leading cause of mortality. The published literature evaluating atherosclerosis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



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

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

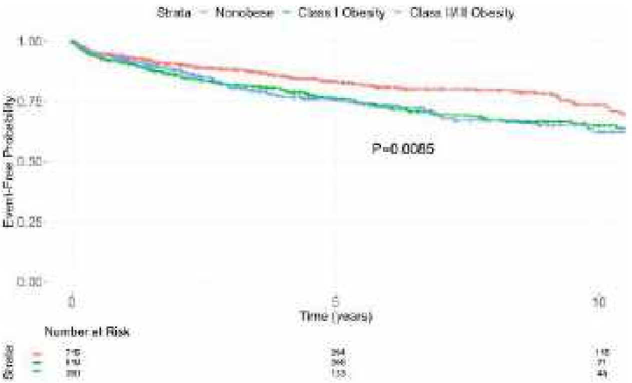

Figure 1: Kaplan-Meier estimator depicting CVD event-free probability in each BMI category over the duration of follow up in all participants. The overall log-rank test p-value is shown. CVD: cardiovascular disease; BMI: body mass index.

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2251-C | RISK OF FATTY LIVER AND HEPATIC FIBROSIS ASSOCIATED WITH LONG-TERM USE OF TAMOXIFEN OR ANASTROZOLE MAY BE OVERESTIMATED IN PATIENTS WITH BREAST CANCER

Mateus Jorge Nardelli[1], Mísia Joyner De Sousa Dias Monteiro[1], Guilherme Grossi Lopes Cancado[1], Tereza Fontes Cal[2], Adriana Maria Lamego Rezende[1], Julia Cunha Vasconcelos[1], Carolina Martins Vieira[1], Paulo Henrique Costa Diniz[1], Juliana De Assis Silva Gomes Estanislau[1], Luciana Faria[1] and Claudia Alves Couto[3], (1)Universidade Federal De Minas Gerais, (2) Universidade Estadual De Campinas, (3)Universidade Federal De Minas Gerais, Belo Horizonte, Brazil

Background: Nonalcoholic fatty liver disease (NAFLD) is highly prevalent among women with breast cancer, particularly those who receive hormone therapy such as tamoxifen and anastrozole. While the survival rates of breast cancer patients have increased, the impact of endocrine therapy on the severity and progression of NAFLD in the long term remains unclear. This study aimed to assess the prevalence and severity of NAFLD in relation to adjuvant hormone therapy in patients with breast cancer, and to investigate the risk factors associated with its occurrence and progression. **Methods:** Cross-sectional study of women with breast cancer recruited from an oncology outpatient clinic. Abdominal ultrasound was used to detect liver steatosis, and transient elastography was used to evaluate hepatic fibrosis. Patients with metastatic disease were excluded. The patients were divided into three groups: no hormone therapy, those exposed to anastrozole, and those exposed to tamoxifen (current or interrupted). **Results:** A total of 233 patients with a mean age of 57 ± 10 years were enrolled, with a follow-up period ranging from 1 to 315 months (median 47, interquartile range [IQR] 79). Comorbidities included diabetes mellitus (22.8%), arterial hypertension (49.1%), dyslipidemia (25.3%), and obesity (44.2%). Of the patients, 71 (30.5%) did not receive hormone therapy, 20 (8.6%) were exposed to anastrozole for a median duration of 24 months (IQR 27), and 142 (60.9%) were exposed to tamoxifen for a median duration of 34 months (IQR 46). Liver steatosis was detected in 56.2% of the patients, with no significant differences between the three groups ($p = 0.340$). Liver stiffness was also similar between groups, with a median of 5.2 (IQR

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

2.2) kPa (p = 0.515), 9.9% of patients having liver stiffness e 8 Kpa (p = 0.372), and 5.0% of patients having a measurement e 12 Kpa (p = 0.338). Body mass index (BMI) and diabetes mellitus were independently associated with liver steatosis, while only BMI positively correlated with advanced fibrosis (liver stiffness e 8 kPa), even after adjustment for hormone therapy duration. **Conclusion:** More than half of the breast cancer patients had fatty liver disease, with around 10% having liver stiffness e 8 Kpa. Common metabolic risk factors, such as body mass index and diabetes mellitus, were independently associated with the occurrence and progression of NAFLD in breast cancer patients, regardless of hormone therapy exposure. The risk of NAFLD progression induced by tamoxifen and anastrozole seems to have been previously overestimated.

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2252-C | SEATTLE MODEL: A NEW NON-INVASIVE SYSTEM BASED ON MACHINE LEARNING MODELS TO IDENTIFY ADVANCED FIBROSIS IN PATIENTS WITH MAFLD

Srikrishna Gurumurthy, Tesla STEM High School and Pankaj Rajvanshi, Swedish Medical Center

Background: Screening for advanced fibrosis (AF) in patients with non-alcoholic fatty liver disease (NAFLD) patients with type 2 diabetes mellitus (T2DM), also called metabolic-associated fatty liver disease (MAFLD), has been recommended. With the magnitude of the problem, resource constraints, costs, and complications of various tests; non-invasive tests that are inexpensive, easy to administer and have a high sensitivity (Sn) and positive predictive value (PPV) are needed. We have shown that machine learning models (MLMs) are superior to FIB-4 in the prediction of advanced liver fibrosis. Here, we report on a new model based on MLMs to predict advanced fibrosis in MAFLD. **Methods:** We analyzed data from the NIDDK NAFLD Adult database for 317 patients with NAFLD and T2DM (MAFLD) who had liver biopsy results available. We first created an MLM using an XGBoost model with 30 parameters. We then ran 5 random runs to identify the top 10 features, in rank of importance. We created our final model (called Seattle Model) using AST/ALT ratio, Platelet count, INR, and Waist Circumference. The performance of this model was internally validated in the dataset by splitting the data into training (20%) and validation (80%) datasets. The performance of Seattle Model was compared with FIB-4. **Results:** Among 317 patients in the NAFLD database, 298 (94%) had BMI > 27, 262 (82.6%) had a BMI > 30. Three features (AST/ALT ratio, Platelet Count, and INR) were consistent in 5 random runs of the initial model. The addition of waist circumference improved the performance of our model, and the final Seattle Model was created using these four parameters. It has an AUROC of 0.73, Sn 84.0%, specificity (Sp) 62.4%, PPV 71.4%, and a negative predictive value (NPV) of 78.1% for prediction of AF (e F3). For cirrhosis (F4), it has an AUROC of 0.783, Sn 91.4%, specificity (Sp) 79.3%, PPV 93.3%, and a negative predictive value of 47.9%. Comparison with FIB-4 is shown in Table 1. For AF (e F3), the Seattle Model was statistically superior (p < 0.05) to FIB-4 in AUROC, Sp and PPV. FIB-4 was statistically superior (p < 0.05) to the Seattle Model in Sn and NPV for F4 only. **Conclusion:** Seattle Model (a new MLM) is better than FIB-4 in prediction of advanced fibrosis and cirrhosis in patients with MAFLD. This new model for MAFLD needs further validation in larger datasets. Because of the excellent PPV of this model, further comparison of this model with imaging and blood tests may provide additional insights.

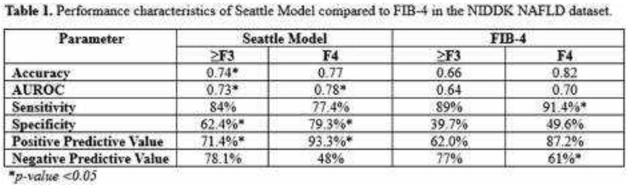

Table 1. Performance characteristics of Seattle Model compared to FIB-4 in the NIDDK NAFLD dataset.

Parameter	Seattle Model		FIB-4	
	≥F3	F4	≥F3	F4
Accuracy	0.74*	0.77	0.66	0.82
AUROC	0.73*	0.78*	0.64	0.70
Sensitivity	84%	77.4%	89%	91.4%*
Specificity	62.4%*	79.3%*	39.7%	49.6%
Positive Predictive Value	71.4%*	93.3%*	62.0%	87.2%
Negative Predictive Value	78.1%	48%	77%	61%*

**p-value <0.05*

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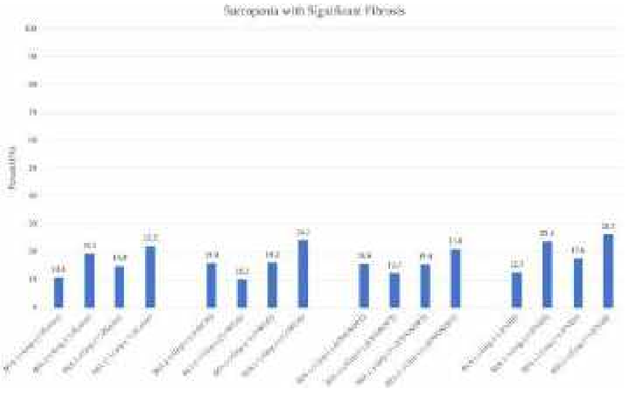
2253-C | SIMULTANEOUS ASSESSMENT OF SKELETAL MUSCLE MASS AND HANDGRIP STRENGTH IDENTIFIES PATIENTS WITH NAFLD AT A HIGH-RISK OF ADVANCED LIVER FIBROSIS

David Sooik Kim[1], Pyo Hyeok Kwon[2], Jae Seung Lee[2], Hye Won Lee[2], Beom Kyung Kim[2], Jun Yong Park[2], Do Young Kim[2], Sang Hoon Ahn[2], Nikolaos T. Pyrsopoulos[1] and Seung Up Kim[2], (1)Rutgers University, New Jersey Medical School, Newark, NJ, (2)Yonsei University College of Medicine, Seoul, Republic of Korea

Background: Although sarcopenia is associated with multiple comorbidities, its diagnosis depends on various diagnostic criteria with different diagnostic modalities. We investigated the association between appendicular skeletal muscle mass (ASM) measured by bioimpedance analysis (BIA) and handgrip strength (HGS) and identified the predictors of discordance between the two modalities in diagnosing sarcopenia. In addition, we investigated whether the combined use of the two diagnostic modalities identifies a high-risk subgroup among patients with nonalcoholic fatty liver disease (NAFLD). **Methods:** Between 2018 and 2023, 2,043 NAFLD patients with ASM by BIA and HGS were recruited. Sarcopenia was diagnosed when ASM/BMI < 0.882 in men and < 0.582 in women or by HGS < 28.9 kg in men and < 16.8 kg in women. Advanced liver fibrosis was defined as liver stiffness value by transient elastography greater than 9.6 kPa. **Results:** Among all patients, 794 (38.8%) and 200 (10.8%) patients had sarcopenia by BIA and HGS, respectively. ASM and HGS showed a positive correlation ($R = 0.79$, $P < 0.001$), that became more prominent when stratified by gender ($R = 0.96$) and by gender and age ($R = 0.98$) (all $P < 0.001$). In multivariate analysis, male gender (odds ratio [OR] = 1.3) and BMI (OR = 1.2) were the independent predictors of discordance between ASM and HGS in diagnosing sarcopenia ($P < 0.05$). Patients with sarcopenia both by BIA and HGS and those with sarcopenia by HGS only demonstrated a significantly higher probability of advanced liver fibrosis than that of patients without sarcopenia by both BIA and HGS (all $P < 0.001$). When adjusted for age, gender, HbA1c, platelet count, serum albumin, and total bilirubin, similar findings were observed (all $P < 0.05$). **Conclusion:** ASM by BIA and HGS showed a significant association and male gender and BMI were independently associated with the discordance between the two diagnostic modalities. In addition, the use of two diagnostic modalities was beneficial in identifying a high-risk population with advanced liver fibrosis among patients with NAFLD.



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2254-C | SURGICAL MENOPAUSE IS ASSOCIATED WITH INCREASED PREVALENCE OF NONALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Aunchalee Jaroenlapnopparat, Mount Auburn Hospital/Harvard Medical School, Ben Ponvilawan, University of Missouri-Kansas City School of Medicine, Pojsakorn Danpanichkul, Chiang Mai University, Jerapas Thongpiya, Texas Tech University Health Science Center and Suchapa Arayakarnkul, University of Minnesota

Background: Natural Menopause is associated with nonalcoholic fatty liver disease (NAFLD). However, data are inconsistent on whether surgical menopause is a risk of NAFLD. We aimed to collect all existing data to determine this association. **Methods:** Potentially eligible studies were identified from EMBASE, MEDLINE, and Web of Science databases from inception to April 2023 using a search strategy that was composed of the terms for “NAFLD” and “oophorectomy” or “surgical menopause”. Eligible study must contain two groups of participants: one

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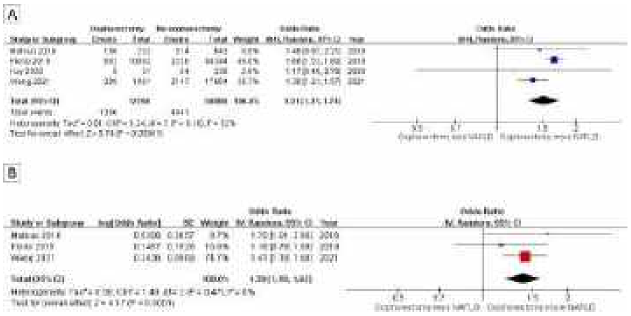
Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

group of postmenopausal women who underwent surgical menopause, and another group of premenopausal women. The study must report the association between surgical menopause and prevalent NAFLD. We extracted such data from each study and calculated pooled odds ratio (OR) by combining effect estimates of each study using a random-effects model. Funnel plot was used to assess for the presence of publication bias. **Results:** A total of 465 articles were identified. After two rounds of independent review by two investigators, 4 cross-sectional studies fulfilled the eligibility criteria. The meta-analysis of 4 studies revealed the significant association between surgical menopause (oophorectomy) and NAFLD with a pooled OR of 1.51 (95% CI, 1.31-1.74; $I^2 = 52\%$). The association remained significant in a sensitivity meta-analysis of 3 studies that reported the association with adjustment for age, BMI, diabetes status, and status of hormone use with a pooled OR of 1.39 (95% CI, 1.19-1.62; $I^2 = 0\%$). The funnel plot was fairly symmetric and was not suggestive of publication bias. **Conclusion:** The meta-analysis reveals that surgical menopause is associated with approximately 1.5 times higher odds of NAFLD. The association remains significant after adjusting for age, BMI, diabetes status, and status of hormone use.



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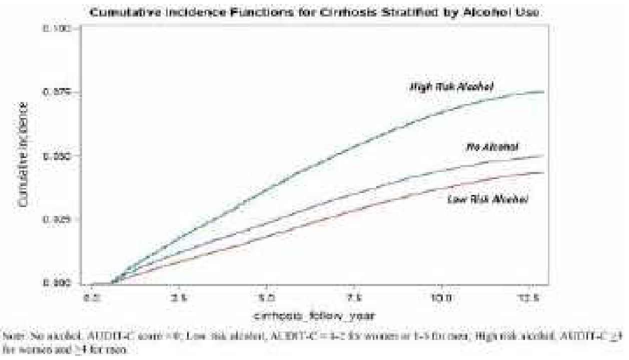
2255-C | THE ASSOCIATION BETWEEN BASELINE ALCOHOL USE AND LONG-TERM RISK OF INCIDENT CIRRHOSIS AMONG A NATIONAL COHORT OF U.S. VETERANS WITH METABOLIC DYSFUNCTION ASSOCIATED FATTY LIVER DISEASE

Robert J. Wong[1,2], Zeyuan Yang[2], Ramsey Cheung[3], Ashwani K. Singal[4], Albert Do[5], Aijaz Ahmed[1] and Aaron Yeoh[6], (1)Stanford University School of Medicine, (2)VA Palo Alto Healthcare System, (3) Veterans Affairs Palo Alto Health Care System, (4) University of South Dakota, (5)Yale University, New Haven, CT, (6)Stanford University - School of Medicine

Background: Metabolic dysfunction associated fatty liver disease (MAFLD) is highly prevalent among U.S. adults, and particularly among U.S. Veterans, a population enriched in metabolic co-morbidities. The association between different levels of alcohol use and risk of disease progression among adults with fatty liver remains unclear, and data specifically in patients with MAFLD are lacking. We aim to evaluate the association between baseline levels of alcohol use and risk of incident cirrhosis among a national cohort of adult Veterans with MAFLD. **Methods:** Adults with MAFLD were identified using the national Veterans Affairs database from 1/1/2010 to 12/31/2022. Patients with cirrhosis or HCC at baseline or within 6 months after index date of MAFLD diagnosis were excluded. Baseline AUDIT-C scores were used to categorize patients into no alcohol (AUDIT-C = 0), low-risk alcohol (AUDIT-C = 1-2 for women and 1-3 for men), and high-risk alcohol (AUDIT-C > 3 for women and > 4 for men). Incidence of cirrhosis (per 100 person-years) was stratified by alcohol use categories and evaluated using Nelson-Aalen methods for estimating cumulative hazards rates. We applied competing risks methods that censored for death. Adjusted multivariate Cox proportional hazards models evaluated for predictors of cirrhosis. **Results:** Among 1,156,189 Veterans with MAFLD, 54.2% reported no alcohol use, 34.6% reported low-risk alcohol, and 11.2% high-risk alcohol. Compared to patients reporting no alcohol, high-risk alcohol users were younger (59.9y vs. 64.0y, $p < 0.01$), had lower proportion with diabetes mellitus (42.5% vs. 62.4%, $p < 0.01$), but had higher FIB-4 scores at baseline (proportion with FIB-4 > 2.67: 15.0% vs. 11.1%, $p < 0.01$). Compared to MAFLD patients with no alcohol use, the incidence of cirrhosis was significantly higher in patients with high-risk alcohol (0.76 vs. 0.53 per 100 person-years, $p < 0.01$), but significantly lower in patients with low-risk alcohol use (0.42 vs. 0.53 per 100 person-years, $p < 0.01$). On adjusted multivariate regression, compared to MAFLD patients with no alcohol use, those with high-risk alcohol use had significantly greater risk of cirrhosis (HR 1.27, 95% CI 1.23-1.32), whereas those with low-risk alcohol use had lower risk of cirrhosis (HR 0.89, 95% CI 0.86-0.91). **Conclusion:** Among a national cohort of U.S. veterans with MAFLD, high-risk alcohol use was associated with significantly higher risk of incident cirrhosis, whereas low-risk alcohol use as determined by AUDIT-C scores, was associated with lower risk of incident cirrhosis when compared to patients reporting no alcohol use.



Note: No alcohol, AUDIT-C score =0; Low risk alcohol, AUDIT-C = 1-2 for women or 1-3 for men; High risk alcohol, AUDIT-C ≥3 for women and ≥4 for men.

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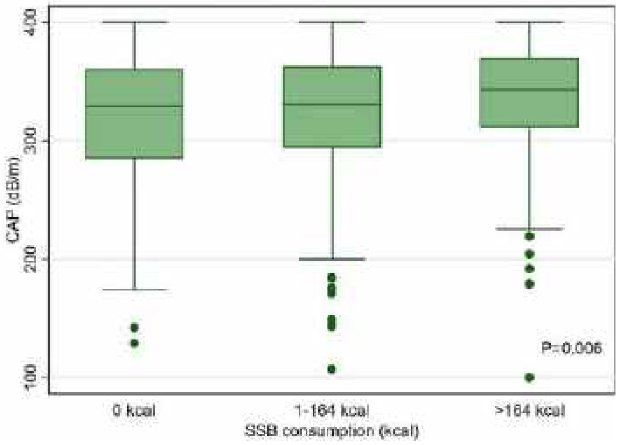
The following people have nothing to disclose: Zeyuan Yang, Ramsey Cheung, Ashwani K. Singal, Albert Do, Aijaz Ahmed, Aaron Yeoh

2256-C | THE ASSOCIATION BETWEEN SUGAR-SWEETENED BEVERAGE CONSUMPTION AND NAFLD SEVERITY MEASUREMENTS

Sameer Khan[1], Laura Wilson[2], Patricia Belt[2], Jeanne M Clark[1], Jeffrey Schwimmer[3], David E Kleiner[4], Emily P. Sharkey[2], James Tonascia[2], Laura A. Miriel[2], Rohit Loomba[5] and Tinsay A. Woreta[6], (1)Johns Hopkins University School of Medicine, (2)Johns Hopkins School of Public Health, (3)UC San Diego, (4) Laboratory of Pathology, National Cancer Institute, Bethesda, MD, (5)University of California, San Diego, San Diego, CA, (6)Johns Hopkins Medicine, Baltimore, MD

Background: The consumption of sugar-sweetened beverages (SSBs) has been shown to be a risk factor for diabetes and obesity. Prior literature examining the association between SSB consumption and NAFLD is based on small, retrospective studies. In this study, we aim to assess the relationship between the intake of SSBs and NAFLD severity using a large, diverse population of adults with biopsy proven NAFLD in the U.S. **Methods:** We studied adult participants from the NASH CRN longitudinal cohort database who underwent vibration controlled elastography (FibroScan) within 6 months of liver biopsy and completed the Beverage Questionnaire (BEVQ-15) at study entry. The BEVQ-15 is a validated food frequency questionnaire that allows for calculation of total SSB calories (kcals). Baseline characteristics were compared across three categories of SSB consumption, none (0 kcal), minimum to moderate (1-164 kcals), and high (> 164 kcals). NAFLD severity was assessed by liver biopsy and FibroScan. Multivariable regression analyses were performed to assess the relationship between the severity of fibrosis and steatosis with SSB consumption (log transformed due to non-normality), controlling for age, sex, race/ethnicity, smoking, alcohol use, hypertension, diabetes, and obesity. **Results:** The 935 participants (60% female, 78% Caucasian) had a mean age of 51 years, mean BMI was 34.8 kg/m^2; and 76% had obesity. 241 (26%) did not consume any calories through SSBs, 462 (49%) consumed 1 to 164 kcal, and 232 (25%) consumed more than 164 kcal. On liver histology, 326 patients (35%) had advanced fibrosis (stage 3 or 4). The mean LSM was 12.0 (± 10.6) kPa. The mean CAP score was 326 (± 52) dB/m. Greater SSB consumption was associated with higher BMI as demonstrated by a mean BMI of 34.2 (± 6.5), 34.4 (± 6.5), and 36.0 (± 7.2) kg/m^2 for the none, minimum to moderate, and high SSB groups, respectively ($p = 0.003$). There was also a significant positive association between greater SSB consumption and higher CAP scores, with median (IQR) scores of 329 (285-360), 330 (294-363), and 343 (311-370) dB/m ($p = 0.006$) for each consecutive SSB group (Figure 1). Multivariable linear regression analysis demonstrated that greater SSB consumption was positively associated with CAP score ($p = 0.02$). However, no significant association was found between SSB consumption and liver stiffness as measured by Fibroscan or liver fibrosis or steatosis severity based on liver histology data. **Conclusion:** This study provides evidence that adults with NAFLD who consume higher amounts of SSBs have higher BMI and CAP scores. SSB consumption did not correspond with higher grade steatosis on histology, which may reflect sampling variability of liver biopsy. Our findings underscore the importance of SSBs as a potential target for lifestyle modification in managing NAFLD. Further research is needed to elucidate the long-term impact of SSB consumption patterns on the trajectory of the disease.

Figure 1. Association between Sugar-Sweetened Beverage (SSB) Consumption Category and Controlled Attenuation Parameter (CAP) Score.



Disclosures: Jeffrey Schwimmer – Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Seraphina: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genfit: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;

Rohit Loomba – Sagimet Biosciences: Consultant, No, No; Pfizer: Consultant, No, No; Merck: Consultant, No, No; NovoNordisk: Consultant, No, No; Novartis: Consultant, No, No; NGM Biopharmaceuticals: Consultant, No, No; Metacrine, Inc.: Consultant, No, No; 89 bio: Stock – privately held company (individual stocks and stock options), No, No; Ionis: Consultant, No, No; Inventiva: Consultant, No, No; Intercept: Consultant, No, No; Inipharma: Consultant, No, No; Hightide: Consultant, No, No; Glympse Bio: Consultant, No, No; Galmed Pharmaceuticals: Consultant, No, No; Eli Lilly: Consultant, No, No; CohBar: Consultant, No, No; Bristol-Myer Squibb: Consultant, No, No; AstraZeneca: Consultant, No, No; Arrowhead Pharmaceuticals: Consultant, No, No; Sagimet Biosciences: Stock – privately held company (individual stocks and stock options), No, No; Altimmune: Consultant, No, No; Aardvark Therapeutics: Consultant, No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; NGM Biopharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; NovoNordisk: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Terns Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; LipoNexus Inc.: Executive role , No, No; Arrowhead Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AstraZeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boehringer-Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol-Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Eli Lilly: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; 89 bio: Consultant, No, No; Terns Pharmaceuticals: Consultant, No, No; Viking Therapeutics: Consultant, No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Hanmi: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Inventiva: Grant/Research Support (research funding from ineligible companies should be disclosed by the

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Disclosure information not available at the time of publication: Laura Wilson, Patricia Belt, Jeanne M Clark, Emily P. Sharkey, James Tonascia, Laura A. Miriel

2257-C | THE ASSOCIATION OF FOOD INSECURITY WITH HEPATIC STEATOSIS VARIES BY BMI AMONG WOMEN LIVING WITH AND WITHOUT HIV INFECTION

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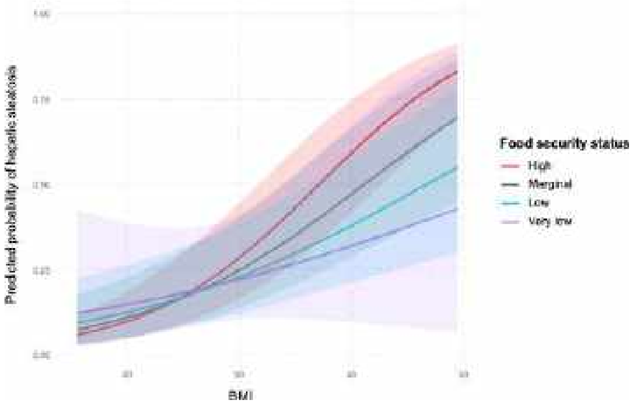
Background: Food insecurity, a key social determinant of health, is a risk factor for hepatic steatosis in the general population. In people living with HIV, food insecurity is associated with worse HIV-related morbidity and metabolic parameters, including obesity and diabetes. However, little is known about the impact of food insecurity on the risk of hepatic steatosis among women with (WWH) and at risk for HIV infection. **Methods:** We measured hepatic steatosis using controlled attenuated parameter (CAP) and food security status using the U.S. Household Food Security Survey Module in women without viral hepatitis. Women with high food security were considered to be food secure and women with marginal, low, or very low food security were considered to be food insecure. Hepatic steatosis was defined as CAP e 248 decibels/m. We performed multivariable logistic regression to examine the association of food insecurity with hepatic steatosis, adjusting for age, sex, race and ethnicity, body mass index (BMI), alcohol use, insulin resistance, and HIV status. Given the potential influence of obesity on the relationship between food insecurity and hepatic steatosis, we also tested for interactions between BMI and food insecurity. **Results:** Among 1533 women (1115 WWH, 418 without HIV), mean age was 50 years, 14% were White, 76% Black, 14% Hispanic, 10% were heavy drinkers, mean BMI was 30 kg/m^2, and 20% reported food insecurity. Participants with food insecurity were more likely to be White (18% vs 14%), heavy drinkers (13% vs 9%), and have a lower BMI (mean 29 vs 31). Food insecurity was associated with lower odds of hepatic steatosis in multivariable analysis (OR: 0.60, CI: 0.2-1.0, $p = 0.05$). We identified a significant interaction between food insecurity and BMI (low food security*BMI $p = 0.02$; very low food security*BMI $p = 0.01$). For every 1-unit BMI increase, there was a 14% (95% CI: 12% to 16%, $p < 0.001$), 10% (95% CI: 6% to 15%, $p < 0.001$), 8% (95% CI: 0.3-16%, $p = 0.001$) and 5% (95% CI: -1% to 11%, $p = 0.10$) greater odds of hepatic steatosis in the high, marginal, low and very low food security groups, respectively. Interestingly, food insecurity was associated with greater hepatic steatosis in women with BMI < 25 kg/m^2 and lower hepatic steatosis in overweight/obese women with BMI e 25 kg/m^2 (Figure). **Conclusion:** In a racially and ethnically diverse cohort of women with and without HIV, women who reported food insecurity with BMI < 25 kg/m^2 had higher odds of hepatic steatosis while women with BMI e 25 kg/m^2 had lower odds of hepatic steatosis. Our findings suggest that food insecurity, in the presence of other factors that might lower BMI, such as chronic inflammatory processes, could worsen hepatic steatosis whereas food insecurity may attenuate the effect of higher BMI on hepatic steatosis. This study lays the groundwork for future efforts exploring potential mechanistic pathways.



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

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

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

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

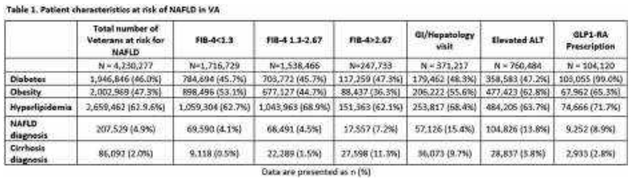

Table 1. Patient characteristics at risk of NAFLD in VA

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

Data are presented as n (%)

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

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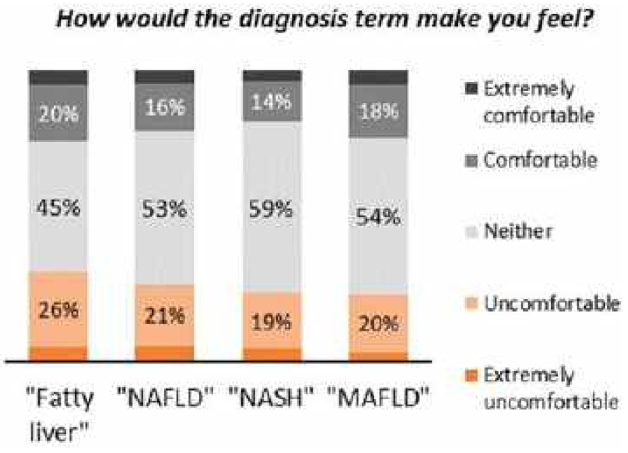
Background: NAFLD can be associated with disease burden and stigma to patients and providers. Aims: To understand the disease burden and stigma related to NAFLD. **Methods:** Members of the Global NASH Council created two surveys (68-item patient and 41-items provider survey) about experiences and attitudes toward NAFLD and related terms. **Results:** The surveys were completed by 895 NAFLD patients (19 countries) and 629 providers (64% GI/hepatologists, 23 countries). Of all patients, 64% ever disclosed having NAFLD to family/friends; the main term used was “fatty liver” (82%) while “metabolic disease” or “MAFLD” were rarely used (never by 88%). 35% of patients reported experiencing stigma or discrimination (at least sometimes) due to obesity/overweight and only 12% due to their liver disease of NAFLD. From the Liver Disease Burden (LDB) survey (35 items, 7 domains; range 1-4, higher scores indicate greater burden), the total mean burden score was the highest in USA (1.97 ± 0.57) and lowest in Middle East and North Africa (MENA) region (1.74 ± 0.53). The Stigma domain score was also the highest in the USA (2.51 ± 0.71) and the lowest in MENA (1.84 ± 0.60). In multivariate analysis adjusted for country of enrollment, independent predictors of higher total LDB and Stigma scores were female sex, living outside urban areas, history of medical weight loss, having e 2 chronic comorbidities, and having severe fibrosis or cirrhosis ($p < 0.05$). Regarding how various diagnostic terms were perceived by patients, there were no substantial differences between “NAFLD”, “fatty liver disease”, “NASH”, or “MAFLD” (Figure). In contrast, provider discomfort while taking care of patients with NAFLD was primarily related to the perceived patients’ lack of willpower for lifestyle changes and taking care of their diabetes (43-48%). Furthermore, 40% of providers believed that the word “fatty” in the name of the disease was stigmatizing for patients (similar across regions and specialties) while 35% believed that the term “non-alcoholic” was stigmatizing (more commonly in the MENA region and among GI/hepatologists). Finally, 45% of providers (49% GI/hepatologists vs. 36% other specialties) believed that a name change may reduce the disease stigma. **Conclusion:** Drivers of stigma and disease burden varies between NAFLD patients, providers, and regions of the world. Female sex, non-urban living, comorbidities (cirrhosis, and medical weight loss) are predictors of greater disease burden and stigma scores in patients with NAFLD.



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2260-C | THE PREVALENCE AND CLINICAL CHARACTERISTICS OF CHINESE ADULTS WITH METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

Ming Yang[1], Huixin Liu[2], Shunmin Guo[3], Pingqiu Shen[3], Ying Qiao[3], Wurong Chen[3], Yanqiu Gu[3], Rao Teng[3], Guiping Li[3], Jianzeng Qin[3], Xiaoran Yang[3], Zhi Qi[3], Yi Feng[3], Mengqi He[3], Zhe Liu[3], Wenyao He[3] and Lai Wei[1], (1)Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, (2)Department of Clinical Epidemiology and Biostatistics, Peking University People's Hospital, (3)Meinian Onehealth Healthcare Holding Co., Ltd

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a newly proposed diagnosis which is different from nonalcoholic fatty liver disease (NAFLD). We aimed to investigate the prevalence and clinical characteristics of Chinese adults with MAFLD. **Methods:** We consecutively enrolled 2,019 Chinese adults in 31 health check-up centers from 11 cities in 2022. A detailed questionnaire and the results of blood biochemical examinations and transient elastography were collected. **Results:** The prevalence of MAFLD and NAFLD among the health examination cohort was 45.8% (925 of 2019) and 42.6% (861 of 2019) ($P = 0.43$). The prevalence of MAFLD among subjects with $BMI < 23$, 23-24.9 and e 25 kg/m^2 was 9.25%, 43.95% and 77.88%, respectively. The corresponding prevalence of NAFLD was 16.30%, 39.53% and 66.47%, respectively. The proportions of subgroup 1 (overweight/obese), 2 (lean/normal weight with metabolic abnormalities), and 3 (diabetes) in the MAFLD subjects were 92.8%, 6.9%, and 13.4%, respectively. The mean age of MAFLD subjects was 45.8 years, and 65.9% subjects were male. 13.4%, 31.4%, and 41.3% of MAFLD subjects had diabetes mellitus, hypertension, and metabolic syndrome. Compared with NAFLD subjects, MAFLD subjects had higher body mass index, waist circumference, liver enzymes, triglyceride, but similar AST-to-platelet ratio index, Fibrosis-4 index, NAFLD fibrosis score and liver stiffness measurement. **Conclusion:** MAFLD is highly prevalent in the general population. The definition of MAFLD may better reflect the pathogenesis related to metabolism but not improve the identification of patients at risk for fibrosis.

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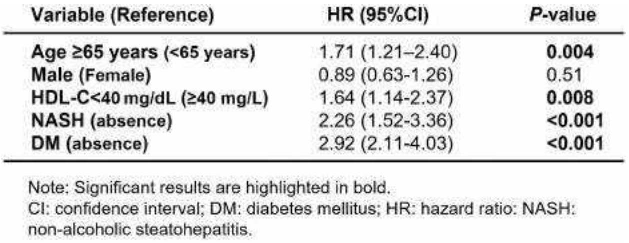
2261-C | THE ROLE OF HDL-CHOLESTEROL ON THE DEVELOPMENT OF LIVER FIBROSIS IN PATIENTS WITH NASLD

Hideki Fujii, Osaka Metropolitan University, Yoshihiro Kamada, Osaka University Graduate School of Medicine, Miwa Kawanaka, Kawasaki Medical School, Hirokazu Takahashi, Division of Metabolism and Endocrinology, Faculty of Medicine and Yoshio Sumida, Aichi Medical University

Background: The impact of HDL-cholesterol (HDL-C) on liver fibrosis in patients with nonalcoholic steatohepatitic liver disease (NASLD) remains unknown. We examined the role of HDL-C in patients with NASLD using data from a multicenter registry. **Methods:** This study was one of the sub-analyses of the CLIONE (Clinical Outcome Nonalcoholic Fatty Liver Disease) study. CLIONE study is a multicenter, registry-based, retrospective cohort study from fifteen hepatology centers in Japan. We identified 1,204 patients with biopsy-proven NASLD from for whom baseline HDL-C levels were recorded between 1994 and 2020. Liver biopsy specimens were digitized, pathologically diagnosed, and histologically scored using the NASH Clinical Research Network system. Stages 3 and 4 were defined as advanced fibrosis. **Results:** Clinical characteristics of the patients (N = 1,204) were as follows: median (interquartile range) age; 57 (45-66) years, male 520 (43%), BMI; 27.4 (24.9-30.8) kg/m^2, platelet count; 214 (176-262) ×10^9/L, diabetes mellitus (DM); 441 (37%), presence of NASH; 792 (66%), and advanced fibrosis; 191 (16%). When a cutoff of 40 mg/dL of HDL-C is used, the low HDL-C group had significantly lower age [52.5 (38-64) vs. 58 (47-66), $P < 0.001$], higher proportion of males (60% vs. 38%, $P < 0.001$), higher percentage of DM (42% vs. 35%, $P = 0.037$), significantly lower albumin [4.3 (4.0-4.6) vs. 4.4 (4.1-4.6) mg/dL, $P < 0.001$] and platelet counts [209 (164-255) vs. 217 (179-264) ×10^9/L, $P = 0.040$] than the high HDL-C group. Pathologically, the low HDL-C group had a significantly higher proportion of NASH (72% vs. 65%, $P = 0.027$) and a significantly higher proportion of advanced fibrosis (22% vs. 14%, $P = 0.004$) than the high HDL-C group. In a multivariate analysis using age, DM, presence of NASH, and gender as covariates, the low HDL-C group was significantly associated with advanced fibrosis [Odds ratio (95% confidence interval): 1.64 (1.14-2.37), $P = 0.008$]. **Conclusion:** Low HDL-C levels were an independent risk factor for advanced fibrosis in patients with biopsy-confirmed NASLD.



Variable (Reference)	HR (95%CI)	*P*-value
Age ≥65 years (<65 years)	1.71 (1.21–2.40)	**0.004**
Male (Female)	0.89 (0.63-1.26)	0.51
HDL-C<40 mg/dL (≥40 mg/L)	1.64 (1.14-2.37)	**0.008**
NASH (absence)	2.26 (1.52-3.36)	**<0.001**
DM (absence)	2.92 (2.11-4.03)	**<0.001**

Note: Significant results are highlighted in bold.
CI: confidence interval; DM: diabetes mellitus; HR: hazard ratio: NASH: non-alcoholic steatohepatitis.

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2262-C | TRACKING FACTORS ASSOCIATED WITH ADVANCED FIBROSIS IN NAFLD IN A HIGHLY DIVERSE URBAN POPULATION–INSIGHTS FROM THE MOUNT SINAI LONGITUDINAL REGISTRY

Xiaotao Zhang[1], Christian Near[1], Vikram Sivakuma[1], Dakota Trick[1], Helen Adams[2], Alyson L. Harty[3], Aryana Chan[1], Ritu Agarwal[1], Douglas T. Dieterich[1], Linda W. Law[4], Tatyana Kushner[5], Rebecca Roediger[1], John C. Bucuvalas[3], Jaime Chu[5], Asher Leviton[1], Scott L. Friedman[1], Augusto Villanueva[1] and Meena B. Bansal[1], *(1)Icahn School of Medicine at Mount Sinai, (2)Mount Sinai Institute for Liver Medicine, (3)Icahn School of Medicine at Mount Sinai (ISMMS), (4)Icahn School of Medicine at Mount Sinai, Englewood Cliffs, NJ, (5)Icahn School of Medicine at Mount Sinai, New York, NY*

Background: The Mount Sinai NAFLD/NASH registry and biobank, launched in May 2022, is a longitudinal study aimed at identifying real-world factors related to fibrosis progression/non-progression and developing predictive algorithms for liver and cardiac clinical outcomes. Baseline profiles were characterized, and factors associated with advanced fibrosis stage identified. **Methods**: Patients who presented for standard of care visits for the management of NAFLD, and who had no evidence of other chronic liver diseases or excessive alcohol consumption were offered enrollment and consented. Baseline characteristics, including demographic information, lifestyle factors, fibrosis stage, comorbidities, metabolic profiles, and relevant laboratory values, were evaluated. Fibrosis stage was assessed using Fibroscan^{TM} (F2: 8-10kPa; F3: 10-14kPa; F4: > 14kPa). Univariate ordinal logistic regression analyses were conducted to examine the association between baseline characteristics and the severity of fibrosis stage and simple logistic regression was performed to determine the association between baseline characteristics and advanced fibrosis stages (e F2 vs. F0/F1). **Results**: As of April 2023, 304 patients were included in the study. Mean age was 53.8 years (SD = 14.6) with 51% female. Racial/ethnic distribution consisted of Whites (24%), Black or African American (11%), and Asian (8%); 56% identified as Hispanic. 34% of patients were former or current smokers and 32% reported mild-moderate alcohol consumption. Almost 20% had cirrhosis, 40% had e F2 fibrosis, 61% were obese, and 42% had type 2 DM. In the ordinal logistic regression analysis, a statistically significant association ($p < 0.05$) was found between multiple variables and a higher odds of advanced fibrosis stage. These variables included age, BMI, obesity, FIB-4 score, SAFE score, GGT levels, MELD, TSH, IgA, and current medication use (Metformin, Aspirin, GLP-1, and PPI). Consistent associations were observed when comparing patients with e F2 fibrosis to F0/F1 (Table 1). **Conclusion**: In our diverse NAFLD registry, where 40% of patients had significant fibrosis, both expected predictors (e.g., high FIB-4) but also higher TSH, higher IgA, and PPI usage were associated with higher fibrosis stage. Data from this unique registry will enable real-world risk-stratification, sub-phenotyping, predictive modeling, and identification of patients who should be prioritized for emerging NASH therapeutics and HCC screening.

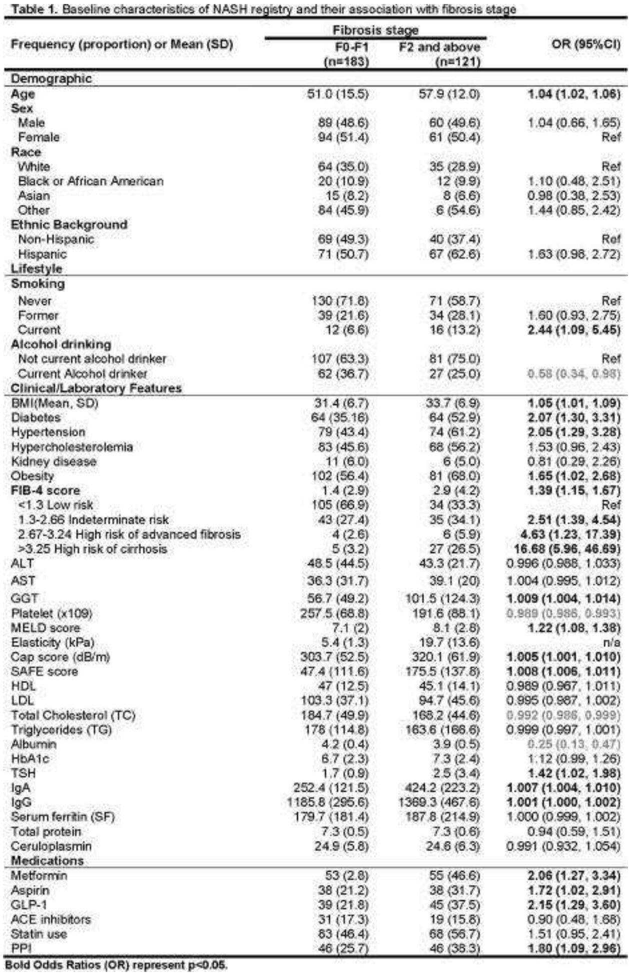

Table 1. Baseline characteristics of NASH registry and their association with fibrosis stage

Frequency (proportion) or Mean (SD)	Fibrosis stage F0-F1 (n=183)	Fibrosis stage F2 and above (n=121)	OR (95%CI)
Demographic			
Age	51.0 (15.5)	57.9 (12.0)	**1.04 (1.02, 1.06)**
Sex			
Male	89 (48.6)	60 (49.6)	1.04 (0.66, 1.65)
Female	94 (51.4)	61 (50.4)	Ref
Race			
White	64 (35.0)	35 (28.9)	Ref
Black or African American	20 (10.9)	12 (9.9)	1.10 (0.48, 2.51)
Asian	15 (8.2)	8 (6.6)	0.98 (0.38, 2.53)
Other	84 (45.9)	6 (54.6)	1.44 (0.85, 2.42)
Ethnic Background			
Non-Hispanic	69 (49.3)	40 (37.4)	Ref
Hispanic	71 (50.7)	67 (62.6)	1.63 (0.98, 2.72)
Lifestyle			
Smoking			
Never	130 (71.8)	71 (58.7)	Ref
Former	39 (21.6)	34 (28.1)	1.60 (0.93, 2.75)
Current	12 (6.6)	16 (13.2)	**2.44 (1.09, 5.45)**
Alcohol drinking			
Not current alcohol drinker	107 (63.3)	81 (75.0)	Ref
Current Alcohol drinker	62 (36.7)	27 (25.0)	0.58 (0.34, 0.98)
Clinical/Laboratory Features			
BMI(Mean, SD)	31.4 (6.7)	33.7 (6.9)	**1.05 (1.01, 1.09)**
Diabetes	64 (35.16)	64 (52.9)	**2.07 (1.30, 3.31)**
Hypertension	79 (43.4)	74 (61.2)	**2.05 (1.29, 3.28)**
Hypercholesterolemia	83 (45.6)	68 (56.2)	1.53 (0.96, 2.43)
Kidney disease	11 (6.0)	6 (5.0)	0.81 (0.29, 2.26)
Obesity	102 (56.4)	81 (68.0)	**1.65 (1.02, 2.68)**
FIB-4 score	1.4 (2.9)	2.9 (4.2)	**1.39 (1.15, 1.67)**
<1.3 Low risk	105 (66.9)	34 (33.3)	Ref
1.3-2.66 Indeterminate risk	43 (27.4)	35 (34.1)	**2.51 (1.39, 4.54)**
2.67-3.24 High risk of advanced fibrosis	4 (2.6)	6 (5.9)	**4.63 (1.23, 17.39)**
>3.25 High risk of cirrhosis	5 (3.2)	27 (26.5)	**16.68 (5.96, 46.69)**
ALT	48.5 (44.5)	43.3 (21.7)	0.996 (0.988, 1.033)
AST	36.3 (31.7)	39.1 (20)	1.004 (0.995, 1.012)
GGT	56.7 (49.2)	101.5 (124.3)	**1.009 (1.004, 1.014)**
Platelet (x109)	257.5 (68.8)	191.6 (88.1)	0.989 (0.986, 0.993)
MELD score	7.1 (2)	8.1 (2.8)	**1.22 (1.08, 1.38)**
Elasticity (kPa)	5.4 (1.3)	19.7 (13.6)	n/a
Cap score (dB/m)	303.7 (52.5)	320.1 (61.9)	**1.005 (1.001, 1.010)**
SAFE score	47.4 (111.6)	175.5 (137.8)	**1.008 (1.006, 1.011)**
HDL	47 (12.5)	45.1 (14.1)	0.989 (0.967, 1.011)
LDL	103.3 (37.1)	94.7 (45.6)	0.995 (0.987, 1.002)
Total Cholesterol (TC)	184.7 (49.9)	168.2 (44.6)	0.992 (0.986, 0.999)
Triglycerides (TG)	178 (114.8)	163.6 (166.6)	0.999 (0.997, 1.001)
Albumin	4.2 (0.4)	3.9 (0.5)	0.25 (0.13, 0.47)
HbA1c	6.7 (2.3)	7.3 (2.4)	1.12 (0.99, 1.26)
TSH	1.7 (0.9)	2.5 (3.4)	**1.42 (1.02, 1.98)**
IgA	252.4 (121.5)	424.2 (223.2)	**1.007 (1.004, 1.010)**
IgG	1185.8 (295.6)	1369.3 (467.6)	**1.001 (1.000, 1.002)**
Serum ferritin (SF)	179.7 (181.4)	187.8 (214.9)	1.000 (0.999, 1.002)
Total protein	7.3 (0.5)	7.3 (0.6)	0.94 (0.59, 1.51)
Ceruloplasmin	24.9 (5.8)	24.6 (6.3)	0.991 (0.932, 1.054)
Medications			
Metformin	53 (2.8)	55 (46.6)	**2.06 (1.27, 3.34)**
Aspirin	38 (21.2)	38 (31.7)	**1.72 (1.02, 2.91)**
GLP-1	39 (21.8)	45 (37.5)	**2.15 (1.29, 3.60)**
ACE inhibitors	31 (17.3)	19 (15.8)	0.90 (0.48, 1.68)
Statin use	83 (46.4)	68 (56.7)	1.51 (0.95, 2.41)
PPI	46 (25.7)	46 (38.3)	**1.80 (1.09, 2.96)**

Bold Odds Ratios (OR) represent p<0.05.

Disclosures: Douglas T. Dieterich – Novo Nordisk: Speaking and Teaching, Yes, No; Novo Nordisk: Speaking and Teaching, Yes, No; Gilead Sciences: Speaking and Teaching, No, No;

Tatyana Kushner – Bausch: Consultant, No, Yes; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; AbbVie: Consultant, No, Yes; Eiger: Advisor, No, No;

Jaime Chu – Albireo: Consultant, No, No;

Meena B. Bansal – Madrigal: Advisor, No, No; NOVO Nordisk: Advisor, No, No; The Kinetix Group: Consultant, No, No; Histoindex: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Fibronostics: Advisor, No, No;

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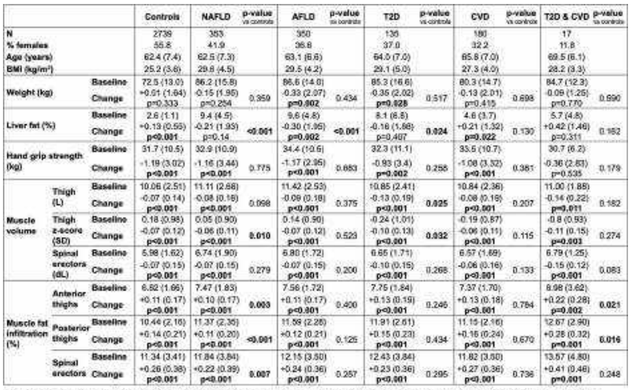
2263-C | TWO YEARS OF WASTING WITH METABOLIC DISORDERS - INITIAL RESULTS ON MUSCLE COMPOSITION FROM THE LONGITUDINAL UK BIOBANK

Jennifer Linge[1,2], Mikael Fredrik Forsgren[1,2] and Olof Dahlqvist Leinhard[1,2], (1)Amra Medical AB, (2) Linköping University

Background: Adverse muscle composition (low muscle volume [MV] with high muscle fat infiltration [MFI]) assessed with magnetic resonance imaging (MRI) is common in general population (10%) and has been linked to poor functional performance, comorbidity, and all-cause mortality in non-alcoholic fatty liver disease (NAFLD), as well as increased hospitalization and all-cause mortality in general population. The aim of this study was to describe changes in muscle composition in different metabolic disorders in the longitudinal UK Biobank imaging study. **Methods:** 3761 participants were scanned twice approximately 2.2 years apart using a 6-minute MRI protocol. Images were analyzed for liver fat, fat-free MV and MFI of the thighs and spinal erectors using AMRA® Researcher, Linköping, Sweden. For each participant, a sex-, weight- and height invariant thigh MV z-score was calculated. Muscle composition changes were described in participants with NAFLD (without type 2 diabetes [T2D] and cardiovascular disease [CVD], AFLD (without T2D and CVD), T2D (without CVD), CVD (without T2D), comorbidity (T2D and CVD), and controls (without NAFLD, AFLD, T2D and CVD). Paired t-tests were used to test for significant changes within each group. Linear regressions adjusted for sex, baseline age and BMI, and weight change were used to test differences in change between controls and the other groups. **Results:** The cohort consisted of 51% females, with mean (SD) age 62.7 (7.3) years and BMI 26.2 (4.2) kg/m^2 at baseline. All groups were weight stable except AFLD and T2D that showed significant annualized weight loss (Table 1). All groups except the comorbidity group showed a significant decrease in hand grip strength, but none of the disease groups showed more rapid functional decline compared to the control group. Significant muscle wasting was observed for all groups (both reductions of MV and increases of MFI). Compared to the controls, NAFLD (without T2D and CVD) showed slower wasting (significantly less reduction of thigh MV z-score and increase in MFI), T2D showed larger loss of muscle volume (both thigh MV and MV z-score), while the comorbidity group showed larger increase of MFI (significantly so for anterior/posterior thigs). **Conclusion:** Significant changes in muscle composition (MV and MFI) can be observed across 2 years. Results indicate that individual's with metabolic disorders experience more rapid wasting and that different diseases may be associated with different wasting profiles.



			Controls	NAFLD	p-value vs controls	AFLD	p-value vs controls	T2D	p-value vs controls	CVD	p-value vs controls	T2D & CVD	p-value vs controls
N			2739	353		350		136		180		17	
% females			55.8	41.9		36.8		37.0		32.2		11.8	
Age (years)			62.4 (7.4)	62.5 (7.3)		63.1 (6.6)		64.0 (7.0)		65.8 (7.0)		69.5 (6.1)	
BMI (kg/m²)			25.2 (3.6)	29.8 (4.5)		29.5 (4.2)		29.1 (5.0)		27.3 (4.0)		28.2 (3.3)	
Weight (kg)		Baseline	72.5 (13.0)	86.2 (15.8)		86.6 (14.0)		85.3 (16.6)		80.3 (14.7)		84.7 (12.3)	
		Change	+0.01 (1.64) p=0.333	-0.15 (1.95) p=0.254	0.359	-0.33 (2.07) **p=0.002**	0.434	-0.35 (2.02) **p=0.028**	0.517	-0.13 (2.01) p=0.415	0.698	-0.09 (1.25) p=0.770	0.690
Liver fat (%)		Baseline	2.6 (1.1)	9.4 (4.5)		9.6 (4.8)		8.1 (6.8)		4.6 (3.7)		5.7 (4.8)	
		Change	+0.13 (0.55) **p<0.001**	-0.21 (1.93) p=0.14	**<0.001**	-0.30 (1.95) **p=0.002**	**<0.001**	-0.16 (1.88) p=0.407	**0.024**	+0.21 (1.32) **p=0.022**	0.130	+0.42 (1.46) p=0.311	0.182
Hand grip strength (kg)		Baseline	31.7 (10.5)	32.9 (10.9)		34.4 (10.6)		32.3 (11.1)		33.5 (10.7)		30.7 (6.2)	
		Change	-1.19 (3.02) **p<0.001**	-1.16 (3.44) **p<0.001**	0.775	-1.17 (2.95) **p<0.001**	0.653	-0.93 (3.4) **p=0.002**	0.258	-1.08 (3.32) **p<0.001**	0.361	-0.36 (2.83) p=0.535	0.179
Muscle volume	Thigh (L)	Baseline	10.06 (2.51)	11.11 (2.68)		11.42 (2.53)		10.85 (2.41)		10.84 (2.36)		11.00 (1.85)	
		Change	-0.07 (0.14) **p<0.001**	-0.08 (0.16) **p<0.001**	0.098	-0.09 (0.18) **p<0.001**	0.375	-0.13 (0.19) **p<0.001**	**0.025**	-0.08 (0.16) **p<0.001**	0.207	-0.14 (0.22) **p=0.011**	0.182
	Thigh z-score (SD)	Baseline	0.18 (0.98)	0.05 (0.90)		0.14 (0.90)		-0.24 (1.01)		-0.19 (0.87)		-0.8 (0.93)	
		Change	-0.07 (0.12) **p<0.001**	-0.06 (0.11) **p<0.001**	**0.010**	-0.07 (0.12) **p<0.001**	0.523	-0.10 (0.13) **p<0.001**	**0.032**	-0.06 (0.11) **p<0.001**	0.115	-0.11 (0.15) **p=0.003**	0.274
	Spinal erectors (dL)	Baseline	5.98 (1.62)	6.74 (1.90)		6.80 (1.72)		6.65 (1.71)		6.57 (1.69)		6.79 (1.25)	
		Change	-0.07 (0.15) **p<0.001**	-0.07 (0.15) **p<0.001**	0.279	-0.07 (0.15) **p<0.001**	0.200	-0.10 (0.15) **p<0.001**	0.268	-0.06 (0.16) **p<0.001**	0.133	-0.15 (0.12) **p<0.001**	0.083
Muscle fat infiltration (%)	Anterior thighs	Baseline	6.52 (1.66)	7.47 (1.83)		7.56 (1.72)		7.75 (1.84)		7.37 (1.70)		8.98 (3.62)	
		Change	+0.11 (0.17) **p<0.001**	+0.10 (0.17) **p<0.001**	**0.003**	+0.11 (0.17) **p<0.001**	0.400	+0.13 (0.19) **p<0.001**	0.246	+0.13 (0.18) **p<0.001**	0.784	+0.22 (0.28) **p=0.002**	**0.021**
	Posterior thighs	Baseline	10.44 (2.16)	11.37 (2.35)		11.59 (2.28)		11.91 (2.61)		11.15 (2.16)		12.67 (2.90)	
		Change	+0.14 (0.21) **p<0.001**	+0.11 (0.20) **p<0.001**	**<0.001**	+0.12 (0.21) **p<0.001**	0.125	+0.15 (0.23) **p<0.001**	0.434	+0.16 (0.24) **p<0.001**	0.670	+0.28 (0.32) **p=0.001**	**0.016**
	Spinal erectors	Baseline	11.34 (3.41)	11.84 (3.84)		12.15 (3.50)		12.43 (3.84)		11.82 (3.60)		13.57 (4.80)	
		Change	+0.26 (0.38) **p<0.001**	+0.22 (0.39) **p<0.001**	**0.007**	+0.24 (0.36) **p<0.001**	0.257	+0.23 (0.36) **p<0.001**	0.295	+0.27 (0.36) **p<0.001**	0.736	+0.41 (0.46) **p=0.001**	0.248

Table 1 Baseline characteristics and annualized changes of muscle composition in disease groups and controls. Values are mean and standard deviations. p-values for change within each group are from paired t-test. p-values for difference between each disease group and controls are from linear regression adjusted for sex, baseline age, baseline body mass index (BMI), and annualized weight change.

Disclosures: Jennifer Linge – AMRA Medical AB: Employee, Yes, No; Eli Lilly: Consultant, No, No; BioMarin: Speaking and Teaching, No, Yes;
Mikael Fredrik Forsgren – AMRA Medical AB: Employee, Yes, No;
Olof Dahlqvist Leinhard – AMRA Medical AB: Employee, Yes, No; Eli Lilly: Consultant, No, No; Fulcrum Therapeutics: Consultant, No, No; AMRA Medical AB: Stock – privately held company (individual stocks and stock options), Yes, No;

2264-C | UNCOVERING THE GENETIC LINK: ASSOCIATION OF PNPLA3_rs738409 VARIANT WITH METABOLIC-ASSOCIATED FATTY LIVER DISEASE IN A SRI LANKAN POPULATION

Madunil Anuk Niriella[1], Anuradhani Kasturiratne[1], Dileepa Senajith Ediriweera[1], Shamila Thivanshi De Silva[1], Anuradha Supun Dassanayake[1], Arjuna Priyadrshin De Silva[1], Arunasalam Pathmeswaran[1], Ananda Rajitha Wickramasinghe[1], Norihiro Kato[2] and Hithanadura Janaka De Silva[1], (1)Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka, (2)National Center for Global Health and Medicine, Toyama, Shinjuku-Ku, Tokyo, Japan

Background: The PNPLA3_rs738409 variant has been identified globally as a potential genetic risk factor for non-alcoholic fatty liver disease (NAFLD). In the Ragama Health Study (RHS), a randomly selected population cohort of Sri Lankan adults, we have previously shown an association between the PNPLA3_rs738409 variant and NAFLD (OR = 1.25, 95% CI 1.08–1.44, P = 0.003) [1].

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

There is renewed interest in redefining fatty liver disease as metabolic-associated fatty liver disease (MAFLD). In this case-control study, we examined the association of the PNPLA3_rs738409 variant with MAFLD in the RHS population. **Methods:** The genotypes of the PNPLA3_rs738409 variant were determined using a polymerase chain reaction. In addition, the association of the PNPLA3_rs738409 variant with MAFLD vs controls was analysed using the Cochran–Armitage trend test. The genotype and allele frequencies of the PNPLA3_rs738409 variant were in Hardy-Weinberg equilibrium in MAFLD and control groups. **Results:** Genotype data of 3002 participants were analysed. There were 987 with MAFLD and 1212 controls. A significant association was observed for the PNPLA3 (rs738409) polymorphism with susceptibility to MAFLD (OR = 1.22, 95% CI 1.06–1.41, P = 0.006). Due to sample size limitation, there seems to be no significant differences in effect allele frequencies between NAFLD and MAFLD patients (OR = 0.98. 95% CI 0.85–1.14, P = 0.80). **Conclusion:** This study suggests that although the definitions of fatty liver disease (NAFLD and MAFLD) are phenotypically diverse, the genetic association with the PNPLA3_rs738409 variant and fatty liver seems consistent. **Reference**

1. Kasturiratne A, Akiyama K, Niriella MA, et al. Association of genetic variants with non-alcoholic fatty liver disease in an urban Sri Lankan community. Liver Int. 2015 Feb;35(2):676-9. doi: 10.1111/liv.12624. Epub 2014 Jul 10. PMID: 24947803.

Disclosures: The following people have nothing to disclose: Madunil Anuk Niriella, Anuradhani Kasturiratne, Dileepa Senajith Ediriweera, Shamila Thivanshi De Silva, Anuradha Supun Dassanayake, Arjuna Priyadrshin De Silva, Arunasalam Pathmeswaran, Ananda Rajitha Wickramasinghe, Norihiro Kato, Hithanadura Janaka De Silva

2265-C | UNDERSTANDING THE INCREMENTAL COST OF NONALCOHOLIC STEATOHEPATITIS AND DIABETES USING ELECTRONIC HEALTH RECORDS AND CLOSED CLAIMS DATA

Jesse Fishman[1], Elliot B. Tapper[2], Stephen Dodge[1], Keith Miller[1], Dave Lewandowski[3], Alina Bogdanov[3] and Machaon Bonafede[3], (1)Madrigal Pharmaceuticals, (2)University of Michigan, (3)Veradigm

Background: Nonalcoholic steatohepatitis (NASH) and type 2 diabetes (T2D) are both linked to substantial healthcare casts. However, the incremental cost of each condition is not well understood. We, therefore, aim to quantify the incremental cost of NASH and T2D using real-world data. **Methods:** Patients with e 2 diagnosis codes for NASH and/or e 2 diagnosis codes for T2D were identified in electronic health records or claims between 1/1/2016 and 12/31/2021 in the Veradigm Integrated Dataset. Patients with viral hepatitis, alcohol-use disorder or alcoholic liver disease, type 1 diabetes, or gestational diabetes were excluded. Patients had to be e 18 years old on the index date and have e 24 months of continuous claims enrollment encompassing the index date (study period). The index date was the earliest diagnosis (after 1/1/2016) when the patient met all study criteria. Patients were stratified into 3 cohorts: NASH-only, T2D-only, and NASH+T2D. We calculated annualized costs from actual costs during the 24-month study period and then fit a generalized linear model, controlling for disease cohort, age, sex, and modified Charlson comorbidity index, to estimate the per year all-cause healthcare costs and incremental cost of adding T2D to a NASH diagnosis (or vice versa). Incremental costs were estimated by changing the disease indicator variable from NASH-only or T2D-only to NASH+T2D and observing the change in cost. **Results:** We identified 23,111 patients with NASH-only, 3,548,786 patients with T2D-only, and 30,339 patients with NASH+T2D. Mean (SD) age and percentage female was 52.1 (14.2) years and 57.4% for the NASH-only cohort, 62.0 (14.0) years and 56.4% for the T2D-only cohort, and 59.0 (12.2) years and 65.5% for the NASH+T2D cohort. First, we calculated adjudicated costs for all patients, and then, after excluding outliers (patients with costs in the top 1%) and selecting a random sample of 100,000 patients with T2D, the model-predicted mean cost per year was $7,668 for patients with NASH-only, $11,226 for patients with T2D-only, and $16,812 for patients with NASH +T2D. The incremental increase in cost per year of adding T2D to NASH was 63% (+$4,846) and the incremental increase in cost per year of adding NASH to T2D was 42% (+$4,692). **Conclusion:** Both NASH and T2D contribute to the high healthcare costs among patients with a dual diagnosis. Results from our analysis indicate that NASH comprises a higher portion of total healthcare costs among patients with NASH and T2D.

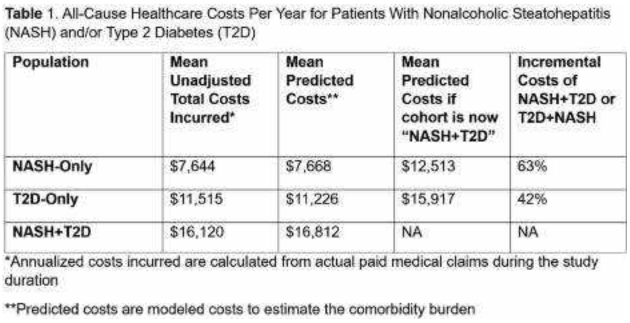


Table 1. All-Cause Healthcare Costs Per Year for Patients With Nonalcoholic Steatohepatitis (NASH) and/or Type 2 Diabetes (T2D)

Population	Mean Unadjusted Total Costs Incurred*	Mean Predicted Costs**	Mean Predicted Costs if cohort is now "NASH+T2D"	Incremental Costs of NASH+T2D or T2D+NASH
NASH-Only	$7,644	$7,668	$12,513	63%
T2D-Only	$11,515	$11,226	$15,917	42%
NASH+T2D	$16,120	$16,812	NA	NA

*Annualized costs incurred are calculated from actual paid medical claims during the study duration

**Predicted costs are modeled costs to estimate the comorbidity burden

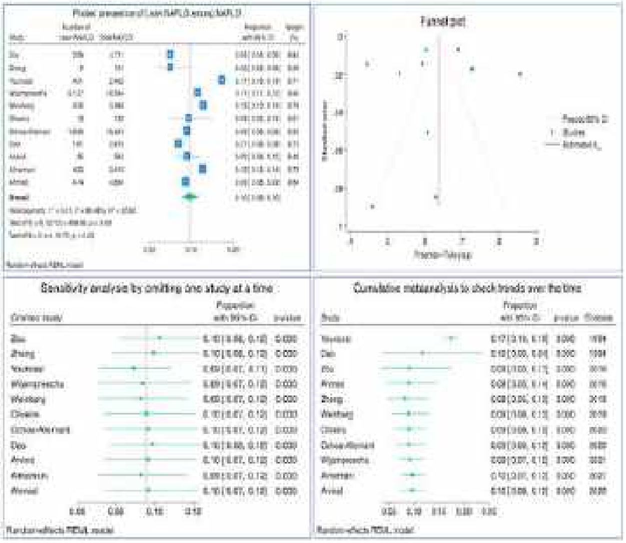
Disclosures: Jesse Fishman – Madrigal Pharmaceuticals: Employee, Yes, No;

Alina Bogdanov – Madrigal Pharmaceuticals: Consultant, Yes, No;
The following people have nothing to disclose: Elliot B. Tapper
Disclosure information not available at the time of publication: Stephen Dodge, Keith Miller, Dave Lewandowski, Machaon Bonafede

2266-C | UNRAVELING THE PREVALENCE AND SUBGROUP PROPORTIONS OF LEAN NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) IN THE UNITED STATES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Anvesh Narimiti[1], Vinay Jahagirdar[2], Mithil Suresh Gowda[3], Moulika R Bandaru[3], Kaanthi Rama[4], Amrutha Jagaragallu[4] and Deepika Devuni[5], (1)Harvard School of Public Health, (2)University of Missouri Kansas City, (3)Saint Vincent Hospital, (4)Gandhi Medical College & Hospital, (5)UMass Chan Medical School

Background: Nonalcoholic fatty liver disease (NAFLD) is mainly seen in obese and/or individual's with type 2 diabetes mellitus. Lean NAFLD is defined as NAFLD in non-overweight individual's (BMI < 25 kg/m^2 or < 23 kg/m^2 in Asians). It is associated with higher cardiovascular, liver, and all-cause mortality compared to healthy individual's. Prevalence of lean NAFLD is as high as 19% in Asia. Several individual studies report the prevalence of lean NAFLD from various states in the United States (US). We aimed to look at the overall pooled prevalence of lean NAFLD in the US and pooled prevalence by sex and race, which has not yet been reported. **Methods:** Multiple databases, including MedLine and Embase, were searched from inception to April 2023. Outcomes of interest were pooled prevalence of lean NAFLD among NAFLD patients and among the general population, pooled proportion by sex and race, and pooled prevalence of comorbid conditions. Random effects model was employed. Freeman-Tukey double arcsine-transformed proportion was applied to stabilize variance. Sensitivity analysis was performed by omitting one study at a time. A cumulative meta-analysis in ascending chronological order of study year was also done to observe for changes in pooled prevalence over time. **Results:** Initial database search yielded 711 articles of which 11 were finally included. The cumulative study population was 68,931,874 patients. The pooled rates were as follows: prevalence of lean NAFLD among NAFLD patients 0.10 (0.08,0.12, $I^2 = 98.5\%$), prevalence among general population 0.01 (0.00,0.03, $I^2 = 99.9\%$). On subgroup analysis, pooled rates were as follows: Females 0.66 (0.56,0.75), Caucasians 0.69 (0.53,0.83), African Americans 0.03 (0.01,0.06), Hispanics 0.17 (0.05,0.35). Proportion of co-morbid conditions included diabetes 0.25 (0.11, 0.42), hypertension 0.22 (0.13,0.34) and hyperlipidemia 0.37 (0.12,0.66). Sensitivity analysis confirmed the robustness of our findings. Cumulative meta-analysis demonstrated a declining trend in lean NAFLD prevalence until the early 2000s followed by stabilization from 2016. No significant publication bias was detected, ensuring the reliability of our results. **Conclusion:** In the US the pooled prevalence of lean NAFLD among NAFLD patients is around 10% and among general population is around 1%. Prevalence of lean NAFLD among NAFLD patients appears to be lower in US than in the global population. Another noteworthy finding was the declining prevalence of lean NAFLD since the late 1980's, which may be due to the obesity pandemic contributing to increase in proportion of NAFLD individual's with obesity.



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The following people have nothing to disclose: Anvesh Narimiti, Vinay Jahagirdar, Mithil Suresh Gowda, Moulika R Bandaru, Kaanthi Rama, Amrutha Jagaragallu

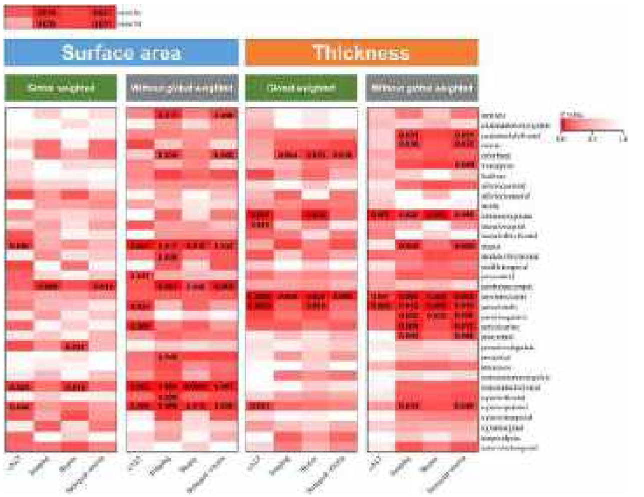
2267-C | UNRAVELLING THE LIVER-BRAIN CONNECTION: A TWO-SAMPLE MENDELIAN RANDOMIZATION STUDY INVESTIGATING THE CAUSAL RELATIONSHIP BETWEEN NAFLD AND CORTICAL STRUCTURE

Shitao Jiang, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

Background: Non-alcoholic fatty liver disease (NAFLD) represents a growing public health concern due to its increasing prevalence, association with obesity and type 2 diabetes, and potential progression to advanced liver diseases. NAFLD has also been linked to cognitive decline and neuropsychiatric conditions, highlighting the possibility of a liver-brain axis. However, the causal relationship between NAFLD and cortical changes remains uncertain. This study aimed to explore the causal impact of NAFLD on cortical structures using a two-sample Mendelian randomization (MR) approach, providing crucial insights into the potential interaction between NAFLD and brain health. A better understanding of this relationship could have significant implications for preventing and treating cognitive deficits and neuropsychiatric disorders in patients with NAFLD. **Methods:** Summary data from genome-wide association studies (GWAS) for NAFLD were gathered from large-scale cohorts, ensuring a robust dataset for analysis. Surface area (SA) and cortical thickness (TH) measurements were derived from the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium magnetic resonance imaging (MRI) data of 33,992 participants. This extensive sample size increased the statistical power and generalizability of our findings.

The inverse-variance weighted (IVW) method served as the primary method for our analysis, while additional sensitivity analyses were conducted to detect potential heterogeneity and pleiotropy. These analyses included the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO), MR-Egger, and weighted median procedures, providing a comprehensive evaluation of the causal effect of NAFLD on cortical structures. **Results:** Our MR analysis revealed that NAFLD led to notable alterations in cortical structures, particularly in the pars orbitalis gyrus. This brain region plays a crucial role in cognitive functions, such as language processing and decision-making, which could be adversely affected by these structural changes. Specifically, genetically predicted NAFLD was linked to a decrease in TH ($\beta = -0.008$ mm, 95% CI: -0.013 mm to -0.004 mm, $P = 3.00 \times 10^{-4}$) within this region.

Importantly, no significant heterogeneity and pleiotropy were identified in our analysis. This finding strengthens the validity of our results and bolsters the argument for a causal relationship between NAFLD and cortical changes. **Conclusion:** The results of this two-sample MR study provide robust evidence for a liver-brain axis, as demonstrated by the causal association between NAFLD and changes in cortical structures. These findings emphasize the potential interaction between NAFLD and brain health, which could have far-reaching implications for preventing and treating cognitive deficits and neuropsychiatric conditions in patients with NAFLD.

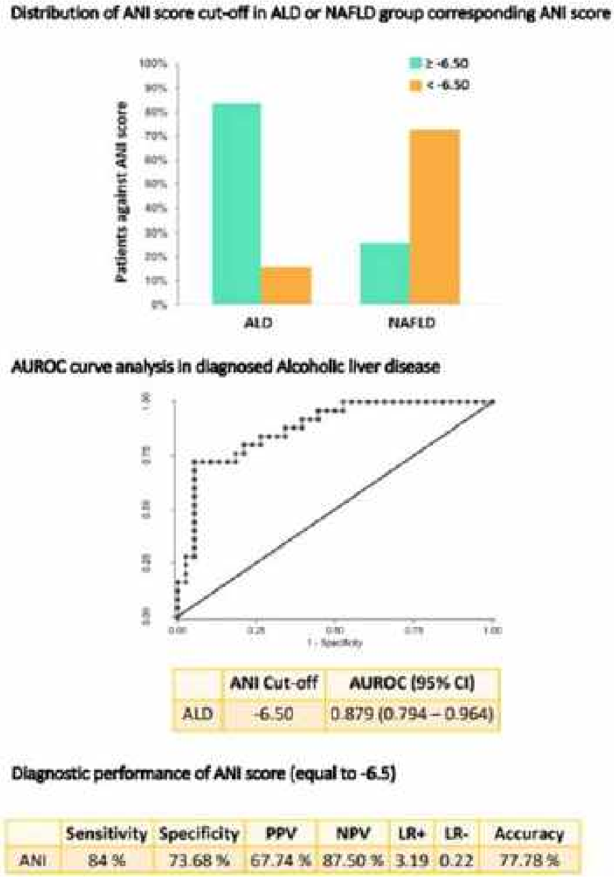


Disclosures: The following people have nothing to disclose: Shitao Jiang

2268-C | VALIDATION OF ALD/NAFLD INDEX TO DIAGNOSE AN ALCOHOL BASIS FOR STEATOHEPATITIS – MULTICENTER STUDY

Pongsakorn Tantigovit[1], Noppamate Preechathammawong[1], Mongkon Charoenpitakchai[1], Sombat Treeprasertsuk[2] and Sakkarin Chirapongsathorn[1], (1)Phramongkutklao Hospital and College of Medicine, (2)Chulalongkorn University, Bangkok, Thailand

Background: Distinguishing alcohol related liver disease (ALD) basis from a nonalcoholic fatty liver disease (NAFLD) basis for the clinical and histologic spectrum of steatohepatitic liver disease is difficult because of unreliability of alcohol consumption history. ALD/NAFLD Index (ANI) was create to diagnose ALD in patients with steatohepatitis. However, information regarding alcohol predictor is still lacking in outside North America populations. We aimed to validate a model to diagnose ALD in patients with steatohepatitis. **Methods:** A cross-sectional cohort study was performed at two tertiary care medical centers in Thailand, Phramongkutklao Hospital and King Chulalongkorn Memorial Hospital, to validate an ANI model using multivariable analysis and diagnostic accuracy of the test. This model was validated in 2 independent data sets comprising patients of varying severity of steatohepatitis spanning over 3 years. **Results:** Logistic regression identified mean corpuscular volume, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, body mass index, and gender as the most important variables that separated patients with ALD from NAFLD. These variables were also used to validate in the ALD/NAFLD Index (ANI), with ANI of greater than -6.5 incrementally favoring ALD and ANI of less than -6.5 incrementally favoring a diagnosis of NAFLD, thus making ALD unlikely. ANI had a c-statistic of 0.879 in the validation sample. ANI performance characteristics were significantly better than several conventional and recently proposed biomarkers used to differentiate ALD from NAFLD, including the histopathologic feature, AST/ALT ratio, gamma-glutamyl transferase, and mean corpuscular volume of red cell. **Conclusion:** Regarding Asian patients, ANI accurately differentiates ALD from NAFLD in hospitalized, ambulatory, and pretransplantation patients and compares favorably with other traditional and proposed biomarkers.



Distribution of ANI score cut-off in ALD or NAFLD group corresponding ANI score

AUROC curve analysis in diagnosed Alcoholic liver disease

	ANI Cut-off	AUROC (95% CI)
ALD	-6.50	0.879 (0.794 – 0.964)

Diagnostic performance of ANI score (equal to -6.5)

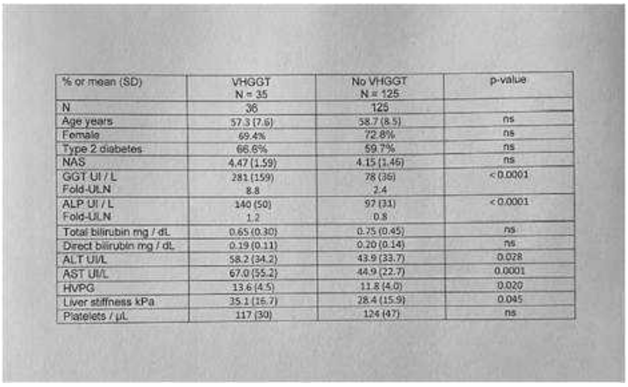
	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Accuracy
ANI	84 %	73.68 %	67.74 %	87.50 %	3.19	0.22	77.78 %

Disclosures: The following people have nothing to disclose: Pongsakorn Tantigovit, Noppamate Preechathammawong, Mongkon Charoenpitakchai, Sombat Treeprasertsuk, Sakkarin Chirapongsathorn

2269-C | VERY HIGH ELEVATION OF GAMMA-GLUTAMYL TRANSPEPTIDASE IN NASH CIRRHOSIS. A NEW PROGNOSIS FACTOR?

Pol Boudes, Galectin Therapeutics, Eric Lawitz, Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX, USA and Naga P. Chalasani, Indiana University Medical Center

Background: When monitoring patients with NASH, including NASH cirrhosis, an unexplained very high elevation of Gamma Glutamyl Transpeptidase VHGGT) is frequently encountered. Increased GGT has been linked to increased mortality in type 2 diabetes[1] and is associated with a worst prognosis in Primary Biliary Cholangitis[2]. We investigated patients with portal hypertension due to NASH cirrhosis to establish the frequency of VHGGT and whether this characteristic individualizes a clinically relevant subgroup of patients. **Methods:** The population consisted of 161 patients with NASH cirrhosis enrolled in a double-blind, placebo-controlled study of belapectin (NCT02462967). The mean age was 58.2 (8.4), 70% females. Cirrhosis was confirmed by liver histology (Ishak 5 or 6, Brunt F4) and the NAS score was reported. Portal hypertension was confirmed by a hepatic venous pressure gradient (HVPG) > 6 mm Hg. Liver stiffness was measured by Fibroscan. Patients had no current or recent history of alcohol consumption and no cirrhotic decompensation (varix bleeding, ascites, encephalopathy). Transaminases were < 10-fold the ULN, platelets e 60 000 / μL, and direct bilirubin < 2 mg/dL. There was no eligibility restriction on ALP and GGT. The definition of VHGGT was an elevation e 5-fold ULN (CTC Adverse Event grade 3 and above). **Results:** A VHGGT was present in 36/161 (22.4%) patients. Characteristics of interest between VHGGT and non-VHGGT patients are presented in the table. **Conclusion:** While patients with VHGGT may have some degree of cholestasis, the GGT increase is out of proportion with the increase in ALP and not associated with an increase in direct bilirubin. As a subgroup, VHGGT patients appears to be more cytolytic and have a higher degree of portal hypertension when compared to non-VHGGT patients. Further studies should establish the prognostic relevance of VHGGT. 1 Lee DY, et al. Sci Reports 2020;10:15375 2 Gerussi A, et al. Clin Gastroenterol Hepatol 2021;19:1688



% or mean (SD)	VHGGT N = 35	No VHGGT N = 125	p-value
N	36	125	
Age years	57.3 (7.6)	58.7 (8.5)	ns
Female	69.4%	72.8%	ns
Type 2 diabetes	66.6%	59.7%	ns
NAS	4.47 (1.59)	4.15 (1.46)	ns
GGT UI / L Fold-ULN	281 (159) 8.8	78 (36) 2.4	< 0.0001
ALP UI / L Fold-ULN	140 (50) 1.2	97 (31) 0.8	< 0.0001
Total bilirubin mg / dL	0.65 (0.30)	0.75 (0.45)	ns
Direct bilirubin mg / dL	0.19 (0.11)	0.20 (0.14)	ns
ALT UI/L	58.2 (34.2)	43.9 (33.7)	0.028
AST UI/L	67.0 (55.2)	44.9 (22.7)	0.0001
HVPG	13.6 (4.5)	11.8 (4.0)	0.020
Liver stiffness kPa	35.1 (16.7)	28.4 (15.9)	0.045
Platelets / µL	117 (30)	124 (47)	ns

Disclosures: Eric Lawitz – 89Bio Inc., AbbVie, Akero Therapeutics, Allergan, Alnylam Pharmaceuticals Inc., Amgen, Ascelia Pharma, AstraZeneca, Axcella Health, Boehringer Ingelheim, Bristol-Myers Squibb, Conatus Pharmaceuticals, Cymabay Therapeutics, CytoDyn, DSM, Durect Corporation: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Akero, Boehringer Ingelheim, BMS, Intercept, Novo Nordisk, Metacrine, Sagimet, Terns: Advisor, No, No; Abbvie, Gilead Sciences, Intercept: Speaking and Teaching, No, No;

The following people have nothing to disclose: Pol Boudes, Naga P. Chalasani

2270-C | A RAT MODEL FOR METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

Mutsumi Tsuchishima, Mikihiro Tsutsumi and Joseph George, Department of Hepatology, Kanazawa Medical University, Uchinada, Ishikawa 920-0293, Japan

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a major health problem worldwide. It is characterized by intense deposition of fat globules in the hepatic parenchyma and is accompanied with fibrosis that could potentially progress to liver cirrhosis and hepatocellular carcinoma (HCC). We developed a rat model to evaluate the molecular mechanisms associated with the pathogenesis of MAFLD and to screen appropriate modalities to prevent MAFLD. **Methods:** SHRSP5/Dmcr rats (spontaneously hypertensive rats / stroke prone) were fed a high-fat and cholesterol (HFC) diet for a period of 12 weeks and evaluated for the development of steatosis, steatohepatitis, fibrosis, and cirrhosis. The same set of control animals received normal diet. A group of animals were sacrificed at the end of the 4th, 6th, 8th, and 12th weeks from the beginning of the experiment. Blood and liver samples were collected for biochemical and histopathological evaluations. Immunohistochemical staining was performed for α-SMA, TNF-α, 4-hydroxy-2-nonenal (4-HNE), collagen type I, and type III. **Results:** Histopathology and trichrome staining demonstrated steatosis at 4th week, steatohepatitis with progressive fibrosis at 6th week, advanced fibrosis with bridging at 8th week, and cirrhosis *at* 12th week of HFC diet administration. Biochemical markers and immunohistochemical staining for α-SMA, TNF-α, 4-HNE, and collagens type I and type III demonstrated the progression of MAFLD from simple steatosis to liver cirrhosis. The animals that received normal diet did not show any biochemical or pathological alterations. **Conclusion:** The results of the current study demonstrated that HFC diet administration to SHRSP5/Dmcr rats is a good and reproducible animal model for MAFLD and is suitable to study the molecular mechanisms associated with the pathogenesis of MAFLD and to screen appropriate therapeutic modalities. *Email: georgej@kanazawa-med.ac.jp*

Disclosures: The following people have nothing to disclose: Mutsumi Tsuchishima, Mikihiro Tsutsumi, Joseph George

2271-C | ABHD5 OVEREXPRESSION PROTECTS PNPLA3-148M PRIMARY HUMAN HEPATOCYTES FROM STEATOSIS IN LIVER CHIMERIC MICE WITH NAFLD

Ype P de Jong[1], Mohammad Kabbani[2], Aditya Upadhyay[1], Chenhui Zou[1], Corrine Quirk[3], Maha Maaliki[2], Antonis Athanasiadis[4], Luis Chiriboga[5], Fulmer G Clifton[6] and Eleftherios Michailidis[4], (1)Weill Cornell Medicine, NY, (2)Mhh, (3)Rockefeller University, (4)Emory, (5)NYU, (6)Cleveland Clinic

Background: The methionine variant at position 148 of patatin-like phospholipase domain-containing protein 3 (PNPLA3-148M) is associated with advanced fatty liver disease. Previous studies have proposed a mechanism by which PNPLA3-148M sequesters alpha/beta-hydrolase domain containing 5 (ABHD5), thereby impairing adipose triglyceride lipase (ATGL) activity on lipid droplets. Here we test the hypothesis that ABHD5 overexpression in primary human hepatocytes (PHH) with PNPLA3-148M can overcome sequestration and improve steatosis in liver chimeric mice with NAFLD. **Methods**: PHH from a homozygous PNPLA3-148M donor (PHH-148M) were lentivirally transduced with ABHD5 prior to transplantation into immunodeficient *Fah-/-* liver injury mice. To link the PNPLA3 genotype to steatosis, PNPLA3-148M and ABHD5 were co-transduced in PHH from a homozygous PNPLA3-148I donor (PHH-148I). After reaching peak liver humanization animals were challenged with a Western-style diet (WD, 60% kcal from lard, 23% sucrose, 0.03% cholesterol) and regular drinking water for four weeks. **Results**: PHH-148M developed more severe steatosis in response to WD than PHH-148I, which was confirmed in PNPLA3-148M transduced PHH-148I that, in addition, displayed widespread microvesicular steatosis. ABHD5 overexpression in PHH-148I did not affect steatosis. In contrast, ABHD5 overexpression in PHH-148M resulted in $>$ 4-fold lower steatosis compared to control mice. While ABHD5 minimally improved steatosis in PNPLA3-148M transduced PHH-148I, it nearly completely resolved microvesicular steatosis. **Conclusion**: These findings support a model where sequestration of ABHD5 by PNPLA3-148M impairs triglyceride lipolysis by ATGL, leading to excess steatosis upon hypercaloric feeding. Overexpression liver chimeras with PHH-148I or PHH-148M grafts provide mechanistic insights on how PNPLA3 and ATGL maintain human lipid homeostasis under hypercaloric conditions.

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Disclosure information not available at the time of publication: Mohammad Kabbani, Aditya Upadhyay, Chenhui Zou, Corrine Quirk, Maha Maaliki, Antonis Athanasiadis, Luis Chiriboga, Fulmer G Clifton

2272-C | ACCELERATION OF AN ADVANCED NASH MODEL BY ACUTE AND TOXIC EFFECTS OF PHENOBARBITAL

Nico Kraus[1], Magnus Moeslein[1], Robert Schierwagen[1,2], Wenyi Gu[1,2], Maximilian Joseph Brol[1,2], Frank Erhard Uschner[1,2], Pierre-Emmanuel Rautou[3,4], Sophie Lotersztajn[5,6], Roger Flores-Costa[7], Joan Claria[7,8], Jonel Trebicka[1,2,8] and Sabine Klein[1,2], (1)University Hospital Frankfurt, (2)University Hospital Münster, (3)Hôpital Beaujon, (4)Université Paris-Cité, (5)Inserm, (6)Sorbonne Paris Cité, (7)Hospital Clínic-Idibaps, Barcelona, Spain, (8)European Foundation for the Study of Chronic Liver Failure

Background: Non-alcoholic steatohepatitis (NASH) is an increasing cause for liver cirrhosis globally. NASH-cirrhosis is responsible for liver related complications and no specific treatment is currently available. Animal models for the development of new therapeutic approaches are an unmet need. The aim of this study was to develop ananimal model of advanced NASH-cirrhosis in rats mimicking the human situation in a shorter period of time. **Methods:** Liver cirrhosis was induced by repetitive carbon tetrachloride (CCl_4) injections in combination with high fat and high-cholesterol western diet (WD). To boost liver injury animals received Phenobarbital in the drinking water using a short-term (ST) high (3d of 0.3g/L) or a long-term (LT) low dose (6 wks of 0.06g/L) treatment. **Results:** Rats developed advanced NASH-cirrhosis characterized by blood biochemistry, hepatic steatosis, inflammation and fibrosis. However, LT rats showed ascites as a definite sign of portal hypertension after around 6 weeks, whereas ST rats developed ascites after a median of 8 weeks. All rats showed increased portal pressure and concomitantly a decreased systemic arterial pressure compared to CCl_4 alone. Whereas all rat models develop NASH cirrhosis, only rats with LT treatment developed hepatocyte ballooning, which is a sign of parenchymal cell damage/death and also present in human NASH cirrhosis. **Conclusion:** The LT administration of low dose Phenobarbital in combination with CCl_4 intoxication and WD represents a novel rat model with accelerated development of advanced liver fibrosis mimicking all key characteristics of decompensated NASH-cirrhosis in humans.

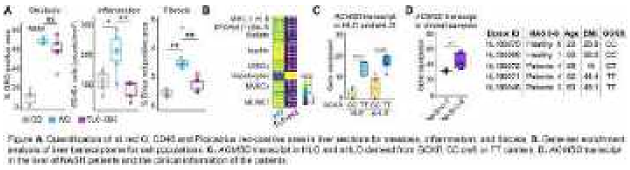
Disclosures: Jonel Trebicka – Versantis: Consultant, No, No; Gore: Speaking and Teaching, No, No; Boehringer-Ingelheim: Consultant, No, No; Alexion: Consultant, No, No; Falk: Consultant, No, No; Mallinckrodt: Consultant, No, No; Grifols: Consultant, No, No; CSL Behring: Consultant, No, No;

The following people have nothing to disclose: Nico Kraus, Magnus Moeslein, Robert Schierwagen, Wenyi Gu, Maximilian Joseph Brol, Frank Erhard Uschner, Pierre-Emmanuel Rautou, Sophie Lotersztajn, Roger Flores-Costa, Joan Claria, Sabine Klein

2273-C | ACMSD INHIBITION REDUCES HEPATIC INFLAMMATION AND FIBROSIS IN A MURINE THERMONEUTRALITY MODEL OF NASH

Yasmine Liu[1], Masaki Kimura[2], Sandra Rodríguez-López[1], Angelique M.L. Scantlebery[3], Keno Strotjohann[1], Xiaoxu Li[1], Krisztian Homicsko[4], Archana Vijayakumar[5], Robert P. Myers[5], Maroun Bou-Sleiman[1], G. Mani Subramanian[5], Riekelt H Houtkooper[3], Takanori Takebe[2] and Johan Auwerx[1], (1)École Polytechnique Fédérale De Lausanne, (2) Cincinnati Children's Hospital Medical Center, Cincinnati, OH, (3)Amsterdam University Medical Center, Amsterdam, Netherlands, (4)Lausanne University Hospital, (5)Orsobio, Inc

Background: α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD) is a branch point enzyme in the *de novo* NAD+ biosynthetic pathway in liver and kidney. TLC-065 is a potent ACMSD inhibitor that enhances fatty acid oxidation, and reduces *de novo* lipogenesis (DNL), lipotoxicity, and oxidative stress in murine hepatocytes and induced pluripotent stem cell (iPSC)-derived, steatotic human liver organoids (sHLO)[1]. Here, we evaluated therapeutic efficacy of TLC-065 in a murine model of NASH and assessed ACMSD expression in carriers of the glucokinase regulatory protein (GCKR) TT risk variant, which is characterized by increased DNL and NASH susceptibility[2]. **Methods:** C57BL/6J mice fed a western diet (WD) or chow were housed at thermoneutrality (TN; 30°C) for 23 weeks and treated with TLC-065 (25 mg/kg/day dosed in WD) from week 9-23. Hepatic fibrosis and inflammation were assessed histologically. *ACMSD* expression was assessed in HLO (± oleic acid) derived from, and livers of, GCKR CC (ref) or TT carriers. **Results:** In the WD/TN mouse model, TLC-065 was well-tolerated over 14 weeks of dosing and led to pronounced NASH regression, evidenced by normalization of hepatic inflammation and fibrosis to levels observed in chow mice without affecting hepatic steatosis (Fig A). Decreased abundance of non-parenchymal cells including Kupffer cells and stellate cells were seen in liver transcriptome analysis (Fig B). *ACMSD* transcript levels were significantly higher in GCKR TT donor sHLO (Fig C) and with increasing NAS score in NASH subjects which was also associated with presence of the GCKR TT variant (Fig D). **Conclusion:** ACMSD inhibition reduced fibrosis and inflammation in a mouse TN model of NASH. Further, ACMSD expression was significantly increased in the presence of the GCKR TT risk variant which has increased NASH susceptibility providing an opportunity for precision medicine. In sum, these data support the development of novel ACMSD inhibitors to treat liver injury due to NASH and other etiologies. References: [1]YJ Liu, et al., Hepatology (CONF), 2022; [2]Kimura, M. et al., Cell, 2022



Disclosures: Robert P. Myers – OrsoBio: Employee, No, No;
G. Mani Subramanian – OrsoBio, Inc: Employee, No, No;
Johan Auwerx – NovMetaPharma Co., Ltd.: Executive role , Yes, No;
The following people have nothing to disclose: Yasmine Liu, Keno Strotjohann, Xiaoxu Li
Disclosure information not available at the time of publication: Masaki Kimura, Sandra Rodríguez-López, Angelique M.L. Scantlebery, Krisztian Homicsko, Archana Vijayakumar, Maroun Bou-Sleiman, Riekelt H Houtkooper, Takanori Takebe

2274-C | ADIPOSE TISSUE NAT10 IS ESSENTIAL FOR THE DEVELOPMENT OF NAFLD

Qianren Zhang[1], Rui Xue[1], Ren Tianyi[1] and Jiangao Fan[2], (1)Department of Gastroenterology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, (2)Department of Gastroenterology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China

Background: Adipose tissue dysfunction has been closely linked with nonalcoholic fatty liver disease (NAFLD), but the underlying mechanisms remain to be elucidated. N-4 cytidine acetylation (ac4C) is a novel epi-transcriptomic modification catalyzed by N-acetyltransferase 10 (NAT10). Our preliminary

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

experiment showed that 12-week HFD feeding induced significant upregulation of NAT10 in mouse epididymal fat. Here, we aimed to investigate the significance of adipose NAT10 in NAFLD development. **Methods:** Adipocyte-specific *Nat10*-knockout mice (*Nat10*^{AKO}) and wild-type littermates (*Nat10*$^{fl/fl}$) were fed with HFD (60% fat) for 16 weeks to induce NAFLD. After NAFLD modeling, all mice were euthanized for morphological, biochemical, histopathological and metabolic evaluations. Transcriptomic-wide mapping of ac4C modification was performed on mRNA samples isolated from primary epididymal adipocytes, with the aid of RNA-seq and acetylated RNA immunoprecipitation sequencing (acRIP-seq). **Results:** While being fed with HFD, *Nat10*^{AKO} mice gained much more weight than *Nat10*$^{fl/fl}$ mice and significant differences began to appear since week 3 of HFD feeding. After 16-week HFD feeding, glucose tolerance and insulin tolerance were improved in*Nat10*^{AKO} mice when compared with *Nat10*$^{fl/fl}$ mice. Due to metabolic chamber records, *Nat10*^{AKO} mice showed markedly higher oxygen consumption, carbon dioxide production, respiratory exchange ratio, heat production and movement than *Nat10*$^{fl/fl}$ mice. In addition, fasting *Nat10*^{AKO} mice had significantly lower levels of triglyceride, cholesterol, free fatty acids, insulin, glucose and leptin in serum when compared with fasting *Nat10*$^{fl/fl}$ mice. Masses of epididymal white adipose tissue, inguinal white adipose tissue, brown adipose tissue and liver were significantly smaller in *Nat10*^{AKO} mice than *Nat10*$^{fl/fl}$ mice. According to histological analyses, *Nat10*^{AKO} epididymal adipocytes were not only smaller in size than *Nat10*$^{fl/fl}$ epididymal adipocytes, but also infiltrated with fewer macrophages and neutrophils, which was in line with the downregulation of proinflammatory cytokines. Moreover, hepatic steatosis was remarkably reduced in *Nat10*^{AKO} mice than *Nat10*$^{fl/fl}$ mice. Combined analysis of RNA-seq and acRIP-seq demonstrated that *Nat10* deletion in adipocytes led to reduced ac4C abundance in cyclin A2 (*Ccna2*) and cyclin-dependent kinase 2 (*Cdk2*) mRNAs, which further decreased mRNA stability and transcriptional efficacy. Lower expressions of CCNA2 and CDK2 in *Nat10*^{AKO} adipocytes arrested cell cycle progression, thereby inhibiting adipogenesis. Besides, reduced ac4C modifications in *Pparg*, *Dgat1*, and *Srebp1c* mRNAs also contributed to *Nat10*^{AKO} phenotypes via hindering lipogenesis, adipocyte maturation and adipocyte proliferation. **Conclusion:** Elevated adipocyte NAT10 expression serves as an important pathogenic factor as well as a potential therapeutic target of NAFLD.

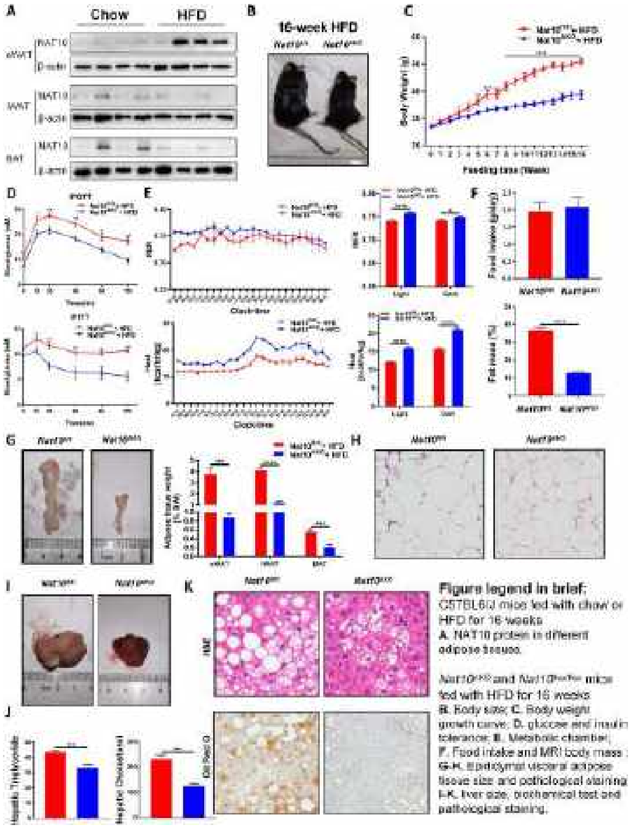


Figure legend in brief:
C57BL6/J mice fed with chow or HFD for 16 weeks
A. NAT10 protein in different adipose tissues.

Nat10^{AKO} and *Nat10*$^{fl/fl}$ mice fed with HFD for 16 weeks
B. Body size; **C.** Body weight growth curve; **D.** glucose and insulin tolerance; **E.** Metabolic chamber; **F.** Food intake and MRI body mass ; **G-H.** Epididymal visceral adipose tissue size and pathological staining **I-K.** liver size, biochemical test and pathological staining.

Disclosures: The following people have nothing to disclose: Qianren Zhang, Rui Xue, Ren Tianyi, Jiangao Fan

2275-C | AI MODELS TO PREDICT THE INFLUENCE OF NAFLD-ASSOCIATED RISK VARIANTS ON MOLECULAR PHENOTYPES

Henry Pratt, UMass Medical School and Daniel S. Pratt, Massachusetts General Hospital

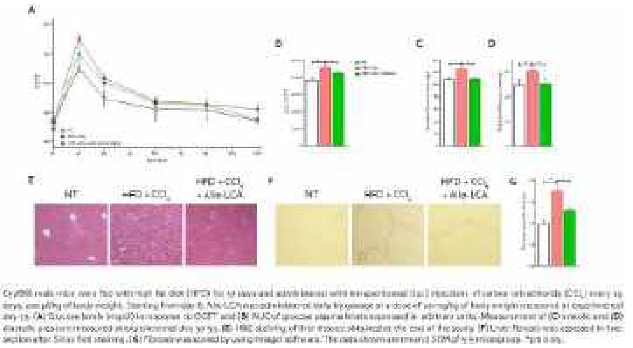
Background: Genome-wide association studies (GWAS) have identified tens of risk loci for NAFLD, but the mechanism by which most of these variants confer risk is poorly-understood owing in large part to many of these variants lying outside of coding genes, and thus do not directly impact the structure and function of proteins. These non-coding risk variants may instead impact the expression of risk genes, but predicting which genes are impacted and in what biological contexts is challenging. **Methods:** We trained several AI models to predict the impact of sequence variants on regulatory element activity in twenty different cell and tissue types with potential pathophysiological relevance to fatty liver disease, including hepatocytes, adipocytes, pancreatic endocrine cells, and various immune cells, as well as eight control cell types less likely to have involvement such as testicular cells and motor neurons. We then applied these models to sequence variants from two NAFLD GWAS encompassing 13,195 NAFLD patients and 1,143,407 healthy controls. We aimed to (1) identify cell and tissue types in which NAFLD variants are statistically more likely to regulate gene expression than expected by chance and (2) prioritize high-confidence candidate risk variants for future study. **Results:** Our models predicted effects on regulatory element activity for NAFLD-associated risk variants at 11 distinct genomic loci. Of these, 8 were predicted to be important by models trained in T cell lineages, including Th1 cells, Th2 cells, and Th17 cells, and 3 were predicted to be important by models trained on data from cells of the endocrine pancreas. This represented a significant enrichment for these cell types; we did not observe significant enrichment in other cell types tested. Of the 11 loci, 6 are predicted to influence activity of gene promoters and 5 are predicted to influence gene expression by modulating the activity of enhancers. NAFLD-associated risk alleles were equally likely to increase enhancer and promoter activity as to decrease it relative to protective alleles. **Conclusion:** We predict molecular phenotypes for 11 NAFLD-associated genomic loci. We link these loci both with predicted impacts on enhancers and promoters and with candidate cell types in which those impacts are most likely relevant. Our models support the hypotheses that both immune and endocrine pathways play roles in NAFLD pathophysiology and provide a targeted framework for further investigation of these loci.

Disclosures: The following people have nothing to disclose: Henry Pratt, Daniel S. Pratt

2276-C | ALLO-LCA, A BILE ACID DERIVATIVE WITH DUAL ACTIVITY ON GPBAR1 AND RORΓT, ALLEVIATES NASH-INDUCED LIVER FIBROSIS

Michele Biagioli[1], Cristina Di Giorgio[1], Martina Bordoni[1], Silvia Marchianò[1], Carmen Massa[1], Rachele Bellini[1], Ginevra Urbani[1], Eleonora Distrutti[2], Angela Zampella[3] and Stefano Fiorucci[1], (1)University of Perugia, (2) Azienda Ospedaliera Di Perugia, (3)University of Naples, Federico II

Background: NAFLD is due to the pathological accumulation of lipids in hepatocytes. When lipid accumulation exceeds the protective mechanisms, hepatocytes become injured, process known as lipotoxicity, and release a number of inflammatory mediators that lead to recruitment and activation of ECM-forming cells with excessive deposition of a distorted ECM, leading to liver fibrosis. Liver fibrosis, is a late contributor to NASH pathogenesis. Upon liver injury, hepatocytes and non-parenchymal liver cells release pro-fibrogenetic mediators that binds to, and activate, HSCs. Bile acids (BAs) are amphipatic molecules synthesized in the liver. Beside their role in nutrient absorption, BAs are signaling molecules exerting a variety of regulatory function by activating a family of receptro called “bile acid activated receptors” (BARs). Recently identified derivatives of bile acids (called tertiary bile acids), have shown the ability to act simultaneously on GPBAR and also on RORγt on which some of them exert an inverse agonist activity. The action on RORγt makes these tertiary bile acids attractive therapeutic compounds with the ability to act on both the innate and adaptive immune systems. The aim of the study was to evaluate the effect the dual action on GPBAR1 and RORγt, by the administration of Allo-LCA, in preventing the development of NASH inflammation and fibrosis. **Methods:** In this study Allo-LCA will be used in rodent model of NASH, induced by the use of high fat diet (HFD) and intraperitoneal (i.p.) injections of carbon tetrachloride (CCl_4) (every 15 d, 200 μl/kg of body weight). Allo-LCA was administered at the dose of 10 mg/kg daily. The total duration of the experiment was 57 days. **Results:** Allo-LCA binds to GPBAR1 acting as an agonist with an EC50 of 2.7 μM and also acts as an inverse agonist of RORγt with an IC50 of 1.5 μM. The data demonstrated that Allo-LCA administration increased insulin sensitivity in mice exposed to HFD + CCl_4. Allo-LCA also reduced systolic and diastolic blood pressure compared to the experimental group treated with HFD + CCl_4 alone. Microscopic analysis of the liver by H&E and Sirius Red showed that the administration of HFD + CCl4 induced hepatic steatosis and severe fibrosis. Both processes were reversed by the administration of Allo-LCA. Furthermore, analysis of liver inflammation by qPCR showed that Allo-LCA decreased the expression of pro-inflammatory cytokines and markers of both macrophages and T lymphocytes indicating a decreased influx of immune cells in the liver. Moreover, the hepatic expression of Col1a1 and αSma were reduced by Allo-LCA indicating less HSC activation. **Conclusion:** Allo-LCA, with its potent dual action on GPBAR1 and RORγt, reduces liver inflammation induced by an HFD + CCl_4 increasing insulin sensitivity and reducing liver fibrosis, suggesting that this compound may represent a potent new treatment for NASH and related fibrosis.



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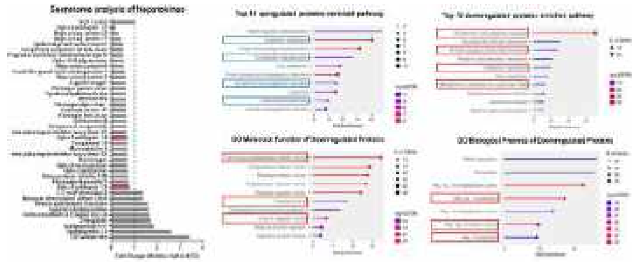
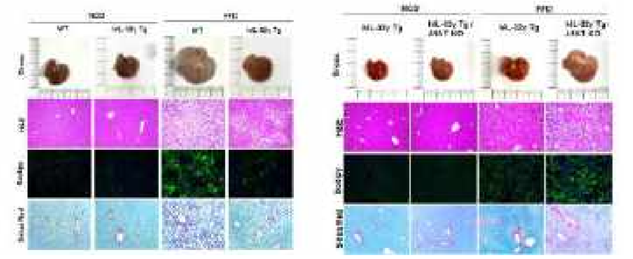
Disclosure information not available at the time of publication: Eleonora Distrutti, Angela Zampella, Stefano Fiorucci

2277-C | ALPHA-1 ANTITRYPSIN/ PROTEINASE 3 IMBALANCE EXERTS PROTEOLYTIC REGULATION ON INTERLEUKIN-32 GAMMA TO PROMOTE NONALCOHOLIC STEATOHEPATITIS

JeongSu Park[1], Jin Lee[2], Feng Wang[1], Hwan Ma[1], Yong-Sun Lee[3], SangKyu Lee[4], Yoon Mee Yang[5], Hwan-Soo Yoo[1], Sang-Bae Han[1], Bumseok Kim[6], Jin Tae Hong[1] and Yoon-Seok Roh[1], (1)Chungbuk National University, (2)University of California, San Diego, (3) National Institute of Food and Drug Safety Evaluation, South Korea, (4)Kyungpook National University, (5) Kangwon National University, (6)Biosafety Research Institute and College of Veterinary Medicine, Jeonbuk National University, Iksan 54596, Korea.

Background: Excessive proteolytic activity is one of the key clinical aspects of nonalcoholic steatohepatitis (NASH). Alpha-1-antitrypsin (A1AT) has the main function of balancing the action of protease enzymes. However, the regulatory and downstream mechanism of A1AT in NASH remains unclear. **Methods:** Quintuple *Serpina1a–e* knockout (A1AT KO) mice, human IL-32γ transgenic (hIL-32γ Tg) mice, and hIL-32γ Tg/A1AT KO mice were fed with fast food diet (FFD). Liver tissues, hepatocytes, and Kupffer cells (KCs) were collected and analyzed by histology, RNAseq, secretome profiling, and cytokine array. **Results:** A1AT was found to be the most downregulated secreted protein in hepatocytes from FFD-fed mice by secretome profiling, and its expression was transcriptionally regulated by hepatocyte nuclear factor 4 alpha (HNF4A) with response to IL1β. In both humans and mice with NASH, the serum levels of A1AT were significantly decreased, whereas those of proteinase 3 (PR3), a pro-inflammatory serine protease, were increased. Consistently, the PR3/A1AT ratio was positively correlated with ALT and AST in human subjects. We approved similar trends in the correlation between IL1B, HNF4A, and SERPIINA1 expressions in patients with NASH using the RNAseq dataset. *In vivo* deletion of A1AT markedly increased expression of PR3, inducing more severe inflammatory responses and liver fibrosis. Pharmacological modulation of A1AT and PR3 alleviated the severity of NASH in mice. According to the PR3-bound cytokine array, IL-32γ was identified as a major target of PR3-mediated proteolytic cleavage. IL-32γ treatment decreased expression of pro-inflammatory cytokines in KCs. Consistently, in vivo overexpression of IL-32γ markedly alleviated FFD diet-induced hepatic inflammation, and liver fibrosis. Moreover, additional deletion of A1AT enhanced PR3 activity and dampened IL-32γ-mediated protective actions against NASH. Imbalance of A1AT and PR3 levels induced excessive degradation of IL-32γ in mice liver. The blockade of PR3-mediated IL-32γ cleavage by V104A mutation sustained its anti-inflammatory function in KCs. Furthermore, the cleaved IL-32γ (C-terminus) by PR3 induced profound inflammation, suggesting PR3 increases proteolytic processing of IL-32γ promoting liver inflammation and fibrosis. **Conclusion:** The hepatic A1AT maintains IL-32γ-mediated protective actions through inhibition of PR3-dependent proteolytic processing which could be a novel therapeutic strategy against NASH.





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2278-C | ALTERED EphA2 SIGNALING IN NON-ALCOHOLIC FATTY LIVER DISEASE PROGRESSION

Brenna Pearson-Gallion[1], Alexandra Finney[1], Elizabeth Cockerham[1], Kelley Nunez[2], Chowdhury Abdullah[1], Eshika Tandon[1], Dhananjay Kumar[1], Richa Aishwarya[1], Matthew Scott[1], Cyrine Ben Dhaou[1], Kaylea Reeves[1], Paul Thevenot[3], Ari J. Cohen[4], James Traylor[1], Md Shenuarin Bhuiyan[1], Arif Yurdagul[1], Oren Rom[1] and Anthony W Orr[1], (1)Lsuhs-Shreveport, (2)Ochsner Health System, (3)Alton Ochsner Medical Foundation, (4)Ochsner Health System, New Orleans, LA

Background: Nonalcoholic fatty liver disease (NAFLD), the leading cause of chronic liver disease worldwide, results from diet-induced hepatic steatosis that can result in hepatocyte ballooning, inflammation and fibrosis driving nonalcoholic steatohepatitis (NASH). The Eph receptors, the largest family of receptor tyrosine kinases in the mammalian genome, affect inflammation and fibrosis in other model systems, and we have shown that EphA2 deletion reduces atherosclerosis despite increasing plasma cholesterol levels. While a GWAS study has linked EphA2 to NAFLD, the potential role of EphA2 in NAFLD has never been investigated. **Methods:** EphA2 expression and signaling was assessed in mice fed a high fat diet (HFD) for 8 and 24 weeks, in human liver samples from NASH patients, and in HuH7 cells treated with palmitic acid (FA), low density lipoprotein (LDL), and/or fructose. Global EphA2 KO mice were fed the FPC diet for 8 and 16 weeks followed by histological and molecular analyses. Primary hepatocytes and mitochondria were isolated from global EphA2 KO mice and used for Seahorse analysis. **Results:** Mice with early-stage non-alcoholic fatty liver disease (NAFLD) showed elevated EphA2 expression along with markers of EphA2 ligand-dependent signaling (EphA2 tyrosine phosphorylation). Consistently, HuH7 cells treated with FA, LDL, and/or fructose displayed a similar enhancement of EphA2 expression upon treatment. However, a mouse model of late-stage NASH exhibited reduced expression of the EphA2 ligand ephrinA1 and elevated markers of ligand-independent EphA2 signaling (Ser897 phosphorylation). Similarly, human liver samples from NASH patients show reduced ephrinA1 expression and elevated markers of EphA2 ligand independent signaling. Consistent with a role for EphA2 in NAFLD/NASH, global EphA2 KO mice show significantly lower indices of NAFLD following high fat diet feeding, including reduced hepatic steatosis and inflammation. RNA sequencing and Seahorse analysis illustrated enhanced metabolism in EphA2 KO mice. **Conclusion:** Taken together, our data demonstrate that EphA2 expression and signaling are altered during NAFLD/NASH pathogenesis and suggest that EphA2 inhibition may reduce NAFLD/NASH disease progression.

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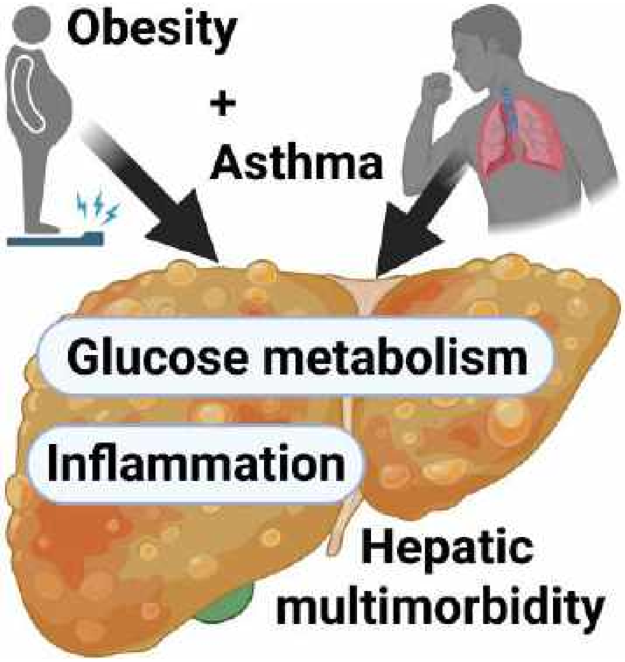
2279-C | ASTHMA AND OBESITY - SYNERGISTIC EFFECTS ON HEPATIC METABOLISM IN A MOUSE MODEL

Tim Westhoff[1], Holger Garn[2], Sarah Miethe[2], Verena Von Bülow[3], Martin Roderfeld[3] and Elke Roeb[3], (1) Justus-Liebig-University, (2)Philipps University, (3) Justus-Liebig-University, Giessen

Background: Obesity, as a component of the metabolic syndrome, is a widespread disease with steadily increasing case numbers in industrialized countries and serious health consequences such as non-alcoholic fatty liver disease (NAFLD). The prevalence of NAFLD is currently estimated at 26% worldwide. Asthma is the most common chronic respiratory disease, affecting approximately 350 million people worldwide. Asthma and obesity frequently co-occur and usually negatively influence the respective disease course. Recent epidemiological studies suggest a pathomechanistic link between obesity and asthma, but studies on mechanistic interactions at the cellular and molecular level are missing. **Methods:** The aim of our study was to analyze the comorbidity of NAFLD & asthma on molecular parameters of the hepatic metabolism in a mouse model. Therefore, four groups of C57BL/6 mice ($n = 6$ animals each) were fed either a high-fat diet (HFD) or normal diet (ND) until 20 weeks of age and additionally exposed to house dust mite extract (HDM) or PBS as a control in the last 4 weeks by repeated intranasal applications. Liver samples were analyzed by qRT-PCR and immunohistochemistry for biochemical markers with regard to glucose metabolism and inflammatory parameters. Differences between experimental groups were extracted by Kruskal-Wallis test (using SPSS29.0). **Results:** In all groups with HFD or HDM exposure, genes of glucose metabolism were differentially regulated as compared to healthy controls. In particular, expression of glycolysis associated enzymes such as phosphofructokinase 1 and aldolase was decreased in the HDM/HFD group. In addition, a decrease in succinyl-CoA synthetase was detected in liver tissue at both levels, mRNA (qRT-PCR) and protein (immunohistochemistry) expression. While

IL-10 as a parameter of hepatic anti-inflammatory immune mechanisms was increased in the HDM group, markers for Th1 immune responses were found to be downregulated in the HDM/HFD group. **Conclusion:** Our results demonstrate potentiated effects of asthma and obesity on parameters of the hepatic glucose metabolism and hepatic inflammation. Thereby, we verified a synergistic negative impact on liver function in succession with increased liver injury in the presence of both disease conditions.



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2280-C | BILE SALT EFFLUX PUMP (BSEP) MEMBRANE-LOCALIZED ZONAL ABUNDANCE IN HUMAN LIVER TISSUE FROM PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)★

William A. Murphy[1], Anna Mae Diehl[2], Matthew S. Loop[3], Dong Fu[1], Cynthia D. Guy[2], Manal F. Abdelmalek[4], Georgia Sofia Karachaliou[5], Noora Sjöstedt[6], Sibylle Neuhoff[7], Paavo Honkakoski[8] and Kim L.R. Brouwer[1], (1)University of North Carolina at Chapel Hill, (2)Duke University, (3)Auburn University, (4)Mayo Clinic, Rochester, MN, (5)Duke University Medical Center, (6)University of Helsinki, (7)Certara UK Ltd., (8)University of Eastern Finland

Background: Zonal differences in NAFLD pathophysiology may be an important factor in disease progression and therapeutic response. Systemic and enterohepatic bile acids (BAs) are elevated in NAFLD and pericentral microcholestasis was reported in early nonalcoholic steatohepatitis (NASH). However, the mechanisms responsible for these changes are not well understood. BSEP, a canalicular membrane transporter, is the rate-determining step in hepatic BA secretion. BSEP has been implicated in cholestatic disease and is positively regulated by farnesoid X receptor, a pericentrally active NAFLD drug target. While no change in BSEP abundance in NAFLD was reported previously, quantitative estimates of membrane-localized BSEP are lacking, particularly across hepatic regions. To assess BSEP membrane-localized abundance (BSEP_{MA}) in NAFLD, we developed a machine learning image classification method to quantify BSEP canalicular membrane localization and tissue zonation using 3D liver biopsy images. **Methods:** Human liver biopsy sections were obtained from the Duke NAFLD Biorepository. Fibrosis stage and NAFLD-associated histologic features were assessed by board-certified pathologists to inform histologic-based diagnosis in accordance with current NASH Clinical Research Network criteria: Non-diseased liver (NDL; $n = 10$), NAFL ($n = 9$), NASH ($n = 11$). Biopsies underwent immunofluorescence staining for BSEP, a canalicular membrane marker (CD-13), and nuclei (DAPI) followed by 40X confocal imaging (3 random areas were imaged per sample). To quantify membrane localization, hepatocellular BSEP fluorescence was segmented into 3D surfaces using the Imaris machine learning classifier and volumetric overlap (within 0.4 μm) with CD-13 was measured. To evaluate zonal abundance for each sample, BSEP fluorescence was quantified to reflect relative proportions across three equidistant hepatic zones between the portal tract and central vein (PT-to-CV axis). BSEP_{MA} was obtained by adjusting zonal abundance measures for plasma membrane localization within a sample. A two-way repeated measures ANOVA was used for statistical analysis. **Results:** Relative periportal increases and pericentral decreases in BSEP_{MA} were observed with NAFLD progression (Fig. 1A) and were associated with steatosis (Fig. 1B), lobular inflammation (Fig. 1C), and hepatocellular ballooning (Fig. 1D). Observed zonal differences in BSEP_{MA} with fibrosis were inconclusive. **Conclusion:** Changes in periportal and pericentral BSEP_{MA} occur with NAFLD progression. These findings provide novel insight into altered BA homeostasis in NAFLD. Increased periportal BSEP_{MA} may protect from hepatotoxicity due to higher BA exposure in this region, while decreased pericentral BSEP_{MA} may explain previous findings of microcholestasis. Thus, therapeutic approaches to increase pericentral BSEP_{MA} could improve microcholestasis and pericentral NASH.

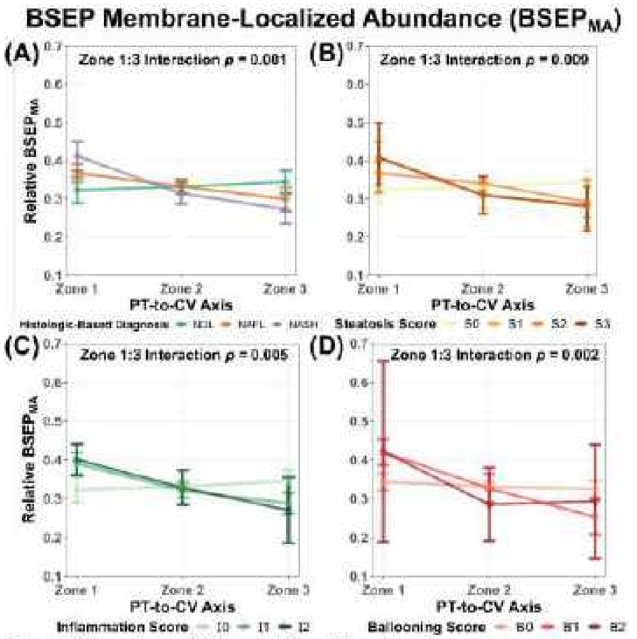

Figure 1. Mean (arithmetic) $BSEP_{MA}$ and 95% confidence intervals.
Observed p values for interaction effect between hepatic zones 1 and 3 and histologic subgroups. Only two zones could be compared at once because groupwise relative $BSEP_{MA}$ values across the three zones are constrained to a total sum of 1.
(A) NDL (n=10), NAFL (n=9), NASH (n=11); **(B)** S0 (n=10), S1 (n=7), S2 (n=8), S3 (n=5); **(C)** I0 (n=10), I1 (n=17), I2 (n=3); (D) B0 (n=20), B1 (n=7), B2 (n=3).
CV, central vein; *PT*, portal tract

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Dong Fu – Frontera Therapeutics: Employee, No, Yes;

Cynthia D. Guy – Madrigal: Consultant, No, No; 89Bio: Consultant, No, Yes; NGM Biopharma: Consultant, No, Yes; HitoIndex: Consultant, No, No; CymaBay: Consultant, No, Yes;

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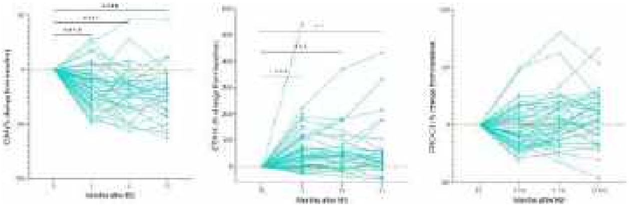
2281-C | BIOMARKERS TARGETING DIFFERENT EPITOPES OF THE SAME PROTEIN - TYPE III COLLAGEN - PROVIDE INFORMATION ABOUT BOTH FIBROGENESIS AND FIBROLYSIS IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE UNDERGOING BARIATRIC SURGERY

Thomas Wiggers Møller[1], Ida Lønsmann Sorribes[2], Julie Steen Pedersen[3], Morten Karsdal[4], Flemming Bendtsen[5] and Diana J. Leeming[2], (1)Nordic Bioscience a/S, (2)Nordic Bioscience A/S, (3) Copenhagen University Hospital of Koege, (4)Nordic Bioscience a/S, Denmark, (5)Hvidovre Hospital

Background: One characteristic of liver fibrosis is increased degree of enzymatic cross-linking of collagens as well as collagen remodeling. We aimed to investigate differences in measuring the same protein in three different ways using serological biomarkers: MMP driven fibrolysis of cross-linked type III collagen (CTX-III), MMP driven fibrolysis of type III collagen (C3M), and fibrogenesis of type III collagen (PRO-C3). **Methods:** 70 patients had blood samples and liver biopsies collected on the day of bariatric surgery. Additional blood samples were collected at 3-, 6- and 12-months after bariatric surgery. 40 of the patients had a liver biopsy at twelve months. Serum CTX-III, C3M, and PRO-C3 were measured using fully validated immunoassays, and the markers were analyzed using a linear mixed-effect analysis on log-transformed data. **Results:** 61% of the included 70 patients were females and mean age and mean BMI were 44 years and 42 kg/m2, respectively. Patients had a median NAFLD activity score of 3 and mild-to-moderate fibrosis F0 (3%), F1 (86%), and F2 (11%). The general percent change of MMP degraded cross-linked type III collagen (CTX-III) from baseline was significantly elevated in patients with bariatric surgery ($p < 0.0001$), with the most dramatic change observed between baseline and 3-months follow-up ($p < 0.001$). Interestingly, the general percent change of MMP degraded type III collagen (C3M) from baseline was significantly decreased ($p < 0.0001$), with the biggest change observed from baseline to the 3-months follow-up ($p < 0.0001$), while type III collagen formation (PRO-C3) remained statistically unchanged.

Conclusion: This study indicates that in NAFLD patients undergoing bariatric surgery, induction of resolution may only be monitored assessing a cross-linked fragment generated by MMP, potentially being more specific to fibrotic tissue due to the increase in degree of collagen cross-links with fibrosis severity. A non-crosslinked version did not provide the same value but rather decreased potentially reflecting the inflammatory pathway.



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Disclosure information not available at the time of publication: Ida Lønsmann Sorribes, Julie Steen Pedersen, Flemming Bendtsen, Diana J. Leeming

2282-C | BREAKING THE LINK BETWEEN AGING AND NAFLD: UNRAVELING THE ROLE OF FERROPTOSIS

Kuo Du[1], Ji Hye Jun[1,2], Raquel Maeso Díaz[3], Rajesh Kumar Dutta[3], Seh-Hoon Oh[3], Jen-Tsan Ashley Chi[1] and Anna Mae Diehl[3], (1)Duke Universty, NC, (2)Duke Universty, Durham, NC, United States, (3)Duke University

Background: Non-alcoholic fatty liver disease (NAFLD) is a growing public health concern, and its prevalence is projected to increase due to the growing elderly population. Ferroptosis, a recently discovered form of regulated cell death, has been implicated in various age-related diseases such as cardiovascular diseases. However, the role of ferroptosis in aging-associated NAFLD susceptibility remains unclear. **Methods:** Liver tissues and primary hepatocytes were harvested from chow-fed aged (24 mo) and young (3 mo) mice to examine the role of aging on basal ferroptotic stress, inflammation and fibrosis. RNA sequencing was performed to characterize aged hepatocyte transcriptomes and define how aging affects the gene signatures associated with ferroptosis, NAFLD and insulin signaling. Aged and young mice were also fed with CDA-HFD diet to determine if/how aging impacts NAFLD, and aged mice were further treated with ferroptosis inhibitor Ferrastatin-1 to examine whether inhibiting ferroptosis improves aging-associated NAFLD susceptibility. **Results:** Aged liver exhibited increased basal steatosis, fibrosis, and inflammation, and this phenotype was associated with increased ferroptotic stress in hepatocytes. Characterization of aged hepatocytes revealed upregulation of gene signatures associated with aging, ferroptosis, and NAFLD, while gene signatures associated with insulin signaling were downregulated. When fed with a NAFLD-inducing diet, aged mice exhibited an exacerbated NAFLD phenotype, as evidenced by worse liver function and increased liver fibrosis and inflammation. These mice also demonstrated exaggerated ferroptotic stress, and inhibiting ferroptosis significantly protected against the exacerbated NAFLD phenotype in aged mice. **Conclusion:** Our study demonstrates that aging-associated ferroptosis is a fundamental pathogenic mechanism of NAFLD susceptibility. Targeting the ferroptosis pathway and its associated pathobiology holds promise to treat NAFLD in the aging population. These findings have significant implications for developing novel therapeutic strategies to manage NAFLD and improve liver health in the elderly.

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2283-C | CATBOOST OUTPERFORMS OTHER MACHINE LEARNING METHODS TO PREDICT FATTY LIVER DISEASE IN THE UK BIOBANK

Yousif Alyousifi[1], Elizabeth K. Speliotes[2], Chinmay Raut[1], Antonino Oliveri[3], Ali Turfah[1] and Steven Dunne[1], (1)University of Michigan, (2)University of Michigan Medical School, (3)University of Michigan, Ann Arbor, MI

Background: Non-alcoholic Fatty Liver Disease (NAFLD) is a condition characterized by the accumulation of fat in the liver, unrelated to alcohol consumption, which can lead to potential health complications. Magnetic Resonance Imaging Proton Density Fat Fraction (MRI PDFF) is one of the most accurate measures for assessing fatty liver disease. However, obtaining MRI scans can be expensive or impractical. This study aims to predict MRI PDFF-measured liver fat using blood assay measurements and baseline data from the UK Biobank. **Methods:** We used the UK Biobank cohort individual's with MRI-PDFF measured 43,293, average age = 55.19, Male = 48.5% and Females = 51.5%. We used MRI PDFF > 3% to denote fatty liver disease. 248 predictors were taken from the baseline characteristics, physical measures, and serum values of these participants. We split the data into training (34,634) and testing (8,659) groups and applied machine learning methods including CatBoost, Support Vector Machine, Decision Tree, Random Forest, and Logistic Regression to estimate fatty liver disease. **Results:** CatBoost achieved the best performance with the highest accuracy of 0.776, second highest precision of 0.739, highest recall of 0.647, highest F1 score of 0.690 and highest ROC-AUC of 0.844 compared to the other methods (Table 1). The worst performing method was Decision Trees with an accuracy of 0.675, precision of 0.571, recall of 0.599, F1 score of 0.570 and ROC-AUC of 0.654 **Conclusion:** Using machine learning methods, we were able to predict the presence of fatty liver disease with high accuracy, precision, and recall. We are working to reduce the predictors to generalizable parameters that can be used more broadly to determine hepatic steatosis in other populations.

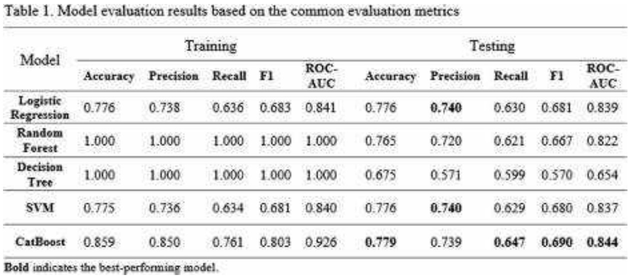

Table 1. Model evaluation results based on the common evaluation metrics

Model	Training					Testing				
	Accuracy	Precision	Recall	F1	ROC-AUC	Accuracy	Precision	Recall	F1	ROC-AUC
Logistic Regression	0.776	0.738	0.636	0.683	0.841	0.776	**0.740**	0.630	0.681	0.839
Random Forest	1.000	1.000	1.000	1.000	1.000	0.765	0.720	0.621	0.667	0.822
Decision Tree	1.000	1.000	1.000	1.000	1.000	0.675	0.571	0.599	0.570	0.654
SVM	0.775	0.736	0.634	0.681	0.840	0.776	**0.740**	0.629	0.680	0.837
CatBoost	0.859	0.850	0.761	0.803	0.926	**0.779**	0.739	**0.647**	**0.690**	**0.844**

Bold indicates the best-performing model.

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Elizabeth K. Speliotes:
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2284-C | CHARACTERIZING DEVELOPMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE IN HUMAN PRECISION-CUT LIVER SLICES

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Background: Non-alcoholic fatty liver disease (NAFLD) is a growing healthcare problem, ranging from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) and often leading to fibrosis and cirrhosis along with hepatocellular carcinoma. Progress in this field depends on the availability of reliable preclinical models. Precision-cut liver slices (PCLS) provide a preserved multicellular environment that allows for the interaction of various liver cell types. In this study we characterized the development of NAFLD in human PCLS. **Methods:** Healthy human PCLS were cultured for up to 96 hours in either GFIPO medium (William's E Medium supplemented with Glucose (36 mM), Fructose (5 mM), Insulin (1 nM), Palmitic acid (0.24 mM) and Oleic acid (0.48 mM)) to mimic NAFLD-inducing conditions, or WEGG medium (William's E Medium supplemented with Glucose (25 mM)) as a control. PCLS and media were collected every 24 hours to assess viability and fat accumulation by measuring ATP levels and triglyceride (TG) content. Gene expressions of inflammatory and fibrotic markers were evaluated by RT-qPCR. Inflammatory cytokines and pro-collagen 1a1 secretion were measured using ELISA and a Luminex assay. Additionally, RNA-sequencing was performed to identify and evaluate significantly changed genes and pathways in response to incubation process. **Results:** Liver slices remained viable for up to 96 hours of incubation in both WEGG and GFIPO mediums as evidenced by ATP levels. The TG content was increased with 92% in the GFIPO group. In GFIPO, mRNA expression of the inflammatory biomarker interleukin 6 (*IL6*) was significantly upregulated compared to WEGG (6-fold), as well as interleukin 1b (*IL1β*) (42-fold). However, no significant differences were observed in the expression of tumor necrosis factor alpha (*TNFα*). Nevertheless, the protein levels of TNFα and IL6 produced and secreted during the culture were significantly up-regulated (2-fold and 14-fold, respectively) in GFIPO medium. Regarding pro-fibrogenic gene expression, the secretion of pro-collagen 1a1 was increased significantly (2-fold) as well, while no difference was found at the mRNA level except for

ACTA2, which was significantly increased (2-fold). RNA-sequencing data indicated that initially, carbohydrate metabolism and lipid metabolism were significantly elevated in PCLS incubated in GFIPO, followed by a subsequent decrease in the later stages (72h and 96h). However, pathways associated with the immune system and signal transduction initially showed a downward trend but demonstrated an upward trend in GFIPO upon longer incubation. **Conclusion:** GFIPO increased the TG content and enhanced the development of inflammatory and pro-fibrogenic signaling at the gene and protein levels in human PCLS mimicking human NAFL development. RNA sequencing data revealed a metabolic response at the early stage, and an immune response at the later stage of NAFL development in this model.

Disclosures: The following people have nothing to disclose: Mei Li

Disclosure information not available at the time of publication: Vincent De Meijer, Anika Nagelkerke, Peter Olinga

2285-C | CHOLESTEROL-ASSOCIATED LOCUS EHBP1 PROTECTS AGAINST NASH FIBROSIS

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Background: Elevated hepatic cholesterol content is frequently seen in human NASH and high-cholesterol diets have been found to promote NASH progression in mouse models. However, the regulation of cholesterol accumulation in hepatocytes during NASH is not completely understood. Genome-wide association studies (GWAS) have revealed that several single nucleotide polymorphisms (SNPs) in *EHBP1* are associated with LDL cholesterol. However, the mechanisms underlying this association and the role of EHBP1 in hepatic cholesterol metabolism is unknown. **Methods:** Wild type (WT) mice were injected (i.v.) with AAV8-H1-shEhbp1 and AAV8-TBGS1-EHBP1 viruses to knockdown or overexpress EHBP1 in hepatocytes. The mice were fed a Fat/NASH diet for 10 weeks and plasma cholesterol, hepatic free cholesterol, fibrosis, inflammation and steatosis were analyzed. **Results:** EHBP1 expression was decreased in NASH liver of human and mouse as well. Our mouse studies showed that hepatocyte-specific EHBP1 deficiency increased liver free cholesterol, liver fibrosis, inflammation, and steatosis. In contrast to EHBP1 silencing, EHBP1 overexpression alleviated NASH progression. Mechanistic study with primary hepatocytes revealed that EHBP1 promotes sortilin (SORT1)-mediated PCSK9 secretion, leading to LDLR degradation and less LDL uptake. Regarding the decreased EHBP1 expression in NASH livers, we demonstrated that NASH-relevant cytokine TNFa reduced the expression of PPARa, a novel transcription factor for EHBP1. These data not only provide new mechanistic insight into the role of EHBP1 in hepatic cholesterol metabolism and NASH fibrosis by uncovering the interaction between EHBP1 and other LDL cholesterol-related loci including SORT1, PCKS9, and LDLR, but also elucidate a novel interplay between inflammation and EHBP1-mediated cholesterol metabolism in the context of NASH. **Conclusion:** At the homeostasis status, cholesterol-associated GWAS locus EHBP1 protects against NASH by promoting PCSK9 secretion and LDLR degradation, which prevents LDL uptake into hepatocytes and alleviates liver fibrosis. However, as NASH progresses, TNFa abolishes the beneficial effect of EHBP1 by suppressing PPARa and EHBP1 expression.

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2286-C | CircZBTB46 ALLEVIATES NON-ALCOHOLIC FATTY LIVER DISEASE BY TARGETING MIR-326/FGF1/AMPK AXIS

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Background: Non-alcoholic fatty liver disease (NAFLD) is currently the most prevalent cause of chronic liver diseases worldwide. Due to its complex pathogenesis and limited treatment methods, further research is urgently needed. The role of circular RNA (circRNA) in NAFLD is increasingly being discovered, but the mechanism behind it is not yet fully understood. This study aims to explore the role and molecular mechanism of circZBTB46 in NAFLD by regulating the miR326/FGF1/AMPK signaling pathway. **Methods:** RNA-sequencing and bioinformatics analysis were conducted on liver tissues obtained from 3 healthy controls, 3 NAFLD, and 3 NASH patients to identify differentially expressed circRNA. Western diet (WD)-fed mice were used as the NAFLD model in vivo, and free fatty acid (FFA)-treated LO2 cells were used as the NAFLD model in vitro. The circRNA-miRNA binding site was predicted using miRanda and TargetScan, and the interaction was verified through dual-luciferase reporter gene assays, RNA immunoprecipitation, and RNA pull-down experiments. mRNA expression levels were measured using qRT-PCR, while protein expression levels were detected by western blot, immunohistochemistry, and immunofluorescence. Triglyceride (TG) and cholesterol levels were quantified using

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

ELISA, and lipid deposition was detected with Oil Red O and BODIPY 493/503 staining. **Results:** We identified a circular RNA, named circZBTB46, which is generated from ZBTB46 gene and is downregulated in NAFLD patients as well as in vitro and in vivo NAFLD models. Overexpression of CircZBTB46 significantly reduced hepatic lipid deposition and TG secretion. Mechanistically, circZBTB46 alleviates NAFLD progression through the circZBTB46/miR-326/FGF1 pathway. miR-326 is upregulated in NAFLD and inhibits FGF1 expression by binding to the 3' UTR region of FGF1, leading to hepatic lipid deposition. CircZBTB46 counteracts the inhibitory effect of miR326 on FGF1/AMPK by acting as a miR-326 sponge, promoting the expression of FGF1, and thus reducing hepatic lipid deposition. **Conclusion:** The circZBTB46-miR326-FGF1/AMPK signaling axis has a significant role in non-alcoholic fatty liver disease. Investigating the expression of circZBTB46 in the bloodstream of NAFLD patients may offer new insights for non-invasive diagnosis of this condition.

Disclosures: The following people have nothing to disclose: Qingmin Zeng, Chang-Hai Liu, Wei Jiang, Dongbo Wu, Hong Tang

2287-C | CLINICAL TRANSLATABILITY OF LDLR-/-. LEIDEN MOUSE MODEL FOR NON-ALCOHOLIC STEATOHEPATITIS

Eveline Gart, José A. Inia, Martine M.C. Morrison, Robert Kleemann and Anita M. Van Den Hoek, The Netherlands Organization for Applied Scientific Research (TNO)

Background: Non-alcoholic steatohepatitis (NASH) is one of the most prevalent chronic liver diseases, which is closely associated with obesity, insulin resistance, dyslipidemia and cardiovascular disease. Preclinical validation of novel drug candidates for the treatment of NASH requires a translational animal model that should recapitulate these hallmarks of the human disease. The present study aimed to further investigate the translatability of the Ldlr-/-.Leiden mouse as translational NASH model. **Methods:** Ldlr-/-.Leiden mice fed a translational HFD without cholesterol supplementation were compared with human NASH patients on (a) obesity and insulin resistance; (b) lipoprotein profiles, endogenous cholesterol synthesis and de novo lipogenesis (DNL); (c) liver transcriptome and metabolome profile; (d) histological NASH endpoints and (e) atherosclerosis. In addition, the response to treatments with obeticholic acid (OCA), cenicriviroc and semaglutide was analyzed and compared to clinical trial results. **Results:** Ldlr-/-.Leiden mice fed a HFD develop severe obesity (with adipose tissue inflammation), insulin resistance and hyperlipidemia with humanized lipoprotein profiles (high triglycerides and LDL, low HDL). Similar to human NASH patients, Ldlr-/-.Leiden mice on HFD (without cholesterol supplementation) exhibit endogenous cholesterol synthesis and DNL. The mice recapitulate human NASH transcriptome and metabolome profiles and reveal a translational histopathology in the liver with steatosis, inflammatory aggregates and bridging fibrosis, as well as atherosclerosis development. Furthermore, the mice respond to the different treatments with NASH resolution (OCA & semaglutide, not with cenicriviroc) and improvement with fibrosis (OCA only), in line with clinical trials. **Conclusion:** Overall, the Ldlr-/-.Leiden mouse model shows good clinical translatability and accurately mimics the etiology and pathology of NASH and fibrosis in humans.

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Disclosure information not available at the time of publication: José A. Inia, Martine M.C. Morrison, Robert Kleemann

2288-C | COFFEE COMPOUNDS MODULATE ANTIOXIDANT RESPONSE AND LIPID DROPLETS FORMATION AGAINST PALMITATE-INDUCED LIPOTOXICITY IN HEPATOCYTES

Johanna C Arroyave Ospina[1,2], *Magnolia Martínez*[1], *Manon Buist-Homan*[1], *Victoria Palasantzas*[1] *and Han Moshage*[3], *(1)University Medical Center of Groningen, (2)Universidad De Antioquia, (3)University Medical Center Groningen*

Background: Metabolic dysfunction associated fatty liver disease (MAFLD) is the result of disturbed lipid metabolism. Accumulation of free fatty acids (FFAs) in hepatocytes causes lipotoxicity mediated by oxidative stress. Coffee compounds are known for its beneficial effects in MAFLD, however the mechanisms still need to be further explored. The aim of this study was elucidate the protective mechanisms of coffee compounds against palmitate-induced lipotoxicity in primary hepatocytes. **Methods:** Primary hepatocytes were isolated from Wistar male rats and treated with palmitate (1 mmol/L) in combination with caffeine (CF: 1 mmol/L) or chlorogenic acid (CGA: 5 μmol/L). Mitochondrial ROS production, palmitate-induced necrosis, antioxidant response markers SOD1, SOD2, HO-1 and GPx1, ER stress markers CHOP, ATF4 and GRP78 and, lipid droplets (LDs) formation were assessed. Monoacylglycerols 2-SG (2-Stearolylglycerol), 2-OG (2-Oleoylglycerol) and SCD-1 (Stearoyl-CoA Desaturase 1) Inhibitor were used to modulate LD formation. LD formation in steatotic Zucker hepatocytes was also investigated. **Results:** CF and CGA prevented palmitate-induced cell death and reduced ROS production. CF and CGA were found to induce the antioxidant response, especially HO-1 expression was increased, but did not significantly reduce palmitate-induced ER stress markers. CF and CGA increased LD formation in palmitate treated cells. This effect was significantly reduced by 2-SG and SCD-1 inhibitor, but enhanced by 2-OG. Lipid droplets accumulation was associated with lower palmitate toxicity and reduced ROS production. **Conclusion:** CF and CGA protect hepatocytes from lipotoxicity via inducing the antioxidant response and enhancing lipid droplet formation, likely via a SCD-1 dependent mechanism. Oxidative-stress related toxicity in hepatocytes can be prevented by enhancing LDs formation.

Disclosures: The following people have nothing to disclose: Johanna C Arroyave Ospina, Magnolia Martínez, Manon Buist-Homan, Victoria Palasantzas, Han Moshage

2289-C | COMPARATIVE ANALYSIS OF iPSC-DERIVED HEPATOCYTES (iPSC-HEPS) FROM NAFLD PATIENTS AND HEALTHY CONTROLS REVEALS IMPAIRED MITOCHONDRIAL FUNCTION IN NAFLD iPSC-HEPS

Dounia Le Guillou[1], *Chris S. Her*[1], *Kevin Siao*[1], *Simaron K. Dhillon*[1], *Caroline C. Duwaerts*[2], *Jacquelyn J. Maher*[3] *and maher, (1)University of California, San Francisco, (2)University of California, San Francisco, Richmond, CA, (3)University of California, San Francisco, San Francisco, CA*

Background: Mitochondria play a central role in the development and progression of NAFLD to NASH. We recently showed that NAFLD iPSCs differentiated into hepatocytes (iPSC-Heps) display a disease-specific gene expression profile with altered expression of genes related to lipid metabolism, inflammation, and insulin sensitivity. In this study, we investigated and compared mitochondrial function in NAFLD *vs.* control iPSC-Heps. **Methods:** iPSCs were differentiated to iPSC-Heps over 22 days. Mitochondrial function was assessed using the Seahorse XF Analyzer, measuring oxygen consumption rate (OCR) in the presence of either glucose or galactose, the latter designed to enhance oxidative phosphorylation. Endogenous and exogenous fatty acid oxidation (FAO) were evaluated by measuring OCR in the presence or absence of etomoxir (a FAO inhibitor) or palmitate, respectively. The generation of reactive oxygen species (ROS) in response to a 2h-palmitate treatment was measured using MitoSOX dye. Mitochondrial mass was determined by citrate synthase activity assay. **Results:** We investigated at least 9 NAFLD and 9 control patient-specific iPSC lines in this study. NAFLD iPSC-Heps spontaneously exhibited elevated triglycerides compared to control iPSC-Heps (129 *vs.* 71 nmol triglyceride/mg protein, $p = 0.02$). Seahorse experiments revealed that while mitochondrial respiration did not significantly differ between NAFLD and control iPSC-

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Heps under glucose conditions, NAFLD iPSC-Heps showed a significant increase in OCR when exposed to galactose. NAFLD iPSC-Heps exhibited higher endogenous FAO compared to controls (difference of 2772 pmol O_2/min/10^6 cells, $p = 0.006$). On the contrary, exogenous FAO was higher in control iPSC-Heps compared to NAFLD iPSC-Heps (difference of 2051 pmol O_2/min/10^6 cells, $p = 0.039$). Additionally, NAFLD iPSC-Heps displayed more ROS generation in response to palmitate than controls (155 % *vs*. 98 % MitoSOX intensity in response to palmitate *vs*. vehicle, $p = 0.012$)). Previous RNAseq data also revealed that even in the absence of any palmitate challenge, NAFLD iPSC-Heps already exhibited higher expression of genes involved in the oxidative stress response compared to controls. Assessment of mitochondrial mass did not reveal significant differences between NAFLD and control iPSC-Heps. **Conclusion:** Our results highlight distinct mitochondrial phenotypes in NAFLD iPSC-Heps, including an increased reliance on mitochondrial respiration, elevated endogenous FAO, and impaired utilization of exogenous fatty acids associated with enhanced ROS production, suggesting mitochondrial dysfunction when exposed to excess fatty acids. These findings support the notion of mitochondrial dysfunction in NAFLD, particularly in NASH, and highlight potential therapeutic targets for restoring normal hepatic metabolism in the disease.

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The following people have nothing to disclose: Dounia Le Guillou, Kevin Siao, Simaron K. Dhillon

2290-C | CONCOMITANT OBESOGENIC DIET AND ALCOHOL INDUCE A PRO-INFLAMMATORY ENVIRONMENT WITHOUT HISTOLOGIC STEATOHEPATITIS IN MICE

Joseph L Dempsey[1], Delfin Buyco[2], Joe Lim[1], Sina A. Gharib[1] and Rotonya M. Carr[1], (1)University of Washington, (2)Northwestern University

Background: Non-alcoholic fatty liver disease (NAFLD) and alcohol-associated liver disease (ALD) share many risk factors and have a similar histologic disease progression. However, the mechanisms by which fatty liver disease progresses to inflammatory conditions from concomitant obesity and alcohol consumption (here, termed the “syndrome of metabolic and alcoholic fatty liver disease” (SMAFLD)) are not fully known. **Methods:** We developed an experimental model of SMAFLD to examine the initial molecular changes that occur during early steatosis. Namely, we fed C57BL6/J mice a chow (Chow) or high-fat, fructose, cholesterol (FFC) diet and co-administered either saline or EtOH. EtOH-treated mice were given 5% EtOH in drinking water and 2.5 g EtOH/kg body weight per week for 8 weeks by gavage. We measured ALT, sectioned the liver for histology, and analyzed the hepatic transcriptome for immune signatures. We performed targeted lipidomics of hepatic ceramides (Cers) by LC-MS because of their established role in inflammation. Finally, we performed a glucose tolerance test and quantified hepatic levels of protein kinase B (AKT) given the known inhibitory role of inflammatory genes on insulin signaling. **Results:** FFC and FFC-EtOH diets induced steatosis and increased ALT compared to Chow. Despite the absence of histologic evidence of steatohepatitis or fibrosis, Gene Set Enrichment Analysis (GSEA) of RNA-seq data showed that FFC-EtOH had increased immune signaling, oxidative stress response, and energy and fatty acid metabolism compared to EtOH alone. STRING analysis showed that FFC and FFC-EtOH significantly upregulated genes that are associated with inflammasome activation. FFC diet is associated with CTP binding, sulfonylurea receptor binding, and dATP binding, whereas FFC-EtOH is associated with complement component C3b binding and RAGE receptor binding. Lipidomics revealed upregulation of the anti-inflammatory ceramide pre-cursor sphingolipids, dyhydrosphingosine and dyhydrosphingosine-1-phsophate, in FFC and FFC-EtOH diets. Finally, compared to Chow, glucose tolerance was impaired and protein levels of AKT were reduced in FFC-EtOH. **Conclusion:** Similar to NAFLD and ALD, SMAFLD induces immune signaling, an inflammatory environment, and glucose intolerance prior to histologic inflammation. The FFC and FFC-EtOH hepatic transcriptome have increased inflammatory signaling, specifically with inflammasome activation. However, at early stages of disease development, hepatic metabolites and other compensatory mechanisms may prevent histologic inflammation. Our study reveals the molecular and transcriptomic profile of early SMAFLD by the dysregulation of Cers, metabolic signaling, and inflammation. These metabolic targets at this early stage of SMAFLD may be used to develop therapeutics to prevent disease progression.

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2291-C | DASATINIB AND QUERCETIN AS SENOLYTICS ATTENUATE FAT DEPOSITION AND HAVE ANTIFIBROTIC EFFECTS IN MEDAKA NONALCOHOLIC STEATOHEPATITIS MODEL

Hiroyuki Abe[1], Shunta Yakubo[1], Norihiro Sakai[1], Yusuke Watanabe[1], Naruhiro Kimura[1], Toru Setsu[1], Takeshi Yokoo[1], Akira Sakamaki[1], Hiroteru Kamimura[1], Atsunori Tsuchiya[1], Kenya Kamimura[2] and Shuji Terai[1], (1)Graduate School of Medical and Dental Sciences, Niigata University, (2)School of Medicine, Niigata University

Background: Non-alcoholic steatohepatitis (NASH) is known to cause cellular senescence due to the effects of oxidative stress, endoplasmic reticulum stress, and autophagy in the liver caused by ectopic fat deposition. Recently, senolytic drugs to eliminate senescent cells have been reported, including a combination of dasatinib, an antitumor agent, and quercetin, a flavonoid used as a dietary supplement. In the present study, we evaluate the efficacy of dasatinib and quercetin as senolytic drug in NASH medaka model. **Methods:** Medaka fish were fed high-fat diet (HFD) for 7 weeks inducing to NASH. The models were kept in the tank with and without dasatinib (1.0 mg/L) and quercetin (0.01 mg/L) dissolved for the last week of treatment. Body weight, liver weight ratio, and histological fat deposition were evaluated to validate treatment efficacy. Fibrosis-related genes were analyzed by quantitative PCR. **Results:** Body weight was 0.41 ± 0.07 g in the normal diet group, 0.49 ± 0.05 g in HFD group, and 0.40 ± 0.06 g in the treatment group, showing an improvement in the treatment group ($P < 0.001$). Hepatic weight ratio was 0.016 ± 0.008 in the normal diet group, 0.034 ± 0.010 in HFD group, and 0.019 ± 0.006 in the treatment group, indicating improved hepatomegaly in the treatment group compared to HFD group ($P < 0.01$). Histologically, area of fat deposition in the liver was 21.4 ± 8.9% in the normal diet group, 40.1 ± 13.2% in HFD group, and 18.4 ± 13.9% in the treatment group, indicating improved fat deposition in the treatment group compared to HFD group ($P < 0.01$). The transcript levels of Col1 were 1.31 ± 0.39 fold in HFD group and 0.26 ± 0.29 fold in the treatment group compared to the normal diet group ($P < 0.001$). The transcript levels of Timp2b was 21.78 ± 36.11 fold in HFD group and 0.12 ± 0.08 fold in the treatment group compared to the normal diet group ($P < 0.01$). The transcript levels of TGF1 was 122.06 ± 171.03 fold in HFD group and 0.47 ± 0.51 fold in the treatment group compared to the normal diet group ($P < 0.05$). **Conclusion:** Dasatinib and quercetin improve body weight, liver weight ratio, and histological fat deposition in NASH, and decrease fibrosis-related gene expression, suggesting that they may be useful in the treatment of hepatitis and its associated fibrosis. Both drugs have been used as clinical therapeutic agents or supplements, which are expected to have potential for clinical application.
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2292-C | DEFINITIVE SENESCENCE PHENOTYPES OF HEPATIC STELLATE CELLS (HSCs), AND EXPRESSION OF SENOLYTIC TARGETS IN MURINE AND HUMAN NONALCOHOLIC STEATOHEPATITIS

Chittampalli N Yashaswini, Icahn School of Medicine at Mount Sinai

Background: Recent studies implicate senescent HSCs as a driver of NASH and HCC, which has led to efforts to deplete these cells using CAR-T cells that target urokinase plasminogen activator, a candidate marker of senescence. However, the expression of uPAR may not be restricted to HSCs. Our aims were to determine the cellular distribution of uPAR expression in murine and human NASH, and to establish the definitive phenotype of senescent HSCs. **Methods:** Immunofluorescence, immunohistochemistry, senescence-associated beta galactosidase assays, bulk RNA sequencing, single nuclear RNA sequencing and single cell RNA sequencing were used to characterize patterns of HSC senescence and uPAR expression in human NASH and in a well validated mouse model of NASH (doi: 10.1016/j.jhep.2018.03.011). **Results:** Senescence markers are increased in murine and human NASH compared to healthy samples; regions of senescence in murine NASH overlap with HSC distribution. Senescent HSCs are in close proximity to macrophages, and single nuclear RNA sequencing indicates the presence of senescent HSCs in murine and human datasets that express uPAR. Expression of uPAR fluctuates in intensity and cell-specificity throughout the progression of human and murine NASH. uPAR expression is strongest in early NASH, when it is most restricted to HSCs, but as NASH progresses, it is increasingly detectable in cells of myeloid lineage. Based on single cell RNA sequencing of murine NASH, uPAR is strongly expressed by neutrophils and non-inflammatory macrophages. Anti-uPAR CAR T cell treatment in murine NASH slightly reduces fibrosis, along with efficient depletion of neutrophils and macrophages. In patients with NASH there is increased HSC senescence, with significantly more HSCs expressing uPAR. Cells of monocyte lineage strongly express uPAR in patients with NASH as well. **Conclusion:** We have documented the presence of senescent cells in murine and human NASH. These data are the first comprehensive characterization of hepatic uPAR expression in human and murine NASH, demonstrating that uPAR is not only present in senescent HSCs, but also expressed by myeloid cells (neutrophils and non-inflammatory macrophages), proportionate to the severity of NASH. Our findings reinforce the therapeutic potential of anti-uPAR CAR T cell therapy in patients with NASH, but also suggest that CAR T-mediated clearance of both senescent HSCs and immune cells may contribute to its efficacy.

Disclosures: The following people have nothing to disclose: Chittampalli N Yashaswini

2293-C | DELETION OF CARNITINE PALMITOYLTRANSFERASE 1a FROM THE LIVER REDUCES HEPATIC POLYUNSATURATED FATTY ACIDS AND DRIVES MICROVESICULAR STEATOSIS IN FEMALE MICE

Mikala M. Zelows[1], Corissa Cady[1], Zachary Kipp[1], Evelyn Bates[1], Anna Mead[1], Nikitha Dharanipragada[1], Se-Hyung Park[1], Harrison A. Clark[2], Tara R. Hawkinson[2], Terrymar Medina[2], Ramon C. Sun[2], Todd A. Lydic[3], Terry Hinds[1], Samir Softic[1], Gregory A. Graf[1] and Robert N. Helsley[1], (1)University of Kentucky, (2) University of Florida, (3)Michigan State University

Background: Loss-of-function mutations in carnitine palmitoyltransferase 1a (CPT1a) associate with reductions in circulating polyunsaturated fatty acids (PUFAs). Loss of hepatic PUFAs contributes to the progression from nonalcoholic fatty liver disease (NAFLD) to more severe nonalcoholic steatohepatitis (NASH). Therefore, the goal of this study was to determine the impact of liver-specific CPT1a deletion (LKO) on PUFA metabolism and NAFLD. **Methods:** Eight-week old male and female LKO (*Cpt1a*$^{\Delta Alb}$) and littermate controls (*Cpt1a*$^{F/F}$) were placed on a low-fat or high-fat diet (HFD; 60% kcal fat) for 15 weeks. Glucose and insulin tolerance tests were completed after 10 and 12 weeks on the diet, respectively. Mice were necropsied after a 16 hour fast to induce hepatic fatty acid oxidation, and tissues and serum were collected and utilized for shotgun lipidomics, matrix-assisted laser desorption ionization for mass spectrometry imaging (MALDI-MSI), bulk RNA sequencing, histology, transmission electron microscopy, and protein expression by immunoblotting. **Results:** Male and female LKO mice did not exhibit a difference in total body weight or adiposity. Male LKO mice displayed improved insulin sensitivity, had lower circulating alanine aminotransferase (ALT) levels, but did not exhibit changes in hepatic triglycerides or cholesterol levels as compared to male control mice. Female LKO mice, however, displayed significant increases in serum ALT levels which associated with greater deposition of hepatic triglycerides and cholesterol, as compared to female control mice. Histologically, female LKO mice displayed diffuse, panlobular microvesicular steatosis, while male LKO mice exhibited slight periportal steatosis. Shotgun lipidomics revealed female LKO mice exhibited reductions in EPA and DHA-containing phospholipids. Utilizing MALDI-MSI, we observed spatial heterogeneity of 38:6 and 40:6 PE species in control mice, which was absent with *Cpt1a* deficiency. Bulk RNA-sequencing analysis revealed that male LKO mice increased PPARα-target genes involved in mitochondrial (*Cpt2*, *Acadm*) and peroxisomal oxidation (*Acaa1b*, *Acox1*), while female LKO mice increased genes more involved in lipid droplet formation (*Plin2*, *Plin5*, *Cidec*) and inflammation (*Tnfa*, *Cd63*, *Mmp12*). Consistent with gene expression, protein levels of PLIN2, PLIN5, and G0S2 were significantly elevated in female LKO mice, which associated with impaired protein kinase a (PKA)-mediated triglyceride hydrolysis in these mice. **Conclusion:** Liver specific deletion of CPT1a promotes sexually dimorphic NAFLD in female mice without influencing body weight or adiposity. Mechanistically, female LKO deplete their hepatic PUFAs and increase expression of genes involved in lipid droplet metabolism and inflammation, which collectively contribute to the more severe NAFLD observed in these mice.

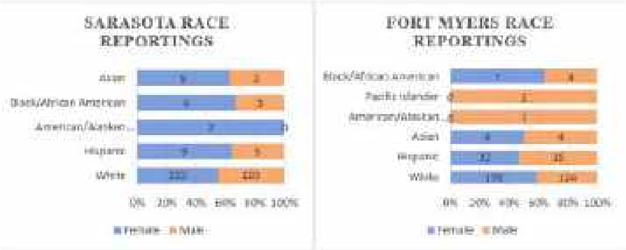
Disclosures: The following people have nothing to disclose: Mikala M. Zelows, Robert N. Helsley

Disclosure information not available at the time of publication: Corissa Cady, Zachary Kipp, Evelyn Bates, Anna Mead, Nikitha Dharanipragada, Se-Hyung Park, Harrison A. Clark, Tara R. Hawkinson, Terrymar Medina, Ramon C. Sun, Todd A. Lydic, Terry Hinds, Samir Softic, Gregory A. Graf

2294-C | DEMOGRAPHIC OUTCOMES INVOLVING PRESCREENING FOR NAFLD

Jessica Kiarra King[1], Austin Vaughn[1], Joshua T. Ghansiam[1], Anna H.T. Nguyen[1], Gabrielle Bachtel[1], Brandon A Kapalko[1], Guy W. Neff[2] and Jasmine Tidwell[1], (1)Covenant Metabolic Specialists, LLC, (2) Tampa General Medical Group, Bradenton, FL

Background: As the prevalence of NAFLD increases, challenges are fraught with diagnosing this silent epidemic. Improvements are needed in noninvasive testing to identify NAFLD. And because few NAFLD patients present with disease state symptoms, the prevalence of NAFLD is continuing to increase. Work to educate and raise awareness has been disappointing which has led to vast demographic changes in clinical patients, with limited therapeutic options. The purpose of this project is to evaluate demographic settings of at risk NAFLD patients within a large clinical site network. **Methods:** A retrospective review of medical records of patients referred for NAFLD prescreening from 11/1/2021 to 4/30/2023 was conducted. Demographic information was collected and included gender, age, ethnicity, and BMI. Reports for overall NAFLD groups were broken into, White, Black/African American, Asian, American/Alaskan American, Non-Hispanic, and Hispanic. Total patients included in the study at the Sarasota location was 449, while at the Fort Myers location, it was 375. Patient demographic outcomes were collected from patient intake forms. **Results:** Total patients included in the study at the Sarasota location was 449, while at the Fort Myers location, it was 375. The review of data reveals an average age reporting of 59.4 and 56.2 at the Sarasota (SRQ) and Fort Myers (FTM) locations respectively. While average BMI found was 32.8 (SRQ) and 34.5 (FTM). Total female patients referred to both locations amounted to 469, while male patients referred to both locations totaled 315. Patients reporting as Non-Hispanic were 388 (SRQ) and 260 (FTM), totaling 648. While Patients reporting as Hispanic/Latino were 31 (SRQ) and 109 (FTM), totaling 140. While no correlation could be drawn from BMI or age, the data provided indicates a higher percentage of Non-Hispanic White women seeking treatment for NAFLD. **Conclusion:** The above results show a striking contrast to reported NAFLD prevalence data. The data is comparable to general medicine prevalence outcomes with Non-Hispanic white women presenting for healthcare utilization at a much greater rate than other groups. This above data collected suggests NAFLD population may vary geographically, and white females tend towards healthcare utilization for NAFLD assistance.



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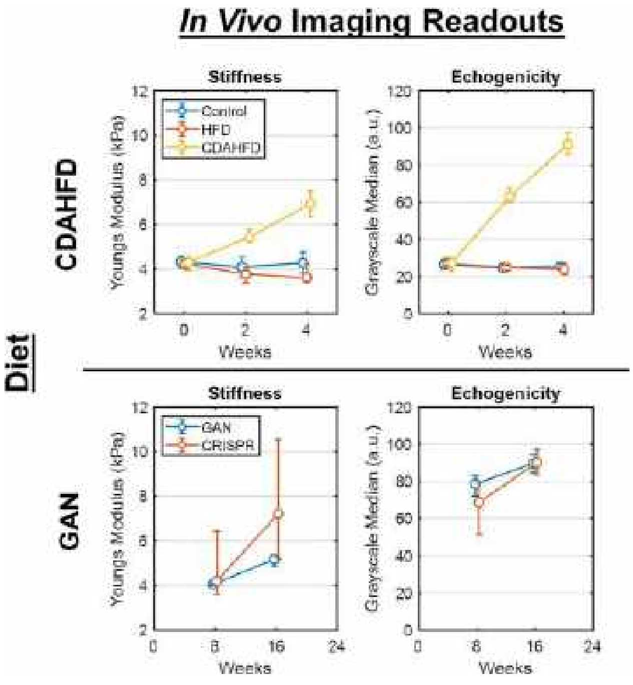
2295-C | DEMONSTRATION OF AN AUTOMATED IN VIVO RESEARCH TOOL FOR QUANTITATIVE NON-INVASIVE 3D ASSESSMENT OF LIVER DISEASE PHENOTYPES IN MULTIPLE NASH MOUSE MODELS

Tomasz Czernuszewicz[1], Alvin Chan[2], Kelsey Jarrett[2], Christopher Hamad[2], Zara Mamouei[1], Juan D Rojas[1], Thomas Kierski[1], Brian Velasco[3], Phillip G Durham[3], Kevin Francis[1], Nicholas Bernthal[2], Paul A Dayton[3], Thomas Vallim[4] and Ryan Gessner[1], (1)Revvity, (2) UCLA, (3)UNC Chapel Hill, (4)University of California, Los Angeles

Background: Ultrasound can be used to non-invasively stage NASH-related phenotypes (e.g. steatosis and fibrosis). These imaging tools are widely implemented in the clinic, and have recently been adapted for small animal use in a flatbed robotic in vivo imaging system. Our goal was to extend this platform's existing capabilities to enable 3D shear wave elastography (SWE) captures for more comprehensive whole-organ scanning, and high throughput acquisition. Noninvasive evaluation is of particular interest in rodent models, as individual mice can be tracked over time, each being their own controls in longitudinal studies. **Methods**: A prototype Vega system (Revvity, Inc.) was programmed to include 3D wide-field SWE region-of-interest (ROI) placement and stepped scanning. The 3D SWE workflow consisted of: (1) a wide-field multi-focal-zone 3D B-mode continuous scan to locate the liver; (2) a 3D ROI bounding box encompassing the left lateral/medial lobes using the gall bladder and stomach as landmarks; (3) a 3D SWE stepped scan acquired. B-mode and SWE capture regions were approximately 40x30 mm and 15x5 mm, respectively (1.0 mm step size). Reconstruction included voxel filling with importance-

mask blending. For analysis, 3D segmentations were defined to quantify median liver stiffness and median grayscale intensity for each liver. To demonstrate feasibility, the system was tested in several different preclinical rodent models for liver disease, including Controls (N = 8), HFD (N = 16), CDAHFD (N = 16), GAN diet (N = 5), and novel CRISPR modified mice (N = 5) over 5 timepoints between 0 and 16 weeks on diet. **Results**: The 3D images collected with the Vega scanner revealed significant increases in both liver brightness and stiffness (both have been shown previously to correlate with steatosis and fibrosis respectively) in the CDAHFD and CRISPR models of liver disease ($p < 0.05$). The HFD model had not yet increased either parameter within the first month of the study. The system was also high throughput, with median scan and analysis time per animal of < 6 min (including analysis). The 3D SWE acquisition required over half the time per animal due to stepped scanning approach and transducer cool down delays between each step. **Conclusion**: 3D SWE scanning using hands-free stepped scanning is feasible, and produces consistent liver stiffness and echogenicity measurements in different mouse models of liver disease. Future studies will look to improve throughput speed and evaluate the sensitivity of the instrument in treatment response studies.



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Disclosure information not available at the time of publication: Tomasz Czernuszewicz, Christopher Hamad, Zara Mamouei, Juan D Rojas, Thomas Kierski, Brian Velasco, Phillip G Durham, Kevin Francis, Nicholas Bernthal, Paul A Dayton, Thomas Vallim

2296-C | DEVELOPING A TRANSLATIONAL BIOMARKER PANEL FOR USE IN PRE-CLINICAL ADVANCED IN VITRO STUDIES OF NON-ALCOHOLIC STEATOHEPATITIS

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Background: Significant effort has been made to identify non-invasive clinical biomarkers for non-alcoholic steatohepatitis (NASH) and to profile proteomic and transcriptomic changes in the different stages of disease progression. Pre-clinical animal models predominantly used to study NASH often express irrelevant pathways and expression profiles that do not mirror the human disease and therefore many translational biomarkers cannot be used consistently in these studies. The need for more human relevant pre-clinical models has led to the development of microphysiological systems (MPS) that model the human liver and NASH. For MPS NASH models to be effective tools in assessing the efficacy of novel therapeutics they must express a wide range of translational biomarkers. In this study we evaluated the profile of a collection of translational biomarkers in a well characterised NASH MPS model and determined whether their expression was altered following treatment with several probe anti-NASH compounds. **Methods:** Here we used the PhysioMimix™ MPS NASH assay that comprised a mix of highly differentiated primary hepatocytes with primary Kupffer and stellate cells, which are challenged with a media containing free fatty acids to induce a NASH phenotype. The profiles of twenty soluble (e.g. IL-6, IL-8, MCP-1 MMP1, CRP, TIMP-1) and microscopy biomarkers (e.g. collegen-type-1) with evidence of expression in clinical studies were assessed in up to six different donor combinations of primary cells in the NASH MPS model. We explored what effects ASK1 inhibition, SCD1 inhibition or CCR2/5 inhibition would have on the expression of these biomarkers in the NASH MPS model. **Results:** We observed dynamic changes in the expression of inflammasome markers in the MPS NASH model, with significant expression of IL-6, IL-8 and MCP-1 whilst levels of MMP1 and Lipocalin-2 were found to decrease at longer timepoints, as more advanced fibrosis occurred. Fibrotic biomarkers were also expressed with profiles in the NASH MPS consistent with clinical findings. For example, thrombospondin-2 which is highly predictive for advanced fibrosis in patients (> F3) was found to increase over time in the MPS NASH model. Anti-NASH compounds tested on the MPS NASH model demonstrated efficacy on both inflammasome and fibrosis biomarkers, with most significant changes observed following SCD1 inhibition and CCR2/5 inhibition but limited effects of ASK-1 inhibition. **Conclusion:** Here we profile a range of clinically relevant NASH biomarkers in a MPS human liver model and demonstrate the expression of many of these biomarkers are altered, following therapeutic intervention, in a similar manner as observed clinically. We propose the set of biomarkers identified here could be used more widely across other pre-clinical models of NASH to standardise experimental design and data generation.

Disclosures: The following people have nothing to disclose: Tudor Petreus, Ovidiu Novac, Raul Silva, Yassen Abbas, Tomasz Kostrzewski

2297-C | DEVELOPMENT OF A NOVEL IN VITRO MITOCHONDRIAL TOXICITY TEST BASED ON ATP INHIBITION SUBSTRATE ASSAY

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Background: Mitochondrial toxicity has led to the withdrawal of numerous drugs from the market, highlighting the importance of assessing mitochondrial dysfunction during drug development. However, there is currently a lack of globally accepted methods for evaluating mitochondrial toxicity. Therefore, the objective of this study was to propose a protocol for assessing mitochondrial toxicity. **Methods:** Mitochondrion-associated transcriptome analysis was conducted on liver samples obtained from patients with non-alcoholic fatty liver disease (NAFLD) and healthy individual's. Mitochondrial dysfunction was induced in H9C2 and HepG2 cells through treatment with doxorubicin, a chemotherapeutic agent known to cause mitochondrial dysfunction. The ATP inhibition substrate test, as well as mitochondrial DNA (mtDNA) copy number analysis, was performed on peripheral blood samples collected from patients before and after chemotherapy administration. **Results:** Analysis of hepatic mRNA transcriptome revealed upregulated expression of genes associated with the mitochondrial tricarboxylic acid (TCA) cycle and mitochondrial envelope in NAFLD patients, who exhibit characteristic mitochondrial dysfunction. Treatment with doxorubicin led to concentration-dependent cytotoxicity and decreased ATP levels in H9C2 and HepG2 cells. Furthermore, increased levels of reactive oxygen species (ROS) and disrupted mitochondrial cristae were observed, contributing to a significant reduction of ATP by more than 40-50%. In addition, the proposed ATP inhibition substrate test demonstrated decreased ATP levels in the peripheral blood of patients before and after chemotherapy administration. The mtDNA copy number, an indicator of mitochondrial dysfunction, was also reduced. **Conclusion:** The ATP inhibition substrate test represents a promising approach for assessing mitochondrial toxicity. By measuring ATP levels, this novel assay provides a valuable tool for evaluating drug-induced mitochondrial dysfunction and its potential implications in drug development and patient care.

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2298-C | DIFFERENTIAL ANTI-FIBROTIC EFFECTS OF SEMAGLUTIDE AND LANIFIBRANOR DEMONSTRATED BY AI-DIGITAL PATHOLOGY IN THE BIOPSY-CONFIRMED GAN DIO-NASH MOUSE MODEL WITH ADVANCED FIBROSIS AND HCC

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Background: Non-alcoholic steatohepatitis (NASH) increases the risk for the development of liver fibrosis which may progress to cirrhosis and hepatocellular carcinoma (HCC). Semaglutide (glucagon-like-receptor 1 agonist) and lanifibranor (pan-peroxisome proliferator-activated receptor agonist) are currently in late-stage clinical development for NASH. The present study aimed to evaluate the efficacy of semaglutide and lanifibranor monotherapy on disease progression in the Gubra Amylin NASH (GAN) diet-induced obese (DIO) model with biopsy-confirmed advanced fibrosing NASH and HCC (GAN DIO-NASH-HCC), using both stain and stain-free artificial intelligence (AI)-digital pathology. **Methods:** Paired-biopsy samples from the GAN DIO-NASH-HCC model (52 weeks of diet) treated for 16 weeks with either vehicle, 30 mg/kg lanifibranor or 30 nmol/kg semaglutide (N = 15-17 animals/group) were included. Histopathological NAFLD Activity Score and Fibrosis Stage were first evaluated by Gubra Histopathological Objective Scoring Technique (GHOST) AI-deep learning-based image analysis on HE and PSR stained images. Next, more nuanced features of fibrosis and steatosis were also examined using stain-free images captured by Second-harmonic generation/two-photon excitation fluorescence (SHG/TPEF) microscopy (Genesis®200, HistoIndex Pte Ltd, Singapore) from formalin-fixed paraffin-embedded liver tissues, where AI-based algorithms recognized three zones, namely portal tract (PT), central vein (CV) and peri-sinusoidal (PS) for zonal analysis. Multiple parameters of steatosis and fibrosis, including their distribution, composition as well as co-localization changes, were quantified and compared among intervention groups. **Results:** Semaglutide and lanifibranor promoted e 2-point significant improvement in NAFLD Activity Score, via reduced numbers of hepatocytes with lipids and inflammatory foci evaluated by GHOST deep-learning. Neither semaglutide nor lanifibranor significantly improved fibrosis stages; however, SHG/TPEF AI-based microscopy revealed that lanifibranor improved fibrosis in the PS zone and in the portion that is colocalized with both macro- and micro-steatosis, while semaglutide improved fibrosis specifically in the area colocalized with macro-steatosis, which is one of the key features to characterize human NAFLD and is also the majority of steatosis found in this animal model. **Conclusion:** Our study demonstrated that stain-free AI digital pathology provides the sensitivity to detect differential fibrosis improvement in the GAN DIO-NASH-HCC mouse model treated with lanifibranor or semaglutide, which may have not been evident by fibrosis staging alone. Fibrosis zonal and co-localization analyses have the potential in providing insights into disease biology and drug mechanisms of action.

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Susanne E. Pors – Gubra: Employee, Yes, No;

Michael Feigh – Gubra: Employee, Yes, No; Gubra: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No; Gubra: Executive role , Yes, No;

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f 2299-C | DISSECTING THE ROLES OF THE TWO HOMOLOGOUS PHOSPHOLIPID SCRAMBLASES: TMEM41B AND VMP1, IN NAFLD/NASH

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Background: Transmembrane Protein 41B (TMEM41B) and Vacuolar Membrane Protein 1 (VMP1) are homologous endoplasmic reticulum (ER)-resident scramblases with important roles in autophagy and VLDL secretion. Hepatic loss of these proteins leads to defective autophagy and rapid development of non-alcoholic steatohepatitis (NASH) in mice. Previous studies showed that VMP1 over-expression alleviates choline-deficient amino acid-defined high-fat diet (CDAHFD)-induced NASH in mice (PMID:35452693). However, whether TMEM41B has related, albeit distinct roles from VMP1 in regulating autophagy and VLDL secretion in mouse livers is unknown. **Methods:** Liver-specific TMEM41B knockout (L-TMEM41B KO), TMEM41B KO/VMP1 KI (KOKI), and TMEM41B/VMP1 double knockout (DKO) mice were generated by crossing with Albumin-Cre mice. Serum and liver were assayed at 1, 2, and 4 months for short-and long-term changes associated with scramblase expression changes. **Results:** L-TMEM41B single KO mice had massive hepatic steatosis by 1 month with a decrease in VLDL secretion. L-TMEM41B KO mice also had increased liver LC3-II and p62 levels, confirming autophagy defect. Lipidomics analysis revealed decreased hepatic phospholipids in L-TMEM41BKO mice. Transmission electron microscopy and western blot in TMEM41B KO hepatocytes revealed decreased MAM structure and levels of PSD1 and PEMT, two enzymes critical for mitochondrial-associated ER membrane (MAM) phospholipid (PL) synthesis. Cellular fractionation identified TMEM41B and VMP1 are localized on MAM. Strikingly, defective VLDL secretion, hepatic steatosis, and LC3-II and p62 accumulation significantly resolved in 2- and 4-month-old L-TMEM41B KO mice. Impaired VLDL secretion and hepatic steatosis partially resolved in 1-month-old KOKI mice, but not increased LC3-II and p62, suggesting VMP1 may improve impaired VLDL secretion but not autophagy defect. DKO mice had impaired VLDL secretion, hepatic steatosis, and inflammation at 1 month, though they also recovered from hepatic steatosis and impaired VLDL secretion, suggesting adaptive response for VLDL secretion. Lineage tracing assay revealed clonal expansion of hepatocytes possibly derived from hepatic progenitor cells that may assist in L-TMEM41B KO and DKO mice recovery. **Conclusion:** Lack of VMP1 or TMEM41B leads to impaired VLDL secretion and steatosis that can be reversed via selective clonal hepatocyte expansion. VMP1 overexpression may partially compensate for loss of TMEM41B with respect to lipid accumulation, though it has little effect on autophagy.

Disclosures: Wen-Xing Ding: WEN-XING DING, Hong-Min Ni

2300-C | DOXAZOSIN INHIBITS PALMITIC ACID-INDUCED LIPOTOXICITY IN PRIMARY RAT HEPATOCYTES BY INHIBITING THE GENERATION OF REACTIVE OXYGEN SPECIES

Sandra A. Serna Salas[1], Magnolia Martínez[2], Aniek Vlasma[3], Manon Buist-Homan[2] and Han Moshage[1], (1) University Medical Center Groningen, (2)University Medical Center of Groningen, (3)Umcg

Background: Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) is the most common liver disorder worldwide. It is associated with excessive accumulation of lipids in the liver. The deleterious effects of this accumulation of lipids is termed lipotoxicity. Lipotoxicity can induce cell death, persistent inflammation and eventually lead to fibrosis, cirrhosis and hepatocellular carcinoma. Doxazosin is a synthetic drug with alpha-1 adrenergic antagonistic properties. Moreover, it has anti-inflammatory properties and has been shown to reduce fibrogenesis. Aim: to elucidate whether doxazosin can protect against palmitic acid-(PA)-induced lipotoxicity in primary rat hepatocytes. **Methods:** Primary rat hepatocytes (rHeps) were challenged with PA at 1 mmol/L or 250 µmol/L. Cell death was determined by Sytox green staining and caspase-3 activity. Lipid accumulation was assessed by Oil Red O and Bodipy staining using oleic acid as a positive control. Triglyceride (TG) content was also measured. ROS generation was analyzed by MitoSox and endoplasmic reticulum stress markers were determined using qPCR and Western blot. **Results:** Cell necrosis and apoptosis were significantly induced by PA in a dose dependent manner. Doxazosin (DX) protected rHep from PA-induced cell death by either apoptosis or necrosis. Lipid accumulation was slightly increased by PA and strongly by OA. DX did not modulate the accumulation of lipids within rHeps. ROS generation by PA was abolished by DX. ER stress markers were not diminished by DX in rHep in the presence of PA, but phosphorylated JNK was significantly reduced by DX in PA-treated hepatocytes **Conclusion:** DX protects rHep against PA-induced cytotoxicity. DX reduces the generation of mitochondrial ROS and the phosphorylation of JNK which explains the protective effect of DX against hepatocyte cell death.

Disclosures: The following people have nothing to disclose: Sandra A. Serna Salas, Magnolia Martínez, Aniek Vlasma, Manon Buist-Homan, Han Moshage

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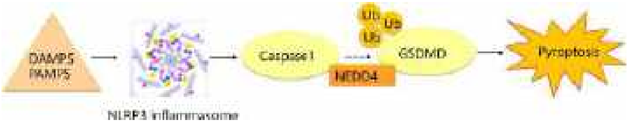
2301-C | E3 UBIQUITIN LIGASE NEDD4 IS A KEY NEGATIVE REGULATOR FOR GSDMD-MEDIATED PYROPTOSIS IN NON-ALCOHOLIC STEATOSIS

Rui Jin, Xiaoxiao Wang, Baiyi Liu, Zilong Wang, Yuyun Song, Xiaohe Li, Feng Liu and Huiying Rao, Peking University People's Hospital, Peking University Hepatology Institute, Beijing Key Laboratory of Hepatitis C and Immunotherapy for Liver Diseases, Beijing International Cooperation Base for Science and Technology on NAFLD Diagnosis

Background: Pyroptosis mediated by GSDMD is thought to be involved in NASH development, but the roles of GSDMD in the pathogenesis of NASH are not fully understood. In this study, we aim to illustrate the exact regulation mechanisms of GSDMD in NASH. **Methods:** We knocked down hepatocellular GSDMD and Caspase-1 in mice via the CRISPR-AAV-Sacas9 system respectively, and mice fed a methionine-choline deficient (MCD) diet to induce NASH. After confirming the pathway of pyroptosis in NASH mice, Co-IP and multidimensional mass spectrometry(MS) was performed to identify the ubiquitinates/deubiquitinases co-acting with GSDMD. NEDD4 was knocked known or overexpressed in mice livers by injection of AAV vectors. 293T and AML12 cells were used for in vitro studies. **Results:** We confirmed the canonical inflammasome pathway in MCD-induced NASH mice by detecting the increased protein levels of NLRP3, GSDMD, GSDMD-N, Caspase-1, and Caspase-1 P20 in NASH mice. The knockdown of hepatocellular GSDMD or Caspase-1 could ameliorate pathological manifestations in NASH mice. Interestingly, we found that GSDMD mRNA levels were downregulated in NASH mice compared with control mice, a discrepancy between GSDMD mRNA levels and GSDMD protein levels indicated that GSDMD protein might undergo post-translational modifications. And we found that ubiquitination levels of GSDMD, especially K48 polyubiquitination levels of GSDMD were decreased in the liver of NASH mice compared with control ones. The knockdown of Caspase-1 could decrease the protein level of GSDMD and increase the ubiquitination levels of GSDMD but did not affect GSDMD mRNA, indicating that Caspase-1 might not directly regulate GSDMD. Multiple ubiquitinates/deubiquitinases co-acting with GSDMD were identified by co-IP combined with MS. The interaction between NEDD4 and GSDMD was confirmed by further co-IP both in vivo and in vitro. It was found that the knockdown of NEDD4 in AML12 cells can up-regulate the protein expression level of GSDMD, and the overexpression of NEDD4 can reduce the protein expression level of GSDMD. We also confirmed the overexpression of NEDD4 can increase the k48-linked polyubiquitination of GSDMD in 293T cells and AML12 cells, the ubiquitination of GSDMD was significantly reduced after PA and LPS treatment in AML12 cells. Besides, the knockdown of Caspase-1 could increase the protein levels of NEDD4. The overexpression of NEDD4 in mice liver could decrease the protein levels of GSDMD, and increase the the k48-linked polyubiquitination of GSDMD while. In NASH mice, the overexpression of NEDD4 effectively reduced the protein levels of GSDMD and GSDMD-N compared with OE-Vector group. **Conclusion:** NEDD4 directly interacts with GSDMD, and mediates k48-linked polyubiquitination of GSDMD, regulating the protein level of GSDMD in NASH. Our findings revealed NEDD4 is a key negative regulator of GSDMD, GSDMD ubiquitination may be considered as a novel therapeutic target for NASH.



Disclosures: The following people have nothing to disclose: Rui Jin, Xiaoxiao Wang, Baiyi Liu, Zilong Wang, Yuyun Song, Xiaohe Li, Feng Liu, Huiying Rao

2302-C | EFFECTS OF HEPATOCYTE-SPECIFIC DELETION OF EGFR IN A DIET-INDUCED NAFLD MOUSE MODEL

Shehnaz Bano, Matthew Avery Copeland, Anne Orr, Silvia Liu, Joseph Locker, John Stoops, Wendy M. Mars, George K. Michalopoulos and Bharat Bhushan, University of Pittsburgh

Background: Nonalcoholic fatty liver disease (NAFLD) is a most prevalent liver disorder that is linked to an increased risk of developing liver fibrosis and hepatocellular carcinoma. Epidermal growth factor receptor (EGFR) is well known to regulate hepatocyte proliferation and regeneration in liver. In our previous study, we found that chemical inhibition of EGFR utilizing Canertinib, dramatically reduced hepatocyte steatosis, liver injury, and fibrosis, in a murine fast-food diet (FFD) model, indicating a potential role for EGFR in regulating NAFLD. **Methods:** We extended our studies of the EGFR role in NAFLD by investigating the effect of hepatocyte-specific EGFR deletion in a murine NAFLD model. 8-10 weeks old EGFR$^{flox/flox}$ mice were injected adeno associated virus 8 (AAV-8) expressing Cre recombinase with a thyroxin binding globulin (TBG) promoter (hepatocyte-specific promoter) to knockout EGFR in hepatocytes (EGFR KO). The EGFR KO or wild-type (WT) mice were fed normal chow diet or FFD for 2 months. **Results:** FFD-fed EGFR KO mice displayed significant reduction in serum triglyceride levels with histologically evident lower fat accumulation, mainly in the periportal areas of liver, compared to WT mice. At transcriptional level, EGFR deletion significantly reduced expression of SREBF1 (a major transcriptional regulator of fatty acid synthesis) along with its downstream fatty acid synthase gene and increased expression of lipolysis genes such as PNPLA2. FFD-fed EGFR KO mice showed lower protein expression of PPARγ compared to FFD-fed WT mice. Further, our transcriptomic analysis via RNA sequencing and subsequent Ingenuity Pathway Analysis revealed significant alteration of hepatic fibrosis/stellate cell activation pathways along with inhibition of TGFβ1 signaling (a key driver of liver fibrosis) in EGFR KO mice compared to FFD-fed WT mice. However, the overall effect of hepatocyte-specific EGFR deletion on steatosis and gene signatures associated with NAFLD was much weaker compared to systemic pharmacological inhibition observed in our previous study. Lastly, deletion of EGFR enhanced expression and phosphorylation of the other ErbB family members (HER2 and HER3), indicating a potential compensatory mechanism for the loss of EGFR signaling in hepatocytes. **Conclusion:** The hepatocyte-specific deletion of EGFR alters lipid metabolism and fibrosis signaling in a murine FFD model of NAFLD, but is much less effective compared to pharmacological inhibition of EGFR.

Disclosures: The following people have nothing to disclose: Shehnaz Bano, Bharat Bhushan

Disclosure information not available at the time of publication: Matthew Avery Copeland, Anne Orr, Silvia Liu, Joseph Locker, John Stoops, Wendy M. Mars, George K. Michalopoulos

2303-C | EFFECTS OF INDIVIDUAL BILE ACID FEEDING ON NON-ALCOHOLIC STEATOHEPATITIS DEVELOPMENT IN LOW BILE ACID MOUSE MODEL

Rulaiha E Taylor[1], Vik Meadows[2], Gina Capece[1], Veronia Basaly[1], Zakiyah Henry[1], Katherine D Otersen[1], Bo Kong[3] and Grace L. Guo[2], (1)Rutgers University, (2) Rutgers University, Piscataway, NJ, (3)Environmental and Occupational Health Sciences Institute, Rutgers, the State University of New Jersey, Piscataway, NJ

Background: Bile acids (BA) are synthesized in the liver from cholesterol and function as signaling molecules that aid in fat absorption and regulate lipid and glucose homeostasis. BA species selectively activate nuclear receptors, including the farnesoid X receptor (FXR), to regulate their synthesis and induce target gene expression including fibroblast growth factor 19 (FGF19). BA dysregulation is a key feature of liver diseases, such as nonalcoholic steatohepatitis (NASH), with modulation of the FXR-FGF19 axis as a promising therapeutic target for treatment. Acute feeding of individual BAs differentially affects lipid, inflammation, and oxidative stress pathways in low BA mice, *Cyp7a1/Cyp27a1* double knockout (DKO). The current study determines effects of individual BAs in the DKO mice on NASH development. **Methods:** Eight-week old male wild-type (WT) and DKO mice were fed a low-fat (LFD) or high-fat-high-sugar-high-cholesterol (HFHSD) diet composed of 49% sucrose, 20% fat, and 1.25% cholesterol containing vehicle (0% w/w) or individual BAs DCA (0.1% w/w); UDCA (0.1% w/w); CA (0.2% w/w) for 16 weeks. Serum and tissues were collected following feeding. Hepatic injury, steatosis, inflammation, and fibrosis were assessed by H&E, IHC, hepatic lipid extraction (cholesterol, triglycerides), and qPCR. **Results:** DKO mice on HFHSD were found to be insulin sensitive compared to WT diet controls. HFHSD DKO mice were resistant to weight gain and accumulation of white adipose tissue compared to WT mice, which was unaffected by BA feeding. DKO mice fed LFD CA and DCA had increased hepatic cholesterol and triglycerides compared to WT and DKO vehicle, while DKO mice fed HFHSD with CA or DCA only had elevated hepatic cholesterol compared to respective to vehicle. IHC and mRNA data suggest dietary exposure to CA or DCA, in LFD or HFHSD, induced inflammation in DKO mice compared to vehicle. Fibrosis was promoted in WT LFD CA and DKO HFHSD CA and DCA compared to respective vehicle groups per genotype. Individual BA feeding significantly altered classical BA synthesis pathway and subsequent downstream FXR gene expression in LFD treatments. UDCA acts as an intestinal FXR activator, while CA and DCA activate liver and intestinal FXR. **Conclusion:** UDCA may act as an intestinal FXR agonist in low BA states. Individual BAs, CA and DCA, promoted fibrosis and inflammation in WT mice on LFD and DKO mice on HFHSD. Significant alterations in lipid uptake and metabolism following BA feeding indicate differences in cholesterol and lipid handling across genotypes.

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Grace L. Guo: Grace guo

Disclosure information not available at the time of publication: Vik Meadows, Gina Capece, Katherine D Otersen

2304-C | EFFECTS OF URSODEOXYCHOLIC ACID ON NASH DEVELOPMENT IN MICE WITH HEPATIC DEFICIENCY OF FXR

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Background: Farnesoid X Receptor (FXR) has been identified as a therapeutic target for non-alcoholic steatohepatitis (NASH). FXR agonism and antagonism have both proven to be beneficial in the mitigation of NASH, leading to much controversy in the field, particularly regarding FXR signaling in the gut. The objective of this study was to determine the effects of ursodeoxycholic acid (UDCA), a postulated gut FXR antagonist, on the mitigation and prevention of NASH development in mice. **Methods:** Six- to eight-week-old male and female Liver FXR knockout ((*Fxr*$^{\text{floxed/floxed}}$, albumin Cre (+), *Fxr* LKO) and control (Cre-) mice were fed either a low-fat control diet or a NASH “Fast Food” (FF) diet (Western diet with 21% milk fat, 1.25% cholesterol, and 34% sucrose) both supplemented with 0.1% (w/w) UDCA for 16 weeks. Body weights were recorded weekly, and an oral glucose tolerance test (GTT) was performed at 3 months. Serum biochemistry was analyzed, and liver-to-body weight ratio was calculated. The expression levels of genes involved in NASH development were determined. Moreover, liver pathology was assessed, and immunohistochemistry staining was conducted for activated macrophages as an indirect measurement of inflammation. **Results:** Over the course of treatment, no alterations were seen in body weight, food intake, GTT, and serum biochemistry from UDCA feeding. Gene expression data showed that UDCA feeding resulted in a significant induction of *Fxr* in the ileum and a trending increase in the liver. The FXR target gene, *Fgf15*, was also significantly increased in the ileum of UDCA-fed mice. Lipocalin 2 (*Lcn2*) was induced by FF + UDCA-feeding, whereas lipocalin 13 (*Lcn13*) was obliterated by FF + UDCA feeding. Regarding bile acid synthesis, the gene expression results suggested that the classical pathway is upregulated in UDCA-fed mice. Furthermore, total serum levels of bile acids were significantly increased in FF-fed mice. **Conclusion:** The data strongly suggest that in contrast to the report that UDCA is a gut FXR antagonist, in this study, UDCA seems to act as an FXR agonist, especially in the ileum. In addition, UDCA may not be as protective in NASH development in male mice as originally reported, manifested by the increase in Lcn2, an inflammation indicator, and decrease in Lcn13, an FXR function indicator in male mouse livers, upon FF + UDCA feeding. This effect will be determined in female mice in the future.

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Grace L. Guo: Grace guo

Disclosure information not available at the time of publication: Syeda Maliha

2305-C | EFFECTS OF VERTICAL SLEEVE GASTRECTOMY IN MICE WITH INTESTINE SPECIFIC DEFICIENCY OF FIBROBLAST GROWTH FACTOR 15

Katherine Otersen[1,2], Bo Kong[3], Monica D. Chow[1,4], Andrew Wassef[1], Daniel Rizzolo[1,5], Somwya Yamathy[1], Vik Meadows[1], Rulaiha E Taylor[1], Laura Armstrong[6], Leonid Kagen[2], Yi-Horng Lee[7] and Grace L. Guo[2,3,8], (1) Rutgers University, Piscataway, NJ, (2)Department of Pharmacology and Toxicology, Rutgers, the State University of New Jersey, Piscataway, NJ, (3) Environmental and Occupational Health Sciences Institute, Rutgers, the State University of New Jersey, Piscataway, NJ, (4)University of Miami Leonard M. Miller School of Medicine, Miami, FL, (5)Charles River Laboratories, Wilmington, MA, (6)Bristol Myers Squibb, (7)Rutgers Robert Wood Johnson Medical School, Rutgers, the State University of New Jersey, New Brunswick, NJ, (8)Rutgers Center for Lipid Research, Rutgers, the State University of New Jersey, New Brunswick, NJ

Background: Obesity prevalence is rising and comorbidities like non-alcoholic liver disease (NAFLD), which impairs liver function and bile acid signaling, are of growing concern. Vertical sleeve gastrectomy (SGx), the surgical removal of 80% of the stomach, is the main medical intervention for weight reduction. The molecular mechanisms by which SGx improves liver disease in morbidly obese patients remains elusive. A key finding associated with SGx shows increased circulating bile acids (BAs) and fibroblast growth factor 19 (FGF19). The endocrine factor FGF15/19 (mouse FGF15, human FGF19) is highly expressed in ileal enterocytes and released postprandially to critically suppress BA synthesis in the liver. Emerging studies show that FGF15/19 improves energy expenditure and decreases body weight, providing a therapeutic strategy for obese patients. Therefore, we hypothesize that the resolution of NAFLD in mice undergoing SGx is due to the induction of FGF15 by increased BAs. **Methods:** The current study used wild-type (WT) and intestine-specific *Fgf15* knockout (*Fgf15*$^{ile-/-}$) mice fed a high-fat diet (HFD) for 3 months to induce obesity, at which point mice underwent sham surgery or SGx and were continued on HFD for 1-3 months. Following feeding determination of metabolic effects and gene expression changes were measured in all mice. **Results:** In obese WT mice, SGx produced improved metabolic effects including decreased weight and adiposity, improved insulin sensitivity, and diminished NAFLD progression. Interestingly, *Fgf15*$^{ile-/-}$ mice showed a marked improvement of metabolism including NAFLD characteristics compared to WT mice post-SGx. This improvement was also seen in the relative expression of genes involved in BA and lipid homeostasis. This includes decreased expression of genes associated with BA transport in the intestine and liver, increased BA synthesis and improved lipid metabolism. Despite improved NAFLD progression, *Fgf15*$^{ile-/-}$ mice showed increased inflammatory and fibrotic gene expression following SGx compared to WT mice. **Conclusion:** The marked improvement seen in Fgf*15*$^{ile-/-}$ suggests that the metabolic benefits and reversal of NAFLD progression may be associated with, but independent of, FGF15 induction. Since the *Fgf15*$^{ile-/-}$ mice had a larger BA pool size and maintained higher serum concentrations of BAs post-SGx, the improved metabolic effects associated with SGx may be due to increased serum levels and altered composition of BAs post-SGx.

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2306-C | ENDOGENOUS Has2-MEDIATED HYALURONAN SYNTHESIS LIMITS AGE-ASSOCIATED WEIGHT GAIN, ADIPOSE HYPERTROPHY, AND HEPATIC TRIGLYCERIDE CONTENT

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Background: Advanced physiologic age is often associated with increased body mass, fat to lean body mass ratio, and hepatic triglycerides (TG), and this can promote metabolic perturbations characteristic of non-alcohol associated fatty liver disease (NAFLD). Hyaluronan (HA), an extracellular matrix glycosaminoglycan, is increased in non-alcohol-associated steatohepatitis patient liver and blood, HA increases in parallel with fibrosis score, and hyaluronan synthase (*Has)2* mRNA correlates with increased plasma and hepatic HA content. While overexpressing *Has2* in hepatic stellate cells enhances liver fibrosis in mice, overexpressing *Has2* in hepatocytes and/or adipocytes reduces body mass, liver TG and adipocyte hypertrophy in a diet-induced mouse fatty liver disease model. Here, we tested the hypothesis that mice expressing only endogenous *Has2* (no functional Has1 or Has3) would be protected from age-associated weight gain, adipocyte hypertrophy, and hepatic steatosis. **Methods:** Female wild-type (WT) and *Has1,Has3* double knockout (*Has1,3* dko) mice were aged to 7 weeks (young) or 17 months (old) and fed normal mouse chow (5% calories from fat). Liver, white adipose tissue (WAT), and blood were collected; whole body and organ mass was measured. Liver TG was quantified using a biochemical assay. Adipocyte area

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was determined using ImageJ. Plasma HA was measured using an ELISA-like assay. **Results:** Plasma HA content did not differ between genotypes or with age but tended to be lower in *Has1,3* dko mice. All following study parameters were not different between young WT and young *Has1,3* dko mice. While both strains increased body mass with age, body mass doubled in old relative to young WT mice. Body mass increased only 30% in old *Has1,3* dko mice and was less than old WT mice. With age, WAT/body weight ratios increased in WT mice (0.8 +/- 0.1% young, 4.1 +/- 0.3% old) and *Has1,3* dko mice (0.8 +/- 0.01% young, 2.3 +/- 0.2% old) but this increase was 44% less in old *Has1,3* dko mice. Consistently, average adipocyte area doubled in WT mice while it increased only 1.5-fold with age in *Has1,3* dko mice and was less than WT mice. Finally, hepatic TG content increased with age in WT mice, but not in *Has1,3* dko mice. **Conclusion:** Together, these data suggest that HA synthesized by Has2 protects mice from age-associated alterations of liver and adipose tissue. Thus, increasing Has2-mediated HA production may offer therapeutic promise to limit progressive age-associated changes in metabolic tissues.

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2307-C | ENDOPLASMIC RETICULUM STRESS INDUCES HEPATIC STEATOSIS VIA CHAPERONE-MEDIATED AUTOPHAGY INHIBITION

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Background: Nonalcoholic fatty liver disease (NAFLD) progresses from steatosis (nonalcoholic fatty liver, NAFL) to nonalcoholic steatohepatitis (NASH). NAFL is characterized by the accumulation of lipids in hepatocytes, and endoplasmic reticulum (ER) stress is associated with hepatic lipid accumulation. Chaperone-mediated autophagy (CMA), a specific type of autophagy, facilitates the breakdown of lipid droplets (LD) by lysosomes. Using ER stress inducers and diet-induced NASH in mice, we investigated the molecular mechanism by which ER stress leads to impaired CMA activity and hepatic lipid accumulation. **Methods:** C57BL/6 mice were injected with tunicamycin through intraperitoneal injection. C57BL/6 mice were fed with a methionine-choline deficient diet (MCD) for 4 weeks, or a choline-deficient L-amino acid-defined high-fat diet (CDHFD) for 8 weeks for diet-induced NASH mice models. **Results:** Treatment of tunicamycin and thapsigargin (ER stress inducers) significantly decreased the protein level of LAMP2A, the critical regulator of CMA in primary mouse hepatocytes. Intraperitoneal injection of tunicamycin into mice led to reduced LAMP2A expression, along with an increase in CMA substrates, including LD-coated protein perilipin 2 (PLIN2), in the liver tissues. Treatment of CMA activator, AR7, or ER stress inhibitor, taurodeoxycholic acid, in primary mouse hepatocytes restored the level of PLIN2 induced by tunicamycin. Activating transcription factor 3 (ATF3), one of the transcription factors involved in regulating ER stress, was responsible for the reduction of LAMP2A expression under the ER stress condition. Knockdown of ATF3 with siRNA significantly induced the expression of LAMP2A, and overexpression of ATF3 decreased the expression of LAMP2A in primary mouse hepatocytes. Based on the GEO dataset (GSE48452), an inverse correlation was observed between the expression of LAMP2A and the severity grade of NASH in human liver samples from patients. We confirmed an increase in ER stress markers, including ATF3, and a decrease in LAMP2A expression in NASH livers induced by MCD or CDHFD in mice. **Conclusion:** Our findings revealed that ER stress induces lipid accumulation through the inhibition of CMA in liver. The upregulation of ATF3, caused by ER stress, led to the inhibition of CMA and subsequent hepatic lipid accumulation.

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Disclosure information not available at the time of publication: Karin Diggle, Tatiana Kisseleva, David A. Brenner, Byung-Hoon Lee

2308-C | ESCHERICHIA COLI PROMOTES ENDOTHELIAL TO MESENCHYMAL TRANSFORMATION OF LIVER SINUSOIDAL ENDOTHELIAL CELLS AND EXACERBATES NON-ALCOHOLIC FATTY LIVER DISEASE VIA ITS FLAGELLIN

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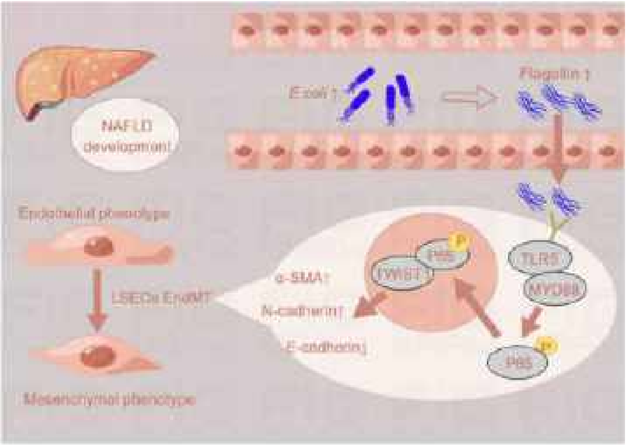
Background: Gut bacteria translocate into liver through disrupted gut vascular barrier, which is an early common event in the development of non-alcoholic fatty liver disease (NAFLD). Liver sinusoidal endothelial cells (LSECs) are directly exposed to the translocated gut microbiota in portal vein blood. *Escherichia coli* (*E.coli*), a gut commensal bacteria with flagella, is significantly enriched in gut microbiota in NAFLD patients. However, whether and how *E.coli* affect NAFLD progression remain unclear. **Methods:** The abundance of *E.coli* in a cohort of NAFLD patients and healthy controls was analyzed by 16S ribosomal RNA sequencing. The role of *E.coli* was estimated in NAFLD mice after 16 weeks of administration, and features of NAFLD were assessed. *E.coli*–derived epithelial to mesenchymal transition (EndMT) in LSECs was also analyzed by western blot and immunofluorescence. **Results:** The abundance of gut *Enterobacteriaceae* was increased in NAFLD patients with severe fat deposition and fibrosis. Importantly, the translocated *E.coli* in the liver aggravated hepatic steatosis, inflammation and fibrosis in NAFLD mice. Mechanistically, *E.coli* induced EndMT in LSECs via TLR5/MYD88/TWIST1 pathway during NAFLD development. TLR5 inhibitor attenuated *E.coli*-induced EndMT in LSECs and liver injury in NAFLD mice. Interestingly, flagellin-deficient *E.coli* promoted less EndMT in LSECs and liver injury in NAFLD mice. **Conclusion:** *E.coli* promoted the development of NAFLD and promoted EndMT in LSECs through TLR5/NF-κB-dependent activation of TWIST1 mediated by flagellin. Therapeutic interventions targeting *E.coli* and/or flagellin may represent a promising candidate for NAFLD treatment.



Disclosures: The following people have nothing to disclose: Bo Shen, Lungen Lu

2309-C | ESCULETIN PROTECTS AGAINST LIPOTOXICITY IN PRIMARY RAT HEPATOCYTES VIA ATTENUATING JNK-MEDIATED OXIDATIVE STRESS AND AMPK-MEDIATED LIPID ACCUMULATION

Mengmeng Xia, Zongmei Wu, Manon Buist-Homan and Han Moshage, University Medical Center Groningen

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is currently the most prevalent chronic liver disease and the major indication for liver transplantation. There is no effective drug-based therapy for it. Impaired lipid metabolism, leading to lipotoxicity, is the main contributor to MAFLD, making lipotoxicity an important therapeutic target. There is evidence that both JNK and AMPK play critical roles in regulating lipotoxicity. Coumarin-like compounds, e.g. esculetin, have been shown to regulate activation of JNK and AMPK in liver injury and to exhibit hepatoprotective effects. This study aims to explore the potential protective effect of the coumarin-derivative esculetin in lipotoxicity. **Methods:** Primary rat hepatocytes were isolated using two-step collagenase perfusion. Palmitate (PA) and free fatty acids (FFAs, a mixture of thepalmitate and oleate) were used to mimic lipotoxicity. Oxidative stress was measured *via* detection of cellular ROS and mitochondrial superoxide. Cell necrosis was assessed by SYTOX green nuclear staining and LDH release assay. Lipid accumulation was determined by Oil Red O, BODIPY-LD staining and triglyceride measurement. The levels of anti-oxidant genes Nrf2, GpX1 and Sod1 and lipid metabolism-associated genes Srebp1c, Ppar-α, and Cd36 were measured by RT-PCR. Activation (phosphorylation) of JNK and AMPK were detected by Western Bot. **Results:** Esculetin significantly alleviated oxidative stress in PA-treated primary hepatocytes by reducing ROS production and increasing expression of anti-oxidant genes, including Nrf2 and Gpx1. Esculetin suppressed PA-induced necrosis in primary hepatocytes. Compared to PA, FFA induced lipid accumulation rather than toxicity in primary hepatocytes. Esculetin improved lipid metabolism in FFA-treated primary hepatocytes by decreasing expression of Srebp1c and increasing expression of Ppar-α as well as reducing lipid accumulation. The protective effect of esculetin was dependent on the inhibition of JNK and activation of AMPK. Treatment with the JNK inhibitor SP600125 reduced oxidative stress and necrosis and treatment with the AMPK inhibitor Compound C increased lipid accumulation. **Conclusion:** Esculetin prevented lipotoxicity via reducing JNK-induced oxidative stress and improving AMPK-dependent lipid metabolism. Esculetin might be a promising compound to target lipotoxicity in MAFLD.

Disclosures: The following people have nothing to disclose: Mengmeng Xia, Zongmei Wu, Manon Buist-Homan, Han Moshage

2310-C | EXACERBATION OF LIVER INJURY IN A MOUSE MODEL OF NON-ALCOHOLIC FATTY LIVER DISEASE THROUGH INDUCTION OF GUT FUNGAL DYSBIOSIS

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

Background: Non-alcoholic fatty liver disease (NAFLD) is projected to become the leading cause for liver transplantation within the next 30 years. However, there are currently no approved therapies for NAFLD other than targeted weight loss. Recently, the gut microbiota has gained attention as a potentially modifiable risk factor for disease due to its association with obesity. Despite being present in smaller quantities, fungi, an often-overlooked component of the gut microbiota may play a significant role in liver pathophysiology. Our objective therefore was to understand the impact of manipulating the gut mycobiota on the development or progression of NAFLD. **Methods:** In our study we employed a long-term high fat/high sugar feeding animal model of NAFLD. To manipulate the gut mycobiota, we utilized amphotericin B or fluconazole in the animal's drinking water. Additionally, we employed a genetic knockout of Caspase Recruitment Domain-9 (CARD9), which impairs the immune response against fungi. After a 6-month feeding period, animals were sacrificed. Liver, blood and stool samples were collected for analysis. Liver histology was performed to evaluate the amount of steatosis and fibrosis. Stool samples collected from these mice were subjected to next-generation sequencing analysis targeting both bacterial and fungal populations. **Results:** Our study revealed significant findings regarding the impact of specific interventions on gut fungal populations in mice. Administration of fluconazole or presence of a CARD9 knockout resulted in a notable reduction in fungal alpha-diversity while mice consuming amphotericin B had preserved fungal alpha-diversity. Importantly, mice with reduced fungal alpha-diversity displayed elevated markers of liver injury and fibrosis. Analysis of the taxonomic composition of the gut microbiota found in the stool revealed variations in the abundance of several mold genera in the groups with lower fungal alpha-diversity. Reductions were seen in the following mold genera: Aspergillus, Cladosporium, Penicillium, Trichoderma and Ustilago. When bacterial alpha-diversity is taken into account, groups with a reduced fungal to bacterial alpha diversity ratio exhibited the most severe disease. **Conclusion:** Our study establishes an association with fungal dysbiosis and liver injury in the context of a diet-induced obesity animal model of NAFLD. Specifically, we observed a correlation between reductions in fungal alpha-diversity and liver injury markers. However, further research is warranted to elucidate the underlying mechanisms that drive this phenomenon. Future studies should focus on the interaction of specific fungal species or the crosstalk between gut fungi and bacteria. Extending these results to human cohorts will be important to determine the relevance of these findings. Targeting and manipulating gut mycobiota could therefore hold promise as a novel approach to treating NAFLD.

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The following people have nothing to disclose: Vijay Pandyarajan

2311-C | EXPOSURE TO PERFLUOROALKYL SUBSTANCES ALTERS LIPID METABOLISM AND TRIGGERS CANCER PATHWAYS IN HUMAN LIVER SPHEROIDS

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Background: Exposure to steatogenic environmental pollutants increases the risk of non-alcoholic fatty liver disease (NAFLD) development and progression to non-alcoholic steatohepatitis (NASH). Poly- and perfluoroalkyl substances (PFAS) are highly stable synthetic chemicals widely used in industry and consumer products. PFAS persist in the environment, contaminating air, soil, and drinking water throughout the United States. Perfluorooctane sulfonate (PFOS) is associated with changes in metabolism and an increased risk of non-viral hepatocellular carcinoma (HCC), although the mechanisms remain elusive. Perfluorohexane sulfonate (PFHxS), a PFAS analogous to PFOS, has raised concerns as potentially hazardous. However, its effects on human health are not defined. Our study explores the molecular mechanisms whereby PFOS/PFHxS disrupt liver metabolism and facilitate NAFLD development. **Methods:** We combined 3D human primary liver spheroids and single-cell RNAseq (scRNA-Seq) analysis to investigate metabolic disruption induced by PFOS/PFHxS. 3D InSight^{TM} human liver spheroids (InSphero) are composed of hepatocytes (10 donors: 5 males and 5 females), endothelial cells, and macrophages (1 donor). Liver spheroids were maintained in low glucose medium (lean medium) and exposed to 20μM of PFOS or 20μM of PFHxS for 7 days. Control spheroids were cultured in lean medium for the same time. We dissociated spheroids with Trypsin, generating suitable cells for 10x genomics scRNAseq (kit 3' v3.1). **Results:** PFOS modified the expression of almost 2,000 genes in liver spheroids, while PFHxS only affected 205 genes. Both PFAS changed the global gene expression of hepatocytes and macrophages. We observed a significant upregulation of pathways involved in lipid metabolism, with PFHxS affecting mainly the hepatocytes. Regarding the inflammatory pathways in macrophages, PFOS inhibited overall cell activation, while PFHxS upregulated oxidative stress and IL-10 signaling. PFOS induced significant enrichment of cancer-related pathways, especially in macrophages. PFOS inhibited the expression of metallothioneins in hepatocytes, a family of peptides involved in cell detoxification. **Conclusion:** Our findings suggest that PFOS and PFHxS have distinct effects on liver spheroids. PFOS remarkably induced cancer-related pathways, while PFHxS primarily affected the lipid metabolism of hepatocytes. Metallothioneins may be involved in counteracting the pro-oncogenic effects of PFAS in the liver.

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2312-C | EXTRACELLULAR VESICLES DERIVED FROM LIVER SINUSOIDAL ENDOTHELIAL CELLS INHIBIT THE ACTIVATION OF HEPATIC STELLATE CELLS AND KUPFFER CELLS IN VITRO

Junyu Wang, Zongmei Wu, Mengmeng Xia, Sandra A. Serna Salas, Johanna C Arroyave Ospina, Manon Buist-Homan, Martin C. Harmsen and Han Moshage, University Medical Center Groningen

Background: Liver sinusoidal endothelial cells (LSECs) play a crucial role in maintaining liver microcirculation and homeostasis. In chronic liver diseases, hepatic stellate cells (HSCs) and Kupffer cells (KCs) become activated and LSECs undergo dedifferentiation and capillarization, hampering their normal function. Although KCs and HSCs are intimately involved in the onset and progression of inflammation and fibrosis in chronic liver disease, the role of LSECs in the development of chronic liver diseases remains unclear. Extracellular vesicles (EVs) are released from a variety of cells and contain a plethora of bioactive molecules, including proteins and RNAs and are important mediators of intercellular communication. Aim: to investigate the effect of LSEC-derived EVs on the activation of KCs and HSCs. **Methods:** Primary rat LSECs, HSCs and KCs were isolated from male Wistar rats. EVs were isolated from condition medium (CM) of LSECs by ultracentrifugation and evaluated by nanoparticle tracking analysis, transmission electron microscopy and determination of specific markers. EVs were added to target cells for 24/72 hours. Gene expression was determined by qPCR and protein expression was determined by Western blot and immunofluorescence and proliferation of cells by Xcelligence and BrdU assay. **Results:** LSECs-derived EVs reduced the expression of the fibrotic markers collagen type 1 and α-smooth muscle actin (αSMA) in activated HSCs. LSECs-derived EVs significantly suppressed proliferation of activated HSCs. EVs also decreased the expression of inflammatory genes in activated KCs *in vitro*: *iNOS* by 72.6%, *TNF-α* by 54.9%, *IL-6* by 35.6%, and *IL-1β* by 59.5%. **Conclusion:** EVs released from normal LSECs inhibit the activation of HSCs and the inflammatory phenotype of KCs. LSECs are therefore crucial in maintaining normal liver homeostasis. Elucidating the content of these EVs may lead to the identification of novel therapeutic and/or diagnostic targets for chronic liver diseases.

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2313-C | EXTRAHEPATIC/INTRAPANCREATIC CYTOKINE PRODUCTION PROMOTES HEPATOCARCINOGENESIS FROM NONALCOHOLIC STEATOHEPATITIS

Seita Kataoka[1], Atsushi Umemura[1], Kanji Yamaguchi[1], Yuya Seko[1], Michihisa Moriguchi[1], Toshihide Shima[2], Takeshi Okanoue[3] and Yoshito Itoh[1], (1)Kyoto Prefectural University of Medicine, (2)Saiseikai Suita Hospital, Suita, Osaka, Japan, (3)Saiseikai Suita Hospital

Background: Nonalcoholic fatty liver disease (NAFLD), the leading etiology of chronic liver disease, is mainly caused by insulin resistance and can lead to hepatocellular carcinoma (HCC). Hyperglycemia, a risk factor for NAFLD, induces *KRAS* mutations in pancreatic cells; thus, NAFLD and pancreatic *KRAS* mutations can exist simultaneously. Here, we aimed to determine the impact of pancreatic *Kras* mutations on the pathogenesis of nonalcoholic steatohepatitis (NASH) in mice. **Methods:** MUP-uPA mice (MUP mice) were used as the NASH model, and a conditional KrasG12D model (KC mice: *LSL-Kras*$^{G12D/+}$*;PDX-1-Cre*) was used as the pancreatic

Kras mutation model. MUP, KC, and MUP-KC mice (progeny from a cross between KC and MUP mice) were fed a high-fat diet until 24 weeks of age for analysis. **Results:** HCC developed in 33 of 34 MUP-KC mice, 6 of 45 MUP mice, and 1 of 14 KC mice, with a significantly higher rate in MUP-KC mice. In RNA analysis using next-generation sequencing, 236 genes involved in the inflammatory pathways were significantly upregulated in MUP-KC mice compared with MUP mice. Interestingly, 125 of these genes were transcriptional targets of signal transducer and activator of transcription 3 (STAT3). In western blotting analysis, STAT3 phosphorylation was significantly increased in noncancerous areas in MUP-KC mice. Antibody microarray analysis of the portal vein showed increased expression of cytokines, such as regenerating family member 3 gamma, representing inflammatory changes in the pancreas. **Conclusion:** *Kras* mutations may increase STAT3 phosphorylation in the liver via cytokine production, accelerate HCC cell proliferation, and promote HCC development in the NASH liver.

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The following people have nothing to disclose: Seita Kataoka, Atsushi Umemura, Kanji Yamaguchi, Michihisa Moriguchi, Toshihide Shima, Takeshi Okanoue

f 2314-C | Fgl2-C3aR AXIS MEDIATED NEUTROPHIL EXTRACELLULAR TRAPS PROMOTE INTRAVASCULAR COAGULATION AND LIVER FIBROSIS IN NASH PROGRESSION

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Background: Procoagulant imbalance was observed in non-alcoholic steatosis (NASH) patients with liver fibrosis, but the role of coagulation in NASH fibrosis remains largely unclear. Neutrophil extracellular traps (NETs) served as an essential factor in immuno-thrombosis. Here, we aim to study the role of NETs-mediated coagulation in NASH fibrosis and the underlying mechanism. **Methods:** NETs were depleted by intraperitoneal injection of DNase 1. Anti-Ly6G was used to deplete neutrophils. Wild type (WT) and *fgl2*$^{-/-}$ C57BL/6 mice were treated either with 60% high fat diet (HFD) or methionine/choline-deficient (MCD) diet to induce NASH fibrosis. To explore the role of C3aR in NASH fibrosis, MCD mice received C3aR antagonist (SB290157). Whole transcriptome sequencing of hepatic tissues or liver leukocytes were conducted in WT and fgl2-/- mice. For in vitro study, bone marrow neutrophils from WT and *fgl2*$^{-/-}$ mice were subjected to palmitic acid (PA) and LPS, NETs formation and related proteins were detected following treatment. **Results:** Abundant neutrophil accumulation and NETs formation were observed in NASH progression. NETs depletion improved liver fibrosis, inflammatory response and lipid accumulation both in HFD and MCD mouse models. Meanwhile, decreased hepatic fibrin deposition, plasma thrombin-anti-thrombin complex and fibrinogen expression were observed following DNase 1 treatment. Fibrinogen-like protein 2 (FGL2) was highly expressed on hepatic neutrophils in NASHmodels. *Fgl2*$^{-/-}$ mice showed significant reduction of NETs levels and hepatic fibrin deposition, along with decreased complement and coagulation factors, including TAT, fibrinogen, C3a and C5a expression. Combined with RNA-sequencing results, we found that *fgl2*$^{-/-}$ mice showed significantly decreased C3aR expression. *In vitro* experiment showed C3aR mediated NETs formation following PA and LPS

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treatment. C3aR antagonist treatment showed improved liver fibrosis and alleviated inflammatory response *in vivo*. In detail, decreased NETs formation, hepatic fibrin deposition as well as complement and coagulation factors expression were observed in NASH models following C3aR antagonist treatment. **Conclusion:** NETs mediated coagulation dysregulation promotes NASH fibrosis progression. FGL2 mediated NETs formation was regulated by C3aR. NETs act as amplifiers of immune-thrombosis in NASH fibrosis progression, and targeting NETs might serve as a potential therapeutic target in NASH fibrosis.

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2315-C | GENOME-WIDE ANALYSIS OF DNA METHYLATION CHANGES ASSOCIATED WITH NAFLD PROGRESSION TO ADVANCED FIBROSIS OR NASH

Jin Li, Texas a&M University and Robert Tsai, Texas a&m University

Background: Non-alcoholic fatty liver disease (NAFLD) has become a leading cause of hepatocellular carcinoma (HCC) in western countries. NAFLD includes a wide spectrum of liver diseases, ranging from simple steatosis to HCC. The majority of NAFLD-related HCCs (f-HCC) are detected at an advanced stage when cure is rarely possible. Hence, there is an urgent unmet need to understand the molecular events driving the progression of NAFLD for risk assessment and prevention of f-HCC. Two major risk factors preceding f-HCC are advanced liver fibrosis (ALF) and non-alcoholic steatohepatitis (NASH). To date, the mechanisms driving NAFLD progression remain unclear. To address this question, we analyzed DNA methylation changes that occurred as simple steatosis developed into ALF or NASH. **Methods:** Genome-wide methylomic data using the Human Methylation 450K Beadchip on human NAFLD samples were collected from datasets of five independent cohorts (2 in Germany, 2 in US, 1 in Japan), processed and analyzed using the ChAMP package. Meta-analyses were performed to identify differentially methylated regions (DMRs) associated with f-ALF (by comparing NAFLD-F3/4 to NAFLD-F0/1) and non-fibrotic NASH (by comparing NASH-F0/1 to NAFLD-F0/1). Genomic distributions of DMRs were determined by Hotspot analysis. Pathways of DMR-associated genes were analyzed using Gene Set Enrichment Analysis (GSEA) and Gene Ontology (GO). **Results:** 263 f-ALF hypo-DMRs and 444 hyper-DMRs were identified by comparing NAFLD-F3/4 (n = 38) against NAFLD-F0/1 (n = 61). Eight non-fibrotic NASH hypo-DMRs and three hyper-DMRs were identified by comparing NASH-F0/1 (n = 22) to NAFLD-F0/1 (n = 61). The majority (~90%) of those DMRs were distributed in the promoter region within 1 kb of the transcriptional start site (TSS). Analysis of age/sex-matched samples revealed 18 f-ALF hypo-DMRs and 732 hyper-DMRs. GO analyses showed that genes associated with the 732 hyper-DMRs are highly enriched in metabolic pathways, such as RNA metabolism, fatty acid oxidation, and lipid oxidation. Homer analysis discovered five transcription factors associated with f-ALF hyper-DMRs (KLF1, KLF3, KLF6, Sp2, and Isl1). Notably, 23 f-ALF hypo-DMRs and 30 hyper-DMRs were also found differentially methylated in viral HCC compared to normal tissue adjacent to the tumor. **Conclusion:** This study identified novel targets that might regulate the progression of NAFLD from simple steatosis to advanced fibrosis and/or NASH via DNA methylation mechanisms, thereby increasing the risk of HCC formation.

Disclosures: The following people have nothing to disclose: Jin Li, Robert Tsai

2316-C | GPNMB CONTRIBUTES TO NASH PROGRESSION WITH M2 POLARIZATION OF HEPATIC MACROPHAGES AND ACTIVATION OF HEPATIC STELLATE CELLS

Kenji Fukumoto[1], Hayato Hikita[1], Shusuke Kumazaki[1], Seiya Kato[1], Yoichi Sasaki[1], Kazuhiro Murai[1], Takahiro Kodama[2], Tomohide Tatsumi[1] and Tetsuo Takehara[2], (1)Osaka University, Graduate School of Medicine, (2) Osaka University Graduate School of Medicine

Background: Recently, with the advent of single cell RNA analysis, NASH-associated macrophages (NAMs) characterized by high expression of TREM2 and GPNMB have attracted much attention. However, the details of the effects of NAMs and GPNMB on the pathogenesis of NASH have not been elucidated, and we aimed to clarify these effects. **Methods:** In vivo experiments, wild-type mice were fed western diet for 12 or 24 weeks to induce NASH. STAM mice were used as a model of NASH carcinogenesis, in which wild-type mice were treated with streptozotocin and fed a high-fat diet for 14 weeks. We performed single cell RNA analysis of liver tissue from NASH patients and measured serum GPNMB levels of NAFLD patients. In vitro experiments were performed using THP-1, a human monocytic cell line, HepG2, a human hepatocellular carcinoma cell line, and LX-2, a human stellate cell line. **Results:** Single cell analysis of liver tissues from NASH model mice showed that GPNMB was highly expressed in CD68-positive macrophages. GPNMB gene expression was markedly upregulated in

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macrophages isolated from liver tissues of NASH model mice compared to that of normal diet group. Fluorescent immunostaining of NASH model mouse liver tissue showed a Hepatic Crown-like structure with TUNEL-positive cells surrounded by GPNMB-positive cells. Serum GPNMB levels in the NASH mouse model showed a high positive correlation with GPNMB and COL1A1 gene expression levels in liver tissue. Gene expression of GPNMB was upregulated in the liver tumor area of STAM mice compared to the non-tumor area. Single-cell RNA sequencing of liver tissue from two NASH patients showed that GPNMB was highly expressed in CD68-positive macrophages. Serum GPNMB levels were measured in 467 NAFLD patients and were significantly higher in the NASH group compared to the NAFL group. Serum GPNMB levels increased with the progression of NAFLD activity score and liver fibrosis stage. Gene expression and protein levels of GPNMB increased when THP-1 macrophages were treated with palmitic acid and cholesterol, and also increased when THP-1 macrophages phagocytosed apoptotic bodies prepared by irradiating HepG2 with UV light. Administration of recombinant GPNMB enhanced gene expression of COL1A1, ACTA2, and TGFB1, which are activation markers of LX-2. The expression of M2 macrophage marker genes such as TGFB1 and CD163 in THP-1 macrophages was enhanced by treatment with recombinant GPNMB. On the other hand, knockout of GPNMB gene by CRISPR-Cas9 system suppressed the expression of these genes. **Conclusion:** GPNMB derived from liver macrophages was suggested to contribute to the development of liver fibrosis and carcinogenesis in NASH by promoting macrophage differentiation into M2 type and activating hepatic stellate cells.

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2317-C | HEPATIC MITOCHONDRIAL QUALITY CONTROL AMELIORATES RESPONSIVENESS TO EXERCISE THROUGH DOWNREGULATION OF SELENOPROTEIN P IN NASH-RELATED HEPATOCARCINOGENIC MICE

Keisuke Hino[1,2], Kyo Sasaki[2], Yuichi Hara[2] and Sohji Nishina[2], (1)Shunan Memorial Hospital, Ube, Japan, (2) Kawasaki Medical School

Background: Exercise is an important therapeutic intervention for NASH, since no drug for NASH has been recognized. The hepatokine, selenoprotein P (SeP) has been reported to cause "exercise resistance" through reduced ROS production in skeletal muscle, and to be elevated in serum in NASH patients. Meanwhile, mitochondrial dysfunction is closely associated with pathogenesis of NASH. Therefore, we aimed to investigate whether hepatic mitochondrial quality control (mitophagy) attenuates SeP production and consequently ameliorates responsiveness to exercise. **Methods:** Iron chelator, deferiprone (DFP) was used as mitophagy trigger via mitochondrial ferritin (FTMT) induction, as reported previously (EMBO Rep 2020). The 7,12-dimethylbenz[a] anthracene (DMBA)-treated mice fed a high fat diet was used as an obesity-related HCC mouse model (NASH-HCC mice). Responsiveness to exercise was assessed by running endurance test in NASH-HCC mice treated with/without DFP. **Results:** Running distance in endurance test was significantly longer in control mice (C57/BL6 mice) than NASH-HCC mice after training for 4 weeks, suggesting that NASH-HCC mice have "exercise resistance". Hepatic *Sep* mRNA levels were significantly lower in NASH-HCC mice with DFP treatment than those without. FTMT knockdown by siRNA abrogated DFP-induced reduction of SeP expression in Huh7 cells and HepG2 cells, suggesting mitophagy-related reduction of SeP expression. Treatment with SeP repressed mitochondrial basal and maximal respiration in mouse myoblast cell line, C2C12 cells in a dose dependent manner. DFP significantly increased 2-thiobarbituric acid reactive substances (TBARS) level in skeletal muscle in exercised NASH-HCC mice, but not in non-exercised NASH-HCC mice. In parallel with increased TBARS production, peroxisome proliferators-activated receptor-γ co-activator 1α (PGC1α), which regulates mitochondrial biogenesis, was also increased in skeletal muscle in NASH-HCC mice treated with DFP. Grip strength significantly increased by exercise in NASH-HCC mice with DFP treatment, but not in those without. Finally, running distance in endurance test was significantly longer in NASH-HCC mice with DFP treatment than those without after training for 4 weeks. **Conclusion:** Mitophagy induction in the liver ameliorates responsiveness to exercise through downregulation of SeP in NASH-HCC mice.

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2318-C | HEPATIC STELLATE CELLS ARE ACTIVATED AND AVOID DEATH UNDER NECROPTOSIS STIMULI: HEPATIC FIBROSIS DURING NECROPTOSIS

Sang Bong Ahn[1], Eileen Yoon[2], Huiyul Park[3], Hyunwoo Oh[4], Hyo Young Lee[4], Joo Hyun Sohn[2] and

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

Dae Won Jun[2], (1)Eulji Medical Center, (2)Hanyang University College of Medicine, (3)Hanyang University, (4)Uijeongbu Eulji Medical Center

Background: Necroptosis is an emerging cell death pathway that allows cells to undergo "cellular suicide" in a caspase-independent manner. We investigated the fate of hepatic stellate cells under necroptotic stimuli. **Methods:** Anti-fibrotic effects were assessed using common bile duct ligation (BDL) models in wild-type (WT) and mixed lineage kinase domain-like protein knockout (MLKL-KO) mice. Necroptosis was induced by tumor necrosis factor-α, pan-caspase inhibitors, and inhibitor of apoptosis protein inhibitors in HT-29 (colorectal cancer cells), U937 (monocytes), and LX-2 (hepatic stellate cells). LX-2 cell activation and death were evaluated after necroptosis with and without the MLKL inhibitor (necrosulfonamide). **Results:** The immunoreactive score of MLKL was higher in patients with non-alcoholic fatty liver disease than in healthy controls. Hepatic fibrosis was significantly decreased in MLKL-KO BDL mice compared to WT BDL mice. Necroptotic stimuli caused death of HT-29 and U937 cells. But necroptotic stimuli activated LX-2 cells instead of cell death. Necroptosis inhibitors attenuated fibrogenic change of LX-2 cells during necroptosis. Unlike HT-29 and U937, MLKL phosphorylation and oligomerization were not observed during necroptosis in LX-2 cells. Ribonucleic acid sequencing data showed that NF-κB signaling-related genes were increased in LX-2 cells after necroptosis stimuli. Stimulation of necroptosis in LX-2 cells increased nuclear expression of NF-κB, which decreased after necrosulfonamide treatment. Induction of necroptosis in LX-2 cells led to activation and autophagosome formation, attenuated by necrosulfonamide treatment. **Conclusion:** Hepatic stellate cells avoided necroptosis due to a lack of MLKL phosphorylation and oligomerization and activated via autophagosome and NF-κB pathways.

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2319-C | HEPATIC YBX1 PROMOTES NAFLD AND NASH BY DIRECTLY ACTIVATING THE ADIPOGENIC C/EBPA:PPARG AXIS

James M. Jordan[1], Jixuan Qiao[1,2], Fahrettin Haczeyni[1] and Baran A. Ersoy[1], (1)Weill Cornell Medicine, NY, (2) University of North Carolina at Chapel Hill

Background: Y box-binding protein 1 (Ybx1), a nucleic acid-binding protein primarily known for its role in early development and stress-induced activation related to innate immunity and cancer, has also been implicated in metabolic disorders. Our prior studies have linked elevated YBX1 expression with non-alcoholic fatty liver disease (NAFLD). Using a hepatocyte-specific conditional knockout mouse model ($Ybx1^{LKO}$) in a diet-induced obesity (DIO) context, we found that Ybx1 contributes to the accumulation of hepatic triglyceride and cholesterol. Subsequent profiling studies revealed that Ybx1 regulates genes involved in adipocyte differentiation and lipid droplet formation, most of which are downstream of peroxisome proliferator-activated receptor gamma (PPARγ). Ybx1 also plays a role in hepatic cholesterol clearance and demonstrates anti-inflammatory properties, as shown by decreased macrophage infiltration following its suppression in a NASH mouse model. The aim of this study is to uncover the mechanism through which Ybx1 enhances adipogenic gene expression downstream of PPARγ. **Methods:** We implemented siRNA and adenovirus-mediated Ybx1 overexpression in primary human and mouse hepatocytes, as well as continuous hepatocytes, to investigate the effect of Ybx1 modulation on PPARγ mRNA levels. LC-MS/MS was used to identify proteins that coimmunoprecipitate (coIP) with YBX1 from nuclear lysates of hepatocytes isolated from DIO mice. The functional impact of PPARγ-related coIP hits were confirmed with siRNA in palmitate-treated hepatocytes. **Results:** We observed that Ybx1 is both necessary and sufficient to stimulate PPARγ transcription in response to palmitate-induced lipotoxicity in human and mouse primary hepatocytes. Furthermore, we showed that YBX1 binds to C/EBPα, a known transcriptional activator of PPARγ in differentiating preadipocytes. The suppression of C/EBPα entirely counteracted the transcriptional regulation of Ybx1 over PPARγ, affirming the critical role of a Ybx1/C/EBPα complex in DIO hepatocytes. **Conclusion:** While a significant increase in Ybx1 expression in differentiating preadipocytes may support healthy adipogenesis, our findings reveal a detrimental mechanism in which the maladaptive activation of Ybx1 within hepatocytes directly stimulates the C/EBPα:PPARγ pathway, leading to an increase in adipogenic gene expression that becomes lipotoxic within the liver. Given that YBX1 expression was found to surge by over 8-fold in the livers of obese NAFLD patients, YBX1 presents itself as a potential therapeutic target for NAFLD and NASH.

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2320-C | HEPATOCYTE DEPLETION OF ERK5 IMPAIRS THE RESPONSE TO LIPOTOXIC OXIDATIVE STRESS RESULTING IN DEFECTIVE INSULIN RECEPTOR SIGNALING

Alessio Menconi[1], Giovanni Di Maira[1], Giulia Lori[1], Nadia Navari[1], Maria Letizia Taddei[1], Salvatore Petta[2], Rosaria Maria Pipitone[3], Claudia Campani[4], Cathy Tournier[5], Elisabetta Rovida[1] and Fabio Marra[1], (1) University of Florence, (2)Sezione Di Gastroenterologia, Dipartimento Promozione Della Salute, Materno-Infantile, Di Medicina Interna e Specialistica Di Eccellenza "G. D'alessandro", Università Di Palermo, Palermo, Italy, (3)University of Palermo, (4)University of Florence, Italy, (5)University of Manchester

Background: Insulin resistance is an early event in nonalcoholic fatty liver disease (NAFLD), but the molecular mechanisms underlying the reduced response to insulin are still elusive. The mitogen-activated protein kinase ERK5 has been implicated in the development of hepatic fibrosis and cancer. Aim of this study was to investigate the role of ERK5 in the regulation of hepatocyte sensitivity to insulin. **Methods:** A murine hepatocyte cell line (MMH) was silenced using lentiviral vectors encoding shRNA for the ERK5 gene. Mitochondrial depolarization was assayed using the TMRE staining protocol. OXPHOS was measured by Seahorse. Mice with hepatocyte-specific deletion of ERK5 (ERK5ΔHep) were fed with a high-fat diet (HFD) for 16 weeks. For Glucose and insulin tolerance tests were conducted injecting 1 g/kg BW glucose or 0.8 U/kg BW insulin, respectively, i.p. **Results:** MMH stably silenced for ERK5 showed reduced Akt activation following insulin stimulation. When ERK5-silenced cells were exposed to palmitic acid and then stimulated with insulin, Akt activation was abrogated, and expression of the insulin receptor (IR) reduced. Additionally, ERK5 silencing induced phosphorylation and activation of JNK, resulting in phosphorylation of IRS-1 on inhibitory residues (S307). In parallel, an increase of mitochondrial ROS generation was observed in ERK5-depleted MMH. ERK5 is known to induce a NRF2-dependent anti-oxidative stress response. Expression of the NRF2-target genes HMOX1 and NQO1 was reduced in ERK5-silenced MMH. Treatment with NAC, a free-radical scavenger, prevented the downregulation of the IR and the increase in IRS1 phosphorylation on S307. Measurement of the mitochondrial membrane potential indicated a strong depolarization in ERK5-silenced cells, together with an impairment of mitochondrial OXPHOS, associated with up-regulated expression of PGC-1alpha and TRIB3, a negative regulator of insulin signalling through inhibition of Akt. ERK5ΔHep mice exhibited impaired glucose tolerance and reduced insulin sensitivity. Hepatocyte depletion of ERK5 in vivo was also associated with reduced expression of IR, and increased expression of PGC-1α and TRIB3. **Conclusion:** We have elucidated a new role of ERK5 in maintaining hepatocyte insulin sensitivity, via an antioxidant response involving IRS-1, PGC-1α, and TRIB3, and converging on Akt activation.

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2321-C | HEPATOCYTE HEDGEHOG ACTIVITY CONTROLS NAFLD SEVERITY BY REGULATING SENESCENCE-ASSOCIATED SECRETOME

Ji Hye Jun[1], Kuo Du[2], Seh-Hoon Oh[2], Raquel Maeso Díaz[2], Rajesh Kumar Dutta[3], Anna Mae Diehl[2] and Duke University, (1)Duke Universty, NC, (2)Duke University, (3)Duke University, Durham, NC

Background: NAFLD and other inflammatory liver diseases induce hepatocyte DNA damage and senescence. NAFLD severity correlates with the burden of senescent hepatocytes but the mechanisms driving hepatocyte senescence, and how this exacerbates NAFLD, are unknown. We recently discovered hepatocytes become senescent when Smoothened (Smo, an obligatory Hedgehog pathway component) is disrupted. Smo-depleted hepatocytes remain viable but their state change has a robust effect on hepatocyte-secreted proteins. Therefore, we hypothesized hepatocyte Smo activity controls NAFLD severity via the hepatocyte senescence-secretome. **Methods:** Adult Smo$^{flox/flox}$ mice were treated with control- or AAV8-TBG-Cre vectors to delete Smo specifically in hepatocytes, and fed with CDAA-HFD for 8 weeks to induce NAFLD; blood and livers were harvested for serological, histological, molecular and proteome-profiler analysis. Secreted proteins that were differentially abundant in sera of chow-fed Smo(-) and Smo(+) mice, and that were also differentially expressed in hepatocyte lysates from these two groups, were identified. AML-12 hepatocytes and primary Smo(-) hepatocytes were cultured with oleic and palmitic acid to model lipotoxic stress and treated with vehicle or proteins that were suppressed by Smo deletion; effects on lipotoxicity and senescence were compared. **Results:**

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

Depleting Smo in hepatocytes increased markers of DNA damage (8OHDG, γH2AX) and senescence (p16, p21), and exacerbated the effects of CDAA-HFD, increasing markers of steatosis (Oil-red O), lipotoxicity (4-HNE), and fibrosis (α-SMA, Sirius red). Compared to sera of Smo(+) mice, sera of Smo(-) mice were depleted of several proteins that are known to inhibit senescence, including FGF-1, P-selectin, and thymidine phosphorylase-TP. These proteins were also decreased in Smo(-) hepatocyte lysates. When added to AML-12 cells and Smo(-) primary hepatocytes during culture under lipotoxicity-inducing conditions, these proteins inhibited markers of lipotoxicity (4-HNE) and senescence (p16, p21, β-galactosidase) and enhanced viability. In AML-12 cells, TP increased Gli2, a down-stream transcription factor that is normally activated by Smo. **Conclusion:** Inhibiting Hedgehog signaling in hepatocytes exacerbates NAFLD by suppressing hepatocyte production of proteins that normally protect cells from lipotoxicity and senescence during metabolic stress.

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2322-C | HEPATOCYTE-DERIVED EVS MEDIATES PATHOPHYSIOLOGICAL CHANGES IN GASTROCNEMIUS OF NASH MICE AS WELL AS SKELETAL MUSCLE CELLS

Akiko Eguchi[1], Motoh Iwasa[1], Hiroshi Yukawa[2,3], Naonobu Fujita[4], Satoru Noguchi[5], Shinichiro Hayashi[5], Yosky Kataoka[6], Hiroshi Kitamura[7], Ryuta Shigefuku[1], Yasuyuki Tamai[1], Ryo Nakagawa[3], Sanae Fukuda[8], Yoshinao Kobayashi[1], Masatoshi Watanabe[1], Yoshinobu Baba[2], Ariel E. Feldstein[9], Yoshiyuki Takei[1] and Hayato Nakagawa[1], (1)Mie University, (2)Nagoya University, (3)Chiba University, (4)Tokyo Institute of Technology, (5)National Center of Neurology and Psychiatry, (6)Riken Biosystems Dynamics Research, (7)Rakuno Gakuen University, (8)Kansai University of Welfare Sciences, (9)University of California, San Diego

Background: Sarcopenia is a common and potentially serious complication of chronic liver disease while potential humoral factors involved in liver-muscle cross-talk are not fully understood. We have demonstrated that hepatocyte-derived extracellular vesicles (HC-EV) from damaged hepatocytes are intercellular pathological mediators that contribute to the progression of liver disease. Here, we investigate whether HC-EV is an inter-organ disease mediator involved in skeletal muscle injury. **Methods:** Gastrocnemius injury in NASH mice fed with a choline-supplemented amino acid diet were accessed via qPCR, histological staining and electron microscopy. Pharmacokinetics of fluorescently labeled HC-EV were assessed by imaging. The characterization of HC-EVs isolated from NASH mice were performed by FACS, nanotracking and miR-array. The internalization and effects of HC-EV on skeletal muscle cells (C2C12 myotube) were assessed via laser confocal microscopy and qPCR. Circulating EV-miRs in human NASH with low skeletal muscle mass (LMM), NASH and healthy individual's ($n = 3$) were detected by miR-array. **Results:** Liver and spleen weights were increased ($p < 0.01$) in NASH mice associated with an increase of liver collagen1 and TNF-a mRNA levels ($p < 0.01$). Gastrocnemius muscle/body weight ratio was decreased in NASH mice ($p < 0.01$) associated with abnormal mitochondrial morphology and reduction of mRNA levels related to muscle differentiation (myogenin], metabolism (uncoupling protein 3, UCP3), repair (forkhead box protein O1, FOXO1) and mitochondrial function (cytochrome c oxidase subunit 2, mtCOX2) ($p < 0.05$). Imaging analysis revealed that a part of HC-EVs, which were increased ($p < 0.05$) in the blood of NASH mice, propagated to the gastrocnemius muscle. The number of HC-EVs isolated from mice was elevated in NASH mice compared to control mice ($p < 0.01$), consistent with the large size of EVs with a diameter of 250 nm. HC-EVs were efficiently internalized into C2C12 myotubes and induced a reduction of mRNA levels related to muscle metabolism, repair and mitochondrial function (UCP3, FOXO1 and mtCOX2) ($p < 0.05$), which were consistent with those induced in the gastrocnemius muscles of NASH mice. The miR-array analysis detected 127 up-regulated and 140 down-regulated miRs ($p < 0.05$) in NASH-HC-EVs. 68 circulating EV-miRs were significantly changed in human NASH-LMM vs. NASH vs. healthy individual's ($P < 0.05$) and identified human NASH-LMM with a specificity of 0.98 and a sensitivity of 0.96. HC-EV-miRs were also detected in human NASH-LMM. **Conclusion:** HC-EVs contribute the development of skeletal muscle damage associated with chronic liver disease as an interorgan disease mediator. HC-EV-miR is a novel biomarker and may be involved in the progression of hepatic sarcopenia in NASH patients, while further investigations are warranted.

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2323-C | HEPATOCYTE-SPECIFIC CK1ε DELETION IMPROVES FATTY LIVER AND AMELIORATES IN VITRO STEATOHEPATITIS IN MICE

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Background: The liver plays a major role as the body's glucose reservoir. However, excessive amounts of dietary refined sugar and high fructose are among the known causes of fatty buildup that can lead to fatty liver disease, which in turn is a diabetic chief determinant. Non-alcoholic fatty liver disease (NAFLD) is the usual outcome of obesity, dyslipidemia, and insulin resistance. Regardless of the rise in dietary trends linked to NAFLD, the most effective therapeutic strategy to combat liver disease is currently unavailable. Casein kinase 1 epsilon (CK1ε), a member of the serine/threonine family of protein kinases, may be a potential target for drug development as they are mostly overexpressed in various disease models. Its role in the development of acute and chronic liver diseases remains elusive. **Methods:** To identify the role of CK1ε in the progression of NAFLD, hepatocyte-specific CK1ε knockout mice (CK1ε $^{\Delta HEP}$) were first generated by crossing CK1ε $^{fl/fl}$ mice with Alb-Cre mice. An F2 generation of hepatocyte-specific CK1ε $^{fl/fl}$ Alb-Cre^{+} knock-out mice were then obtained. CK1ε $^{fl/fl}$ mice and CK1ε $^{\Delta HEP}$ were fed a Western diet (WD) and a normal chow diet (CD) for 16 weeks, respectively. **Results:** Compared with CK1ε $^{fl/fl}$ WD-fed mice, CK1ε $^{\Delta HEP}$ WD-fed mice gained significantly less body weight with improved oral glucose tolerance. As evidenced by histological changes, early-stage steatosis severity in CK1ε $^{\Delta HEP}$ WD-fed mice was also reduced. Strikingly, CK1ε $^{\Delta HEP}$ WD-fed mice showed significantly lower hepatic concentrations of total triglycerides and total cholesterol relative to CK1ε $^{fl/fl}$ WD-challenged mice. To further validate the novel function of CK1ε, primary hepatocytes were isolated from CK1ε $^{\Delta HEP}$ and treated with 0.4mM palmitic acid (PA). The results showed that CK1ε $^{\Delta HEP}$ decreased PA-induced inflammatory responses and lactate dehydrogenase compared to the counterpart CK1ε $^{fl/fl}$ PA control. Also, intracellular accumulation of lipids was significantly reduced in PA-induced CK1ε $^{\Delta HEP}$ and affected lipid metabolism. CK1ε $^{\Delta HEP}$ further attenuated PA-induced lipo-apoptosis in primary hepatocytes. As a molecular mechanism underlying CK1ε action, the non-canonical JNK/MAPK signaling pathway was considered, and phosphorylated c-Jun proteins were reduced significantly in the CK1ε $^{\Delta HEP}$ positive control than CK1ε $^{fl/fl}$ positive control (both *in-vitro* and *in-vivo*). **Conclusion:** This work highlighted the role of CK1ε as a NAFLD modulator via stimulating the JNK/MAPK signaling pathway. Therefore, CK1ε played a pivotal role in hepatic lipid accumulation. This role enables us to establish better therapeutic strategies targeting NAFLD. Keywords: Casein kinase 1 epsilon, Non-alcoholic steatohepatitis, Hepatocyte-specific, Inhibition

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2324-C | HEPATOCYTE-SPECIFIC GROWTH DIFFERENTIATION FACTOR 15 OVEREXPRESSION AMELIORATES HIGH-FAT DIET-INDUCED OBESITY AND LIVER STEATOSIS VIA INDUCTION OF FIBROBLAST GROWTH FACTOR 21 IN MICE

Kento Takeuchi, Kanji Yamaguchi, Takao Shirono, Yusuke Takahashi, Kota Yano, Seita Kataoka, Yuya

Seko, Michihisa Moriguchi and Yoshito Itoh, Kyoto Prefectural University of Medicine

Background: Growth Differentiation Factor (GDF) 15 is a stress-response endocrine growth factor that belongs to the TGFβ family and also has both hepatokine and mitokine aspects together with Fibroblast Growth Factor (FGF) 21. GDF15 is also induced by various cancer cells and platinum drugs, and is known to induce anorexia via its receptor GFRAL-RET, which is expressed in the in brainstem neurons. From a different point of view, it has been reported to improve glucose intolerance due to its potent anti-obesity effect, and NAFLD by enhancing metformin action in diabetic mouse models. Recently demonstrated, CNOT6L (CCR4-NOT Transcription Complex Subunit 6 Like), which is involved in deadenylation-dependent mRNA degradation, is expressed in a diet-induced manner and is involved in suppression of GDF15 and FGF21 expression at the transcription level. In this study, we examined the synergistic effects of GDF15 and FGF21 in a mouse NAFLD model. **Methods:** We examined hepatocyte-specific enhancer/promoter of GDF15 or FGF21 expression plasmids in high-fat diet (HFD)-fed male mice. One week after hydrodynamic injection of those plasmids via the tail vein of 8-week-old male B6 mice, the mice were divided into two groups and fed a normal diet and a HFD for 8 weeks to induce NAFLD. A control plasmid group was also established for each of these diets. After treatment, blood, liver and epididymal fat samples were collected and analyzed for the glycose and lipid metabolism-related gene expression **Results:** Once hydrodynamic injection for GDF15 or FGF21 delivery sustained high circulating levels of those respectively, resulting in marked reductions in body weight, epididymal fat mass, insulin resistance, and liver steatosis. The amount of food intake per mouse was unchanged in the first 4 weeks, but decreased in the GDF15-treated group in the latter 4 weeks. However, no difference was observed in food intake per body weight. Hepatic steatosis canceled in the GDF15-treated group. HFD increased hepatic CNOT6L and FGF21 mRNA expression but had no effect on GDF15 expression. On the other hand, HFD induced serum GDF15 and FGF21 levels. In addition, GDF15 treatment increase hepatic FGF21 mRNA expression but FGF21 treatment had no effect on GDF15 expression. GDF15 suppressed CNOT6L mRNA expression and stimulated ER stress-related pathways, which may have contributed to the increased expression of FGF21. **Conclusion:** GDF15 and FGF21, both liver-derived cellular stress response mitokines, have their blood levels increased in NAFLD. Recently, direct effects of GDF15 on the liver were reported, and in this study, induction of FGF21 expression in the liver was demonstrated under GDF15 overexpression.

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2325-C | HEPATOCYTE-SPECIFIC UBC13 DELETION DRIVES NAFLD PROGRESSION VIA CELLULAR SENESCENCE AND GLUTAMINOLYSIS

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Background: Non-alcoholic fatty liver disease (NAFLD) is a complex and multifactorial disease characterized by a buildup of lipids in hepatocytes, to the more advanced non-alcoholic steatohepatitis (NASH) with inflammation and fibrosis. The incidence of NAFLD increases with age, and aging-related mechanisms such as cellular senescence have been proposed as pathogenic drivers. Cellular senescence is defined by permanent and irreversible cell cycle arrest and enhanced glutaminolysis improves survival of senescent cells. UBC13, a ubiquitin E2 conjugating enzyme, plays a crucial role in K63-linked polyubiquitination and promotes DNA repair. DNA damage accumulation is reported as a commonly underlying cause of cellular senescence. We hypothesize that UBC13 acts as a negative regulator of cellular senescence and glutamine metabolism during the development of NAFLD. **Methods**: Wild-type and hepatocyte-specific UBC13 knockout (UBC13 KO) developed NAFLD by high fat diet (HFD) feeding for 6 weeks. For senolytic treatments, (1) vehicle or Dasatinib (D:5 mg kg^{-1}) and Quercetin (Q:10 mg kg^{-1}) were administered via oral gavage or (2) intraperitoneally injected with vehicle or CB-839 (Glutaminase inhibitor; 10 mg kg^{-1}). To investigate ageing, mice were housed for various periods up to 15 months. **Results:** We identified that hepatocyte-specific deletion of UBC13 increased liver injury and hepatic steatosis. UBC13 KO induced DNA damage, marked by the presence of nuclear γ-H2AX foci and upregulation of cell cycle markers (p16, p21 and p53), leads to cellular senescence. We found that UBC13 deletion increased Glutaminase 1 (GLS1) expression, suggesting that overactivated glutaminolysis may contribute to hepatic cellular senescence. We demonstrated that inhibiting glutaminolysis by blocking GLS1 using CB-839 and senolytic combination of D/Q significantly mitigated liver injury, hepatic steatosis and senescence. Increased fat deposition severely impairs liver function and exacerbates the aging phenotype. Consistent with these findings, we discovered senescent hepatocytes accumulate in parallel with age which can be ameliorated by senolytic combination of D/Q and glutaminase targeting using CB-839. **Conclusion:** Together, these data indicate that UBC13 plays a causal role in the development of NAFLD pathogenesis, and that senescence can cause steatosis by inducing glutaminolysis. These findings support a cogent argument of targeting senescent cells for the treatment of NAFLD/NASH.

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The following people have nothing to disclose: Lien Reolizo

f 2326-C | HEPATOPROTECTION THROUGH REMOVAL OF MITOCHONDRIAL S-GLUTATHIONYLATION BY A CYSTEINE MUTANT ON THE COMPLEX I SUBUNIT

Suyavaran Arumugam, Yan Zhang, Yingdong Zhu, Wajahat Z. Mehal and Xinshou Ouyang, Yale University, New Haven, CT

Background: S-glutathionylation (SSG), a prevailing redox sensor, regulates mitochondrial metabolism and function. The significance of mitochondrial protein S-Glutathionylation (SSG) in hepatic metabolism and function remains understudied despite its crucial role. Aim: To provide a comprehensive review of oxidative stress-induced mitochondrial protein modifications, with a particular focus on SSG, and its effects on hepatic metabolism and function. **Methods:** Mouse primary hepatocytes were treated with MitoPQ, a mitochondria-targeted redox cycler followed by mitochondria isolation coupled LC-MS/MS analysis. Bioinformatic analysis identified protein modifications and further homology search. The human NDUFS6^{-C87S} mutant transgenic gene (Tg) mice were generated by retrieving the transgene cassette from the plasmid backbone, followed by standard pronuclear microinjection, embryo transfer, gestation, weaning, and genotyping. Lipid metabolism by BODIPY staining, MitoROS by mitoSOX staining, mitochondrial membrane potential (MMP) by JC-1, and Glucose tolerance test (GTT) on a High Fat Diet (HFD) were measured. **Results:** Proteome-wide analysis of mitochondrial protein modifications in mitoPQ-treated mouse hepatocytes revealed multiplex modifications with over 65 differentially expressed proteins with SSG modification. Gene Ontology (GO) classification has revealed complex I as a significant SSG target. The selective reduction of Cys87 residue containing NDUFS6 fragments is particularly interesting since NDUFS6 is a subunit of the first enzyme complex of ETC. Homology search indicates that C87 residue containing DNA sequence (CTGCGATGG) of NDUFS6 is highly conserved among species. The expression of SSG-resistant human NDUFS6^{-C87S} mutant in hepatocytes resulted in reduced lipid accumulation (over 50% reduction, $P < 0.01$), reduced mitoROS (over 80% reduction of mitoSOX, $P < 0.01$) and prevented the loss of MMP ($P < 0.01$) in response to palmitate stimulation. The human NDUFS6^{-C87S} Tg mice and littermates exhibited significant improvement in metabolic dysfunction as evidenced by significant enhancements in glucose tolerance through the GTT (Blood glucose level Tg vs WT, $P < 0.01$) when subjected to a HFD condition. Furthermore, the mitochondrial protein SSG in the Cys87 residue of NDUFS6 was lost in hepatocyte specific PKM2 knockout condition in response to mitoPQ, PKM2 is known a glycolytic rate enzyme in the regulation of mitochondrial metabolism and function. **Conclusion:** The removal of SSG in ETC complex I protein NDUFS6 by C87S mutation in hepatocytes improved mitochondrial oxidative reactions related to hepatic metabolism and function. Manipulation of NDUFS6^{-C87} such as through site mutation holds great potential as a therapeutic target for improving hepatic metabolism and mitigating steatosis in NAFLD/NASH.

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2327-C | HIGH-FAT DIET INCREASES SUSCEPTIBILITY TO LIPOPOLYSACCHARIDE-INDUCED LIVER INJURY IN OBESE KK-AY MICE

Satoshi Sakuma, Kazuyoshi Kon, Kumiko Arai, Akira Uchiyama, Hiroo Fukada, Toshifumi Sato, Shunhei Yamashina and Kenichi Ikejima, Juntendo University School of Medicine

Background: Obesity and metabolic syndrome are the prominent risk factors for the multi-organ damage and mortality during systemic infectious diseases. Cytokine storm is a key event for the organ damage including severe liver injury, but the mechanism underlying the sensitization by metabolic dysfunction is still unclear. We investigated the impact of metabolic syndrome and high-fat diet (HFD) load in exacerbation of cytokine storm and liver damage following lipopolysaccharide (LPS) challenge using obese diabetic KK-A^{y} mice. **Methods:** Male KK-A^{y} mice were fed a diet containing high-fat (HFD) or control diet for 4 weeks. C57Bl6/J mice (BL6) was used as a control strain. Mice were sacrificed at 1-24 hr after intraperitoneal injection of LPS 5 mg/kg BW or saline. Apoptotic cell death was detected by TUNEL staining. Hepatic mRNA was measured by RT-PCR. **Results:** KK-A^{y} fed an HFD showed prominent hepatic steatosis after HFD feeding, whereas Bl6 mice developed trivial steatosis even after HFD. After a single injection of LPS, all Bl6 fed a control diet survived for 24hr, indicating that this dose was sublethal. HFD-fed BL6 died within 24 hr after injection of LPS nearly 20%. In sharp contrast, the mortality rate 24 hr after LPS injection reached 86% in HFD-fed KK-A^{y}, which was significantly higher than 16% of control diet-fed KK-A^{y} given LPS. Serum ALT levels 12 h after LPS in HFD-fed KK-A^{y} increased to 673 ± 191 IU/L, which were obviously higher than those in HFD-fed BL6 reaching 193 ± 58 IU/L. Indeed, HFD-fed KK-A^{y} showed marked apoptotic cell expression after LPS. Hepatic expression of TNFα mRNA 1 hr after LPS were almost doubled in HFD-fed KK-A^{y} as compared to control diet-fed KK-A^{y}. IL1β mRNA was also significantly higher in HFD-fed KK-A^{y} 1-3 h after LPS than those in control diet-fed KK-A^{y}. Prior to LPS, HFD-loaded KK-A^{y} showed increased hepatic expression of TLR-4 and CD-14 nearly 3-fold and 7.5-fold, respectively. Further, KK-A^{y} fed an HFD showed marked induction in hepatic LPS-binding protein (LBP) mRNA, the levels reaching 2.6-fold higher than those in control diet-fed KK-A^{y}. In contrast, HFD-induced increases in TLR-4, CD-14, and LBP were not observed in Bl6. Moreover, HFD-feeding elicited overexpression of IL-6 in the liver only in KK-A^{y} but not in Bl6. **Conclusion:** These findings clearly indicate that KK-A^{y} mice, which develop obesity and severe fatty liver following HFD-feeding, are obviously vulnerable to LPS, showing higher mortality and severer liver injury. The underlying mechanisms most likely involve sensitization of hepatic macrophages by upregulation of pattern-recognition receptors and inflammasome-related reactions against LPS, as well as induction of LBP production in hepatocytes caused by IL-6. It is therefore concluded that metabolic dysfunction-associated fatty liver appears to be an important risk factor of exacerbation in multiple organ failure including severe liver damage under condition of cytokine storm.

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f 2328-C | HSD17B13 MODULATES HEPATOCYTE-TO-HEPATIC STELLATE CELL COMMUNICATION THROUGH DIHOMES AND INTERFERON SIGNALING

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Background: Loss-of-function variants in *HSD17B13* protect against non-alcoholic steatohepatitis (NASH)-related fibrosis in humans. While HSD17B13-targeted therapies already show promising results in clinical trials, the molecular mechanism for protection and substrates of HSD17B13 remain largely unknown. We hypothesized that HSD17B13 regulates the communication between hepatocytes and hepatic stellate cells (HSC). **Methods:** *Hsd17b13* knockout (KO) and littermate control mice (n = 13-14) were fed with choline-deficient amino acid-defined high fat diet (CDAA-HFD) for 12 weeks to establish NASH fibrosis. A hepatocytes-to-HSCs conditioned media (CM) *in vitro* model was used to study HSD17B13-regulation of hepatocyte-to-HSC communication. RNA-seq with pathway analysis, metabolomics, and qPCR were utilized. Hepatic gene expression was examined in a cohort of NASH patients undergoing bariatric surgery and genotyped for *HSD17B13* variants. **Results:** *Hsd17b13* knockout (KO) attenuated NASH fibrosis by 34% ($p = 0.003$) while upregulating hepatic interferon (IFN) signaling in CDAA-HFD fed mice, as previously reported. *In vitro,* silencing hepatocyte *Hsd17b13* upregulated IFN stimulated genes (ISG) (*Cxcl10*, 2.6-fold, $p = 0.03$; *Irf7*, 1.7-fold, $p = 0.004$; *Isg15*, 1.6-fold, $p = 0.001$) and exposing HSCs to CM from these hepatocytes decreased HSC activation ($p < 0.05$). LPS induction of hepatocyte IFN signaling was sufficient to decrease HSC activation by CM (50% reduction, $p < 0.05$). In patients with NASH ($n = 244$), hepatic expression of multiple ISGs was significantly upregulated (e.g. *ISG15*, 1.7-fold, $p < 0.0001$) in carriers of the protective *HSD17B13* rs72613567 TA variant. Metabolomic analysis revealed that hepatic levels of the linoleate metabolites 9,10-DiHOME and 12,13-DiHOME were lower in CDAA-HFD-fed KO mice (46%, $p < 0.02$ & 28%, $p < 0.02$, respectively). Treating hepatocytes *in vitro* with 9,10-DiHOME or 12,13-DiHOME significantly suppressed the induction of ISGs by *Hsd17b13* knockdown. **Conclusion:** We found that intact HSD17B13 impairs hepatic IFN signaling and that loss of HSD17B13 can restore this signaling *in vitro*, in mice, and in humans with NASH. Restoration of hepatocyte IFN signaling is sufficient to ameliorate HSC activation and subsequent fibrogenesis. We show that the suppression of IFN signaling by HSD17B13 is likely mediated by DiHOMEs, which are potential enzymatic products of HSD17B13. Taken together, our findings provide new insights on how HSD17B13 and HSD17B13-targeted therapies may affect NASH-related fibrosis.

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The following people have nothing to disclose: Wenqi Cui, Yaron Rotman

Disclosure information not available at the time of publication: Yanling Ma, Diego Miranda

2329-C | HUMAN NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) PROMOTING GCKR GENETIC VARIANT P446L PROMOTES GLYCOGEN AND TRIGLYCERIDE ACCUMULATION IN HUMAN LIVER HUH-7 CELLS

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Background: Nonalcoholic fatty liver disease (NAFLD) is caused by the accumulation of excess fat in liver and leads to cirrhosis. NAFLD is heritable, affects about 30% of the general population and is becoming the leading cause of liver disease. Human genome wide association studies have identified a genetic variant in GCKR(P446L) that promotes NAFLD but how this variant changes GCKR function to cause NAFLD is not known. Glucokinase regulator (GCKR) encodes glucokinase regulatory protein (GKRP) is expressed in liver and interacts with and inhibits glucokinase (GCK) to negatively regulate glucose utilization and storage. GKRP is a key player in regulation of hepatic GCK and glycogen synthesis in human hepatocyte. GKRP forms a complex with GCK, inhibiting GCK while also maintaining a stable pool of GCK available when needed. Prior in vitro studies have shown that the effect of GKRP on glycogen synthetic flux is nearly perfectly reciprocal to the effect of GCK on this flux. **Methods:** Using lentiviral integration, we created stable human Huh-7 cell lines with wildtype and mutant P446L GCKR overexpressed or knocked down using shRNAs. We measured intracellular triglyceride and glycogen levels using biochemical assays as well as lipid dyes and microscopy and quantitated it using cell profiler. We measured GYS2, GCK, GKRP, FASN and ACC protein levels using Western blot under various glucose concentrations. **Results:** GCKR(P446L) increased triglyceride and glycogen accumulation compared with GCKR(WT) overexpressed or control Huh-7 cells across different doses of glucose (0, 2, 5 and 25mM) after 8 hours of incubation. The most significant difference between WT and P446L occurred at 2mM glucose ($p < 0.05$). Overexpression of wild-type GCKR significantly decreased glycogen content compared with control cells only at 25mM glucose ($p < 0.01$). Knockdown of GCKR significantly increased cellular glycogen compared with control cells at 2 and 5mM glucose. Western blot results showed P446L variant significantly increased protein level of glycogen synthase (GYS2), Fatty Acid Synthase (FASN) and Acetyl- CoA Carboxylase (ACC) and glucokinase (GCK) compared to cells expressing vector and GCKR(WT) at 2 and 5mM glucose. Knockdown GCKR significantly increased GYS2 protein levels at 2mM glucose ($p < 0.0001$). **Conclusion:** GCKR (P446L) increased triglyceride and glycogen accumulation compared with GCKR (WT) in Huh-7 cells suggesting a cell autonomous effect of triglyceride and glycogen accumulation. GCKR (P446L) mimics the knockdown of GCKR in phenotypically in these assays suggesting that P446L mutation is a loss of function change. At least one-way GCKR(P446L) increases TG in liver is by increasing ACC and FASN levels to increase de novo lipogenesis. GCKR (P446L) may also increase glycogen accumulation at 2mM glucose by up-regulating GYS2. These experiments help explain how P446L causes liver damage.

Disclosures: The following people have nothing to disclose: Yue Chen

Elizabeth K. Speliotes:

Disclosure information not available at the time of publication: Brahmpreet Saini, Jason Chen, Brian D Halligan

f 2330-C | HYDROPHOBIC BILE ACIDS ACCELERATE NAFLD-ASSOCIATED HCC DEVELOPMENT IN A MOUSE MODEL WITH HUMAN-LIKE BILE ACID COMPOSITION

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Background: The mechanisms of developing hepatocellular carcinoma (HCC) in non-alcoholic fatty liver disease (NAFLD) remain unclear. Feeding a high-fat/high-sucrose diet (HFHSD) without cholesterol loading or a carcinogen to conventional mice rarely results in severe fibrosis or HCC development. Mice possess a highly hydrophilic and cytoprotective bile acid (BA) composition due to Cyp2a12 and Cyp2c70 genes, which are absent in humans. Therefore, we hypothesized that NAFLD disease progresses in mice as it does in humans when BAs are modified to be hydrophobic. **Methods:** Eleven-week-old C57BL/6J wild-type (WT) and C57BL/6J derived Cyp2a12/Cyp2c70 double knockout (DKO) mice were used. The mice from each strain were divided into two groups; one was given a normal diet (ND), and the other was administered an HFHSD. Samples were collected at 26, 41, 59, and 70 weeks of age for histopathological, biochemical, and immunological analyses. **Results:** No differences in body weight gain were observed between WT and DKO mice after feeding an HFHSD. Hepatic steatosis and insulin resistance were less severe in DKO mice than in WT mice, and no significant differences in hepatic inflammation markers were discovered between the two groups. However, hepatic fibrosis was more advanced in DKO mice than in WT mice, and HCC (a pathologically well-differentiated type) developed in 70% of the HFHSD-fed DKO mice at 59 weeks. Furthermore, at 70 weeks, HFHSD-fed DKO mice demonstrated severe hepatic fibrosis with the disappearance of hepatic lipid droplets and a 100% incidence of HCC. The BA pool of DKO mice was smaller than that of WT mice regardless of diet up to 26 weeks but was greater than that of WT mice at 59 weeks with increases in chenodeoxycholic acid and lithocholic acid. Hepatic oxysterol concentrations were higher in DKO mice than in WT mice and in HFHSD as compared to ND. RNA sequencing analysis of the liver at 41 weeks revealed significant differences in the expressions of several genes related to fatty acid metabolism, oxidative stress, and carcinogenesis between WT and DKO mice treated with HFHSD. **Conclusion:** Hydrophobic BA composition is necessary to induce severe fibrosis and HCC in mice without modifying genes essential in humans or administering non-physiological amounts of cholesterol or carcinogens. Increased hydrophobic BAs mitigate insulin resistance and hepatic inflammation, presumably by activating Takeda G protein-coupled receptor 5. However, hydrophobic BAs promote hepatic fibrosis and hepatocarcinogenesis, especially under conditions of NAFLD.

Disclosures: The following people have nothing to disclose: Hajime Ueda, Akira Honda, Teruo Miyazaki, Tadashi Ikegami

2331-C | INCREASED BAS WAS ASSOCIATED WITH CHOLESTATIC GENE PROFILE IN PATIENTS WITH NASH

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Background: Increased serum bile acids (BAs) was observed in NASH patients but the pathogenesis was unclear. Through examine human serum and hepatic tissue samples, we dissected the profile of serum BAs and BA-related genes in NASH patients and examined its clinical significances. **Methods:** We prospectively collected hepatic tissues and serum samples from NASH patients and healthy living liver donors. By investigated tissue mRNA levels of BA related genes and measured their serum BAs levels, we established the pathophysiology in NASH related cholestasis. **Results:** We had collected 69 NASH patients and 10 healthy living liver donors (as control). Serum BAs were significantly increased in NASH patients, especially the primary and conjugated BAs ([NASH vs. control, mean (SEM): 3.94 (0.38) μM vs. 1.55 (0.71) μM, $p < 0.0001$]). Tissue mRNA analysis revealed that level of BA-related genes from NASH patients favoring cholestasis. Specifically, mRNA level of *CYP7A1* was significantly increased in NASH patients (relative expression level in NASH patients = 10.87 times of control $p < 0.001$). Fasting serum FGF19 was positively correlated with serum total primary BAs level (Rho = 0.38, $p < 0.001$). Clinically, the conjugated primary BA: glycocholic acid (GCA) was the most conspicuous BA that positively correlated with hepatitis markers, including ALT (Rho = 0.34, $p = 0.003$), AST (Rho = 0.43, $p = < 0.0001$), Alk-P (Rho = 0.24, $p = 0.04$) and GGT (Rho = 0.41, $p = 0.0002$). Clinical parameters of metabolic syndromes, including BMI, serum lipid and glucose profile were not correlated with serum GCA. **Conclusion:** In NASH patients, dysregulated BA homeostasis was noted and favoring cholestasis. Serum GCA was the most obviously increased serum BAs which positively correlated with serum hepatitis markers.

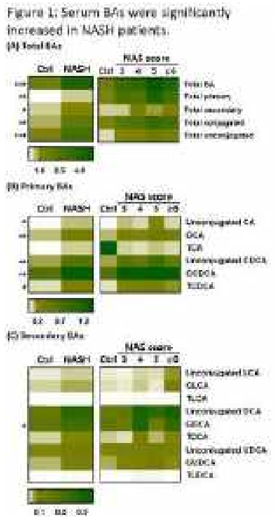

Figure 1: Serum BAs were significantly increased in NASH patients.

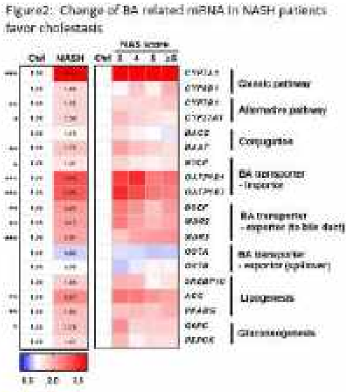

Figure2: Change of BA related mRNA in NASH patients favor cholestasis

Disclosures: The following people have nothing to disclose: Shih-Chieh Chien, Chiung-Yu Chen, Yau-Sheng Tsai, Pin-Nan Cheng, Hung-Wen Tsai, Yih-Jyh Lin, Shu-Chu Shiesh, Yen-Cheng Chiu, Toad Chiu

2332-C | INHIBITING SARM1 IS MORE EFFICACIOUS THAN NICOTINAMIDE RIBOSIDE SUPPLEMENTATION FOR THE TREATMENT OF A MOUSE MODEL WITH NAFLD/NASH

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Background: NAD+, nicotinamide dinucleotide, is a central metabolite for cellular redox balance and a pivotal cofactor for proteins regulating metabolism and health. NAD+ levels decline in a range of metabolic diseases including NAFLD/NASH. Boosting NAD+ levels, i.e.,through nicotinamide riboside (NR) supplementation, reverses the disease in mice. SARM1 (Toll/interleukin-1 receptor motif-containing 1) is a new NAD+-cleaving enzyme highly expressed in neurons. SARM1 activation consumes NAD+ and induces axon degeneration, specifically hepatic sympathetic neuropathy in NAFLD/NASH. Therefore, inhibiting SARM1 holds great promise to treat the disease. Despite their comparable activity on the hepatic NAD+ levels, a head-to-head comparison of the therapeutic outcomes between NR supplementation and SARM inhibition is lacking. Here, we examined the therapeutic effects of NR and a SARM inhibitor (SARMi) in a mouse model of NAFLD/NASH. **Methods:** C57BL/6J mice fed a western diet (WD) or chow were housed at thermoneutrality (TN; 30°C) for 23 weeks and treated with NR (500 mg/kg/day) and SARM1i (60 mg/kg/day) from week 9-23. Body weight was measured bi-weekly. Body composition, plasma circulating factors were assessed by EcoMRI and a Luminex system. Hepatic fibrosis and inflammation were assessed histologically. **Results:** Boosting NAD + levels with NR and SARM1i in NAFLD/NASH mice comparably attenuated the body weight gain and increased the percentage of lean mass (Fig A-B). SARM1i, but not NR, reversed the hyper-glycemia and decreased the liver weight (Fig C-D). Hepatic inflammation and fibrosis were reduced by both NR and SARM1i (Fig E). Further, a significant reduction in the plasma levels of the liver damage marker ALAT/ASAT ratio, the fibrosis marker TIMP-1 and the mitokine GDF-15 levels were seen after the SARM1i therapy but not with the NR treatment (Fig F). These data suggest a better therapeutic effect of SARM1i on the global metabolic stress in NAFLD/NASH. Lastly, liver transcriptome analysis substantiated the therapeutic effect of SARM1i, with the pathogenic changes underlying NAFLD/NASH including inflammatory responses, fibrotic processes, mitochondrial dysfunction among others being suppressed. **Conclusion:** SARM1i therapy is more efficacious than NR supplementation in reversing NAFLD/NASH in mice. The superior therapeutic effect of SARM1i supports the development of SARM1i to treat liver injury due to NASH and other etiologies.

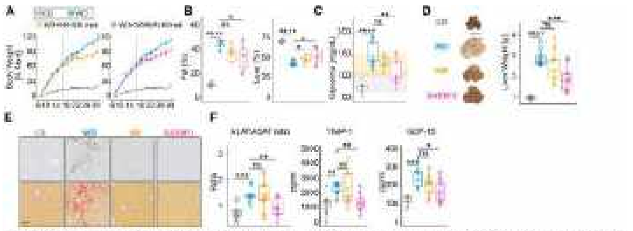

Figure A. Body weight gain curves (expressed as percentage from the starting body weight for each treatment group. B. Fat and lean mass percentage. C. Fasting glycemia. D. Liver gross morphology and weight. E. CD45 and Picrosirius red staining of liver sections. F. Plasma circulating biomarkers.

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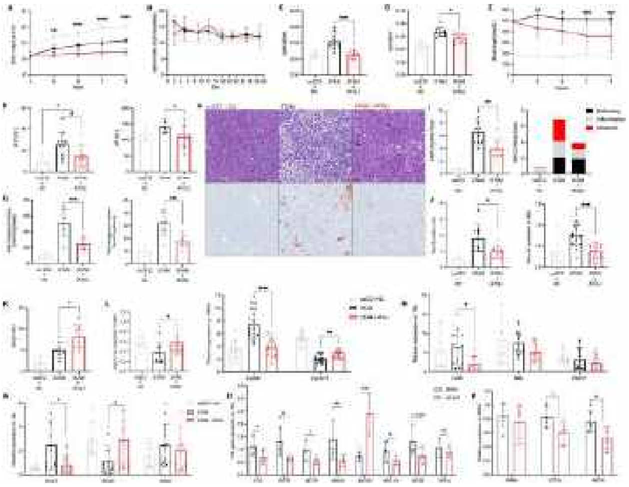
Disclosure information not available at the time of publication: Angelique M.L. Scantlebery, Sandra Rodríguez-López, Krisztian Homicsko, Karen Smith, Jeffrey Ciavarri, Maroun Bou-Sleiman, Riekelt H Houtkooper

2333-C | INHIBITION OF ADIPOSE TRIGLYCERIDE LIPASE ALLEVIATES NON-ALCOHOLIC STEATOHEPATITIS IN DIABETIC MICE VIA IMPAIRED PPAR-ALPHA SIGNALLING FAVOURING HYDROPHILIC BILE ACID COMPOSITION

Emmanuel Dauda Dixon[1], Thierry Claudel[1], Alexander Nardo[1], Claudia Daniela Fuchs[2], Veronika Mlitz[1], Hubert Scharnagl[3], Tatjana Stojakovic[3], Gernot Grabner[4], Henkjan J. Verkade[5], Guenter Haemmerle[4], Robert Zimmermann[4] and Michael Trauner[2], (1) Medical University of Vienna, (2)Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, (3) University Hospital Graz, (4)University of Graz, (5) University of Groningen, Beatrix Children's Hospital/ University Medical Centre Groningen, Groningen, Netherlands

Background: Inhibition of adipocyte triglyceride lipase (ATGL/PNPLA2) activity in insulin resistance and non-alcoholic fatty liver disease is an attractive therapeutic target via reducing fatty acid flux from adipose tissue to the liver. This study evaluated the impact of Atglistatin-mediated ATGL inhibition on the development of non-alcoholic steatohepatitis (NASH) in diabetic and hyper-lipidaemic mice. **Methods:** Streptozotocin-injected male mice were fed an HFD to induce NASH. Atglistatin was administered on week 4 for four weeks. We analysed liver histology, hepatic lipid content, immunohistochemistry, RNA sequencing, and serum biochemistry. Mechanistically, we treated Caco2 cells and human primary extrahepatic cholangiocyte organoids with the human ATGL inhibitors NG-497. **Results:** Atglistatin reduced body weight (-2.54 g), fat (-40%), and liver mass (-23%) and significantly improved fasting blood glucose levels (-12%). In line with a trend for reduced ALT (-45%), AP (-25%), total acylglycerol (TAG), and cholesterol contents, we observed a significant improvement in histological liver injury assessed by H&E staining and NAFLD score (-45%). The NAFLD score revealed improvement of steatosis (-60%) and inflammation (-35%) but not ballooning in the Atglistatin group. The improved inflammation was consistent with the significant reduction of Mac2-positive cells in the liver (-50%) and gonadal white adipose tissues (gWAT) (-60%). Mechanistically, Atglistatin reduced *Cpt1α* and *Abca1*, suggesting impaired Pparα signalling that favours hydrophilic bile acid synthesis. In line, *Cyp7a1, Cyp27a1,* and *Cyp2c70* were increased while *Cyp8b1* was reduced. Intestinal lipid transporters in the Atglistatin-treated mice, like *Abca1* and *Cd36,* were reduced, consistent with the reduction of liver TAG species, mostly linoleic acids. To validate the *in vivo* findings in human cells, we used the novel human-specific ATGL inhibitor NG-497. Caco2 cells treated with NG-497 showed reduced *ATGL, ABCA1, FATP5,* and *MTTP*. Furthermore, PPARα signalling was impaired in extra-hepatic cholangiocyte organoids treated with NG-497, as reflected by the significant reduction of *CPT1α* and *ABCA1*. **Conclusion:** Inhibition of ATGL activity reduces the availability of bona fide ligands for Pparα activation leading to impaired Pparα signalling, which translates into hydrophilic bile acid synthesis that interferes with dietary lipid absorption, improving the metabolic disturbances in the STAM model of NASH. The validation with the human-specific ATGL inhibitor should open a new clinical avenue for NAFLD clinical trial and treatment.



Disclosures: Henkjan J. Verkade – Ausnutria BV, Albireo, Danone Nutricia Research, Intercept, Mirum, Orphalan, and Vivet: Consultant, No, No;
The following people have nothing to disclose: Emmanuel Dauda Dixon, Thierry Claudel, Alexander Nardo, Claudia Daniela Fuchs, Veronika Mlitz, Hubert Scharnagl, Tatjana Stojakovic, Gernot Grabner, Guenter Haemmerle, Robert Zimmermann, Michael Trauner

2334-C | INHIBITION OF LEUKOTRIENE B4 RECEPTOR 1 DOES NOT PROTECT FROM NASH AND LIVER FIBROSIS IN THE CHOLINE-DEFICIENT AMINO ACID-DEFINED HIGH FAT DIET MOUSE MODEL

Erin Coyne[1], Yilin Nie[1], Desiree Abdurrachim[2], Yongqi Zhou[2], Asad Abu Bakar Ali[2], Stacey Meyers[3], Jeff Grein[3], Wendy Blumenschein[3], Brendan Gongol[1], Yang Liu[1], Cedric Hugelshofer[4], Ester Carballo-Jane[5] and Saswata Talukdar[1], (1)Cardiometabolic Diseases, Merck & Co., Inc., South San Francisco, CA, (2) Cardiometabolic Diseases, MSD, Singapore, (3) Molecular Profiling, Merck & Co., Inc., South San Francisco, CA, USA, (4)Discovery Chemistry, Merck &

Co., Inc., South San Francisco, CA, USA, (5) Quantitative Biosciences, Merck & Co., Inc., Kenilworth, NJ, USA

Background: Nonalcoholic steatohepatitis (NASH) is a prevalent disease affecting 2-6 % of the global population and is expected to be a $10-35 billion market by 2030 but there are currently no approved therapies for this chronic liver disease. NASH can progress to more severe forms of disease including fibrosis, cirrhosis, hepatic decompensation, hepatocellular carcinoma, and death. The pro-inflammatory leukotriene B4 (LTB4)/leukotriene B4 receptor 1 (Ltb4r1) axis is a potential therapeutic target for the treatment of NASH and liver fibrosis. **Methods:** To understand the role of the LTB4/Ltb4r1 axis and validate the therapeutic efficacy of Ltb4r1 inhibition in a highly inflammatory and pro-fibrotic mouse model of NASH and fibrosis, we challenged mice with a choline-deficient, amino acid-defined high fat diet, treated with an Ltb4r1 antagonist at 30 or 90 mg/kg for 8 weeks, and evaluated liver function, histology, and gene expression at the end of the study. **Results:** We found that treatment with the Ltb4r1 antagonist had no impact on liver function enzymes, however we observed a significant reduction is plasma triglyceride and leptin levels compared to vehicle control. On histological endpoints, we observed no effect of Ltb4r1 inhibition on steatosis, inflammation, or ballooning scores. In addition, there was no significant difference in liver fibrosis with Ltb4r1 inhibition. Whole liver RNA-seq and pathway analysis revealed significant changes in fatty acid, arachidonic acid, and eicosanoid metabolic processes however this was not sufficient to influence histological endpoints, NAFLD activity score, and liver fibrosis. **Conclusion:** Overall, the data from this study suggests that targeting the LTB4/Ltb4r1 axis in highly inflammatory and pro-fibrotic conditions of chronic liver disease should be considered with caution.

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Desiree Abdurrachim – MSD: Employee, No, No;
The following people have nothing to disclose: Yang Liu
Disclosure information not available at the time of publication: Yilin Nie, Yongqi Zhou, Asad Abu Bakar Ali, Stacey Meyers, Jeff Grein, Wendy Blumenschein, Brendan Gongol, Cedric Hugelshofer, Ester Carballo-Jane, Saswata Talukdar

f 2335-C | INTESTINAL IL-33-HIF-1α AXIS MEDIATES NAFLD PROGRESSION BY INCREASING GUT MICROBIOTA-DERIVED TMAO SYNTHESIS

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Background: Gut microbiota and its metabolites play a critical role in the occurrence and development of non-alcoholic fatty liver disease (NAFLD). As a dual-function protein, IL-33 performs distinct intracellular and extracellular functions. In this study, we investigated the effect of IL-33-Hif-1α axis mediated alteration of gut microbiota-derived metabolites on the regulation of NAFLD. **Methods:** Global IL-33 knockout mice ($Il33^{-/-}$) and intestinal epithelial-specific IL-33 knockout mice ($Il33^{\Delta IEC}$) and their control mice were fed either a chow diet or a 60% high-fat diet (HFD) for 24 weeks. 3,3-dimethyl-1-butanol (DMB) was administered to HFD-fed mice to inhibit gut microbiota-derived TMAO synthesis. Wild-type mice after gut microbiota depletion by antibiotic treatment were transplanted with suspension of gut microbiota from HFD-fed knockout mice and wild-type mice to determine the direct role of IL-33 in regulating gut microbiota in NAFLD. The bacterial community composition was determined by 16S rRNA sequencing. The serum metabolites were analyzed by liquid chromatography-mass spectrometry (LC-MS) metabolomics. Mouse spleen naïve CD4+ T cells and the intestinal epithelial cell line, Caco-2, were used for in vitro studies. **Results:** Intestinal IL-33 aggravated glucolipid metabolism disorders, inflammatory injury and fibrosis progression in NAFLD by disrupting the intestinal microenvironment. High-fat diet stimulated intestinal epithelial cells to produce a large amount of IL-33, and the increased IL-33 enters the epithelial nucleus, inhibiting the synthesis of Hif-1α and the activation of its downstream pathways, *Tff3* and *Adora2b*, which directly damaged the intestinal barrier. IL-33 released after intestinal epithelial cell damage promoted the expression of Hif-1α in intestinal lamina propria T lymphocytes through ST2, which directly up-regulated T-bet to promote Th1 differentiation, leading to the secretion of inflammatory cytokine IFN-γ and indirectly damaged the intestinal barrier. The dual regulatory effect of intestinal IL-33 lead to gut microbiota dysbiosis, that was, the up-regulation of TMA and its synthesis bacteria *Lachnoclostridium*, *Providencia*, *Desulfovibrio*, *Blautia* and *Prevotella*. Soon, the increased TMA is oxidized to TMAO in the liver, which caused hepatic oxidative stress injury and aggravated NAFLD progression. Transplantation of gut microbiota from IL-33 knockout mice into wild-type mice could reverse NAFLD phenotype. **Conclusion:** Intestinal IL-33 mediates the dual regulation of intestinal Th1 cells and intestinal epithelial cells on Hif-1α function to induce gut microbiota derived TMAO synthesis and finally aggravate the progression of NAFLD. Targeting intestinal IL-33 may provide a new strategy for the treatment of NAFLD.

Disclosures: The following people have nothing to disclose: Xiaojing Wang, Suping Hai, Xitang Li, Wenhui Wu, Qiang Gao, Binghui Yu, Erliang Xie, Qin Ning

2336-C | KNOCKDOWN OF HYDROGEN PEROXIDE-INDUCIBLE CLONE-5 AMELIORATES LIVER FIBROSIS IN A MOUSE MODEL OF NASH

Masahito Noguchi[1], Masashi Sakaki[2], Aya Miyauchi[1], Momoko Kobayashi-Tanabe[1], Akira Miyazaki[1] and Joo-Ri Kim-Kaneyama[1], (1)Showa University, (2)Showa University, Tokyo, Japan

Background: Hydrogen peroxide-inducible clone-5 (Hic-5), also named transforming growth factor beta-1-induced transcript 1 protein (Tgfb1i1), was found to be induced by TGF-b. We previously reported that Hic-5 expression was strongly upregulated in activated hepatic stellate cells (HSCs) of human fibrotic liver tissue and BDL- or CCl_4-induced mouse liver fibrosis. Additionally, Hic-5 deficiency significantly attenuated mouse liver fibrosis and HSC activation through inhibition of the TGF-b/Smad2 signaling pathway in the activated HSCs (J. Hepatol. 2016). Against this background, here we investigated the involvement of Hic-5 in the regulation of NASH pathogenesis. **Methods:** We examined Hic-5 expression levels with the progression of hepatic fibrosis in a choline-deficient, methionine-depleted high-fat-diet (CDAHFD)-induced NASH mouse model. NASH models were also developed in Hic-5-knockout and wild-type mice to compare the pathological changes in NASH as well as the pathological changes induced by the suppression of Hic-5 after the induction of fibrosis. We also analyzed the distribution of Hic-5 expression in fibrotic liver tissue using tissue immunostaining and single-cell RNA-seq data from patients with cirrhosis from public databases. **Results:** Hic-5 mRNA expression was induced with an increase in liver fibrosis area in the NASH mouse model. Three weeks after the start of the NASH diet, a 3.7-fold ($p = 0.007$) increase in the level of Hic-5 compared with that in the control diet group was observed. Hic-5 deficiency significantly attenuated mouse liver fibrosis and Hic-5 knockdown by siRNA in vivo also suppressed liver fibrosis in the NASH mouse model. Single-cell RNA-seq analysis showed that Hic-5 expression was particularly induced in a specific cell population among HSCs of cirrhotic patients. **Conclusion:** The suppression of fibrosis progression by Hic-5 inhibition after the induction of liver fibrosis indicates that Hic-5 has potential as a therapeutic target molecule for NASH liver fibrosis.

Disclosures: The following people have nothing to disclose: Masahito Noguchi, Masashi Sakaki, Aya Miyauchi, Momoko Kobayashi-Tanabe, Akira Miyazaki, Joo-Ri Kim-Kaneyama

2337-C | KUPFFER CELL-DERIVED IL-6 PROTECTS HUMAN HEPATOCYTES AGAINST LIPID DROPLET ACCUMULATION

Marisa Carbonaro, Regeneron Pharmaceuticals and Zhe Li, Regeneron Pharmaceuticals, Inc.

Background: Abnormal accumulation of lipid droplets in liver is a major feature of fatty liver disease, an increasing health issue in developed countries. It has been widely observed that, in humanized liver mice, in which donor human hepatocytes repopulate recipient rodent livers, engrafted human hepatocytes show defects including hepatosteatosis. Ameliorating such defects would improve the accuracy of the models to recapitulate normal human liver biology and shed light on some of the underlying mechanisms that regulate lipid accumulation in hepatocytes. **Methods:** Humanized liver mice were generated through engraftment of human hepatocytes into the livers of *FSRG* ($Fah^{-/-}$, $Sirpa^{hu/hu}$, $Rag2^{-/-}$, $Il2rg^{-/-}$) mice. Human Kupffer cells that produce hIL6 were engrafted through implantation of human hematopoietic stem cells (huHSC) into FSRG mice. Impaired IL6-GP130 signalling in engrafted human hepatocytes was restored through transduction of primary human hepatocytes with lentivirus carrying mouse IL6R or constitutively active GP130 expression vectors before implantation, or by systemic supplementation of hIL6 via either AAV dosing or genetic humanization of the murine *Il6* allele. **Results:** Abnormoal lipid droplet accumulation occurred in mouse liver engrafted with human, but not rodent hepatocytes. Providing human Kupffer cells via hematopoietic stem cell engraftment in humanized liver mice also corrected the abnormality. Restoration of hepatic IL6-GP130 signaling, through ectopic expression of mouse IL6R or constitutive activation of GP130 in human hepatocytes, or humanization of *Il6* allele in recipient mice, substantially reduced hepatosteatosis. **Conclusion:** Hepatosteatosis in humanized liver mice is associated with impaired IL6 receptor signaling in human hepatocytes, which is a result of incompatibility between murine IL6 expreesed in recipent mice and human IL6R expressed on donor hepatocytes. Hepatic GP130 signaling, maintained by IL6 that is normally provided by non-parenchymal liver cells, plays an important role in protecting hepatocytes from excessive lipid accumulation. Our observations provide not only a method to improve humanized liver models, but also suggest therapeutic potential for manipulating GP130 signaling in human liver steatosis.

Disclosures: Marisa Carbonaro – Regeneron Pharmaceuticals: Employee, No, No;
Zhe Li – Regeneron Pharmaceuticals, Inc.,: Employee, No, No;

2338-C | LIPOLYTIC HORMONES GLUCAGON AND ISOPROTERENOL DO NOT ENHANCE DEFATTING EFFECT IN NUTRIENT-RESTRICTED EX VIVO STEATOTIC RODENT LIVERS ON NORMOTHERMIC MACHINE PERFUSION

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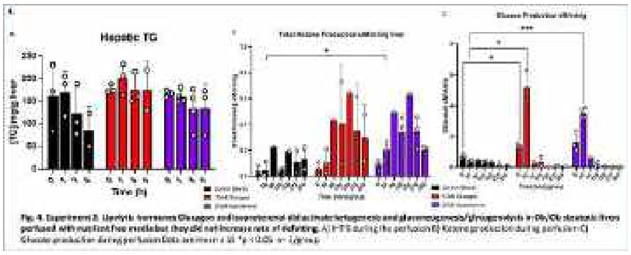
Background: Discard of steatotic donor grafts continue to contract the previous liver organ pool. It is projected that liver graft utilization will decrease from 78% to 44% by 2030. Normothermic machine perfusion has enabled researchers to explore the rehabilitation of these organs using pharmacological agents. However, many of these agents lack FDA approval for human use or ex vivo organ applications. Here we present the effects of nutrient restriction and the use of lipolytic hormones to induce defatting in rodent models of hepatic steatosis. Our research has demonstrated that steatotic livers exhibit elevated oxidative metabolism and turnover in the tricarboxylic acid (TCA) cycle. We hypothesize that by restricting Free Fatty Acids (FFA) and other nutrient substrates in an ex vivo perfusion system, livers will utilize their excessive intrahepatic triglycerides (IHTG) as a fuel source. Additionally, we aim to determine whether the addition of lipolytic hormones, namely Glucagon and Isoproterenol, can enhance lipolysis. **Methods:** Male Ob/Ob mice aged 16-20 weeks were perfused under physiological temperature and pH using a solution devoid of FFA or glucose, containing 3% BSA, 25mM NaHCO3, 118mM NaCl, 4.7mM KCl, 1.2mM MgSO4, 1.2mM KH2PO4, and 0.8mM l-carnitine. Two groups received the addition of lipolytic hormones (10nM Glucagon and 20mM Isoproterenol) to the perfusate. Membrane oxygenation provided a 95/5% mixture of oxygen and CO2. The livers were perfused for 6 hours, and a liver lobe was ligated and snap-frozen at specified intervals for IHTG quantification. **Results:** Although Glucagon (red) and Isoproterenol (purple) activated ketogenesis and increased endogenous glucose production, the steatotic livers perfused without any hormones lost 33% of their IHTG over the 6-hour perfusion period, compared to only 5% in the Glucagon group and 20% in the Isoproterenol group. **Conclusion:** Modest reductions in IHTG were observed with a perfusion solution devoid of nutrient substrates. The addition of lipolytic hormones did not enhance lipid disposal. This suggests that the Ob/Ob model may represent chronically steatotic livers that have undergone reprogramming, making them resistant to defatting even when exposed to lipolytic hormones. Further investigations are currently underway in our laboratory to elucidate these mechanisms.



Disclosures: The following people have nothing to disclose: Amin Mamoon Amin, Shawn Burgess, Justin Fletcher

2339-C | LIVER AND ADIPOSE TISSUE TRANSCRIPTOMICS IDENTIFY IMMUNE NETWORKS THAT REGULATE DISEASE SEVERITY IN PEOPLE WITH NASH AND NAFLD

Allison Wing, National Institutes of Health, Regina Umarova, National Institute of Diabetes and Digestive and Kidney Diseases, Maren Podszun, University of Hohenheim and Yaron Rotman, National Institute of Diabetes and Digestive and Kidney Diseases, Nih

Background: A subset of people with non-alcoholic fatty liver disease (NAFLD) progress to non-alcoholic steatohepatitis (NASH) but the pathways underlying this progression are unclear. The close association of NAFLD with obesity suggests an important role for adipose tissue in NAFLD severity and progression. Using transcriptomics and gene co-expression analysis, we aim to discover tissue crosstalk and identify pathways in the liver and adipose tissue that underlie NAFLD severity. **Methods**: Paired same-day liver and subcutaneous adipose tissue samples were obtained from adult subjects with NAFLD participating in a clinical trial (NCT01792115). Gene expression was quantified by RNA sequencing, and co-expression networks within each tissue were constructed using Weighted Gene Co-expression Analysis (WGCNA). Genes associated with histological scores (NASH-CRN scoring system) and networks were integrated using Mergeomics software to identify causal NAFLD gene networks and predict key regulatory (driver) genes within the co-expression networks. Ingenuity Pathway Analysis

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

was used to map co-expression networks to biological pathways. **Results**: Samples with histological scores were available from 17 subjects (median age 50, median NAS 3, 53% with NASH). In the liver, pathway analysis predicted an association of NAFLD activity score (NAS) with downregulation of interferon (*IFN*)-g signaling, with *MSR1* and *MRC1* identified as some of the key driver genes. In adipose tissue, a modest association between NAS and mitochondrial activity pathway was observed with no significant key drivers identified. However, several adipose tissue gene networks were significantly and highly correlated with hepatic portal inflammation scores. In the top three networks (FDR q < 1e-30 for all three), key driver genes *CD3D* and *RAC2*; *IKZF1* and *RGS18*; and *IRF5* and *CD45* were identified. These are predicted to be downstream of downregulated IFN-g signaling, as in the liver, and decreased T-cell pathways. **Conclusion**: We have identified gene co-expression networks which predict roles for downregulated IFN-g pathways across tissues in driving the severity of NAFLD. Importantly, adipose tissue inflammatory pathways were strongly associated with hepatic portal inflammation, suggesting a unique role for adipose-derived factors. Our findings highlight a role for hepatic and adipose aberrant IFN signaling in the progression of NAFLD.

Disclosures: The following people have nothing to disclose: Allison Wing, Regina Umarova, Yaron Rotman

Disclosure information not available at the time of publication: Maren Podszun

f 2340-C | LOSS OF KUPFFER CELL TIM4-DEPENDENT EFFEROCYTOSIS PROMOTES LIVER FIBROSIS IN NONALCOHOLIC STEATOHEPATITIS★

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Background: Nonalcoholic steatohepatitis (NASH) is an advanced stage of nonalcoholic fatty liver disease (NAFLD) and the leading cause of human chronic liver disease. Apoptosis in hepatocytes is a key feature during NASH progression, but precisely how apoptotic hepatocyte contributes to NASH progression, particularly the most important feature, liver fibrosis, remains incompletely understood. Cell death generally causes disease when clearance of dead cells by macrophages (efferocytosis) is impaired, leading to leakage of disease-causing factors. Herein, we investigate the role of liver resident Kupffer cell (KC)-dependent efferocytosis in the progression of NASH. **Methods:** KC-TIM4 expression was assayed in liver tissue sections obtained from humans and mice with normal and NASH. For mouse NASH, male C57BL/6J mice were fed either a high-fat choline-deficient L-amino-defined (HF-CDAA) diet for 4 weeks to induce early NASH, 10 weeks to induce advanced NASH, or a fructose-palmitate-cholesterol (FPC) diet for 16 weeks. For all mouse models, causation was tested by administering anti-TIM4 antibodies to wild-type mice, KC-*Timd4* knockout mice, or liver macrophages TIM4 restoration mice, followed by assessment of efferocytosis by liver macrophages and NASH fibrosis. For *ex vivo* studies, the engulfment of human and mouse apoptotic hepatocytes by primary human and mouse liver KCs was assayed. **Results:** We have shown that the accumulation of apoptotic hepatocytes in human and mouse NASH liver is associated with decreased KCs efferocytosis receptor TIM4 expression, which is consistent with impaired efferocytosis of apoptotic hepatocytes during NASH progression. The administration of anti-TIM4 inhibited the engulfment of apoptotic hepatocytes by primary human and mouse liver KCs *ex vivo*, which suppressed efferocytosis and accelerated liver fibrosis in the early experimental NASH model. Moreover, liver KC-*Timd4* deficiency caused impaired efferocytosis and accelerated liver fibrosis. In contrast, the restoration of TIM4 in liver macrophages improved impaired efferocytosis and decreased liver fibrosis in advanced NASH in our two models of diet-induced NASH. **Conclusion:** Decreased expression of KC-TIM4 occurs in NASH liver and is associated with impaired efferocytosis, and blocking TIM4-mediated efferocytosis accelerated liver fibrosis in early NASH, while restoration of TIM4 in macrophages recovered impaired efferocytosis and mitigated liver fibrosis in advanced NASH. These findings define a new mechanism contributing to NASH progression with potential therapeutic implications.

Disclosures: The following people have nothing to disclose: Hongxue Shi, Luca Valenti

Disclosure information not available at the time of publication: Xiaobo Wang, Mary P Moore, Ira Tabas

2341-C | LOSS OF OVARIAN HORMONE EXACERBATES DIET-INDUCED NAFLD

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Background: Non-alcoholic fatty liver disease (NAFLD), a common metabolic disease whose incidence is significantly increased by obesity, is characterized by excessive fat deposition in hepatocytes (steatosis). Simple steatosis progresses to non-alcoholic steatohepatitis (NASH), the advanced form of NAFLD, when the liver displays overt inflammatory damage. Much evidence indicates that the prevalence of obesity-induced NAFLD in women is much lower than that in men while

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

comparable findings are obtained from rodent studies. This demonstrates the prevalence disparity in NAFLD, which is attributable to, in large part, different levels of sex hormone especially estrogen between females and males. The present study aimed to explore the effect of loss of ovarian hormone on diet-induced NAFLD phenotype in mice. **Methods:** To achieve this, female wild type (WT) C57BL/6J mice were subjected to either sham operation or ovariectomy (OVX), at 5-6 weeks of age. After recovery for 1 week, the mice were fed a high-fat diet (HFD, 60% fat calories) for 12 weeks. Age-matched male mice were fed an HFD identically. Liver steatosis and inflammation, as well as systemic insulin sensitivity were examined. **Results:** Compared with HFD-male mice, HFD-female/sham mice displayed smaller degrees in hepatic steatosis as indicated the results of liver histology. However, the degrees of hepatic steatosis in HFD-female/OVX mice were much greater than those in HFD-female/sham mice, and comparable with those in HFD-male mice. Biochemical analysis indicated decreased expression of hepatic genes/enzymes in fatty acid oxidation. When liver inflammation was analyzed, liver sections from HFD-female/OVX mice and HFD-male mice displayed comparable numbers of F4/80 cells, but significant more F4/80 cells than those from HFD-female/sham mice. In addition, the phosphorylation levels of proinflammatory signaling through NF-kB p65 and JNK p46 in HFD-female/OVX mice were significantly higher than those in HFD-female/sham mice, but were comparable with those in HFD-male mice. These changes were likely attributable to increased hepatic expression of stimulator of interferon gene (STING), which is a critical mediator promoting macrophage proinflammatory activation. Consistent with NAFLD phenotype, the severity of diet-induced systemic insulin resistance in female/OVX mice was greater than that in female/sham, but comparable with that in male mice. **Conclusion:** Taken together, these results demonstrated that loss of ovarian hormone abolishes sex-based protective effects on diet-induced NAFLD in female mice. As such, enhancing estrogen actions may be viable for managing NAFLD in males.

Disclosures: The following people have nothing to disclose: Xinlei Guo, Minji Koo, Honggui Li, Chaodong Wu

2342-C | LOSS OF SULT2B1b PREVENTS HEPATIC STEATOSIS AND INSULIN RESISTANCE BY REGULATING ENERGY EXPENDITURE AND METABOLISM

Jingyuan Wang, Gregory M. Young and Wen Xie, University of Pittsburgh

Background: Obesity and Type II Diabetes (T2D) and their related comorbidities are one of the leading causes of loss of life and disability globally. The need to find potential therapeutic targets to help curb growing insulin resistance and obesity rates will be vital to stop this health crisis. Sult2b1b is a sulfotransferase that preferentially conjugates a sulfate group onto cholesterol to form cholesterol sulfate. Our previous study showed that over expression of Sult2b1b or treatment with cholesterol sulfate improved energy metabolism by reducing lipogenesis and gluconeogenesis. In this study, we aimed to investigate whether and how Sult2b1b inhibition affects the development of obesity and T2D. **Methods:** WT and Sult2b1b$^{-/-}$ male mice were fed with high-fat-diet (HFD) for 12 weeks to induce obesity and T2D. We also introduced the Sult2b1b$^{-/-}$ allele into the ob/ob mice by cross-breeding. Body weight and composition were monitored weekly. Glucose and insulin tolerance tests were performed every four weeks. Metabolic cage study, histological and biochemical analysis was conducted at the end point. **Results:** Sult2b1b knockout protected mice against hepatic steatosis and insulin resistance in both HFD-induced obesity and ob/ob background mice. Furthermore, the loss of Sult2b1b significantly decreased liver steatosis, hyperlipidemia, and white adipose tissue (WAT) inflammation. Metabolic cage study showed a significant increase of energy expenditure in the Sult2b1b$^{-/-}$ mice without changes in their locomotive activities. Transcriptome analysis indicated reduced gluconeogenesis in liver, increased fatty acid oxidation in WAT, and increased thermogenesis in skeletal muscle. **Conclusion:** Our results demonstrated that Sult2b1b played a regulatory role in the development of obesity and T2D. Given the protection provided through genetic ablation, inhibiting Sult2b1b may be a promising target to combat obesity and T2D.

Disclosures: The following people have nothing to disclose: Jingyuan Wang, Gregory M. Young, Wen Xie

2343-C | MANNOSE ATTENUATES HEPATIC STEATOSIS IN A MOUSE NAFLD/NASH MODEL AND HEPATOCYTES IN VITRO THROUGH MODULATION OF KHK EXPRESSION

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Background: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide, yet there are no approved therapies. We have previously shown that mannose, a simple sugar, can dampen hepatic stellate cell activation *in vitro*, but its role in NAFLD-induced steatosis has not been studied. **Methods**: We used the well-validated FAT-NASH model (Tsuchida et al, J. Hepatology 2018) to induce hepatic steatosis. Mice were fed normal diet or FAT-NASH regimen (high fat, fructose, and cholesterol, and low dose CCl4) for 12 weeks. Mannose was supplied in drinking water (5% or 20%) for either the full 12 weeks to assess for preventative effects against steatosis development, or after a 6-week delay when steatosis and fibrosis are already present. Effectiveness was determined through standard histological assessment (hematoxylin and eosin (H&E) and oil red O (ORO) staining) and quantification of liver triglycerides (TG) and cholesterol. We further used an unbiased, AI-based approach to quantify steatosis phenotypes in liver sections (Fibro-Nest^{TM}). Human hepatocytes (THLE-5B) were conditioned *in vitro* with 750 µM oleic + palmitic acid (2:1) without or with 100mM fructose to induce steatosis and treated with 25mM mannose for 72 hours. *In vitro* efficacy was assayed by ORO staining and western blot analysis. Mouse liver bulk RNAseq and western blots were performed. **Results**: *In vivo,* steatosis prevalence was reduced in all mannose-treated NASH mice groups, evident qualitatively with H&E and ORO staining and quantitatively with AI-based histological assessment ($p < 0.05$). Liver TG and cholesterol were also decreased in all treatment groups with the greatest reduction of liver TG seen in delayed 5% and 20% mannose treatments ($p = 0.002$ and 0.001 respectively). *In vitro,* 25 mM mannose decreased steatosis by 33% ($p < 0.05$). Interestingly, steatosis reduction with mannose treatment was only seen in fructose-conditioned hepatocytes and not in oleic + palmitic acid alone. Mouse bulk liver RNAseq and validating qPCR revealed fructolytic enzyme ketohexokinase (*Khk)* was increased in NASH mice compared to normal diet ($p < 0.01$) but was decreased with 5% and 20% mannose treatments ($p < 0.05$ and $p < 0.001$ respectively). Western blot assays confirmed reduction of KHK in all treatment groups with the greatest decrease in 20% mannose prophylactic treatments in mouse livers (66% reduction, $p = 0.01$) and with 25 mM mannose in human hepatocytes ($p = 0.01$). **Conclusion**: Our findings uncover mannose as a novel therapeutic for NAFLD/NASH, possibly acting through modulation of fructose metabolizing pathways. Ongoing studies will test the role of mannose and KHK in liver steatosis.

Disclosures: Li Chen – PharmaNest Inc: Employee, Yes, No; PharmaNest: Stock – privately held company (individual stocks and stock options), Yes, No;

Mathieu M. Petitjean – PharmaNest Inc: Stock – privately held company (individual stocks and stock options), Yes, No; PharmaNest: Executive role , Yes, No;

Jaime Chu – Albireo: Consultant, No, No;

The following people have nothing to disclose: John Hong, Joshaya Trotman, Yvette Carbajal, Mariel Glass, Peng Zhang, Liheng Wang, Charles DeRossi

2344-C | MATERNAL OBESOGENIC DIET PROMOTES OFFSPRING NON-ALCOHOLIC FATTY LIVER DISEASE PROGRESSION WITH MICROBIOME DEPENDENT ALTERATIONS IN THE WEANING REACTION

Vung Lian[1]*, Holly Hinrichs*[1]*, Monica Young*[1]*, Phillip I Tarr*[1]*, Nicholas Davidson*[2] *and Michael Thompson*[1]*, (1) Washington University School of Medicine in St. Louis, (2)Washington University Medical School, Departments of Medicine and Molecular Biology and Pharmacology, Saint Louis, MO*

Background: Maternal obesity is associated with development of hepatic steatosis in offspring and maternal obesogenic diet exposure promotes worse NAFLD in animal models. The mechanisms driving this programming event are not fully defined. One mechanism of transmission of developmentally programmed phenotypes is via transfer of an altered microbiome from Mom to offspring. The specific mechanism for how an altered offspring microbiome increases susceptibility to NAFLD is not clear. One path may be via a critical early life event termed the 'weaning reaction' that is dependent on the early microbiome and when altered results in worse pathologic inflammation in the offspring. Given that the microbiome is altered following maternal obesogenic diet exposure, we hypothesized that maternal obesogenic diet would affect the weaning reaction in offspring with an associated increase in progressive offspring NAFLD. **Methods:** Female mice were fed chow (CON) or high fat-fructose-cholesterol (HFFC) diet for 6 weeks and bred with lean males. A subset of these mice were cross-fostered with the opposite dam to evaluate the impact of the early microbiome. Terminal ileum was collected from offspring at 2, 3, 4, and 5 weeks of age to evaluate expression of *Tnfa* and *Ifng*. 16S sequencing of cecal contents of 3 week old offspring was performed. Offspring from each group were weaned to HFFC diet for 7 weeks to induce development of non-alcoholic steatohepatitis. Liver was collected for histopathologic analysis. **Results:** Ileal *Tnfa* and *Ifng* expression peaked at 3 weeks in CON offspring consistent with the pattern seen previously. A rise in ileal *Tnfa* and *Ifng* expression was not observed in HFFC offspring suggesting a loss of the weaning reaction. 16S sequencing at 3 weeks identified shifts in the microbiome in HFFC offspring. Alpha-diversity was decreased in HFFC offspring. Shifts in abundance of multiple genera were identified included increased *Lactobacillus* and increased *Akkermansia* in HFFC offspring. *Bacteroides* were decreased in HFFC offspring. In offspring weaned to HFFC diet, the degree of steatosis, inflammation, and fibrosis was increased in HFFC offspring compared to CON offspring. Cross-fostering HFFC offspring with CON dam induced a weaning reaction while conversely cross-fostering CON offspring with HFFC dam attenuated the weaning reaction. Preliminary findings in male and female offspring show that cross-fostering HFFC offspring with a CON dam reduced hepatic inflammation and fibrosis during HFFC diet feeding. **Conclusion:** These findings provide preliminary evidence that maternal obesogenic diet exposure affects the weaning reaction with associated shifts in the offspring microbiome. This effect on the weaning reaction is associated with worse susceptibility to NAFLD in mice. Preliminary data show that this phenotype is dependent on early changes in the gut microbiome.

Disclosures: The following people have nothing to disclose: Michael Thompson

Disclosure information not available at the time of publication: Vung Lian, Holly Hinrichs, Monica Young, Phillip I Tarr, Nicholas Davidson

2345-C | MICRORNA-206-3p MIMICS THE FUNCTIONS OF LIPID-LOWERING MEDICATIONS, STATINS, AND LXRA AGONISTS

Ningning Liu, Chinese Academy of Sciences and Guisheng Song, University of Minnesota

Background: Hepatosteatosis, hypertriglyceridemia, and hypertriglyceridemia are interconnected metabolic disorders. This study is designed to characterize how MicroRNA-206-3p (miR-206) simultaneously prevents *de novo* lipogenesis (DNL), cholesterol synthesis, and VLDL production in hepatocytes but drives cholesterol efflux in macrophages. **Methods:** Mice were treated with a high-fat-high-cholesterol (HFHC) diet to induce hepatosteatosis, hypertriglyceridemia and hypercholesterolemia. MimiR-206 mimic was used to elevate levels of miR-206 in hepatocytes and macrophages of mice. AAV8 was used to specifically express miR-206 in hepatocytes. To calculate the VLDL production rate, mice were injected with Triton WR1339 and ^{35}S-methionine/cysteine to inhibit lipolysis and to label newly synthesized proteins. ^{3}H-cholesterol-labeled and acLDL-loaded J774 cells were used to determine if miR-206 drives cholesterol efflux. **Results:** Overload of cholesterol and triglycerides reduced miR-206 in hepatocytes and macrophages. A negative feedback between LXRα (liver X receptor) and miR-206 is formed to maintain high LXRα and low miR-206 in hepatocytes. Systemic administration of miR-206 alleviated hepatosteatosis, hypertriglyceridemia and hypercholesterolemia in mice. A significant reduction in LDL-cholesterol and VLDL-cholesterol but unaltered HDL-cholesterol was observed in miR-206-treated mice. Consistent with these observations, miR-206 reprogrammed the transcriptome of hepatocytes towards inhibition of DNL, cholesterol synthesis, and assembly and secretion of VLDL. In macrophages, miR-206 activated expression of genes regulating cholesterol efflux. Hepatocyte-specific expression of miR-206 reduced hepatic and circulating triglycerides and cholesterol as well as VLDL production, while transplantation of macrophages bearing miR-206 facilitated cholesterol efflux. Mechanistically, miR-206 impaired expression of *Lxrα* and *Hmgcr* by interacting with their respective 3'untranslated regions in hepatocytes but facilitated expression of *Lxrα* by directly targeting macrophage-specific TRPS1 (tricho-rhino-phalangeal syndrome 1), a transcription repressor of *Lxrα*, in macrophages. Disrupting the interaction of miR-206 with *Hmgcr* and *Lxrα* prevented miR-206 from inhibiting DNL, cholesterol synthesis and VLDL production. **Conclusion:** MiR-206 inhibits DNL and drives cholesterol efflux via differentially modulating LXRα in hepatocytes and macrophages, in addition to impairing cholesterol synthesis and VLDL production. MiR-206 simulates the functions of lipid-lowering medications, statins and LXRα agonists.

Disclosures: The following people have nothing to disclose: Ningning Liu, Guisheng Song

2346-C | MIR-122 OVEREXPRESSION INDUCES AUTOPHAGY VIA PKM2 DOWNREGULATION IN NON-ALCOHOLIC FATTY LIVER DISEASE

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Background: Non-alcoholic Fatty Liver Disease (NAFLD) has emerged as a leading global cause for chronic liver disease and results in a serious public health problem. microRNA-122, an abundant miRNA present in the liver, is downregulated in different cancers including hepatocellular carcinoma (HCC). Pyruvate Kinase (PK) is a rate limiting enzyme in the last physiologically irreversible step of glycolysis. Emerging evidence showed that PKM2 plays a significant role in HCC and is highly expressed in tumor tissues. Overexpression of PKM2 induces inflammation and inhibits autophagy and apoptosis in cancer cells. miR-122 targets PKM2 and it was hypothesized that PKM2 inhibition may downregulate in NAFLD, while inducing autophagy. Thus, PKM2 may represent a new target for monitoring and treatment of NAFLD. **Methods:** After animal ethics committee's approval, C57BL/6 mice were fed with control diet, choline sufficient L-amino acid (CSAA) diet and choline deficient L-amino acid (CDAA) diet. After 6, 18, 32 and 54 weeks, these

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

mice were euthanized, both protein and RNA were isolated from the liver tissues. The change in miR-122, PKM2, Atg7, Beclin-1, LC3B expression was analyzed by RT-PCR and Western blotting. The role of PKM2 and miR-122 regulation was elucidated in in-vitro studies. HepG2 cells were treated with free fatty acids (Oleic acid, Palmitic acid, Linoleic acid, 650 µM each). After 48 hours, miR-122 and PKM2 mRNA expression were analyzed using RT-PCR. Proteins were analyzed by immunoblotting technique after 72 hours. miR-122 mimic were used for miR-122 overexpression in HepG2 cells. PKM2 and autophagy marker proteins were analyzed. Knockdown of PKM2 was achieved using PKM2 specific siRNAs and autophagy markers were determined by immunoblotting. **Results:** In NAFLD mice model system, CDAA diet fed mice showed a downregulation of miR-122 expression, upregulation of PKM2 (p d 0.05) and the autophagy marker proteins Atg7, Beclin-1, LC3B was downregulated (p d 0.05). In FFAs-induced HepG2 cells, PKM2 expression was increased, while autophagy markers were downregulated significantly (p d 0.05). In miR-122 over-expressing HepG2 cells, the expression of PKM2 was downregulated by two-fold (p d 0.05), while the autophagy markers were increased significantly. PKM2 downregulation resulted in HepG2 cells, reversed the miR-122 induced changes. **Conclusion:** These results down regulation of miR-122 resulted in increased PKM-2 expression, and inhibiting PKM-2 resulted in an enhanced autophagy, suggesting that targeting PKM-2 could provide a novel strategy for regulating NAFLD progression leading to HCC.

Disclosures: The following people have nothing to disclose: Md Musa Hossain, Amrendra Kumar Sah, Amit Mishra, Akanksha M, Senthil Kumar Venugopal

2347-C | MODELLING THE BIOLOGICAL MECHANISMS OF A PNPLA3 AND HSD17B13 POLYMORPHISMS IN A 3D HUMAN LIVER SPHEROID OF NASH

Radina Kostadinova, Jesus Glaus, Angelina Freitag, Philipp Vonschallen, Arumugham Raghunathan and Francisco Verdeguer, Insphero

Background: Non-alcoholic steatohepatitis (NASH) is a progressive severe disease characterized by lipid accumulation, inflammation and fibrosis in the liver. Single nucleotide polymorphisms (SNPs) at specific loci have revealed differential propensity to develop NASH. Among them, “GG” rs738409 located in PNPLA3 results in the I148M amino acid change and increase the odd ratio to develop NASH. On the other hand, a truncating mutation in HSD17B13 leads to a protection from liver fibrosis in NASH. The mechanism of both PNPLA3 and HSD17B13 is not clearly understood. The aim of this study was to provide a human spheroid model carrying either PNPLA3 or HSD17B13 SNPs to phenotypically characterize their role in NASH development. **Methods:** Human 3D NASH model of spheroidal, scaffold free co-culture was developed of single donors from primary hepatocytes, Kupffer cells, liver endothelial cells and hepatic stellate cells. Single donor of primary hepatocytes were genotyped and selected for PNPLA3 rs738409 GG, GC or CC genotyes and HSD17B13 for major allele or minor T:A allele. **Results:** We show that steatotic and proinflammatory conditions lead to increased intracellular triglycerides levels and secretion of inflammatory markers IL-6, MIP-1α, TNF-α, IL-10, MCP-1 and IL-8 and increased secretion of procollagen peptides I and III. These results show a recapitulation of the hallmarks of NASH. PNPLA3(I148M) genotype in liver spheroids resulted in an increased levels of steatosis and fibrosis measured by triglyceride content and collagen secretion compared to the major allele. In line with these results, transcriptomics analysis show that both de-novo lipogenesis and fibrotic pathways are elevated in the PNPLA3(I148) donors compared to major allele. These results are in agreement with the expected phenotypic propensity to develop NASH in the human population carrying the PNPLA3(I148M) variant. We showed in addition an elevation of intracellular triglycerides but protection of fibrosis indicated by decreased procollagen 1 levels in the mutant HSD17B13 T:A variant. **Conclusion:** We show that genetically defined spheroid models containing relevant SNPs are a good tool to understand their biological mechanisms of action and would in addition help predicting drug responses for patients stratification.

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Disclosure information not available at the time of publication: Jesus Glaus, Angelina Freitag, Philipp Vonschallen, Arumugham Raghunathan

2348-C | MOLECULAR PATHOGENESIS OF NASH THROUGH THE DYSREGULATION OF METABOLIC ORGAN NETWORK IN THE NASH DERIVED HCC MODEL MOUSE TREATED WITH STREPTOZOTOCIN-HIGH FAT DIET

Taishi Hashiguchi, SMC Laboratories, Inc.

Background: Non-alcoholic steatohepatitis (NASH) is an increasingly prevalent chronic liver disease. NASH patients often exhibit gut dysbiosis, and dysfunction in adipose tissue and metabolism. Although the mechanism of NASH progression has not been fully elucidated, the multiple parallel hits hypothesis suggests abnormalities in adipocytokines, intestinal microflora, and endotoxins are intertwined, and could contribute to development of NASH. The STAM™ model is a clinically-correlated murine NASH model which shows the same pathological progression as human NASH patients, and has been widely used for pharmacological and basic research. However, analysis of the model has focused on the liver. Considering organ crosstalk, mutual biological communication between organs, interactions between the liver, and the gut and adipose tissue in the model should be clarified. **Methods:** NASH was induced in male mice by a single subcutaneous injection of 200 μg streptozotocin solution 2 days after birth and feeding with high-fat diet after 4 weeks of age. The mice were sacrificed at NASH stage, sampling colon and adipose tissue. Colon samples were snap frozen in liquid nitrogen and stored at -80˚C for tight junction-related protein analysis. Adipose tissue was prepared into paraffin blocks for HE staining. Blood adiponectin was analyzed to confirm changes in adipocytokine profile. **Results:** Tight junction-related proteins in the intestine of STAM™, analyzed by ELISA, showed that expression of ZO-1 decreased with the progression of disease. Increased expression of endotoxin in the blood was also observed in STAM™ mice. HE staining of adipose tissue revealed hypertrophy of adipocytes. Adiponectin expression was decreased in STAM™. **Conclusion:** Decreased expression of ZO-1 in the intestine of STAM™ mice suggests the occurrence of leaky gut, and abnormalities in adipocytokine secretion were also observed. Together with the liver, phenotypes in these organs are highly similar to human NASH patients, and might be involved in the pathogenesis of NASH.

Disclosures: Taishi Hashiguchi – SMC Laboratories,Inc: Employee, No, Yes;

2349-C | MUTATION OF PXR PHOSPHORYLATION MOTIF AT Ser347 IS ASSOCIATED WITH MORE SEVERE LIVER DAMAGE IN DIET-INDUCED NON-ALCOHOLIC STEATOHEPATITIS IN MICE.

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Background: Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disorders initially manifested as hepatic steatosis and may progress into inflammation (non-alcoholic steatohepatitis; NASH), fibrosis, cirrhosis, and hepatocellular carcinoma. Hepatic nuclear receptors (NRs) are a large group of transcription factors that regulate a variety of liver functions and affect NASH pathogenesis. Pregnane X Receptor (PXR, NR1I2) is a ligand-activated NR critical in regulating drug metabolizing enzymes and transporters and playing a key role in maintaining bile acid, glucose, lipid, and cholesterol homeostasis in the liver. The function and transcriptional activity of PXR can be regulated in a ligand-independent manner through post-translational modifications, such as phosphorylation at Ser347 in mice or Ser350 in humans. Mutation of this conserved phosphorylation motif of PXR *in vitro* alters human PXR transcriptional activity; however, the mechanism remains elusive. In this study, we utilized mice with a PXR Ser347Ala knock-in mutation (PXR-KI) to investigate the effects of blocking this phosphorylation site in NASH development. **Methods:** Six-week old wild-type (WT) and PXR-KI male mice, both on the C57BL/6J genetic background, were fed a high fat diet (HFD; diet with 40 Kcal% palm oil fat, 20 kcal% fructose, and 2% cholesterol), a low fat diet (LFD; 10 kcal% fat and carbohydrate mainly as corn starch), or a chow control diet (CCD) for 16 weeks. Hepatic injury, steatosis, inflammation, and fibrosis were assessed biochemically (ALT, ALP, triglycerides, total cholesterol, total bile acids), by H&E staining, hepatic lipid extraction (cholesterol, triglycerides), and qPCR. **Results:** On HFD, PXR-KI mice showed an increase in liver/body weight ratio compared to WT HFD, PXR-KI CCD, and LFD. Additionally, PXR-KI HFD mice displayed a trend of increased serum total bile acids, serum ALT, and hepatic triglycerides compared to WT HFD. Serum total cholesterol was significantly elevated in PXR-KI HFD as compared to WT-HFD and PXR-KI groups. Moreover, hepatic mRNA expression of genes related to lipid metabolism, *Cd36* (fatty acid uptake), *Fasn* (fatty acid synthase), and fibrosis *Col1a1* (collagen type 1), were elevated in PXR-KI HFD compared to WT HFD and PXR-KI CCD groups. Interestingly, the mRNA levels of *Fasn* were also increased in WT LFD compared to WT HFD. Further, the expression of PXR target gene, *Cyp3a11*, was decreased in mice fed HFD compared to CCD mice, while *G6pase* (glucose 6 phosphatase), was decreased in WT HFD compared to WT CCD and LFD. **Conclusion:** These data suggest that blocking PXR ser347 phosphorylation motif may exacerbate NASH progression, indicating the importance of this phosphorylation motif in regulating PXR functions including maintenance of bile acid, glucose, and lipid homeostasis and thus the development of NASH.

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Disclosure information not available at the time of publication: Rulaiha E Taylor, Masahiko Negishi

2350-C | NLRP3 INFLAMMASOME ACTIVATION IN NEUTROPHILS DRIVES HEPATIC STELLATE CELL ACTIVATION IN MURINE NON-ALCOHOLIC STEATOHEPATITIS

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Background: Chronic inflammation represents a central driver of disease progression in Nonalcoholic Steatohepatitis (NASH). Activation of the NLRP3 inflammasome, a cytosolic multiprotein complex that mediates sterile inflammatory responses, in leukocytes has been proposed to be a key driver of murine and human NASH. However, the relevance of NLRP3 inflammasome activation in either macrophages or neutrophils that contribute to the pathology of NASH remains unknown. In this study the contribution of neutrophil specific NLRP3 inflammasome activation in NASH was investigated. **Methods:** Neutrophil specific Nlrp3 knock-out mice were generated to investigate the role of NLRP3 inflammasome activation in neutrophils. A chronic (choline-deficient, L-amino acid-defined high-fat diet (CDAA-HFAT)) liver injury model was used to induce in vivo NLRP3 activation and fibrotic-non-alcoholic steatohepatitis (NASH). Mice were put on CDAA-HFAT diet for 10 weeks and liver steatosis, inflammation and fibrosis were analysed by immunohistochemistry and RT-PCR. **Results:** Neutrophil-specific Nlrp3 knock-out did not show a difference in the degree of steatosis compared to WT mice. Furthermore, population of Kupffer cells, the resident macrophages in the liver, was similar in both neutrophil-specific Nlrp3 knock-out and WT mice analysed by immunohistochemistry and RT-PCR. Interestingly, Neutrophil-specific Nlrp3 knock-out resulted in reduced mRNA levels of α-SMA and vimentin, markers for HSC activation, compared to WT mice analysed by RT-PCR. Furthermore, α-SMA expression was decreased on protein level in neutrophil-specific Nlrp3 knock-out mice compared to WT mice analysed by immunohistochemistry. Liver fibrosis, a key feature of NASH, was reduced in neutrophil-specific Nlrp3 knock-out mice compared to WT mice. Levels of mRNA of Col3a and CTGF were reduced in neutrophil-specific Nlrp3 knock-out mice compared to WT mice. **Conclusion:** This study provides novel insights in the cell-specific role of NLRP3 activation in neutrophils in the pathogenesis of NASH. NLRP3 inflammasome activation in neutrophils was identified as crucial for the progression to fibrotic-NASH.

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The following people have nothing to disclose: Benedikt Kaufmann, Ola Leszczynska, Helmut Friess, Daniel Hartmann
Disclosure information not available at the time of publication: Laela Booshehri, Lori Broderick

2351-C | OAT BETA-GLUCAN AMELIORATES NON-ALCOHOLIC FATTY LIVER DISEASE IN A PREBIOTIC MANNER

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Background: The gut and liver have a close bilateral relationship that influences both liver pathology and hemostasis. Oat beta-glucan, a non-digestible polysaccharide, has shown promising effects on metabolic syndrome hallmarks such as hyperlipidemia. However, its impact on non-alcoholic fatty liver disease (NAFLD), particularly NAFLD fibrosis, remains unknown. Therefore, we investigated the effect of oat beta-glucan on NAFLD progression. **Methods:** We examined the effect of beta-glucan on NAFLD progression using a Western-style diet (WSD)-induced NAFLD model. We characterized the metabolic profile, including fat distribution, glucose tolerance, and lipid metabolism, as well as hepatic inflammation and fibrosis. Additionally, we analyzed gut microbiota and bile acid composition. The gut microbiota was modulated using broad-spectrum antibiotics (Abx). **Results:** Oat beta-glucan supplementation did not affect the metabolic phenotype. However, treatment with beta-glucan reduced intrahepatic inflammation, which was associated with a significant reduction in infiltrating monocyte-derived macrophages (MoMFs), fibroinflammatory pathways, and hepatic fibrosis. This protective effect depended on the gut microbiota and was lost with Abx treatment. Oat beta-glucan modulated the gut microbiota composition in a prebiotic manner, partially reversing unfavorable changes associated with WSD and promoting protective taxa, including *Ruminococcus* and *Lactobacillus*. Consistent with these findings, we observed significantly reduced translocation of Toll-like receptor ligands after beta-glucan treatment. **Conclusion:** Our study identifies oat beta-glucan as a novel and potent dietary component that improves intrahepatic inflammation and fibrosis in diet-induced NAFLD. These results suggest that beta-glucan may be a cost-effective and well-tolerated new agent for preventing NAFLD progression, warranting assessment in clinical studies.

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2352-C | ORAL SUPPLEMENTATION OF DIMETHYL FUMARATE AMELIORATES STEATOSIS AND FIBROSIS IN MOUSE MODEL OF NASH

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Background: Metabolic dysregulation, such as an imbalance of free fatty acids and amino acids (AAs), is involved in the development of steatosis and fibrosis in NASH. We previously showed that, in NASH model mice fed with a high-fat, methionine (Met)-restricted and Tyrosine (Tyr)-deficient diet, hepatic fumarate quantity and Nrf2 expression were decreased, resulting in the reduction of VLDL excretion from the liver. In this study, we aimed to evaluate the impact of the supplementation of fumarate ester, dimethyl fumarate (DMF), on the pathogenesis of NASH and disclose its metabolic mechanisms in NASH mouse model. **Methods:** In order to clarify the relationship between 24 plasma AAs and lipoprotein profiles, we enrolled 41 patients diagnosed with NAFLD by needle biopsy. In mouse experiments, C57BL/6 mice were fed with a high fructose, saturated fatty acid and cholesterol (FFC) diet for 20 weeks. We compared biochemical data, plasma lipoprotein profiles, and pathology among normal chow fed mice, FFC diet fed mice (FFC) and FFC diet plus DMF fed mice (FFC+DMF). Metabolites and metabolic genes in the liver were assessed using metabolomics (CE-TOFMS) and RNA-seq at short-term (2 weeks) and long-term (20 weeks), respectively. In order to elucidate antioxidant mechanism by DMF, intracellular reactive oxygen species (ROS), Nrf2 and AAs in hepatocytes were measured *in vitro* by fluorescent microscopy and HPLC, respectively. **Results:** In early-stage NAFLD patients, fumarate related AAs; Met, phenylalanine (Phe) and Tyr were positively correlated with the large VLDL-TG level and HOMA-R, supporting for the rationale of the fumarate supplementation. In mice, the FFC group became obese, hyperglycemic and exhibited pathological changes of NASH liver (steatosis, inflammation, ballooning and fibrosis) at 20 weeks. Metabolomics and RNA-seq revealed that the FFC group decreased the level of fumarate and increased beta oxidation (the elevation of acetyl CoA, Acaa1a and Hadh) at 2 weeks. Interestingly, at 20 weeks, beta oxidation was inversely decreased and then increased gluconeogenesis (the increase of NADH / NAD ratio and the decrease of fumarate related AAs), and then large VLDL-TG was significantly decreased. On the other hand, in the FFC +DMF group, obesity and hyperglycemia were prevented, and pathological changes of NASH liver were ameliorated and the lipoprotein profiles were normalized. Metabolomics analysis revealed that DMF supplementation restored these AAs levels and then improved beta oxidation and excess gluconeogenesis in the liver. *In vitro*, Monomethyl fumarate, derivate of DMF, resulted in the nuclear translocation of Nrf2 and decreased ROS and the fumarate related AAs consumption in hepatocytes treated with fatty acids. **Conclusion:** Oral supplementation of DMF could serve as one of the dietary interventions to NASH, the mechanisms of which are the restoration of metabolic imbalance of AAs and enhancing VLDL excretion from the liver.

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The following people have nothing to disclose: Masaaki Mino, Eiji Kakazu, Akitoshi Sano, Toshihiro Sakata, Taiji Yamazoe, Michitaka Matsuda, Taizo Mori, Sachiyo Yoshio

2353-C | ORGAN-ON-A-CHIP NAFLD/NASH MODEL EXPRESSING PNPLA3-I148M AND TM6SF2-E167K ALLOWS FOR BIOMARKER DISCOVERY THROUGH UNTARGETED METABOLOMIC PROFILING.

Émanuel Paré, Claudia Carpentier, Maxim Maheux, Jérémy Loehr, Émilie Pic and Jacques Corbeil, Université Laval

Background: NASH is a disease with multiple causes ranging from genetic background, lifestyle, nutrition, and drugs. While most of the efforts are concentrated at detecting and treating the advanced forms of the disease, the lack of physiologically relevant models limits our ability to identify and treat at risk populations at the early stages. Moreover, current diagnostic and prognostic methods require invasive biopsies and expensive imaging devices with limited success. In this study, we used organ-on-a-chip to create a model that reproduces the main cellular characteristics of the disease: intracellular fatty acid accumulation, inflammation, apoptosis and fibrosis in a 3D co-culture of differentiated hepatic and stellate cells. We introduced the two primary genetic mutations associated with NAFLD/NASH to mimic genetic subgroups of the disease. New NASH biomarkers can be identified by treating the cells with fatty acids, diet-associated molecules and drugs and monitoring their impact on the abundance of specific metabolites. **Methods:** Clonal populations of HepaRG cells expressing PNPLA3-I148M or TM6SF2-E167K were generated using CRISPR-Cas9. The model was developed using the commercially available Organ-on-a-chip system from Mimetas®. A mixture of HepaRG and LX2 cells (ratio 9:1) was seeded in a type I collagen gel on a 2-lane Organoplate. Culture media and cell samples were analysed on an Acquity I-class UPLC system with either a BEH Amide or a CSH C18 column coupled to a Synapt G2-si mass spectrometer in MSe mode. Confocal microscopy was used to perform 3D imaging of cell and disease-relevant markers. **Results:** Treating the model with palmitic acid (PA) and oleic acid (OA) caused an accumulation of lipid droplets in hepatocytes without affecting other cell subtypes in the co-culture. Caspase 3/7 assays revealed that PA increased the number of apoptotic cells while OA did not. Moreover, a combination of PA and OA did not affect the number of apoptotic cells, suggesting a protective role for unsaturated fatty acids. Untargeted metabolomics and lipidomics analysis revealed distinct metabolic signatures between the mock-transfected and mutant cell lines. We identified 168 features that allow distinction of PNPLA3-I148M and 262 features for TM6SF2-E167K mutants. Preliminary functional analysis using Metaboanalyst 5.0 associated some of those features to amino acid-related metabolic pathways and further analysis and identification is under way. **Conclusion:** 1)Our model exhibits the main characteristics of the NAFLD/NASH. 2) We recapitulated the most common genetic background associated with NASH in a high-throughput model compatible with untargeted mass spectrometry. 3) This proof-of-concept established our ability to identify putative novel disease-related metabolomic biomarkers associated with specific genetic backgrounds.

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Disclosure information not available at the time of publication: Claudia Carpentier, Maxim Maheux, Jérémy Loehr, Émilie Pic, Jacques Corbeil

2354-C | PATHOGENETIC ANALYSIS OF NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND NONALCOHOLIC STEATOHEPATITIS (NASH) WITH MULTI-CELL-LINEAGE HUMAN LIVER ORGANOIDS

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Background: Nonalcoholic fatty liver disease (NAFLD) and its advanced form, nonalcoholic steatohepatitis (NASH), are prevalent liver diseases with no effective treatment available. Currently, there is a lack of a realistic *ex vivo* modeling system that recapitulates some of the *in vivo* pathophysiological microenvironment for studying the pathological response of different hepatic lineage cells during the progression of NAFLD/NASH. **Methods:** Primary human hepatocytes, hepatic stellate cells (HSCs), liver endothelial cells (LECs), cholangiocytes (CHOs), and Kupffer cells (KC) were isolated from liver explants of healthy donors and NAFLD livers. Scaffold-free 3D human liver organoids (3D-HLOs) were created by co-culturing 5 major human hepatic cells (HC+LEC+HSC+CHOL+KC) in a low attachment 96-well plate. Normal 3D-HLOs were subjected to the different concentrations of free fatty acid treatment (FFA, oleic acid:palmitic acid, 2:1) with or without lipopolysaccharide (LPS) for 14 days to induce steatosis, fibrosis, LEC dysfunction, and inflammation. As a comparison, individual cell lines including HCs, CHOLs, and LECs were treated with different concentrations of FFA for 48 hours. Normal 3D-HLOs+FFA ± LPS and NAFLD 3D-HLOs were subjected to the treatment of leading compounds in clinical development for NASH including obeticholic acid (OCA, 1mM), lanifibranor (LAN, 10mM), FGF19 (10ng/ml) and Tirzeptide (200nM) for 7 days to assess the functionality of organoids and drug responses. RT-qPCR (PCR), immunoreactivity, EIA, and biochemistry assays were performed to determine 3D-HLO functional phenotype, fibrosis, angiogenesis, and secretion of albumin (ALB) and total bile acids (TBA). **Results:** FFA treatment induces a robust lipid accumulation in HCs and CHOLs, but much less in LECs. We found that FFA treatment significantly upregulated the expression of the genes in LECs that are related to angiogenesis (CDH5), epithelial-mesenchymal transformation (TGF-β2 and TGF-β3), cellular stress (P53), and inflammation (IL-32). 3D-HLOs treated with FFA+LPS had increased lipid accumulation, collagen deposition, and functional deterioration compared to FFA treatment alone. We found that OCA, LAN, FGF19, and Tirzeptide all failed to rescue the FFA+LPS-instigated reduction of ALB production. However, both OCA and LAN, but not FGF19 repressed the FFA+LPS-upregulated fibrosis (COL1A1, ACTA2) and angiogenesis (PECAM). **Conclusion:** Our muti-cellular 3D-HLOs provide a unique *in vitro* platform that is suitable for studying the pathogenic cellular interactive process in NAFLD/NASH that will help to interrogate the involvement of different hepatic lineages in the progression of NAFLD/NASH, which will augment the development of targeted and effective treatments.

Disclosures: The following people have nothing to disclose: Wenjun Zhang, Burcin Ekser

Disclosure information not available at the time of publication: Yujin Park, Deepthi Thadasina, Thi Minh Uyen Le, Ping Li

2355-C | PCKS9 INHIBITION ATTENUATES STEATOSIS AND INFLAMMATION BY AMELIORATING ER STRESS IN NONALCOHOLIC FATTY LIVER DISEASE MOUSE MODEL

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Background: Nonalcoholic fatty liver disease (NAFLD) causes significant morbidity and mortality, and pharmacological treatment options are limited. Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes the degradation of the low-density lipoprotein receptor (LDL-R) thereby elevating plasma LDL cholesterol levels and the risk of coronary heart disease. Therefore, we investigated the role of PCSK9 inhibitor Evolocumab, a monoclonal antibody in liver fat accumulation and injury for the treatment of NAFLD **Methods:** In this study, we investigated the role of PCSK9 in diet-induced mouse model. Evolocumab (50 mg/kg) or vehicle was administered weekly for 12 weeks to mouse receiving a high fat diet or an isocaloric control diet. At the end of the treatment of PCSK9 inhibition, serum and liver samples were obtained for molecular characterization and histopathological analysis. **Results:** PCSK9 inhibition with evolocumab reduced high fat-induced hepatic triglyceride accumulation through regulation of lipid metabolism (modulation of the transcription factors (SREBP-1c) in liver and oxidation (PPARα and CPT1)), hepatocellular injury (ALT), hepatic inflammation (pro-inflammatory cytokines/chemokines (IL-1β, IL-6, TNFα, IL-10, and MCP-1). In line with these findings, a metabolic challenge using a high-fat diet attenuates severe hepatic steatosis, ER stress inflammation and fibrosis in the liver of mice treated with evolocumab compared to controls. **Conclusion:** We demonstrated that anti-PCSK9 treatment using evolocumab attenuated diet-induced steatohepatitis in the mouse model. Anti-PCSK9 treatment that spares liver metabolism may be a viable new therapeutic possibility for the treatment of NAFLD. Further studies are needed to elucidate the exact role of PCSK9 in NAFLD and to evaluate efficacy and safety of anti-PCSK9 treatment in patients with NAFLD.

Disclosures: The following people have nothing to disclose: Myeong Jun Song

2356-C | PEROXIREDOXIN 2 DRIVES HEPATOCARCINOGENESIS IN METABOLIC LIVER DISEASE

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Background: Metabolic liver disease and hepatocellular carcinoma (HCC) are major global health burdens with unsatisfactory treatment options. HCC is the third most common cause of cancer-related death and the leading cause of death among cirrhotic patients. While new treatments for HCC have been recently approved, chemopreventive strategies for HCC are lacking. Aiming to discover novel therapeutic targets, we combined genome wide transcriptomic analysis of liver tissues from patient with advanced liver disease and HCC and a cell-based system predicting liver disease progression and HCC risk. Computational analysis identified peroxiredoxin 2 (PRDX2) as a candidate driver of hepatocarcinogenesis. **Methods:** The role of PRDX2 in liver disease progression and HCC development was investigated by *Prdx2* KO in a state-of-art CRIPSR/Cas9 mouse model for NASH-induced hepatocarcinogenesis and a cell-line-derived xenograft (CDX) mouse model. The mechanism of action was explored using RNA-Seq analyses of mouse liver tissues and validated by perturbation studies in human liver cell-based models. **Results:** In vivo perturbation studies in a mouse model for NASH driven hepatocarcinogenesis showed that *Prdx2* KO robustly reduces steatosis and decreases HCC development. RNA-Seq analyses of mouse liver tissues with validation at the protein level showed that loss of *Prdx2* function suppresses oncogenic signaling (i. e. p38/MAPK, PI3K/AKT, STAT3 signaling) and improves metabolic liver functions (i.e cholesterol, fatty acid and bile acid metabolism) through activation of the AMPK. Finally, PRDX2 loss-of-function studies in hepatoma cell-based models and a CDX mouse model unraveled that PRDX2 mediates cancer cell proliferation, migration, invasion, and survival. **Conclusion:** Our findings demonstrate an important functional role of PRDX2 in metabolic liver disease and hepatocarcinogenesis. Targeting PRDX2 is a previously undiscovered therapeutic opportunity for the treatment of metabolic liver diseases and prevention of NASH-induced HCC.

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Thomas F. Baumert – Alentis Therapeutics: Advisor, No, No;

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2357-C | PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONIST IVA337 AMELIORATES LIVER FIBROSIS IN 2D AND 3D NASH CELL CULTURE MODELS

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Background: Nonalcoholic steatohepatitis (NASH) is advanced from nonalcoholic fatty liver disease (NAFLD), and it is characterized with severe hepatic fibrosis. The pan-peroxisome proliferator-activated receptor (pan-PPAR) agonist IVA337, and PPARγ agonist rosiglitazone (ROSI) are promising anti-NASH compounds, but the underlying mechanisms remain uncharacterized. **Methods:** Liver fibrosis models were established in 2D primary human hepatic stellate cells by adding TGFß1, and in 3D mouse liver spheroids containing primary hepatocytes, hepatic stellate cells, and non-parenchymal cells. The anti-fibrosis effects of IVA337 in these NASH models were evaluated by RT-qPCR, RNA sequencing and immunostaining. **Results:** In TGFß-stimulated hepatic stellate cells, IVA337 was more effective than ROSI in suppressing the expression of fibrosis-related genes expression (PAI1, COL1A1, and SMA). We successfully constructed a 3D mouse liver spheroids NASH model, which is characterized by low lipid content and high expression of fibrotic genes. We found that administration of either IVA337 or ROSI not only reduced the expression of fibrosis genes, but

also restored lipid content in the NASH spheroids as shown by bodipy staining. Additionally, immunostaining analysis showed that IVA337 was more effective than ROSI in reducing the expression of smooth muscle actin (SMA) and collagen. Furthermore, we performed bulk RNA-sequencing, and GO analysis identified several lipid pathways as the major effectors downstream of IVA treatment. Together, our results show that that pan-PPAR agonist IVA337 is effective in suppressing fibrosis development in the 2D and 3D NASH cell culture models, and our findings indicate that IVA337 exerts its anti-NASH effect by restoring the balance between lipogenesis and fibrogenesis. **Conclusion:** IVA337 is effective in suppressing liver fibrosis by modulating lipid metabolism.

Disclosures: The following people have nothing to disclose: Na Li, Shuai Wu, Xiaodan Li, Ling-Juan Zhang, Xiao Liu

2358-C | PNPLA3-148M IS ASSOCIATED WITH INCREASED CELLULAR METHYLATION ACTIVITY AND REDUCED ANTIOXIDATIVE STRESS CAPACITY IN THE PROGRESSION OF NON-ALCOHOL FATTY LIVER DISEASE

Zheyun Peng and Wanqing Liu, Wayne State University

Background: The PNPLA3 148I > M variant is associated non-alcoholic fatty liver disease (NAFLD) and its advanced stage non-alcoholic steatohepatitis (NASH). However, the detailed mechanism underlying this association remains incompletely understood. **Methods:** This study aims to further explore the molecular pathogenic mechanism of PNPLA3-148M-driven NASH via an integrated metabolomic and transcriptomic analysis in a humanized PNPLA3 mouse model. DNA 5-mC level was measured in the liver tissues. Transgenic mice carrying the human PNPLA3-148I or PNPLA3-148M gene isoform were fed a NASH-inducing AMLN diet for 24 weeks. Metabolomic analysis was conducted for the liver tissue and serum samples and transcriptome of the liver tissue was also analyzed via RNA-seq. **Results:** A total of 843 and 774 metabolites were profiled in mouse liver and serum samples, respectively. In the liver, levels of 101 metabolites were found to be significantly changed in the PNPLA3-148M group compared to the PNPLA3-148I mice ($p < 0.05$). Enrichment analysis revealed that pathways involving folate metabolism, choline metabolism, citric acid cycle, glutamate metabolism, and methionine metabolism were significantly different between the two strains. Remarkably, PNPLA3-148M was associated with a significantly decreased cellular methylation activity indicated by the decreased ratio of S-Adenosyl-L-homocysteine and S-adenosylhomocysteine (SAM/SAH) as compared to the PNPLA3-148I mice, which is in line with a downregulated Dnmt3b expression. In addition, the γ-glutamylcysteine, the precursor of GSH, was significantly reduced in PNPLA3-148M mice, along with a decreased ratio of GSH/GSSG, indicating a reduced capacity of response to oxidative stress in the PNPLA3-148M mice. In the serum, there were 109 metabolites found to be significantly changed between the two groups ($p < 0.05$) with the most of those metabolites being free fatty acids and intermediate metabolites of the fatty acid metabolism. The metabolites related to the above pathway (methylation and anti-oxidative stress) showed a trend of decreasing. Notably, a significant increase of acyl choline species was observed in the liver of PNPLA3-148M mice, while the serum choline level was found significantly reduced, indicating a choline-deficient situation in the PNPLA3-148M mice. **Conclusion:** Besides its role in lipids metabolism, PNPLA3-148M may also contribute to the development of NASH via modulating cellular methylation activity, which may further lead to genome-wide epigenetic regulation of both DNA and protein modification. The PNPLA3-148 isoform may also be associated with a reduced capacity in rescuing liver cells from oxidative stress.

Disclosures: The following people have nothing to disclose: Zheyun Peng, Wanqing Liu

2359-C | POTENTIAL THERAPEUTIC SIGNIFICANCE OF CHIT1 INHIBITION IN NASH-LIVER FIBROSIS

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Background: According to recent research findings, macrophage activation and cytokine release play a central role in liver fibrosis. The secretion of human chitotriosidase (CHIT1) by inflammatory macrophages was observed, and this study primarily emphasized the relationship between CHIT1 and liver fibrosis. **Methods:** The concentration of CHIT1 in the serum of a cohort of liver fibrosis patients ($n = 62$) was assessed using ELISA. Furthermore, the gene expression levels of CHIT1 in liver tissues from a separate cohort of liver fibrosis patients ($n = 94$) were evaluated using the nCounter assay. The objective of this study was to investigate the underlying mechanism of CHIT1 and explore the therapeutic potential of inhibiting CHIT1 using OATD-01 in the treatment of NASH-liver fibrosis mice. Combination of Streptozocin (STZ) injection and high fat and high cholesterol diet (HFHC) was used to establish NASH-liver fibrosis model. **Results:** An increase in the concentration of CHIT1 in the serum of liver fibrosis patients was evaluated, as determined by ELISA, in the F3-F4 fibrosis stage compared to the F0-F2 stage ($P = 0.007$). Furthermore, gene expression of CHIT1 in liver tissue was assessed using the nCounter assay, demonstrating an increase as fibrosis stage progressed ($P = 0.006$). In the STZ-HFHC mouse model, liver fibrosis induction was confirmed, and increased CHIT1 expression was observed through immunohistochemistry (IHC). FACS analysis revealed an upregulation of CHIT1 expression in macrophages in the livers of the STZ-HFHC group compared to the control group. Treatment of STZ-HFHC mice with OATD-01 resulted in improved liver fibrosis, as confirmed by IHC, and a reduction in inflammation indicated by decreased serum levels of ALT and AST ($P = 0.05$). OATD-01 treatment also led to downregulation of fibrosis-related genes and immune-related genes in the liver of STZ-HFHC mice, as determined by qRT-PCR. Dose-dependent improvements in hepatic fibrosis were observed with OATD-01 treatment in the STZ-HFHC mouse model. The results strongly support the efficacy of OATD-01 in significantly improving hepatic fibrosis, with higher doses demonstrating a more pronounced effect. **Conclusion:** Our study provides compelling evidence for the significant involvement of CHIT1 in liver fibrosis, supported *by elevated CHIT1 expression observed in both human patients and mouse models. Notably, treatment with the CHIT1 inhibitor, OATD-01, exhibited a dose-dependent amelioration of hepatic fibrosis in the STZ-HFHC mouse model. These results* strongly indicate that targeting CHIT1 inhibition holds promise as a potential therapeutic approach for addressing NASH-associated liver fibrosis in human patients.

Disclosures: The following people have nothing to disclose: Si Hyun Bae, Jung Hoon Cha, Na Ri Park, Sung Woo Cho, Pil Soo Sung

2360-C | PREDICTION OF CLINICAL NASH CANDIDATES WITH A HUMAN IN-VITRO AND SCREENING COMPATIBLE LIVER SPHEROID MODEL

Francisco Verdeguer, Radina Kostadinova, Thomas Hofstetter, Olivier Frey, Jesus Glaus, Angelina Freitag, Arumugham Raghunathan and Philipp Vonschallen, Insphero

Background: Non-alcoholic steatohepatitis (NASH) is a progressive severe disease characterized by lipid accumulation, inflammation, and fibrosis in the liver which lacks any approved drug therapy. Novel approaches to identify therapeutic candidates that predict clinical responses are needed. Human preclinical models, including organoids/spheroids, are powerful for translational drug discovery, however, the use of high-throughput scalable methods including drug screening is a current challenge. We aim at generating a spheroid NASH model amenable for high-throughput drug screening for a better prediction of clinical candidates. **Methods:** We developed a human 3D NASH model of spheroidal, scaffold free co-culture derived from primary hepatocytes, Kupffer cells, liver endothelial cells and hepatic stellate cells. We have defined specific steatotic and proinflammatory culture media conditions (NASH cocktail) containing high levels of sugars, free fatty acids and a LPS pulse compared to physiological control conditions. Spheroids were incubated with the NASH cocktail for 10 days and several clinical trial candidates were added during this period. We measured total intracellular triglycerides, a panel of inflammatory cytokines and pro-collagen 1 collected from media supernatants to investigate the therapeutic effect of the tested compounds including Firsocostat, Selonsertib, Resmetirom, GC1, Obeticolic acid, Elafibranor, Lanifibranor and combinations of those. **Results:** We have analysed the robustness of triglycerides and pro-collagen 1 assays to measuruing the Z' factors of control versus NASH. The data show Z' > 0.5 suggesting optimal conditions for throughput screening. Our pilot study with known clinical compounds predicts the expected clinical effects showing a good translation of steatotic, inflammatory or fibrotic phenotypes in liver spheroids. **Conclusion:** We have achieved conditions and drug predictions of NASH with a spheroid model for its use in high-througput screening of clinical candidates in NASH.

Disclosures: The following people have nothing to disclose: Francisco Verdeguer, Radina Kostadinova

Disclosure information not available at the time of publication: Thomas Hofstetter, Olivier Frey, Jesus Glaus, Angelina Freitag, Arumugham Raghunathan, Philipp Vonschallen

2361-C | PREVALENCE OF INTRANUCLEAR LIPID DROPLETS IN NONALCOHOLIC FATTY LIVER DISEASE

Norihiro Imai[1], Yuki Ohsaki[2], Jinglei Cheng[1], Jingjing Zhang[1], Fumitaka Mizuno[1], Taku Tanaka[1], Shinya Yokoyama[1], Kenta Yamamoto[1], Takanori Ito[1], Yoji

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

Ishizu[1], Takashi Honda[1], Masatoshi Ishigami[1], Hiroaki Wake[1] and Hiroki Kawashima[1], (1)Nagoya University Graduate School of Medicine, (2)Sapporo Medical University

Background: Lipid droplets (LDs) are organelles found in not only adipocytes but also various cells throughout the body, and they store excess energy while also fulfilling a multitude of physiological functions. In our recent report, we described two distinct types of intranuclear LDs observed in hepatocytes: one characterized by cytoplasmic and nuclear membrane invagination, and the other lacking such features. The objective of this study is to investigate the occurrence of these two types of intranuclear LDs in nonalcoholic fatty liver disease (NAFLD). **Methods:** This study included 27 patients with NAFLD who underwent liver biopsies. A part of the liver biopsy specimen was dissected and fixed for electron microscopic observation. Electron microscopy observations of liver biopsy samples were conducted independently from light microscopy-based clinical diagnosis. Depending on the presence of adjacent cytoplasmic invagination of the nuclear membrane, LDs in the nuclei were classified into two types: "true" nucleoplasmic LDs (nLDs) and cytoplasmic LD invagination with nucleoplasmic reticulum (cLDs in NR). **Results:** Liver biopsies were performed in 12 men and 15 women. The mean age was 56 years (range: 22 to 89 y). Liver biopsy-proven liver diseases included nonalcoholic steatohepatitis (NASH) in 16 patients and nonalcoholic fatty liver (NAFL) in 11 patients. Hematoxylin and eosin staining revealed that the severity of liver steatosis was 5–33% in 19 patients, 33–66% in five patients, and $>66\%$ in three patients. The mean NAFLD activity score was three (range: 1 to 5). Hepatocyte ballooning was confirmed in all patients with NASH. Electron microscopy revealed the presence of nLDs in 65% of the liver biopsy samples from patients with NAFLD, and cLDs in NR were observed in 23% of the samples. No significant correlations were found between the frequency of nLDs or cLDs in NR and the severity of liver steatosis, suggesting that the presence of nLDs or cLDs in NR does not directly reflect cytoplasmic lipid accumulation. Although the prevalence of nLDs in liver biopsies did not differ significantly between patients with NASH and NAFL (NASH: 63% vs. NAFL: 70%), the presence rate of cLDs in NR was significantly higher in patients with NAFL compared to those with NASH (NASH: 6% vs. NAFL: 50%, $P=0.018$). **Conclusion:** This study unveiled the presence of two types of intranuclear LDs in patients with NAFLD, leading us to speculate about two distinct pathophysiological roles of nLDs and cLDs in NR in NAFLD.

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f 2362-C | RECAPITULATING THE LIVER SINUSOID PHYSIOLOGY OF FULLY POLARIZED HEPATOCYTES, VASCULAR PLEXUS, STELLATE CELLS AND IMMUNE CELLS FOR ANTI FIBROTIC COMPOUND SCREENING

Flavio Bonanini, Roelof Dinkelberg, Vincent Van Duinen, Tessa Hagens, Nienke Kortekaas, Manuel Caro Torregrosa, Dorota Kurek, Paul Vulto and Kristin Bircsak, Mimetas

Background: Modelling the complex biology and physiology of the liver is imperative to unravel the pathogenic mechanisms of liver diseases and thus enable drug development. This requires biological models that closely mimic liver biology in its cellular composition, architecture and function. Yet, most multicellular systems result in a rather disorganized aggregate of different cell types or depend on their forceful confinement in separate microfluidic channels, often separated by artificial membranes. **Methods:** Human primary or stem cell-derived hepatocytes, liver endothelial cells, stellate cells and immune cells were introduced within a microfluidic setup of 64 parallel chips in a microtiter plate format. Confocal microscopy and transcriptomics were used to characterize and compare the model to native liver. We challenged the system with lipids or cytokines to induce steatotic and fibrotic phenotypes. High content confocal imaging and cytokine release measurements were used to evaluate the effect of clinically-relevant tool compounds in a fully automated setup. **Results:** Liver-derived endothelial cells self organized into sinusoidal-like structures, with dimension and marker expression consistent with and in close basolateral interaction with stellate cells. Hepatocytes were fully polarized and organized in distinct plate-like structures, separating interconnected endothelial vessels associated with functional macrophages. Transcriptomics analysis revealed fidelity with the diversity of gene expression levels found in liver tissue with clear representation of all major liver cell types. Steatosis and fibrosis phenotypes could be induced as presented by visible hepatic lipid accumulation, stellate cell activation marker increase and cytokine release. Implementation of benchmark compounds led to a highly reproducible assay with performance within industry requirements for high-throughput screenings. A fully automated, multiplexed small scale anti-fibrotic drug screen identified eleven compounds that were able to revert the fibrotic phenotype, with two compounds also able to restore hepatocyte function and modulate vascular plexus morphology. **Conclusion:** We believe this comprehensive liver model reflects the cellular organization and interactions found within the liver lobule in an unprecedented manner. The system holds the potential for groundbreaking progress in liver disease modelling which, in addition to the steatosis and fibrosis modelling presented here, will be extended to infectious diseases and cancer. In conjunction with its high throughput capability, this has the potential to revolutionize drug discovery and develop therapies for complex liver diseases.

Disclosures: Flavio Bonanini – Mimetas: Employee, Yes, No;

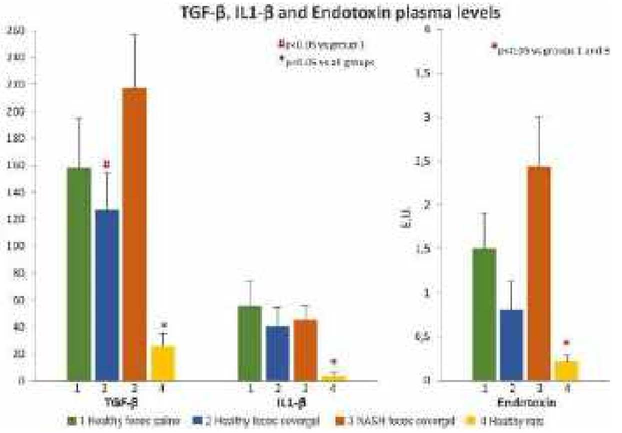
Paul Vulto – Mimetas: Executive role , Yes, No;

Disclosure information not available at the time of publication: Roelof Dinkelberg, Vincent Van Duinen, Tessa Hagens, Nienke Kortekaas, Manuel Caro Torregrosa, Dorota Kurek, Kristin Bircsak

2363-C | REDUCTION OF TGF-Β AND IMPROVEMENT OF FIBROSIS AFTER OPTIMIZATION OF FECAL MICROBIOTA TRANSPLANT WITH AN ENDOSCOPIC-PLACEMENT HYDROGEL IN A MURINE MODEL OF STEATOHEPATITIS WITH FIBROSIS

Ramon Bartoli Sole[1,2], Ignacio Iborra[3], Maria Torner Simó[3], Alba Ardevol Ribalta[3], Helena Masnou[2,3] and Rosa Maria Morillas[1,2,3], (1)Ciberehd, (2)Germans Trias I Pujol Research Institute (IGTP), (3)Hospital Germans Trias I Pujol

Background: Gut microbiota dysbiosis has become a key factor in the development and progression of nonalcoholic steatohepatitis (NASH) by influencing the immune and metabolic systems and increasing gut mucosa permeability to bacterial products, which in turns, activates the secretion of proinflammatory and profibrotic cytokines. Although fecal microbiota transplant (FMT) has been proposed as a new therapeutic strategy, effective colonization is difficult to achieve. Our group has developed an endoscopic-placement hydrogel (covergel) that, used as a vehicle, could improve FMT. Our aim was to compare the efficacy of FMT using covergel versus the standard method on gut permeability and plasma levels of proinflammatory (IL1-β) and profibrotic (TGF-β) cytokines and its effect on steatosis and fibrosis in a rat model of NASH with fibrosis **Methods:** 24 rats received a high-fat/cholesterol/fructose diet throughout the study (15 weeks) and CCl_4 for 12 weeks (NASH rats). 6 rats received standard chow (healthy rats). Feces from NASH and healthy rats were collected for FMT. At week 13, NASH rats were randomized into 3 groups for FMT by colonoscopy. Group 1: healthy feces in saline (HF-standard-FMT); group 2: healthy feces in covergel (HF-covergel-FMT); group 3: NASH feces in covergel (NASH-covergel-FMT). At week 15, rats were sacrificed to assess liver/body weight ratio, degree of liver fibrosis (Mason's trichromic) and steatosis (oil red), and plasma endotoxin, IL1-β and TGF-β levels (ELISA) **Results:** All NASH rats increased in body weight, whereas liver/body weight ratio normalized in group 2. Standard FMT showed a non-significant improvement in reversing fibrosis (groups 1 vs 3; p = 0.084). In contrast, HF-covergel-FMT reduced fibrosis (groups 2 vs 3; p = 0.001) and also showed a significant improvement compared to HF-standard-FMT (groups 2 vs 1; p = 0.034). FMT did not modify steatosis, being higher in all NASH groups. Endotoxemia and TGF-β levels decreased with HF-covergel-FMT vs. NASH-covergel-FMT (groups 2 vs 3; p = 0.046), being similar to healthy controls. In addition, TGF-β levels correlated with fibrosis degree (Pearson = 0.797, p < 0.01). However, FMT was unable to reduce IL1-β levels, being similar in all NASH groups **Conclusion:** FMT optimized with covergel significantly reduces fibrosis compared to the standard method, without changes in steatosis. In addition, it reduces the liver/weight ratio, endotoxemia, and TGF-β levels. The use of covergel improves the efficacy of standard FMT



Disclosures: Rosa Maria Morillas – Intercept Pharmaceuticals: Consultant, Yes, Yes;

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

The following people have nothing to disclose: Ramon Bartoli Sole, Ignacio Iborra, Maria Torner Simó, Alba Ardevol Ribalta, Helena Masnou

2364-C | REGULATION OF LIVER FGF21 SECRETION BY THE INNATE IMMUNE SYSTEM

Neethu Alex[1], Samuel Piaker[1], Sudha Varadaraj[1], Nufar Edinger[2], Jay D. Horton[3] and Suraj J. Patel[1], (1)UT Southwestern Medical Center, (2)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (3)UT Southwestern Medical Center, Dallas, TX

Background: Inflammation and metabolic dysfunction are both known to play a role in alcohol-related liver disease. However, evidence for causal relationships between the two are sparse. The expression of interferon regulatory factor 3 (IRF3), a classical mediator of the innate immune response to viral infection, increases with the severity of alcohol-induced liver injury in human and mouse livers. In this study, we report a robust repression of the metabolic hormone fibroblast growth factor 21 (FGF21) by IRF3. **Methods:** Transgenic mice expressing a constitutively active (phospho-mimetic) mutant allele of IRF3 were used for gain-of-function studies, while liver-specific IRF3 knockout mice and WT mice injected with IRF3 antisense oligonucleotides (ASOs) were used for loss-of-function studies. FGF21 levels in the serum were measured by ELISA, following a single binge of ethanol without or after chronic binge ethanol feeding. Overexpression of constitutively active IRF3 and transcriptionally inactive IRF3 mutants in primary hepatocytes was carried out using an adenoviral expression system. RNA-Seq and CUT&RUN were used to determine the dataset consisting of the IRF3 transcriptome and cistrome, respectively. Plasmids expressing luciferase under the control of truncated versions of the FGF21 promoter region were used in combination with the luciferase assay system for linker scanning mutagenesis. **Results:** Transgenic mice expressing constitutively active IRF3 maintained lower circulating FGF21 levels compared to their wild-type littermates, even under the influence of alcohol – one of the most potent inducers of FGF21. Concordantly, loss of hepatocyte IRF3 in ethanol-binged mice increased FGF21 secretion. Moreover, the suppression of FGF21 by IRF3 slowed recovery from ethanol-induced intoxication in mice. IRF3-mediated inhibition of FGF21 was also seen in the presence of other triggers of FGF21 such as diet-induced obesity. Using a combination of RNA-Seq and IRF3 CUT&RUN analyses from primary hepatocytes overexpressing constitutively active IRF3, we determined that IRF3 is not a direct transcriptional repressor of FGF21. IRF3 mutants that do not translocate into the nucleus and bind to chromatin were used to demonstrate that transcriptionally active IRF3 is essential for suppression of FGF21. Using linker scanning mutagenesis of the FGF21 promoter, we identified a ~200bp region of DNA upstream of the transcription start site of FGF21, where the suppressive action of IRF3 occurs. **Conclusion:** Our data demonstrates the existence of a novel IRF3-FGF21 inhibitory axis that could be targeted to increase endogenous FGF21 secretion, decrease alcohol preference and reduce the severity of liver injury.

Disclosures: The following people have nothing to disclose: Neethu Alex

Disclosure information not available at the time of publication: Samuel Piaker, Sudha Varadaraj, Nufar Edinger, Jay D. Horton, Suraj J. Patel

2365-C | ROLE OF HEPATIC STELLATE AND LIVER SINUSOIDAL ENDOTHELIAL CELLS IN A HUMAN PRIMARY CELL 3D MODEL OF NASH

Philip Tan[1], Traci Ostertag[1], Sara Brin Rosenthal[2], Daisy Chillin-Fuentes[3], Haylee Aidnik[1], Sara Linker[4], Keith Murphy[1], Jeffrey N Miner[1] and David A. Brenner[5], (1)Viscient Biosciences, (2)University of California, San Diego School of Medicine, (3)University of California, San Diego, (4)Salk Institute, (5)Sanford Burnham Prebys Medical Discovery Institute

Background: Nonalcoholic steatohepatitis (NASH) is an inflammatory and fibrotic liver disease that has reached epidemic proportions and has no pharmacological therapies. Research and drug development efforts are hampered by inadequate preclinical models. **Methods:** Three dimensional (3D) bioprinted liver disease tissues were built using primary human hepatocytes and non-parenchymal hepatic stellate cells (HSC), liver sinusoidal endothelial cells (LSEC), and macrophage/Kupffer cells (KC) from either healthy or NASH-diseased donors. Fibrosis was determined by measuring fibrotic markers using ELISA-based assays and histology, and by snRNAseq gene-expression analysis. Chimeric tissues composed of mixtures of diseased and healthy cell types were made and analyzed to assess the contribution of each individual cell type in NASH. **Results:** 3D bioprinted tissues with cells sourced from NASH-diseased patients exhibited a NASH phenotype including markers of fibrosis and fibrotic deposition. Importantly, this effect occurs without the addition of disease inducing agents. Bioprinted tissues composed entirely of healthy cells exhibit significantly less fibrosis. Chimeric tissues revealed a direct contribution for both HSCs

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

and LSECs in the development of NASH. Thus, the epigenetic changes in these two cell types persist from the diseased donor liver. **Conclusion:** This model represents a fully human system with potential to detect clinically active targets and eventually therapies.

Disclosures: Jeffrey N Miner – Organovo: Employee, No, No; Viscient Biosciences: Employee, Yes, No;

The following people have nothing to disclose: Philip Tan

Disclosure information not available at the time of publication: Traci Ostertag, Sara Brin Rosenthal, Daisy Chillin-Fuentes, Haylee Aidnik, Sara Linker, Keith Murphy, David A. Brenner

2366-C | ROLE OF PREGNANE X RECEPTOR IN TYPE 1 AND TYPE 2 DIABETES

Daniel Okuwdili Nnamani[1], Sora Choi[2], Malvin Ofosu-Boateng[1], Elizabeth Twum[1], Lidya H Gebreyesus[1], Frank J. Gonzalez[3] and Maxwell Gyamfi[1], (1)The University of Tennessee Health Science Center, (2) North Carolina Central University, (3)National Cancer Institute

Background: Diabetes mellitus is a chronic metabolic disease with high morbidity and mortality rates. Type 1 diabetes accounts for 5-10% of cases of diabetes and is associated with loss of pancreatic beta cells and insulin deficiency. In contrast, type 2 diabetes is associated with obesity, insulin resistance, beta cell impairment, and insulin insufficiency. The pregnane X receptor (PXR) is a nuclear receptor involved in the regulation of enzymes that detoxify drugs and other xenobiotics in the liver and intestine. Studies have shown that PXR promotes obesity and suppresses gluconeogenesis and hyperglycemia. However, it is unknown whether PXR mediates the pathogenesis of diabetes. **Methods:** Adult male C57BL/6J (wild-type, WT) and *Pxr*-null mice were fed either normal chow or high-fat diet (HFD) for 16 weeks. At week 14, chow-fed and HFD-fed mice were each divided into two groups and administered either a single dose of streptozotocin (STZ, 100 mg/kg, ip) or vehicle. Blood was harvested at 1 and 2 weeks post-STZ and all mice were killed. Serum parameters, liver histopathology, immunoblotting, and gene expression analysis were examined. **Results:** Unexpectedly, STZ alone and HFD +STZ significantly increased blood glucose levels, but reduced serum insulin levels in WT mice, but not in *Pxr*-null mice, suggesting that PXR promotes the development of both type 1 and type 2 diabetes. In agreement with the observed hyperglycemia in WT mice, STZ suppressed the hepatic mRNA levels of both the glycolytic enzyme glucokinase (*Gck)* and glucose suppressor hormone fibroblast growth factor 21 (*Fgf21*). Interestingly, HFD alone-fed WT mice have metabolic syndrome characterized by obesity, dyslipidemia, hyperinsulinemia, hyperleptinemia, and marked liver injury in association with increased hepatic lipogenic gene mRNAs (*Pparg*, *Srebf1*, *Srebf2* and their target genes). Furthermore, HFD also increased hepatic mRNA levels of *Fgf21* and acyl-CoA oxidase 1 (*Acox1*) which might have protected obese HFD-fed WT mice against hyperglycemia. Importantly, inhibition of STZ-induced hepatic *Gck* mRNA expression may protect *Pxr*-null mice against T1DM and T2DM. **Conclusion:** Collectively, these results indicate that PXR deficiency protects against STZ-induced hyperglycemia, while PXR promotes obesity, T1DM, and T2DM development by inhibiting gene expression of *Gck* and *Fgf21* involved in glucose and insulin signaling. These data suggest PXR as a potential target for the treatment of diabetes.

Disclosures: The following people have nothing to disclose: Daniel Okuwdili Nnamani, Sora Choi, Malvin Ofosu-Boateng, Elizabeth Twum, Lidya H Gebreyesus, Frank J. Gonzalez, Maxwell Gyamfi

2367-C | SESN2 MAINTAINS HEPATIC IMMUNE HOMEOSTASIS AND REDOX BALANCE BY INHIBITING RIPK3-MEDIATED NECROPTOSIS IN NON-ALCOHOLIC STEATOHEPATITIS

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Background: Necroptosis, a novel type of programmed cell death, is intricately associated with the inflammatory response. Currently, most studies focus on the activation of necroptosis, while the mechanisms underlying the negative regulation of necroptosis remain poorly understood. Here, we aimed to explore the functional significance and molecular mechanisms of Sestrin2 (SESN2), a highly evolutionarily conserved stress-inducible protein, in regulating necroptosis in non-alcoholic steatohepatitis. **Methods:** The effects of SESN2 overexpression or SESN2 knockdown on the regulation of necroptosis were assessed in the TNFα/Smac-mimetic/Z-VAD-FMK (T/S/Z)-induced cell necroptosis model. Western-blot, co-Immunoprecipitation, GST pull-down, and confocal assays were employed to explore the regulatory mechanisms including protein-protein interactions and post-translational modification (e.g., phosphorylation and ubiquitination). Additionally, we used GSK'872, a specific inhibitor of receptor-interacting serine/threonine-protein kinase 3 (RIPK3), to determine which phenotypes of steatohepatitis in SESN2 knockout HepG2 cells/mice were due to RIPK3-mediated necroptosis in palmitic acid (PA)-induced *vitro* model and high-fat diet (HFD)-induced *vivo* model. **Results:** Our findings revealed that SESN2 was upregulated under conditions that induce necroptosis and functioned as a negative regulator of necroptosis. Mechanistically, we found that SESN2 interacted with RIPK3 and tuned down necroptosis by inhibiting the phosphorylation of RIPK3, promoting the ubiquitination of RIPK3 and preventing the formation of the RIPK1/RIPK3 necrosome. The depletion of SESN2 resulted in excessive necroptosis, accompanied by increased fat accumulation, inflammation, and oxidative stress in the experimental steatohepatitis model. Blocking necroptosis by RIPK3 inhibitor, GSK'872, prevented the liberation of pro-inflammatory cytokines and ROS generation, but not hepatocyte fat deposition, in both PA-treated SESN2-KO HepG2 cells and HFD-fed SESN2-KO mice, demonstrated that the hyperinflammation and excessive oxidative stress induced by a genetic deficiency in SESN2 is due to RIPK3-mediated necroptosis. **Conclusion:** Collectively, our results suggested that SESN2 inhibits RIPK3-mediated necroptosis; this regulation is an important for the immune homeostasis and the redox balance in the liver.

Disclosures: The following people have nothing to disclose: Zhang Jianbin, Jiangao Fan

2368-C | SEXUAL DIMORPHISM IN THE GUT MICROBIOME OF NAFLD: ANALYSIS OF DOWNSTREAM TISSUE-SPECIFIC BACTERIAL COLONIZATION OF JEJUNUM AND DESCENDING COLON

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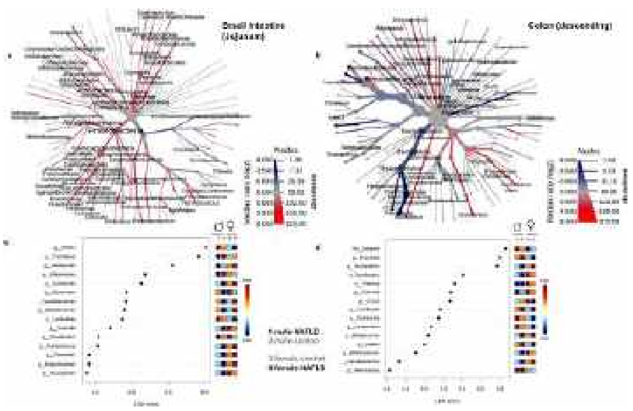
Background: Evidence suggests that the gastrointestinal microbiome exerts a crucial role in the biology of NAFLD. Likewise, NAFLD pathophysiology is modified by gender differences that affect complex regulatory pathways. However, whether sexual dimorphism in the gut microbiome can contribute to the pathogenesis of NAFLD remains unknown. **Methods:** We performed sex-specific analyses of microbiome composition (high throughput 16S sequencing) in two structurally and functionally distinct anatomical gut regions, the small intestine and colon, in an experimental model of NAFLD and metabolic syndrome. We developed a high-fat diet (HFD)-induced NAFLD in the SHR (spontaneously hypertensive rat) and its control WKY (Wistar-Kyoto) rat strain. Eighteen-weeks old male and female SHR and WKY rats were divided into two experimental groups: standard chow diet and HFD (12 weeks, (n = 6/group). HFD-fed rats, irrespective of the strain, developed NAFLD. Tissues were snap frozen and stored at −80 °C. High-quality sequences were assigned to operational taxonomic units using the QIIME pipeline. Results are expressed at the genus level. **Results:** The overall microbiome composition of females and males with NAFLD differed significantly, including differences between topographical gut regions (Figure shows a hierarchical tree with abundance ratio in NAFLD vs. controls indicated by colors; a: distal jejunum; b: descending colon). Compared to males, female rats showed higher jejunal (F-value: 15; R-squared: 0.15, PC2 21%, PC3 13.2%) and colon microbiome beta diversity (F-value: 14; R-squared: 0.14; PC2 26.3%, PC3 12.9%); Bray-Curtis index [PERMANOVA] $p = 0.001$. Sex-specific analysis of relative bacterial abundances shows differences, including significant features in the jejunum ($n = 35$) and colon ($n = 30$). Identification of differentially abundant features by linear discriminant analysis effect size (LEfSe) showed distinctive differences between females and males with NAFLD (Figures c and d; top 15 significant features). **Conclusion:** This study demonstrates that there is sexual dimorphism in the gut microbiome of NAFLD, with microbial heterogeneity within different intestinal compartments. Gaining insight into the sex-specific differences in the microbiome composition between gut anatomical and functional regions, including the small intestine -the primary site for absorption of all nutrient-derived components, and the distal colon, may be used to tailor treatment strategies.



Disclosures: The following people have nothing to disclose: Maria Silvina Landa, Adrian Salatino, Silvia Ines Garcia, Silvia C. Sookoian
Carlos Jose Pirola:

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f 2369-C | SINGLE-CELL EXPRESSION OF HUMAN LIVER NASH INDICATES A LDB2-EXPRESSING NATURAL KILLER CELL POPULATION SUSCEPTIBLE TO FIBROTIC NICHE VIA ARREST OF CELL CYCLE

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Background: Fibrosis is the principal driver of outcomes in NASH and yet there remains a lack of single-cell profiling efforts in NASH investigating immune and stromal cellular niches associated with cirrhosis. **Methods:** We profiled liver samples from 14 patients, five NASH (fibrosis stage 4), and nine pathologically normal livers (fibrosis stage 0). Liver tissue was from freshly collected biopsy specimens, explanted liver tissue collected during transplantation for NASH, or donor material surplus to transplantation requirements. For cell sequencing, fresh tissue was used to prepare single-cell suspensions by enzymatic dissociation, enrichment of hepatocytes and cell sorting for live cells. cDNA libraries were prepared using 10x Chromium solution and sequenced using Illumina Nextseq 500. Cellranger v7.0 and Scanpy v1.9.3 pipelines were used to align reads, count gene transcripts and identify the comprising cell-types, for which tissue composition and gene-expression differences were modelled. **Results:** We obtained > 40k high-quality single cells comprising T-lymphocytes, myeloid, endothelial/mesenchymal, hepatocytes, cholangiocytes and B-lymphocytes. We identified changes in tissue composition and cellular phenotype associated with cirrhosis. We identified an expansion of CD9-expressing and antigen-presenting myeloid cells in liver cirrhosis associated with a downregulation of the Interleukin-1 and TNF pathways. We observed perturbation of the T-lymphocyte compartment in fibrosis with underrepresentation of the NK populations and expansion of CD4/CD8 cells. We also detected the reduction of the LDB2-expressing NK population, which was associated with the repression of a cell-cycle-associated gene programme and enrichment of endothelium towards a subpopulation associated with the up-regulation of the IL27 and Rho signalling pathways. Finally, we observed that induction of extracellular-matrix-associated genes in cirrhosis was not restricted to the stellate cells, as cholangiocytes and hepatocytes also displayed up-regulation of several extracellular matrix components. **Conclusion:** Our results identify an NK population susceptible sensitive to the fibrotic niche, a role for the IL27 and Rho signalling pathways in fibrosis-associated vascular remodelling and suggest a multi-cell-type source of extracellular matrix components. These results constitute the most extensive single-cell transcriptomic profiling of T-lymphocytes of human NASH.

Disclosures: Cesar Prada – Novo Nordisk: Employee, Yes, No;

Philip N. Newsome – Novo Nordisk: Advisor, No, No; B Ingelheim: Advisor, No, No; Gilead: Advisor, No, No; Pfizer: Advisor, No, No;

The following people have nothing to disclose: Sanne Veidal

Disclosure information not available at the time of publication: Nguyet T Luu, Thomas Monfeuga, Paul Horn, Reenam Khan, Celine Hernandez, Dominik Pfister, Markus Latta, Enrique Toledo, Chris J Weston, Patricia Lalor

2370-C | SPATIAL AND SINGLE-CELL TRANSCRIPTOMICS REVEAL THE REGIONAL DIVISION OF THE SPATIAL STRUCTURE OF NASH FIBROSIS

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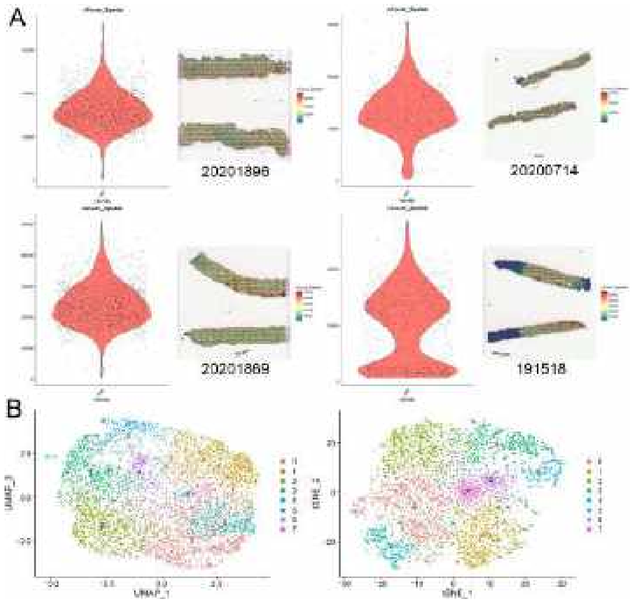
Background: To reveal the regional division of the spatial structure of NASH fibrosis and the communication relationship between cells in different regions and to analyse specific marker genes as potential therapeutic targets for NASH fibrosis. **Methods:** The liver sections of healthy controls, NAFL patients and NASH patients were measured by spatial transcriptomics, and integration analysis was performed with single-cell RNA-seq. Differential expression, functional pathway prediction, and deconvolution analysis revealed lineage-specific changes in gene expression, subpopulation composition and intercellular communication in NASH and identified key genes involved in HSC activation. The role of key genes in NASH fibrosis was verified in vitro and in vivo. **Results:** Descending and clustering analysis of 4114 nuclei from liver tissues of healthy controls, NAFL, and NASH showed that the distribution of cluster5 (fibrotic region) is dominated by lobules, and a small amount of fibrosis can be seen in the sink area. Functional analysis suggested that differentially expressed genes of cluster5 were concentrated in ECM structural components and signalling molecules. Six cell types were obtained by integrating the single-cell sequencing dataset (GSE189175). Compared with the healthy control and NAFL groups, the NASH group had significantly increased proportions of HSCs and myofibroblasts, which were distributed in the lobule and the portal area around the fibrotic area. Simultaneously, the infiltration of Kupffer cells around the fibrotic area also increased. The cell communication analysis showed that diffusive cell communication was the main type, including endocrine, paracrine and autocrine communication, followed by ECM-receptor cell communication. According to the analysis of differentially expressed genes in the subsets, AEBP1 and DPT are relatively highly expressed in cluster5, as well as in HSCs and myofibroblasts. SCENIC analysis found that AEBP1+ and DPT+ myoblasts were involved in the activation of HSCs and fibrosis formation. Immunohistochemistry verified the high expression of AEBP1 and DPT in patients with NASH fibrosis. After transfection of AEBP1 and DPT interference fragments in LX2 cells in vitro, the mRNA level of Collagen I in cells was significantly lower than that of the siRNA-NC group and blank control group. **Conclusion:** Our study is the first to reveal lineage-specific changes in gene expression, subpopulation composition and cell communication in NASH fibrosis, providing new directions for potential therapeutic targets for NASH fibrosis.



Disclosures: Calvin Pan Pan – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
The following people have nothing to disclose: Min-Ran Li, Li-Hong Ye, Ni Li, Er Hei Dai

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

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

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

Downregulation of StarD5 with hepatic lipid excess is an unappreciated key physiologic function directing lipid storage for future needs. Conversely, impaired StarD5 with prolonged lipid/cholesterol excess initiates/accelerates fatty liver's transition to fibrosis; mediated via dysregulation in the oxysterol signaling pathway.

Disclosures: The following people have nothing to disclose: Daniel Rodriguez-Agudo, Genta Kakiyama, Nanah Bai-Kamara, William M. Pandak

2372-C | STATINS IMPROVE LIVER FUNCTION AND MINIMIZE THE DEGREE OF LIVER DAMAGE BY MODULATING CELL DEATH

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

Background: Patients with advanced liver fibrosis are frequently treated with statins. However, how statins modulate liver cell function remains elusive. In the present work, we hypothesized that statins can modulate cell death, thereby ameliorating advanced chronic liver failure (ACLF). **Methods:** Carbon tetrachloride (CCl4) was used to induce liver fibrosis in Wistar and Sprague Dawley rats and rodents were treated with Simvastatin and Atorvastatin, respectively. After sacrifice, qRT-PCR, Western blot, and IF analysis were performed. Functional experiments were carried out with a human hepatocyte cell line (HepG2), and primary isolated hepatocytes from cirrhotic patients, treated with TNF/D-GalN in the presence or absence of statins. Finally, Western blot and qPCR analysis were performed in liver biopsies of twelve obese patients following bariatric surgery with NAFLD activity scores (NAS) ranging from 0 to 3, and a microarray analysis of ACLF patients was examined. **Results:** Cell death markers of apoptosis and necroptosis (phospho-MLKL and cleaved caspase 3 (CC3)) were overexpressed in liver extracts of patients with higher NAS scores and ACLF. Statins reduced CCl$_4$-induced overexpression of markers of liver fibrosis and inflammation, and apoptosis in animals with ACLF, thereby attenuating the expression of CC3, CC8 and TUNEL-positive cells. Moreover, statins therapy protected both HepG2 cells and cirrhotic primary hepatocytes from acute -induced cell death. **Conclusion:** Statin therapy enhanced liver function and reduced systemic inflammation in human cell lines and rat models of ACLF, thereby mitigating the severity of the condition. We describe a novel mechanism by which statins specifically protected against cell death.

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Disclosure information not available at the time of publication: Zoe Boyer-Diaz, Javier Vaquero, Rafael Bañares, Jaime Bosch, Yulia Nevzorova, Francisco Javier Cubero

2373-C | SUBCELLULAR DISPOSITION OF ADENOSINE A3 RECEPTOR IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE: INSIGHTS INTO INTRANUCLEAR TRANSLOCATION

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

Background: Recent studies have shown decreased expression of adenosine A3 receptor (A3AR) in the liver of patients with non-alcoholic fatty liver disease (NAFLD), suggesting its potential involvement in NAFLD pathogenesis. However, the significance and role of intranuclear translocation of A3AR have not been thoroughly investigated. Thus, the aim of this study was to explore the differences in A3AR expression between NAFLD patients and healthy controls, specifically focusing on its subcellular distribution. **Methods:** A total of 163 NAFLD cohorts (Control: n = 61, NAFLD: n = 76, NASH: n = 26) were examined to compare A3AR expression in liver tissue and peripheral blood mononuclear cells (PBMCs). Immunofluorescence expression and cell fractionation techniques were utilized to analyze the subcellular distribution of A3AR following treatment with palmitic acid (PA) and oleic acid (OA). **Results:** Analysis of in-house and public RNA sequencing data revealed no significant differences in A3AR expression between healthy controls and NAFLD patients. Consistently, A3AR expression in PBMCs showed no variation between the two groups. Intriguingly, differential expression of A3AR in intracellular compartments was observed in the liver tissue of healthy controls and NAFLD patients. Cytoplasmic A3AR was predominantly expressed in healthy controls, whereas nuclear A3AR was mainly observed in NAFLD patients. Furthermore, increased nuclear A3AR expression was detected in PA and OA-induced HepG2 cells, indicating its translocation from the cytoplasm. **Conclusion:** The findings suggest that steatosis may trigger the translocation of A3AR from the cytoplasm to the nucleus. Further investigations are warranted to elucidate the mechanisms underlying A3AR translocation and its functional implications in NAFLD pathophysiology.

Disclosures: The following people have nothing to disclose: Huiyul Park, Sang Bong Ahn, Eileen Yoon, Hyunwoo Oh, Hyo Young Lee, Joo Hyun Sohn, Dae Won Jun

2374-C | TARGETING CHRONIC VEGF-C SIGNALING MITIGATES DISEASE PROGRESSION IN NON-ALCOHOLIC STEATOHEPATITIS

Jason Eng[1,2], Seock-Won Youn[1], Bhairavi Swaminathan[1], Rahul Vadakath[1] and Jan Kitajewski[1,3], (1)University of Illinois at Chicago, (2)Cleveland Clinic Foundation, (3)University of Illinois Cancer Center

Background: The sinusoidal endothelial cells (LSECs) are critical regulators of homeostasis within the liver. In fact, disruption of normal LSEC physiology is one of the earliest hallmarks of liver disease. Thus, strategies which target factors involved in LSEC dysregulation may improve hepatic recovery and prevent the progression of certain pathological conditions, including non-alcoholic steatohepatitis (NASH). **Methods:** Using human and murine tissues, we observed drastically increased levels of vascular endothelial growth factor-C (VEGF-C) in NASH livers compared with non-diseased samples. To investigate the role of VEGF-C during disease progression, we performed additional studies in murine NASH models. In mice fed a western diet with carbon tetrachloride, overexpression of VEGF-C was accomplished with adeno-associated viral (AAV) infection. Conversely, blockade of the receptors for VEGF-C, VEGFR2 and VEGFR3, was achieved with lenvatinib, a tyrosine kinase inhibitor which primarily inhibits R2/R3 signaling at low doses. NASH severity was monitored by histology and serum liver chemistry analysis. To identify the potential mechanism in which VEGF-C drove disease progression, we performed single nuclei RNA sequencing on vehicle and lenvatinib treated NASH livers, and validated targets with qPCR and immunofluorescent studies. **Results:** We discovered that chronic VEGF-C expression exacerbated NASH progression in mice. Interestingly, we observed that VEGFR3-specific activation led to worsening steatosis, while VEGFR2/VEGFR3 activation enhanced both fibrosis and steatosis. Administration of low dose lenvatinib significantly delayed NASH progression by decreasing fibrosis, steatosis, and tumor nodule formation. Lastly, transcriptomic analysis revealed downregulation of several pathways associated with extracellular matrix interactions, angiogenesis, and inflammation. Several known molecules involved in NASH pathogenesis such as VCAM1, Notch receptors, and collagen proteins were simultaneously confirmed to be downregulated in response to lenvatinib treatment. **Conclusion:** Taken together, these findings indicate that chronic VEGF-C production in NASH plays a role in promoting liver fibrosis and steatosis, and that blockade of the downstream receptors, VEGFR2 and VEGFR3, may be a promising therapeutic strategy to mitigate disease severity and cancer development.

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The following people have nothing to disclose: Jason Eng, Seock-Won Youn, Bhairavi Swaminathan, Rahul Vadakath

2375-C | TARGETING EFHD1 FOR LIVER DISEASE

David R Eberhardt, Sandra H Lee, Ashley R Bratt, Xue Yin, William L Holland, Sihem Boudina and Dipayan Chaudhuri, University of Utah

Background: New treatments for liver disease may arise by examining genes identified in genome-wide association studies (GWAS). Variation in one such gene, *EF-hand domain family member D1* (*EFHD1*), has been associated with liver injury biomarkers in multiple GWAS analyses. In these studies, higher serum biomarkers correlate with increased EFHD1 expression. EFHD1 is a poorly studied mitochondrial Ca^{2+}-binding protein, and how it regulates liver function is unknown. We sought to assess whether inhibiting hepatic EFHD1 could represent a novel therapy for treating metabolic liver disease. In human and mouse livers, EFHD1 is expressed at low levels preferentially in hepatocytes, with little to no expression in other cell types. It is found primarily on the outer mitochondrial membrane and inter-membrane space. **Methods:** To study the effects of EFHD1 inhibition on liver injury, we subject wild-type (WT) and

EFHD1 whole body knockout (*Efhd1*$^{-/-}$) mice to a high fat diet (HFD) and analyze their livers for disease markers. We also performed live-cell imaging using hepatocytes isolated from WT and *Efhd1*$^{-/-}$ mice. **Results:** In wild-type animals, hepatic EFHD1 levels increased during HFD, and male *Efhd1*$^{-/-}$ mice gained less weight (10.6 ± 1.6% less after 28 weeks HFD), despite similar levels of food intake, activity, and insulin resistance. RNA sequencing of *Efhd1*$^{-/-}$ livers from mice fed a HFD revealed a significant reduction in genes associated with inflammation, relative to wild-type animals, which was confirmed by histological analysis. We also observed fewer hepatocyte large lipid droplets (32.9 ± 3.1%, WT; 21.1 ± 3.5%, *Efhd1*$^{-/-}$) but not small lipid droplets. Mitochondria continuously undergo fission and fusion, and increased fission has been correlated with liver injury. We found EFHD1 was present at sites of ER-mitochondrial contact on the outer membrane, where fission and fusion occur. In fact, mitochondria in *Efhd1*$^{-/-}$ hepatocytes were around 100.03 ± 0.32% larger than controls, and showed less remodeling after activating cytoplasmic Ca^{2+} signals. Mechanistically, this may be due to interactions we identified between EFHD1 and the mitochondrial fission/fusion machinery. Thus, reducing fission by deleting EFHD1 may prevent mitochondrial damage and subsequent liver injury. **Conclusion:** These findings demonstrate that EFHD1 inhibition may be a promising therapy for liver injury.

Disclosures: The following people have nothing to disclose: David R Eberhardt

Disclosure information not available at the time of publication: Sandra H Lee, Ashley R Bratt, Xue Yin, William L Holland, Sihem Boudina, Dipayan Chaudhuri

2376-C | TARGETTING HEPATIC CALPAIN ACTIVITY PROTECTS AGAINST EXPERIMENTAL NASH FIBROSIS IN MICE

Jiang Li[1], Olivia B Bannister[1], Charis-Marie Vanderpuye[1], Juliane I Beier[1,2], Silvia Liu[1,2], Michael Merchant[3], Panagiotis V Benos[4], Andres Duarte-Rojo[5] and Gavin E. Arteel[1,2], (1)University of Pittsburgh, (2) Pittsburgh Liver Research Center, (3)University of Louisville, Louisville, KY, (4)University of Florida, (5) Northwestern University Feinberg Scho

Background: We recently showed that the pattern of degraded proteins in plasma samples from experimental and human NASH fibrosis differs dramatically from healthy livers; informatic analysis suggested robust elevated activation of the cysteine proteases Calpains 1 and/or 2 (Capn1/2) in both human and experimental NASH fibrosis (PMID: 36778394). Although Calpain 1/2 have been identified as key players of remodeling in other organs, they have not been investigated in NASH fibrosis. The purpose of the current study was to investigate the impact of targeted disruption of hepatic Calpain 1/2 activity in a preclinical mouse model of NASH fibrosis. **Methods:** 4 wk old C57Bl6/J mice were injected with recombinant adeno-associated virus type 8 vectors (rAAV8; 1×10^{11} PFU/mouse, i.p.) encoding shRNA against Capn4 (*Capns1*), or control scrambled rAAV8 vectors. After 4 wks, mice were fed ad libitum either a low-fat control diet (LFD: 13% saturated fat) or a 'Western'-style high-fat, high-fructose diet (HFD: 42% saturated fat) for 12 weeks. Liver tissue portions were frozen immediately in liquid nitrogen or preserved for FFPE or frozen tissue sectioning. Major endpoints were assessed by histology, biochemical analyses and/or gene expression. The expression of Capn1 and Capn2 in human NASH fibrosis was explored, using data from public study (GSE135251) of RNA-seq analysis of human NASH fibrosis, which includes patients at METAVIR fibrosis stage from 0 to 4. **Results:** rAAV8-mediated knockdown of Capn4 mediated a robust and stable suppression of hepatic *Capns1* expression, coupled with a nearly complete abrogation of detectable Capn1/2 enzyme activity. As expected, HFD caused obesity and insulin resistance (HOMA-IR) under these conditions. HFD also caused severe fatty liver, as determined by histological assessment and by biochemical analysis. HFD also induced expression of indices of fibrogenesis and collagen accumulation and caused the formation of "chicken-wire" fibrosis within the hepatic lobule, as determined by Sirius red staining. Knocking down Capn4 did not impact systemic indices of obesity and adiposity, but dramatically attenuated increases in all indices of steatosis and fat accumulation in the liver. Moreover, the increase in fibrosis caused by HFD was attenuated by knocking down Capn4. Analysis of human NASH fibrosis indicated that expression of Capn2 (but not Capn1) increased significantly with each fibrosis stage. **Conclusion:** Taken together, these results indicate that blocking calpain activity by targeting a key regulatory protein (Capn4) protects against lipid accumulation caused by HFD, despite not impacting overall weight gain. Moreover, knocking down Capn4 also attenuated fibrogenesis under these conditions. These data indicate that Capn1/2 activity may be critical in the transition from NAFLD to NASH fibrosis.

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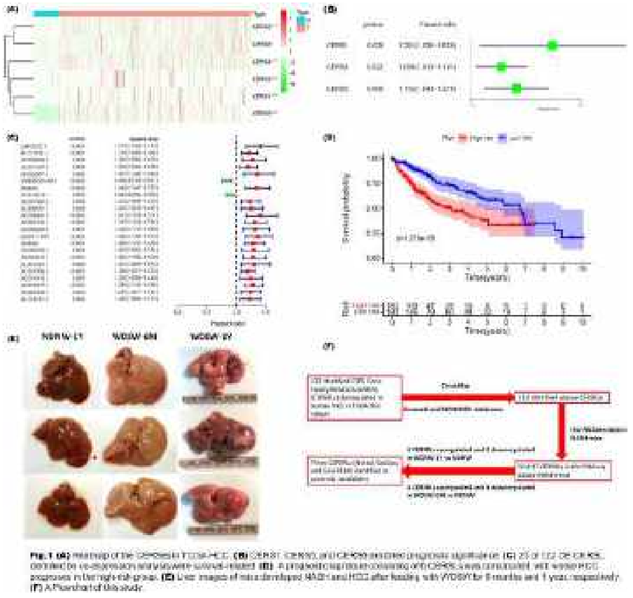
The following people have nothing to disclose: Jiang Li, Juliane I Beier, Michael Merchant, Panagiotis V Benos, Gavin E. Arteel
Disclosure information not available at the time of publication: Olivia B Bannister, Charis-Marie Vanderpuye, Silvia Liu

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

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

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



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

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

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

administration elevated the LPC 16:0 levels almost to those of wild-type mice. In addition, lysophosphatidylethanolamine (LPE) 16:0, 18:2, 18:0, 20:4, and 22:6 were also decreased in the liver tissue of PTEN KO, and all but 22:6 were significantly increased by glycine. After 24 weeks, PTEN KO developed 2.6 ± 1.0 liver tumors, while glycine completely suppressed tumorigenesis to 0 ± 0. At this hepatocarcinogenic stage, hexosylceramide (HexCer) d18:1/16:0, d18:1/22:0, d18:1/24:0, lactosylceramide (LacCer) d18:1/24:0, sphingomyelin (SM) d18:1/16:0, 18:1/22:0, and 18:1/24:0 were significantly lower in PTEN KO than wild-type mice. By administration of glycine, HexCer and LacCer were almost completely increased to levels of wild-type mice, and SM was significantly increased only at 18:1/24:0. In contrast, the amount of ceramide (Cer) contained in the liver of PTEN KO was generally higher than that of wild-type mice, especially d18:1/22:0 and d18:1/22:0, which were more than twice that of wild-type mice. Administration of glycine completely suppressed these increases to levels comparable to wild-type mice. **Conclusion:** In the liver of hepatocyte-specific PTEN knockout mice, lysophospholipids such as LPC and LPE are decreased in the phase of steatohepatitis, and sphingolipids such as HexCer, LacCer, and SM are decreased and Cer are accumulated as instead in the stage of hepatocarcinogenesis. Glycine significantly ameliorates the alteration of lipid metabolism and is effective in suppressing steatohepatitis-related hepatocarcinogenesis.
Disclosures: The following people have nothing to disclose: Kazuyoshi Kon, Hyeon-Cheol Lee-Okada, Kumiko Arai, Akira Uchiyama, Toshifumi Sato, Hiroo Fukada, Takehiko Yokomizo, Kenichi Ikejima

2379-C | THE EFFECTS OF FLUORENE EXPOSURE IN CONJUNCTION WITH HIGH FAT DIET ON TOXICANT-ASSOCIATED FATTY LIVER DISEASE

Jianzhu Luo[1], Banrida Wahlang[1], Loretta Jophlin[1], Walter Watson[1], Collin M. M White[1], Shikshita Singh[2], Oluwanifemi Esther Bolatimi[1], Ngozi Victoria Adiele[1] and Matthew Cave[1], (1)University of Louisville, Louisville, KY, (2)University of Ottawa

Background: Fluorene belongs to the class of polycyclic aromatic hydrocarbons (PAHs) and is a major component of particulate matter ($PM_{2.5}$). Previous studies have demonstrated positive associations between PAH mixtures and risk for fatty liver disease (FLD). However, the impact of fluorene in the context of toxicant-associated FLD (TAFLD) remains to be elucidated. This study is to investigate the effects of fluorene exposure in TAFLD and identify mechanisms contributing to hepatic and metabolic disruption. **Methods:** Male C57BL/6 mice were fed either a low fat (CD) or high fat diet (HFD,42%) for 10 weeks; each diet group was then administered corn oil (control) or fluorene (50 mg/kg/day, daily gavage, 4 weeks). Mice were then euthanized; plasma and tissues were collected for downstream analysis. Results were analyzed using 2-Way ANOVA for two factors: ‘diet” and “fluorene”; followed by contrast test analyses for different subgroup comparisons. **Results:** HFD-fed mice showed hepatic steatosis (H&E staining of liver sections), while fluorene exposure resulted in increased liver inflammatory infiltration. Consistently, assessment of hepatic gene expression demonstrated fluorene upregulation of mRNA levels for the inflammatory/fibrotic marker (*Tgfb1*) in HFD-fed mice. In terms of lipid metabolism, HFD upregulated hepatic expression of genes involved in lipid uptake (*Cd36*) and decreased expression of genes for de novo lipogenesis (*Fasn*) and lipid binding (*Fabp1*). Fluorene decreased *Fasn* and increased *Fabp1* mRNA levels only in CD-fed mice. Additionally, fluorene altered hepatic expression of genes involved in glucose and glycogen metabolism (increased gluconeogenic *Pck1*, decreased *Gck* expression) in CD-fed mice although this group exhibited lower fasting glucose levels and reduced hepatic glycogen storage, further implicating fluorene’s disruption of glucose metabolism. While HFD feeding decreased mRNA levels of genes involved in hepatic recovery/function (*HNF4a, Egfr*), fluorene exposure further decreased *Egfr* mRNA levels in HFD-fed mice. Moreover, fluorene also decreased *Fgf21* mRNA levels in HFD-fed mice, suggesting possible liver damage in this group. Lastly, assessment of hepatic xenobiotic receptor activation demonstrated fluorene-mediated induction of target genes for the AhR (*Cyp1a2*), CAR (*Cyp2b10*), PXR (*Cyp3a11*). **Conclusion:** The current findings suggest that fluorene is a metabolism-disrupting chemical that can contribute to TAFLD, partially through diet-interactions and hepatic receptor activation.
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2380-C | THE HEPATIC PROTEOME CHANGES IN NASH-SUSCEPTIBLE C57Bl6/J MICE INDUCED BY AN OBESOGENIC DIET.

Jiang Li[1], Toshifumi Sato[2], Daniel Wilkey[3], Panagiotis V Benos[4], Andres Duarte-Rojo[5], Gavin E. Arteel[1] and Michael Merchant[3], (1)University of Pittsburgh, (2) Juntendo University School of Medicine, (3)University of Louisville, Louisville, KY, (4)University of Florida, (5) Northwestern University Feinberg Scho

Background: Non-alcoholic steatohepatitis (NASH)-associated cirrhosis is an indication for liver transplant (LT). Post-LT NASH reoccurrence is associated with accelerated progression to fibrosis/cirrhosis and increased mortality. Efforts to study NASH relying on mouse models with ad libitum feeding of high-fat chow are confounded by strain-dependent effects. We hypothesized that hepatic proteomic comparisons of the western diet on obesogenic susceptible (C57Bl6/J) versus non-susceptible (AJ) mouse strains would yield novel and important insights the mechanisms of NASH development or disease progression. **Methods:** 8wks old, male AJ and C57Bl/6J mice were fed ad libitum either a low-fat control diet (LFD: 13% saturated fat) or a 'Western'-style high-fat, high-fructose diet (HFD: 42% saturated fat) for 12 weeks then fasted for 4h prior to sacrifice. Liver tissue was snap frozen immediately for proteomic and immunoblot analyses. Tissue (C57 or AJ mice LFD or HFD; $n = 4$ per group) were analyzed using a 2DLC-MS workflow and TMTPro isobaric reagents in a SP3 method on a Thermo Lumos tribrid instrument (UC, Davis Proteomics Core Facility). LCMS data were analyzed using ProteomeDiscoverer 2.4 with the TMTPro and SP3 nodes. Differences in protein abundance were estimated by ANOVA with FDR correction ($q < 0.05$ considered significant). **Results:** As expected, whereas sensitive C57Bl6/J mice gained dramatic weight on an HFD, insensitive AJ mice did not. This effect was coupled with an increase indices of insulin resistance (HOMA-IR), liver injury and fibrosis in the C57Bl6/J mice, but not in the AJ mice. 1,604 differentially abundant proteins (DAP) were observed by ANOVA correlating with Gene Ontological (GO) differences in fatty acid & amino acid metabolism (biological), acetyl CoA, long chain fatty acid and kynurenine metabolism (molecular), and mitochondrial electron transport function (cellular component). HFD to LFD induced 1,094 DAP in C57 and 59 in AJ mice. GO comparison of C57(HFD) to AJ (HFD) DAP identified roles for adenine, AMP and purine metabolism (biological); transporter associated with antigen processing (TAP) function (molecular); and mitochondrial respiratory chain and MHC I class I peptide loading (cellular). **Conclusion:** The western diet induces strain-dependent changes in the mouse hepatic proteome. Obesogenic susceptible C57Bl6/J mice responses suggests GO roles for altered adenine/AMP metabolism, antigen presentation, and mitochondrial function in susceptibility to NASH development.

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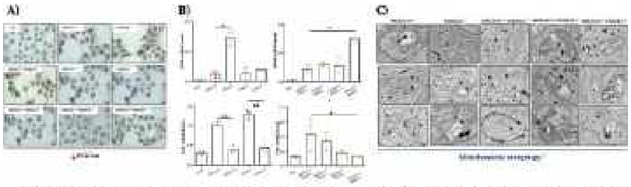
The following people have nothing to disclose: Jiang Li, Toshifumi Sato, Daniel Wilkey, Panagiotis V Benos, Gavin E. Arteel, Michael Merchant

2381-C | THE OVEREXPRESSION OF TM6SF2 AND/OR MBOAT7 WILD-TYPE GENES RESTORES THE MITOCHONDRIAL LIFECYCLE AND ACTIVITY IN AN IN VITRO NAFLD MODEL

Erika Paolini[1], Miriam Longo[2], Marica Meroni[3], Giada Tria[1], Roberto Piciotti[4], Massimiliano Ruscica[5], Anna Ludovica Fracanzani[5] and Paola Dongiovanni[3], (1) Fondazione Irccs Ca Granda, Milano, Italy, (2) Fondazione Italiana Fegato, (3)Fondazione Irccs Cà Granda Ospedale Maggiore Policlinico, (4)General Medicine and Metabolic Diseases, Fondazione Irccs Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, Milano, Italy, (5)Università Degli Studi Di Milano

Background: Mitochondrial dysfunction plays a pivotal role in the transition from NASH up to HCC. The knockout (KO) of *MBOAT7* and/or *TM6SF2* hampers the mitochondrial dynamics in Hepg2 cells resulting in an enrichment of misshapen and failed mitochondria. The overexpression of *MBOAT7* and/or *TM6SF2* wild-type genes in KO models through lentiviral vectors decreases the number of damaged-globular mitochondria, while increases the normo-shaped ones. To deepen the impact of *PNPLA3*/*MBOAT7*/*TM6SF2* loss-of-function mutations on mitochondrial aberrances, we investigated the mitochondrial lifecycle and activity in KO cells overexpressed for the wild-type forms of *MBOAT7* and/or *TM6SF2*. **Methods:** Mitochondrial lifecycle and activity were assessed through RT-PCR, Western Blot, Seahorse assay, immunohistochemistry, and transmission electron microscopy (TEM). **Results:** The overexpression of *MBOAT7*, *TM6SF2* or both decreased PGC1α levels, the master regulator of mitobiogenesis, which was activated in KO cells in response to fusion-fission unbalance, boosted the expression of Mfn1, Mfn2 (mitochondrial outer membranes proteins involved in fusion) and OPA1 (inner mitochondrial membranes fusion protein) whereas decreased FIS1 and DRP1 (fission proteins) levels, thus re-establishing the mitochondrial turnover. Consistently, the mitophagy pathways (PINK/PARKIN/BNIP3/BNIP3-L/LC3/phospho-UBIQUITIN) increased after the *MBOAT7* and/or *TM6SF2* overexpression, encouraging the disruption of damaged mitochondria that results in high number of intracellular autophagic structures assessed by TEM. The balance of mitochondrial biogenesis is essential for organelles' homeostasis and activity. Indeed, the overexpressed models augmented the COX-I/SDHA ratio, COX-III, and citrate synthase activity paralleling the mitochondrial oxygen consumption rate, thus recovering the OXPHOS capacity and Krebs cycle which were impaired in KO cells. Finally, lactate levels decreased after the upregulation of *MBOAT7* and/or *TM6SF2* wild-type genes together with the glycolytic extracellular acidification rate, thereby inhibiting the switch to anaerobic glycolysis which was promoted in KO cells to trigger tumorigenesis. **Conclusion:** Genetics impacts on mitochondrial maladaptation during NAFLD and the overexpression of *MBOAT7* and/or *TM6SF2* wild-type genes in KO HepG2 cells re-balances the mitochondrial lifecycle and turnover, thus ensuring the organelles' function and possibly reversing hepatocellular damage.



The overexpression of *MBOAT7* and/or *TM6SF2* rebalances the mitochondrial lifecycle by decreasing PGC1α activity (A), increasing *Mfn2* mRNA levels implicated in fusion (**B**), lowering the mRNA expression of *Fis1* involved in fission (B) and triggering mitophagy (C: autophagic structures are indicated by black stars).

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2382-C | THE ROLE OF LIVER EPSINS IN NONALCOHOLIC STEATOHEPATITIS

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Background: Nonalcoholic steatohepatitis (NASH) is a common chronic liver disease that can advance to fibrosis, cirrhosis, and liver failure; however, no effective therapy is currently available. Epsin is an evolutionarily conserved protein family that involved in clathrin-mediated endocytosis. We found that both Epsin1/2 expressions in liver are significantly up-regulated by Western Diet (WD) induced NASH mice model, as well as in the liver biopsy from NASH patients. We hypothesize that the expressions of Epsin1 and Epsin2 in the liver are required for NASH progression. In this study, we aim to investigate the novel roles Epsin1 and Epsin2 in the liver during NASH pathogenesis and progression. **Methods:** We conditionally delete Epsin1/2 using Albumin-Cre (Liver-DKO). We then induce a mouse model of NASH by feeding both WT and Liver-DKO mice a WD+20%fructose for 52 weeks. We used single cell multiome, combined with molecular approaches to study the mechanisms. As a proof-of-concept, we test a strategy to deliver Epsin1/2 siRNAs encapsulated nanoparticles (NPs) targeting the liver via intravenous injection to treat diet induced NASH in mice. **Results:** We found WD-fed Liver-DKO mice have significant reductions in hepatic fibrosis formation and less lipid accumulation, and this associate with better glucose and insulin tolerance, as well as lower serum aspartate transaminase (AST) and alanine aminotransferase (ALT) when compare with WD-fed WT mice. Through analysis of the single cell multiome from the WT and Liver-DKO livers, we found more immune cells population with high amount of cytokines and chemokines expression in WT NASH mice compared with Liver-DKO. Interestingly, monocyte-derived inflammantory Kupffer cell (KCs) are enriched in WD-fed WT mice, however, embryonic-derived KCs are the enriched in liver DKO, and associate with dramatically reduced total KCs population. Mechanistically, we found more zone 2 hepatocytes identified in Liver-DKO compared with in WT-NASH mice. We also found that Liver-DKO has more diploid hepatocytes , and NASH mice have more aneuploid hepatocytes, suggesting that the Liver-DKO hepatocytes under NASH diet are more regenerative. We also found that HNF4a dramatically reduced in WD-fed WT mice, but its expression preserved in WD-fed Liver-DKO mice, suggesting the loss of hepatocyte identity was inhibited by Epsins deletion. Therapeutically, we found significant resolution of hepatic fibrosis after knockdown of Epsin1/2 siRNA NP treatment. **Conclusion:** We discovered the novel roles of liver Epsins in promoting NASH progression and outcome in mice. Liver specific deletion of Epsin1/2 significantly suppress NASH progression by preventing immune cells infiltration that protect hepatocytes from severe chronic injury. Our preclinical data suggests specially targeting Epsin1 and Epsin2 in the liver could be a promising therapeutic strategy for NASH treatment.

Disclosures: The following people have nothing to disclose: Bo Zhu, Hao Wu, BeiBei Wang, YaoWei Lu, Hong Chen

2383-C | THE ROLE OF MITOCHONDRIAL QUALITY CONTROL FACTOR CLPP IN ADIPOCYTE-HEPATOCYTE CROSSTALK IN THE PROGRESSION OF NAFLD

Yoonsu Ha[1], Taek Kyong Kim[2] and Seung-Jin Kim[2], (1) Kangwon National University, (2)Global/Gangwon Innovative Biologics-Regional Leading Research Center (GIB-RLRC)

Background: Mitochondria are critical to cellular metabolism and stress responses, and their dysfunction is linked to human disease and pathology. Adipose tissue is a specialized connective tissue that stores energy in the form of lipids and has several other important functions in the human body such as an endocrine role and production of numerous bioactive factors. Liver is responsible for many important functions in the body that include detoxification, protein synthesis, and the production of chemicals that help digest food. These multiple functions of adipose tissue and liver contribute to the progression of NAFLD. Mitochondrial dysfunction can lead to inadequate mitochondrial quality control mechanisms and also it is associated with the dysfunction of adipose tissue and liver. In addition, recent studies indicate mitochondrial dysfunction in the pathology and etiology of hepatic steatosis, such as the adaptation and remodeling of mitochondria. However, it is still unclear whether inadequate mitochondrial quality control mechanisms are responsible for dysfunction of adipose tissue and liver. **Methods:** Primary adipocyte, hepatocyte cells were isolated from adipose tissues and livers of adult mice (6-8 wk) respectively. Isolated primary adipocytes were reprogrammed to become mature adipocytes. Mouse preadipocyte cell lines (3T3-L1) and primary adipocytes were transfected with a lentivirus that expresses shClpP. Transwell co-culture system was used to investigate the cell-cell interaction in vitro. **Results:** In this study, we found that loss of the function of ClpP, which is a key mitochondrial quality control factor, impairs adipogenic differentiation in adipocytes via senescence and subsequently induces proinflammatory-senescence-associated secretory phenotype (SASP) secretion. Interestingly, the conditioned media collected from ClpP depleted adipocytes were characterized by high MCP-1 content and led to hepatic inflammation in hepatocytes. **Conclusion:** Our findings establish a pivotal role for ClpP involved in mitochondrial quality control in adipocyte metabolism and provide new insights into therapeutic approaches to NAFLD associated with mitochondrial dysfunction.

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2384-C | THE ROLE OF SERPINE1 IN HEPATIC STELLATE CELLS AS A THERAPEUTIC TARGET FOR NONALCOHOLIC STEATOHEPATITIS

Hyun Young Kim[1], Cuijuan Han[1], Sara Brin Rosenthal[1], Xiao Liu[1], Wonseok Lee[1], Haeum Jang[1], Karin Diggle[1], Tatiana Kisseleva[1] and David A. Brenner[1,2], (1) University of California, San Diego School of Medicine, (2)Sanford Burnham Prebys Medical Discovery Institute

Background: Nonalcoholic steatohepatitis (NASH) progresses from steatosis to steatohepatitis and fibrosis. Hepatic Stellate Cells (HSCs) are the major source of Collagen Type I-producing myofibroblasts in fibrotic liver. Using complimentary single nucleus (sn)RNA- and snATAC-sequencing analysis of HSCs from normal, NAFL, and NASH human livers, we identified a group of genes in which transcriptional and epigenetic activity was closely linked to the regulation of extracellular matrix organization network. The role of selected genes in fibrogenic activation of human HSCs was investigated using 3D human liver spheroids composed of all liver cells (isolated in our laboratory) and HSC-specific gene knockout in mice. **Methods:** NASH was induced in human liver spheroids generated by co-culturing human liver cells (60% hepatocytes, 40% non-parenchymal cells, and enriched HSCs at physiological ratios) in a growth factor-enriched media for 7 days, followed by stimulation with a NASH cocktail (oleate, palmitate, glucose, fructose, LPS, and TGFβ1) for additional 7 days. **Results:** Human liver NASH (vs control) spheroids upregulated G6Pase and CYP2E1 (indicative of hepatotoxic injury), lipid droplets, fibrogenic genes (Collagen Type I, αSMA). This effect was associated with increased SERPINE1 and SPON1 expression in activated Desmin^{+}αSMA^{+} aHSCs/myofibroblasts, suggesting that human NASH liver spheroids closely recapitulate responses of human liver to metabolic injury. The role of selected targets, SERPINE1, SPON1, GAS7, and LTBP2 in HSC activation was tested using dsiRNA. Transfection of human HSCs with gene-targeting (vs scrambled) dsiRNA knockdown of SERPINE1 significantly decreased the expression of markers of fibrosis, COL1A1 and ACTA2, in the human NASH liver spheroids. We hypothesized that genetic deletion of SERPINE1 (plasminogen activator inhibitor-1) can attenuate development of toxic liver fibrosis in mice. HSC-specific Serpine1 knockout mice, Lrat$^{\Delta \mathrm{Serpine1}}$ mice, were generated by crossing of Lrat^{Cre}×Serpine1$^{\mathrm{flox/flox}}$ mice. HSC activation and development of CCl$_4$-induced liver fibrosis was strongly reduced in Lrat$^{\Delta Serpine1}$ mice (vs Serpine1$^{flox/flox}$ mice). **Conclusion:** Human liver spheroids serve as a useful tool to study NASH in a dish. Although SERPINE1 is expressed in different cell populations, our findings in human spheroids and HSC-specific Serpine1 knockout mice suggest that SERPINE1 in HSCs can become a target for anti-fibrotic therapy.

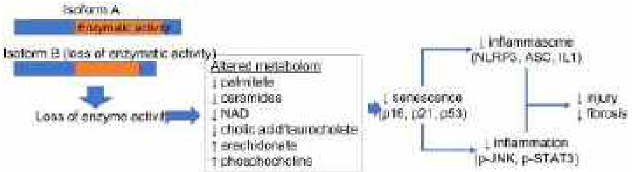
Disclosures: The following people have nothing to disclose: Hyun Young Kim, Wonseok Lee

Disclosure information not available at the time of publication: Cuijuan Han, Sara Brin Rosenthal, Xiao Liu, Haeum Jang, Karin Diggle, Tatiana Kisseleva, David A. Brenner

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

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

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



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

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Patricia J. Sime – Boehringer Ingelheim, Consultant/Advisory Board; UCB Biosciences Inc, Grant/Contract; Fibrogen, Consultant/Advisory Board; Galecto, Stockholder; VYNE pharmaceuticals, Consulting/ advisory; American Thoracic Society, Board and journal editor; Three Lakes F: Consultant, No, No;

The following people have nothing to disclose: Mulugeta Seneshaw, Hae-Ki Min, Faridoddin Mirshahi, Michael Idowu, Prakash Ramachandran, John Min, Huiping Zhou, Siddharth Ghosh, Lauren Cowart, Yang Yue, Ekaterina Smirnova, Amon Asgharpour, Mohammad S. Siddiqui

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

Kapil K Upadhyay[1], Brandon Buscher[1], Xiaomeng Du[1], Yanhua Chen[2], Antonino Oliveri[1], Elizabeth K. Speliotes[3,4] and Graham F Brady[1], (1)Division of Gastroenterology and Hepatology, Department of Internal Medicine;, (2)University of Michigan, (3) University of Michigan Medical School, (4)University of Michigan Medical School, Ann Arbor, Michigan, USA

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

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

and *ELOVL5* (encoding fatty acid elongases), while *ACOX1* (encoding a key β-oxidation pathway enzyme) was downregulated. **Conclusion:** Taken together, these data validate the previously reported associations of rs6461378-T with hepatic steatosis and NAFLD-related traits and suggest cell-autonomous mechanisms by which SUN1 H118Y may contribute to human NAFLD by promoting hepatocyte lipid uptake and storage and downregulating fatty acid β-oxidation.

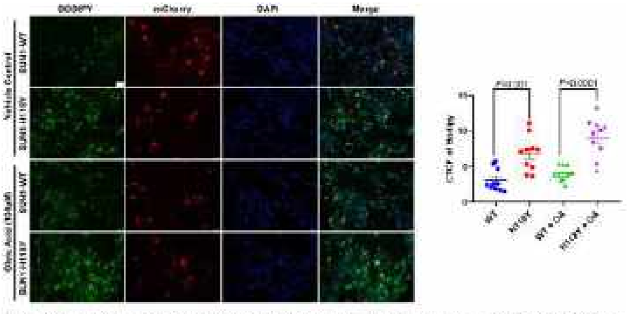

Figure 1. SUN1 H118Y increased lipid accumulation in HuH7 cells. Left panel, representative images of BODIPY 493/503-stained HuH7 cells after transfection with mCherry-tagged SUN1 WT or H118Y for 24h and vehicle or oleic acid treatment (100μM, 24h); scale bar=50μm. Right panel, quantitation of lipid staining (n=3 experiments, 20 fields per condition per experiment) as total BODIPY fluorescence per 20× field (CTCF); statistical analyses were performed via one-way ANOVA and Tukey's multiple comparison test.

Disclosures: Graham F Brady – Orphalan: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;
The following people have nothing to disclose: Kapil K Upadhyay, Antonino Oliveri
Elizabeth K. Speliotes:
Disclosure information not available at the time of publication: Brandon Buscher, Xiaomeng Du, Yanhua Chen

f 2387-C | THIOESTERASE SUPERFAMILY MEMBER 2 INTERACTS WITH PHOSPHATIDYLCHOLINE TRANSFER PROTEIN IN SKELETAL MUSCLE TO PROMOTE NON-ALCOHOLIC FATTY LIVER DISEASE

Yang Xie[1,2] and David E Cohen[1,2], (1)Brigham and Women's Hospital, (2)Harvard Medical School

Background: Interactions between thioesterase superfamily member 2 (Them2), a long-chain fatty acyl-CoA thioesterase, and phosphatidylcholine transfer protein (PC-TP), a cytosolic lipid binding protein, regulate cellular fatty acid and glucose metabolism, as well as insulin signaling. We have demonstrated that global or skeletal muscle-specific, but not liver-specific deletion of Them2 protects mice against high-fat diet (HFD)-induced hepatic steatosis and insulin resistance characteristic of non-alcoholic fatty liver disease (NAFLD). Moreover, restoration of Them2 expression in skeletal muscle in *Them2*$^{-/-}$ mice is sufficient to promote NAFLD. The aim of this study was to elucidate whether Them2-PC-TP interactions in skeletal muscle are necessary for Them2 to induce NAFLD. **Methods:** *Them2*$^{-/-}$ mice received continuous administration of compound A1, an inhibitor of Them2-PC-TP interactions, via implanted mini-infusion pumps. Skeletal muscle-specific Them2 expression was then restored using recombinant adeno-associated virus serotype 8 driven by the muscle creatine kinase promoter, with LacZ as a control. Mice were fed a HFD (60% kcal from fat) for 12 w. Protein expression was ascertained by immunoblotting. Tolerance tests to glucose and insulin were conducted to assess glucose control. Hepatic steatosis was evaluated by H&E and oil red O staining, as well as enzymatic measurements of hepatic triglyceride concentrations. Membrane localization of glucose transporter type 4 (Glut4) in skeletal muscle was analyzed by confocal immunofluorescence imaging. Glucose uptake in the soleus muscle was measured using ^{3}H-2-deoxy-D-glucose. **Results:** Compound A1 administration abrogated the capacity for skeletal muscle-specific Them2 expression to promote hepatic steatosis and insulin resistance. For mice expressing Them2 relative to those expressing LacZ in skeletal muscle, this was evidenced by the absence of increased hepatic steatosis, of worsened glucose control or of decreased Glut4 membrane translocation and glucose uptake by skeletal muscle. **Conclusion:** The interaction of Them2 with PC-TP is critical to the capacity of skeletal Them2 to promote hepatic steatosis and insulin resistance. We speculate that both Them2 and PC-TP in skeletal muscle represent attractive targets in the clinical management of NAFLD.

Disclosures: David E Cohen – Esperion: Advisor, No, No; Amryt: Advisor, No, No; Pfizer: Advisor, No, No; Saliogen: Consultant, No, No; Editas: Consultant, No, Yes; PTC Therapeutics: Advisor, No, No;
The following people have nothing to disclose: Yang Xie

2388-C | THYROID HORMONE RESCUES NON-ALCOHOLIC FATTY LIVER DISEASE IN MICE FED WESTERN DIET BY INCREASING HEPATIC SIRT3 EXPRESSION

Raghu Ramanathan, Sarah Ashley Johnson and Jamal A. Ibdah, University of Missouri-Columbia

Background: The therapeutic options for non-alcoholic fatty liver disease (NAFLD) are limited. Reduced hepatic mitochondrial fatty acid oxidation (FAO) and mitochondrial dysfunction play an important role in the pathogenesis of NAFLD. Thyroid hormone (TH) regulates lipid metabolism in the liver and may have important therapeutic potential in NAFLD. The goal of this study is to test whether thyroid hormone rescues NAFLD in mice fed western diet by increasing the expression of Sirtulin-3 (SIRT3), a master regulator of mitochondrial FAO. **Methods:** Six-month old wild-type male mice with C57BL/6 background were fed

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

Western diet (Research Diets Inc, D12451 Rodent Diet, 45 kcal% fat, 1% cholesterol) for 16 weeks to induce NAFLD. The control mice (n = 6) received phosphate buffered saline (PBS), while the treatment group (n = 6) received triiodothyronine (T_3) 25μg/100g weight intraperitoneal (ip) for 7 days. After sacrifice, complete FAO were measured in fresh liver lysate. Sirtulin-3 (SIRT-3) gene and protein expression, as well as expression of other genes affecting mitochondrial function and mitophagy, were assessed along with histology and transmission electron microscopy (TEM). **Results:** T_3 resulted in 2-fold increase in complete hepatic CO_2 production compared to control PBS ($p < 0.01$, Fig. 1A). The levels of SIRT-3 in both gene and protein expression were significantly increased ($p < 0.05$, Fig. 1B & C) with TH treatment. T_3 increased expression of mitochondrial markers OPA-1 ($p < 0.01$) and COX-IV ($p < 0.05$) compared to control (Fig. 1D, F). In addition, T_3 increased expression of the mitophagy markers BNIP-3 ($p < 0.01$) compared to control (Fig. 1E). Liver histology showed that T_3 rescued NAFLD with significant reduction in steatosis and inflammation markers as compared to control mice (Fig. 1G). The TEM revealed significant improvements in mitochondrial structure compared to control (Fig. 1H). **Conclusion:** TH increases SIRT3 expression which leads to enhanced FAO and rescue of NAFLD in mice. Our study suggests that TH and SIRT-3 are potential targets for treatment of NAFLD by improving mitochondrial function and quality. (Supported by VA Merit 1BX 004710).

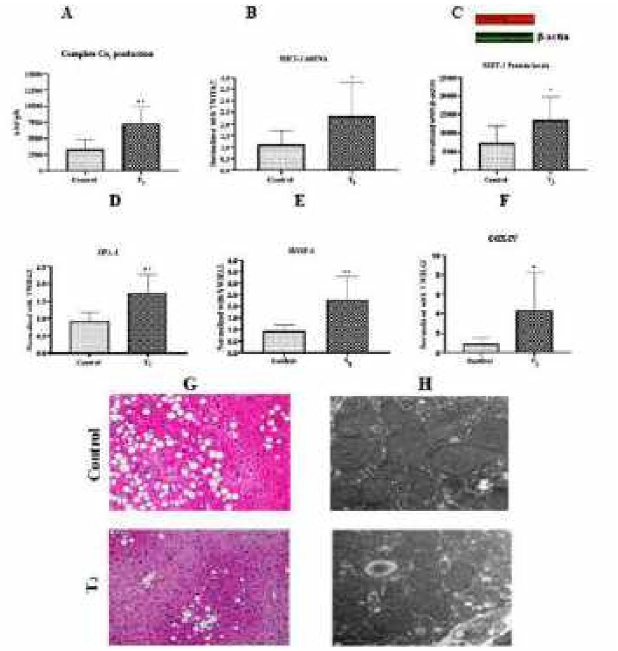


Figure 1. A: Hepatic FAO; B & C: SIRT-3 gene and protein expression; D, E & F: qPCR of mitochondrial markers; G & H: Histology and TEM analysis. Control: PBS treated, T3: treated with 25μg/100g weight T3. Values presented as Mean ± S.D. * p<0.05; ** p<0.01.

Disclosures: The following people have nothing to disclose: Raghu Ramanathan, Sarah Ashley Johnson, Jamal A. Ibdah

2389-C | TIR8 AMELIORATES NASH PROGRESSION BY MAINTAINING PPARA EXPRESSION AND REDUCING THE SENSITIVITY OF HEPATOCYTES TO LPS

Ying Shi[1], Xiao Guang Yang[2], Xiao Dan Zhong[1], Xu Shi[1], Ya Nan Li[1], Junqi Niu[1] and Yanhang Gao[1], (1)The First Hospital of Jilin University, (2)Northeast Normal University

Background: PPARα (peroxisome proliferator-activated receptor-α) serves as the primary regulatory factor in hepatic lipid metabolism. Its expression level influences beta-oxidation and lipid accumulation, making it a crucial target for ameliorating the onset and progression of nonalcoholic fatty liver disease (NAFLD). Moreover, aside from PPAR small molecule agonists, other hepatic endogenous molecular that can maintain the expression of PPARα during free fatty acid stress remain unclear. **Methods:** Bioinformatics was used to compare the gene transcription profiles of liver tissue in NASH patients and normal individual's in the GES database, in which TIR8 was identified. To determine the role of TIR8 in maintaining PPARα gene expression under conditions of lipid accumulation, a high-fat, high-cholesterol diet (HFHCD) induced NASH mouse model and the human liver cell line HepRG were used to investigate the effects of TIR8 on PPARα mediated hepatic lipid metabolism and inflammatory signaling pathways. Immunoprecipitation was used to study the reasons for TIR8 downregulation in hepatocytes under free fatty acid treatment. **Results:** This study found that the expression of TIR8 in the livers of NASH patients was significantly lower than in normal individual's, and the TIR8 gene level was also significantly downregulated in the livers of NASH mice induced by a high-fat, high-cholesterol diet. Knockout of the TIR8 gene accelerated the progression of NASH in mice, with more severe liver lipid deposition and damage than in wild-type mice. Exogenous TIR8 gene overexpression had a protective effect on the mouse liver, with significant improvements in lipid deposition, liver damage, and inflammation factor levels. In vitro studies showed that TIR8 overexpression could maintain PPARα levels in the HepRG liver cell line under free fatty acid stress and reduce the accumulation of triglycerides and formation of lipid droplets induced by palmitic acid/oleic acid. Mechanistically, we found that under the action of free fatty acids and LPS, proteasome 20sα subunit 4 (PMSA4) mediated the degradation of TIR8, which may be a key reason for further activation of inflammatory pathways and the decline of PPARα levels. **Conclusion:** In summary, the expression level of TIR8 is highly correlated with the progression of NASH. The degradation of TIR8 in hepatocytes may be a key reason for PPARα downregulation , leading to lipid metabolism disorder and inflammation mediated by PPARα. Therefore, stimulating the expression of TIR8 is beneficial for maintaining the level of hepatic PPARα, which helps alleviate the progression of NASH.

Disclosures: The following people have nothing to disclose: Ying Shi, Xiao Guang Yang, Xiao Dan Zhong, Xu Shi, Ya Nan Li, Junqi Niu, Yanhang Gao

2390-C | TRANSCRIPTOMIC PROFILING FOR AUTOPHAGY PATHWAY IN HUMAN FATTY LIVERS

Yiing Lin, William C. Chapman and Jae-Sung Kim, Washington University in St. Louis

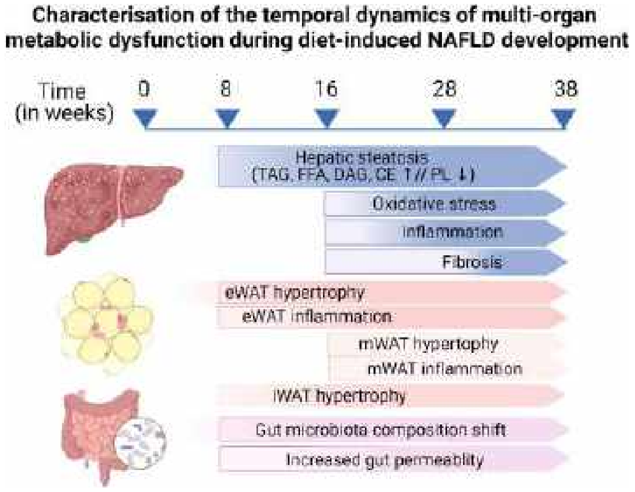
Background: Nonalcoholic fatty liver disease (NAFLD) has become the most common liver disorder in the world, and its global prevalence increases steadily. Autophagy is a cellular process that clears unnecessary cellular constituents. How steatosis affects autophagy in non-parenchymal liver cells remains unknown. **Methods:** We obtained 10 discarded organ livers deemed unsuitable for liver transplant, including 4 mild (< 5 % steatosis), 4 moderate (5-50% steatosis), and 2 severe (> 50% steatosis) fatty livers. Using the Chromium Next GEM Single Cell 3' reagent kit and Chromium Next GEM Chip G Single Cell kit (10x Genomics, Pleasanton, CA), we conducted single-nuclei RNA-sequencing (snRNA-seq) targeting 11,000 nuclei per sample. Changes in autophagy genes involved in the stage of initiation, phagophore formation, elongation, and completion were analyzed in hepatocytes, Kupffer cells, stellate cells, sinusoidal endothelial cells, and cholangiocytes. **Results:** In hepatocytes, the SQSTM1/p62 gene, a marker of autophagic clearance, progressively increased with the severity of steatosis. Compared to mildly steatotic livers, SQSTM1/p62 expression levels in hepatocytes were 64% higher in severely steatotic livers. In striking contrast, its levels in non-parenchymal liver cells were substantially lower in severely steatotic livers than in mildly steatotic livers. Levels of SQSTM1/p62 expression in Kupffer cells, stellate cells, sinusoidal endothelial cells, and cholangiocytes of severely steatotic livers were 14%, 24%, 33%, and 43% of values in mildly steatotic livers, respectively. These results suggest that severe hepatic steatosis increases autophagy in non-parenchymal cells but decreases autophagy in hepatocytes. Analysis of the individual stages in the autophagy pathway revealed that the factors involved in the initiation (DEPTOR and TBK1), phagophore formation (VSP34, ATG14, and BIF1), elongation (ATG14), and completion (ATP6V1D and ATP6V1H) of autophagy were elevated in Kupffer cells, stellate cells, and sinusoidal endothelial cells of severely steatotic livers. Levels of DEPTOR, PRKN, NBR1, TBK1, ATG14, ATG3, ATG4B, ATG14, ATP6V1C1, ATP6V1H, and CTSD were elevated in cholangiocytes of severely steatotic livers. **Conclusion:** Autophagic response to steatosis in non-parenchymal liver cells differs from that in hepatocytes.

Disclosures: The following people have nothing to disclose: Yiing Lin, William C. Chapman, Jae-Sung Kim

2391-C | TRANSLATIONAL CHARACTERIZATION OF THE TEMPORAL DYNAMICS OF METABOLIC DYSFUNCTIONS IN LIVER, ADIPOSE TISSUE AND THE GUT DURING DIET-INDUCED NASH DEVELOPMENT IN LDLR-/-.LEIDEN MICE

Eveline Gart, Tno

Background: >NAFLD progression, from steatosis to inflammation and fibrosis, results from an interplay of intra- and extrahepatic mechanisms. Disease drivers likely include signals from white adipose tissue (WAT) and gut. However, the temporal dynamics of disease development remain poorly understood. **Methods:** High-fat-diet (HFD)-fed Ldlr-/-.Leiden mice were compared to chow-fed controls. At t = 0, 8, 16, 28 and 38w mice were euthanized, and liver, WAT depots and gut were analyzed biochemically, histologically and by lipidomics and transcriptomics together with circulating factors to investigate the sequence of pathogenic events and organ cross-talk during NAFLD development. **Results:** HFD-induced obesity was associated with an increase in visceral fat mass, plasma lipids and hyperinsulinemia at 8 weeks, along with an increase in liver steatosis and circulating biomarkers indicative of liver damage (ALT, AST, CK18-M30, TIMP1). Liver steatosis was mainly attributable to increased triacylglycerols and to a lesser extent free-fatty acids, cholesteryl esters and diacylglycerols. In parallel, regulators involved in lipid catabolism (e.g., ACOX1) were deactivated and in lipid synthesis (e.g., SREBF1) activated by HFD. Subsequently, hepatocyte hypertrophy, oxidative stress (4-HNE) and hepatic inflammation developed. Hepatic collagen accumulated at t = 16w and became particularly prominent after 28-38 weeks. Epididymal WAT adipocytes were maximally hypertrophic from t = 8w, which coincided with inflammation development in this depot. Mesenteric and subcutaneous WAT hypertrophy developed slower and did not appear to reach a maximum within the period studied, with minimal inflammation. In the gut, HFD significantly increased permeability, induced a major shift in microbiota composition (ileum and colon) from t = 8w and associated with circulating gut-derived metabolite changes (short-chain fatty acids and bile acids). **Conclusion:** Ldlr-/-.Leiden mice on a HFD develop obesity, dyslipidemia and insulin resistance, essentially as observed in obese NASH patients. We demonstrate that marked epididymal-WAT inflammation, and gut permeability and dysbiosis precede the development of NAFLD stressing the importance of a multiple-organ approach in the prevention and treatment of NAFLD.


Characterisation of the temporal dynamics of multi-organ metabolic dysfunction during diet-induced NAFLD development
Time (in weeks)
0
8
16
28
38
Hepatic steatosis (TAG, FFA, DAG, CE ↑/ PL ↓)
Oxidative stress
Inflammation
Fibrosis
eWAT hypertrophy
eWAT inflammation
mWAT hypertophy
mWAT inflammation
iWAT hypertrophy
Gut microbiota composition shift
Increased gut permeablity

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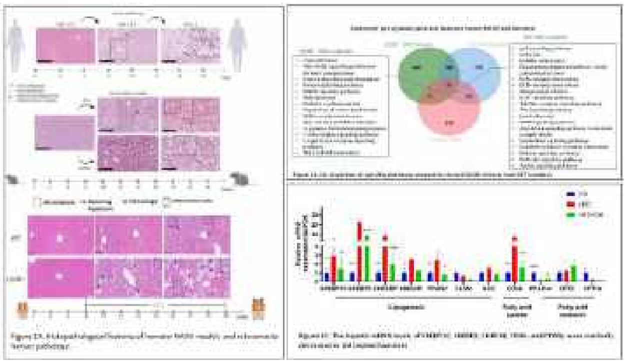
2392-C | TREATMENT OF GROWTH HORMONE ATTENUATES HEPATIC STEATOSIS IN NASH HAMSTERS BY REGULATING PATHWAY OF LIPID METABOLISM AND INFLAMMATION

Wei Zhang[1], Yijun Tao[2], Xiao Lin[2], Ping Ma[2], Gonglie Chen[2], Ling Zhang[2], Wei Huang[2], Xunde Xian[2], George Liu[2] and Yuhui Wang[2], (1)Peking University People's Hospital, Peking University Hepatology Institute, Beijing, China, (2)Institute of Cardiovascular Sciences and Key Laboratory of Molecular Cardiovascular Sciences, Ministry of Education, Peking University, Beijing, China.

Background: Non-alcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease. However, most available animal models fail to mimic the spectrum of the disease from steatosis (NAFL) alone to steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma. Our present study defines wild type hamster with feeding high-fat diet (HFD) as a pre-clinical model of moderate steatohepatitis that mimics the human disease, including pathophysiologic characteristics and transcriptomic signature. Additionally, the reduction in hepatocyte growth hormone (GH)-signaling promotes the development of NAFLD, but the direct effects of GH on hepatocyte function have not been well characterized. We aimed to explore the mechanism of it in our hamster model. **Methods:** Wild type hamsters were fed a healthy chow diet or fed a HFD containing 5% lard and 0.5% cholesterol. The response to GH treatment for four weeks was evaluated in these models. RNA sequencing technology was used to test liver transcriptional differences. Human transcriptomic analysis were defined using a publicly available NASH gene expression profiling dataset (GSE48452 and 126848) allowing the comparison of biopsy-confirmed NAFL and NASH patients with normal controls. **Results:** The 16-weeks HFD induced obesity, hyperlipidemia, and increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Histological analysis in our hamsters exhibited: moderate-severe steatosis, hepatocellular ballooning necrosis, inflammation but mild hepatic fibrosis (Figure1A). Pathway enrichment analysis showed that our hamster model shared a relevant number of important pathways involved in NASH pathophysiology (Figure1B). Exogenous GH treatment decreased liver/body weight without affecting serum lipid profiles. Importantly, GH treatment attenuated hepatic steatosis and inflammation, and also reduced macrophage accumulation in liver. The hepatic mRNA levels of SREBP1C, SREBP2, CHREBP, CD36, and PPARγ were markedly decreased in GH treated hamsters without significant changes in other molecules related to lipid metabolism (Figure1C). And the hepatic expression IL-1β mRNA were decreased by GH treatment. **Conclusion:** Our study defines a translational model of NASH and found GH treatment could attenuate hepatic steatosis and inflammation with downregulation of genes involving lipogenesis /oxidation and inflammation in hyperlipidemic condition.



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Disclosure information not available at the time of publication: Yijun Tao, Xiao Lin, Ping Ma, Gonglie Chen, Ling Zhang, Wei Huang, Xunde Xian, George Liu, Yuhui Wang

2393-C | TWO MEALS PER PERIOD PREVENTS FATTY LIVER BY STIMULATING ENERGY EXPENDITURE

Pamela Mattar[1,2], Andressa Reginato[2], Christian Lavados[2], Nuria Martinez-Lopez[1,2], Mridul Sharma[1,2], Gary Schwartz[2], Prashant Rajbhandari[3] and Rajat Singh[1,2,4], (1)University of California, Los Angeles, (2) Albert Einstein College of Medicine, (3)Diabetes, Obesity, Metabolism Institute, Icahn School of Medicine at Mount Sinai, (4)Liver Basic Research Center at University of California Los Angeles

Background: Intermittent fasting has been proposed as a non-invasive approach to reduce body weight and promote insulin sensitivity. Dietary interventions, e.g., caloric restriction has been shown to protect against NAFLD; however, caloric restriction is marred by poor compliance, impacting human translatability. This forms the basis for developing new dietary approaches to provide similar benefits without lowering caloric intake. We have shown that feeding animals twice-a-day (TAD), i.e., during two 2-hr feeding windows in the diurnal phase, without caloric restriction, protects against NAFLD by stimulating autophagy in liver. In ongoing studies, we are exploring how feeding TAD or twice-a-night (TAN) protects against NAFLD. **Methods**: *Animals*: Studies were performed in male mice of varying ages. *Experiments*: We performed comparative analysis of TAD feeding vs. our newly implemented TAN feeding wherein mice were fed during similar two 2-hr feeding windows in the nocturnal phase without eliminating calories. *Statistics*: Unpaired Student's T-test, one-way or two-way ANOVA followed by appropriate multiple-comparisons tests. **Results**: Comparative analysis revealed that TAD and TAN feeding each markedly reduces body weight, promotes insulin sensitivity, lowers liver triglyceride content and blocks liver inflammation. Using functional and histological approaches, lipidomics, and transcriptomics, we reveal that TAN-fed mice show improved systemic lipid catabolism and energy expenditure, thus funneling lipid away from the liver. Indeed, TAN feeding increases oxygen consumption rates in diverse tissues determined via Seahorse respirometry, decreases liver triglycerides and liver inflammatory and senescence markers. Given that autophagy mediates these benefits in TAD-fed mice, we suspect that stimulation of systemic autophagy drives these hepatoprotective benefits in TAN-fed mice. **Conclusion**: Our studies show that the increases in systemic lipid utilization by feeding two meals per period, in absence of caloric restriction, is sufficient to prevent NAFLD and steatohepatitis.

Disclosures: The following people have nothing to disclose: Pamela Mattar, Andressa Reginato, Christian Lavados, Nuria Martinez-Lopez, Mridul Sharma, Gary Schwartz, Prashant Rajbhandari, Rajat Singh

f 2394-C | Ubc13 PROTECTS AGAINST DEFECTIVE MITOPHAGY IN NON-ALCOHOLIC FATTY LIVER DISEASE BY PROMOTING K63-LINKED p62 UBIQUITINATION★

Feng Wang[1], Yoon-Seok Roh[1], Jin Lee[2], Jeong-Su Park[1], Hwan Ma[1] and Ekihiro Seki[3], (1)Chungbuk National University College of Pharmacy, (2)University of California, San Diego, La Jolla, CA, (3)Cedars-Sinai Medical Center, Torrance, CA

Background: Ubiquitination is a post-translational modification and contributes to mitophagy which plays an essential role in nonalcoholic fatty liver disease (NAFLD). Ubc13 is the only known ubiquitin-conjugating enzyme (E2) specialized in K63-linked polyubiquitination. However, the mechanism of how mitochondria quality control is regulated by Ubc13 in NAFLD remains unclear. **Methods:** Hepatocyte-specific Ubc13 knockout (Ubc13$^{\Delta Hep}$) and Ubc13/p62$^{\Delta Hep}$ mice were treated Fast food diet (FFD) for 8 weeks. Mitochondrial functions in hepatocytes were examined by Seahorse bioanalyzer and Mt-Keima system. RNA sequencing and proteomics analysis were performed using liver tissue. Spatial transcriptomics (GeoMX) analysis was performed using normal and NASH human liver tissues. **Results:** Hepatocyte-specific Ubc13 deletion induces cell death and inflammation. Multi-omics analysis (RNA sequencing and Proteomics) revealed that Ubc13 regulates mitochondrial integrity. Ubc13 deletion caused mitochondrial dysfunction. Since mitophagy plays a major role in mitochondrial quality control, we sought to determine how Ubc13 regulates mitophagy. We found that Ubc13 overexpression enhanced mitophagic clearance and Ubc13 deletion decreased it *ex vivo* and *in vitro*, indicating that Ubc13 promotes mitophagy in hepatocytes. Mitochondrial dysfunction is often observed in NAFLD patient livers, and our data showed hepatic expression of Ubc13 was significantly downregulated in livers of NAFLD patients analyzed by GeoMx and IHC, further suggesting the role of Ubc13 in mitochondrial functions in NAFLD. We also found that Ubc13 deletion in hepatocytes aggravated FFD-induced lipid accumulation and subsequent inflammation and fibrosis. Of note, proteomics analysis identified p62 is the most upregulated protein in liver of Ubc13$^{\Delta Hep}$ mice. Mechanistically, Ubc13 directly interacted with p62 at K7A and subsequently induced K63 ubiquitination, promoting mitophagy. We also found defective mitophagy by Ubc13 deletion induced p62 accumulation by suppressing p62

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

degradation. An additional deletion of p62 alleviated hepatic inflammation and fibrosis in Ubc13$^{\Delta Hep}$ mice, suggesting that the aberrant accumulation of p62 is associated with disease progression in Ubc13$^{\Delta Hep}$ mice. **Conclusion:** Our findings revealed that Ubc13-mediated p62 ubiquitination is an essential mechanism for mitochondrial quality control, which may prevent the development of NAFLD.

Figure 1. Ubc13 deletion induces cell death and mitochondrial dysfunction.

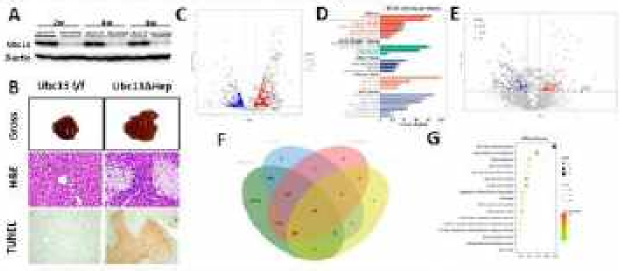


Figure 2. Ubc13 mediates mitochondrial quality control by regulation of mitophagy

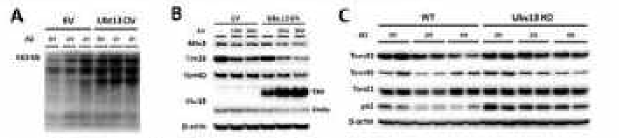
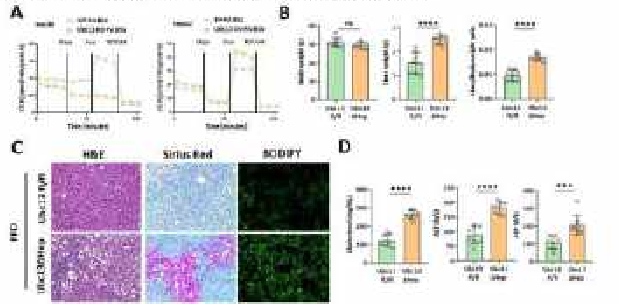


Figure 3. Ubc13 protects against HFD induced Non-alcoholic Fatty Liver Diseases



Disclosures: Ekihiro Seki – Jubilant Theraeputics Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, Yes;
The following people have nothing to disclose: Feng Wang, Yoon-Seok Roh, Jin Lee, Jeong-Su Park, Hwan Ma

2395-C | ULTRASTRUCTURAL ANALYSIS OF VASCULAR ENDOTHELIAL GLYCOCALYX IN NONALCOHOLIC FATTY LIVER DISEASE

Ayumi Kuroda, Kodai Suzuki, Hideshi Okada, Hiroyuki Tomita, Chihiro Takada, Takahiro Yoshida, Shozo Yoshida and Shinji Ogura, Gifu University

Background: Non-alcoholic fatty liver disease (NAFLD) is regarded as a hepatic disease of metabolic syndrome that develops based on obesity, diabetes, dyslipidemia, and hypertension. Fatty liver, in which fat is deposited in the liver tissue, is thought to progress to non-alcoholic steatohepatitis and liver cirrhosis (NASH) when the tissue is exposed to certain stimuli such as oxidative stress and inflammatory cytokines. However, the mechanism of the progress is still unclear. The endothelial glycocalyx which is a glycoprotein on the surface of the vascular endothelial cells plays an important role in regulating vascular homeostasis. Therefore, we hypothesized that the hepatic endothelial glycocalyx injured associated with the progress of NAFLD. In this study, we analyzed the ultrastructure of the hepatic endothelial glycocalyx with scanning electron microscopy. **Methods:** Ten-week-old C57BL6 mice were fed methionine-choline-deficient diet (MCD) as NAFLD group, or standard diet as control group for 4 weeks. MCD diet inhibits triglyceride elimination from the liver and causes fat accumulation in the liver. Intrahepatic fibrosis and lipid droplets were evaluated by HE and Oil Red O staining. In addition to conventional 2.5% glutaraldehyde perfusion fixation, endothelial glycocalyx staining was performed to observe the labile endothelial glycocalyx by electron microscopy. Mice were anesthetized and then perfused with a solution composed of 2% glutaraldehyde, 2% sucrose, 0.1-M sodium cacodylate buffer (pH 7.3), and 2% lanthanum nitrate, at a steady flow rate. The freeze-fracture method was used to prepare samples for scanning electron microscopy. **Results:** MCD group showed a decrease in body weight and an increase in serum aspartate aminotransferase compared to the control group. Histologically, A prominent accumulation of lipid droplets was observed in the liver tissue of MCD group. Conventional scanning electron microscopy results showed destruction of the fenestrated structure of the hepatic sinusoidal endothelial cells, and it was suggested that the accumulation of lipid droplets compressed the bile ducts and inhibited bile excretion. Ultrastructural analysis by the glycocalyx method revealed that detachment of the intrahepatic microvessels in the MCD group compared to the control group. **Conclusion:** In conclusion, our data has shown that the endothelial glycocalyx damage is sustained due to a chronic inflammation at the initial NAFLD. It may lead to liver fibrosis and cirrhosis.

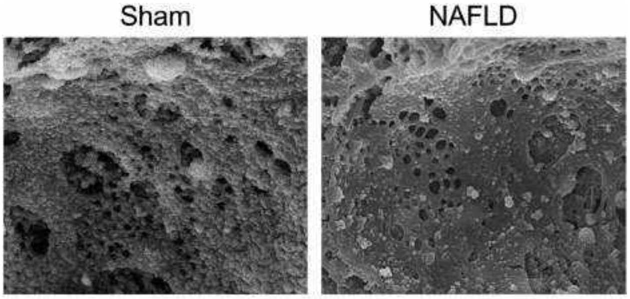


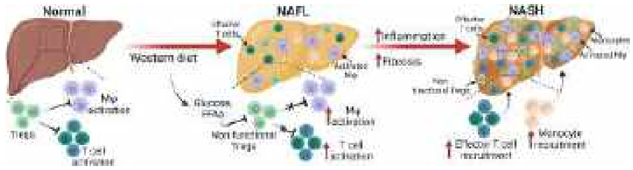
Figure Ultrastructural imaging of hepatic endothelial glycocalyx with scanning electron microscopy. The endothelial glycocalyx of NAFLD was damaged compared to the endothelial glycocalyx of sham.

Disclosures: The following people have nothing to disclose: Ayumi Kuroda, Kodai Suzuki, Hideshi Okada, Hiroyuki Tomita, Chihiro Takada, Takahiro Yoshida, Shozo Yoshida, Shinji Ogura

f 2396-C | WESTERN DIET DAMPENS T REGULATORY CELL FUNCTION TO FUEL HEPATIC INFLAMMATION IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Sudrishti Chaudhary[1], Ravi Rai[1], Pabitra Pal[1], Dana Tedesco[2], Aatur Singhi[3], Satdarshan (Paul) Monga[1], Arash Grakoui[2], Smita Iyer[1] and Reben Raeman[1], (1) University of Pittsburgh, (2)Emory University School of Medicine, (3)University of Pittsburgh Medical Center

Background: The immunosuppressive T regulatory cells (Tregs) regulate immune responses and maintain immune homeostasis, yet their functions in metabolic dysfunction-associated steatotic liver disease (MASLD) pathogenesis remains controversial. **Methods:** Mice were fed a normal diet (ND) or a western diet (WD) for 16 weeks to induce MASLD. Diphtheria toxin injection to deplete Tregs in Foxp3DTR mice or Treg induction therapy in WT mice to augment Treg numbers was initiated at twelve and eight weeks, respectively. Liver tissues from mice and MASH human subjects were analyzed by histology, confocal imaging, and qRT-PCR. **Results:** WD triggered accumulation of adaptive immune cells, including Tregs and effector T cells, within the liver parenchyma. This pattern was also observed in MASH patients, where an increase in intrahepatic Tregs was noted. In the absence of adaptive immune cells in Rag1 KO mice, WD promoted accumulation of intrahepatic neutrophils and macrophages and exacerbated hepatic inflammation and fibrosis. Similarly, targeted Treg depletion exacerbated WD-induced hepatic inflammation and fibrosis. In Treg-depleted mice, hepatic injury was associated with increased accumulation of neutrophils, macrophages, and activated T cells within the liver. Conversely, induction of Tregs using recombinant IL2/aIL2 mAb cocktail reduced hepatic steatosis, inflammation, and fibrosis in WD-fed mice. Analysis of intrahepatic Tregs from WD-fed mice revealed a phenotypic signature of impaired Treg function in MASLD. Ex vivo functional studies showed that glucose and palmitate, but not fructose, impaired the immunosuppressive ability of Treg cells. **Conclusion:** Our findings indicate that the liver microenvironment in MASLD impairs the ability of Tregs to suppress effector immune cell activation, thus perpetuating chronic inflammation and driving MASLD progression. These data suggest that targeted approaches aimed at restoring Treg function may represent a potential therapeutic strategy for treating MASLD.



Disclosures: The following people have nothing to disclose: Sudrishti Chaudhary, Ravi Rai, Pabitra Pal, Dana Tedesco, Aatur Singhi, Satdarshan (Paul) Monga, Arash Grakoui, Smita Iyer, Reben Raeman

2397-C | YKL-40 DEFICIENCY ALTERS INFILTRATING NEUTROPHILS INFLAMMATORY GENE PROFILE IN NLRP3 INDUCED LIVER INFLAMMATION

Lin Kui[1], Andrea D. Kim[1,2], Hal Hoffman[1], Ben Croker[1] and Ariel E. Feldstein[1], (1)University of California, San Diego, (2)Johns Hopkins University, Baltimore, MD

Background: BRP-39 (breast regression protein 39; Chi3L1) and its human homolog YKL-40 is a well-established biomarker of liver fibrosis in NASH patients while the potential mechanistic contribution to NASH pathogenesis remains poorly understood. We have recently identified Chi3L1 as one of the top upregulated genes in the liver of mouse with inducible gain-of-function NOD-like receptor protein 3 (Nlrp3) activation that mimics several liver features of NASH (Hepatology 2022). **Methods:** Using Tamoxifen-inducible Nlrp3 knock-in Muckle wells (MW CRT) mice, Tamoxifen-inducible Nlrp3 knock-in Muckle wells BRP39 deficient mice (MW/BRP CRT), we investigated the consequence of BRP39 deficiency influencing NLRP3 induced liver inflammation, particularly looking at the change in gene expression of infiltrating neutrophils. ***Results:*** MW CRT have reduced bodyweight and increased liver weight (***$p < 0.001$) compared to WT mice. Contrastingly, MW/BRP CRT mice have improved bodyweight and liver weight (*$p < 0.05$) compared to MW CRT mice. Ly6G+ infiltrating neutrophils (**$p < 0.01$) were significantly lowered in MW/BRP CRT mice compared with MW CRT mice, furthermore immunofluorescence imaging revealed MW/BRP CRT mice whole liver having significantly less activated neutrophils with lower Ly6G+ and H3Cit+ expression (*$p < 0.05$) compared with MW CRT. Chemotaxis analysis revealed that MW/BRP CRT neutrophils migration ability is significantly reduced compared with MW CRT. RNA-seq of isolated whole-blood neutrophils revealed that MW/BRP CRT mice have reduced immune activation, migration, aggregation and signaling response compared to MW CRT. Among the top 25 differentially expressed genes (DEG), Complement

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

C1q complex (C1qb and C1qa) essential for classical pathway cascade, Anpep (CD13) important receptor in neutrophils phagocytosis and activating effector function, F12 (factor XII) involved in neutrophils migration are downregulated (logFC > 1 or < -1, FDR < 0.01). Gene Ontology analysis with fgsea (fast gene set enrichment analysis) confirmed that the downregulated gene sets associated with biological processes pathways involved in protein kinase activity, complement activation, cell junction assembly, leukocyte mediated immunity and cytokine production. **Conclusion:** We showed that BRP39 is important in immune activation, cytokine production regulation, kinase activity and signaling in NLRP3 induced liver inflammation and fibrotic NASH.

Disclosures: Hal Hoffman – Novartis and Kiniksa: Consultant, No, No;

Ariel E. Feldstein – Novo Nordisk: Executive role , No, No;

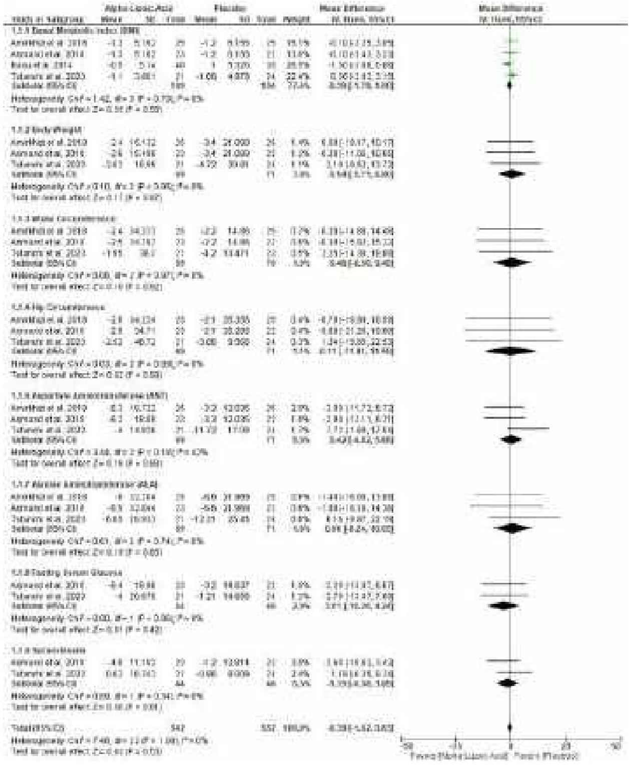
The following people have nothing to disclose: Lin Kui, Andrea D. Kim, Ben Croker

2398-C | ALPHA-LIPOIC ACID SUPPLEMENTATION FOR NON-ALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Islam Mohamed[1], Noor Hassan[2], Ifrah Fatima[3], Mohamed Abuelazm[4], Jagadish Koyi[3], Rawan Rajab[5], Hazem Abosheaishaa[6], Mohamed Ahmed[3], Wael T Mohamed[1], Khaled Elfert[7], Adel Muhanna[1], Laura M. Alba[8], Wendell K. Clarkston[1] and Hassan Ghoz[3], (1) University of Missouri-Kansas City, (2)University of Missouri- Kansas City, Kansas City, MO, (3)University of Missouri- Kansas City, (4)Tanta University, (5)University of Missouri Kansas City, (6)Icahn School of Medicine at Mount Sinai, (7)St. Barnabas Hospital, Bronx, NY, (8) Univeristy of Missouri- Kansas City, Kansas City, MO

Background: Non-alcoholic fatty liver disease (NAFLD) is the most prevalent form of chronic liver disease worldwide, often associated with obesity, type 2 diabetes, and insulin resistance. NAFLD can progress to more severe conditions, including liver cirrhosis and hepatocellular carcinoma. Current understanding of NAFLD pathogenesis is limited, and treatment options beyond weight loss are limited. Insulin resistance and chronic inflammation are known to contribute to NAFLD development and progression. Alpha-lipoic acid (ALA), an antioxidant with potential anti-inflammatory properties, has been investigated as a supplement for NAFLD. However, existing studies have produced conflicting results, making it challenging to determine the efficacy of ALA supplementation in NAFLD treatment. To address this uncertainty, we conducted a meta-analysis and systematic review to assess the efficacy of ALA for NAFLD treatment. **Methods:** We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs). We searched multiple databases, including PubMed, EMBASE, Web of Science, SCOPUS, and Cochrane, up to April 18th, 2023. The search utilized relevant keywords and MeSH terms. Data from eligible studies were analyzed using RevMan version 5.4 software. Continuous outcomes were assessed using the mean difference (MD), and corresponding confidence intervals (CI). The study protocol was registered prospectively in the PROSPERO database.

Results: In our meta-analysis, no significant differences were found between alpha-lipoic acid and placebo in terms of changes in the basal metabolic index (BMI) (MD: -0.39, 95% CI: [-1.78, 1.00], P = 0.58), body weight (MD: 0.54, 95% CI: [-5.71, 6.80], P = 0.87), waist circumference (MD: 0.48, 95% CI: [-8.50, 9.46], P = 0.92), hip circumference (MD: -0.11, 95% CI: [-11.81, 11.59], P = 0.99), aspartate aminotransferase (AST) (MD: 0.42, 95% CI: [-4.82, 5.66], P = 0.88), alanine aminotransferase (MD: 0.90, 95% CI: [-8.24, 10.05], P = 0.85), fasting serum glucose (MD: -3.01, 95% CI: [-10.26, 4.24], P = 0.42), and serum insulin (MD: -1.35, 95% CI: [-6.58, 3.89], P = 0.61). **Conclusion:** Our comprehensive meta-analysis, the first to investigate the effects of ALA for NAFLD, revealed no significant difference between ALA and placebo in the treatment of NAFLD. ALA supplementation did not show significant effects on key metabolic parameters, including BMI, body weight, waist circumference, hip circumference, AST, ALT, fasting serum glucose, and serum insulin levels. Further large-scale RCTs are warranted to obtain a more comprehensive understanding of the potential benefits of ALA in the treatment of NAFLD.



Disclosures: The following people have nothing to disclose: Islam Mohamed, Noor Hassan, Ifrah Fatima, Jagadish Koyi, Hazem Abosheaishaa, Mohamed Ahmed, Khaled Elfert, Hassan Ghoz

Disclosure information not available at the time of publication: Mohamed Abuelazm, Rawan Rajab, Wael T Mohamed, Adel Muhanna, Laura M. Alba, Wendell K. Clarkston

2399-C | ALTERATIONS IN THE ADIPOSE TISSUE TRANSCRIPTOMIC PROFILE ARE ASSOCIATED WITH e F2 LIVER FIBROSIS BUT ARE UNCHANGED BY A SYNBIOTIC INTERVENTION IN NAFLD

Josh Bilson[1], Carolina J. Oquendo[1], Eleonora Scorletti[2], Jenny Lord[1], Paul R. Afolabi[1], Giovanni Targher[3], Diana Baralle[1], Philip C. Calder[1], Christopher D Byrne[1] and Jaswinder K. Sethi[1], (1)University of Southampton, (2)University of Pennsylvania, (3) Universitaria Integrata of Verona

Background: Subcutaneous adipose tissue (SAT) dysfunction may be influenced by gut microbiota and contributes to NAFLD pathogenesis. Whether gene markers of SAT function are associated with liver fibrosis and can be influenced by a synbiotic treatment that changes gut microbiota is unknown. We investigated: (a) whether AT insulin resistance (IR), alterations in SAT transcriptomic profiles and a gene expression signature of SAT fibrosis are associated with the presence of e F2 liver fibrosis; and (b) whether a synbiotic treatment modified (a). **Methods:** Sixty-two patients with NAFLD (60% men) were studied prior to and following 12 months of treatment with synbiotic or placebo. RNA-sequencing was used to assess SAT transcriptomic profiles. A validated composite collagen gene expression (CCGE) score was used as a proxy of SAT fibrosis. Vibration-controlled transient elastography (VCTE)-validated thresholds were used to non-invasively assess liver fibrosis. Regression modelling and receiver operator characteristic curve analysis was used to test associations and risk prediction. **Results:** Patients with NAFLD and e F2 fibrosis (n = 24) had greater AT IR and a SAT gene expression signature characterised by an enrichment in inflammatory and extracellular matrix-associated gene expression compared to those with < F2 fibrosis (n = 38). Synbiotic treatment did not change SAT transcriptomic profiles or inflammatory/adipokine markers. The CCGE score was independently associated with (explaining 32% of the variance) and was a good predictor of e F2 fibrosis (AUROC 0.79, 95%CI 0.68-0.90). Associations between SAT transcriptomics and e F2 fibrosis were further reproduced using end-of-study data. **Conclusion:** A transcriptomic signature in SAT was associated with e F2 liver fibrosis but was unchanged by a synbiotic treatment. CCGE scores in SAT were a good predictor of e F2 liver fibrosis in NAFLD.

Disclosures: The following people have nothing to disclose: Josh Bilson, Eleonora Scorletti

Disclosure information not available at the time of publication: Carolina J. Oquendo, Jenny Lord, Paul R. Afolabi, Giovanni Targher, Diana Baralle, Philip C. Calder, Christopher D Byrne, Jaswinder K. Sethi

2400-C | ARTIFICIAL INTELLIGENCE BASED DIGITAL PATHOLOGY REVEALS FATTY ACID SYNTHASE (FASN) INHIBITOR ALONE OR IN COMBINATION WITH SEMAGLUTIDE IMPROVES FIBROSIS IN DIET-INDUCED OBESE MICE WITH BIOPSY-CONFIRMED NASH AND FIBROSIS

Wen-Wei Tsai[1], Mie Berke[2], Michael Feigh[2], Louis Petitjean[3], Li Chen[3], Eduardo Bruno Martins[1], George Kemble[1] and Marie O'Farrell[1], (1)Sagimet Biosciences, (2)Gubra Aps, (3)Pharmanest

Background: Increased *de novo* lipogenesis (DNL) drives the development of nonalcoholic steatohepatitis (NASH) and fatty acid synthase (FASN) is the rate-limiting enzyme in the DNL pathway. FASN inhibition not only reduces liver fat but also acts directly on immune and hepatic stellate cells reducing inflammation and fibrosis. Denifanstat (TVB-2640), a first in class FASN inhibitor, has demonstrated improvements in liver fat and biomarkers associated with inflammation and fibrosis in NASH trials. Semaglutide, a GLP-1 analog, reduced body weight and demonstrated NASH resolution in a recent NASH trial; however, it did not improve fibrosis compared to placebo. Aim: This study was designed to evaluate a FASN inhibitor alone and in combination with semaglutide on liver pathology, including NAFLD activity score (NAS) and fibrosis, in biopsy-confirmed NASH mice. **Methods:** Male C57BL/6J Gubra-Amylin-NASH (GAN) diet-induced obese mice with histologically-confirmed NAS (e 5) and fibrosis stage (F2-F3) were randomized and treated with either TVB-3664 (a surrogate FASN inhibitor for denifanstat, 10 mg/kg, PO, QD) or semaglutide (30 nmol/kg, SC, QD) alone or in combination for 12 weeks (Gubra, Denmark). High resolution phenotypic FibroNest analysis (PharmaNest, NJ) was used to evaluate changes in fibrosis. **Results:** Semaglutide significantly reduced body

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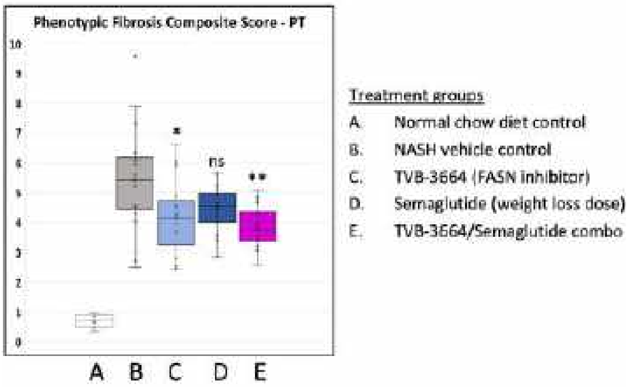
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

weight alone or in combination with TVB-3664. TVB-3664 and the TVB-3664/semaglutide combination improved plasma ALT and AST, reduced total liver triglycerides and cholesterols, and decreased hepatocytes with lipid droplets and galectin-3 staining area. TVB-3664 and semaglutide significantly improved NAS (NAS e 1 point, 47% & 56%, respectively) and the combination showed further improvement (94%). Combination of TVB-3664/semaglutide decreased total liver area of picosirius red (PSR), collagen 1a1 and smooth muscle actin staining. Digital AI pathology algorithm assessment of post-treatment PSR staining (FibroNest) showed that TVB-3664 alone and the TVB-3664/semaglutide combination significantly reduced the phenotypic fibrosis composite severity score ($p < 0.05$ & $p < 0.01$, respectively, Figure 1) and parenchymal steatosis area ratio ($p < 0.01$) compared to vehicle. **Conclusion:** Combination treatment of FASN inhibitor and semaglutide showed further histological improvement of NAS and fibrosis compared to single agent treatment in a translational mouse model of NASH. These results support future clinical evaluation of denifanstat/GLP-1 combination therapy.

Figure 1



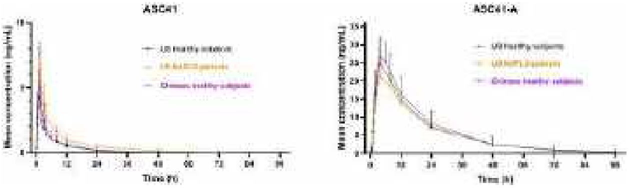
*$p<0.05$, **$p<0.01$, ns: no significant, compared to NASH vehicle control

Disclosures: Wen-Wei Tsai – Sagimet Biosciences: Employee, Yes, No; Sagimet Biosciences: Stock – privately held company (individual stocks and stock options), Yes, No;
Michael Feigh – Gubra: Executive role , Yes, No; Gubra: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No; Gubra: Employee, Yes, No;
Li Chen – PharmaNest Inc: Employee, Yes, No; PharmaNest: Stock – privately held company (individual stocks and stock options), Yes, No;
The following people have nothing to disclose: Louis Petitjean
Disclosure information not available at the time of publication: Mie Berke, Eduardo Bruno Martins, George Kemble, Marie O'Farrell

2401-C | ASC41, A THYROID HORMONE RECEPTOR Β AGONIST, SHOWED LITTLE DRUG INTERACTION, SIGNIFICANT LIPID REDUCTION AND COMPARABLE PHARMACOKINETIC PROFILES AMONG CHINESE AND US HEALTHY SUBJECTS AND PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD): RESULTS FROM TWO PHASE 1 STUDIES

Jinzi Wu, Handan He and Yuemei Yan, Gannex Pharma Co., Ltd.

Background: ASC41 is a small molecule prodrug of thyroid hormone receptor β (THR-β) agonist. ASC41 is converted to its pharmacologically active metabolite ASC41-A by CYP3A4 in the liver. Here we report results of ASC41 drug-drug interaction (DDI) study in US healthy subjects and pharmacokinetic (PK), safety and pharmacodynamic (PD) in Chinese healthy subjects or US subjects with non-alcoholic fatty liver disease (NAFLD). **Methods:** NCT04527250 was a randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, PK and PD of single and multiple ascending oral doses of ASC41. NCT04845646 was an open label, DDI study to evaluate effect of itraconazole (CYP3A strong inhibitor) and phenytoin (CYP3A strong inducer) on PK of ASC41 following a single dose of 5 mg ASC41 tablet and PK in NAFLD patients. **Results:** The active metabolite ASC41-A concentrations in plasma were approximately 20 times higher than those of ASC40 after oral dosing of ASC41. Both AUC and C_{max} of ASC41 and ASC41-A showed linear PK after single (1-20 mg) or multiple (1-5mg) doses. There were no clinically significant changes in the exposure of ASC41-A in the presence or absence of itraconazole (CYP3A4 strong inhibitor) or phenytoin (CYP3A4 strong inducer). PK profiles of ASC41-A were similar among US and Chinese healthy subjects, as well as NAFLD patients following a single dose of 5 mg ASC41 tablet (Figure 1). ASC41 induced significant reduction of lipid parameters, such as low-density lipoprotein cholesterol, triglycerides, and total cholesterol, but has no effect on high-density lipoprotein cholesterol after multiple ascending-dose range of 1-5 mg. No serious adverse events were reported across studies, and most adverse events were mild (grade 1) in severity and all were resolved with no sequelae. **Conclusion:** PK of ASC41-A was comparable among US and Chinese healthy subjects and NAFLD patients. ASC41 demonstrated significant reductions of lipids. ASC41 exhibited satisfactory safety and tolerability. Drug-Drug interactions of ASC41/ASC41-A with strong CYP3A4 inhibitor or inducer were low, showing competitiveness to other THR-β agonists in the late stage clinical development. It is unlikely that there will be clinically significant drug-drug interactions between ASC41/ASC41-A and the most frequently used antidepressants and statins, indicating broad application in patients with NASH. ASC41 is currently in a 52-week Phase 2 trial to treat biopsy-confirmed NASH patients.



Disclosures: The following people have nothing to disclose: Jinzi Wu, Handan He, Yuemei Yan

2402-C | ASSESSMENT OF LIVER FIBROSIS IN INDIVIDUALS WITH METABOLIC SYNDROME OR TYPE 2 DIABETES MELLITUS USING NON-INVASIVE TESTS

Robert Nastasa, Carol Stanciu, Ermina Stratina, Sebastian Zenovia, Cristina Muzica, Remus Stafie, Rotaru Adrian, Horia Minea, Laura Huiban, Stefan Chiriac, Catalin Sfarti, Camelia Cojocariu, Tudor Cuciureanu, Ana-Maria Singeap, Irina Girleanu and Anca Trifan, University of Medicine and Pharmacy "Grigore T. Popa", Iasi, Romania

Background: Individual's with metabolic syndrome (MS) or type 2 diabetes mellitus (T2DM) are at high risk for developing non-alcoholic fatty liver disease and advanced liver fibrosis. Although, there are currently no recommendations for screening patients with MS or T2DM. This study aimed to assess the diagnostic accuracy of non-invasive tests in predicting advanced liver fibrosis (e F3) in patients with MS or T2DM using the novel non-invasive score namely Agile 3+ score, which is done by combining straightforward clinical parameters with common laboratory biomarkers and liver stiffness measurements by vibration-controlled transient elastography. **Methods:** We prospectively enrolled patients with MS or T2DM which have been evaluated using non-invasive tests such as aspartate aminotransferase to platelet ratio index (APRI) score, fibrosis-4 (FIB-4) index, NAFLD fibrosis score (NFS), and Agile 3+ score in the Gastroenterology and Hepatology Institute Iasi, between August to October 2022. We calculated the area under the receiver operating curve (AUROC), specificity, sensitivity, negative predictive value (NPV), and positive predictive value (PPV) for each of these biomarkers in the detection of advanced liver fibrosis (e F3) compared with Agile 3+ score. In addition, we used Controlled Attenuation Parameter (CAP) with a cut-off ³ 274 dB/m for diagnosed non-alcoholic fatty liver disease (NAFLD). **Results:** Among 96 patients with T2DM and MS enrolled with a mean BMI of 26.98 ±4.73 kg/m2, 58 (60.4%) were females. According to Agile 3+ score, 28 (29.2%) individual's had at least advanced fibrosis (e F3) using a cut-off e 0.679. Moreover, 73 (76%) of the patients included in our study had NAFLD, according to a CAP ³ 274 dB/m. A significant correlation was found between Agile 3+ score and FIB-4 index ($r = 0.578$), NFS ($r = 0.591$), and APRI score ($r = 0.644$) ($p < 0.001$). The FIB-4 index had the highest NPV (90.12%) followed by the NFS score (86.61%). In comparison with Agile3+ score, all the biomarkers had relatively low specificity (<80%) and PPV (<75 %). Although, the major finding of our analysis was that all these biomarkers had relatively high NPV (>85%) and accuracy (>83%) for predicting advanced liver fibrosis. **Conclusion:** Novel non-invasive score, namely Agile 3+ score appear to improve identification of advanced fibrosis and cirrhosis, among MS and T2DM patients, who are at high risk to develop NAFLD and at least advanced fibrosis (e F3). Furthermore, it is possible to increase the PPV and reduce the number of cases with indeterminate results for the identification of cirrhosis and advanced fibrosis in patients with NAFLD, which would minimize the need for liver biopsy.

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f 2403-C | BOS-580, AN INVESTIGATIONAL FGF21 ANALOG, IMPROVED MARKERS OF GLYCEMIC CONTROL AND LIVER STEATOSIS IN A DIABETIC SUB-POPULATION ENROLLED IN A PHASE 2a DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY IN PATIENTS WITH PHENOTYPIC NASH

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Background: Type-2 diabetes (T2D) is commonly associated with NASH. FGF21 is known to improve glucose homeostasis through increase in peripheral insulin sensitivity and suppression of hepatic glucose production. We present below a sub-group analysis of the effect of BOS-580 on glycemia control biomarkers and liver fat reduction in T2D sub-populations enrolled in a phase 2a

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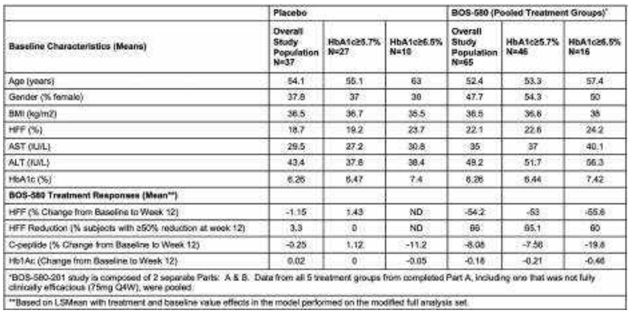
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

study of BOS-580, an investigational FGF21 analog being studied for the treatment of NASH. **Methods:** Part A of phase 2a study BOS-580-201 enrolled 102 patients with obesity at risk for developing NASH, with VCTE liver stiffness measure (LSM) scores of 7-9.9 kPa, AST values of > 20 IU/mL, and body mass index (BMI) from 30-45 kg/m^2. Participants were randomized into 5 different dosing groups (75mg Q4W, 75mg Q2W, 150mg Q4W, a150mg Q2W, and 300mg Q4W) and administered BOS-580, an engineered variant of human FGF-21 fused to human IgG1-Fc, or placebo, for 12 weeks. Two sub-populations were identified based on baseline HbA1c values of e 5.7% (pre-diabetics and diabetics, n = 73) or e 6.5% (diabetics, n = 26). Glycemic markers including C-peptide and Hb1Ac, along with hepatic fat fraction (HFF), were evaluated in these sub-populations and the overall study population. **Results:** Baseline characteristics (age, gender, body weight, BMI, LSM score) were similar in T2D sub-populations to the overall study population. However, baseline HFF and AST values were higher in the HbA1c e 6.5% sub-population. After 12 weeks of treatment with BOS-580, C-peptide levels dropped 19.8% and absolute HbA1c levels decreased by 0.46% in the HbA1c e 6.5% sub-population, compared to decreases of 8.1% and 0.18%, respectively, in the overall study population. In addition, both overall reductions in HFF as well as the proportion of patients demonstrating at least a 50% reduction in HFF, were generally similar across all sub-populations. No treatment emergent adverse events of hypoglycemia were reported in any patient enrolled in the study. **Conclusion:** Once monthly or bi-weekly dosing of BOS-580 in patients with HbA1c > 5.7% had improvements in glycemic markers comparable to the overall study population, while those with HbA1c > 6.5% demonstrated numerically greater improvements in glycemic markers in a 12-week trial. The potential ability of FGF21-based NASH therapies to treat such patients could be particularly important given the prevalence of T2D in NASH patients and the role of FGF21 in improving glycemic control.



	Placebo			BOS-580 (Pooled Treatment Groups)*		
Baseline Characteristics (Means)	Overall Study Population N=37	HbA1c≥5.7% N=27	HbA1c≥6.5% N=10	Overall Study Population N=65	HbA1c≥5.7% N=46	HbA1c≥6.5% N=16
Age (years)	54.1	55.1	63	52.4	53.3	57.4
Gender (% female)	37.8	37	30	47.7	54.3	50
BMI (kg/m2)	36.5	36.7	35.5	36.5	36.8	38
HFF (%)	18.7	19.2	23.7	22.1	22.6	24.2
AST (IU/L)	29.5	27.2	30.8	35	37	40.1
ALT (IU/L)	43.4	37.8	38.4	49.2	51.7	56.3
HbA1c (%)	6.26	6.47	7.4	6.26	6.44	7.42
BOS-580 Treatment Responses (Mean)**						
HFF (% Change from Baseline to Week 12)	-1.15	1.43	ND	-54.2	-53	-55.8
HFF Reduction (% subjects with ≥50% reduction at week 12)	3.3	0	ND	66	65.1	60
C-peptide (% Change from Baseline to Week 12)	-0.25	1.12	-11.2	-8.08	-7.58	-19.8
Hb1Ac (Change from Baseline to Week 12)	0.02	0	-0.05	-0.18	-0.21	-0.46

*BOS-580-201 study is composed of 2 separate Parts: A & B. Data from all 5 treatment groups from completed Part A, including one that was not fully clinically efficacious (75mg Q4W), were pooled.

**Based on LSMean with treatment and baseline value effects in the model performed on the modified full analysis set.

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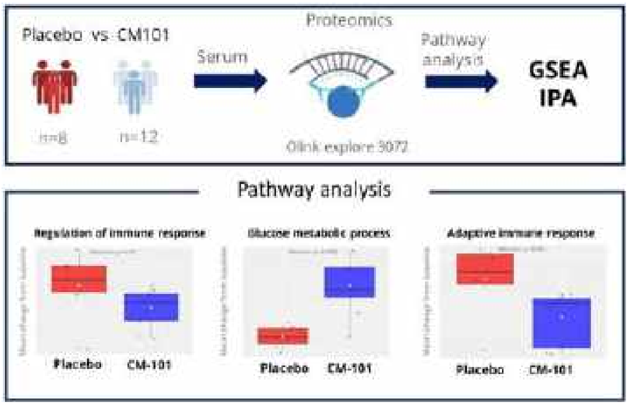
2404-C | CM-101, A CCL24 NEUTRALIZING ANTIBODY, SHOWED IMPROVEMENTS IN INFLAMMATORY, FIBROTIC, AND METABOLIC PATHWAYS IN PATIENTS WITH NASH: PROTEOMICS ANALYSIS OF A PHASE 2a STUDY

Revital Aricha, Ilan Vaknin, Tom Snir, John Lawler, Adi Mor and Matthew Frankel, Chemomab Ltd.

Background: CCL24 (eotaxin-2) is a chemokine that promotes cell trafficking and regulates inflammatory and fibrotic processes. CCL24 plays a central role in the development of hepatic fibrosis and liver injury. Patients with nonalcoholic steatohepatitis (NASH) were noted to have elevated levels of CCL24 and CCR3 in liver and blood samples. Phase 2a study (NCT05824156) of CM-101 in NASH patients, met safety goals and showed improved liver fibrosis biomarkers and physiological assessments. Here, we further elucidate the effect of CM-101 on disease related pathways through an analysis of proteomics data from the serum of patients in the NASH study. **Methods:** Twenty-three patients with NASH, diagnosed by liver biopsy, were randomized to receive 8 administrations of either CM-101 5mg/kg ($n = 14$) or placebo ($n = 9$) subcutaneously, every 2 weeks. End of study (EOS) visit occurred 6 weeks post last treatment, at week 20. Sera from patients were analyzed using the Olink^{TM} proximity extension assay (PEA) of 3072 proteins. Differentially expressed proteins between CM-101 and Placebo treated patients were identified using a mixed effect model fitted to the data. To identify pathways differentially modulated from baseline to EOS between CM-101 and placebo groups, Gene Set Enrichment Analysis (GSEA) and Ingenuity Pathway analysis (IPA®) were performed. CCL24 engagement by CM-101 was assessed in the serum. The level of other CCR3 ligands, eotaxin-1 and eotaxin-3, were evaluated to explore potential compensatory effect. **Results:** Serum proteomics analysis using GSEA showed that CM-101 treatment led to significant downregulation in multiple immune related pathways, suggesting amelioration of inflammation, as well as an increase in several metabolic pathways that represent improved glucose metabolism. IPA demonstrated consistent and significant reduction in liver related pathological pathways such as hepatic steatosis and the activation of hepatic stellate cells. Treatment with CM-101 revealed a strong target engagement-profile. Circulating levels of eotaxin-1 and eotaxin-3, which engage to the same receptor CCR3, were not changed during the clinical trial, suggesting no compensatory effect following CCL24 blockade by CM-101. **Conclusion:** The data suggest that CM-101 attenuates fibrotic and inflammatory pathways while improving metabolic pathways – all essential in mitigating the sequelae associated with progressive NASH and other fibrotic liver diseases. CM-101 is currently being evaluated in a PSC phase 2 study.



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John Lawler – Chemomab: Employee, Yes, No;
Adi Mor – Chemomab: Employee, Yes, No; Chemomab: Executive role , Yes, No;
Matthew Frankel – Chemomab: Employee, Yes, No;

f 2405-C | COMPARING THE EFFICACY OF DIFFERENT FORMS OF INTERMITTENT FASTING IN THE MANAGEMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE: A NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

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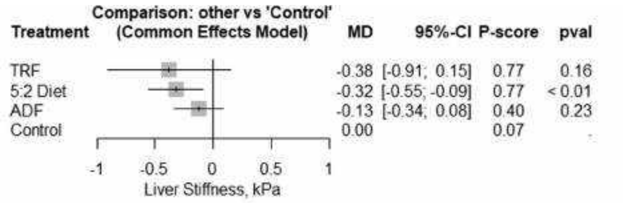
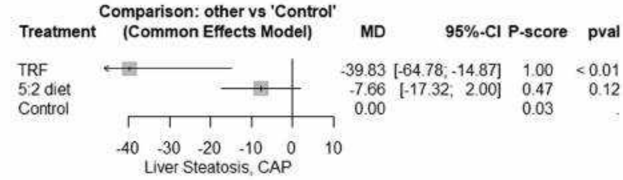
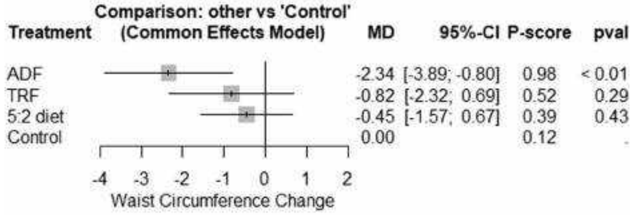
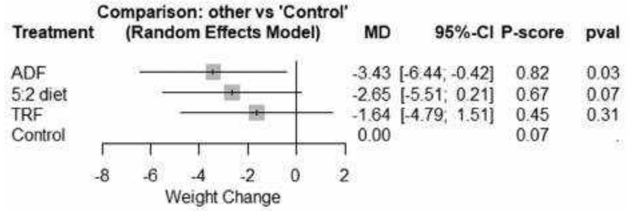
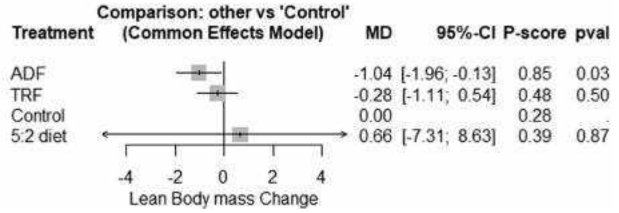
Background: Non-alcoholic fatty liver disease (NAFLD) is a prevalent metabolic disorder characterized by excessive accumulation of fat in the liver. It is strongly associated with obesity, insulin resistance, and other components of metabolic syndrome, making it a significant public health concern. Lifestyle modifications, including dietary interventions, have been suggested as means to improve NAFLD outcomes. Intermittent fasting (IF) has emerged as a potential therapeutic strategy. This network meta-analysis aims to compare the effectiveness of different regimens of IF in the management of NAFLD. **Methods:** A comprehensive literature search identified relevant RCTs investigating different regimens of IF for treating NAFLD. PubMed, EMBASE, Web of Science, SCOPUS, and Cochrane, were searched up to April 10th, 2023, using appropriate keywords and MeSH terms. Network analyses were performed using R software with the N-meta packages, Mean difference (MD) was used to pool continuous outcomes with 95% confidence intervals (CIs). Heterogeneity between studies was assessed using χ^2 and I^2 tests, considering heterogeneity at χ^2 P-value < 0.1 and $I^2 > 50\%$. Homogeneous data were pooled using a fixed-effect model, and heterogeneous data were pooled using a random-effect model. Our meta-analysis was registered in PROSPERO under the identification number CRD42023418467. **Results:** Our meta-analysis included 8 RCTs with a total of 635 participants. The 5:2 diet significantly improved liver stiffness compared to placebo (MD: -0.3403, 95% CI: [-0.6626, -0.0181], p = 0.03). However, both alternate-day fasting (ADF) and time-restricted feeding (TRF) did not show significant reductions in liver stiffness ; (MD: -0.1764, 95% CI: [-0.4728, 0.1200], p = 0.2) and(MD: -0.3817, 95% CI: [-0.9296, 0.1662], p = 0.1), respectively. TRF exhibited a significant improvement in liver steatosis (CAP score) (MD: -39.8267, 95% CI: [-64.7827, -14.8707], p = 0.0018). No significant changes were observed in AST, GGT, LDL cholesterol, total cholesterol, triglyceride levels, BMI, blood pressure, HOMA-IR, fasting blood sugar, lean body mass, or waist circumference across all IF regimens. However, ADF showed positive results in anthropometric measures, including significant improvements in lean body mass, waist circumference, fat mass, and weight reduction ($p < 0.05$). **Conclusion:** Our network meta-analysis demonstrates the efficacy of intermittent fasting as a management strategy for NAFLD. Specifically, the 5:2 diet exhibited a significant improvement in liver stiffness, while TRF showed a significant improvement in liver steatosis. Furthermore, ADF was associated with positive changes in anthropometric measures. These findings have important implications for tailoring the management of NAFLD patients based on pre-dominant specific conditions such as steatosis, fibrosis, or insulin resistance.











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2406-C | COMPARISON OF CIRRHOSIS SURGICAL RISK SCORES AND WEIGHT LOSS AMONG PATIENTS UNDERGOING BARIATRIC SURGERY

Darya Herscovici[1], Avery Pullman[1] and Richard Perugini[2], (1)UMass Memorial, (2)UMass Memorial Medical Center

Background: Nonalcoholic steatohepatitis (NASH) is a leading cause of liver disease for those awaiting transplant. Bariatric surgery (BS) leads to significant and sustained weight loss, correcting metabolic abnormalities associated with NASH, and offers an important intervention in the management of NASH. We present a comparison of surgical risk scores and weight loss outcomes in a population of patients with cirrhosis who underwent longitudinal sleeve gastrectomy (LSG). **Methods:** Inclusion criteria were all patients seen in BS clinic from Oct 2017-Mar 2021 with a concurrent diagnosis of cirrhosis who underwent LSG. Retrospective chart reviews were conducted on 3 groups of patients: Group A: Patients identified with non-alcoholic fatty liver disease (NAFLD), or NASH preoperatively, were evaluated by hepatology, and had a sinusoidal gradient < 8. Group B: Patients where cirrhosis was discovered at the time of BS and there was no evidence of portal hypertension. Group C: Patients who were referred to BS after having undergone a prior liver transplant for NASH. A VOCAL-Penn score measuring 90-day decompensation risk was calculated as a measure of cirrhosis surgical risk. NAFLD fibrosis score was calculated prior to LSG and one year post LSG. **Results:** Four patients met the inclusion criteria for group A. Prior to surgery, mean VOCAL-Penn score was 4.98% (+/- 1.04%) and mean NAFLD fibrosis score was 2.35 (+/- 0.26). One year after surgery, average patients' body weight decreased by 14.4% and mean NAFLD fibrosis score decreased by 0.86 (+/- 0.25). Seven patients met the inclusion criteria for group B. Prior to surgery, mean VOCAL-Penn score was 3.53% (+/- 0.54%) and mean NAFLD fibrosis score was 2.02 (+/- 1.01). One year after surgery, average patients' body weight had decreased by 23.9% and mean NAFLD fibrosis score increased by 0.17 (+/- 0.26). NAFLD fibrosis scores were not significant between groups A or B preoperatively or postoperatively ($p = 0.60$, $p = 0.82$). Four patients met the inclusion criteria for group C. Prior to surgery, mean VOCAL-Penn score was 2.83% (+/- 0.58%). One year after surgery, average patients' body weight had decreased by 26.5%. **Conclusion:** Cirrhosis is an important comorbidity of obesity, and requires the combined efforts of BS, hepatology, transplant surgery, and metabolic weight loss programs. This preliminary study demonstrates that patients who had already undergone a prior liver transplant on average had lower surgical risk and demonstrated greater weight loss than patients

who had not. It also demonstrates that patients who had been evaluated by hepatology had on average improved NAFLD fibrosis scores following LSG, suggesting that multidisciplinary optimization of liver function may be associated with improved outcomes following LSG.
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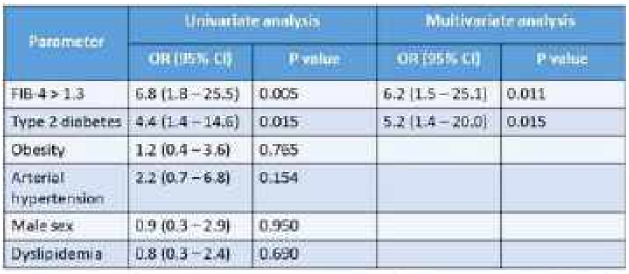
f 2407-C | ECHOCARDIOGRAPHY-BASED MARKERS OF SUBCLINICAL CARDIAC DYSFUNCTION IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND PRESERVED EJECTION FRACTION: INTERIM DATA FROM A PROSPECTIVE COHORT

Angelo Armandi[1,2], Alessandro Andreis[1], Matteo Bellettini[1], Kamela Gjini[1], Irene Poggiolini[1], Gabriele Castelnuovo[1], Gian Paolo Caviglia[1], Chiara Rosso[1], Nuria Perez Diaz Del Campo[1], Davide Giuseppe Ribaldone[1], Giorgio Maria Saracco[1], Davide Castagno[1], Alberto Milan[1], Gaetano Maria De Ferrari[1] and Elisabetta Bugianesi[1], (1)University of Turin, (2) University of Mainz

Background: Individual's with Non-Alcoholic Fatty Liver Disease (NAFLD) have abnormal myocardial energy metabolism and reduced coronary functional capacity, even in the absence of risk factors for cardiovascular disease (CVD), potentially associated with cardiac fibrosis and heart failure. We aimed to evaluate diastolic and systolic function in NAFLD individual's with preserved ejection fraction. **Methods:** We prospectively enrolled patients with ultrasound-diagnosed NAFLD and without overt CVD undergoing screening echocardiography (Philips, Andover, US) including speckle tracking analysis for myocardial fiber deformation (strain) in all four cardiac chambers. Significant diastolic dysfunction was defined as mitral E/E' ratio > 9, while systolic dysfunction was defined by left ventricular global longitudinal strain (GLS) > -18%. Significant liver fibrosis (SLF) was non-invasively assessed by either FIB-4 score > 1.3 or liver stiffness measurement (LSM) > 7 kPa by transient elastography. Severe liver steatosis was defined by Controlled Attenuation Parameter (CAP) > 300 dB/m. **Results:** A total of 94 patients were included (median age 53.0 [44.5 – 62.5] years, male sex 43.2%). SLF was detected in 20.0% by FIB-4 and in 14.9% by LSM. Severe steatosis was present in 53.8% of cases. FIB-4 values were significantly higher in patients with diastolic (p = 0.008) and systolic (p = 0.006) dysfunction. In patients with SLF by either FIB-4 or LSM we found lower absolute values of left atrium reservoir strain (indirect marker of reduced compliance) (p = 0.027 and p = 0.021, respectively), lower values of left atrium conduit strain (indirect marker of impaired passive emptying) (p = 0.020 and p = 0.0003) and lower values of right atrium reservoir strain (p = 0.011 and p = 0.007). Patients with severe steatosis had increased epicardial fat tissue deposition (p = 0.020). In a multiple stepwise logistic regression model including type 2 diabetes (T2D), obesity, arterial hypertension, dyslipidemia, male sex and SLF by FIB-4, both SLF and T2D were significantly associated with diastolic dysfunction (Figure 1). **Conclusion:** NAFLD patients with SLF and without overt CVD have impaired pre-clinical markers of cardiac dysfunction. Increased FIB-4 is associated with diastolic dysfunction independently of major CVD risk factors. *The research was supported by the Italian Ministry for Education, University and Research (MIUR) under the programme "Dipartimenti di Eccellenza 2018-2022" Project code D15D18000410001.*



Parameter	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
FIB-4 > 1.3	6.8 (1.8 – 25.5)	0.005	6.2 (1.5 – 25.1)	0.011
Type 2 diabetes	4.4 (1.4 – 14.6)	0.015	5.2 (1.4 – 20.0)	0.015
Obesity	1.2 (0.4 – 3.6)	0.765		
Arterial hypertension	2.2 (0.7 – 6.8)	0.154		
Male sex	0.9 (0.3 – 2.9)	0.950		
Dyslipidemia	0.8 (0.3 – 2.4)	0.690		

Univariate and multivariate logistic regression analysis for the association with diastolic dysfunction (increased E/E' ratio).

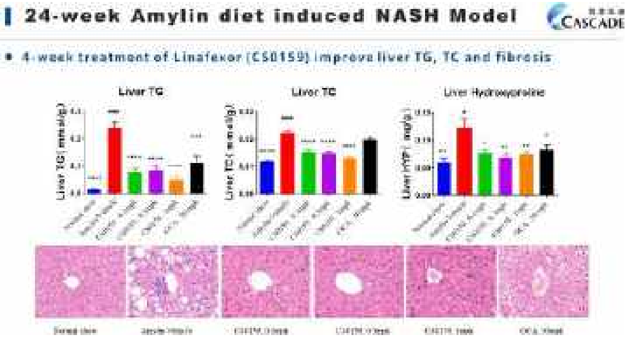
Disclosures: Elisabetta Bugianesi – AstraZeneca: Consultant, No, No; Boehringer Ingelheim: Consultant, No, No; Bristol Myers Squibb: Consultant, No, No; Gilead Sciences: Consultant, No, No; Intercept: Consultant, No, No; Inventiva: Consultant, No, No; Merck Sharp & Dohme: Consultant, No, No; Novo Nordisk: Consultant, No, No;
The following people have nothing to disclose: Angelo Armandi, Alessandro Andreis, Matteo Bellettini, Kamela Gjini, Irene Poggiolini, Gabriele Castelnuovo, Gian Paolo Caviglia, Chiara Rosso, Nuria Perez Diaz Del Campo, Davide Giuseppe Ribaldone, Giorgio Maria Saracco, Davide Castagno, Alberto Milan, Gaetano Maria De Ferrari

2408-C | LINAFEXOR: A PULSE FXR LIGAND THAT FITS METABOLIC CYCLE OF BILE ACIDS TO TREAT NASH

Huaqiang Eric Xu, Simm; Cascade Pharmaceutical

Background: Metabolism in all vertebrate animals is subject to 24-hour circadian control, and non-alcoholic steatohepatitis (NASH) is in part caused by bile acid malmetabolism that is out of circadian control.

Farnesoid X receptor (FXR) ligands have shown promise in treating NASH by modulating bile acid synthesis and metabolism. This study investigates the efficacy and safety of Linafexor (CS0159), a pulse FXR ligand with a short half-life, aligning with the metabolic cycle of bile acids. The importance of considering circadian rhythm and metabolic regulation in drug design is emphasized. **Methods:** In vitro assays assessed Linafexor's FXR agonistic activity and selectivity. A four-week, randomized, placebo-controlled study was performed in 24-week Amylin diet-induced NASH mice, with Linafexor treatment administered daily at three dosage levels (0.1, 0.3, and 1.0 mg/kg). Liver histology, serum bile acid levels, and gene expression involved in bile acid synthesis and metabolism were analyzed. Phase 1 clinical studies included 10 cohorts: 6 single ascending dose (SAD) cohorts (0.2, 0.6, 1.0, 2.0, 4.0, and 8.0 mg/kg) and 4 multiple ascending dose (MAD) cohorts (0.4, 1.0, 2.0, and 4.0 mg/kg). Safety and toxicity were evaluated. **Results:** Linafexor demonstrated potent and selective FXR activation in vitro. In the murine NASH model, Linafexor treatment led to significant reductions in liver steatosis, inflammation, and fibrosis across all dosages, with the 0.3 mg/kg dose showing the greatest efficacy. Serum bile acid levels and gene expression were modulated in a circadian-dependent manner, consistent with Linafexor's short half-life and metabolic rhythms. Linafexor has unique tissue distribution, with a 10-fold enrichment in the liver. Phase 1 studies showed linear exposure of Linafexor with dosing and no adverse effects associated with treatment. **Conclusion:** Linafexor (CS0159), a pulse FXR ligand with a short half-life, demonstrated significant efficacy in treating NASH by modulating the metabolic cycle of bile acids in accordance with circadian rhythms. Circadian-dependent effects on bile acid metabolism may contribute to its enhanced efficacy and safety profile. The excellent safety profile observed in Phase 1 studies, along with an ongoing Phase 2 study, supports further investigation of Linafexor as a promising therapeutic option for NASH. Preliminary Phase 2 efficacy and safety data will be presented in the meeting.



24-week Amylin diet induced NASH Model

- 4-week treatment of Linafexor (CS0159) improve liver TG, TC and fibrosis

Disclosures: Huaqiang Eric Xu – Cascade Pharmaceutical: Executive role , Yes, No;

f 2409-C | LIVER CELL-TYPE SPECIFIC MOLECULAR SIGNATURES MARKING TRANSITION FROM ADVANCED FIBROSIS TO CIRRHOSIS IN HUMAN NON-ALCOHOLIC STEATOHEPATITIS

Michael Feigh[1], Mathias Bonde Møllerhøj[2], Martin Rønn Madsen[2], Mikkel P Werge[3], Mikkel Christensen-Dalsgaard[2], Sanne Veidal[4], Lise C.B. Rudkjær[2], Elisabeth Douglas Galsgaard[5], Lise Lotte Gluud[3] and Henrik B. Hansen[2], (1)Gubra Aps, (2)Gubra, (3)Gastro Unit, (4)Global Drug Discovery, Novo Nordisk a/S, Novo Nordisk Park 1, 2760 Maalov, Denmark, (5)Novo Nordisk

Background: Hepatic fibrosis is the strongest predictor of morbidity and mortality in nonalcoholic steatohepatitis (NASH), establishing fibrosis as a critical therapeutic target in this disease. To improve treatment outcomes in NASH, the specific roles and molecular signaling mechanisms of hepatic cell types in the progression of fibrosis must be clarified. Here, we developed a transcriptomic map at cellular resolution, defining molecular signatures of parenchymal and non-parenchymal cell types across all stages of fibrosis in human NASH. **Methods:** Bulk RNA sequencing (RNAseq) was performed on snap-frozen liver biopsies obtained from a patient cohort of 40 obese individual's with NASH (stages F0-F4, n = 4-10 per fibrosis stage) or no/mild NAFLD (macrovesicular steatosis) without fibrosis (control group, n = 7). Paired single-nucleus (sn) RNA-seq analysis was performed on a subset of biopsies (control, NASH F0-1, NASH F2-3, NASH F4; n = 4 per group). Cell type deconvolution of differentially expressed genes in bulk RNAseq samples was based on corresponding snRNAseq data. **Results:** The transcriptomics platform enabled paired bulk and single-nucleus (sn) RNAseq analysis on small percutaneous/transjugular human liver biopsies (d 5 mg tissue). The number of differentially expressed genes increased progressively with disease severity. Transcriptome signatures were clearly separated from NASH patients with cirrhosis (fibrosis stage 4), demonstrating perturbations in genes associated with extracellular matrix remodeling and the immune system. Bulk RNAseq data were cross-referenced to public bulk RNAseq data sets for further data validation. snRNAseq yielded data from 33,764 nuclei after quality control, recovering all major liver cell types in both control and disease samples based on cell-specific marker genes. Subclustering of snRNAseq datasets revealed multiple subtypes of hepatic stellate cells (HSCs) relevant in the progression of fibrosis. **Conclusion:** We report a state-of-the-art integrative transcriptomics pipeline mapping molecular changes in liver non-parenchymal cell types covering the entire spectrum of fibrosis in NASH patients. Distinct

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

HSC subpopulations and transcriptional programs may play important roles in the transition from advanced fibrosis to cirrhosis in human NASH.

Disclosures: Michael Feigh – Gubra: Employee, Yes, No; Gubra: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No; Gubra: Executive role , Yes, No;

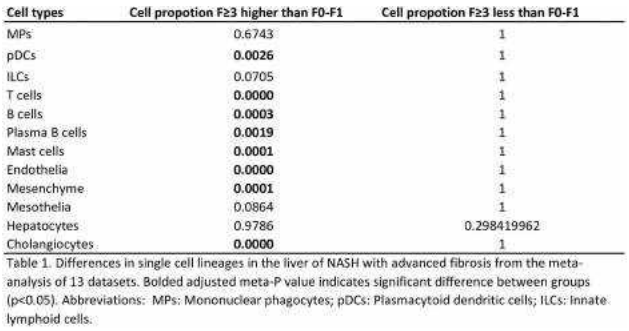
Martin Rønn Madsen – Gubra: Employee, No, No;

The following people have nothing to disclose: Mathias Bonde Møllerhøj, Mikkel P Werge, Mikkel Christensen-Dalsgaard, Sanne Veidal, Lise C.B. Rudkjær, Elisabeth Douglas Galsgaard, Lise Lotte Gluud, Henrik B. Hansen

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

Tingbo Guo[1], Sha Cao[1], Tiebing Liang[2], Prakash Ramachandran[3] and Naga P. Chalasani[2], (1) Deparment of Biostatistics & Health Data Science, Indiana University School of Medicine, Indianapolis, Indiana, USA, (2)Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA, (3) Institute for Regeneration and Repair, Center for Inflammation Research, University of Edinburgh

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



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

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

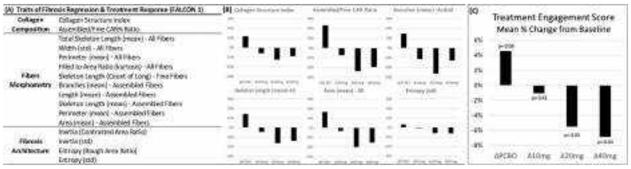
Disclosures: The following people have nothing to disclose: Tingbo Guo, Prakash Ramachandran, Naga P. Chalasani

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

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

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

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



Disclosures: Li Chen – PharmaNest Inc: Employee, Yes, No; PharmaNest: Stock – privately held company (individual stocks and stock options), Yes, No;

Anne Minnich – Bristol Myers Squibb: Consultant, No, No;

Vipul Baxi – Bristol Myers Squibb: Employee, Yes, No;

Edgar D. Charles – Bristol Myers Squibb: Employee, Yes, No; Bristol Myers Squibb: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Mathieu M. Petitjean – PharmaNest Inc: Stock – privately held company (individual stocks and stock options), Yes, No; PharmaNest: Executive role , Yes, No;

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

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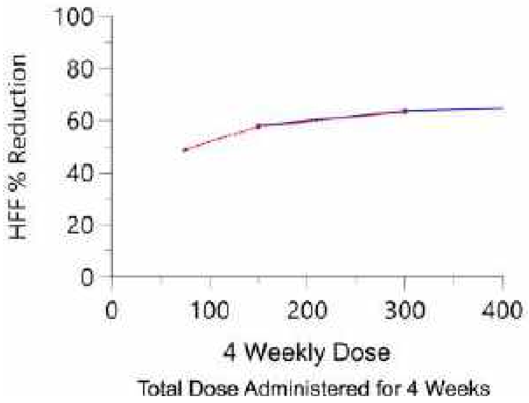
The following people have nothing to disclose: Zachary D. Goodman

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

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

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

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



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Disclosures: Swapan Chowdhury – Boston Pharmaceuticals: Employee, Yes, No;
Aruna Dontabhaktuni – PharmaPro Consulting Inc. / Boston Pharmaceuticals: Consultant, Yes, No;
Tatjana Odrljin – Boston Pharmaceuticals: Employee, Yes, No;
Alicia Clawson – Boston Pharmaceuticals: Employee, Yes, No;
Etienne Dumont – Boston Pharmaceuticals: Employee, Yes, No;
Vijay Bhargava – Nejay Consultant Inc / Boston Pharmaceuticals: Consultant, Yes, No;
Eric Svensson – Boston Pharmaceuticals: Employee, Yes, No;
Serge Guzy – POPPHARM / Boston Pharmaceuticals: Consultant, Yes, No;

2414-C | POSTPRANDIAL PLASMA PROTEOMICS IN NON-ALCOHOLIC FATTY LIVER DISEASE

Maria Mironova, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, Paul S. Blank, National Institute of Child Health and Human Development, Regina Umarova, National Institute of Diabetes and Digestive and Kidney Diseases and Yaron Rotman, National Institute of Diabetes and Digestive and Kidney Diseases, Nih

Background: The drivers of progression from steatosis to non-alcoholic steatohepatitis (NASH) and subsequent fibrosis in non-alcoholic fatty liver disease (NAFLD) are unclear. Most studies focus on long-term energy imbalance and the fasting state, while the acute alterations of metabolism after a single caloric load are relatively unstudied. We previously identified unique postprandial alterations in the plasma lipidome in subjects with NAFLD. We hypothesized that similar unique alterations will be seen in the plasma proteome. **Methods:** A single-center prospective study. Subjects with NAFLD and healthy controls were fed a standardized liquid mixed meal (Ensure Plus). Plasma samples were obtained at fasting, and 2 and 4 hours after the meal. The plasma proteome at each time point was measured using the SomaScan assay. Repeated measures ANOVA was used to assess temporal patterns, focusing on targets that had a significant groupXtime interaction. The KEGG database was used for pathway analysis. **Results:** We included 34 subjects with NAFLD and 7 controls. 1,317 unique proteins were quantified at each of the three time points. Of these, 42 plasma proteins were significant for interaction, i.e. had postprandial temporal patterns that significantly differed between NAFLD and controls, independently of fasting levels. Pathway analysis revealed enrichment of pathways in energy metabolism (as anticipated), cytokine signaling, complement cascade, and acute phase reaction, most likely derived from the liver. At the fasting state, NAFLD subjects had higher levels of chemokines CCL16, CCL21 and CCL23, hepcidin, complement decay accelerating factor (DAF), C1 esterase inhibitor, TNF receptor superfamily member 1B, and IL-1 receptor-like 1. Postprandially, however, there was an increase in these proteins in healthy controls while in NAFLD, they were either decreased or demonstrated a blunted response (Fig. 1). **Conclusion:** In this first study in humans exploring the postprandial plasma proteome in NAFLD, we identified a physiological postprandial upregulation of inflammatory plasma proteins that is impaired in people with NAFLD. Postprandial oxidative stress, endothelial dysfunction, and microbial translocation are all putative drivers of this response and also implicated in NASH. The decrease or blunting of postprandial inflammatory responses in subjects with NAFLD suggest impaired compensatory mechanisms in NAFLD and greater susceptibility to liver injury after a meal.

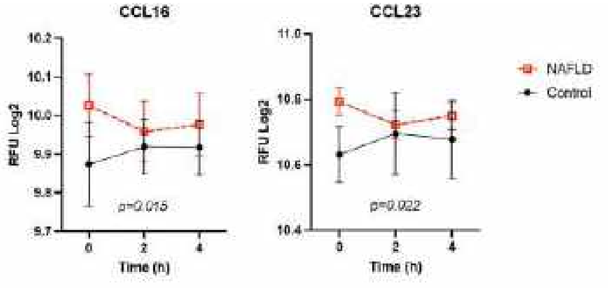

Figure 1. Example of postprandial behavior of chemokines CCL16 and CCL23. Data presented as mean ±SEM, p-values for groupXtime interaction (RFU - relative fluorescence units).

Disclosures: The following people have nothing to disclose: Maria Mironova, Regina Umarova, Yaron Rotman

Disclosure information not available at the time of publication: Paul S. Blank

2415-C | PREVALENCE OF AND FACTORS ASSOCIATED WITH NAFLD AND FIBROSIS DETECTED BY VIBRATION CONTROLLED TRANSIENT ELASTOGRAPHY AMONG TURKISH ADULTS AT-RISK: RESULTS FROM A PROSPECTIVE STUDY

Gediz Dogay Us[1,2], Ozgur Mustafa Koc[3], Francesco Innocenti[1], Ihsan Nuri Akpinar[2] and Ger H. Koek[1,3], (1) Maastricht University, (2)Pax Clinic, (3)Maastricht University Medical Center

Background: Turkey is considered a high-risk region for NAFLD; however, there are limited prospective data available to evaluate its prevalence among at-risk Turkish populations with metabolic risk factors such as obesity, metabolic syndrome, and diabetes. Therefore, we aimed to estimate the prevalence of NAFLD and liver fibrosis, as well as identify associated factors, among Turkish individual's with multiple metabolic disorders. **Methods:** We enrolled 436 adult participants for a single-centered prospective study in an outpatient clinic during a one-year period. All participants presented with at least one component of the metabolic syndrome. Physical examination, anthropometrical assessment and blood analysis were performed in a standardized clinical research visit. Individual's with excessive alcohol consumption ($>$2U/day for women, $>$3U/day for men) were excluded. Controlled attenuation parameter (CAP), and liver stiffness measurements (LSM) by a Vibration controlled transient elastography (VCTE) device (FibroScan®; Echosens, Paris, France) were used to determine NAFLD and fibrosis, respectively. NAFLD was defined as CAP e 248 db/M and fibrosis as LSM e 7.2 kPa in XL probe and e 7.9 kPa in M probe. Multivariable logistic and linear regression models were used to investigate the association of NAFLD and LSM with age, sex, waist circumference (WC), BMI, alcohol, smoking, diabetes, hypertension, dyslipidemia, metabolic syndrome, vitamin D deficiency, insulin resistance, transaminases, and HbA1c. **Results:** Overall, among the 436 individual's included in the analysis, NAFLD and fibrosis prevalence were 48.2% (95% CI: 43.5%, 52.9%) and 6.9% (95% CI: 4.9%, 9.7%), respectively. The mean CAP was 247.3 ± 49.7 db/M and the mean LSM was 5.3 ± 2.7 kPa. Multivariable logistic regression analysis of NAFLD revealed a significant association with obesity (OR = 3.999; 95% CI: 2.293, 6.974), male sex (OR = 0.483; 95% CI: 0.266, 0.876), metabolic syndrome (OR = 6.234; 95% CI: 3.401, 11.428), and vitamin D deficiency (OR = 1.831; 95% CI: 1.057, 3.174). Multivariable linear regression of LSM demonstrated a significant association with obesity (B = 1.079; 95% CI: 0.615, 1.543), insulin resistance (B = 0.070; 95% CI: 0.022, 0.119), and HbA1c (B = 0.273; 95% CI: 0.051, 0.494). **Conclusion:** NAFLD is prevalent in nearly half of the at-risk population studied. Male sex, obesity, metabolic syndrome, and vitamin D deficiency are significant risk factors associated with it. Despite the high NAFLD prevalence, liver fibrosis is less prevalent and is associated with obesity, insulin resistance and HbA1c. Further research is warranted in this population.

Disclosures: The following people have nothing to disclose: Gediz Dogay Us, Ozgur Mustafa Koc, Francesco Innocenti, Ihsan Nuri Akpinar, Ger H. Koek

f 2416-C | PROTEIN BARCODE OF CIRCULATING EXTRACELLULAR VESICLES IN CHILDHOOD OBESITY ASSOCIATES WITH METABOLIC FACTORS FOR NAFLD AND MAY AFFECT THE FUTURE DEVELOPMENT OF MUSCLE AND NERVOUS SYSTEM

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Background: Childhood obesity frequently transitions to adult obesity and is known to be a risk factor for developing metabolic syndrome (MetS) including NAFLD. We had demonstrated that circulating extracellular vesicles (EVs) and EV-protein composition were significantly associated with MetS-related factors in adult. Here, we investigate the association of circulating EV numbers with metabolic factors and perform comprehensive proteomics analysis of EV cargo in children. **Methods:** Weight status of the enrolled 107 children (69 boys, 38 girls, median age, 10 y) with or without obesity was evaluated by both of body mass index (BMI)-for-age and relative body weight (RBW). Various metabolic parameters, including body composition, liver function, lipid and glucose metabolism, were measured. Additionally, the ratio of liver CT attenuation value/spleen CT attenuation value (liver/spleen CT) was measured as an index of hepatic steatosis. Circulating EV number was measured using Calcein AM staining and fluorescence flow cytometry. Comprehensive proteomic analysis was performed using nano liquid chromatography tandem-mass spectrometry. Correlation between circulating EV numbers and metabolic parameters were evaluated using Spearman's test and multiple regression analysis. Anthropometric and laboratory values among multiple groups divided by degrees of obesity were compared using Kruskal-Wallis test. **Results:** Circulating EV number was positively correlated with many physical and laboratory metabolic parameters, comprised BMI-for-age (rho = 0.450, $P < 0.001$), RBW (rho = 0.504, $P < 0.001$), ALT (rho = 0.273, $P < 0.05$) and triglyceride (TG, rho = 0.614, $P < 0.001$), whereas it was inversely correlated with liver/spleen CT (rho = -0.330, $P < 0.05$). TG (standard partial regression (SPRC) = 0.548, $P < 0.001$, 95% CI 0.404-1.041) and RBW (SPRC = 0.469, $P < 0.05$, 95% CI 0.090-0.851) were detected as an independent factor to determine the circulating EV number. Degree of obesity evaluated by RBW was significantly correlated with circulating EV number ($P < 0.001$) and liver/spleen CT ($P < 0.01$). Proteomic analysis identified 31 up-regulated and 45 down-regulated EV proteins in

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childhood obesity. Gene ontology analysis revealed up-regulated proteins to be involved in various biological processes, including intracellular protein transport, protein folding, stress response, inflammation and immune response, which can modulate lipid and glucose metabolism. In addition, several proteins involving in development of skeletal and cardiac muscle and nervous system were up-regulated in childhood obesity. **Conclusion:** Circulating EVs of childhood obesity are significantly associated with MetS-related dysmetabolism including NAFLD. A special “barcode” of EV protein cargo indicates that childhood obesity may affect not only NAFLD, but also the future development of skeletal and cardiac muscles and nervous system.

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2417-C | SAMM50-rs2073082, -rs738491 AND -rs3761472 INTERACTIONS ENHANCEMENT OF SUSCEPTIBILITY TO NON-ALCOHOLIC FATTY LIVER DISEASE

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Background: Genetic single nucleotide polymorphisms (SNPs) play a decisive role in the susceptibility and development of non-alcoholic fatty liver disease (NAFLD). Several studies have identified that three sorting and assembly machinery component 50 (SAMM50) polymorphisms (rs2073082, rs738491, rs3761472) are associated with an increased risk of NAFLD. However, the clinical significance of SAMM50 SNPs in relation to NAFLD remains largely unknown. Therefore, we conducted a clinical study and SNP-SNP interaction analysis to further elucidate the effect of SAMM50 SNPs on the progression of NAFLD in the elderly. **Methods:** Totally 1053 patients over age 65 years were recruited. Fatty liver was detected by abdomen ultrasound. Liver fat content and fibrosis stage were evaluated by Fibro Scan. Genomic DNA was extracted and then genotyped by Fluidigm 96.96 Dynamic Array. A multivariable logistic regression was used to evaluate the association between NAFLD and SNPs. SNP-SNP interactions were analyzed using generalized multivariate dimensionality reduction (GMDR). **Results:** The risk of NAFLD was substantially higher in people who carried SAMM50-rs2073082 G allele and -rs738491 T allele (OR, 1.962; 95% CI, 1.448-2.659; $p < 0.001$; OR, 1.532; 95% CI, 1.246-1.884; $p = 0.021$, respectively) compared to non-carriers. Carriers of the rs738491 T allele and rs3761472 G allele in the cohort showed a significant increase in liver stiffness measurements (LSM). The combination of three SNPs was showed the highest predictive power for NAFLD (cross-validation consistency [CVC], 10/10). Allele G-T-G carriers have a two-fold higher risk of NAFLD compared to haplotype A-C-A. **Conclusion:** Our results demonstrated that SAMM50-rs2073082 G and -rs738491 T allele were significantly associated with NAFLD susceptibility in Chinese elders, while rs738491 T allele and rs3761472 G allele were related to higher fibrosis. Furthermore, we present novel findings that a three-SNP combination model can accurately predict the risk of NAFLD vulnerability.

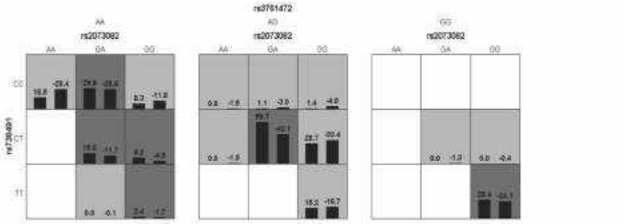

Figure legends:Gene--gene interactions among SAMM50 rs2073082, rs738491 and rs3761472 loci in NAFLD and Control subjects.The score distribution of NAFLD subjects (left black bar in boxes) and control subjects (right black bar in boxes) is shown for each genotype combination. High-risk genotype combinations are represented by dark gray shade cells, while light gray shade cells represent low-risk genotype combinations. Cells with no shading or white cells represent genotype combination for which no data is observed.

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2418-C | SINGLE TESTING WITH MASLD MACHINE LEARNING MODELS (MASMLS) PERFORM EQUALLY TO CURRENT GUIDELINE ALGORITHMS OF SEQUENTIAL TESTING USING FIBROSIS-4 INDEX AND TRANSIENT ELASTOGRAPHY

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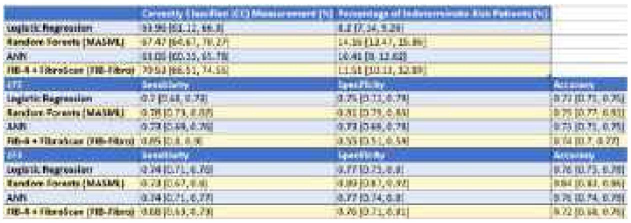
Background: Current guidelines recommend screening patients with NAFLD (or MASLD) risk factors using sequential testing with FIB-4 followed by transient elastography, or FibroScan® (FIB-Fibro) to stratify risk for advanced liver fibrosis. We assessed the performance of a new MASLD machine learning model (MASML) (Chang et al. *Hepatology* 2022) (single test) vs FIB-Fibro (sequential testing) in predicting the risk of significant/advanced liver fibrosis. **Methods:** MASML, a random forests model, was the best model among logistic regression, random forests, and artificial neural network to predict risk of significant/advanced fibrosis (≥F2/≥F3) using 17 routine demographic/clinical features in 1223 MASLD patients at multiple US centers. Patients had ≥1 MASLD risk factors (≥2 metabolic risk factors, type 2 diabetes, steatosis, high aminotransferases) and underwent liver biopsy, FibroScan®, and laboratory testing within a 6-month period. We used 80% of the cohort to train and 20% to test MASML. We assessed the correctly classified (CC) measurement percentage of indeterminate-risk patients, sensitivity (Sn), specificity (Sp), and accuracy (Ac) to compare MASML to FIB-Fibro. **Results:** There was no statistically significant difference between the CCs of MASML and that of FIB-Fibro (67.47% (CI: 64.67%-70.27%) vs 70.53% (CI: 66.51%-74.55%)), or between the percentage of indeterminate patients of MASML vs FIB-Fibro (14.16% (CI: 12.47%-15.86%) vs 11.51% (CI: 10.13%-12.89%)). For ≥F2, there was no significant difference in Sn or Ac between MASML and FIB-Fibro (Sn 0.78 (CI: 0.73-0.82) vs 0.85 (CI: 0.8-0.9); Ac 0.79 (CI: 0.77-0.81) vs 0.74 (CI: 0.7-0.77)). MASML had significantly higher Sp vs FIB-Fibro (0.81 (CI: 0.79-0.83) vs 0.55 (CI: 0.51-0.59)). For ≥F3, there was no significant difference in Sn between MASML and FIB-Fibro (0.73 (CI: 0.67-0.8) vs 0.68 (CI: 0.63-0.73)), and MASML had significantly higher Sp and Ac compared to FIB-Fibro (Sp 0.89 (CI: 0.87-0.92) vs 0.76 (CI: 0.71, 0.81); Ac 0.84 (CI: 0.83-0.86) vs 0.72 (CI: 0.68-0.76)). Other MLs are shown. **Conclusion:** Though there was no difference between MASML and FIB-Fibro in the prediction of risk of significant/advanced liver fibrosis, MASML had higher Sp than FIB-Fibro. Single test MASML may replace sequential FIB-Fibro in guidelines to identify at risk NASH patients, since MASML uses routine demographic/clinical features rather than costly imaging technology and can thus be used in primary care settings.



	Correctly Classified (CC) Measurement (%)	Percentage of Indeterminate-Risk Patients (%)	
Logistic Regression	[illegible]	[illegible]	
Random Forests (MASML)	67.47 [64.67, 70.27]	14.16 [12.47, 15.86]	
ANN	[illegible]	[illegible]	
FIB-4 + FibroScan (FIB-Fibro)	70.53 [66.51, 74.55]	11.51 [10.13, 12.89]	
≥F2	Sensitivity	Specificity	Accuracy
Logistic Regression	0.7 [0.68, 0.73]	0.75 [0.73, 0.78]	0.72 [0.71, 0.75]
Random Forests (MASML)	0.78 [0.73, 0.82]	0.81 [0.79, 0.83]	0.79 [0.77, 0.81]
ANN	0.73 [0.68, 0.76]	0.73 [0.68, 0.78]	0.73 [0.71, 0.75]
FIB-4 + FibroScan (FIB-Fibro)	0.85 [0.8, 0.9]	0.55 [0.51, 0.59]	0.74 [0.7, 0.77]
≥F3	Sensitivity	Specificity	Accuracy
Logistic Regression	0.74 [0.71, 0.76]	0.77 [0.75, 0.8]	0.76 [0.73, 0.78]
Random Forests (MASML)	0.73 [0.67, 0.8]	0.89 [0.87, 0.92]	0.84 [0.83, 0.86]
ANN	0.74 [0.71, 0.77]	0.77 [0.74, 0.8]	0.76 [0.74, 0.78]
FIB-4 + FibroScan (FIB-Fibro)	0.68 [0.63, 0.73]	0.76 [0.71, 0.81]	0.72 [0.68, 0.76]

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2419-C | SPLEEN STIFFNESS IS ASSOCIATED WITH GENDER AND BMI: RESULTS FROM A COHORT AT RISK OF NAFLD

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Background: Spleen stiffness (SS) is a crucial diagnostic tool to rule out and rule in clinically significant portal hypertension, particularly in cases of viral etiology. While its correlation with liver stiffness (LS) has been established in viral liver disease, there is limited knowledge regarding SS and its associated risk factors in other etiologies. Additionally, there is a lack of evidence regarding the normal ranges of SS in populations at risk of NAFLD. Hence, we aimed to assess spleen stiffness and identify factors related to it in a population at risk of NAFLD with multiple metabolic disorders. **Methods:** We enrolled 436 adult participants for a single-centered prospective study in an outpatient clinic during a one-year period. All participants presented with at least one component of the metabolic syndrome. Physical examination, anthropometrical assessment and blood analysis were performed in a standardized clinical research visit. Individual's with excessive alcohol consumption (>2U/day for women, >3U/day for men) were excluded. Controlled attenuation parameter (CAP), liver stiffness measurements (LSM) and spleen stiffness measurement (SSM) by a Vibration controlled transient elastography (VCTE) device (FibroScan®; Echosens, Paris, France) were used to determine NAFLD, liver fibrosis and spleen stiffness, respectively. Spleen was located with the embedded ultrasound probe and the SS was measured with the spleen probe that can produce a 100-Hz wave. Univariable and multivariable linear regression analyses were used to investigate the association of SS with CAP and LS, respectively, adjusting for the following potential confounders: age, sex, WC, BMI, alcohol, smoking, diabetes, hypertension, dyslipidemia, metabolic syndrome, insulin resistance, transaminases, and Hba1c. **Results:** Mean spleen stiffness was 26.34 (± 11.97) kPa in the recruited sample. The univariable analyses showed that spleen stiffness was positively associated with CAP (B = 0.042; 95% CI: 0.017, 0.066) and LSM (B = 1.472; 95% CI: 0.921, 2.023). After adjusting for age, sex, WC, BMI, alcohol, smoking, diabetes, hypertension, dyslipidemia and metabolic syndrome, insulin resistance, transaminases, and Hba1c, the association remained statistically significant with LSM (B = 0.952; 95% CI: 0.353, 1.551) but not with CAP (B = -0.006; 95% CI: -0.039, 0.027). In both adjusted models, SS was also significantly associated with BMI and gender. **Conclusion:** SS is associated with LS, male sex, and BMI in a population at-risk of NAFLD. The observed association between SS and LS reinforces previous evidence, while this study is the first to demonstrate an association between SS, gender and BMI. These findings may serve as a reference point for assessing SS, particularly in patients at risk of NAFLD. Further research is warranted to identify other risk factors that influence spleen stiffness across the spectrum of liver diseases.

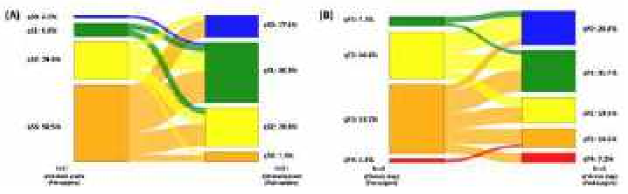
Disclosures: The following people have nothing to disclose: Gediz Dogay Us, Ozgur Mustafa Koc, Francesco Innocenti, Ihsan Nuri Akpinar, Ger H. Koek

2420-C | THE CONCOMITANT ZONAL QUANTIFICATION OF QSTEATOSIS AND QFIBROSIS USING HISTOINDEX AI DIGITAL PATHOLOGY IMPROVES DETECTION OF LIVER INJURY REGRESSION POST-BARIATRIC SURGERY

Vlad Ratziu[1], Raluca Pais[2], Judith Aron-Wisnewsky[3], Frederic Charlotte[4], Dean Tai[5], Elaine Lay Khim Chng[5], Desiree Abdurrachim[6], Chih-Liang Chin[7], Saswata Talukdar[7] and Asad Abu Bakar Ali[6], (1)Sorbonne Université, Assistance Publique-Hôpitaux De Paris, Hôpital Pitié Salpêtrière, Institute of Cardiometabolism and Nutrition (ICAN), (2)Aphp, (3)Pitié-Salpêtrière Hospital, (4)Sorbonne Université, Ican Institute, Hôpital Pitié-Salpêtrière, (5)Histoindex Pte Ltd, Singapore, (6) Cardiometabolic Diseases, MSD, Singapore, (7) Cardiometabolic Diseases, Merck & Co., Inc., South San Francisco, CA

Background: Conventional microscopy histological reads are semi-quantitative and subjective. AI-assisted digital pathology (DP) allows automated and quantitative staging/grading of liver injury in NASH. We aimed to examine the potential of second harmonic generation/two photon excitation fluorescence (SHG/TPEF)-based AI DP to detect histological changes post-bariatric surgery and patterns of fibrosis and steatosis response. **Methods:** Unstained paired liver biopsies (baseline and > 1-year post-surgery) from 41 obese patients with significant liver injury (SAF activity grades 3 or 4 or NASH CRN fibrosis stages 3 or 4, Hepatology Vol 76:456-68) were included. SHG/TPEF provided qualitative (qF-stage and qS-grade) and quantitative (continuous qF and qS scores) measurements of fibrosis and steatosis, respectively. Steatosis was quantified in lobular zones 1, 2 and 3 with concomitant measurement of fibrosis changes around the fat vacuoles. **Results:** The distribution of qF-stages was 0: 13%; 1: 18%; 2: 31%; 3: 33% and 4: 4% and that of qS-grades 0: 10%; 1: 26%; 2: 31%; 3: 33%. Fibrosis regression according to qF-stage was seen in 71% (29/41), stabilisation in 22% (9/41) and progression in 7% (3/41) of patients. The proportion of qF3/qF4 dropped from 56% pre-operatively to 22% at follow-up. The change in qF score documented a more dynamic level of fibrosis changes with only 1 patient (2%) displaying stabilisation while 81% (33/41) had improved fibrosis and 17% (7/41) worsened. qS-grade documented steatosis reduction in 73%, stabilization in 17% and worsening in 10% which was corroborated by the qS score. Co-localisation analysis showed changes in steatosis led to changes in adjacent fibrosis. While pts with qS score reduction had fibrosis regression, those with stable or increased qS score had persistent fibrosis and steatosis in zones 2 and 3. **Conclusion:** SHG/TPEF analyses replicated the findings of conventional pathology (improvement in a majority of patients but persistence of advanced fibrosis despite successful bariatric surgery) while providing important additional insights: 1) continuous scores documenting a larger dynamic range of fibrosis change; 2) co-localization analyses detecting patterns and kinetics of fibrosis improvement in relation to steatosis regression. SHG/TPEF AI-DP provides a more thorough documentation of liver injury improvement post-bariatric surgery than conventional microscopy.

Figure: Sankey diagram showing the proportion of patients in each (A) steatosis grade and (B) fibrosis stage pre- and post-bariatric surgery according to SHG/TPEF AI-DP. Percentages detail the proportion of the total cohort in each stage/grade.



Disclosures: Desiree Abdurrachim – MSD: Employee, No, No;

The following people have nothing to disclose: Vlad Ratziu, Raluca Pais, Judith Aron-Wisnewsky, Frederic Charlotte, Dean Tai, Elaine Lay Khim Chng

Disclosure information not available at the time of publication: Chih-Liang Chin, Saswata Talukdar, Asad Abu Bakar Ali

2422-C | VLDL LIPIDOMIC PROFILING REVEALS ALTERED GLUCOSYLCERAMIDE METABOLISM IN NONALCOHOLIC FATTY LIVER DISEASE RELATED LIVER FIBROSIS

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Background: The secretion of very low-density lipoprotein (VLDL) is the primary mechanism by which hepatocytes remove lipids from its cellular organelles into the circulation. It is produced entirely by the liver and has a short-half life in the circulation. Hereby, lipid composition in VLDL provides a unique window to assess hepatocellular lipid homeostasis. This study aims to evaluate how VLDL lipid changes with liver fibrosis in nonalcoholic fatty liver disease (NAFLD). **Methods:** Fresh frozen plasma from 157 patients with biopsy proven NAFLD were used to prepare VLDL using ultracentrifugation. Lipidomic analysis was performed on lipids extracted from VLDL using Gas Chromatography / Mass Spectrometry (GC/MS). Lipidome values were normalized by total plasma VLDL particle concentration measured by NMR spectroscopy and batch effect was successfully removed using Limma algorithm. The relationship between lipidome and liver fibrosis was analyzed with multivariate regression in LipidR. **Results:** Out of the 1507 analyzed lipid species, we identified 8 significant lipid molecules associated with advanced fibrosis (F3-4) as compared to no or early-stage fibrosis (F0-2). Dihexoacylceramide (CerG2) 39:6, sterol (ST) 44:4 and phosphatidic acid (PA) 32:4 were upregulated, while cholesterol ester (ChE) 18:0, sphingomyelin (SM) 47:3, triacylglycerol (TG) 18:1/17:1/20:4, ceramide (Cer) 18:1/26:0 and SM 34:2 were downregulated (Figure 1). While the inverse association between ChE, TG and liver fibrosis have been reported previously, the correlation with sphingolipids were unexpected. Lipid subspecies analyses revealed a decrease in CerG2 precursors, including ceramides and sphingomyelin among those with advanced fibrosis. Meanwhile, CerG2, a type of glycosylated sphingolipids, showed a significant increase. Lipid set enrichment analysis confirmed the positive enrichment of sterol, monohexoacylceramide (CerG1) and CerG2 lipid species. Furthermore, advanced fibrosis was also associated with a loss of the heterogeneity in lipid hydrocarbon chain length and decrease in the number of unsaturated hydrocarbon bonds. In comparison, no significant lipid features were found to be associated with PNPLA3 rs738409 GG or TM6SF2 rs58542926 TT genotypes. **Conclusion:** Liver fibrosis in NAFLD is associated with distinct changes in VLDL lipid species and properties reflecting altered hepatocellular lipid homeostasis. Among these changes, an increase in CerG2 and a reciprocal decrease in

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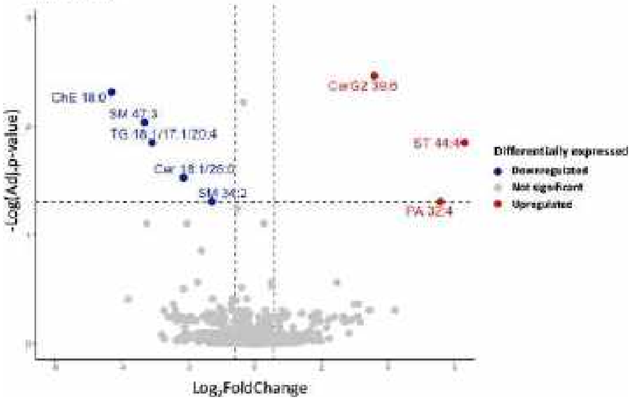
Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

ceramide and sphingomyelin may be of novel biological significance, as recent studies have linked glycosphingolipids accumulation with hepatocellular carcinoma. Further investigations are warranted to elucidate the specific mechanisms through which these molecules contribute to fibrogenesis and carcinogenesis in NAFLD.

Figure 1.



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2423-C | A PHASE I TRIAL OF BETAINE 4 VS 8 G/D ON ALT IN NON-ALCOHOLIC FATTY LIVER DISEASE

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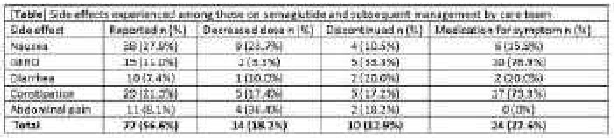
Background: Betaine is a safe and inexpensive nutraceutical that has improved ALT and liver histology in some but not all clinical trials of NASH when administered at 20 g/day. The aim of this phase I trial was to determine whether betaine at a dose of 4 or 8 g/day improved ALT in patients with NAFLD. **Methods:** 44 subjects with clinically diagnosed NAFLD and ALT > 60 IU/L received betaine 4 g/d for 4 weeks and were then randomized to either 4 or 8 g/d for another 8 weeks. 22 patients (10 in 4g/d arm and 12 in 8g/d arm) had T2DM (A1c < 8.5). Primary outcome was change in ALT between Week 0 and Week 12. Laboratory tests and clinical assessments were performed monthly and at 4 and 12 weeks after stopping treatment. A paired-t-test was used to assess change in ALT and lab tests. **Results:** Age (48 ± 15 in 4g/d, 49 ± 13 in 8g/d), gender (95.5% male in 4g/d, 100% male in 8g/d), BMI (34.1 ± 6.5 in 4g/d, 34 ± 5.2 in 8g/d), A1c (among diabetics: 7.2 ± 0.55 in 4g/d, 7.5 ± 1.1 in 8g/d), LDL (117 ± 33 in 4g/day, 107 ± 37 in 8g/day), and ALT (98 ± 66 in 4g/d, 78 ± 26 in 8g/d) did not differ between groups at baseline. At Week 12, ALT improved significantly among both cohorts, with a greater improvement among subjects receiving 8 g/d (not significant vs. 4 g/d). ALT improved similarly among diabetics and non-diabetics. Mean weight loss was 1.5 kilograms and did not differ between groups. Betaine treatment increased HDL (change in HDL [2 ± 1 mg/dL; $p < 0.05$]) while LDL increased 3mg/dL. Betaine non-significantly changed A1c and fructosamine among subjects with DM. ALT increased towards baseline after stopping betaine. Adverse events were minimal. **Conclusion:** Betaine at a dose of 4 or 8 g/day for 12 weeks improved ALT among subjects with a clinical diagnosis of NAFLD and an elevated ALT. Betaine increased HDL and non-significantly changed in A1c, fructosamine, and LDL. Given the low cost and minimal adverse event profile, additional trials of betaine treatment of NAFLD should be considered.

Disclosures: The following people have nothing to disclose: Andrew Steven Lim, Sheena Cruz, Aliya Asghar, Timothy R. Morgan

2424-C | ADVERSE GASTROINTESTINAL EFFECTS OF SEMAGLUTIDE WERE NOT ASSOCIATED WITH MEDICATION DISCONTINUATION OR WEIGHT LOSS OUTCOMES IN PATIENTS WITH NAFLD

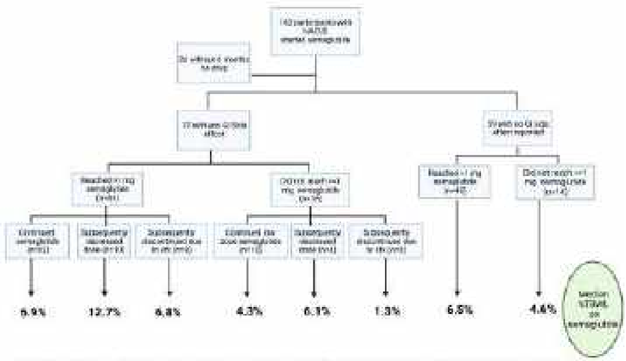
Adam Buckholz[1], Nicole Cornet[1], Lindsay Rogers[1], Aditi Rao[1], Patrick T Magahis[1], Tibor I. Krisko[1], Reem Sharaiha[1], Carolyn Newberry[1] and Sonal Kumar[2], (1) Newyork-Presbyterian/Weill Cornell Medical Center, (2) Weill Cornell Medical College, NY

Background: The GLP1 receptor agonist semaglutide has been purported as an effective treatment tool for patients with NAFLD, as it produces a 7-10% total body weight loss (TBWL). Gastrointestinal side effects (GISFx) related to associated delayed gastric motility may limit reaching approved medication dose. The relationship between side effects and weight loss outcomes is unknown. **Methods:** We retrospectively identified patients with NAFLD who initiated semaglutide in our multidisciplinary metabolic center from 2019-22. Those taking semaglutide for at least 6 months were included. The final measured weight while on drug during the study period was used to calculate % TBWL. Concomitant alternative anti-obesity medication (AOM), GISFx, discontinuation events, dose decrease due to side effects and baseline characteristics were collected. Dose of semaglutide at initiation, peak, and time of GISFx were also collected; reaching a full dose of semaglutide was considered ≥ 1 mg/week. Outcomes of interest were %TBWL and ≥ 7% TBWL at final weight in multivariable (MV) regression adjusting for developing GISFx, discontinuing due to GISFx, dose reducing, and peak semaglutide dose. **Results:** Of 162 NAFLD patients on semaglutide, the majority were female (74%) and 86 had concomitant T2DM (53%). Median baseline BMI was 36.2 (IQR 8.8) and 88 (54%) were on an additional AOM. 136 patients (84%) were on semaglutide at least 6 months; 12 were lost to follow up, 6 stopped early due to GISFx, and 8 stopped for other reasons such as insurance or availability. A majority of patients (77, 57%) reported a GISFx at a median dose 0.5 mg/week, the most common of which was nausea [Table]. There was no difference in discontinuation rates by side effect, but those with GERD and constipation received symptomatic therapy more than those with other symptoms ($p < 0.01$). Overall, 24 participants discontinued or dose reduced due to side effects after at least 6 months [Figure], but most (106, 77%) reached full dose. In MV regression, those who developed side effects did not have lower peak dose, more failure to reach > 1 mg/wk or more discontinuation. Only reaching full dose was significantly associated with TBWL (b = 3.15, 95% CI 0.12, 6.19 p = 0.04) while odds of reaching 7% TBWL neared significance (OR 2.19, 95%CI 0.89, 5.39 p = 0.09). Other factors (age, gender, ethnicity, other AOMs) did not attenuate this association, but were not included to avoid model overfitting. **Conclusion:** In a pragmatic study of weight loss in NAFLD patients on semaglutide, we found that development of side effects was not associated with likelihood of drug discontinuation, dose reduction, or % TBWL. Achieving full dose associated with more weight loss, regardless of development of GISFx. Further studies in a more controlled setting are needed, but this data suggests that semaglutide side effect management may be important to enable dose increase its dose dependent effect.



[Table] Side effects experienced among those on semaglutide and subsequent management by care team

Side effect	Reported n (%)	Decreased dose n (%)	Discontinued n (%)	Medication for symptom n (%)
Nausea	38 (27.9%)	9 (23.7%)	4 (10.5%)	6 (15.8%)
GERD	15 (11.0%)	[illegible]	5 (33.3%)	[illegible]
Diarrhea	10 (7.4%)	1 (10.0%)	2 (20.0%)	2 (20.0%)
Constipation	29 (21.3%)	5 (17.4%)	5 (17.2%)	[illegible]
Abdominal pain	11 (8.1%)	4 (36.4%)	2 (18.2%)	0 (0%)
Total	77 (56.6%)	14 (18.2%)	10 (13.0%)	34 (27.6%)



[Figure] Flow chart demonstrating outcomes regarding side effects, dose reduction/discontinuation and dose escalation among NAFLD patients starting semaglutide, with subsequent % total body weight loss (TBWL)

Disclosures: Sonal Kumar – Gilead Sciences: Speaking and Teaching, No, No; Ipsen: Speaking and Teaching, No, No; Intercept Pharmaceutical: Speaking and Teaching, No, No; Novo Nordisk: Speaking and Teaching, No, No;

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Disclosure information not available at the time of publication: Nicole Cornet, Lindsay Rogers, Aditi Rao, Patrick T Magahis, Tibor I. Krisko, Reem Sharaiha, Carolyn Newberry

2425-C | BENEFICIAL EFFECTS OF LUSEOGLIFLOZIN FOR HEPATIC STEATOSIS AND FIBROSIS INDEXES WITH A REDUCTION OF BODY WEIGHT AND AN INCREASE IN SERUM ALBUMIN LEVELS IN PATIENTS WITH DIABETES: A POOLED META-ANALYSIS OF PHASE III CLINICAL TRIALS USING INVERSE PROBABILITY TREATMENT WEIGHTING PROPENSITY ANALYSIS

Takumi Kawaguchi[1,2], Kenta Murotani[2,3], Yoko Shirouzu[4], Hitoshi Obara[3], Hironori Yamaguchi[4], Yuko Toyofuku[2], Fumi Kaneko[2] and Saeko Uchida[4], (1) Kurume University School of Medicine, (2)Kurume University Hospital, (3)Kurume University, (4)Taisho Pharmaceutical Co., Ltd.

Background: Luseogliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, is known to decrease serum ALT levels in patients with diabetes. We aimed to investigate the effects of luseogliflozin on hepatic steatosis and fibrosis indexes as well as body weight and serum albumin levels in patients with diabetes using a pooled meta-analysis of phase III clinical trials. **Methods**: In this pooled meta-analysis, we included 5 phase III clinical trials from 121 centers. The primary outcomes were fatty liver index (FLI) and aspartate aminotransferase to platelet ratio index (APRI) after 24 weeks. Secondary outcomes were body weight and serum albumin level after 24 weeks. Statistical analysis was performed using propensity scoring analysis by the inverse probability of treatment weighting (IPTW) method. **Results**: Patients' characteristics were adjusted by 20 covariates including age, sex, BMI, FLI and APRI using IPTW. A total of 493 participants (luseogliflozin group n = 302, placebo group n = 191) were enrolled in this pooled meta-analysis. *Primary outcome*: Luseogliflozin significantly decreased FLI compared to placebo after 12/24 weeks (adjusted coefficient -6.804/-5.423, 95%CI -10.258 to -3.349/-8.760 to -2.086, P = 0.0002/.0016). There was no significant difference in APRI between the luseogliflozin and placebo groups at 12 weeks. However, luseogliflozin significantly decreased APRI compared to placebo after 24 weeks (adjusted coefficient -0.024, 95%CI -0.042 to

-0.007, P = 0.0066). Secondary outcomes: luseogliflozin significantly decreased body weight compared to placebo after 12/24 weeks (adjusted coefficient -1.360/-1.406, 95% CI -1.592 to -1.128/-1.728 to -1.084, P < 0.0001/ < 0.0001). No significant difference was observed in serum albumin levels between the two groups at 12 weeks. However, luseogliflozin significantly increased serum albumin levels (adjusted coefficient 0.044, 95%CI 0.001 to 0.087, P = 0.0472) compared to placebo after 24 weeks. **Conclusion**: This pooled meta-analysis demonstrated that luseogliflozin improved non-invasive indexes for hepatic steatosis and fibrosis in patients with diabetes. We also revealed that luseogliflozin reduced body weight and increased serum albumin levels. Thus, luseogliflozin may be beneficial for the regression of hepatic steatosis and fibrosis with the improvement of other prognostic factors including obesity and hypoalbuminemia in patients with diabetes.

Disclosures: Takumi Kawaguchi – Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, No, No;

Disclosure information not available at the time of publication: Kenta Murotani, Yoko Shirouzu, Hitoshi Obara, Hironori Yamaguchi, Yuko Toyofuku, Fumi Kaneko, Saeko Uchida

2426-C | CLINICAL TRANSLATABILITY OF THE GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF NON-ALCOHOLIC STEATOHEPATITIS

Michael Feigh[1], Jacob Nøhr-Meldgaard[1], Martin Rønn Madsen[1], Susanne E. Pors[2] and Henrik B. Hansen[1], (1) Gubra, (2)Gubra a/S, Copenhagen, Denmark

Background: The Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse is a comprehensively validated preclinical model of non-alcoholic steatohepatitis (NASH) with progressive fibrosis. The present study aimed to assess liver histopathological effects of 10 clinical candidates in the GAN DIO-NASH mouse with reference to histological primary endpoints reported in corresponding clinical phase-2/3 trials in NASH patients. **Methods:** Individual drug treatment studies were performed in male DIO-NASH mice fed the GAN diet (40 kcal-% fat, 22% fructose, 10% sucrose, 2% cholesterol) for e 34 weeks and with liver biopsy-confirmed NAFLD Activity Score (NAS e 5) and fibrosis (e stage F1) using the NASH Clinical Research Network (CRN) scoring system. GAN DIO-NASH mice (n = 14-18 per group) were administered resmetirom (THR-β agonist, 3 mg/kg, QD, PO), semaglutide (GLP-1 receptor agonist, 30 nmol/kg, SC, QD), obeticholic acid (FXR agonist, 30 mg/kg, PO, QD), tropifexor (FXR agonist, 0.3 mg/kg, PO, QD), cilofexor (FXR agonist, 30 mg/kg, PO, QD), lanifibranor (pan-PPAR agonist, 30 mg/kg, PO, QD), elafibranor (PPAR-α/δ agonist, 30 mg/kg, PO, QD), seladelpar (PPAR-δ agonist, 10 mg/kg, PO, QD), firsocostat (ACC inhibitor, 5 mg/kg, PO, QD), cenicriviroc (CCR2/5 receptor antagonist, 100 mg/kg, PO, BID), or vehicle for 12 weeks. Histopathological pre-to-post individual assessment of NAS and fibrosis stage was performed and evaluated against FDA/EMA-accepted co-primary/secondary histological endpoints (resolution of NASH with no worsening of liver fibrosis; e 1-stage fibrosis improvement without worsening of NASH). **Results:** Histological outcomes in GAN DIO-NASH mice were comparable to corresponding clinical trials for resmetirom (MAESTRO-NASH), semaglutide (Newsome et al. NJEM 2020), lanifibranor (NATIVE), tropifexor (FLIGHT-FXR), cilofexor (ATLAS) and seladelpar (Harrison et al., AASLD, 2020). Obeticholic acid reversed NASH but not fibrosis in GAN DIO-NASH mice, being line with the FLINT trial, whereas the opposite effect has been reported the pivotal REGENERATE trial. Elafibranor only resolved NASH, being consistent with the GOLDEN-505 trial but contrasting no histological benefits in the pivotal RESOLVE-IT trial. Firsocostat improved both NASH and fibrosis, although these endpoints were not met in the ATLAS trial. While cenicriviroc had no effect in GAN DIO-NASH mice, fibrosis was significantly improved in the AURORA trial. **Conclusion:** GAN DIO-NASH mice faithfully reproduce histological outcomes of several compounds profiled in clinical trials for NASH, highlighting clinical translatability and utility of the model in preclinical drug development.

Disclosures: Martin Rønn Madsen – Gubra: Employee, No, No;

Susanne E. Pors – Gubra: Employee, Yes, No;

The following people have nothing to disclose: Michael Feigh, Jacob Nøhr-Meldgaard, Henrik B. Hansen

2427-C | EFFECT OF METFORMIN ON LIVER TRANSAMINASES IN PATIENTS OF NON-ALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW

Hriday Shah[1], Charmy Parikh[2], Raj Harshadkumar Patel[3], Ramaswamy Sundararajan[4], Henil Upadhyay[5] and Aman Narula[1], (1)Gmers Medical College, Vadodara, (2)Harvard University TH Chan School of Public Health, (3) St. Mary Medical Center, Langhorne, (4)Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, (5) Pramukhswami Medical College, Anand

Background: Simple steatosis and nonalcoholic steatohepatitis are the two primary conditions under the umbrella of nonalcoholic fatty liver disease (NAFLD). Medications that improve insulin sensitivity, like metformin, may be useful in treating NAFLD patients since insulin resistance (IR) plays a crucial role in the development of the disease. Our aim was to determine the effect of metformin use on liver transaminases in patients diagnosed with NAFLD.

Methods: Relevant studies were found by searching PubMed, PubMed Central, Science Direct, and Cochrane Library. The search was done on May 5, 2023. This review was carried out using the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines. Inclusion criteria were: published as randomized clinical trials (RCT) and observational cohort studies in the last eight years (2011-2023), full text in English only. In addition, we included studies in which NAFLD (defined as fatty liver on ultrasonography with alcoholic intake < 140 g and < 210 g per week for women and men, respectively, not treated with medications affecting hepatic steatosis and no history of autoimmune liver disease or viral hepatitis) patients were on Metformin therapy. Outcomes included changes in AST (aspartate aminotransferase), ALT (alanine aminotransferase), BMI (body mass index), and HbA1c (glycated hemoglobin). Studies that had follow-up periods of more than 20 weeks were included. Quality appraisal for publications was done using relevant assessment tools like the Newcastle-Ottawa scale, Cochrane risk-of-bias tool, etc. Articles that scored at least 70% using quality appraisal tools were included.

Results: Five studies were included, encompassing a total of 167 patients. Patients were followed for a range of 4-6 months. Two studies reported a significant reduction in serum AST and ALT concentrations post-metformin therapy ($p < 0.01$). Three of the five studies that evaluated the impact of Metformin on BMI, revealed a decline in this parameter as well, with two studies reporting a statistically significant difference ($p < 0.001$). Two studies investigated the effect of Metformin on HbA1C levels, both of which demonstrated a decrease after therapy.

Conclusion: Overall, this systematic review highlights that higher dosages and prolonged treatment durations of metformin lead to a downward trend in serum concentrations of AST, ALT, BMI, and HbA1C. Future prospective studies with longer follow-up periods can provide more information on this aspect of NAFLD treatment.

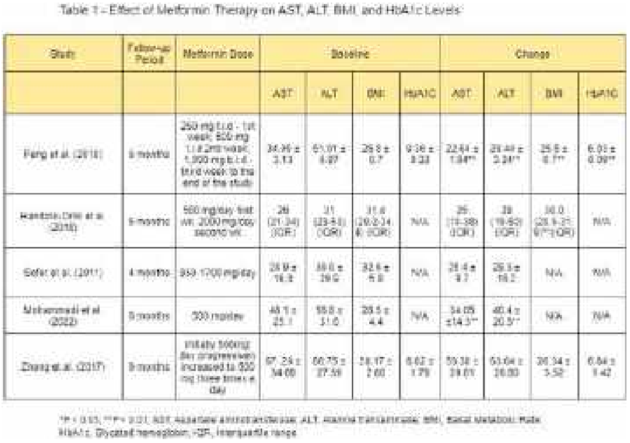


Table 1 – Effect of Metformin Therapy on AST, ALT, BMI, and HbA1c Levels

Study	Follow-up Period	Metformin Dose	Baseline				Change			
			AST	ALT	BMI	HbA1C	AST	ALT	BMI	HbA1C
Feng et al. (2018)	6 months	250 mg t.i.d - 1st week; 500 mg t.i.d 2nd week; 1,000 mg b.i.d - third week to the end of the study	34.36 ± 3.13	51.01 ± 4.87	25.8 ± 0.7	9.36 ± 0.33	22.64 ± 1.84**	28.44 ± 3.24**	25.5 ± 0.7**	6.03 ± 0.09**
Handzlik-Orlik et al. (2019)	6 months	500 mg/day first wk; 2000 mg/day second wk	26 (21-34) (IQR)	31 (23-53) (IQR)	31.6 (29.2-34.6) (IQR)	N/A	25 (19-38) (IQR)	28 (19-50) (IQR)	30.0 (28.6-32.6**) (IQR)	N/A
Sofer et al. (2011)	4 months	850-1700 mg/day	28.9 ± 16.3	46.6 ± 29.6	32.6 ± 5.8	N/A	28.4 ± 9.7	26.3 ± 16.2	N/A	N/A
Mohammadi et al (2022)	3 months	500 mg/day	45.1 ± 25.1	55.8 ± 31.6	28.5 ± 4.4	N/A	34.05 ±14.3**	40.4 ± 20.5**	N/A	N/A
Zhang et al. (2017)	3 months	initially 500mg/day progressively increased to 500 mg three times a day	67.24 ± 34.00	66.75 ± 37.39	28.17 ± 2.60	6.62 ± 1.79	59.38 ± 29.01	63.64 ± 26.00	26.34 ± 3.52	6.84 ± 1.42

*P < 0.05, **P < 0.01; AST, Aspartate aminotransferase; ALT, Alanine transaminase; BMI, Basal Metabolic Rate; HbA1c, Glycated hemoglobin; IQR, Interquartile range

Disclosures: The following people have nothing to disclose: Hriday Shah, Charmy Parikh, Raj Harshadkumar Patel, Ramaswamy Sundararajan, Henil Upadhyay, Aman Narula

2428-C | EFFECT OF WEIGHT LOSS AGENTS ON THE IMPROVEMENT OF LIVER INFLAMMATION AMONG METABOLIC ASSOCIATED FATTY LIVER DISEASE PATIENTS

Takamasa Ohki, Shioda Memorial Hospital

Background: Sodium-glucose co-transporter 2 (SGLT-2) inhibitors and Glucagon like peptide-1 (GLP-1) analogue are diabetes agents available on the market. Important advantage of SGLT-2 inhibitors and GLP-1 analogues are their favorable effects on the reduction of body weight (BW). The aim of this study is to analyze the effectiveness of SGLT-2 inhibitors and GLP-1 analogue as treatments for metabolic associated fatty liver disease (MAFLD) patients with type 2 diabetes mellitus (T2DM). **Methods:** We retrospectively enrolled consecutive 233 Japanese MAFLD patients with T2DM who were administered SGLT-2 inhibitors or GLP-1 analogues between 2010 June 1 and 2021 December 31. The last follow-up date was 2022 December 31. We divided these patients into two groups according to the BW reduction rate after 8 weeks (BW reduction rate equal to 3% or more than 3%; BWR-group $N = 54$, BW reduction rate less than 3%; CON-group $N = 179$). The primary endpoint was cumulative normalization rate of ALT and the secondary endpoint was cumulative re-exacerbation rate of patients who achieved normalization of ALT. We also assessed the factors which contributed to the normalization and re-exacerbation of ALT using COX hazard multivariate analysis. **Results:** There were no significant differences about patients' backgrounds including proportion of initial administration rate of SGLT-2 inhibitors and GLP-1 analogue between BWR-group and CON-group. Normalization of ALT was observed in 47 (87.0%) patients of BWR-group and 137 (76.5%) patients of CON-group ($P = 0.13$) at the end of follow-up. The cumulative normalization rate of ALT was significantly differed between the two groups showing 3, 6 and 12 months of 26.4 %, 45.3%, and 60.5% in BWR-group, 12.3 %, 28.0% and 41.0% in CON group, respectively ($P < 0.01$). Multivariate analysis indicated that BW reduction equal to or for more than 3% within 8 weeks (HR: 0.67, 95%CI: 0.47-0.96, $P = 0.029$), serum albumin level (HR: 0.51 per 1 g/dl, 95%CI: 0.31-0.85, $P = 0.009$, and alteration of T2DM (HR: 0.69, 95%CI: 0.49-0.99, $P = 0.041$) as independent factors

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

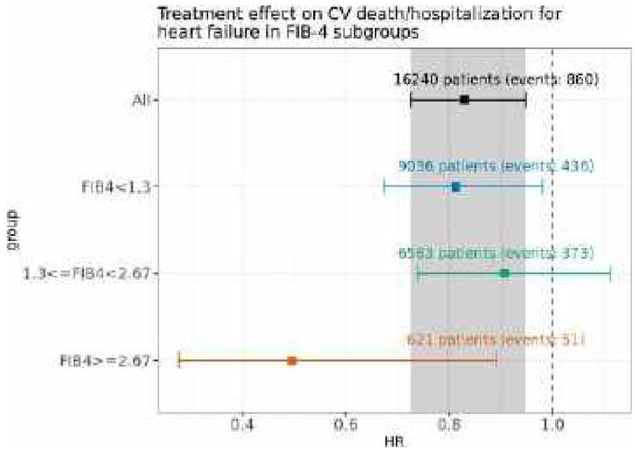
contributed to the normalization of ALT. During the follow-up period, 103 of 184 patients (56.0%) who had achieved improvement of ALT experienced re-exacerbation. The cumulative re-exacerbation rate was 13.2%, 29.6%, and 44.1% at 6, 12 and 24 months, respectively. Multivariate analysis indicated that BW gain (HR: 2.21, 95%CI: 1.48-3.28, P < 0.01), and exacerbation of T2DM (HR: 2.13, 95%CI: 1.43-3.16, P < 0.01) as independent factors related to re-exacerbation. **Conclusion:** The administration of SGLT-2 inhibitors and GLP-1 analogues led not only good glycaemic control but also normalization of ALT with a favorable effect of BW reduction. BW reduction within 8 weeks after administration of these agents was an independent factor contributed to rapid improvement of ALT. Maintenance of BW and T2DM after normalization of ALT was also very important.

Disclosures: The following people have nothing to disclose: Takamasa Ohki

2429-C | EFFECTS OF DAPAGLIFLOZIN ON CARDIOVASCULAR OUTCOMES IN PATIENTS AT HIGH RISK OF ADVANCED LIVER FIBROSIS: POST HOC ANALYSES FROM THE DECLARE-TIMI 58 TRIAL

Jan Oscarsson[1], Monika Huhn[1], Ingrid Am Gause-Nilsson[1], Stephen D Wiviott[2], Filipe A Moura[2], John P. H. Wilding[3], Simona Cernea[4], Luc Van Gaal[5], Avivit Cahn[6], Deepak L Bhatt[7], Darren K McGuire[8], Peter A Johansson[1] and C David Sjöström[9], (1)Astrazeneca, (2) Brigham and Women's Hospital, Harvard Medical School, (3)University of Liverpool, (4)George Emil Palade University of Medicine, (5)Antwerp University Hospital, (6)Hadassah Medical Center, (7)Icahn School of Medicine at Mount Sinai Health System, (8)University of Texas Southwestern Medical Center, (9)Astrazeneca, Hovås, Sweden

Background: The Fibrosis-4 score (FIB-4) was originally developed to evaluate the risk for advanced liver fibrosis in patients with hepatitis C/HIV infection, incorporating age, transaminase levels, and platelet count. More recently, FIB-4 has been used to assess the risk for advanced liver fibrosis in patients with non-alcoholic fatty liver disease. The aim of this post hoc analysis was to investigate the prognostic value of FIB-4 for cardiovascular (CV) outcomes and the effects of dapagliflozin. **Methods**: The DECLARE-TIMI 58 randomized trial investigated the effect of dapagliflozin, a SGLT2 inhibitor, versus placebo in patients with type 2 diabetes with or at high risk for atherosclerotic cardiovascular disease (ASCVD). Baseline FIB-4 was calculated for all participants, with the present analyses stratified by the following FIB-4 categories: < 1.3, 1.3- < 2.67 and e 2.67 and presented as HR (95%CI) for the effect of dapagliflozin versus placebo in the different FIB-4 categories. **Results**: Of 17,160 patients enrolled, a total of 16,240 patients were included in the present analyses, with median follow up of 4.2 years. The number of patients in the different FIB-4 categories were < 1.3; n = 9036 (55.6%), 1.3- < 2.67; n = 6583 (40.6%) and with e 2.67; n = 621 (3.8%). The proportion of patients with established ASCVD at baseline did not differ across FIB-4 subgroups, ranging from 40 to 43%. The annualized event rate for the primary composite outcome of CV death and hospitalization for heart failure (HHF) across the 3 FIB-4 categories among participants receiving placebo was 1.4% in the < 1.3 category, 1.5% in 1.3- < 2.67 category and 2.9% in the e 2.67 category. The corresponding annualized event rate among participants receiving dapagliflozin was 1.1%, 1.4% and 1.4%, respectively. The HR (95% CI) for the effect of dapagliflozin versus placebo on CV death and HHF was 0.81 (0.67-0.98) in the < 1.3 category, 0.91 (0.74-1.11) in the 1.3- < 2.67 category, and 0.50 (0.28-0.89) in the e 2.67 FIB-4 category (see Figure). There was no overall effect modification by FIB-4 ($p_{interaction} = 0.18$). For the components of the composite, the HR (95% CI) for the effect of dapagliflozin versus placebo on CV death was 0.98 (0.76-1.26) and 1.05 (0.80-1.39) in the < 1.3 and 1.3- < 2.67 categories and 0.55 (0.26-1.15) in the e 2.67 category. The effect on HHF was 0.74 (0.57-0.96) in < 1.3 and 0.79 (0.60-1.04) in the 1.3- < 2.67 categories, and 0.40 (0.17-0.97) in the e 2.67 FIB-4 category. Additional adjusting for age, sex, and BMI gave similar results. **Conclusion**: In a randomized placebo-controlled study investigating CV outcomes in persons with type 2 diabetes and high atherosclerotic cardiovascular risk, high FIB-4 score was associated with higher CV risk; whereas dapagliflozin reduced risk for CV death/HHF across FIB-4 categories.



Disclosures: Jan Oscarsson – AstraZeneca: Employee, No, No;

Disclosure information not available at the time of publication: Monika Huhn, Ingrid Am Gause-Nilsson, Stephen D Wiviott, Filipe A Moura, John P. H. Wilding, Simona Cernea, Luc Van Gaal, Avivit Cahn, Deepak L Bhatt, Darren K McGuire, Peter A Johansson, C David Sjöström

2430-C | EFFICACY OF SODIUM GLUCOSE CO-TRANSPORTER 2 INHIBITOR ON A PROGRESSION OF NONALCOHOLIC STEATOHEPATITIS IN A MURINE STEATOHEPATITIS MODEL

Young Chang, Soonchunhyang University

Background: Sodium glucose cotransporter 2 (SGLT2) inhibitors, an antidiabetic drug, have shown positive effects in diabetes and cavdiovascular diseases. It is unclear whether SGLT2 inhibition could exert a beneficial effect on nonalcoholic steatohepatitis (NASH)-associated liver fibrosis and hepatocellular carcinoma. **Methods:** We examined the beneficial effect of SGLT2 inhibitor, empagliflozin, in a murine NASH model. The choline-deficient, amino acid-defined diet (CDAA) with high fat diet was formulated and administered to 8-week-old male C57Bl/6J mice for up to 24 weeks. A total of 21 mice were divided into two groups, the control group and the SGLT2 inhibitor group. Five animals in each group were treated for 12 weeks, and the remaining five in the control group and six in the SGLT2 inhibitor group were treated for 24 weeks. **Results:** There was no significant difference in mean body weight between the control and treatment group after 12 weeks (24.19 g vs. 23.91 g; $P = 0.65$). Laboratory findings, including serum aspartate transaminase, alanine transaminase, creatinine, glucose, and triglyceride, also showed no statistical differences between groups (all $P > 0.1$). When hepatic fibrosis was assess by Sirius red staining, the area of collagen deposition was smaller in the SGLT2 inhibitor group (Figure 1). Moreover, 12 weeks of SGLT2 inhibitor treatment downregulated the expression of various fibrosis-related proteins in the liver compared to the control, indicating that SGLT2 inhibitor treatment attenuated hepatic fibrosis. After 24 weeks, the inhibitory effect of SGLT2 inhibitor on hepatic fibrosis was consistently observed as downregulated fibrosis-related proteins (Figure 2). However, multiple hepatic tumors developed in both groups without significant differences in tumor number and size (Figure 3). **Conclusion:** High fat-CDAA feeding in C57Bl/6J mice was identified as a suitable model of NASH developing robust fibrosis and hepatic tumor within 24 weeks. SGLT2 inhibitor showed the potential to attenuate hepatic fibrosis in the progression of NASH, whereas administration of SGLT2 inhibitor alone was insufficient to suppress the development of hepatic tumors.

Figure 1. The area of collagen deposition (Sirius-red) was smaller in (A) the SGLT2 inhibitor group than in (B) the control group.

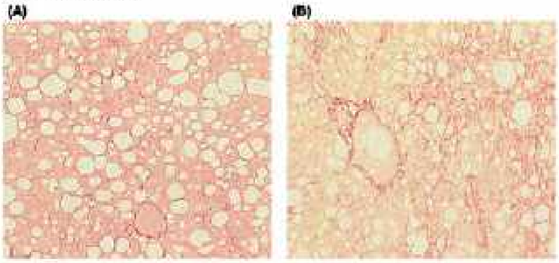


Figure 2. Both after (A) 12 weeks and (B) 24 weeks, SGLT2 inhibitor treatment downregulated the expression of various fibrosis-related proteins in the liver compared to the control.

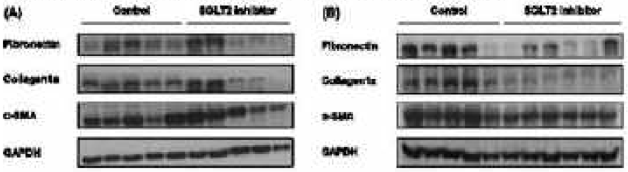
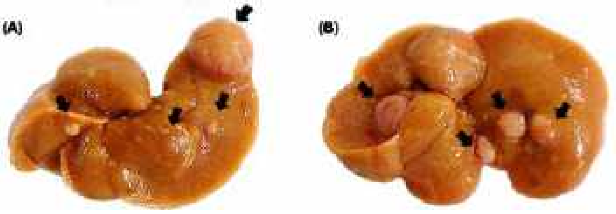


Figure 3. Multiple hepatic tumors developed in both groups without significant differences in tumor number and size. (A) control, (B) SGLT2 inhibitor treated

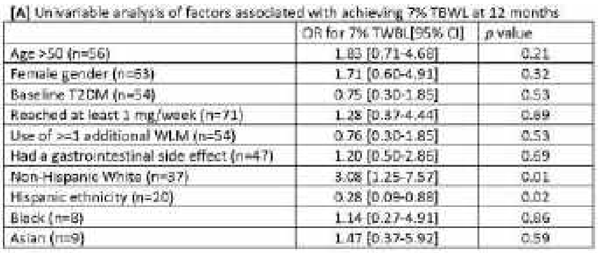


Disclosures: The following people have nothing to disclose: Young Chang

2431-C | HISPANIC PATIENTS WITH NAFLD SHOW LESS TOTAL BODY WEIGHT LOSS AFTER 12 MONTHS ON SEMAGLUTIDE COMPARED TO MATCHED NON-HISPANIC PEERS: DEFINING EFFECTS OF ETHNICITY ON WEIGHT LOSS OUTCOMES

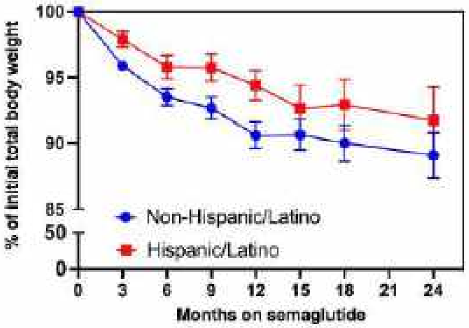
Adam Buckholz[1], Nicole Cornet[1], Lindsay Rogers[1], Aditi Rao[1], Patrick T Magahis[1], Reem Sharaiha[1], Tibor I. Krisko[1], Carolyn Newberry[1] and Sonal Kumar[2], (1) Newyork-Presbyterian/Weill Cornell Medical Center, (2) Weill Cornell Medical College, NY

Background: The GLP1 receptor agonist semaglutide is a commonly used anti-obesity medications (AOM) with growing interest for use in NAFLD, where 7-10% total body weight loss (TBWL) improves outcomes. Demographic factors associated with successful weight loss on semaglutide in real-world settings remain unclear. **Methods:** In our multidisciplinary metabolic center, we retrospectively identified patients initiated on weekly subcutaneous semaglutide between 2019 and 2022. NAFLD was diagnosed by steatosis on imaging and/or FibroScan at initiation. Baseline clinical characteristics, concurrent AOM medication use, and outcomes including peak dose, side effects and need for discontinuation or dose reduction for any reason were collected. Weights were recorded at 3-month intervals (+/- 30 d) when available among those remaining on semaglutide. Weight loss of 7% of TBW at 12-months was considered the primary outcome. Propensity score (PS) analysis with single nearest neighbor matching on age, gender, side effects, and reaching 1 mg/wk was performed to determine the effect of Hispanic status on achieving 7% TBWL. **Results:** A total of 279 patients started semaglutide, of whom 162 (119/74% female) had NAFLD. Of these, mean age was 52.1, 86 (53%) had T2DM (mean A1C 6.7%, IQR 1.8), 82 (50.6%) had HTN, 143 (88.3%) had HLD and mean BMI was 36.2 (IQR 8.8). 107 had baseline FibroScan data, with mean kPa of 7.2 and CAP of 322. The most common starting dose was 0.25 mg/wk (154/95%) with a median peak dose of 1 mg/wk. 136 participants (84%) had at least 6 months of follow up on drug, and 98 participants (61%) had at least 12 months of follow up on drug. 12-month weight was available for 83 participants (51%); 39 (47%) of these achieved at least 7% TBWL. In univariable analysis [A], identifying as Hispanic was associated with significantly reduced odds of achieving 7% TBWL (OR 0.28, 95% CI 0.09-0.88, p = 0.02) and less mean %TBWL (5.6% vs 9.4%, p < 0.05), despite similar baseline characteristics to non-Hispanics, including age, gender, baseline BMI, prevalence of DM, CAP/kPa on FibroScan, use of concurrent AOMs, rate of reaching 1 mg/wk, and development of gastrointestinal side effects. In PS matched analysis, the effect of being Hispanic was 40% lower propensity (95% CI .09, .71 p = 0.01) for reaching 7%TBWL and 3.8% less TBWL overall (p = 0.04). Controlling for additional variables did not attenuate this association. At every “weigh in” date, the mean and median TBWL was lower for Hispanic than non-Hispanic patients [B]. **Conclusion:** In a retrospective analysis of all patients with NAFLD started on semaglutide, roughly half achieved 7% TBWL at 12-months, a clinically significant number. Importantly, however, there was reduced TBWL among Hispanics, the group with the highest NAFLD prevalence, which may lead to worsening disease disparity. Larger controlled studies may help determine the relative contribution of genetic or environmental factors to these findings.



[A] Univariable analysis of factors associated with achieving 7% TBWL at 12 months

	OR for 7% TWBL[95% CI]	p value
Age >50 (n=56)	1.83 [0.71-4.68]	0.21
Female gender (n=53)	1.71 [0.60-4.91]	0.32
Baseline T2DM (n=54)	0.75 [0.30-1.85]	0.53
Reached at least 1 mg/week (n=71)	1.28 [0.37-4.44]	0.69
Use of >=1 additional WLM (n=54)	0.76 [0.30-1.85]	0.53
Had a gastrointestinal side effect (n=47)	1.20 [0.50-2.86]	0.69
Non-Hispanic White (n=37)	3.08 [1.25-7.57]	0.01
Hispanic ethnicity (n=20)	0.28 [0.09-0.88]	0.02
Black (n=8)	1.14 [0.27-4.91]	0.86
Asian (n=9)	1.47 [0.37-5.92]	0.59



[B] At every 3-month time point after initiating semaglutide, those on drug had progressively more total body weight loss (%TBWL). However, at each time point Hispanic/Latino patients had significantly less weight loss as demonstrated by the 3 month average with SEM, although as fewer weights were available later in the study the difference was no longer statistically significant. Total n=162 at initiation, n=83 at 12 months, n=34 at 24 months.

Disclosures: Sonal Kumar – Gilead Sciences: Speaking and Teaching, No, No; Ipsen: Speaking and Teaching, No, No; Intercept Pharmaceutical: Speaking and Teaching, No, No; Novo Nordisk: Speaking and Teaching, No, No;
The following people have nothing to disclose: Adam Buckholz
Disclosure information not available at the time of publication: Nicole Cornet, Lindsay Rogers, Aditi Rao, Patrick T Magahis, Reem Sharaiha, Tibor I. Krisko, Carolyn Newberry

2432-C | INVESTIGATING THE EFFECT OF ESSENTIAL PHOSPHOLIPIDS ON AN IN VITRO MODEL OF HUMAN STEATOSIS

Gina Valentino[1], Branko Popovic[2] and Paola Luciani[1], (1)University of Bern, (2)Sanofi

Background: Non-alcoholic fatty liver disease (NAFLD), the leading cause of liver dysfunction, progresses from steatosis to inflammation and fibrosis with an increasing risk for cirrhosis and liver cancer. The mechanisms underlying this pathophysiology is not fully understood. No approved NAFLD therapies exist, yet essential phospholipids (EPLs) are well-established for the adjunctive management of fatty liver disease, despite an unknow mechanism of action. Here, we assessed the effect of EPL-rich Essentiale® on lipid droplet size distribution and accumulation in an *in vitro* model of steatosis using differentiated HepaRG® cells, a suitable surrogate of

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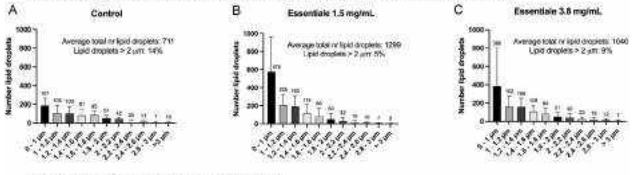
Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

primary human hepatocytes. **Methods:** After differentiation of HepaRG cells per manufacturer´s instruction, we incubated them with a 2:1 molar ratio of oleic acid (OA) to palmitic acid (PA) at 0.75 mM concentration for 24h before further treatment. Liposomes (lipid concentration:1.5 or 3.8 mg/mL) composed of Essentiale® were incubated with steatotic cells in presence of OA/PA (condition A) or co-incubated with OA/PA during the induction of steatosis (condition B). We assessed Essentiale®'s effect on steatotic HepaRG cells, including cell proliferation, mitochondria related cytotoxicity, lactate dehydrogenase leakage and reactive oxygen species production. Lipid droplet quantification performed by labelling with BODIPY 493/503 and confocal microscopy. Immunofluorescence staining assessed ATGL-dependent lipolysis vs LC3B-dependent lipophagy. **Results:** Essentiale® did not change cell proliferation, damage plasma membrane, and increase mitochondria-related cytotoxicity. It did not trigger ROS from HepaRG cells in growth medium. Essentiale® at 1.5 and 3.8 mg/mL after induction of steatosis reduced the percentage of fat droplets (diameter > 2μm) from 14% (untreated cells) to 5% and 9%, respectively. Essentiale® treatment during OA/PA-induced steatosis yielded comparable results (7% and 6%, respectively). The fluorescence signal from ATGL antibody-treated steatotic HepaRG cells indicates lipolysis, as the main contributor to the reduction in lipid droplet count. **Conclusion:** Inducing steatosis on differentiated HepaRG cells mimics human steatosis. Treatment with Essentiale® effectively impacted fat deposits without compromising cell viability, membrane integrity, mitochondria, or oxidative stress This suggests Essentiale® could be safe in human steatosis.

Figure: Diameter droplets profile measured after induction of steatosis in HepaRG cells and further 24 hour incubation with OA:PA (2:1) 0.75 mM.
A) Control cells in HepaRG Growth Medium and OA:PA;
B) HepaRG cells exposed to Essentiale® 1.5 mg/mL in HepaRG Growth Medium and OA:PA;
C) HepaRG cells exposed to Essentiale® 3.8 mg/mL in HepaRG Growth Medium and OA:PA.



Abbreviations: OA, oleic acid; PA, palmitic acid.

Disclosures: Branko Popovic – Sanofi: Employee, Yes, No; Sanofi: Stock – privately held company (individual stocks and stock options), Yes, No;
Paola Luciani – Lipoid GmbH: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Sanofi-Aventis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; DSM Nutritional Products Ltd: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Human Medicines Expert Committee (HMEC) at Swissmedic, the Swiss Agency for Therapeutic Products: Consultant, No, No; Lipoid GmbH: Consultant, No, No; Sanofi-Aventis: Consultant, Yes, No; DSM Nutritional Products Ltd: Consultant, No, No;
The following people have nothing to disclose: Gina Valentino

2433-C | NICLOSAMIDE ETHANOLAMINE (NEN) PROTECTS MOUSE LIVER FROM LIPOTOXICITY BY ACTIVATING NONCANONICAL p62-Keap1-Nrf2 PATHWAY

Yu Seol Lee, Yonsei University College of Medicine

Background: Nonalcoholic steatohepatitis (NASH) is one of most common liver diseases associated with metabolic disturbances, such as obesity, dyslipidemia, and type II diabetes. Despite its increasing prevalence, there is no approved drug for the treatment of NASH. Lipotoxicity-induced reactive oxygen species (ROS) has been known to be a major pathogenesis factor of NASH progression. Therefore, nuclear factor erythroid 2-related factor 2 (Nrf2), a pivotal transcription factor for the elimination of ROS, has been investigated as a potential therapeutic target for the treatment of NASH. Niclosamide ethanolamine (NEN), a FDA-approved drug as an anthelmintic, is recently reported to mitigate obesity-induced hepatic steatosis in high-fat diet (HFD)-fed mice. **Methods:** Male C57BL/6J mice fed a high-carbohydrate diet (HCD) after 24 h of fasting, injected with vehicle or NEN by oral gavage. After 18 h of feeding followed by fasting, the mice were sacrificed. serum alanine aminotransferase (ALT) level were measured and RNA or protein sample of liver tissue from them were analyzed by qRT-PCR or immunoblot assay. Also, to mimic lipotoxic condition, Mouse embryonic fibroblasts (MEFs) and HeLa cells expressing green fluorescent protein-conjugated LC3 (GFP-LC3/HeLa cells) were treated with palmitic acid with or without NEN. **Results:** Here, we revealed that NEN mediates AMPK-mediated phosphorylation of p62 at Ser351, resulting in activation of noncanonical Nrf2 pathway. Furthermore, NEN induces Sesn2-mediated AMPK activation and consequently promotes autophagic Keap1 degradation. We also showed that NEN protects cells and mouse liver from acute lipotoxic

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

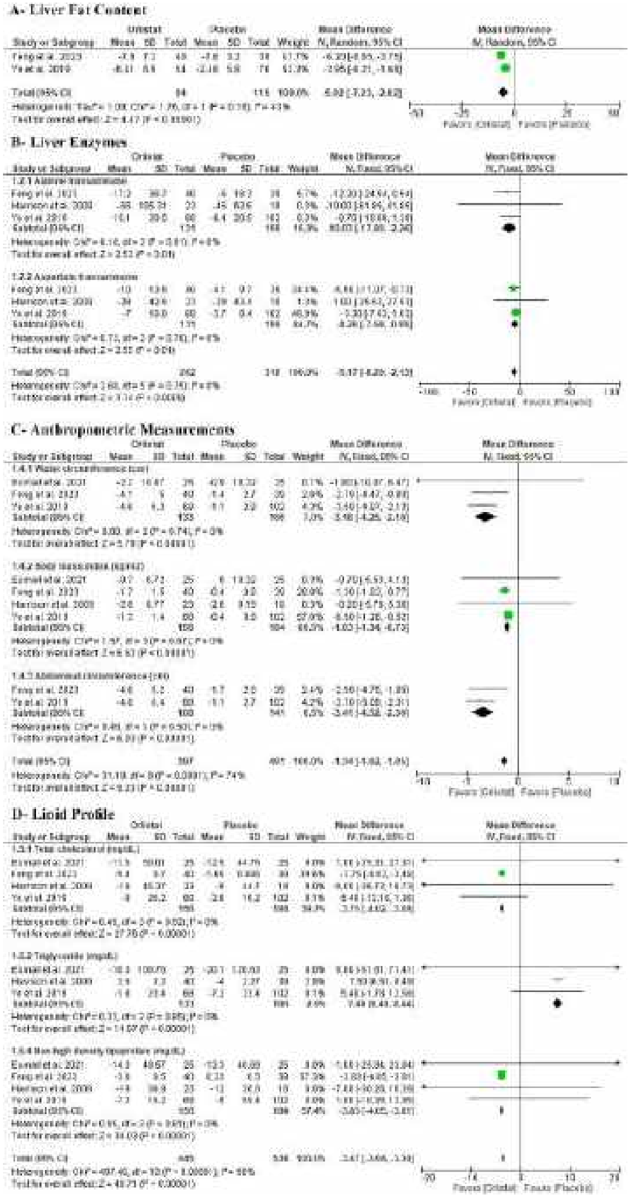
condition by activating noncanonical p62- Keap1-Nrf2 pathway. **Conclusion:** Altogether, these results suggest that NEN could be a novel therapeutic strategy for treatment of NASH.

Disclosures: The following people have nothing to disclose: Yu Seol Lee

2434-C | ORLISTAT FOR OBESE PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

Abdelrahman Mahmoud[1], Islam Mohamed[2], Mohamed Abuelazm[3], Ali Ashraf Salah Ahmed[1], Abdallah Saeed[3], Mahmoud Elshinawy[1], Omar Almaadawy[4], Hassan Ghoz[5] and Basel Abdelazeem[6], (1)Minia University, (2)University of Missouri-Kansas City, (3) Tanta University, (4)Medstar Health-Baltimore, (5) University of Missouri- Kansas City, (6)Mclaren Health Care-Flint

Background: Non-Alcoholic Fatty Liver Disease (NAFLD) is a significant contributor to chronic liver disease worldwide and currently holds the top spot for chronic liver disease in Western countries. In the United States, NAFLD is estimated to affect around 24% of the population. Orlistat blocks intestinal fat absorption leading to decreased liver fat content. Therefore, it is a viable option for NAFLD management. **Methods:** We conducted a systematic review and meta-analysis synthesizing randomized controlled trials (RCTs) which were retrieved by systematically searching: PubMed, EMBASE, Web of Science, SCOPUS, and Cochrane through March 27th, 2023. RevMan version 5.4 software was used to pool continuous outcomes using mean difference (MD) presented with the corresponding confidence interval (CI). Our protocol was prospectively published in PROSPERO with ID: CRD42023411654. **Results:** We included four RCTs with a total of 379 patients. Orlistat was effective in reducing liver fat content (MD: -5.02 with a 95% CI [-7.23, -2.82], P = 0.00001), alanine transferase (MD: -10.03 with a 95% CI [-17.80, -2.26], P = 0.01), aspartate transferase (MD: -4.29 with a 95% CI [-7.59, -0.99], P = 0.01), waist circumference (MD: -3.18 with a 95% CI [-4.25, -2.10], P = 0.00001), body mass index (MD: -1.03 with a 95% CI [-1.34, -0.73], P = 0.00001), total cholesterol (MD: -3.75 with a 95% CI [-4.02, -3.49], P = 0.00001), and low-density lipoprotein (MD: -3.83 with a 95% CI [-4.05, -3.61], P = 0.00001). However, orlistat was associated with increased serum triglycerides (MD: 7.46 with a 95% CI [6.48, 8.44], P = 0. 00001). **Conclusion:** Orlistat is a viable option for NAFLD management; however, it increases triglyceride levels. Which can be a potential limitation of orlistat use in patients with hypertriglyceridemia. More subtle RCTs with larger sample sizes, longer follow-up duration, and including patients with variable metabolic risk factors are still required before endorsement in clinical practice.



Disclosures: The following people have nothing to disclose: Islam Mohamed, Hassan Ghoz

Disclosure information not available at the time of publication: Abdelrahman Mahmoud, Mohamed Abuelazm, Ali Ashraf Salah Ahmed, Abdallah Saeed, Mahmoud Elshinawy, Omar Almaadawy, Basel Abdelazeem

2435-C | STATIN USE IN NONALCOHOLIC FATTY LIVER DISEASE AND EFFECTS ON VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY-DERIVED SCORES - A POPULATION-BASED INVERSE PROBABILITY TREATMENT WEIGHTING ANALYSIS

Natchaya Polpichai, Weiss Memorial Hospital, Sakditad Saowapa, Texas Tech University Health Science Center, Aunchalee Jaroenlapnopparat, Mount Auburn Hospital/Harvard Medical School, Panisara Fangsaard, Bassett Medical Center, Pojsakorn Danpanichkul, Chiang Mai University, Phuuwadith Wattanachayakul, Einstein Medical Center, Vincent Chen, University of Michigan Medical Center, Yu JUN Wong, Department of Gastroenterology & Hepatology, Changi General Hospital, Singapore; Changi General Hospital, Donghee Kim, Stanford University Medical Center and Karn Wijarnpreecha, Banner University Medical Center

Background: Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease globally. While statins have been found to reduce the risk of cardiovascular events in diabetics and chronic kidney disease, the clinical significance of statin use and severity of liver fibrosis in patients with NAFLD remains contentious. **Methods:** We performed a cross-sectional study using the National Health and Nutrition Examination Survey (NHANES) database from 1999-2018. Inverse probability of treatment weighting was introduced to reduce confounding. NAFLD was defined as hepatic steatosis (CAP score e 288 db/m) with negative hepatitis B surface antigen, hepatitis C RNA, Anti-HCV or substantial alcoholic use. The primary predictor was statin use. The outcomes were (1) at-risk steatohepatitis defined as Fibroscan-AST (FAST) score e 0.67, (2) significant or advanced fibrosis defined by liver stiffness measurement (LSM) e 8.8 and e 11.7 respectively, and (3) advanced fibrosis defined by AGILE3+ score e 0.68. **Results:** Out of 1,283 patients who had a diagnosis of NAFLD, 376 were prescribed statins. After adjustment for body mass index and diabetes, statin use was significantly associated with decreased risk for At Risk NASH, significant fibrosis, high AGILE score, with an odd ratio (OR): 0.289 (95% CI: 0.096 to 0.867), OR: 0.540 (95%CI: 0.306 to 0.953) and OR: 0.409 (95%CI: 0.224 to 0.747), respectively. A subgroup analysis was subsequently conducted to examine the effect of lipophilic and hydrophilic statins, but the effect was maintained only in lipophilic statins. **Conclusion:** Statin use was associated with less steatohepatitis and fibrosis in patients with NAFLD using robust casual inference and new Fibroscan™ scores.

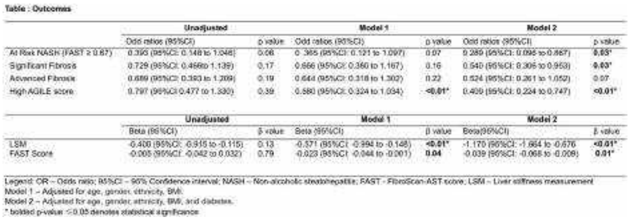


Table : Outcomes

	Unadjusted		Model 1		Model 2	
	Odd ratios (95%CI)	p value	Odd ratios (95%CI)	p value	Odd ratios (95%CI)	p value
At Risk NASH (FAST ≥ 0.67)	0.393 (95%CI: 0.148 to 1.046)	0.06	0. 365 (95%CI: 0.121 to 1.097)	0.07	0.289 (95%CI: 0.096 to 0.867)	**0.03***
Significant Fibrosis	0.729 (95%CI: 0.466to 1.139)	0.17	0.666 (95%CI: 0.380 to 1.167)	0.16	0.540 (95%CI: 0.306 to 0.953)	**0.03***
Advanced Fibrosis	0.689 (95%CI: 0.393 to 1.209)	0.19	0.644 (95%CI: 0.318 to 1.302)	0.22	0.524 (95%CI: 0.261 to 1.052)	0.07
High AGILE score	0.797 (95%CI 0.477 to 1.330)	0.39	0.580 (95%CI: 0.324 to 1.034)	**<0.01***	0.409 (95%CI: 0.224 to 0.747)	**<0.01***

	Unadjusted		Model 1		Model 2	
	Beta (95%CI)	β value	Beta (95%CI)	β value	Beta(95%CI)	β value
LSM	-0.400 (95%CI: -0.915 to -0.115)	0.13	-0.571 (95%CI: -0.994 to -0.148)	**<0.01***	-1.170 (95%CI: -1.664 to -0.676	**<0.01***
FAST Score	-0.005 (95%CI: -0.042 to 0.032)	0.79	-0.023 (95%CI: -0.044 to -0.001)	**0.04**	-0.039 (95%CI: -0.068 to -0.009)	**0.01***

Legend: OR – Odds ratio; 95%CI – 95% Confidence interval; NASH – Non-alcoholic steatohepatitis; FAST - FibroScan-AST score; LSM – Liver stiffness measurement
Model 1 – Adjusted for age, gender, ethnicity, BMI.
Model 2 – Adjusted for age, gender, ethnicity, BMI, and diabetes.
* bolded p-value <0.05 denotes statistical significance

Disclosures: Vincent Chen – KOWA: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AstraZeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
Yu JUN Wong – Gilead: Speaking and Teaching, No, Yes; AbbVie: Speaking and Teaching, No, Yes;
The following people have nothing to disclose: Natchaya Polpichai, Sakditad Saowapa, Aunchalee Jaroenlapnopparat, Panisara Fangsaard, Pojsakorn Danpanichkul, Phuuwadith Wattanachayakul, Donghee Kim, Karn Wijarnpreecha

2436-C | THE EFFECTS OF SEMAGLUTIDE ON NAFLD IN OVERWEIGHT OR OBESE PATIENTS AT A MULTIDISCIPLINARY CLINIC

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Background: Nonalcoholic fatty liver disease (NAFLD) is strongly associated with metabolic syndrome. Current management centers around weight loss reduction as there are no pharmacological therapies approved for the treatment of NAFLD. The Johns Hopkins Healthful Eating, Activity & Weight Program (HEAWP) is a multi-disciplinary clinic with a dedicated focus on the management of metabolic syndrome and NAFLD. In this study, we assessed patients with NAFLD managed at the HEAWP clinic on semaglutide therapy to determine the impact on liver aminotransferases. **Methods:** This study

included adult patients with a clinical diagnosis of NAFLD seen at HEAWP from June 1, 2020 to June 1, 2022. Summary statistics were generated to characterize patients overall and by semaglutide and control groups. To assess significant differences between groups, Wilcox rank-sum tests were performed for continuous variables and Fisher's exact tests for categorical variables. The primary outcome was a change in alanine aminotransferase (ALT) at 6 months. Secondary outcomes included change in weight, BMI, and non-invasive measures of liver fibrosis (NAFLD Fibrosis Score, APRI, FIB-4). **Results:** A total of 70 patients with NAFLD seen at HEAWP were included in the analysis. 51% were female, 9% were Hispanic, and 67% were Caucasian. There were 17 patients in the semaglutide group and 53 in the control group. Median body weight and BMI were higher in the semaglutide group compared to the control group. The median NAFLD fibrosis score was higher at baseline in the semaglutide group compared to controls (0.2 vs -1.9, respectively, p-value 0.035). There was a reduction in ALT at 6 months in both the semaglutide and control groups (30.5 vs 12 IU/L, respectively, p-value 0.11). Median body weight at 6 months decreased by 3.4 kg in the semaglutide group as compared to 0.1 kg in the control group (p-value 0.06) and BMI decreased by 1.02 kg/m2 in the semaglutide group as compared to 0.03 kg/m2 in the control (p-value 0.056) at 6 months. There was a reduction in non-invasive markers of fibrosis at 6 months in both the semaglutide and controls with no difference between the groups (Table 1). **Conclusion:** This retrospective study showed that a multidisciplinary program is an effective treatment for patients with NAFLD which resulted in a significant reduction in ALT and non-invasive markers of liver fibrosis at 6 months. The use of semaglutide in a multidisciplinary program is associated with larger reductions in weight, BMI, and ALT at 6 months.

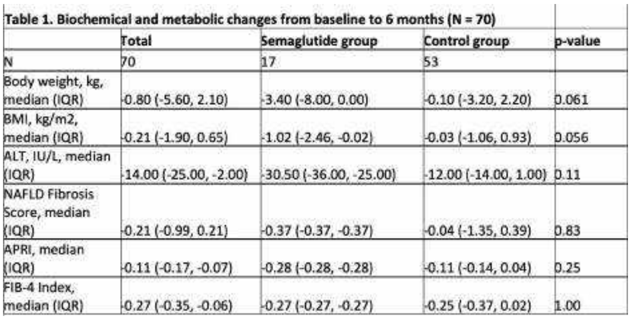


Table 1. Biochemical and metabolic changes from baseline to 6 months (N = 70)

	Total	Semaglutide group	Control group	p-value
N	70	17	53	
Body weight, kg, median (IQR)	-0.80 (-5.60, 2.10)	-3.40 (-8.00, 0.00)	-0.10 (-3.20, 2.20)	0.061
BMI, kg/m2, median (IQR)	-0.21 (-1.90, 0.65)	-1.02 (-2.46, -0.02)	-0.03 (-1.06, 0.93)	0.056
ALT, IU/L, median (IQR)	-14.00 (-25.00, -2.00)	-30.50 (-36.00, -25.00)	-12.00 (-14.00, 1.00)	0.11
NAFLD Fibrosis Score, median (IQR)	-0.21 (-0.99, 0.21)	-0.37 (-0.37, -0.37)	-0.04 (-1.35, 0.39)	0.83
APRI, median (IQR)	-0.11 (-0.17, -0.07)	-0.28 (-0.28, -0.28)	-0.11 (-0.14, 0.04)	0.25
FIB-4 Index, median (IQR)	-0.27 (-0.35, -0.06)	-0.27 (-0.27, -0.27)	-0.25 (-0.37, 0.02)	1.00

Disclosures: The following people have nothing to disclose: Rickisha Berrien-Lopez, Sameer Khan, Tinsay A. Woreta

Disclosure information not available at the time of publication: Sherifatu Abu, James P. Hamilton

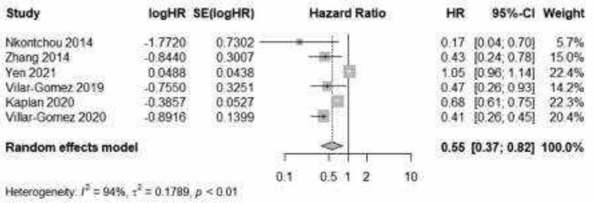
2437-C | THE IMPACT OF METFORMIN USE ON ALL-CAUSE MORTALITY AND HEPATIC DECOMPENSATION IN DIABETIC PATIENTS WITH COMPENSATED CIRRHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Spyridon Peppas[1], Stavros Doumas[2], Jiling Chou[3], Ayah Arafat[3], Maria Gazi[4], Akram I Ahmad[1] and James H Lewis[5], (1)Medstar Washington Hospital Center, (2) Medstar Georgetown University Hospital, (3)Medstar Health Research Institute, (4)251 Air Force General Hospital, (5)Georgetown University Hospital

Background: Patients with cirrhosis have an increased prevalence of diabetes mellitus (DM), which in turn accelerates liver disease progression. The direct impact, however, of antidiabetic medication on the prognosis of this patient group remains unclear. Metformin, a first-line anti-diabetic oral agent, has demonstrated both antiaging and anticancer effects that exceed its impact on glycemic control. Furthermore, recent studies, suggest that metformin use in DM patients with cirrhosis improves mortality and rates of liver decompensation. The aim of this study was to determine the impact of metformin use on all-cause mortality and hepatic decompensation in DM patients with compensated cirrhosis. **Methods:** We performed a systematic review of the literature using Medline, Embase and Cochrane databases from inception to February 2023 to identify studies evaluating the effect of metformin use in DM patients with compensated cirrhosis of any etiology on all-cause mortality or transplantation and liver disease decompensation. We then pooled the identified studies and conducted a large scale meta-analysis. The risk of bias was assessed by ROBINS-I Cochrane tool. The log-transformed adjusted hazard ratios and 95% confidence intervals were evaluated and pooled in R software to conduct the analysis. The inverse variance method was used to calculate the random effects. To account for differences related to the specific etiology of cirrhosis a sensitivity analysis was conducted. **Results:** Six observational studies were identified and 28,332 metformin users and 32,276 non-metformin users were pooled and included in the analysis. Overall, metformin use was associated with reduced all-cause mortality or transplantation (HR: 0.55; 95% CI 0.37-0.82, 6 studies, figure 1) in diabetic patients with compensated cirrhosis. Overall, no benefit was demonstrated for metformin use in the prevention of liver decompensation (HR: 0.97; 95% CI: 0.77-1.22, 4 studies including a total of 60,258 patients, figure 2). Sensitivity analyses were conducted based on the etiology of cirrhosis. In two studies assessing patients with NASH, metformin use was associated with reduced all-cause mortality or transplantation (HR: 0.42 95% CI

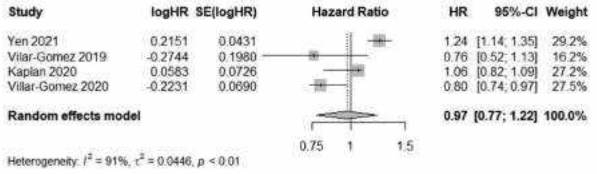
0.33-0.54, total of 505 patients, figure 3). However, no benefit was shown in patients with cirrhosis secondary to hepatitis B or C (HR: 0.49; 95% CI 0.08-2.84, total of 17,324 patients, figure 4). Notably, substantial heterogeneity was appreciated between studies analyzed. **Conclusion:** Metformin use, in diabetic patients with compensated cirrhosis, reduces all-cause mortality or transplantation, but is not associated with prevention of decompensation. This association appears to be particularly strong in patients with NASH cirrhosis. Future studies are called for to define liver-specific metformin effects and identify cirrhotic patients that would benefit from metformin use.

Figure 1. Forest plot depicting the meta-analysis performed using adjusted hazard ratios of all-cause mortality or transplantation in metformin users vs. non-users.



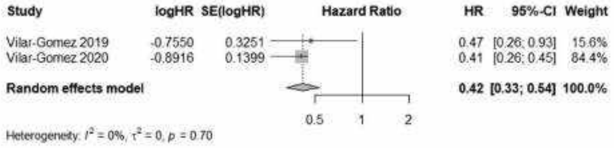
I^2: heterogeneity; HR: hazard ratio; CI: confidence interval; SE: standard error

Figure 2. Forest plot depicting the meta-analysis performed using adjusted hazard ratios of hepatic decompensation in metformin users vs. non-users.



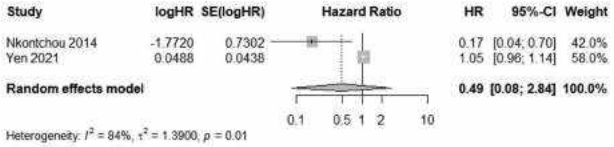
I^2: heterogeneity; HR: hazard ratio; CI: confidence interval; SE: standard error

Figure 3. Forest plot depicting the meta-analysis performed using adjusted hazard ratios of all- cause mortality or transplantation in metformin users vs. non-users for studies that only adjusted for NASH cirrhosis.



HR: hazard ratio; SE: standard error; CI: confidence interval; NASH: non-alcoholic steatohepatitis; I^2: heterogeneity

Figure 4. Forest plot depicting the meta-analysis performed using adjusted hazard ratios of all-cause mortality or transplantation in metformin users vs. non-users for studies that only adjusted for HBV/HCV cirrhosis.



HR: hazard ratio; SE: standard error; CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; I^2: heterogeneity

Disclosures: The following people have nothing to disclose: Spyridon Peppas, Stavros Doumas, Jiling Chou, Ayah Arafat, Maria Gazi, Akram I Ahmad, James H Lewis

2438-C | THREE-DIMENSIONAL PRIMARY CELL BASED LIVER MODEL PREDICTS CLINICAL OUTCOMES OF NASH IN VITRO

Vaidehi Joshi, Rachel Dudum, Payton Olson, Michelle Perez-Arreola, Keith Murphy and Jeffrey N Miner, Viscient Biosciences

Background: Non-alcoholic steatohepatitis (NASH) is a complex liver disease with no approved pharmacological treatments. One of the main challenges in NASH drug discovery is finding in vitro models that accurately recapitulate human NASH disease to offset poor efficacy rates in the clinic. In this study, we developed complex physiologically relevant 3D tissue models of NASH and assessed the ability to predict the response of four clinical compounds *in vitro* for NASH drug discovery. **Methods:** We developed high throughput 3-dimensional healthy and diseased tissues using primary human hepatocytes and non-parenchymal liver cells mixed in physiologically relevant cell ratios. The tissues were characterized using immunofluorescence, gene expression analysis, and functional assays. We then evaluated the ability of these diseased liver tissues to predict the response of clinical compounds with known outcomes in Phase 2 or Phase 3 clinical trials in NASH. **Results:** The 3D NASH tissues exhibited key features of disease and demonstrated a clear separation when compared to healthy liver tissues *in vitro*. Using the diseased 3D liver tissues, we were then able to accurately predict the response of Elafibranor (PPAR inhibitor, Genfit), Emricasan (pan-caspase inhibitor, Conatus/Novartis), Selonsertib (ASK1 inhibitor, Gilead) and OCA (FXR agonist, Intercept) *in vitro* using fibrosis as the primary endpoint. Elafibranor and Selonsertib, both increased markers of disease in our model, matching the outcomes in the Phase 3 clinical studies. OCA showed a significant decrease in collagen deposition while Emricasan failed to show any effect. The 3D liver models accurately predicted the response of clinical compounds on fibrosis. **Conclusion:** Our results demonstrate the advanced potential of our 3D liver tissues as a reliable preclinical screening tool for NASH drug discovery. These models offer a more physiologically relevant platform than traditional 2D cell culture systems or animal models for the evaluation of efficacy of clinical compounds and may accelerate the development of effective therapies for NASH and reduce clinical failures.

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The following people have nothing to disclose: Vaidehi Joshi

Disclosure information not available at the time of publication: Rachel Dudum, Payton Olson, Michelle Perez-Arreola, Keith Murphy

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

2439-C | A FIRST-IN-CLASS GALNAC-siRNA IMPROVES LIVER FUNCTIONS AND FIBROSIS OUTCOMES BY ENHANCING LIVER REGENERATION

Audrey Wang[1], Adelyn Tan[1], Mei Jia Tan[1], Sissi Lin[1], Binxia Yang[1], Torsten Wuestefeld[1,2], Yann Chong Tan[1] and Si Hui Tan[1], (1)Cargene Therapeutics, (2)Genome Institute of Singapore

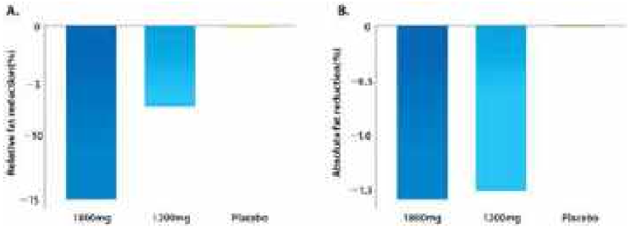
Background: The liver's ability to regenerate itself after damage is unparalleled among all the organs in the body. However, this regenerative ability is impaired in aged and diseased liver, thereby precluding efficient recovery in most patients with liver diseases. In chronic liver diseases, prolonged and repeated insults lead to fibrosis and eventually cirrhosis if left untreated; natural history has shown that liver regeneration can reverse fibrosis. In acute situations, the critical loss of hepatocyte compromises liver functions and eventually leads to liver failure, and liver regeneration replenishes the lost hepatocytes to maintain liver functions. Therefore, enhancing liver regeneration is a viable approach for treating a spectrum of liver diseases. **Methods:** Through our *in vivo* RNAi functional screening and validation platform, we discovered and validated ITFG1 as a therapeutic target for enhancing liver regeneration. Silencing ITFG1 expression in hepatocytes enhances their proliferation in injured or diseased livers, making GalNAc-siRNA the most relevant therapeutic modality for targeting ITFG1. We developed a GalNAc-siRNA therapeutic CG-LR1, with our in-house platforms, and assessed its knockdown potency, safety, durability and therapeutic efficacy to improve liver function and fibrosis outcome in mouse disease models. CG-LR1 was then evaluated for its safety, pharmacodynamics and pharmacokinetics in rats and non-human primates (NHPs). **Results:** CG-LR1 is a first-in-class therapeutic targeting ITFG1, conjugated to our proprietary GalNAc. It has an IC50 of 1.5pM, minimal off targets and high stability. In mice, it has an ED50 of less than 1mg/kg with exquisite liver specificity conferred by the GalNAc ligand. CG-LR1 increases hepatocyte proliferation by more than 50% compared to control in partial hepatectomy, reduces serum biomarkers of liver injury, enhances liver regeneration and attenuates fibrosis in bile duct ligation mouse models with statistical significance. Long term knockdown of ITFG1 *in vivo* does not induce carcinogenicity or hepatomegaly, affirming the safety of this therapeutic approach. Hepatocellular carcinoma patients with low ITFG1 expression also present with better prognosis than those with high ITFG1 expression. In NHPs, CG-LR1 achieved greater than 80% knockdown with sustained silencing activity for more than 3 months with a single dose. **Conclusion:** ITFG1 silencing in hepatocytes with CG-LR1 enhances hepatocyte regeneration in injured and diseased livers to promote liver recovery across etiologies. CG-LR1 is a First-in-Class GalNAc-siRNA that can be broadly applied to acute and chronic liver diseases. CG-LR1's pharmacokinetics also support an infrequent dosing regimen, which helps to improve patient compliance.

Disclosures: The following people have nothing to disclose: Audrey Wang, Adelyn Tan, Mei Jia Tan, Sissi Lin, Binxia Yang, Torsten Wuestefeld, Yann Chong Tan, Si Hui Tan

2440-C | A PHASE 2a, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY, AND SAFETY OF ALS-L1023 IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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

Background: Preclinical data have shown that the herbal extract, ALS-L1023, from Melissa officinalis reduces visceral fat and hepatic steatosis. We aimed to assess the safety and efficacy of ALS-L1023 as the treatment of non-alcoholic fatty liver disease (NAFLD). **Methods:** We conducted a 24-week randomized, double-blind, placebo-controlled 2a study in patients with NAFLD (MRI-proton density fat fraction [MRI-PDFF] e 8% and liver fibrosis e 2.5 kPa on MR elastography [MRE]) in Korea. Patients were randomly assigned to 1800 mg ALS-L1023 (n = 19), 1200 mg ALS-L1023 (n = 21), or placebo (n = 17) groups. Efficacy endpoints included changes in liver fat on MRI-PDFF, liver stiffness on MRE, and liver enzymes. **Results:** For the full analysis set, a relative hepatic fat reduction from baseline was significant in the 1800 mg ALS-L1023 group (-15.0%, p = 0.03). There was a significant reduction in liver stiffness from baseline in the 1200 mg ALS-L1023 group (-10.7%, p = 0.03). Serum alanine aminotransferase decreased by -12.4% in the 1800 mg ALS-L1023 group, -29.8% in the 1200 mg ALS-L1023 group, and -4.9% in the placebo group. ALS-L1023 was well tolerated and there were no differences in the incidence of adverse events among the study groups. **Conclusion:** ALS-L1023 could reduce hepatic fat content in patients with NAFLD.

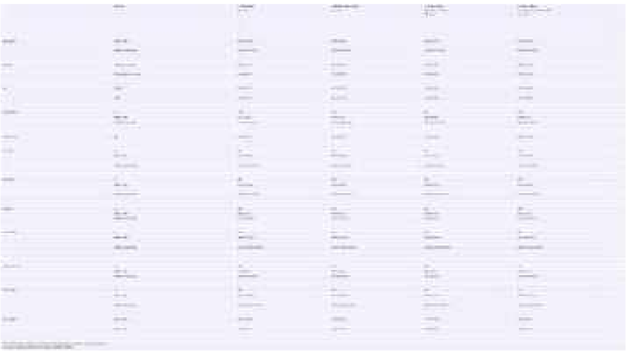


Disclosures: The following people have nothing to disclose: Eileen Yoon, Huiyul Park, Sang Bong Ahn, Hyunwoo Oh, Hyo Young Lee, Joo Hyun Sohn, Dae Won Jun

2441-C | A STEPWISE SCREENING APPROACH USING NONINVASIVE TESTS TO IDENTIFY PHENOTYPIC NONALCOHOLIC STEATOHEPATITIS (NASH) PATIENTS WITH FIBROSIS FOR CLINICAL TRIALS

Rohit Loomba[1], Mazen Noureddin[2], Eric Lawitz[3], Kris V. Kowdley[4], Lois Lee[5], Amnon Schlegel[6], Hiba Graham[6], Lu Zhang[6], Kerry Russell[6] and Naim Alkhouri[7], (1) University of California, San Diego, San Diego, CA, (2) Houston Research Institute, Houston, TX, (3)Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX, (4)Swedish Medical Center, Seattle, WA, (5)Terns Pharma, San Diego, CA, (6)Terns Pharma, Foster City, CA, (7)Arizona Liver Health, Phoenix, AZ

Background: Non-invasive tests (NITs) have become essential to help diagnose and stage nonalcoholic steatohepatitis (NASH). Biopsy-based screen failure (SF) rates are high in NASH trials, which lead to increased cost and extended enrollment durations. Per 2023 AASLD guidance, patients with at least stage 2 fibrosis are at increased risk of cirrhosis and liver-related complications. Patients with specific comorbidities such as type 2 diabetes mellitus (DM2), obesity and hypertension and biomarkers such as PDFF, cT1and other NITs may help define the NASH population. DUET is a randomized double-blind Phase 2a study fully enrolled and currently ongoing in patients with presumed NASH. A stepwise NIT screening approach was implemented to recruit patients likely to have NASH and a high degree of liver fat and fibro-inflammation, reflecting F2 and F3 fibrosis without requiring a biopsy. **Methods:** Initial screening (step 1) required age 18 – 75 years old and BMI ≥ 25 kg/m^2, vibration controlled transient elastography (VCTE) of 7.6 to 21 kPa, and controlled attenuation parameter (CAP) of > 300 dB/m in patients without historical biopsy for fibrotic NASH within 1 year before randomization. Potential subjects remaining eligible after initial screening underwent MRI to assess liver fat content eligibility of ≥ 10% by proton density fat fraction (PDFF) and fibro-inflammation defined as corrected T1 (cT1) ≥ 800 msec (step 2). Common SF reasons were tabulated, and multiparametric MRI SF rates were calculated. Baseline criteria of the enrolled population were compared to the SF population as well as to the AASLD guidance for identifying patients with NASH. **Results:** 591 patients were screened and 162 were randomized; overall SF rate was 73%. The screening duration was 9 months. Of the 591 patients, 291 met step 1 eligibility criteria, with a SF rate of 51%. Of the 291 patients who underwent MRI assessments, 162 met MRI-PDFF and cT1 criteria resulting in a step 2 MRI SF rate of 56%. The randomized population had higher mean values for ALT and AST and a higher proportion of DM2 patients compared to the SF population (Table 1). cT1 values reflect the patients included in the study represent the at-risk NASH population according to the cutoff (≥ 875 msec) provided in the AASLD guidance. **Conclusion**: A stepwise screening approach beginning with clinical assessments, laboratory tests, and VCTE with CAP followed by MRI identified patients that were more likely to meet the eligibility criteria. As a result, fewer MRI assessments were required to fully enroll the study, reducing costs and the need for patients to be scheduled for a separate imaging visit.



Disclosures: Rohit Loomba – Aardvark Therapeutics: Consultant, No, No; Altimmune: Consultant, No, No; Anylam/Regeneron: Consultant, No, No; Amgen: Consultant, No, No; Arrowhead Pharmaceuticals: Consultant, No, No; AstraZeneca: Consultant, No, No; Bristol-Myer Squibb: Consultant, No, No; CohBar: Consultant, No, No; Eli Lilly: Consultant, No, No; Galmed Pharmaceuticals: Consultant, No, No; Gilead: Consultant, No, No; Glympse Bio: Consultant, No, No; Hightide: Consultant, No, No; Inipharma: Consultant, No, No; Intercept: Consultant, No, No; Inventiva: Consultant, No, No; Ionis: Consultant, No, No; Janssen Inc.: Consultant, No, No; Madrigal Pharmaceuticals: Consultant, No, No; Metacrine, Inc.: Consultant, No, No; NGM Biopharmaceuticals: Consultant, No, No; Novartis: Consultant, No, No; NovoNordisk: Consultant, No, No; Merck:

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2442-C | A3907, A CLINICAL SYSTEMIC APICAL BILE ACID TRANSPORTER INHIBITOR, REPROGRAMS FATTY ACID UTILIZATION TOWARDS OMEGA-6 METABOLISM PROMOTING REDUCED INFLAMMATION, FIBROSIS, AND STEATOSIS

Kim Ekroos[1]*, Fredrik Wångsell*[2]*, Martin Rønn Madsen*[3] *and Peter Åkerblad*[2]*, (1)Lipidomics Consulting Ltd., (2) Albireo AB, (3)Gubra*

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

Background: Nonalcoholic steatohepatitis (NASH) is characterized by build-up of fat within liver cells leading to fibrosis, steatosis, and hepatic injury. Inhibition of bile acid (BA) transporters is a potential therapeutic option to treat NASH by restoring lipid homeostasis and reducing inflammatory burden. We investigated the lipidomic modulation of the systemic apical BA transporter inhibitor A3907 in liver and plasma from ob/ob-NASH mice and A3907 phase 1 study subjects and matched this to NASH patients for translational validity. **Methods:** Leptin-deficient ob/ob mice were pre-fed Gubra-Amylin NASH diet, and liver pathology was confirmed by baseline liver biopsy. A3907 or vehicle was given by oral gavage once daily for 4−10 weeks. Lipidomics analyses were performed on mouse liver and plasma and on human plasma from a phase 1 A3907 study in healthy volunteers. **Results:** A3907 showed positive effects on liver weight, fibrosis progression, lobular inflammation, and steatosis scores. NASH leads to elevation of cholesteryl esters (CEs) in liver, which is reversed in a dose-dependent manner by A3907 treatment in ob/ob-NASH mice. After 10 weeks of treatment, liver CE levels dropped 23-fold, reaching concentrations observed in healthy humans. Lipidomics identified a reprogrammed fatty acid (FA) metabolism. In phosphatidyl-choline (PC) and -ethanolamines (PE), the portion of saturated (SFA), diunsaturated (DUFA) and polyunsaturated fatty acids (PUFAs) increased, counterbalanced by a decrease in monounsaturated FAs (MUFAs). A3907-treated animals showed preferences for dietary linoleic acid (FA18:2), activating the omega-6 pathway, leading to elevation of polar and neutral lipid species containing FA18:2 and upstream metabolic products by upregulation of FADS6 and FADS1 genes. The FA metabolic shift is counteracted by decreasing lipid species rich in MUFAs, suggesting that A3907 attenuates utilization of dietary SFAs and omega-9 FAs, supported by downregulation of SCD-1 and ELOVL-1 genes. Similar FA reprogramming was observed in the phase 1 clinical study. **Conclusion:** A3907 administration improves key plasma and liver histological NASH markers and reduces the NASH lipidomic fingerprint. This is triggered by selective FA metabolic reprogramming, restoring liver function by reducing the lipotoxic burden. We identify new mechanisms for treatment of NASH and fibrotic progression and show translational validity by linking effects in animal models with healthy volunteers treated with A3907.

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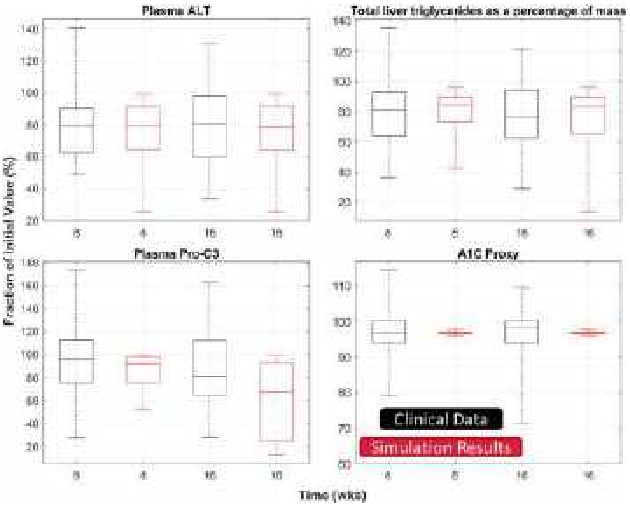
2443-C | ADVANCING THE MULTI-TARGETED MECHANISMS OF ACTION OF A MITOCHONDRIAL ACTIVATOR (AXA-1125) FOR TREATING NASH USING A QUANTITATIVE SYSTEMS PHARMACOLOGY MODEL

Vinal V Lakhani[1], Ming Gao[2], Paul Hinderliter[2], Matthew Russel[2], Karim Azer[2] and Scott Q. Siler[1], (1) Simulations Plus, (2)Axcella Therapeutics

Background: Patients with non-alcoholic steatohepatitis (NASH) do not currently have options for pharmaceutical treatment. AXA-1125 is an endogenous metabolic modulator (EMM), which has shown efficacious potential when administered to patients in early clinical studies. *In vitro* studies and literature review have enumerated several contributing mechanisms of action (MoA's) by which AXA-1125 dosing may be reducing levels of ALT, liver fat, Pro-C3, and HbA1c in patients. To further advance and quantitate the differential multi-targeted mechanisms driving improvements seen in in the clinic, a quantitative systems pharmacology (QSP) model, NAFLDsym, was employed to simulate AXA-1125 under many combinations of candidate MoA's and further substantiate the MoA underlying the clinical benefit observed to date in patients. **Methods:** Clinical trial NCT04073368 was simulated by several software packages. Exposure of AXA-1125 was modeled in Monolix® using a 1-compartment model based on data from a single 22.6 g dose. This model was then used to predict the exposure of multiple doses (24 g BID) for 16 weeks using Simulx®. Separately, various candidate MoA's of AXA-1125 were mechanistically represented in NAFLDsym, including the secretion of incretins (GLP-1 and GIP) and relevant downstream effects, direct reduction of oxidative stress, increased AMPK-responsive enzyme expression, inhibition of hepatic stellate cell activation and proliferation, and decreased TNFα production. Each of these MoA's has the potential to reduce the hepatic lipid burden, lipotoxicity, inflammation and/or fibrosis. NAFLDsym simulations combined the predicted exposure of 24 g BID dosing with various combinations and strengths of candidate MoA's. Simulation results were evaluated against clinical data from a Phase IIa Study (AXA1125-003). **Results:** Simulations with NAFLDsym implicate multiple mechanisms that may be playing a role in the efficacy of AXA-1125. The clinical data were recapitulated in simulations invoking combinations of incretin secretion, and increased AMPK-responsive enzyme expressions. Additional simulations which further invoked direct antioxidant activity, or antioxidant activity and decreased TNFα production, increased fatty acid oxidation, also recapitulated clinical observations. **Conclusion:** NAFLDsym, a QSP model of NAFLD/NASH, was used to investigate the combination of mechanisms playing a role in AXA-1125, a NASH therapeutic candidate. Here, NAFLDsym simulations support the following mechanisms contributing to the clinical response of AXA-1125: incretin effects, AMPK-responsive enzyme expression, antioxidant-mediated reduction of lipotoxicity, and inhibition of TNFα production. This works independently recapitulates previously published MoA findings, including AXA-1125 as a mitochondrial activator, and predicts novel contributions which require additional work to be validated and expanded upon.



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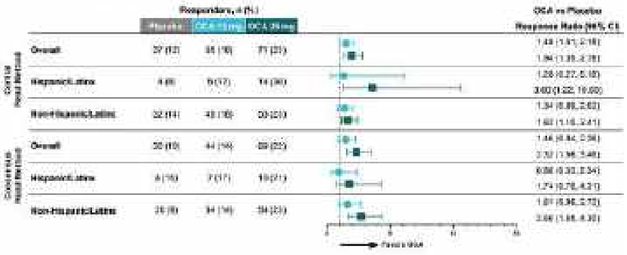
2444-C | ANALYSIS OF HISPANIC/LATINX VS NON-HISPANIC/LATINX SUBGROUPS FROM THE REGENERATE TRIAL OF OBETICHOLIC ACID FOR THE TREATMENT OF NONALCOHOLIC STEATOHEPATITIS

Manal F. Abdelmalek[1], *Lee Feinman*[2], *Jing Li*[2], *Pamela J. Davis*[2], *Amarita Randhawa*[2] *and Julio A. Gutierrez*[3], *(1)Mayo Clinic, Rochester, MN, (2)Intercept Pharmaceuticals, Inc., Morristown, NJ, (3)Verity Medical Foundation*

Background: The prevalence and risk of nonalcoholic steatohepatitis (NASH) is highest in the Hispanic/Latinx (H/L) population. Obeticholic acid (OCA) is a farnesoid X receptor agonist studied as a treatment for pre-cirrhotic liver fibrosis due to NASH. We performed a subgroup analysis of the H/L vs non-H/L populations in the phase 3 REGENERATE trial of OCA in patients with pre-cirrhotic fibrosis due to NASH. **Methods:** Patients with biopsy-confirmed fibrosis stage F2 or F3 were randomized 1:1:1 to once-daily oral placebo, OCA 10 mg, or OCA 25 mg. The primary endpoint of the month 18 interim analysis was improvement in fibrosis e 1 stage with no worsening of NASH by a central or consensus (requiring agreement of 2 out of 3 pathologists) read method using the NASH Clinical Research Network scoring system. Secondary endpoints included change from baseline in serum alanine aminotransferase (ALT) at month 18. Safety was assessed by adverse events. **Results:** Of 931 patients in the intent-to-treat (ITT) population, 141 (15.1%) were H/L. Based on the central read, improvement in fibrosis e 1 stage with no worsening of NASH occurred in 8%, 12%, and 30% of H/L patients vs 14%, 18%, and 23% in the non-H/L patients receiving placebo, OCA 10 mg, and OCA 25 mg, respectively. The magnitude of the response ratios was similar to those observed in the overall ITT population and the consensus read methodology (Figure 1). Despite variability due to the small sample size of the H/L subgroup, the response ratio favored OCA 25 mg compared to placebo (3.60; 95% CI, 1.22–10.60), while a diminished response rate was seen in the non-H/L (1.62; 95% CI, 1.10–2.41). The mean change (SE) from baseline in ALT levels at month 18 in the H/L subgroup was -24.4 [11.4], -10.4 [5.2], and -50.9 [10.7] for placebo, OCA 10 mg, and OCA 25 mg, respectively, compared to -15.2 [3.6], -27.5 [3.0], and -32.1 [3.8], respectively, in the non-H/L subgroup. **Conclusion:** Among the H/L patients, the histological response to OCA was similar to the non-H/L population and consistent with the overall ITT population based on the central read. A larger placebo effect was also noted for the change in ALT levels in the H/L subgroup, as well as a greater reduction from baseline with OCA 25 mg compared to the non-H/L subgroup. The improvement in fibrosis e 1 stage with no worsening of NASH and reduction in ALT support the efficacy of OCA in this high-risk group of patients with pre-cirrhotic fibrosis due to NASH.

Figure 1. Improvement in fibrosis ≥1 stage with no worsening of NASH in Hispanic/Latinx vs non-Hispanic/Latinx patients in the REGENERATE trial



"No worsening of NASH" was defined as no worsening of hepatocellular ballooning grade, no worsening of lobular inflammation grade, and no worsening of steatosis grade.

Abbreviations: CI, confidence interval; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid.

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2445-C | ANTI-INFLAMMATORY AND ANTI-FIBROTIC EFFECTS BY SIMULTANEOUS ACTIVATION OF GLUCAGON, GIP, AND GLP-1 OF EFOCIPEGTRUTIDE (HM15211) IN THIOACETAMIDE-INDUCED MOUSE MODEL OF LIVER INJURY AND FIBROSIS

Jung Kuk Kim, Yohan Kim, Hyunjoo Kwon, Eun Jin Park, Jeong A Kim, Sang Hyun Park, Sungmin Bae, Daejin Kim, Sang Hyun Lee and In Young Choi, Hanmi Pharm. Co., Ltd.

Background: Despite of increase in number of fibrosis due to NASH which becomes a major cause of liver-related outcomes, no approved drug is available. Recently, potential benefit of incretins such as glucagon (GCG), GIP and GLP-1 beyond metabolism has been proposed especially in inflammation and fibrosis. Thus, to optimally implement these incretins, efocipegtrutide, a long-acting GCG/GIP/GLP-1 triple agonist (HM15211), was developed. Here, we evaluated and compared the therapeutic effects of efocipegtrutide with available incretin drugs in TAA (thioacetamide)-induced liver injury and fibrosis mouse. **Methods:** TAA was interperitoneally injected to mouse for 12 weeks to induce liver injury and fibrosis, and efocipegtrutide was administered during last 10 weeks. Semaglutide and tirzepatide were included as comparative controls. At end of treatment, hepatic hydroxyproline content was measured and the liver tissues were subjected to H&E and Sirius red staining followed by histological grading. qPCR and ELISA were performed to evaluate relevant hepatic and blood bio-markers. **Results:** Efocipegtrutide treatment was associated with significant reduction of hepatic hydroxyproline content (231.9 nmol/g vs. 350.4 nmol/g for TAA, vehicle; $p < 0.001$) while that of semaglutide (322.5 nmol/g) or tirzepatide (322.1 nmol/g) had minor effects. Similarly, treatment of efocipegtrutide (0.83 %, $p < 0.001$), significantly reduced Sirius red positive area (vs. 5.75 % for TAA, vehicle), unlike neither semaglutide (4.93 %) nor tirzepatide (3.61 %). To further confirm the potential benefit of efocipegtrutide, histological grading was conducted by using Sirius red and H&E staining, in which efocipegtrutide (1.29, 1.00 vs. 3.00, 3.00 for TAA, vehicle) exhibited greater reduction effects on both fibrosis and portal inflammation score compared to semaglutide (2.14, 2.71) or tirzepatide (2.00, 2.57). Consistent with such histologic analysis, expression of hepatic marker genes for fibrosis and inflammation were significantly/numerically reduced only in efocipegtrutide group. Significant reduction in blood TIMP-1 level was also observed. **Conclusion:** Efocipegtrutide effectively improved liver inflammation and fibrosis in TAA mice. Notably, greater improvement effect over semaglutide and tirzepatide highlights the potential benefit of simultaneous use of GCG, GIP, and GLP-1. Thus, efocipegtrutide could be a novel therapeutic option for fibrosis due to NASH. Phase 2b study is ongoing to assess the clinical relevance of these findings.

Disclosures: Jung Kuk Kim – Hanmi Pharm. Co., Ltd.: Employee, No, No;

Disclosure information not available at the time of publication: Yohan Kim, Hyunjoo Kwon, Eun Jin Park, Jeong A Kim, Sang Hyun Park, Sungmin Bae, Daejin Kim, Sang Hyun Lee, In Young Choi

2446-C | CHARACTERIZATION OF SENESCENT HEPATOCYTE IDENTIFIED NOVEL SENOLYTICS FOR NAFLD TREATMENT

Kuo Du[1], Liuyang Wang[1], Ji Hye Jun[1], Raquel Maeso Díaz[2], Rajesh Kumar Dutta[2], Seh-Hoon Oh[2], Pan Christopher[1], Dennis Ko[1], Xiao-Fan Wang[1] and Anna Mae Diehl[2], (1)Duke Universty, NC, (2)Duke University

Background: NAFLD is rapidly becoming the leading cause of chronic liver disease worldwide. Recent studies demonstrated that senescent hepatocytes accumulate in human NAFLD and correlate with adverse outcomes. However, the characteristics of senescent hepatocytes have not been defined, and it is unclear if/how the senescent phenotype itself affects NAFLD progression. Our study aimed to characterize senescent hepatocytes and identify novel therapeutic targets for NAFLD treatment. **Methods:** We performed RNA-seq and histological analysis on liver biopsies from NAFLD patients to evaluate senescence and correlate it with NAFLD severity. We also induced senescence in hepatocytes using AAV-TBG-p16 vectors in mice and CDK4/6 inhibitor in Huh7 cells, and compared the senescent hepatocyte transcriptome to human NAFLD to evaluate the clinical relevance of these models. The paracrine effects of senescent hepatocytes were studied by harvesting conditional medium and placing it onto proliferating hepatocytes, HSCs, macrophages, and LSECs. We also performed bioactive chemical library screening to identify novel senolytic hits, which were further validated in vitro and in mouse models of NAFLD. **Results:** Senescent markers and gene signatures were upregulated in human NAFLD and positively correlated with disease severity. Transcriptome analysis of senescent hepatocytes revealed a reduced liver-specific gene signature, while gene signatures associated with inflammation and fibrosis were highly upregulated, indicating a pathogenic role of senescent hepatocytes in NAFLD development. The transcriptomes of senescent hepatocytes overlapped with the differentially expressed gene profiles from NAFLD patients, distinguished NAFLD patients from healthy controls, and identified advanced fibrosis from mild fibrosis. The conditioned medium from senescent hepatocytes induced secondary senescence in proliferating hepatocytes and promoted HSC fibrogenesis, macrophage activation, and LSEC capillarization. Bioactive chemical library screening identified multiple senolytic candidates, some of which demonstrated therapeutic potential in mouse models of NAFLD. **Conclusion:** Our study suggests that hepatocyte senescence is a central pathogenic mechanism of NAFLD development, and we identified novel senolytics for NAFLD treatment. These findings provide a foundation

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

for future studies to exploit cellular senescence as a therapeutic strategy to treat liver diseases, including NAFLD.

Disclosures: Anna Mae Diehl – Inventiva: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Tune Therapeutics: Advisor, No, No; NGM: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Hanmi: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; TARGET-NASH: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boehringer-Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Hepta Bio: Advisor, No, No;

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Disclosure information not available at the time of publication: Liuyang Wang, Pan Christopher, Dennis Ko, Xiao-Fan Wang

2447-C | COMBINATORY TREATMENT WITH MIR-22 ASO AND GLP-1 RA INCREASES POSITIVE OUTCOMES ON BODY WEIGHT AND LIVER PARAMETERS IN THE GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF NASH

Riccardo Panella[1,2], Simone Tomasini[1], Michael Feigh[3] and Sakari Kauppinen[1], (1)Aalborg University, (2) Resalis Therapeutics, (3)Gubra Aps

Background: miR-22 was identified as a crucial controller of lipid homeostasis, hepatic steatosis and inflammation. Both genetic and pharmacological inhibition are very effective in reducing body weight and increasing liver health in mouse and non-human primate models. Interestingly, unlike GLP-1 RA, the therapeutic effect of miR-22 inhibition is completely independent from food intake. Our hypothesis is that GLP-1 RA and miR-22 inhibition have two orthogonal mechanisms of action and they can cooperate leading to an increase of the positive effects observed with GLP-1 RA monotherapy **Methods:** Male C57BL/6 mice were fed the GAN diet high in fat, fructose and cholesterol for 38 weeks prior to study start. A liver biopsy was sampled 4 weeks prior to study start. Only animals with biopsy-confirmed NAFLD Activity Score (NAS e 5) and fibrosis stage e F1 were included and stratified into treatment groups. Mice were administered vehicle (n = 18) or Semaglutide (30 nM/kg, n = 18) or Semaglutide and anti-sense oligonucleotide targeting miR-22 (30nM/kg daily; 10mg/kg weekly n = 18) for 24 weeks. Mouse body weight was measured daily and histopathological pre-to-post individual assessment of NAS and fibrosis stage was performed to evaluate the effect of combinatory treatment. Other terminal endpoints in GAN DIO-NASH mice included quantitative liver histology, blood and liver biochemistry. **Results:** Combining GLP-1 RA and miR-22 pharmacological inhibition we prove that those 2 compounds have a strong synergetic effect with a resultant effect of doubling the number of mice that lost at least 20% of their initial body. Moreover our combinatory treatment was preventing the rebound in body weight observed in GLP-1 RA monotherapy. Importantly severe liver parameters (NAFLD, steatosis, lobular inflammation scores) show better improvement in the combinatory group compared to monotherapy **Conclusion:** Our combinatory therapeutic approach was also able to improve the positive effect on body weight and liver parameters already achieved with GLP-1 RA. Combination of GLP-1 RA and miR-22 inhibition was able to prevent the rebound in body weight observed in GLP-1 RA monotherapy, improving the overall effect of GLP-1 RA monotherapy on metabolism while being very well tolerated. Those data are paving the way to the first combinatory treatment for obesity and NAFLD based on targeting a non-coding RNA.

Disclosures: Michael Feigh – Gubra: Employee, Yes, No; Gubra: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No; Gubra: Executive role , Yes, No;

The following people have nothing to disclose: Riccardo Panella, Simone Tomasini, Sakari Kauppinen

2448-C | CVI-2742, A LIVER-DIRECTED AND POTENT THR-BETA SELECTIVE AGONIST, DEMONSTRATES STRONG EFFICACIES IN REDUCING PLASMA CHOLESTEROL AND HEPATIC LIPIDS WITH DESIRABLE TISSUE DISTRIBUTIONS

Jingwen Liu and Zhenyu Wang, CVI Pharmaceuticals Shanghai Limited

Background: Non-alcoholic steatohepatitis (NASH) is characterized by liver steatosis, inflammation, and hepatocyte ballooning with varying degrees of fibrosis. Selective activation of thyroid hormone receptor-beta (THR-β) in liver tissue ameliorates NASH symptoms without causing cardiac abnormalities mediated by THR-α activation. Since THR-β is also expressed in several non-hepatic tissues, penetration of a THR-β agonist into extra hepatic tissues could induce unwanted side effects. Applying a two-step new screening method that combines THR mediated reporter activation assay and an active membrane transporter assay we have discovered a series of novel compounds including CVI-2742 that are liver-directed and potent THR-β selective agonists with EC_{50} in low nmol concentrations. Here we investigated the potency and liver-selectivity of CVI-2742 in biochemical assays and assessed its *in vivo* efficacy and tissue distribution in a hyperlipidemic mouse model. **Methods:** TRE-Luc reporter assays were conducted in HEK293A cells in the presence of THR-β expressing plasmid and a plasmid expressing human hepatic transporter OATP1B1 or a control plasmid pCI-Neo. Mice fed a diet containing 1% cholesterol and 0.5% cholic acid for 3 weeks received vehicle, or CVI-2742 at varying doses (0.5 mkg, 1 mkg and 5 mkg) for 7 days by oral gavage once a day. On day 8, animals were euthanized and blood and tissue samples of heart, brain and liver were collected for biochemical assays and LCMS/MS analysis of CVI-2742. Hepatic and cardiac gene expressions were analyzed by quantitative RT-PCR. **Results:** In the absence of OATP1B1, CVI-2742 activated THR-β with 81% T3 maximal activity at 552 nM EC_{50}, whereas with OATP1B1 being expressed, CVI-2742 activated THR-β with 90% T3 maximal activity at 59 nM EC_{50}, representing a 9.3-fold activity enhancement. In hyperlipidemic mice, compared to baseline, CVI-2742 dose-dependently reduced serum TC by 57% to 75% and TG by maximal 56% after 7-day treatment. Liver TG was reduced to a maximal level of 50% of vehicle control. Serum levels of ALT, AST, TSH and glucose were similar between vehicle and treatment groups. Hepatic mRNA levels of malic enzyme 1 were dose-dependently increased by CVI-2742 whereas mRNA levels of THR-α regulated genes Myh6 and Atp2a2 in heart tissues remained unchanged. Importantly, CVI-2742 were not detected in brain and were showed negligible levels in blood and heart but it was highly concentrated in livers. In mice treated with high dose (5 mpk) of CVI-NP2742, the compound liver to heart partition ratio is 65.5 and liver to plasma ratio is 60, which is superior to reported data from other THR-β agonists under clinical development. **Conclusion:** CVI-2742 is a liver-directed and highly potent THR-β selective agonist *in vitro* and *in vivo*. These preclinical data warrant further investigation of CVI-2742 as a potential treatment for NASH.

Disclosures: Jingwen Liu – CVI Pharmaceuticals Shanghai Limited: Employee, Yes, No;

Zhenyu Wang – CVI Pharmaceuticals Shanghai Limited: Employee, Yes, Yes;

2449-C | CYSTAMINE D4 IMPROVES LIVER INFLAMMATION AND FIBROSIS IN A MURINE MODEL OF FIBROSING STEATOHEPATITIS

Ola Leszczynska, Benedikt Kaufmann, Thibault Alle, Christian Stoess, Hana Sung, Andrea D. Kim, Chelsea Tran, Agustina Reca, Carlo Ballatore, Ranjan Dohil and Ariel E. Feldstein, University of California, San Diego

Background: The development of NASH is greatly influenced by increased oxidative stress, resulting in excessive formation of reactive oxygen species. In this context, glutathione represents a component of antioxidant defense in the liver. Cysteamine supports glutathione synthesis and ameliorates oxidative stress. Further, we developed a deuterated derivative of cystamine to investigate its possible utility as a treatment for NASH. **Methods:** Mice were fed an L-amino acid-defined, high fat diet (CDAAHF) consisting of 60 kcal% fat and 0.1% methionine by weight or control diet for 10 weeks. At 6 weeks of the CDAAHF diet, mice underwent daily gavage for 4 weeks with drug 2 (D2, di-deuterated cystamine) or drug 4 (D4, tetra-deuterated cystamine) in single gavage 200 mg/kg bodyweight. The liver and blood readouts were investigated at 4 weeks post gavage by Western Blot, qPCR, and histological analysis. **Results:** Tissue section quantification revealed a decreased rate of apoptotic staining in D4 gavaged mice when compared to control mice (0.47 ± 0.2 vs 0.13 ± 0.08; 0.16 ± 0.11[%] Positive Area (PA), p d 0.0001). qPCR analysis of mRNA levels of Cxcl1, Ccl9 were significantly decreased in mice gavaged with D4 (0.4-Fold Change (FC), p d 0.0001; 0.6FC, p d 0.05) and D2 (0.4FC, p d 0.01; 0.6FC, p d 0.05) as compared to control animals with concomitant decrease of infiltrating inflammatory cells positive for Ly6c (0.3FC, p d 0.001; 0.1FC, p d 0.0001), and resident cells positive for F4/80 (0.8FC, p d 0.05; 0.8FC, p d 0.001). However, TNF-α mRNA levels were only downregulated in D4 gavaged mice, suggesting greater anti-inflammatory role of D4 over D2 (0.8FC, p d 0.01). Liver fibrosis development was ameliorated in D4 gavaged mice followed by

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

decreased levels of Picrosirius Red staining and mRNA downregulation of Col1a. α-SMA protein levels were significantly lower (2.7[%] PA vs control 4.8[%] PA, p d 0.01), indicating a decrease in hepatic stellate cell activation in D4 gavaged mice. The protein levels of 4HNE (4-hydroxyneonate) were significantly reduced in D4-gavage mice compared to D2 and controls (0.9FC vs 2.5FC, p d 0.05), which suggests D4 plays a role in reduction of oxidative stress in the liver. **Conclusion:** Our studies demonstrate that in the CDAAHF mouse model, compound efficacy increases proportionally with the deuterium content, with D4 being most active. These results show that deuterated cysteamine/cystamine derivatives reduce hepatocyte cell death, liver inflammation, and compensatory proliferation, which holds considerable promise to treat NASH.

Disclosures: Ariel E. Feldstein – Novo Nordisk: Executive role , No, No;

The following people have nothing to disclose: Ola Leszczynska, Benedikt Kaufmann, Thibault Alle, Christian Stoess, Hana Sung, Andrea D. Kim, Chelsea Tran, Agustina Reca, Carlo Ballatore, Ranjan Dohil

2450-C | ECG QT INTERVAL CHANGES IN COMPENSATED NASH LIVER CIRRHOSIS WITH PORTAL HYPERTENSION. EXPERIENCE WITH BELAPECTIN, A GALECTIN-3 INHIBITOR

Pol Boudes, Steven Schoenfeld and Ezra Lowe, Galectin Therapeutics

Background: Liver cirrhosis is associated with prolonged QT/QTc intervals on ECG (> 450 ms in males and 460 ms in females)[1]. However, limited data are available in patients with compensated cirrhosis and portal hypertension (PH) and the clinical relevance of this QT increase is not well known. We describe QT/QTc intervals and clinical status of patients in a phase 2b, randomized trial (NCT 02462967) evaluating the safety and efficacy of belapectin, a galectin-3 inhibitor, in patients with Non-Alcoholic SteatoHepatitis (NASH) cirrhosis and PH. **Methods:** NASH cirrhosis was confirmed by histology. PH was established with a hepatic venous pressure gradient of at least 6 mm Hg. Patients on non-selective beta-blockers, with previous cirrhosis decompensation, medium or large size varices, a MELD e 15, or a Child-Pugh stage B or C, were excluded from the study. There was no eligibility restriction on QT/QTc duration. Patients received biweekly infusions of belapectin 2 mg/kg of lean body mass (LBM), belapectin 8 mg/kg of LBM, or placebo for 52 weeks. 12-lead electrocardiogram were done at screening, on treatment (7th infusion), and post treatment at week 57. QTc used the Bazett's correction. Screening, QTc changes, and increases above relevant thresholds are presented. Correlation between on-treatment QTc changes and belapectin plasma concentrations was explored (7th infusion). Adverse events (AE) and Serious AEs potentially associated with QTc prolongation (syncope, ventricular arrythmia including torsades de pointe, sudden death) were evaluated. **Results:** QTc intervals and changes are presented in the table. None of the QTc elevations were considered clinically relevant by Principal Investigators. There was no apparent correlation between belapectin plasma levels and changes in QTc. Across treatment groups, there were no treatment-emergent AEs that could be linked to a prolonged QT. **Conclusion:** QT/QTc prolongation is frequent in compensated cirrhosis with portal hypertension but does not appear symptomatic. In this study belapectin did not appear to be associated with adverse events related to QTc prolongation. 1 Bernardi, et al. Hepatology 1998;27:28-34

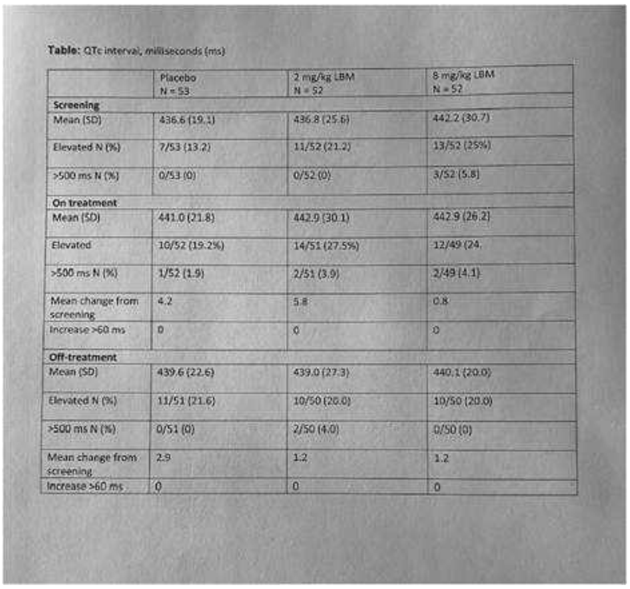


Table: QTc interval, milliseconds (ms)

	Placebo N = 53	2 mg/kg LBM N = 52	8 mg/kg LBM N = 52
Screening			
Mean (SD)	436.6 (19.1)	436.8 (25.6)	442.2 (30.7)
Elevated N (%)	7/53 (13.2)	11/52 (21.2)	13/52 (25%)
>500 ms N (%)	0/53 (0)	0/52 (0)	3/52 (5.8)
On treatment			
Mean (SD)	441.0 (21.8)	442.9 (30.1)	442.9 (26.2)
Elevated	10/52 (19.2%)	14/51 (27.5%)	12/49 (24.
>500 ms N (%)	1/52 (1.9)	2/51 (3.9)	2/49 (4.1)
Mean change from screening	4.2	5.8	0.8
Increase >60 ms	0	0	0
Off-treatment			
Mean (SD)	439.6 (22.6)	439.0 (27.3)	440.1 (20.0)
Elevated N (%)	11/51 (21.6)	10/50 (20.0)	10/50 (20.0)
>500 ms N (%)	0/51 (0)	2/50 (4.0)	0/50 (0)
Mean change from screening	2.9	1.2	1.2
Increase >60 ms	0	0	0

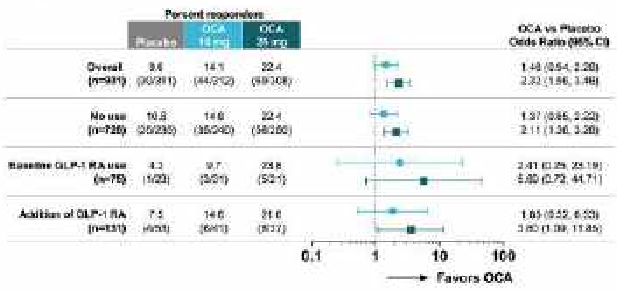
Disclosures: The following people have nothing to disclose: Pol Boudes, Steven Schoenfeld, Ezra Lowe

2451-C | EFFECT OF CONCOMITANT GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS FROM THE REGENERATE TRIAL OF OBETICHOLIC ACID FOR THE TREATMENT OF PRE-CIRRHOTIC FIBROSIS DUE TO NONALCOHOLIC STEATOHEPATITIS

Kris V. Kowdley[1], Amarita Randhawa[2], Jing Li[2], Hiral Patel[2], Christopher Gasink[2], Sangeeta Sawhney[2] and Scott Isaacs[3], (1)Liver Institute Northwest, (2)Intercept Pharmaceuticals, Inc., Morristown, NJ, (3)Emory University School of Medicine

Background: Type 2 diabetes mellitus (T2D) is a common comorbidity associated with nonalcoholic steatohepatitis (NASH). Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are often-prescribed treatments for T2D and are also being investigated as NASH treatments. Obeticholic acid (OCA) is a farnesoid X receptor (FXR) agonist and antifibrotic agent studied as a treatment for pre-cirrhotic liver fibrosis due to NASH, which may often be used with GLP-1 RA. Herein, we assess the efficacy and safety of coadministration of OCA and GLP-1 RA in the phase 3 REGENERATE trial. **Methods:** In this phase 3 multicenter, randomized, double-blind, placebo-controlled study, subjects were randomized 1:1:1 to receive once-daily oral placebo, OCA 10 mg, or OCA 25 mg. The primary histological endpoint of the month 18 interim analysis (intent-to-treat [ITT], n = 931) was improvement in fibrosis ≥1 stage with no worsening of NASH using the NASH Clinical Research Network criteria. Safety was assessed in a larger population (n = 2477). **Results:** In the ITT population, 75 (8.1%) were on a GLP-1 RA for T2D at baseline, and 131 (14.1%) began a GLP-1 RA after the first dose of study drug. Concomitant use of GLP-1 RA was generally balanced across treatment arms. The percentage of subjects receiving OCA 25 mg that achieved the primary endpoint was 23.8% among those with baseline GLP-1 RA use, 21.6% of those who added a GLP-1 RA, and 22.4% in the overall ITT population, compared to 4.3%, 7.5%, and 9.6% receiving placebo, respectively (Figure 1). In the larger safety population, GLP-1 RA use was balanced across treatment arms, with 232 (9.4%) subjects on a GLP-1 RA at baseline and 422 (17.0%) beginning a GLP-1 RA during the trial. The incidence of pancreatitis was numerically higher among those on a GLP-1 RA (2.7% placebo, 1.2% OCA 10 mg, 1.3% OCA 25 mg) compared with the overall safety population (0.8% placebo, 0.6% OCA 10 mg, 1.0% OCA 25 mg). The use of GLP-1 RA in patients treated with OCA was not associated with additional biliary complications. **Conclusion:** Among patients with concomitant GLP-1 RA use and pre-cirrhotic fibrosis due to NASH in REGENERATE, OCA showed consistent efficacy in fibrosis improvement. There were no notable differences in the safety profile of OCA with GLP-1 RA use.

Figure 1. Improvement in fibrosis ≥1 stage with no worsening of NASH in subjects on a GLP-1 R agonist at baseline or began a GLP-1 R agonist after the first dose of study drug



"No worsening of NASH" was defined as no worsening of hepatocellular ballooning grade, no worsening of lobular inflammation grade, and no worsening of steatosis grade.

Abbreviations: CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid.

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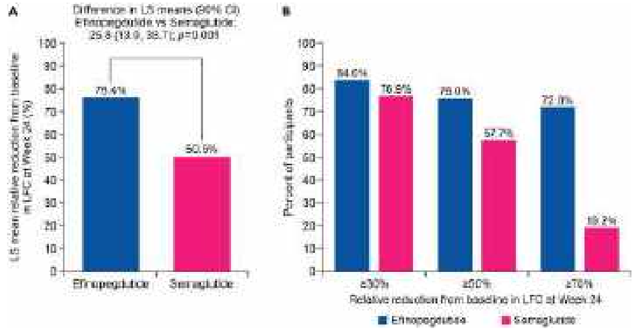
The following people have nothing to disclose: Scott Isaacs

2452-C | EFFICACY AND SAFETY OF EFINOPEGDUTIDE IN HISPANIC PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE: RESULTS FROM AN ACTIVE COMPARATOR-CONTROLLED STUDY

Manuel Romero-Gómez[1], Eric Lawitz[2], R. Ravi Shankar[3], Raymond L.H. Lam[3], Jianxin Lin[3], Keith D. Kaufman[3] and Samuel S. Engel[4], (1)Ucm Digestive Diseases, Virgen Del Rocio University Hospital, Instituto De Biomedicina De Sevilla, Ciberehd, University of Seville, Sevilla, Spain, (2)Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX, USA, (3)Merck & Co., Inc., Rahway, NJ, USA, (4) Global Clinical Development, Merck & Co., Inc., Rahway, NJ, USA

Background: Hispanic (HISP) patients have been reported to have a higher prevalence and severity of nonalcoholic steatohepatitis (NASH) compared to other ethnicities in the USA. We reported robust relative reductions from baseline (RRFB) in liver fat content (LFC) in a broad population of subjects with nonalcoholic fatty liver disease (NAFLD) in a study of efinopegdutide (EFI), a GLP-1/glucagon receptor coagonist, relative to the selective GLP-1 receptor agonist, semaglutide (SEMA). Here, we report RRFB in LFC in the HISP subgroup from this study. **Methods:** In this randomized, active comparator-controlled, open-label study, 145 subjects with NAFLD (18-70 y, BMI 25-50 kg/m^2, stable body weight, without T2DM or with T2DM with an A1C d 8.5% controlled by diet ± stable dose of metformin) and LFC e 10% (measured by MRI PDFF) at screening were randomized 1:1 to EFI 10 mg QW or SEMA 1.0 mg QW (titrated to target doses over 8 weeks) for 24 weeks. The primary efficacy endpoint was the least squares (LS) mean RRFB in LFC (%) at Week 24. **Results:** Among randomized subjects, 25 in the EFI group and 26 in the SEMA group were HISP. In the HISP subgroup, baseline characteristics were generally similar in the two treatment groups. Subjects were predominantly female (58.8%), < 65 years of age (88.2%, mean age: 51.6 y), white (90.2%), and obese (90.2%, mean weight: 96.3 Kg, mean BMI: 36.1 kg/m^2). Mean LFC at baseline was 22.3% in the EFI group and 19.9% in the SEMA group. The LS mean RRFB in LFC at Week 24 was significantly (p = 0.001) greater with EFI (76.4% [90% CI 67.1, 85.7]) than SEMA (50.5% [41.8, 59.3]) (figure). Median RRFB in LFC at Week 24 was 86.6% with EFI and 52.4% with SEMA. More subjects had RRFB in LFC at Week 24 of e 30%, e 50% and e 70% with EFI (84.0%, 76.0% and 72.0%, respectively) than SEMA (76.9%, 57.7% and 19.2%, respectively) (figure). After 24 weeks, 72% in the EFI group had a normal LFC (< 5%) compared with 26.9% in the SEMA group. LS mean RRFB in weight at Week 24 was similar in both groups (EFI 8.1% vs SEMA 7.3%, p = 0.516). In this HISP subgroup there were no meaningful differences between the two treatment groups in the incidences of adverse events (AEs) reported. **Conclusion:** In HISP patients with NAFLD, EFI 10 mg weekly led to a significantly greater reduction in LFC than SEMA 1 mg weekly, with a similar reduction in weight and a comparable incidence of AEs.



Disclosures: Manuel Romero-Gómez – AbbVie, Alphasigma, Allergan, AstraZeneca, Axcella, BMS, Boehringer-Ingelheim, Gilead, Intercept, Inventia, Kaleido, MSD, Novo-Nordisk, Pfizer, Prosciento, RubiÃ³, Siemens, Shionogi, Sobi, and Zydus: Advisor, Yes, No; Gilead, Intercept, Siemens; co-inventor of Hepamet Fibrosis Score, DeMILI, and DeMILI 3.0: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;

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Jianxin Lin – Merck & Co., Inc.: Employee, Yes, No; Merck & Co., Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Keith D. Kaufman – Merck & Co., Inc.: Employee, Yes, No; Merck & Co., Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Samuel S. Engel – Merck & Co., Inc.: Employee, No, No; Merck & Co., Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

2453-C | EFFICACY OF EFINOPEGDUTIDE IN NONALCOHOLIC FATTY LIVER DISEASE: SUBGROUP ANALYSES FROM AN ACTIVE-COMPARATOR-CONTROLLED STUDY

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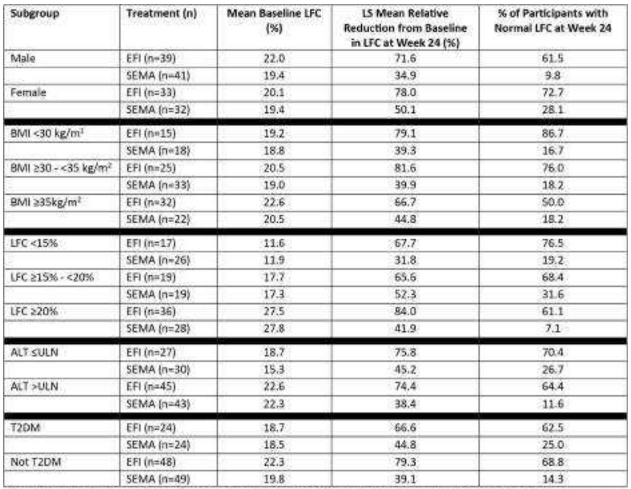
Background: Efinopegdutide (EFI), a GLP-1/glucagon coagonist with ~2:1 GLP-1/glucagon receptor potency, has been shown to provide substantial reduction (72.7%) in liver fat content (LFC) compared to the selective GLP-1 receptor agonist semaglutide (SEMA; 42.3%) in a broad population of subjects with nonalcoholic fatty liver disease (NAFLD), with ~67% (EFI) vs ~18% (SEMA) achieving a normal LFC of < 5%. To further understand subject characteristics that might influence treatment response, we assessed the effects of EFI relative to SEMA on LFC in subgroups of patients from that study. **Methods:** In a Phase 2a, randomized, active-comparator-controlled, parallel-group, open-label study in subjects with NAFLD (18-70 y, body mass index [BMI] 25-50 kg/m^2, stable body weight, without type 2 diabetes [T2DM], or with T2DM with an A1C d 8.5% controlled by diet ± stable dose of metformin), participants with an LFC of e 10% were randomized in a 1:1 ratio to SC EFI 10 mg QW or SC SEMA 1 mg QW for 24 weeks. Both drugs were titrated to the target dose over an 8-week period. The primary efficacy endpoint was the least squares (LS) mean relative reduction from baseline in LFC (%) after 24 weeks of treatment. Subgroup analyses were performed based on the following baseline characteristics – gender, BMI, LFC, alanine aminotransferase (ALT), and presence of T2DM. **Results:** Mean baseline LFC tended to be higher in higher BMI, higher ALT and nondiabetic subgroups (TABLE); no notable difference was seen by gender. LS mean relative reductions in LFC, and between-group differences, in these subgroups were generally consistent with those observed in the overall cohort. Participants in the higher baseline LFC subgroups had greater LS mean relative reductions in LFC but were less likely to achieve an LFC < 5%, compared to the lower baseline LFC subgroup. **Conclusion:** In patients with NAFLD, treatment with EFI 10 mg weekly led to greater reductions in LFC, compared to semaglutide 1 mg weekly, across subgroups defined by demographic and disease-related baseline characteristics.



Subgroup	Treatment (n)	Mean Baseline LFC (%)	LS Mean Relative Reduction from Baseline in LFC at Week 24 (%)	% of Participants with Normal LFC at Week 24
Male	EFI (n=39)	22.0	71.6	61.5
	SEMA (n=41)	19.4	34.9	9.8
Female	EFI (n=33)	20.1	78.0	72.7
	SEMA (n=32)	19.4	50.1	28.1
BMI <30 kg/m^2	EFI (n=15)	19.2	79.1	86.7
	SEMA (n=18)	18.8	39.3	16.7
BMI ≥30 - <35 kg/m^2	EFI (n=25)	20.5	81.6	76.0
	SEMA (n=33)	19.0	39.9	18.2
BMI ≥35kg/m^2	EFI (n=32)	22.6	66.7	50.0
	SEMA (n=22)	20.5	44.8	18.2
LFC <15%	EFI (n=17)	11.6	67.7	76.5
	SEMA (n=26)	11.9	31.8	19.2
LFC ≥15% - <20%	EFI (n=19)	17.7	65.6	68.4
	SEMA (n=19)	17.3	52.3	31.6
LFC ≥20%	EFI (n=36)	27.5	84.0	61.1
	SEMA (n=28)	27.8	41.9	7.1
ALT ≤ULN	EFI (n=27)	18.7	75.8	70.4
	SEMA (n=30)	15.3	45.2	26.7
ALT >ULN	EFI (n=45)	22.6	74.4	64.4
	SEMA (n=43)	22.3	38.4	11.6
T2DM	EFI (n=24)	18.7	66.6	62.5
	SEMA (n=24)	18.5	44.8	25.0
Not T2DM	EFI (n=48)	22.3	79.3	68.8
	SEMA (n=49)	19.8	39.1	14.3

BMI, body mass index; LFC, liver fat content; ALT, alanine aminotransferase; ULN, upper limit of normal; T2DM, type 2 diabetes mellitus.

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2454-C | EVOLUTION OF LIVER FIBROSIS IN TYPE 2 DIABETIC PATIENTS WITH NAFLD IN A FOLLOW-UP STUDY: POSSIBLE HEPATOPROTECTIVE EFFECTS OF SODIUM-GLUCOSE CO-TRANSPORTER-2 INHIBITORS

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Background: Subjects with non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) present high progression of liver disease to fibrosis, which is the main determinant of long-term adverse outcomes. Data are accumulating on the benefits of sodium glucose cotransporter 2 inhibitors (SGLT-2i) on hepatic fibrosis mainly in pharmacologic or retrospective studies. Aim: to prospectively evaluate change in hepatic disease in patients with NAFLD and T2DM and predisposing factors, with particular regard to SGLT-2i. **Methods:** 237 T2DM outpatients (mean age 67 ±9 y, 54% male) were enrolled at the diabetology outpatient clinics and re-evaluated after 52 + 10 months. At baseline and follow-up information about diabetic control, metabolic comorbidities and medications were collected. NAFLD and liver fibrosis (LSM) were detected by ultrasonography and Fibroscan®. **Results:** During follow-up an increase in LSM (6.0 ± 2.8 vs 5.8 ± 2.7 kPa, $p = 0.02$) was registered, despite stability of diabetic control. LSM worsened in 133(56%) subjects, 92 (39%) having a worsening > 10% from baseline. At the end of follow-up, a higher prescription of SGLT2i was seen (20% vs 6%, $p < 0.001$). Patients with worsening versus non worsening of LSM had higher prevalence of increase in BMI during follow-up (45% vs 32%, $p = 0.06$), lower SGLT2i prescription (15% vs 27%, $p = 0.034$) and higher of sulfonylureas (23%vs 11%, $p = 0.016$). In multivariate

analysis adjusted for age, sex, liver enzymes, HbA1c and weight gain, use of SGLT2-inhibitors at follow-up was independently associated with a reduced risk of worsening of LSM (HR 0.34, 95% CI 0.13-0.88), even when considered > 10% from baseline. No impact of sulfonylureas was observed. **Conclusion:** Despite a high prevalence of fibrosis progression in NAFLD subjects with T2DM, we showed a potential effect of SGLT2-inhibitors in reducing the risk of worsening of liver stiffness. Therefore, our data suggest that using this category of antidiabetic drug in NAFLD patients may prevent progression of fibrosis, especially if weight control is obtained in these patients.

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2455-C | EXPLORING THE THERAPEUTIC POTENTIAL OF PROSTAGLANDIN E2 EP4 RECEPTOR TARGETING IN HEPATIC FIBROSIS

Michael Schou Jensen[1], Ke Luo[2], Ann Catrine Daugaard Mikkelsen[1], Karen Louise Thomsen[3], Rajeshwar P. Mookerjee[1], Peter Olinga[2], Rikke Nørregaard[1] and Henricus Antonius Maria Mutsaers[1], (1)Aarhus University, (2)University of Groningen, (3) University College London

Background: Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease globally, affecting approximately one-quarter of the world's adult population. NAFLD occurs as a spectrum from simple steatosis to non-alcoholic steatohepatitis (NASH), a more severe condition marked by steatosis, inflammation, hepatocyte injury (ballooning), and in advanced cases, fibrosis. In patients with NASH, hepatic fibrosis is the main determinant of mortality. However, no approved treatments are available currently, and liver transplantation remains the only curative option for most patients. Our previous studies have shown that modulating PGE2 receptor activity can attenuate renal fibrosis, prompting the investigation of its therapeutic potential in a hepatic context. Thus, we evaluated the anti-fibrotic potential of rivenprost, a PGE2 EP4 receptor agonist, in rat and human fibrotic precision-cut liver slices (PCLS). **Methods:** PCLS were prepared from either NASH rats, which received a high-fat, high-cholesterol diet for 16 weeks, or explanted cirrhotic livers of clinically diagnosed end-stage liver disease patients undergoing liver transplantation. Subsequently, PLCS were incubated with rivenprost (75 mM) for 48h. Fibrogenesis was evaluated on a gene and protein level by qPCR and ELISA, respectively. **Results:** qPCR revealed that treatment with rivenprost markedly reduced the gene levels of fibronectin (*Fn1*), a-smooth muscle actin (*Acta2*), collagen 1A1 (*Col1a1*), and tumor necrosis factor a (*Tnf*) in rat NASH PCLS. Similarly, we observed a decrease in the expression of *FN1*, *COl1A1*, *ACTA2* and *TNF* in human cirrhotic PLCS treated with rivenprost. In addition, rivenprost treatment resulted in a significant reduction in pro-collagen type I carboxy-terminal propeptide release by human cirrhotic PLCS, indicating a reduction in collagen type I production. **Conclusion:** Our results indicate that activation of the PGE2 EP4 receptor effectively reduces fibrosis in both rat and human cirrhotic PCLS. These findings warrant further research into the anti-fibrotic potential of rivenprost for the treatment of liver fibrosis.

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2456-C | INHIBITION OF THE LYSOPHOSPHATIDIC ACID PATHWAY IMPROVES HEPATIC FIBROSIS AND PORTAL HYPERTENSION IN EXPERIMENTAL ADVANCED CHRONIC LIVER DISEASE

Peio Aristu[1], Zoe Boyer-Diaz[1], Anna Zagorska[2], Monika Sharma[2], María Andrés-Rozas[1], Grant Budas[2], Jaime Bosch[3] and Jordi Gracia-Sancho[1,3], (1)Barcelona Liver Bioservices (BLB), (2)Gilead Sciences, Inc., (3)Idibaps - Hospital Clínic Barcelona - Ciberehd, Barcelona, Spain

Background: Hepatic necroinflammatory processes are significant contributors to the progression of advanced chronic liver disease (ACLD), characterized by hepatic microvascular dysfunction, fibrosis, and portal hypertension. Lysophosphatidic acid (LPA), a paracrine factor obtained from the transformation of lysophosphatidylcholine by the enzyme autotaxin (ATX), activates hepatic stellate cells (HSCs) and promotes fibrogenesis. The present project aimed at characterizing the effects of inhibiting LPA in a pre-clinical model of advanced chronic liver disease. **Methods:** Cirrhotic rats with ascites (16 weeks CCl_4) randomly received either an inhibitor of autotaxin (ATXi, GLPG1690; 60 mg/kg/BID), an LPA receptor-1 antagonist (LPAR1i, AM095; 30 mg/kg/BID) or vehicle for 14 days (n = 12/group). *In vivo* hepatic and systemic hemodynamics, and molecular markers of liver injury, fibrosis, inflammation, oxidative stress, cell death, hepatic stellate cells (HSC) activation and liver sinusoidal endothelial cells (LSEC) de-differentiation were determined. **Results:** Cirrhotic animals receiving LPA pathway inhibitors exhibited lower portal pressure compared to vehicle-treated rats (ATXi: 13.4 ± 0.5 Vs 15.1 ± 0.6 mmHg; -11%; LPAR1i: 12.1 ± 0.7 mmHg vs 14.9 ± 0.7; -18%), with no changes in portal blood flow, suggesting decreased intrahepatic vascular resistance. No differences in systemic hemodynamics were observed. Underlying mechanisms of hepatic microcirculatory modulation included improvement in HSCs and LSECs phenotype (ATXi: desmin -24%, Vcam1 -28%; LPAR1i: +35% nitric oxide availability, vWF -25%), and significant fibrosis regression (ATXi: Sirius red area -20%, collagen -35%; LPAR1i: Sirius red -24%, collagen -27%). These were associated with anti-inflammatory (ATXi: IL6 -56%, IL10 -45%; LPAR1i: IL10 -50%), anti-apoptotic (ATXi: cell death -30%, AST -25%; LPAR1i: Casp8 -30%), and antioxidant effects (ATXi: MDA -62%, peroxynitrite -45%; non-significant for LPAR1i). **Conclusion:** This study demonstrates that inhibition of the LPA pathway exerts beneficial effects in a pre-clinical model of decompensated cirrhosis, which lead to marked amelioration in fibrosis and portal hypertension. Our results encourage its clinical evaluation for the treatment of advanced chronic liver disease.

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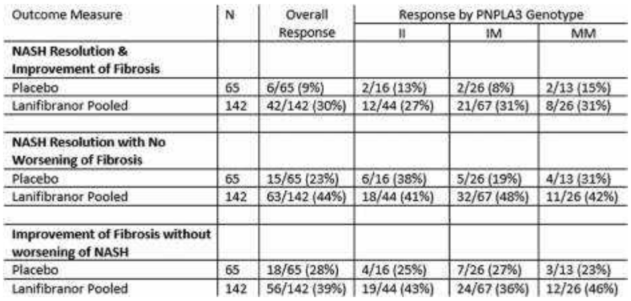
Disclosure information not available at the time of publication: Zoe Boyer-Diaz, Anna Zagorska, Monika Sharma, María Andrés-Rozas, Jaime Bosch

2457-C | LANIFIBRANOR IMPROVES LIVER HISTOLOGY AND MARKERS OF CARDIOMETABOLIC HEALTH IN PATIENTS WITH NASH INDEPENDENT OF PNPLA3 GENOTYPE: A RETROSPECTIVE ANALYSIS OF THE NATIVE STUDY

Louis H Griffel[1], Sven Francque[2], Manal F. Abdelmalek[3], Philippe Huot-Marchand[1], Lucile Dzen[1], Martine Baudin[1], Jean Louis Junien[1], Pierre Broqua[1] and Michael Cooreman[4], (1)Inventiva, (2)University of Antwerp, Edegem, Belgium, (3)Mayo Clinic, Rochester, MN, (4)INVENTIVA

Background: A polymorphism of patatin-like phospholipase domain-containing protein 3 (PNPLA3), I148M, is strongly associated with the risk for and the progression of nonalcoholic steatohepatitis (NASH). Lanifibranor, a pan-PPAR agonist, has shown efficacy on histological disease activity and fibrosis as well as on metabolic-immune markers of NASH in the phase 2b NATIVE study, corresponding to the role of PPAR signaling in the disease biology of NASH. We evaluated the impact of the PNPLA3 variant I148M on the histologic and metabolic-immune response to lanifibranor. **Methods:** NATIVE evaluated lanifibranor 800 and 1200 mg/d versus placebo in 247 patients with non-cirrhotic NASH for 24 weeks of treatment. Of these, 219 patients consented to genotyping for the PNPLA3 rs738409 SNP. 65 were II, 105 IM and 49MM, which is highest risk for disease severity and progression. Paired liver biopsy results were available for 207/219 patients. Histologic and metabolic-immune marker response was evaluated by PNPLA3 genotype. **Results:** There was no significant difference in demographics between the PNPLA3 types, although those with MM genotype were younger (mean age 50.9 vs 55.4 for II and 53.1 for IM) and were more likely to have Type 2 Diabetes (45% MM, 38% II, 41% IM). Pooled lanifibranor and placebo responses are presented in the table. There was no significant difference in response to lanifibranor by PNPLA3 genotype, despite the fact that MM genotype patients had more activity on biopsy than the II or IM patients (82% NAS > = 6, vs 74%, 70%), while there was no difference in fibrosis. Similarly, Improvement of metabolic-immune markers for lanifibranor vs placebo was observed to the same degree in the 3 PNPLA3 genotypes including glycemic control, insulin, HOMA-IR, Hs-CRP, CAP & adiponectin. **Conclusion:** The efficacy of lanifibranor on both liver histology and markers of cardiometabolic health appears to be independent of PNPLA3 status, despite MM genotype patients having more severe activity on liver biopsy.

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient



Outcome Measure	N	Overall Response	Response by PNPLA3 Genotype		
			II	IM	MM
NASH Resolution & Improvement of Fibrosis					
Placebo	65	6/65 (9%)	2/16 (13%)	2/26 (8%)	2/13 (15%)
Lanifibranor Pooled	142	42/142 (30%)	12/44 (27%)	21/67 (31%)	8/26 (31%)
NASH Resolution with No Worsening of Fibrosis					
Placebo	65	15/65 (23%)	6/16 (38%)	5/26 (19%)	4/13 (31%)
Lanifibranor Pooled	142	63/142 (44%)	18/44 (41%)	32/67 (48%)	11/26 (42%)
Improvement of Fibrosis without worsening of NASH					
Placebo	65	18/65 (28%)	4/16 (25%)	7/26 (27%)	3/13 (23%)
Lanifibranor Pooled	142	56/142 (39%)	19/44 (43%)	24/67 (36%)	12/26 (46%)

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Disclosure information not available at the time of publication: Philippe Huot-Marchand, Lucile Dzen, Martine Baudin, Jean Louis Junien, Pierre Broqua

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

2458-C | LANIFIBRANOR-ASSOCIATED ADIPONECTIN INCREASE CORRELATES WITH IMPROVEMENT OF HISTOLOGICAL AND SERUM MARKERS OF NASH SEVERITY BOTH IN TERMS OF ACTIVITY AND FIBROSIS

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Background: Lanifibranor has shown efficacy on liver histology and markers of cardiometabolic health (CMH) in patients with pre-cirrhotic NASH. We previously showed that increases in adiponectin (ADP) with lanifibranor correlated with improvement of CMH markers. We further analyzed the correlation between ADP increase and lanifibranor for 1) histological features of NASH severity, and 2) biomarkers of active NASH and fibrosis. **Methods:** The phase 2 NATIVE study evaluated lanifibranor 800 and 1200 mg/d versus placebo in 247 patients for 24 weeks. Paired samples for histological efficacy were available from 211 patients (72 on placebo, 66 and 73 on lanifibranor 800 and 1200 mg). Serum levels of ADP, pro-C3, and MACK-3 score (a score for active and fibrotic NASH calculated from HOMA, AST and CK-18) were measured at baseline (BL) and end of treatment (EOT). BL ADP levels were divided into low, medium and high (<5, 5-10 and >10 ug/mL); ADP increase at EOT was defined as unchanged, moderate and high (<1.5-fold, 1.5-4-fold and >4-fold change). Histological NASH activity grading (steatosis, inflammation, ballooning) and fibrosis staging were per NASH-CRN and SAF scoring. Histological endpoints were NASH resolution and no worsening of fibrosis (E1), improvement of fibrosis and no worsening of NASH (E2), and NASH resolution AND fibrosis improvement (E3). **Results:** BL ADP levels were low across groups. ADP increase at EOT correlated with all histological endpoints. Responders with lanifibranor (pooled) were for E1: 15, 44 and 57%, E2: 31, 35 and 53%, and E3: 15, 28 and 40% for ADP unchanged, moderate or high increase, respectively. With placebo, a small (10) % of patients had a moderate ADP increase (all <4-fold), which also correlated with histological response, but to a lesser degree. Degree of ADP increase, both absolute and categorical, correlated with improvement of CRN-NAS and SAF-Activity scores as well as with individual components (steatosis, inflammation, ballooning). Lanifibranor-associated ADP increase correlated with improvement in fibrosis stage (38% vs 57% for ADP d 4 vs >4-fold increase, respectively), pro-C3 levels and MACK-3 score. **Conclusion:** ADP increase with lanifibranor in patients with NASH correlated with improvement of histological and serum markers of NASH activity and fibrosis, further supporting that the observed improvements correlate with lanifibranor target engagement. ADP, across the spectrum of NASH, is a biomarker of lanifibranor-associated efficacy.

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2459-C | LEVERAGING NAFLDSYM TO IDENTIFY OPTIMAL COMBINATION THERAPIES FOR NASH PATIENTS

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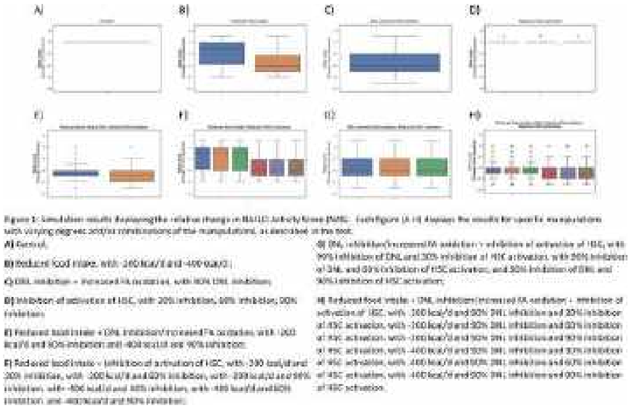
Background: Non-alcoholic steatohepatitis (NASH) is a metabolic disease that is characterized by increased liver fat, inflammation, and fibrosis; if left untreated, results in cirrhosis, hepatocarcinoma, and increased mortality. The many pathways contributing to NASH complicate drug discovery, development, and ultimately treatment of patients with NASH. **Methods:** Here we describe how a Quantitative Systems Pharmacology (QSP) model, NAFLDsym, was leveraged in discovery and development decision-making to select the targets, identify mechanism-based biomarkers, and simulate clinical trials to predict the effects of targets/combination of targets in NASH virtual patients. The mechanisms evaluated included: a) decrease in food intake (FI) leading to 5% or 10% weight loss, b) 90% inhibition of de novo lipogenesis (DNL) with a 60% increase in fatty acid oxidation (FAO), c) inhibition of hepatic stellate cell (HSC) activation by 30%, 60%, or 90%, and d) reductions in lipotoxicity by 20%, 40%, or 60%. **Results:** Simulated decreases in FI or DNL/FAO resulted in comparable reductions in liver fat, alanine aminotransferases (ALT), NAFLD Activity Score (NAS). Effects of the two mechanisms on liver fat and fibrosis endpoints were additive, suggesting the mechanisms may be combined to provide greater benefits than as a monotherapy (Figure 1). The reduction in HSC activation had no effect on liver fat, ALT, or NAS when administered as a monotherapy. The reduction of lipotoxicity led to improvements in fibrosis stage, collagen, plasma Pro-C3, and plasma ALT but not liver fat. The effects of decreased FI or DNL/FAO on fibrosis score, liver collagen, and plasma Pro-C3 were enhanced when combined with the inhibition of HSC activation or reductions in lipotoxicity. **Conclusion:** These explorations confirm there are many pathways that contribute to the pathophysiology of NASH. Agents that reduce hepatic fat are foundational for NASH patients and adding drugs that reduce lipotoxicity/ HSC activation may be key to optimal therapy.



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2460-C | microRNA-21: A NOVEL THERAPEUTIC OPTION THAT PROTECTS FROM HIGH-FAT-DIET-INDUCED LIVER DISEASE PROGRESSION

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Background: Liver disease is a leading cause of morbidity and mortality worldwide. MicroRNAs play crucial roles in regulating the pathophysiological functions of the liver. MicroRNA-21-5p (miR-21) is known to be dysregulated in liver metabolism, non-alcoholic fatty liver disease, fibrosis, and hepatocellular carcinoma. Conversely, the protective effects of miR-21 have also been reported in liver disease. Owing to the huge heterogeneity and variability of miR-21, it has not been approved as a biomarker or therapeutic option for liver disease. In this study, we aim to understand the role of miR-21 in all stages of liver disease and identify its potential as a therapeutic target. **Methods:** Three-week-old B6/129S (WT) and miR-21 KO mice were administered a one-time intraperitoneal injection of carcinogen-diethylnitrosamine, fed either standard (Chow) or choline-deficient high-fat diet (HFD) and were monitored over 32 weeks. To evaluate miR-21 as a potential therapeutic target, WT mice were administered with negative control or miR-21 mimic through tail-vein injection at week 16. **Results:** WT mice on Chow showed no noticeable abnormalities. However, mice on HFD developed obesity early in the experiment. At week 16, HFD-fed mice displayed signs of liver injury, hyperglycemia, and insulin resistance. Histologic evaluation revealed features of NASH manifested by varying severity of steatosis, ballooning degeneration, lobular inflammation, and fibrosis. By week 24, a significant number of tumors were observed in the liver, identified as fatty adenomas. By week 32, all the phenotypes advanced to a more severe stage. As the disease progressed, interestingly, a striking downregulation was observed in miR-21 transcript levels. We observed that the knockout of miR-21 alone was sufficient to cause hepatomegaly, hyperglycemia, insulin resistance, and steatosis. Exposure to HFD in this background caused even worse and accelerated phenotypes in obesity, steatosis, NASH, and the highest levels of fibrosis. By 24 weeks, a huge tumor burden was observed, identified as hepatocellular carcinoma. Administration of miR-21 mimics rescued insulin sensitivity and showed a prominent reduction in steatosis, fibrosis, and tumor burden in WT mice. **Conclusion:** Our results suggest that the knockout of miR-21 is sufficient to cause a metabolic syndrome with steatosis and NASH in mice. These effects, when coupled with HFD, accelerate the rate and severity of liver disease, indicating that loss of miR-21 causes increased susceptibility to the manifestation of HFD-induced hepatic disease. We further show that the administration of miR-21 mimics in this background was able to ameliorate the liver disease phenotypes, highlighting its protective role and signifying its potential as a therapeutic agent.

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2461-C | NONCLINICAL EFFICACY, PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD), AND TOXICOLOGY PROFILE OF ALG-055009, A NOVEL AND POTENT THYROID HORMONE RECEPTOR Β AGONIST, FOR THE TREATMENT OF NON-ALCOHOLIC STEATOHEPATITIS (NASH)

Dinah Misner[1], Kusum Gupta[1], Xuan Luong[1], Jerome Deval[1], Kha Le[2], Doug Clark[1], David McGowan[3], Meenakshi Venkatraman[1], Matthew McClure[1], David B. Smith[2], Tse-I Lin[1], Julian Symons[2], Lawrence M. Blatt[2], Leonid N. Beigelman[2] and Sushmita Chanda[2], (1)Aligos Therapeutics, Inc., (2)Aligos Therapeutics, Inc., South San Francisco, CA, USA, (3) Aligos Belgium BV

Background: NASH is characterized by hepatic inflammation/damage as a reaction to build-up of fat in the liver. Although no drugs are approved to treat NASH, thyroid hormone receptor β (THRβ) agonists have reduced liver fat, restored liver function and reversed inflammation/fibrosis in clinical trials. Here we present the preclinical development of ALG-055009, a second-generation THRβ agonist with improved potency and favorable selectivity. **Methods:** ALG-055009 was profiled in in vitro efficacy, ADME, and toxicology assays, and in vivo pharmacokinetic studies across species. The in vivo activity of ALG-055009 was evaluated in a diet induced obesity (DIO) mouse model where male C57BL/6J mice were fed with a high fat diet for 14 weeks, followed by once daily (QD) or twice daily (BID) oral administration of ALG-055009 for 28 days. Pharmacodynamic endpoints included total/LDL cholesterol, liver enzymes, and thyroid hormones. Liver and heart gene expression was determined by qPCR. Repeat-dose toxicology studies were conducted in rats and dogs, up to 13-weeks in duration, and clinical pathology endpoints including thyroid hormones were assessed at 2-, 6-, and 13-weeks, as well as following 2- to 4-weeks of recovery. **Results:** In the DIO mouse model, where ALG-055009 was administered QD or BID for 28 days, dose-dependent increases in selective THRβ-induced liver gene expression were observed and were associated with reductions in serum total and LDL-C. In this model, 0.15 mg/kg BID was defined as the minimal efficacious dose, corresponding to ALG-055009 plasma C_{max} of 82.5 ng/mL, AUC_{0-24} of 515 ng™h/mL and C_{min} of 2.01 ng/mL. ALG-055009 is projected to have low potential for drug-drug interactions in humans, either as a perpetrator or victim. Additionally, ALG-055009 was well tolerated in both rats and dogs in repeat dose toxicology studies up to the highest doses tested. Dose-dependent changes in lipid parameters were observed in repeat-dose toxicology studies, whereas changes in total circulating thyroid hormones levels were observed at supratherapeutic exposures. **Conclusion:** ALG-055009 is a potent and selective THR-β agonist with favorable in vitro safety and ADME properties and repeat-dose toxicity profile in rats and dogs. ALG-055009 also dose-dependently reduced levels of atherogenic lipids. Combined, this profile indicates ALG-055009 has the potential to be a best-in-class THR-β agonist for the treatment of NASH.

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

Naim Alkhouri[1], Pierre Bedossa[2], Cynthia D. Guy[3], Jörn M. Schattenberg[4], Rohit Loomba[5], Rebecca A. Taub[6], Dominic Labriola[6], Sam Moussa[7], Guy W. Neff[8], Arun Sanyal[9], Mazen Noureddin[10], Meena B. Bansal[11], Vlad Ratziu[12] and Stephen A Harrison[13], (1) Arizona Liver Health, Phoenix, AZ, (2)Newcastle University, (3)Duke University, (4)University of Mainz, (5)University of California, San Diego, San Diego, CA, (6)Madrigal Pharmaceuticals, (7)University of Arizona for Medical Sciences, (8)Tampa General Medical Group, Bradenton, FL, (9)Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA, (10)Houston Research Institute, Houston, TX, (11)Icahn School of Medicine at Mount Sinai, (12)Assistance Publique-Hôpitaux De Paris, Paris, France, (13)Pinnacle Clinical Research Center, San Antonio, TX

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

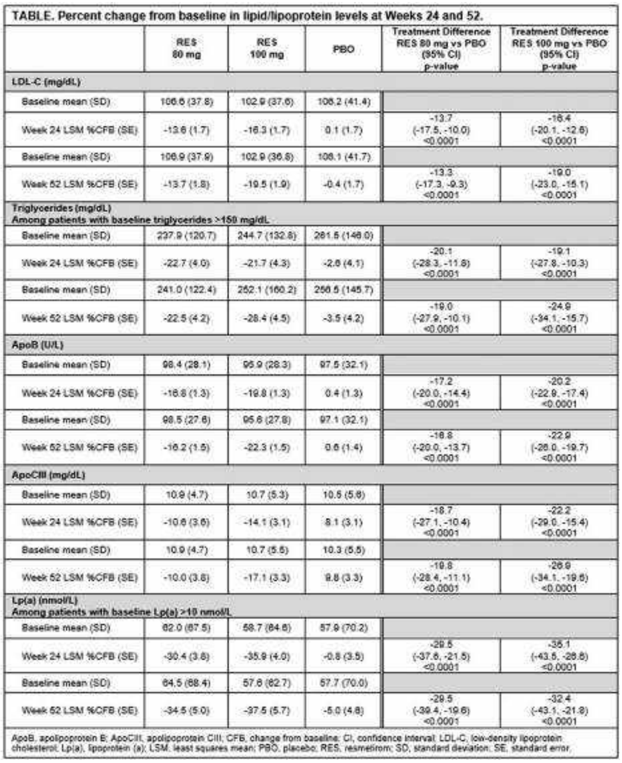

TABLE. Percent change from baseline in lipid/lipoprotein levels at Weeks 24 and 52.

	RES 80 mg	RES 100 mg	PBO	Treatment Difference RES 80 mg vs PBO (95% CI) p-value	Treatment Difference RES 100 mg vs PBO (95% CI) p-value
LDL-C (mg/dL)					
Baseline mean (SD)	106.6 (37.8)	102.9 (37.6)	106.2 (41.4)		
Week 24 LSM %CFB (SE)	-13.6 (1.7)	-16.3 (1.7)	0.1 (1.7)	-13.7 (-17.5, -10.0) <0.0001	-16.4 (-20.1, -12.6) <0.0001
Baseline mean (SD)	106.9 (37.9)	102.9 (36.6)	106.1 (41.7)		
Week 52 LSM %CFB (SE)	-13.7 (1.8)	-19.5 (1.9)	-0.4 (1.7)	-13.3 (-17.3, -9.3) <0.0001	-19.0 (-23.0, -15.1) <0.0001
Triglycerides (mg/dL) **Among patients with baseline triglycerides >150 mg/dL**					
Baseline mean (SD)	237.9 (120.7)	244.7 (132.8)	261.5 (146.0)		
Week 24 LSM %CFB (SE)	-22.7 (4.0)	-21.7 (4.3)	-2.6 (4.1)	-20.1 (-28.3, -11.8) <0.0001	-19.1 (-27.8, -10.3) <0.0001
Baseline mean (SD)	241.0 (122.4)	252.1 (160.2)	256.5 (145.7)		
Week 52 LSM %CFB (SE)	-22.5 (4.2)	-28.4 (4.5)	-3.5 (4.2)	-19.0 (-27.9, -10.1) <0.0001	-24.9 (-34.1, -15.7) <0.0001
ApoB (U/L)					
Baseline mean (SD)	98.4 (28.1)	95.9 (28.3)	97.5 (32.1)		
Week 24 LSM %CFB (SE)	-16.8 (1.3)	-19.8 (1.3)	0.4 (1.3)	-17.2 (-20.0, -14.4) <0.0001	-20.2 (-22.9, -17.4) <0.0001
Baseline mean (SD)	98.5 (27.6)	95.6 (27.8)	97.1 (32.1)		
Week 52 LSM %CFB (SE)	-16.2 (1.5)	-22.3 (1.5)	0.6 (1.4)	-16.8 (-20.0, -13.7) <0.0001	-22.9 (-26.0, -19.7) <0.0001
ApoCIII (mg/dL)					
Baseline mean (SD)	10.9 (4.7)	10.7 (5.3)	10.5 (5.6)		
Week 24 LSM %CFB (SE)	-10.6 (3.6)	-14.1 (3.1)	8.1 (3.1)	-18.7 (-27.1, -10.4) <0.0001	-22.2 (-29.0, -15.4) <0.0001
Baseline mean (SD)	10.9 (4.7)	10.7 (5.6)	10.3 (5.5)		
Week 52 LSM %CFB (SE)	-10.0 (3.6)	-17.1 (3.3)	9.8 (3.3)	-19.8 (-28.4, -11.1) <0.0001	-26.9 (-34.1, -19.6) <0.0001
Lp(a) (nmol/L) **Among patients with baseline Lp(a) >10 nmol/L**					
Baseline mean (SD)	62.0 (67.5)	58.7 (64.6)	57.9 (70.2)		
Week 24 LSM %CFB (SE)	-30.4 (3.6)	-35.9 (4.0)	-0.8 (3.5)	-29.5 (-37.6, -21.5) <0.0001	-35.1 (-43.5, -26.6) <0.0001
Baseline mean (SD)	64.5 (68.4)	57.6 (62.7)	57.7 (70.0)		
Week 52 LSM %CFB (SE)	-34.5 (5.0)	-37.5 (5.7)	-5.0 (4.6)	-29.5 (-39.4, -19.6) <0.0001	-32.4 (-43.1, -21.8) <0.0001

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

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

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

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

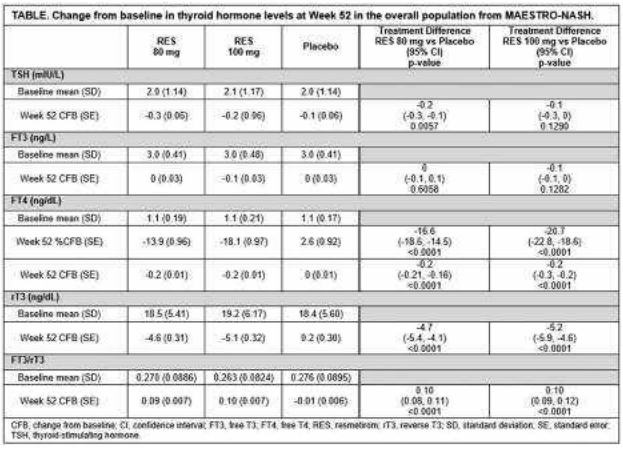

TABLE. Change from baseline in thyroid hormone levels at Week 52 in the overall population from MAESTRO-NASH.

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

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

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

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

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

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

presents hamsters with a choice between control chow or high fat/cholesterol diet, and normal water or 10% fructose water. After a 20-week diet induction, hamsters were maintained on the same diet with the 10% fructose water supplemented without or with 15% alcohol, and animals were simultaneously treated with vehicle, SEMA 0.06mg/kg s.c. QD or LANI 30mg/kg p.o. QD for 5 weeks. **Results:** When no alcohol was provided, SEMA induced a 17% body weight loss ($p < 0.01$ vs. vehicle) with a transient food intake lowering, but a continuous reduction in 10% fructose water intake and a higher normal water intake. Although SEMA did not reduce NAFLD Activity Scoring (NAS), including hepatocyte ballooning and fibrosis scores, it reduced liver triglycerides levels (-25%, $p < 0.01$). When alcohol was provided, SEMA had similar effects on body weight, food intake and normal water intake, while it significantly reduced fructose and alcohol intake during the 5-week treatment. However, SEMA had no effect on NAS and did not lower hepatic triglycerides levels anymore. When no alcohol was provided, LANI induced body weight loss (-5%), a gradual reduction in 10% fructose water intake and a higher normal water intake. LANI reduced liver lipids levels, NAS, and fibrosis score (all $p < 0.05$ vs. vehicle). As well, when alcohol was provided, LANI significantly reduced fructose and alcohol intake, liver lipids levels and NAS. **Conclusion:** SEMA and LANI both reduced fructose and alcohol intake but had different effects on NASH and liver fibrosis in obese NASH hamsters. This preclinical model will help to evaluate drugs targeting NASH on alcohol intake and their potential benefits in humans.

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2465-C | SEMAGLUTIDE NORMALIZE SERUM TRANSAMINASE IN ABOUT HALF OF GLP1-RA NAÏVE TYPE 2 DIABETES (T2D) PATIENTS WITH NON-ALCOHOLIC-FATTY-LIVER-DISEASE (NAFLD)

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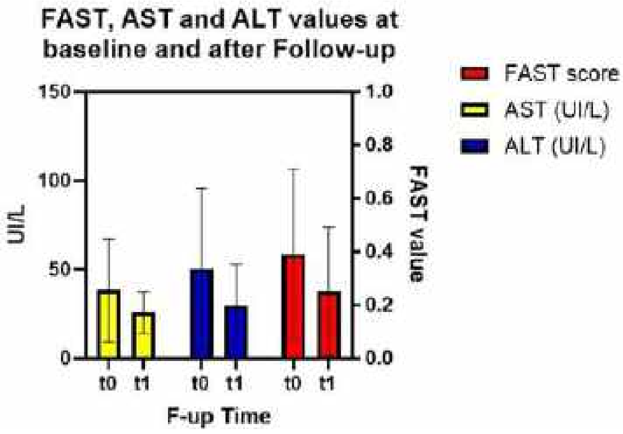
Background: NAFLD patients (pts) with T2D are at higher risk of liver disease progression. Until now GLP-1 receptor agonists (GLP1-ra) and Semaglutide demonstrated histological proven effects on Non-Alcoholic Steatohepatitis (NASH) in phase 2 trials, with a higher efficacy at a daily subcutaneous dosage of 0.4 mg (NASH-resolution in 59% of pts vs. 17% in the placebo group, 60% diabetic). We measured the same biomarkers of liver disease at baseline and after 6 months (t1) of Semaglutide treatment in a small cohort of GLP1-ra naïve T2D patients with NAFLD. **Methods:** Anthropometric characteristics, serum transaminases (AST,ALT), transient elastography (TE) by Fibroscan, and FibroScan-AST score (FAST) were analyzed at baseline (t0) and after 6.6 ± 0.9 months (t1) of Semaglutide titration (to 0.5-1.0 mg weekly if subcutaneous) or (to 7-14 mg daily if oral) in 42 consecutive overweight/obese T2D pts with NAFLD (age 60.5 ± 12.6 yrs, females 28.6%, BMI 31.5 ± 5.5 kg/m^2). **Results:** A significant ($p < 0.005$) t0-t1 reduction was found for Glycated Hemoglobin [9.0 (16-4) mmol/mol], body weight [5.1 ± 3.7 %], AST [5 (26-1) UI/L], ALT [13 (41-0) UI/L], and FAST [39.6 (54.8-20.4) %] while CAP and TE values did not vary significantly. At baseline ALT were elevated in 15/26 pts (57.7%) and normalized in 8/15 (53.0%) of them at t1. The baseline FAST score was 0.39 ± 0.32, with 9 (30%) patients classified as "at-risk" NASH and 5 (23.3%) as gray zone; a one class down-stepping was observed in 37.5% during follow-up, resulting in a significant distribution difference at the end of follow-up ($p = 0.004$). "At-risk" NASH was present in 2/24 (8.3%) of the pts at t1 and 7/24 (29.1%) were classified in the gray zone. The changes of FAST percentage were strongly correlated with AST, ALT, and CAP basal and variation values ($p < 0.005$), but not with Glycated Hemoglobin, Body Weight, and TE reductions. We observed a lower baseline BMI (31.1 ± 5.2 vs 38.0 ± 3.7 kg/m^2, $p = 0.026$) in pts with a FAST zone down-stepping during follow-up, whereas FAST changes were not correlated with body weight reduction e 5% or e 10%. Conversely, FAST down-stepping group presented a higher reduction of AST (42.0 ± 12.6% vs 12.4 ± 22.7%, $p = 0.001$) and ALT (49.8 ± 18.7% vs 14.2 ± 40.0%, $p = 0.023$) than the one without down-stepping. No significant difference was observed between these groups for body weight reduction (-5.2 ± 3.9 vs -4.2 ± 2.7). **Conclusion:** Semaglutide treatment for T2D in pts with NAFLD associates with a significant decline of AST, ALT and FAST as proxies of liver necroinflammation. Noteworthy, this amelioration was not related to glycemic control, nor to weight loss.

Semaglutide effects appear to be more pronounced in patients with grade I vs grade II obesity.



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2466-C | THE GALECTIN-3 INHIBITOR GB1211 DOSE DEPENDENTLY REDUCES INFLAMMATION AND FIBROSIS IN A HIGH FAT DIET RABBIT MODEL OF NASH

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Background: Galectin-3 (Gal-3) is a pro-fibrotic β-galactoside binding lectin highly expressed in fibrotic liver & implicated in hepatic fibrosis. GB1211 is a novel orally active Gal-3 small molecule inhibitor that has high affinity for Gal-3 (human $K_D = 25$nM; rabbit $K_D = 12$nM) & high oral bioavailability in rabbits & man. In this study the efficacy of GB1211 was investigated in a high fat diet (HFD) rabbit model of non-alcoholic steatohepatitis (NASH). **Methods:** Male New Zealand White rabbits were individually caged under standard conditions in a temperature & humidity-controlled room on a 12h light/darkness cycle. After 1 week of regular diet (RD), rabbits were randomly assigned to 7 different groups (n = 6-10/group): RD/vehicle, HFD (8 weeks) & HFD/GB1211 (0.3, 1, 5 or 30 mg/kg GB1211 with vehicle/GB1211 *p.o.* dosed therapeutically *q.d.* 5 days per week from week 9) for 8 or 12 weeks. Liver inflammation, steatosis, ballooning, and fibrosis was measured via blood metabolic markers (glucose, cholesterol, triglycerides & transaminases) and histomorphological analysis (Masson's trichome, Giemsa, oil red O & picrosirius red (PSR)). Plasma concentrations of GB1211 were determined by LC-MS. **Results:** Inflammation score, steatosis (binomial score & % area oil red O), ballooning score & fibrosis (% PSR) were all significantly increased from RD to HFD vehicle groups. GB1211 demonstrated target engagement by significantly decreasing Gal-3 levels in the liver as measured via IHC and mRNA analysis. GB1211 dose dependently reduced biomarkers of inflammation (TLR4, IL-1β), liver function (AST, ALT, bilirubin) and fibrosis (PSR, vimentin). Doses of 1 mg/kg or above demonstrated consistent efficacy across the majority of biological endpoints and further supported the dosing regimens progressed into the clinic. **Conclusion:** GB1211 normalized inflammation & fibrosis in a HFD rabbit model of NASH & liver fibrosis following therapeutic dosing for 4 weeks in a dose dependent manner. This data supports the human GB1211 dose of 100 mg *b.i.d.* that has been shown to reduce key biomarkers of disease in a phase 2b study in liver cirrhosis (NCT05009680).

Disclosures: Ian Holyer – Galecto Biotech AB: Employee, Yes, No;

Fredrik Zetterberg – Galecto Biotech: Employee, Yes, No; Galecto Biotech: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No; Galecto Biotech: Stock – privately held company (individual stocks and stock options), Yes, No;

Robert Slack – Galecto Biotech: Employee, Yes, No; Galecto Biotech: Stock – privately held company (individual stocks and stock options), Yes, No; GSK: Stock – privately held company (individual stocks and stock options), No, Yes;

The following people have nothing to disclose: Linda Vignozzi, Sandra Filippi, Paolo Comeglio, Annamaria Morelli, Ilaria Cellai, Giulia Guarnieri, Mario Maggi

2467-C | THE IPS-DERIVED MESENCHYMAL STEM CELLS AMELIORATED LIVER FIBROSIS AND LIVER FATTY DEPOSITION IN NAFLD/MAFLD-RELATED CIRRHOTIC MICE

Naoki Yamamoto[1,2], Ami Enomoto[1], Tsuyoshi Fujioka[1], Shizuka Aritomi[3], Daiki Kawamoto[1], Kaori

Hamamoto[1], Shuhei Shinoda[1], Toshihiko Matsumoto[1], Koichi Fujisawa[4] and Taro Takami[5,6], (1)Yamaguchi University Graduate School of Medicine, (2) Yamaguchi University, (3)Ajinomoto Co., Inc, (4) University of Occupational and Environmental Health, (5)Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi, Japan, (6)-

Background: Recently, Nonalcoholic fatty liver disease (NAFLD) and Metabolism-associated fatty liver disease (MAFLD) was the major prevalent liver disease worldwide and MAFLD, which could be defined with fatty liver, obesity, diabetes and metabolic syndrome was increased. Nonalcoholic steatohepatitis (NASH) has become the severe problem to make severe liver cirrhosis and hepatocellular carcinoma. However, the radical treatment was not still established for these diseases. We developed the iPS-derived mesenchymal stem cells (iMSCs) which induced undifferentiated iPS cells into mature and higher quality MSCs. The aim of this study is to investigate therapeutic effects of iMSCs on NAFLD/MAFLD in vivo and the mechanisms of ameliorating fatty deposition and fibrosis in liver. **Methods:** C57BL/6 mice were fed by the Gubra-Amylin-NASH (GAN) diet and with carbon tetrachloride by intraperitoneal administration per a week. The total study periods were 20 weeks. We divided into three groups, GAN diet only (GAN group), GAN diet with iMSCs-infusion via spleen (iMSC group), GAN diet with the iMSC-derived exosome intravenous injection (EXO group). We analyzed these livers by Masson trichrome (MT), Sirius–red, Alpha-SMA expression. The oxidative stress was analyzed by hepatic 8OHdG content. We analyzed some serum data and the mRNA-expressions of Type I procollagen, TIMP1, TIMP2, TGF-beta, alpha-SMA, MMP9, TNF-alpha, MCP-1, AFP,Hmox1, XBP1, ATF6, SREBP1, FAS, FGF21 were analyzed using both Real Time-PCR and DNA array. **Results:** After 20 weeks, iMSC and EXO-infused livers showed significantly reduced fibrosis ($p < 0.05$) and fatty deposition ($p < 0.05$), consistent with the lower number of D-PAS-positive cells ($p < 0.05$). Serum data also showed that iMSC and EXO mice significantly could show improved liver function and hyperlipidemia. Administration of iMSC and EXO group significantly reduced levels of 8OHdG ($p < 0.05$). iMSC and EXO group significantly inhibited fibrosis related genes (Type 1 procollagen, TIMP1, TGF-beta), ROS related genes (XBP1, ATF6), inflammation related genes (TNF-alpha, MCP1) mRNA expressions ($p < 0.05$). **Conclusion:** Our results indicated that iMSCs ameliorated fibrosis and fatty deposition in the liver and improved liver functions. The exosome derived from iMSCs was also crucial factor to improve liver environment. Our iMSCs will be the new cell source for the treatment for NAFLD/MAFLD related cirrhotic patients

Disclosures: The following people have nothing to disclose: Naoki Yamamoto, Tsuyoshi Fujioka, Daiki Kawamoto, Toshihiko Matsumoto, Taro Takami

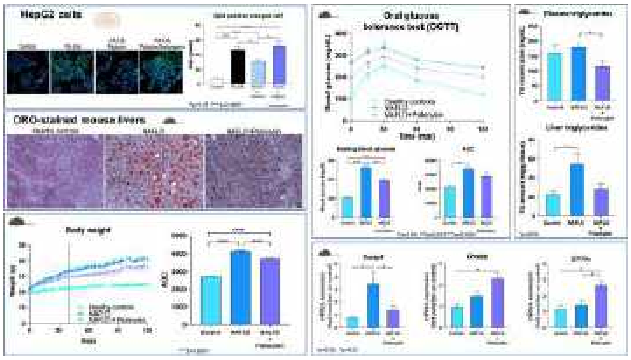
Disclosure information not available at the time of publication: Ami Enomoto, Shizuka Aritomi, Kaori Hamamoto, Shuhei Shinoda, Koichi Fujisawa

2468-C | THE SEROTONIN RECEPTOR AGONIST PSILOCYBIN AS A NOVEL THERAPEUTIC APPROACH FOR NAFLD: PRECLINICAL STUDIES

Sara De Martin[1], Daniela Gabbia[2], Martina Colognesi[2], Ilaria Zanotto[2], Katia Sayaf[2], Stefano Comai[1], Andrea Mattarei[1], Marco Banzato[1], Franco Folli[3], Lucia Centofanti[3], Sergio Traversa[4], Marco Pappagallo[5] and Paolo L. Manfredi[5], (1)University of Padua, (2) University of Padova, (3)University of Milan, (4) Relmada Therapeutic Inc, (5)Relmada Therapeutics Inc

Background: Although NAFLD prevalence is rising globally, paralleling other metabolic disorders including obesity, there are no drugs approved for its cure. The serotonin receptor (5-HT2AR) agonist psilocybin, an alkaloid of *Psilocybe* mushrooms, reduced obesity in animal models. This study assessed the effects of non-psychedelic doses of psilocybin in mice with high-fat-high-fructose diet (HFHFD)-induced NAFLD. Mechanistic studies were performed on HepG2 cells and 3T3L1-derived adipocytes. **Methods:** The *in vitro* effect of psilocin was assessed on HepG2 cells treated with palmitic/oleic acid and on spheroids of 3T3L1-derived adipocytes w/ or w/o the 5-HT2AR antagonist ketanserin. Psilocybin was tested *in vivo* on C57BL/6 male mice fed with HFHFD (60% kcal from fat) for 17 weeks. One group ($n = 10$) received daily 0.05 mg/Kg*bw psilocybin and the other ($n = 10$) received vehicle by oral gavage. Standard diet-fed mice ($n = 10$) were used as controls. Body weight and food intake were assessed weekly. T-maze and Light-Dark-box tests were used to assess anxiety-like behavior and memory. Fasting glucose and triglycerides were measured before sacrifice. Liver histology was assessed by H&E and ORO staining. Blood immunophenotyping was performed by FACS and mRNA expression was evaluated by qPCR. **Results:** Psilocin decreased lipid accumulation in HepG2 cells and 3T3-derived spheroids ($p < 0.05$). These effects were reverted by ketanserin. In NAFLD mice psilocybin, beside ameliorating liver histology, reduced body weight by 12% and restored the levels of plasma and liver triglycerides of standard-diet fed mice. A significant decrease of fasting glucose ($p < 0.001$) and AUC was observed in the

OGTT. Without reducing food intake, psilocybin reduced anxiety-like behavior and improved memory ($p < 0.05$), modulated hepatic genes involved in de novo lipogenesis, glycolysis, b-oxidation, i.e., SREBP1 (2-fold decreased, $p < 0.05$), ChREBP (2-fold increased, $p < 0.05$ vs controls) and CPT-1 (3-fold increased, $p < 0.05$), and restored the phenotype of circulating NK cells, by reverting the increase of PD-1 expressing exhausted NK cells of NAFLD mice ($p < 0.01$). **Conclusion:** Oral 0.05 mg/Kg*bw psilocybin significantly reduced hepatic steatosis, blood glucose levels and body weight in NAFLD mice without detrimental CNS effects, by exerting a pleiotropic action on lipid and glucose metabolism. Psilocybin at low non-psychedelic doses may be a novel candidate therapy for NAFLD and associated metabolic disorders.



Disclosures: Sara De Martin – MGGM LLC: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Neuroarbor LLC: Consultant, No, No; Aesculapius Farmaceutici: Speaking and Teaching, No, No;
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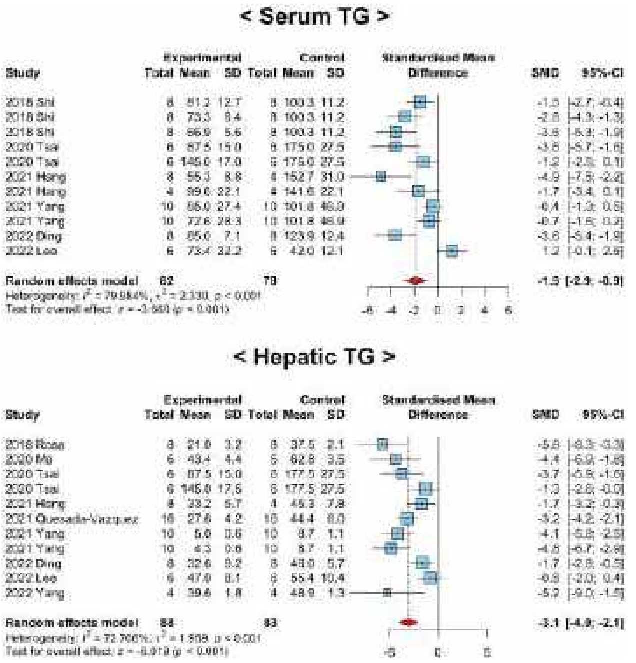
Sergio Traversa – Relmada Therapeutics Inc: Employee, No, No;
Marco Pappagallo – Relmada Therapeutics Inc: Consultant, No, No;
Paolo L. Manfredi – Relmada Therapeutics Inc: Consultant, No, No;
The following people have nothing to disclose: Daniela Gabbia, Martina Colognesi, Ilaria Zanotto, Katia Sayaf, Marco Banzato, Lucia Centofanti

2469-C | THE THERAPEUTIC POTENTIAL OF N-ACETYLCYSTEINE IN NONALCOHOLIC FATTY LIVER DISEASE: A COMPREHENSIVE SYSTEMATIC REVIEW AND META-ANALYSIS OF PRECLINICAL STUDIES, INCORPORATING COMPREHENSIVE TRANSCRIPTOMIC ANALYSIS

Keungmo Yang, Hyun Yang, Si Hyun Bae and Chang Wook Kim, The Catholic University of Korea

Background: Nonalcoholic fatty liver disease (NAFLD) is continuously developed from simple steatosis to inflammation, fibrosis, and hepatocellular carcinoma. Although NAFLD has become the most prevalent chronic liver disease worldwide, there is still no definitive treatment, except for lifestyle interventions, which can be challenging to achieve. Over the past decades, several studies have reported the protective effects of N-acetylcysteine (NAC), an antioxidant, against drug-induced liver injury. However, it is still unclear whether NAC has therapeutic potential in NAFLD. **Methods:** Therefore, the present meta-analysis aimed to investigate the efficacy of NAC on NAFLD in preclinical studies. By searching PubMed, Web of Science, and Cochrane Library, a total of 13 studies were included. The methodological quality was assessed based on the SYstematic Review Centre for Laboratory animal Experimentation guideline, and heterogeneity was evaluated with I^2 and P values. Publication bias was assessed by Egger's test, and sensitivity analysis was performed. **Results:** The results demonstrated that NAC treatment significantly improved systemic and hepatic lipid metabolism ($P < 0.01$), inflammatory liver injury ($P < 0.01$), glucose intolerance ($P < 0.05$), and hepatic steatosis ($P < 0.01$) by restoring hepatic levels of glutathione (GSH) ($P < 0.05$) and GSH reductase ($P < 0.05$) compared to control groups in NAFLD-induced animals. However, the administration of NAC did not alter the hepatic levels of GSH peroxidase, catalase, and superoxide dismutase in animals with NAFLD. Furthermore, a comprehensive analysis of bulk, single-cell, and spatial transcriptomics data consistently revealed significant upregulation of the target pathways of NAC in the liver tissues from mice and patients with NAFLD, thereby reinforcing the potential application of NAC in clinical settings. **Conclusion:** In conclusion, to the best of our knowledge, this is the first study to investigate the efficacy of NAC in preclinical studies of NAFLD through a meta-analysis. Our findings indicate the potential application of NAC in future clinical trials for NAFLD, either as a stand-alone treatment or in combination with other drugs.



Disclosures: The following people have nothing to disclose: Keungmo Yang, Hyun Yang, Si Hyun Bae, Chang Wook Kim

2470-C | THERAPEUTIC EFFECTS OF MOUSE BONE MARROW MESENCHYMAL STEM CELL-DERIVED EXTRACELLULAR VESICLES IN A MURINE MODEL OF NON-ALCOHOLIC STEATOHEPATITIS

Xinlei Li, Sherri Kemper and David Brigstock,
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Background: Extracellular vesicles (EVs) are important intercellular conduits for transport and delivery of molecular signals that drive pathogenic processes in the liver such as inflammation, fibrosis, and tumorigenesis. On the other hand, certain populations of EVs may have beneficial properties that offer new approaches for treating liver disease. Here we investigated the therapeutic actions of EVs from mouse primary bone marrow mesenchymal stem cells (BM-MSC) in a mouse model of non-alcoholic steatohepatitis (NASH). **Methods:** BM-MSC were isolated from the tibia and femurs of Swiss Webster mice, cultured in specialized growth medium, and identified by the presence of BM-MSC markers using Western blot. EVs were collected from 48-hr serum-free medium, purified by sequential centrifugation, and characterized by Western blot and Nanosight Tracking Analysis (NTA). EVs (1e+9 particles) were administered i.p. three times/week in 8-wk male C57Bl6J mice that received either normal chow diet or a choline-deficient L-amino-defined diet containing high (60%) fat (HF-CDAA). After 4 weeks, mice were sacrificed and analyzed for hepatic damage (serum ALT), liver histology and hepatic production of NASH-related molecules by immunofluorescence or RT-qPCR. Additionally, human LX-2 hepatic stellate cells (HSC) were treated with BM-MSC EVs for 48hr prior to analysis of fibrotic, proinflammatory gene expression by RT-qPCR, or erastin-induced ferroptosis. **Results:** BM-MSC were positive for MSC markers (CD146/MCAM, CD44, and CD29). BM-MSC EVs (mean Ø = 126 nm) expressed MSC and EV markers (CD146, CD9, Tsg101), but not cell-associated markers (calnexin). Mice receiving HF-CDAA diet exhibited elevated serum ALT, steatosis, reduced expression of FASN or SREBP1c, enhanced expression of SCD2 and SREBP2, interstitial fibrosis, elevated hepatic αSMA protein and mRNA levels (indicative of activated HSC) and increased expression of CCN2 (CTGF) and Col1A1. Concurrent administration of BM-MSC EVs during 4 weeks of HF-CDAA diet resulted in reversal of NASH-associated changes including attenuated ALT levels, reduced histological damage to the liver, reversal of lipid metabolism transcript expression towards normal, and attenuated production and/or expression of αSMA, CCN2, or Col1A1 protein and/or mRNA. Treatment of LX-2 cells with BM-MSC EVs consistently reduced the expression of CCN2, Col1A1, αSMA, and TIMP3 but did not alter proinflammatory gene expression. Lastly, BM-MSC EVs and erastin co-treatment in LX-2 cells induced efficient ferroptosis. **Conclusion:** BM-MSC EVs are therapeutic for NASH liver damage, steatosis-related gene expression, and fibrosis-related gene expression, the latter of which appear attributable at least in part to direct suppressive actions of EVs on activated HSC.

Disclosures: The following people have nothing to disclose: Xinlei Li, David Brigstock

Disclosure information not available at the time of publication: Sherri Kemper

2471-C | THERAPEUTIC EFFECTS OF OGB21502, A NOVEL TETRA-SPECIFIC DRUG, IN NON-ALCOHOLIC STEATOHEPATITIS (NASH) MICE MODELS

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Onegene Biotechnology

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

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

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

Benson Lu, Alkahest

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

Disclosures: Benson Lu – Grifols: Employee, Yes, No;

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

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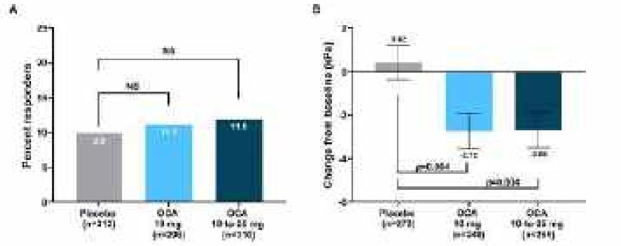
Background: Obeticholic acid (OCA) is a first-in-class farnesoid X receptor agonist and antifibrotic agent in development for treatment of liver fibrosis due to nonalcoholic steatohepatitis (NASH). This phase 3 randomized, double-blind, placebo-controlled multicenter study evaluated the efficacy and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

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



(A) "No worsening of NASH" was defined as no worsening of hepatocellular ballooning grade, of lobular inflammation grade, or of steatosis grade. (B) Data are least squares mean ± SE calculated using mixed effect repeated measure model with treatment group, visit, visit by treatment interaction, and stratification factors (type 2 diabetes at enrollment) as fixed effects, and baseline as a covariate. Mean (SD) baseline liver stiffness (kPa) was 22.11 (12.18), 22.81 (12.51), and 23.13 (12.38) for placebo, OCA 10 mg, and OCA 10-to-25 mg, respectively.

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

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2474-C | TYROSOL REDUCES NASH-ASSOCIATED STEATOSIS, FIBROSIS AND INFLAMMATION BY MODULATING THE HEPATIC IMMUNE PHENOTYPE: PRECLINICAL EVIDENCES

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

Background: The management of NAFLD and NASH represents a clinical challenge. Beneficial effects on liver health have been demonstrated by tyrosol (Tyr), a phenolic compound extracted from extra virgin olive oil. This study aims at evaluating Tyr effects on the hepatic and extrahepatic manifestations of metabolic liver diseases by using experimental 2D and 3D *in vitro* cellular models and a mouse model of NASH. **Methods:** The effect of Tyr *in vitro* was evaluated in 1) HepG2 cells treated with a palmitic:oleic acid mixture to induce fatty acid (FA) accumulation (fatty HepG2), 2) a co-culture of THP1-derived M1 macrophages and fatty HepG2, 3) multicellular spheroids of fatty HepG2, LX2 and THP1-derived macrophages mimicking the inflammatory NASH microenvironment. NASH was induced to C57BL6 mice with a high fructose-high fat diet administered for 14 weeks, combined to CCl_4 treatment (IP 0.05 ml/kg) in the last 4 weeks ($n = 12$). Tyr (10 mg/kg) was administered daily by oral gavage from week 4 ($n = 6$). A group of mice fed with standard diet ($n = 6$) was used as control. The open field, grid and rotarod tests were performed to evaluate NASH-related CNS disorders and sarcopenia. Liver histology was performed by H&E, Masson's trichrome, and ORO stainings. The protein expression of profibrotic αSMA and pro-oxidant NADPH oxidase isoform NOX1 was evaluated by IHC. Hepatic infiltration of CD4+, CD8+ lymphocytes, Tregs, M1- and M2- macrophages was assessed by means of FACS. **Results:** Tyr reduced FA accumulation in HepG2 cells in all the in vitro models ($p < 0.05$. In vivo, Tyr reduced steatosis, fibrosis, and the increase of aSMA expression observed in NASH animals ($p < 0.01$), as well as the number of hepatic inflammatory foci ($p < 0.05$). Tyr reduced NOX1 expression ($p < 0.05$). A drop of proinflammatory CD45+ F4/80+ CD86+ M1-type macrophages ($p < 0.05$), CD4+ ($p < 0.05$) and T helper effector CD4+ FoxP3- CD62L-lymphocytes ($p < 0.05$), and a concomitant increase of Treg CD4+ FoxP3+ cells ($p < 0.05$) was induced by Tyr. Moreover, Tyr attenuated fatigue and anxious behavior in NASH mice, restoring behavioral performances similar to those of healthy animals. **Conclusion:** In preclinical models, Tyr is effective in reducing steatosis, fibrosis, oxidative stress and inflammation, helping the resolution of NASH.

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

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

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

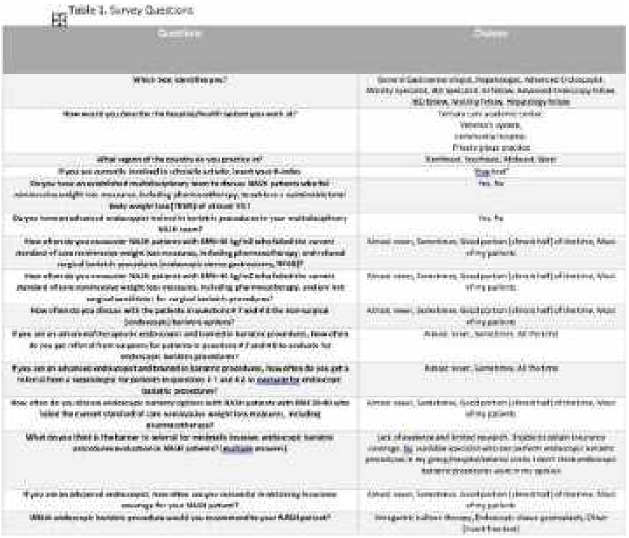

Table 1. Survey Questions

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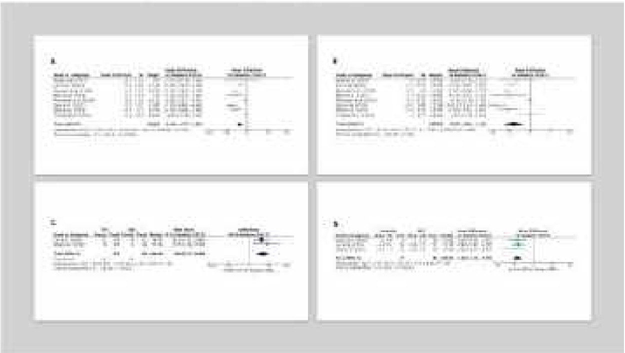
2476-C | DIGITAL THERAPEUTICS LEAD TO CLINICALLY SIGNIFICANT BODY WEIGHT LOSS IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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

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

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

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



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

Disclosures: Rohit Loomba – Aardvark Therapeutics: Consultant, No, No; Altimmune: Consultant, No, No; Anylam/Regeneron: Consultant, No, No; Amgen: Consultant, No, No; Arrowhead Pharmaceuticals: Consultant, No, No; AstraZeneca: Consultant, No, No; Bristol-Myer Squibb: Consultant, No, No; CohBar: Consultant, No, No; Eli Lilly: Consultant, No, No; Galmed Pharmaceuticals: Consultant, No, No; Gilead: Consultant, No, No; Glympse Bio: Consultant, No, No; Hightide: Consultant, No, No; Inipharma: Consultant, No, No; Intercept: Consultant, No, No; Inventiva: Consultant, No, No; Ionis: Consultant, No, No; Janssen Inc.: Consultant, No, No; Madrigal Pharmaceuticals: Consultant, No, No; Metacrine, Inc.: Consultant, No, No; NGM Biopharmaceuticals: Consultant, No, No; Novartis: Consultant, No, No; NovoNordisk: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Sagimet Biosciences: Consultant, No, No; Theratechnologies: Consultant, No, No; 89 bio: Consultant, No, No; Terns Pharmaceuticals: Consultant, No, No; 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2477-C | DIY CLINIC: DEVELOPMENT AND IMPLEMENTATION OF A SUCCESSFUL NON-ALCOHOLIC FATTY LIVER WEIGHT MANAGEMENT CLINIC WITHIN THE VA

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

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

on AOM. Overall, patients lost mean (SD) 8.5 (10) lbs over a mean follow-up of 4.5 months. 33 patients were started on GLP-1 agonists, and 5 on other agents, most commonly metformin. Of the 9 patients not on therapy, 2 declined, 3 had contraindications, 3 were lost to follow-up and one has therapy pending. Among patients treated with AOM who had at least four weeks of therapy prior to analysis and reported a follow-up weight (n = 24), 37% achieved 5% or greater total body weight loss with mean follow-up of 6.3 months. 33 patients (70%) had baseline lipids, liver enzymes and A1c available and 36 (75%) had baseline fibrosis staging (25 pts transient elastography, 8 biopsy, 3 magnetic resonance elastography). Only 8 patients had follow-up metabolic parameter testing during study period. **Conclusion:** Our clinic has obtained pharmacotherapy for three quarters of patients seen. Founding this clinic with a bottom up approach allowed us to revise our process iteratively and successfully recruit clinicians from other key specialties who were more inclined to join an established clinic. The ability to see patients and host our multi-disciplinary panel virtually enhanced ease of care. Coming together as a NAFLD clinician panel provided leverage to address barriers to pharmacotherapy within our institution. Future plans include addition of a pharmacist and dietician to our multi-disciplinary team, increased follow-up of fibrosis stage and metabolic parameters, and continued periodic quality improvement assessments.

Disclosures: The following people have nothing to disclose: Atoosa Rabiee, Jessica Davis

Disclosure information not available at the time of publication: Craig Casella, Jennifer Kerns, Marianna Papademetriou, Shruti Gandhi, Sabyasachi Sen

2478-C | EFFECT OF 12-WEEK INTERMITTENT CALORIE RESTRICTION ON LIVER FAT CONTENT IN COMPARISON WITH STANDARD-OF-CARE IN PATIENTS WITH NAFLD

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Background: Current guidelines do not recommend specific diet other than hypocaloric diet for patients with nonalcoholic fatty liver disease (NAFLD) because of insufficient data. This trial compared the effect of 12-week intermittent calorie restriction (ICR) and standard of care (SOC) on the changes in liver fat content. **Methods:** In this open-label randomized controlled trial (NCT05309642), NAFLD patients with magnetic resonance imaging-proton density fat fraction (MRI-PDFF) e 8% were included. Sample size was calculated with the effect of ICR from previous study, 80% power and 20% dropout rate. Patients were randomly assigned in a 1:1 ratio to receive 12-week ICR (the 5:2 diet) or SOC (80% of recommended total calorie), and stratified according to their BMI e 25 kg/m^2 or < 25 kg/m^2. The primary outcome was the proportion of patients who achieved the reduction of liver fat content measured by MRI-PDFF e 30%. **Results:** Of the total 72 participants who underwent randomization (n = 36, the obese group; n = 36, the non-obese group), 63 patients (n = 34 [obese]; n = 29 [non-obese]) completed 12-week follow-up visits. A significantly greater proportion of patients in the ICR group achieved liver fat content reduction e 30% compared to the SOC group (n = 24/32 [75.0%] vs. n = 15/31 [48.4%]; $P = 0.030$); obese group had a significant difference between the ICR and SOC groups (n = 11/17 [64.7%] vs. n = 5/17 [29.4%]; $P = 0.039$), however, non-obese group had not (n = 13/15 [86.7%] vs. n = 10/14 [71.4%]; $P = 0.311$). The relative reduction of body weight was comparable between the ICR and SOC groups (-5.5% vs. -4.0%; $P = 0.197$). There were no differences in the changes of liver stiffness measured using MR elastography (-0.1 kPa vs. -0.1 kPa), waist circumference (-7.0 cm vs. -6.5 cm), appendicular skeletal muscle mass (-0.6 kg vs. -0.3 kg), body fat (-3.0 kg vs. -2.2 kg), and levels of ALT (-19.0 IU/L vs. -14.0 IU/L), AST (-9.0 IU/L vs. -4.5 IU/L), triglyceride (-40.0 mg/dL vs. -32.5 mg/dL), total cholesterol (-3.0 mg/dL vs. -10.0 mg/dL), fasting glucose (-3.0 mg/dL vs. -1.0 mg/dL), HbA1c (-0.2% vs. -0.2%), and HOMA-IR (-1.0 vs. -0.1) between the ICR and SOC group (all $P > 0.05$). **Conclusion:** The ICR diet was more effective in reducing liver fat content in patients with NAFLD than SOC, suggesting its potential as an effective and feasible dietary intervention for this population. In addition, the impact of ICR diet was more prominent in the obese group compared to the non-obese group in our study.

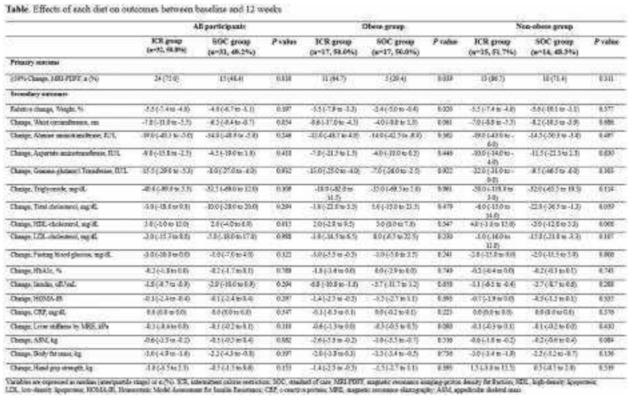

Table. Effects of each diet on outcomes between baseline and 12 weeks

Disclosures: The following people have nothing to disclose: Hwi Young Kim, Han Ah Lee, Hyeyoung Moon, Yuri Kim, Jeong Kyong Lee, Hye Ah Lee

2479-C | EVOLUTION OF DISEASE CHARACTERISTICS OF NAFLD PATIENTS WITH AND WITHOUT DIABETES: A META-ANALYSIS OF THE PLACEBO ARMS

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Background: The natural course of nonalcoholic fatty liver disease (NAFLD) is incompletely understood, particularly in relation to the presence of diabetes. This meta-analysis aims to measure the changes in the severity of NAFLD over time by analyzing data from the placebo arms of randomized controlled trials (RCTs), in order to investigate the natural history of NAFLD. **Methods:** We systematically searched 4 databases (PubMed, Medline, Embase, and Cochrane), until December 2021 to identify RCTs of NAFLD that included a placebo treatment arm. Primary outcome was the progression or regression of NAFLD assessed with histology. The pooled mean differences were estimated using a generalized linear mixed model. **Results:** The meta-analysis incorporated 8 RCTs involving 386 patients without diabetes and 24 RCTs involving 637 patients with diabetes, respectively. The pooled estimate of median intervention period was 24.0 weeks. The pooled estimate of mean change in steatosis grade by histology was -0.1 (95% CI -0.3 to 0.1, $I^2 = 49.3\%$) in patients without diabetes, and -0.4 (95% CI -0.5 to -0.2, $I^2 = 0.0\%$) in patients with diabetes. The pooled estimate of mean change in liver fat content measured using magnetic resonance imaging in patients with diabetes was -1.3% (95% -2.2% to -0.4%, $I^2 = 46.5\%$). The pooled estimate of mean change in fibrosis grade by histology was 0.0 in both patients without (95% CI -0.1 to 0.2, $I^2 = 43.5\%$) and with diabetes (95% CI -0.2 to 0.1, $I^2 = 0.0\%$). The pooled estimate of mean change in NAFLD activity score was -0.5 (95% CI -0.8 to -0.3, $I^2 = 32.0\%$) in patients without diabetes, and -1.5 (95% CI -2.1 to -0.9, $I^2 = 46.5\%$) in patients with diabetes; specifically, 0.0 in both patients without (95% CI -0.2 to 0.0, $I^2 = 44.8\%$) and with diabetes (95% CI -0.3 to 0.4, $I^2 = 41.8\%$) for changes in lobular inflammation; -0.1 (95% CI -0.2 to 0.0; $I^2 = 46.5\%$) in patients without diabetes, and -0.2 (95% CI -0.3 to 0.0; $I^2 = 10.8\%$) in patients with diabetes for changes in ballooning. The pooled estimate of changes in mean body weight was +0.3 kg (95% CI -0.3 to 0.9 kg, $I^2 = 0.0\%$) in patients without diabetes, and -1.0 kg (95% CI -1.6 to -0.3 kg, $I^2 = 43.5\%$) in patients with diabetes. The pooled estimates of changes in serum aminotransferases in patients without and with diabetes were -20.2 IU/L (95% CI -26.4 to -14.0 IU/L, $I^2 = 44.6\%$) vs. -4.5 IU/L (95% CI -8.5 to -0.4 IU/L, $I^2 = 45.2\%$) for ALT, and -10.7 IU/L (95% CI -14.9 to -6.5 IU/L, $I^2 = 48.9\%$) vs. -2.6 IU/L (95% CI -5.0 to -0.1 IU/L, $I^2 = 45.7\%$) for AST, respectively. **Conclusion:** In the placebo arm, neither patients without diabetes nor those with diabetes showed a significant improvement in histology. However, patients without diabetes had a greater decrease in ALT and AST levels than those with diabetes. This finding suggests that the pooled analysis of studies with longer duration might be necessary to capture the potential difference in the evolution of characteristics of NAFLD according to the presence or absence of diabetes.

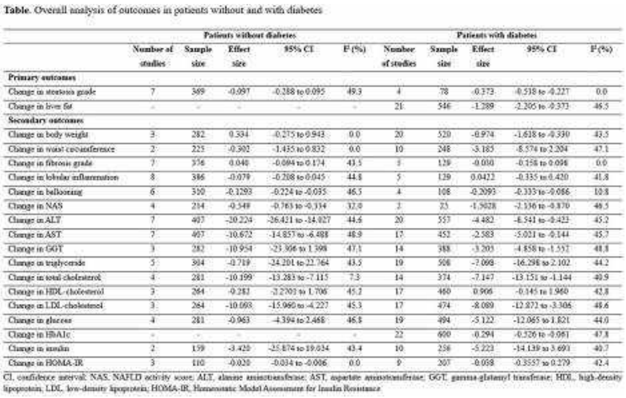

Table. Overall analysis of outcomes in patients without and with diabetes

	Patients without diabetes					Patients with diabetes				
	Number of studies	Sample size	Effect size	95% CI	I^2 (%)	Number of studies	Sample size	Effect size	95% CI	I^2 (%)
Primary outcomes										
Change in steatosis grade	7	369	-0.097	-0.288 to 0.095	49.3	4	78	-0.373	-0.518 to -0.227	0.0
Change in liver fat	-	-	-	-	-	21	546	-1.289	-2.205 to -0.373	46.5
Secondary outcomes										
Change in body weight	3	282	0.334	-0.275 to 0.943	0.0	20	520	-0.974	-1.618 to -0.330	43.5
Change in waist circumference	2	225	-0.302	-1.435 to 0.832	0.0	10	248	-3.185	-8.574 to 2.204	47.1
Change in fibrosis grade	7	376	0.040	-0.094 to 0.174	43.5	5	129	-0.030	-0.158 to 0.098	0.0
Change in lobular inflammation	8	386	-0.079	-0.208 to 0.045	44.8	5	129	0.0422	-0.335 to 0.420	41.8
Change in ballooning	6	310	-0.1293	-0.224 to -0.035	46.5	4	108	-0.2093	-0.333 to -0.086	10.8
Change in NAS	4	214	-0.549	-0.763 to -0.334	32.0	3	73	-1.5028	-2.136 to -0.870	46.5
Change in ALT	7	407	-20.224	-26.421 to -14.027	44.6	20	557	-4.482	-8.541 to -0.423	45.2
Change in AST	7	407	-10.672	-14.857 to -6.488	48.9	17	452	-2.583	-5.021 to -0.144	45.7
Change in GGT	3	282	-10.954	-23.306 to 1.398	47.1	14	388	-3.203	-4.858 to -1.552	48.8
Change in triglyceride	5	304	-0.719	-24.201 to 22.764	43.5	19	508	-7.098	-16.298 to 2.102	44.2
Change in total cholesterol	4	281	-10.199	-13.283 to -7.115	7.3	14	374	-7.147	-13.151 to -1.144	40.9
Change in HDL-cholesterol	3	264	-0.282	-2.2703 to 1.706	45.2	17	460	0.906	-0.145 to 1.960	42.8
Change in LDL-cholesterol	3	264	-10.093	-15.960 to -4.227	45.3	17	474	-8.089	-12.872 to -3.306	48.6
Change in glucose	4	281	-0.963	-4.394 to 2.468	46.8	19	494	-5.122	-12.065 to 1.821	44.0
Change in HbA1c	-	-	-	-	-	22	600	-0.294	-0.526 to -0.061	47.8
Change in insulin	2	159	-3.420	-25.874 to 19.034	43.4	10	256	-5.223	-14.139 to 3.693	40.7
Change in HOMA-IR	3	110	-0.020	-0.034 to -0.006	0.0	9	207	-0.058	-0.3557 to 0.279	42.4

CI, confidence interval; NAS, NAFLD activity score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance

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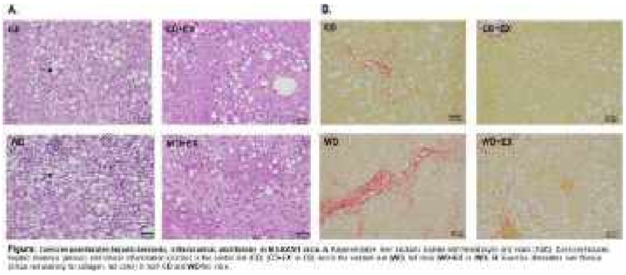
2480-C | EXERCISE ATTENUATES WESTERN DIET AGGRAVATED HEPATIC STEATOSIS AND FIBROSIS IN MS-NASH MICE WITHOUT WEIGHT LOSS

Fatiha Nassir, University of Missouri

Background: Metabolic-associated fatty liver disease (MAFLD) consists of fat accumulation in the liver due to obesity and insulin resistance-associated metabolic dysfunction. Current non-pharmacological therapeutic options for MAFLD focused on reducing or preventing weight gain through lifestyle modifications such as exercise, but little is known about the underlying mechanisms. Therefore, reproducible animal models to recapitulate the pathophysiology of MAFLD in humans are needed to improve our understanding of the mechanisms for the beneficial effect of exercise on the disease, and to explore novel therapeutic options. **Methods:** MS-NASH is a mouse model for lipotoxicity-induced metabolic dysfunction clinically relevant to human MAFLD progression. Six-week-old male mice were fed a control (CD) or western diet (WD) for twenty weeks. The mice remained sedentary or exercised via free access to running wheels. At the end of the 20 weeks, measures of glucose tolerance, blood glucose, triglyceride, hepatic steatosis, and fibrosis were assessed. **Results:** Compared to the CD, the WD increased body weight over the twenty weeks of dietary treatment, starting at three weeks of age. However, voluntary exercise did not alter body weight. The WD fed mice exhibited glucose intolerance compared to CD-fed mice, which was ameliorated with exercise. Exercise did not affect glucose tolerance in CD fed MS-NASH mice. Liver and fat weight increased in WD compared to CD fed mice. Exercise normalized the WD associated increase in fat mass but did not affect liver weight. The increase in blood glucose and triglyceride with WD was also normalized with exercise. Importantly, voluntary exercise improved hepatic steatosis (liver triglyceride, H&E staining, and Oil red-O staining) and fibrosis (serious-red staining) in both CD and WD fed mice. **Conclusion:** These data provide the first direct experimental evidence that voluntary running wheel exercise, independent of weight loss, prevents the aggravation of diet-induced hepatic steatosis and fibrosis in a clinically relevant mouse model of MAFLD. Ongoing studies will determine the mechanisms involved.



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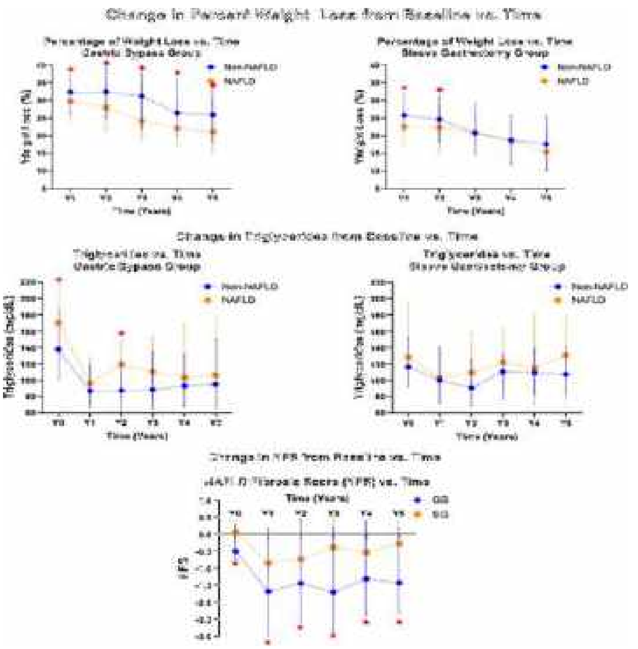
2481-C | IMPACT OF NONALCOHOLIC FATTY LIVER DISEASE ON WEIGHT LOSS AFTER BARIATRIC SURGERY: 5-YEAR POST-OPERATIVE ANALYSIS OF 714 PATIENTS ENROLLED IN A BARIATRIC SURGERY COHORT

Monica A. Tincopa[1], Mohammed Abu-Rumaileh[2], Raad Haddad[3], Matheos Yosef[3], Nazanene Esfandiari[3], Andrew Kraftson[3], Corey Lager[3], Shafaq Khairi[3], Jordan Bushman[3], Shokoufeh Khalatbari[3], Oliver Varban[3] and Elif Oral[3], (1)University of California San Diego, (2)University of Toledo, (3)University of Michigan

Background: Long-term longitudinal data on outcomes for non-alcoholic fatty liver disease (NAFLD) patients following bariatric surgery is limited and the sustainability of improvement in hepatic outcomes is not well established. The aim of this study was to assess the impact of bariatric surgery stratified by type of bariatric surgery and presence of NAFLD on weight, metabolic and hepatic outcomes over 5-years of follow-up. **Methods:** Adults who underwent sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (GB) at our center between 2008-2013 were analyzed. Weight, lipids, A1c, liver enzymes, NAFLD Fibrosis score (NFS) and imaging data were obtained at baseline and yearly for up to 5-years post-surgery via retrospective chart review. NAFLD at baseline was assessed based on liver biopsy, imaging, or clinical diagnosis (ICD-9 or 10 codes) prior to surgery. Persistent NAFLD was defined based on evidence of hepatic steatosis on abdominal imaging (ultrasound, CT or MRI) over follow-up period. Descriptive and bivariate analyses were performed. **Results:** The cohort included 714 patients, 79% female, median age 45, median BMI 47.4 and 36% with diabetes. 221 patients had data confirming NAFLD at baseline (SG = 93, GB = 128). The SG group had significantly higher weight while the GB group had significantly higher A1c, cholesterol and triglycerides (TG). Individual's with NAFLD were older (47 vs 44), more often male (72.9 vs 81.7% female) and had a higher prevalence of diabetes, hypertension and dyslipidemia ($p < 0.001$). Figure 1 demonstrates trends in outcome parameters over 5-years of follow-up by surgery type and NAFLD status. At all-time points, the median weight loss was highest in the GB group. Individual's with NAFLD lost less total weight with the impact more pronounced in the GB group. The effect of NAFLD on reduction in TG was only significant in the GB during year two post-surgery. There were no statistically significant differences in change in LDL based on NAFLD status. Among those with NAFLD, those in the GB group had more improvement in NFS. In a multivariable model for percent total weight loss adjusted for baseline BMI, age, sex, surgery type, and follow-up time, only baseline diabetes and NAFLD were statistically significant covariates (p 0.002 and 0.006 respectively). Overall, 83 NAFLD patients (37.5%) had follow-up imaging with 28 (33.7%) having evidence of persistent NAFLD. Among those with persistent NAFLD, imaging post-surgery was done at 1-2 years in 28.7%, 2-4 years in 16.3%, and > 4 years in 55%. In a multivariable model, only baseline hyperlipidemia was independently associated with persistent NAFLD ($p = 0.04$). **Conclusion:** Patients with NAFLD undergoing bariatric surgery experienced less weight loss over 5-years of follow-up with GB having more beneficial impact on hepatic and metabolic outcomes. One-third of NAFLD patients with follow-up imaging had persistent NAFLD with baseline dyslipidemia as the only independent predictor.



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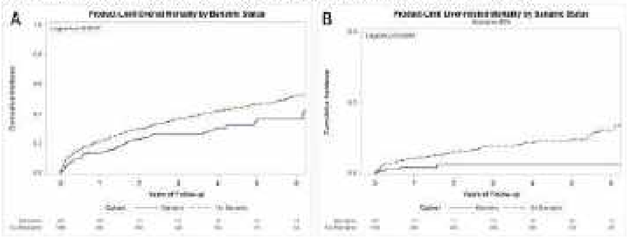
f 2482-C | LONG-TERM ALL-CAUSE AND LIVER-RELATED MORTALITY OF PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)-RELATED LIVER CIRRHOSIS WHO UNDERWENT BARIATRIC SURGERY: A POPULATION-BASED STUDY

Nicholas Ajit Rouillard[1], Leslie Yeeman Kam[2], Scott D. Barnett[2], Richie Manikat[3], Ramsey C. Cheung[4] and Mindie H. Nguyen[2], (1)Stanford University Medical Center, (2)Stanford University Medical Center, Palo Alto, CA, (3)Stanford University - School of Medicine, (4)Veterans Affairs Palo Alto Health Care System

Background: NAFLD affects over one in three Americans and is a major cause of end-stage liver disease in the U.S., paralleling the obesity epidemic. Bariatric surgery is a treatment option for obesity that can lead to liver steatosis and fibrosis regression. However, long-term outcome data of bariatric surgery remains sparse, especially in cirrhosis patients. Therefore, we aimed to evaluate the long-term all-cause and liver-related mortality of a large population-based cohort of NAFLD patients with cirrhosis undergoing bariatric surgery in California, USA. **Methods:** We identified 101,651 patients with NAFLD (via ICD-9 codes) from the California's Department of Healthcare Access and Information database from 2005 to 2013 with linked data to the California Death Statistical Master File. Of these, 30,037 had cirrhosis (767 underwent bariatric surgery and 29,270 did not). Propensity score matching (PSM, on age, sex, race/ethnicity, health insurance type, Charlson comorbidity index [CCI], liver decompensation, and hospital size/setting) in a 1:5 ratio was performed to balance the background risks between bariatric and non-bariatric patients, yielding a PSM cohort of 636 bariatric and 3,180 non-bariatric patients. **Results:** At baseline, compared to the non-bariatric group, bariatric patients were 5 years younger (50.7 vs. 55.7 y; $p < 0.0001$), more likely female (70.3% vs. 54.6%; $p < 0.0001$), White (62.9% vs. 52.5%; $p < 0.0001$), with private insurance or seen at a large, academic, or urban hospital setting (all $p < 0.05$), while having lower CCI scores (1.62 vs. 2.78; $p < 0.0001$) and lower decompensated cirrhosis prevalence (57.8% vs. 82.4%; $p < 0.0001$). After PSM, the two study groups had similar age ($p = 0.88$), sex ($p = 0.96$), race/ethnicity ($p = 0.88$), and comparable insurance ($p = 0.58$) and decompensated cirrhosis distributions ($p = 0.59$), and hospital characteristics (all $p > 0.05$), though with lower CCI scores (1.58 vs. 1.68; $p < 0.0001$). Among the PSM cohort, the 5-year cumulative mortality rates were significantly lower for bariatric patients compared to non-bariatric controls for both all-cause mortality (36.4% vs. 46.7%; $p = 0.0047$) and liver-related mortality (2.39% vs. 9.52%; $p = 0.0064$; Figures 1AB). On multivariable Cox's regression analysis adjusted for age, sex, and CCI, bariatric surgery was independently associated with a 32% and 70% reduction in all-cause (aHR = 0.68, 95% CI: 0.53-0.88) and liver-related mortality (aHR = 0.30, 95% CI: 0.12-0.75), respectively. **Conclusion:** Patients with NAFLD and cirrhosis undergoing bariatric surgery experienced significant long-term benefits with lower all-cause and liver-related mortality and should be considered for obese patients who are reasonable surgical candidates.

Figure 1: Cumulative incidence of (A) overall mortality and (B) liver-related morality among NAFLD patients with baseline cirrhosis by bariatric status after PSM (N=3,816)



Disclosures: The following people have nothing to disclose: Nicholas Ajit Rouillard, Leslie Yeeman Kam, Scott D. Barnett, Richie Manikat, Mindie H. Nguyen

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

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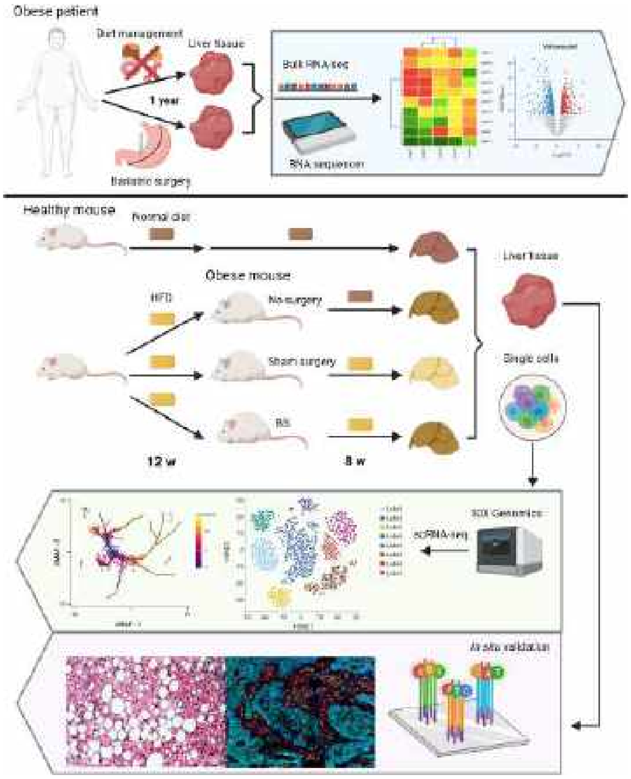
2483-C | NO FUNDING SOURCE

Shuai Chen[1], Xiurong Cai[2], Peng Song[1], Frank Tacke[2], Adrien Guillot[2], Liming Tang[1] and Hanyang Liu[1,2], (1) Nanjing Medical University, China, (2)Charité – Universitätsmedizin Berlin

Background: Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide, composed of metabolic dysfunction, steatosis, inflammation and fibrosis. Importantly, nonalcoholic fatty liver (NAFL) caused by elevated hepatic lipid deposition acts as not only the consequence of obesity, but also the early stage of the NAFLD. It has been reported that morbidly obese patients represent more than 90% of patients with NAFLD. Till now, no effective resolutions have been approved to effectively prevent the disease progression. Current evidence suggests that weight loss has been considered as a potential treatment for NAFLD by remising hepatic steatosis, inflammation and fibrosis. Weight loss approaches include lifestyle alterations (mainly diet management), metabolic medicine and bariatric surgery (BS). Recently, BS is considered to be a novel disease-modifying therapy for NAFLD, according to clinical studies. Despite physiological alterations, underlying mechanisms of cellular cross-talk and microenvironment remain indeterminate. **Methods:** In this study, we gathered open bulk RNA-seq datasets from patient cohorts. Gene alterations of metabolism, inflammation and carcinogenesis were compared according to liver-derived transcriptomic data from post-surgery and diet-managed patients. Furthermore, we established mouse BS models (including sleeve gastrectomy and bypass surgery). As an ongoing work, we perform the single-cell transcriptomic analysis on liver tissues from mouse models [healthy, high-fat diet (HFD) + regression, HFD + sham surgery and HFD + BS mice). Furthermore, we will identify metabolism reprogramming and immune landscape according to cell clustering, cellular interactions and functional enrichment analysis. To reveal the metabolism-related immune modulation, the metabolism-immune association and key factors will be demonstrated. **Results:** We demonstrated that the post-BS livers show more improvements in metabolism-, inflammation- and carcinogenesis-related markers, compared to the diet management. In addition, differences were disclosed in immune cell infiltration (especially macrophage populations) in post-BS patients' livers. Accordingly, we speculate that the immune modulation in post-surgery livers might contribute to metabolic improvement, exerting superior effectiveness than the diet-management. On this basis, we will be able to reveal the metabolism reprogramming and immune modulation, aiming to characterize metabolism-inflammation interactions and key molecules in BS-intervened NAFLs. **Conclusion:** This study determined superior functions of BS on metabolism improvement and NAFL attenuation, compared to diet management. Furthermore, this study will disclose novel mechanisms and clinical potentials of the BS intervenes nonalcoholic fatty liver.



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2484-C | OPTIMISTIC TRIAL: WEIGHT LOSS AND BODY COMPOSITION CHANGES FROM ALTERNATE-DAY MODIFIED FASTING AND CONTINUOUS LOW-CALORIE DIET: A FEASIBILITY TRIAL IN CIRRHOSIS PATIENTS WITH OBESITY

Winston Dunn[1], Felicia Steger[2], Joseph Donnelly[2], Jessica C. Rachman[2], Robert Montgomery[2] and Steve Herrman[2], (1)University of Kansas Medical Center, Kansas City, KS, (2)University of Kansas Medical Center

Background: Patients with advanced liver disease face challenges in achieving weight loss while preserving skeletal muscle mass. This pilot study aimed to evaluate the feasibility of alternate-day modified fasting (ADMF) and continuous low-calorie diet (LCD) interventions in promoting weight loss and preserving Fat Free Mass (FFM) in patients with Child-Pugh Class A cirrhosis and obesity. **Methods:** An open-label, randomized controlled trial was conducted involving 20 adult patients with cirrhosis and obesity. Participants were randomized to either the ADMF ($n = 11$) or LCD group ($n = 9$). Changes in body composition, sarcopenia measures, and functional outcomes were assessed over a 24-week period. **Results:** Thirteen participants completed the 24-week trial (ADMF: age = 54.4 ± 8.0; BMI = 35.9 ± 4.8; Body Fat Percent = 44.3 ± 5.1%, Female = 4; LCD: age = 54.7 ± 6.6; BMI = 39.5 ± 7.6; Body Fat Percent = 45.0 ± 8.9%, Female = 4). The ADMF group lost an average of 14.5 ± 6.9kg (13.4%) of total body weight, while the LCD group lost 11.4 ± 6.7kg (10.8%). Total body fat percent decreased in both groups (ADMF: -3.6 ± 3.2%; LCD = -2.5 ± 2.0%). Fat-free mass (FFM) accounted for 34.9 ± 17% of the total weight loss in the ADMF group and 32.1 ± 20% in the LCD group. The Liver Frailty Index (LFI) with a decreased in both group of (ADMF: 0.5 ± 0.3; LCD: 0.5 ± 0.2). Functional measures, such as Timed Chair Stands, showed improvement in both groups. **Conclusion:** This pilot study demonstrates the feasibility of the ADMF and LCD interventions in producing significant weight loss while improving body composition in patients with cirrhosis and obesity. Further research is needed to validate these findings in larger cohorts and to assess specific measures related to muscle quality and visceral fat.

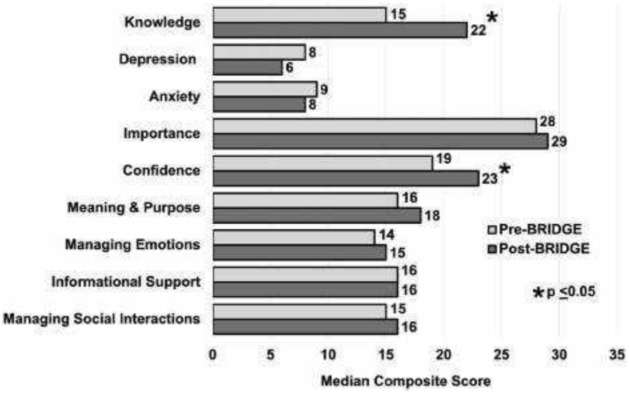
Disclosures: The following people have nothing to disclose: Winston Dunn, Felicia Steger, Joseph Donnelly, Jessica C. Rachman, Robert Montgomery, Steve Herrman

2485-C | OPTIMIZING PATIENT MANAGEMENT FOR NONALCOHOLIC FATTY LIVER DISEASE THROUGH BEHAVIORAL RESOURCES & INTERVENTION THROUGH DIGITAL GROUP EDUCATION (BRIDGE)

Nghiem B. Ha[1], Lisa L. Catalli[1], Sara A. Miller[1], Eliana Z. Agudelo[2], Simone K. Madan[1], Riley Tan[1], Thomas J. Hoffmann[1], Miranda E. Surjadi[1], Danielle Brandman[3] and Jennifer C. Lai[1,4], (1)University of California, San Francisco, (2)University of California, San Francisco, San Francisco, CA, (3)Weill Cornell Medical College, New York, NY, (4)University of California-San Francisco, San Francisco, CA

Background: Managing nonalcoholic fatty liver disease (NAFLD) requires lifestyle and dietary modifications, but providers often lack the time and resources to offer effective counseling at each patient visit. A holistic, multicomponent group approach involving patient engagement can enhance the effectiveness of provider counseling. We developed BRIDGE, a novel small group program led by advanced practice providers (APPs) to enhance knowledge, confidence, and self-efficacy among patients with NAFLD regarding lifestyle management. **Methods**: BRIDGE is a video-based, 6-session (90 min each), bi-weekly, small group psychoeducational program led by APPs. Each session includes didactics, group discussion for peer-to-peer learning/support, and individual consultations to develop personalized behavioral-change strategies using motivational interviewing and cognitive behavioral techniques. Patients rated their knowledge, importance, and confidence to make health-habit changes on a 5-point scale survey. Mental and social health changes were measured using 6 Patient-Reported Outcome Measurement Information System (PROMIS) short forms 2-week before and after the program. **Results**: Included were 15 adults with NAFLD who completed BRIDGE from 9/2022-4/2023, with available pre-/post-surveys: 73% women, median age 62 years and BMI of 34 kg/m^2; 87% obese, 27% diabetes, 67% hypertension, and 67% hyperlipidemia. Race/ethnicity: 33% non-Hispanic white, 40% Hispanics, 26% Asian/Native American. All had severe steatosis with median (IQR) CAP of 339 dB/m (324-374); 20% had advanced fibrosis/cirrhosis. After completing BRIDGE, patients reported notable improvements in various life domains, including recognizing the importance of healthy habits, meaning and purpose, managing emotions/mental health, and seeking support, with significant improvements in knowledge and confidence in lifestyle changes to improve NAFLD (Figure). Most (73%) achieved weight loss (mean ± SD of 2.6 ± 4.7 kg) with significant improvement in muscle strengthening exercise frequency (mean ± SD increased of 2 ± 2 d, $p = 0.02$). Qualitative feedback from patients indicated high satisfaction with BRIDGE. **Conclusion**: Our novel telehealth psychoeducational program enhanced patients' knowledge, confidence, and understanding of health-related behavioral changes for those with NAFLD, while also improving mental well-being and social support. Future research should identify the optimal program length for achieving and sustaining lifestyle changes, which can ultimately improve clinical outcomes.

Figure. Pre- and post-BRIDGE median composite score of patients' knowledge, importance and confidence in changing health habits, including change in mental and social domains of health



Disclosures: Jennifer C. Lai – Novo Nordisk: Advisor, No, No; Genfit: Consultant, No, No; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Vir: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gore: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Flagship Pioneering: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Nghiem B. Ha, Lisa L. Catalli, Sara A. Miller, Eliana Z. Agudelo, Simone K. Madan, Riley Tan, Thomas J. Hoffmann, Miranda E. Surjadi, Danielle Brandman

2486-C | PERK AMELIORATES HEPATIC LIPOTOXICITY VIA ACTIVATING THE p62-ULK1 AXIS-MEDIATED NONCANONICAL KEAP1-Nrf2 PATHWAY

Da Hyun Lee, Severance Biomedical Science Institute, Yonsei University College of Medicine

Background: Hepatic lipotoxicity is a crucial factor in nonalcoholic steatohepatitis resulting from excessive saturated fatty acid-induced reactive oxygen species (ROS)-mediated cell death, which is associated with the accumulation of endoplasmic reticulum (ER) stress in the liver. The unfolded protein response (UPR) alleviates ER stress by restoring ER protein folding homeostasis. However, whether UPR contributes ROS elimination under lipotoxicity remains unclear. The Kelch like ECH-associated protein 1 (KEAP1)-nuclear factor, erythroid 2 like 2 (Nrf2) pathway provides antioxidant defense against lipotoxic stress by eliminating ROS and can be activated by the p62-Unc-51 like autophagy activating kinase 1 (ULK1) axis. However, the upstream molecular regulator of the p62-ULK1 axis-induced KEAP1-Nrf2 pathway in the same context remains unidentified. **Methods:** PKR-like ER kinase (PERK) depleted mice were subjected to fasting followed by refeeding with high-carbohydrate, fat-free diet (HCD) and the effects on the KEAP1-Nrf2 pathway and autophagy were analyzed. Furthermore, the molecular mechanism of this pathway was assessed using *in vitro* samples. **Results:** Here, we demonstrated that PKR-like ER kinase (PERK), a UPR sensor, directly phosphorylates p62 and ULK1, thereby activating the noncanonical KEAP1-Nrf2 pathway. We elucidated the molecular mechanism underlying the PERK-mediated p62-ULK1 axis-dependent noncanonical KEAP1-Nrf2 pathway, which could represent a promising therapeutic strategy against hepatic lipotoxicity. **Conclusion:** Therefore, our findings suggest the next line of defense against ER stress-mediated lipotoxicity. In addition, we elucidated the molecular mechanism underlying the p62-mediated noncanonical KEAP1-Nrf2 pathway, which may serve as a promising new therapeutic target strategy against lipotoxicity in NASH treatment

Disclosures: The following people have nothing to disclose: Da Hyun Lee

2487-C | ROLE OF HONEY EXOSOME-LIKE NANOPARTICLES IN AGING-RELATED NON-ALCOHOLIC STEATOHEPATITIS

Baolong Liu and Jiujiu Yu, University of Nebraska Lincoln

Background: Non-alcoholic steatohepatitis (NASH), a progressive form of non-alcoholic fatty liver disease, has become a leading cause of liver failure. No therapeutics is currently approved to specifically treat this condition. We recently identified exosome-like nanoparticles in honey (H-ELNs) with potent anti-inflammatory functions. In this study, we assessed the role of H-ELNs in aging-related NASH. **Methods:** H-ELNs were isolated from honey using the standard ultracentrifugation method, and orally administered to 1-year-old C57BL/6J mice once a week for one year. When the mice reached two years old, they were sacrificed and their livers were collected for further analysis.

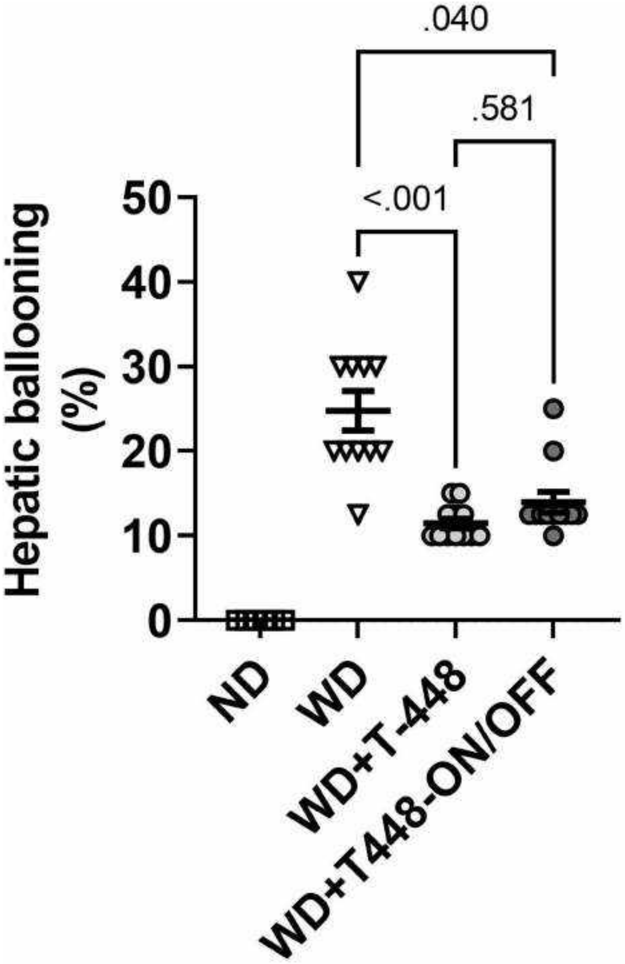
The target cells of H-ELNs in aged liver were assessed. Finally, the biomolecules in H-ELNs were analyzed to elucidate the active components. **Results:** In naturally aged mice, the liver demonstrated extensive inflammation, fibrosis, and formation of nodules, which are typical manifestations of NASH. Interestingly, H-ELNs largely curbed this aging-related hepatic inflammation, fibrosis, and nodule formation. In the aged liver, Kupffer cells were mainly responsible for taking up H-ELNs. Further mechanistic studies showed that H-ELNs suppressed the functions of two transcription factors c-Jun and nuclear factor-kappaB (NF-kB), as well as the NLRP3 inflammasome in the aged liver. Luteolin, miR-5110, and miR-5108 in H-ELNs were found to potently inhibit both c-Jun and NF-kB activities. **Conclusion:** H-ELNs could serve as a promising user-friendly new agent to prevent NASH development.

Disclosures: The following people have nothing to disclose: Baolong Liu, Jiujiu Yu

2488-C | SUSTAINABILITY OF TOTUM-448 BENEFICIAL EFFECTS FOLLOWING INTERRUPTION OF SUPPLEMENTATION IN A HAMSTER MODEL OF DIET-INDUCED NASH

Vivien Chavanelle[1], Yolanda F. Otero[1], Doriane Ripoche[1], Marie Vallier[1], Cédric Langhi[1], Clément Besqueut-Rougerie[1], Valérie Hervieu[2], Béatrice Morio[3], Gaël Ennequin[4], Florian Le Joubioux[1], Thierry Maugard[5], Sebastien Peltier[1] and Pascal Sirvent[1], (1) Valbiotis, (2)Hospices Civils De Lyon, (3)Université Lyon1, (4)Université Clermont Auvergne, (5)Université La Rochelle

Background: Totum-448 is a patented combination of 5 plant extracts and choline. We previously showed that 12 weeks of supplementation with Totum-448 improved steatosis, inflammation, and fibrosis markers in hamsters with diet-induced NASH. In this work, we aimed at assessing the sustainability of Totum-448 associated beneficial effects on NASH by interrupting treatment after a 12-week supplementation period, in western-diet (WD)-fed hamsters. **Methods:** Male golden Syrian hamsters were fed a WD (high-fat, high-cholesterol) supplemented or not with Totum-448 (5%, WD+T-448) for 18 weeks. A 3rd group of hamsters was fed WD+T-448 for 12 weeks before switching to non-supplemented WD for 6 more weeks (WD+T-448-ON/OFF) and a 4th group of hamsters fed a normal diet (ND) was used as control. Food intake, body weight and body composition were monitored continuously. NASH was evaluated using circulating and hepatic biochemical and histological markers of steatosis, inflammation, and fibrosis. **Results:** After 18 weeks, Totum-448 supplemented animals displayed significantly lower liver lipids compared to WD (triglycerides, TG, total cholesterol, TC, and free fatty acids, FFA), as well as decreased area of Oil-Red-O-stained liver sections. Interruption of supplementation for 6 weeks in WD+T-448-ON/OFF resulted in a moderate increase in all liver lipids, compared to WD-T448, though remaining significantly lower than WD. Histological scoring of paraffin-embedded liver sections revealed a significant improvement of hepatic ballooning in 18-week supplemented animals (WD+T-488) that remained significantly ameliorated in WD+T-448-ON/OFF, compared to WD, although to a lesser extent. Finally, in WD+T-448, perirenal, inguinal, and mesenteric fat pad weights were increased and serum FFA levels were decreased, compared to WD, suggesting improved fat storage capacity and reduced lipolysis in adipose tissue. Group WD+T-448-ON/OFF exhibited an intermediate profile, in-between WD+T-448 and WD. **Conclusion:** Supplementation with Totum-448 for 18 weeks resulted in major improvements in several hallmarks of NASH development, including reduction of liver lipid content (steatosis) and ballooning, in WD-fed hamsters. Despite interruption of supplementation, group WD+T-448-ON/OFF displayed an intermediate profile, with most benefits conserved to a lesser degree. The improvement of lipid storage capacity in adipose tissue may constitute a first explanatory hypothesis.

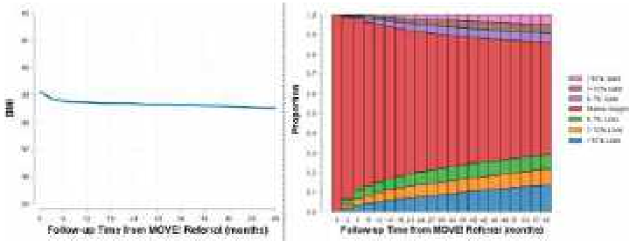


Disclosures: Vivien Chavanelle – Valbiotis: Employee, Yes, No;
Yolanda F. Otero – Valbiotis: Employee, Yes, No;
Doriane Ripoche – Valbiotis: Employee, Yes, No;
Marie Vallier – Valbiotis: Employee, Yes, No;
Cédric Langhi – Valbiotis: Employee, Yes, No;
Clément Besqueut-Rougerie – Valbiotis: Employee, Yes, Yes;
Béatrice Morio – Valbiotis: Independent contractor (including contracted research), Yes, No;
Florian Le Joubioux – Valbiotis: Employee, Yes, No;
Thierry Maugard – Valbiotis: Consultant, Yes, No;
Sebastien Peltier – Valbiotis: Executive role , Yes, No;
Pascal Sirvent – Valbiotis: Employee, Yes, No;
The following people have nothing to disclose: Valérie Hervieu, Gaël Ennequin

2489-C | THE IMPACT OF WEIGHT LOSS PROGRAMS ON BMI TRAJECTORY IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE: A VETERANS HEALTH ADMINISTRATION STUDY

Nadim Mahmud, Hospital of the University of Pennsylvania and David E. Kaplan, Division of Gastroenterology and Hepatology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Background: Weight loss is the mainstay of management for patients with non-alcoholic fatty liver disease (NAFLD), and first-line recommendations advise lifestyle changes incorporating diet and exercise. The impact of formal weight loss programs has not been studied at a population level in NAFLD patients. This is of interest given that delays in achieving significant weight loss will increase the risk of progressive fibrosis, metabolic and cardiovascular morbidity, and cancer risk. We studied the impact of referral to MOVE!, a nationally-implemented, behavioral weight loss program in the Veterans Health Administration (VHA), on weight trajectories in NAFLD patients. **Methods:** This was a retrospective cohort study of VHA patients with body mass index (BMI) > 35 and NAFLD, identified using a validated algorithm, who were referred to MOVE! between 1/2008-12/2022. Baseline demographic, BMI, and comorbidity data were collected. Time-updated BMI was ascertained every 90 days through 5 years of follow-up. A median spline curve of BMI over time was plotted; bariatric surgery events were identified, and BMI trajectory data were censored at time of surgery. Stacked bar charts depicting percentage weight loss or gain (cut points 5%, 7%, 10%) over time were evaluated. **Results:** A total 87,469 NAFLD patients were included from 125 VHA centers. The cohort had median age 56 years (IQR 46, 64), 87.4% male, 61.0% white, with baseline BMI 39.1 (IQR 36.8, 42.5), and 51.1% had diabetes. Through 5 years, 2,137 (2.4%) received bariatric surgery, at median 20.6 months follow-up (IQR 11.1, 37.0). Median BMI for the cohort decreased minimally over 5 years, from ~39.1 to ~38.5 (Figure panel left). The majority of patients had no meaningful weight loss or weight gain through maximum follow-up (Figure panel right). At 5 years, 13.7% achieved > 10% weight loss, 8.0% achieved 7-10% weight loss, 7.4% achieved 5-7% weight loss, and 70.9% experienced either no meaningful weight loss or had significant weight gain. **Conclusion:** In this large VHA cohort of NAFLD patients referred to the MOVE! weight loss program, the majority (70.9%) experienced either no meaningful weight loss or gain significant weight. Bariatric surgery is utilized very infrequently in this cohort. Future studies should aim to identify factors associated with good response to lifestyle modification programs; our data also argue for more aggressive utilization of bariatric surgery when patients develop appropriate indications.



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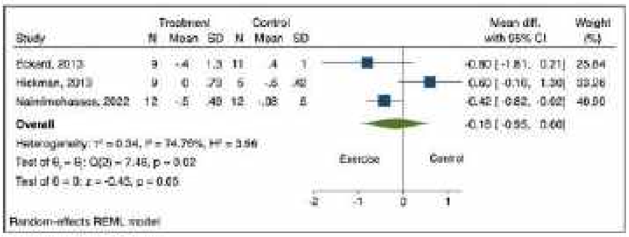
2490-C | THE INDEPENDENT EFFECT OF EXERCISE ON HISTOLOGICAL OUTCOMES IN BIOPSY-PROVEN NON-ALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

George Chen, Bubu A Banini, Albert Do, Craig Gunderson, Saif Zaman and Joseph K. Lim, Yale University, New Haven, CT

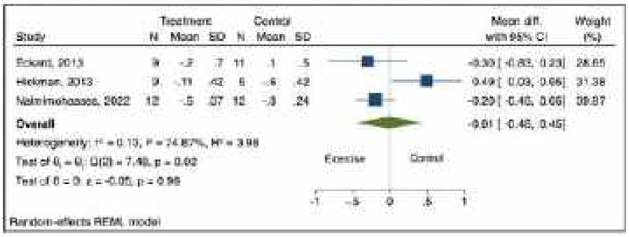
Background: In patients with non-alcoholic fatty liver disease (NAFLD), weight reduction achieved via lifestyle modification including exercise and dietary interventions has been shown to improve histological outcomes. However, the independent effect of exercise on liver histology in NAFLD remains unclear. As such, we conducted a systematic review and meta-analysis of the independent effect of exercise on histological endpoints in biopsy-proven NAFLD. **Methods:** A systematic literature search of Embase, PubMed, and Web of Science databases was performed from inception to October 2022 in accordance with PRISMA guidelines. Articles were selected based on the following inclusion criteria: (1) involved human subjects with biopsy-proven NAFLD, (2) analyzed the independent effect of exercise on histological endpoints, and (3) were interventional studies. Meta-analysis was performed for histological outcomes with complete pre- and post-intervention data reported by at least three studies. The pooled effect of exercise on histological outcome was estimated by calculating the standardized mean difference in a random-effects model. Statistical heterogeneity between studies was quantified using Cochran's Q test. **Results:** Our initial literature search yielded 271 unique articles. After removing studies not meeting the inclusion criteria, we identified a total of four interventional studies that assessed the independent effect of exercise on histological outcomes in biopsy-proven NAFLD. Two studies showed significant exercise-induced improvement in both liver fibrosis and hepatocyte ballooning, while two studies did not detect significant changes in histological parameters. Among measured histological outcomes, liver fibrosis, Brunt grade, and NAS met criteria for meta-analysis with data available from a minimum of three studies. The pooled effect size of exercise on liver fibrosis (mean difference [MD] -0.18; 95% confidence interval [CI] -0.95 to 0.60; p = 0.65), Brunt grade (MD -0.01; CI -0.48 to 0.45, p = 0.96), and NAS (MD 0.61; 95% CI -0.44 to 1.66; p = 0.26) was not statistically significant compared to the control groups (Figure 1A-C). High heterogeneity was observed between the studies for all three histological outcomes ($I^2 = 75\%$ for liver fibrosis; 75% for Brunt grade; 71% for NAS). **Conclusion:** This is the first meta-analysis to investigate exercise-induced changes in liver histology in patients with NAFLD. Based on the current literature, we found that exercise does not independently affect histological outcomes in NAFLD. Additional well-powered randomized controlled trials are needed to better understand the impact of exercise on histological and clinical endpoints in NAFLD.

Figure 1

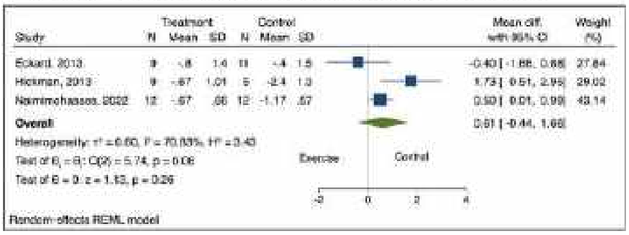
A. Pooled effect of exercise on liver fibrosis in biopsy-proven NAFLD



B. Pooled effect of exercise on Brunt grade in biopsy-proven NAFLD



C. Pooled effect of exercise on NAFLD activity score in biopsy-proven NAFLD



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Joseph K. Lim:

f 2491-C | The WELL Study: Very Low-Carbohydrate diet and mindful eating training reduces liver fat and multiple cardiometabolic risk factors in high risk PNPLA3 adults: A Pilot Study

Laura Saslow[1], Jamie Krinock[1], Alison O'Brien[1], Kate Raymond[1], Judith Moskowitz[2], Jennifer Daubenmier[3], Hovig Bayandorian[4], Deanna J. M. Isaman[1], Dina H. Griauzde[1] and Elizabeth K. Speliotes[5], (1)University of

Michigan, (2)Northwestern University, (3)San Francisco State University, (4)None, (5)University of Michigan Medical School

Background: No medications are currently available for treatment of nonalcoholic fatty liver disease (NAFLD), an increasingly prevalent disease afflicting about 25% of US adults and more than 50% of people with type 2 diabetes. Our preliminary data suggests that insulin resistance and the G allele of rs738409 interact to create a much greater risk of developing NAFLD. One promising way to reduce insulin resistance is using a very low-carbohydrate (VLC) eating pattern, also known as a ketogenic or “keto” dietary pattern, which is a VLC, moderate protein, higher fat eating pattern. **Methods:** This was a single-arm, online trial in adults with rs738409-GG or -CG. Participants completed measures related to intervention feasibility, acceptability, and physical and patient-reported outcomes. Participants were taught to follow an ad libitum very low-carbohydrate eating pattern (20-35 net or non-fiber grams) of carbohydrates per day for 4 months, as well as supplementary psychological tools to support adherence. **Results:** Of the 11 participants who were enrolled, 9/11 (82%) completed study outcomes, and 8/11 (73%) attended at least half of the sessions. Across all participants, the following reduced by a statistically significant amount: body weight decreased 10.9% ($p < 0.001$), HbA1c reduced 9.4% ($p = 0.001$), insulin reduced 30.7% ($p = 0.020$), insulin resistance reduced 36.8% ($p = 0.007$), triglycerides reduced 14.3% ($p = 0.021$), abdominal symptoms reduced 33.2% ($p = 0.044$), emotional function improved 22.6% ($p = 0.16$) and fatigue reduced 27.1% ($p = 0.024$). Six participants were adherent to the eating pattern (defined based on their 4-month 24-hour dietary recalls), 3 participants were not adherent, and 2 had no 4-month 24-hour dietary recall. For the participants who were adherent, the following reduced by a statistically significant amount: body weight decreased 12.0% ($p < 0.001$), average liver lobe fat percent decreased 53.1% ($p = 0.001$), AST reduced 33.9% ($p = 0.006$), ALT reduced 47.5% ($p = 0.003$), HbA1c reduced 7.7% ($p = 0.014$), insulin reduced 40.5% ($p = 0.023$), and insulin resistance reduced 44.0% ($p = 0.019$); LDL-cholesterol levels were not significantly changed. Of the 9 participants who provided 4-month self-report information, intervention satisfaction was high (mean 6.22, 95% CI 5.58 to 6.85), with 5/9 (56%) rating the intervention the top score. Only 11% reported that they would stop the assigned eating pattern as soon as `the study was over, and 44% stated that they did not plan to ever stop following it. **Conclusion**: Results support the feasibility, acceptability, and preliminary efficacy of the VLC intervention in adults thought to have a higher genetic risk for NAFLD. Overall, the results of this pilot study suggest that a VLC eating pattern may be a safe and efficacious approach for this population.

Disclosures: Elizabeth K. Speliotes:

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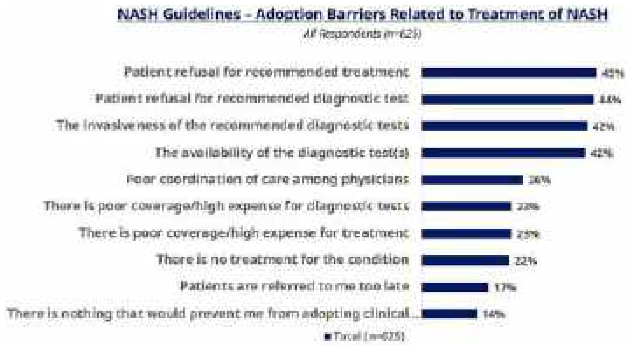
2492-C | UNDERSTANDING BARRIERS IN NON-ALCOHOLIC LIVER DISEASE (NAFLD) MANAGEMENT: INSIGHTS FROM A MULTI-DISCIPLINARY SURVEY OF PHYSICIANS IN EUROPE (BARRIERS-NAFLD)

Laurent Castera[1], William Alazawi[2], Elisabetta Bugianesi[3], Cyrielle Caussy[4], Massimo Federici[5], Manuel Romero-Gómez[6], Jorn Schattenberg[7], Ron Basuroy[8], Preethy Prasad[8], Dmitry Estulin[9] and Jeffrey V. Lazarus[10], (1)Department of Hepatology, Beaujon Hospital, AP-HP, Université Paris Cité, Inserm UMR1149, Clichy, France., (2)Queen Mary University of London, UK, (3)University of Turin, (4)Lyon 1 University and Lyon South Hospital, (5)University of Rome Tor Vegata, (6)Ucm Digestive Diseases, Virgen Del Rocio University Hospital, Instituto De Biomedicina De Sevilla, Ciberehd, University of Seville, Sevilla, Spain, (7) University Medical Center Mainz, (8)Novo Nordisk a/S, (9)Novo Nordisk Health Care AG, (10)Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Barcelona, Spain

Background: Management of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) remain challenging due to several factors including awareness of the diseases, availability of treatments, and lack of adoption and adherence to clinical practice guidelines. As a result, patients may not receive appropriate interventions such as lifestyle modifications, contributing to disease progression and increased risk of complications. This study aimed to identify insights and key challenges physicians face when managing NASH. **Methods:** A real-world, cross-sectional, quantitative survey was conducted from March to May 2023, among hepatologists/gastroenterologists with a subspecialty in hepatology and metabolic physicians (MPs) who are actively managing at least 30 patients with type 2 diabetes and/or obesity per month (endocrinologists, general practitioners, family physicians and internal medicine physicians without a subspecialty in hepatology) in five European countries (France, Germany, Italy, Spain and United Kingdom). Participants completed an anonymous online survey, and descriptive statistics were used to analyse the data.

Results: Among 249 hepatologists and 376 MPs, respondents cared for an average of 143 patients per month with or suspected to have NAFLD/NASH. The majority of hepatologists (62%) and MPs (60%) reported patient comorbidities influenced the diagnosis of NASH. Hepatologists were predominantly influenced by the availability of diagnostic methods (63%) followed by national guidelines (58%), whereas MPs were most influenced by the availability (56%) and invasiveness (49%) of the diagnostic method. Hepatologists reported being more aware of EASL (2021) guidelines (55%) for diagnosing and treating/managing NASH, whereas MPs reported being aware of ADA guidelines (34%). Additionally, 11% of participants reported not being aware of any clinical guidelines for NASH. The factors most commonly preventing adoption of clinical guidelines in NASH diagnosis, treatment and management were patient refusal of recommended treatments (44% hepatologists, 46% MPs), patient refusal for recommended diagnostic tests (42% hepatologists, 45% MPs), the invasiveness of recommended diagnostic tests (39% hepatologists, 43% MPs), and the availability of diagnostic tests (33% hepatologists, 47% MPs) (Figure 1). **Conclusion:** This study found that physicians report multiple challenges associated with managing NASH and further highlights the different influences and approaches taken by physicians to diagnose, monitor, and treat patients with NASH. The findings emphasize the need for increased awareness, definitive guidance and education to assist hepatologists and MPs treating NASH in adopting and adhering to clinical practice guidelines and non-interventional treatments and diagnostic tools.



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Massimo Federici – Novo Nordisk: Consultant, Yes, No; Eli Lilly: Consultant, No, No; Amarin: Consultant, No, No; Organon: Consultant, No, No; Boehringer Ingelheim: Speaking and Teaching, No, No; Novo Nordisk: Speaking and Teaching, Yes, No;

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Jeffrey V. Lazarus – AbbVie, Gilead Sciences, MSD and Roche Diagnostics: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AbbVie, Gilead Sciences, MSD and Roche Diagnostics: Speaking and Teaching, No, No; Intercept, Janssen, and ViiV: Speaking and Teaching, No, No; Novo Nordisk: Speaking and Teaching, Yes, No; AbbVie, Gilead Sciences and Novavax: Consultant, No, No;

2500-A | CHANGING PA STUDENTS MEDICAL BIASES AGAINST PATIENTS WITH LIVER DISEASE

Amanda DeVoss, University of Wisconsin-Madison

Background: Patients with alcohol-induced liver disease are often blamed for their disease and receive poor health care due to bias. Training physician assistants (PAs) to recognize their biases towards patients with liver disease plays an important role in decreasing the unintentional acts of bias that influence the care that patients with liver disease will receive. **Methods:** Between 2020-2023, PA students were asked about biases towards patients with liver disease, specifically about alcohol-induced liver disease. Students were also asked whether they think patients with alcohol-induced liver disease should undergo a liver transplant. Students then underwent a liver related curriculum, which was designed to discuss evidence-based medical decisions regarding all types of liver disease and liver transplantation. Following this curriculum, PA students were again assessed on their biases for patients with liver disease. **Results:** PA students were asked if they had a bias against patients with liver disease. On average from 2020-2023, 35.5% of students identified a bias against patients with liver disease. Students were also asked whether they think patients with alcohol-induced liver disease should undergo a liver transplant. On average, 39% of students believed these patients should not have a liver transplant. Students participated in lectures and interactive sessions about a variety of liver diseases. Evidence based medicine is brought into the curriculum to specially address transplantation for patients with alcohol-induced liver disease. Open discussions on bias against patients with liver disease is fostered by the faculty. After completing the curriculum PA students were again assessed on their biases for patients with liver disease. On average, 18% of students identified a bias against patients with liver disease, showing a 17.5% reduction. Students were also asked if they think patients with alcohol-induced liver disease should undergo a liver transplant. On average, 13% of students believed these patients should not have a liver transplant, a 26% reduction. **Conclusion:** Open-discussions aimed at biases towards patients with alcohol-induced liver disease prove to be a means of reducing medical bias. Each year there is an overwhelming positive change, with students acknowledging less bias against patients with liver disease and advocating for patients with alcohol-induced liver disease to receive a liver transplant.

Disclosures: The following people have nothing to disclose: Amanda DeVoss

f 2501-A | EVALUATION OF SAFETY OF A NURSE-LED PARACENTESIS MODEL FOR PATIENTS WITH DECOMPENSATED LIVER DISEASE IN AMBULATORY CARE: A RETROSPECTIVE REVIEW★

Molly McDonald[1], Carmen Fang[1], Colina K. Yim[2], Pam Hubley[1], Ina Cherepaha-Kantorovich[1], Sharlene Camaya[1], Christine Song[1] and Elizabeth Lee[1], (1) University Health Network, (2)University of Toronto

Background: Ascites is a common symptom of decompensated liver disease, managed by large volume paracentesis (LVP) when low-sodium diets and diuretics are ineffective. Typically LVPs are performed by a physician (MD) or a nurse practitioner (NP), and treatment delays can occur due to limited personnel and competing clinical responsibilities. An ambulatory liver clinic located in a quaternary care hospital in

Toronto, Canada, opened a procedure room staffed by a trained registered nurse (RN) to perform LVPs for the purposes of accommodating increasing numbers of patients requiring LVPs to reduce Emergency Room (ER) and General Internal Medicine (GIM) admissions for ascites management. This study evaluates the safety of this RN-led paracentesis model and examines the geographic range served by this hospital for ambulatory LVPs. **Methods:** A retrospective chart review (June 6, 2022 - Feb 28, 2023) was conducted on patients who underwent LVPs in this hospital's designated ambulatory settings (Medical Day Unit (MDU) and the liver clinic's procedure room). A frequency analysis of post-LVP complications subgrouped by the type of healthcare practitioner who performed the procedure (RN, NP, MD) was completed. Post-LVP complications were reviewed: skin infection, bowel perforation, abdominal wall abscess, hematoma/hemorrhage, arterial injury, and catheter fragment left in the abdominal wall/cavity. Spontaneous bacterial peritonitis was not considered a post-LVP complication. Other data collected for this study included: disease etiology, procedure location, proceduralist's designation, post-LVP related hospital admissions, and the patient's residential postal code. **Results:** 124 unique patients underwent LVPs in the designated ambulatory settings. A total of 580 LVPs were performed. 55.2% (n = 320) were performed in the liver clinic's procedure room, and 44.8% (n = 260) were performed in MDU. Disease etiologies included: alcohol associated liver disease (40.3%), nonalcoholic fatty liver disease (22.6%), viral hepatitis infection (13.7%), autoimmune liver disease (5.6%), and other etiologies (17.7%). Out of the 580 LVPs, 55.5% (n = 322) were performed by an RN, 33.6% (n = 195) were performed by an MD; and 10.9% (n = 63) were performed by an NP. There were no identified post-LVP complications, regardless of the proceduralist. 118 of the 124 patients live within the city of Toronto and the Greater Toronto Area (GTA), areas that are notably served by at least 15 academic and community hospitals. Of note, patients are currently travelling up to 360 km (224mi) to undergo LVPs due to limited local access to care. **Conclusion:** This RN-led paracentesis model demonstrated an equivalent level of safety to their NP and MD counterparts. This data could lead to the adoption of similar models of care in centers that deliver ambulatory care for patients with decompensated liver disease as a strategy for readmission avoidance and timely access to local care.

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2600-A | BENEFICIAL EFFECTS OF BUSHEN FORMULA ON CHRONIC HEPATITIS B PATIENTS BY REGULATING TFH AND B-CELL SUBSETS

Longshan Ji, Rongjie Zhang, Jinghan Wei, Xin Zhang, Yating Gao, Miao Fang, Zhuo Yu, Lin Cao, Yueqiu Gao and Man Li, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine

Background: Bushen Formula (BSF) is the effective traditional Chinese medicine (TCM) for chronic hepatitis B(CHB). Our previous studies have suggested that the combination treatment of BSF with entecavir results in significant decrease of serum hepatitis B virus (HBV) DNA, increase of HBeAg and HBsAg negative conversion in CHB patients without serious adverse events. However, the special effectiveness of BSF treating CHB and its relevant mechanism were not clear. We aimed to confirm the therapeutic effects and explore the pharmacological mechanisms of BSF on CHB. **Methods:** 266 CHB patients were enrolled into the retrospective study, which were categorized into treatment group (T-Group: receiving BSF plus Peg-IFN-α for 24 weeks) and control group (C-Group: receiving Peg-IFN-α for 24 weeks). Patients in T-Group and C-Group were grouped into subgroups including T1/C1 groups (Peg-IFN-α for the first time) and T2/C2 groups (Peg-IFN-α for more than 6 mo). Serum HBV markers and HBV DNA levels were tested. Chinese medicine symptom complex score was evaluated and recorded. Ultra-high performance liquid chromatography-quadrupole-orbitrap-high resolution mass spectrometry (UPLC-Q-Orbitrap-MS) and network pharmacological analysis were conducted to obtain the potential target pathways of BSF on CHB. Characteristics of peripheral follicular helper T cells (Tfh) and B-cell subtypes in CHB patients were analyzed by flow cytometry. In vitro, the co-culture system of CXCR5$^+$ cells and HepG2.2.15 cells was used to explore the immunoregulatory roles of BSF. **Results:** The rate of HBsAg decline e 1lg IU/ml in T2-Group was higher than that in C2-Group (35.7% vs 15.9%, $P < 0.05$). The rate of HBsAg decline e 1lg IU/ml and the HBeAg negative rate in T2-Group were higher than those in T1-Group (35.7% vs 14.7%, $P < 0.05$; 58.6% vs 6.3%, $P < 0.05$). The Clinical efficacy of TCM Syndrome in T-Group is significantly better than that in C-Group. BSF up-regulated the frequencies of Tfh and its IL-21 level and IL-21R level on B-cell. BSF reduced HBsAg and HBeAg levels in the co-culture system of CXCR5$^+$ cells and HepG2.2.15 cells, and up-regulated Tfh frequencies and down-regulated B-cell frequencies. **Conclusion:** Taken together, our findings indicated that BSF contributed to the decrease of HBsAg and the clearance of HBeAg, and improved TCM symptoms in CHB patients with partial response to Peg-IFNα, which maybe correlated with the differentiation of Tfh through IL-21/IL-21R signaling.

Disclosures: The following people have nothing to disclose: Longshan Ji, Rongjie Zhang, Jinghan Wei, Xin Zhang, Yating Gao, Miao Fang, Zhuo Yu, Lin Cao, Yueqiu Gao, Man Li

2601-A | CELLULAR IMMUNE RESPONSE TO A SINGLE DOSE OF LIVE ATTENUATED HEPATITIS A VIRUS VACCINE IN OBESE CHILDREN AND ADOLESCENTS

Voranush Chongsrisawat[1], Tanatchabhorn Soponkanabhorn[1] and Supranee Buranapraditkun[2,3], (1)Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, (2)Division of Allergy and Clinical Immunology, Faculty of Medicine, Chulalongkorn University, and King Chulalongkorn Memorial Hospital, (3)Center of Excellence in Vaccine Research and Development (Chula Vaccine Research Center-Chula VRC), Faculty of Medicine, Chulalongkorn University

Background: Obese children are at an increased risk of developing nonalcoholic fatty liver disease. Individual's with chronic liver disease may have a compromised immune system, which can make them more susceptible to hepatitis A virus (HAV) infection. There is limited data available on the cellular immune response to a live attenuated HAV vaccine, especially in children with obesity. This study aimed to compare antigen-specific interferon (IFN)-γ+ T cell activation in obese children/adolescents with healthy counterparts before and after immunization with a single dose of live attenuated HAV vaccine. **Methods:** This study obtained blood samples from our previous study titled "Impact of Obesity and Being Overweight on Immunogenicity to Live Attenuated Hepatitis A Vaccine in Children and Young Adults". Prior to enrollment, all 212 subjects had never received any HAV vaccine and were seronegative for anti-HAV. Participants were vaccinated with the H2 strain, freeze dried, live attenuated HAV vaccine. For this study, we analyzed stored peripheral blood mononuclear cells (PBMCs) collected from 30 obese subjects aged 8-14 years (15 males) and 30 normal-weight healthy controls of the same age and sex. PBMCs were collected before and 8-9 weeks after HAV vaccination for analysis. Recombinant antigen from HAV-VP3 was used to stimulate PBMCs and the IFN-γ enzyme-linked immunospot (ELISpot) assay was performed to evaluate the immune response. **Results:** The between-group analysis revealed that the T cell response of obese participants was comparable to that of normal controls both before and after vaccination (Figure). The change in IFN-γ production from before to after vaccination in the obese group was not significantly different from that of the control group. In the obese group, there was no correlation between IFN-γ production and clinical characteristics such as sex, BMI, waist circumference, truncal obesity, and acanthosis nigricans. **Conclusion:** Testing for cellular immune response offers a comprehensive understanding of the overall immune response to vaccination, especially for intracellular pathogens such as viruses. The present study, which represents the first exploration of this significant aspect, suggests that obesity does not have an impact on short-term cellular immune response to live attenuated HAV vaccination.

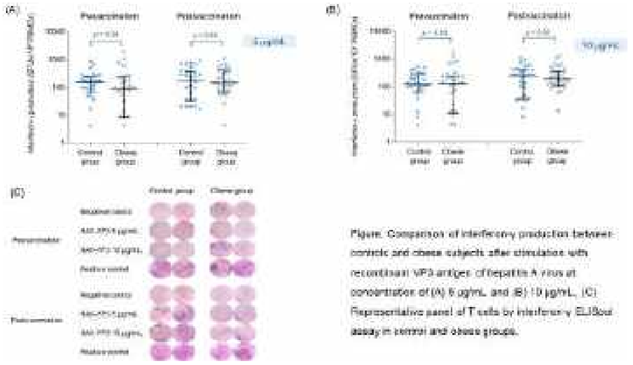

Figure. Comparison of interferon-γ production between controls and obese subjects after stimulation with recombinant VP3 antigen of hepatitis A virus at concentration of (A) 5 μg/mL and (B) 10 μg/mL. (C) Representative panel of T cells by interferon-γ ELISpot assay in control and obese groups.

Disclosures: The following people have nothing to disclose: Voranush Chongsrisawat, Tanatchabhorn Soponkanabhorn, Supranee Buranapraditkun

f 2602-A | CHARACTERIZATION OF THE ANTIBODY REPERTOIRE AGAINST mAChR3 IN PATIENTS WITH PBC AND PSC★

Anne Olbrich[1], Asis Mousa[1], Madlen Oelsner[1], Danilo Deichsel[1], Toni Herta[2], Madlen Matz-Soja[1,2], Beate Preuss[3], Reinhild Klein[3], Tobias Müller[4], Barbara Malik[5], Julia Benckert[5] and Thomas Berg[6], (1) University Hospital Leipzig, (2)Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany, (3)University Hospital Tübingen, (4)Kliniken Berlin, (5)Charité Berlin, (6) University Hospital of Leipzig

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

Background: Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are rare chronic inflammatory biliary diseases. Specific auto-antibodies against the muscarinic acetylcholine receptor type 3 (mAChR3) may contribute to the pathogenesis of these biliary inflammation by modulating mAChR3-mediated signaling. **Methods:** We analyzed the sera from PBC (n = 95) and PSC patients (n = 47) for the presence of functional active mAChR3 auto-antibodies. Subsequently, peripheral blood from 32 patients was examined for mAChR3-binding memory B cells using the labeled mAChR3-peptides. Using FACS, we isolated CD19+CD27+IgG+ memory B cells that bind to mAChR3 peptide on a single-cell level from one index patient with small duct PSC. We amplified the heavy chain (IgH) and corresponding light chain (IgL) gene transcripts for each cell using nested reverse transcription PCR and expressed them *in vitro*. **Results:** We detected mAChR3 auto-antibodies in 6% of the PBC patients and in 17% of the PSC patients. We found circulating anti-mAChR3 memory B cells in all patients and CD19+CD27+IgG+mAChR3+ cells from a subset of these patients on a single-cell level. PBC patients exhibited a significantly higher number of mAChR3+-peptide reactive memory B cells compared to PSC patients. Sequence analyses revealed a substantial proportion of mutated and hypermutated antibodies. Moreover, we could show that CDR3 regions of the mAChR3-specific B cells were elongated compared to our healthy control group. After recombinant expression, the antibodies were tested in a cell culture model, demonstrating their ability to inhibit or stimulate *in vitro*. **Conclusion:** Our investigation of mAChR3 autoantibody expression in PBC and PSC patients could be of significant importance for understanding the etiopathogenesis of these diseases. The identified antibodies will undergo further testing to determine their impact on the bicarbonate umbrella.

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f 2603-A | IL-33/AMPHIREGULIN-MEDIATED REGULATION OF ACUTE IMMUNE-MEDIATED HEPATITIS

Selina Wachtendorf, Fitriasari Jonin, Aaron Ochel, Fabian Heinrich, Gisa Tiegs and Katrin Neumann, University Medical Center Hamburg-Eppendorf

Background: In acute immune-mediated hepatitis, the alarmin IL-33 is released by necrotic hepatocytes to activate type 2 innate lymphoid cells (ILC2s) and regulatory T cells (Tregs) expressing the IL-33 receptor ST2. We have previously shown that ILC2s aggravate liver injury in acute immune-mediated hepatitis. Since IL-33 induces expression of amphiregulin (AREG), which has been linked with tissue repair and immunosuppression, we investigated the immunoregulatory role of the IL-33/AREG axis in acute immune-mediated hepatitis. **Methods:** Mice were treated with concanavalin (Con)A to induce acute immune-mediated hepatitis. ST2-deficient (*Il1rl1*$^{-/-}$) and *Areg*$^{-/-}$ mice were used for functional analyses. The immunosuppressive function of Tregs was analyzed in vitro and in vivo. Phenotype analyses were done by flow cytometry. **Results:** We showed that hepatic *Il33* and *Areg* expression was induced in acute immune-mediated hepatitis. IL-33-responsive ST2$^+$ Tregs constituted an effector Tregs subset in the liver, which was highly activated in hepatic inflammation. *Il1rl1*$^{-/-}$ mice developed more severe liver injury, that was associated with an overall reduced Treg activation due to lack of ST2$^+$ Tregs. Hepatic ILC2s and ST2$^+$ Tregs expressed AREG in response to IL-33 and in acute immune-mediated hepatitis. Interestingly, *Areg*$^{-/-}$ mice developed more severe liver injury than wild-type mice, which correlated with stronger activation and IL-13 expression of hepatic ILC2s, while the frequency of ST2$^+$ Tregs was reduced. Importantly, this Treg subset was characterized by a high potential to protect from acute immune-mediated hepatitis. We further demonstrated that AREG suppressed the expression of IL-13 by hepatic ILC2s in vitro. In contrast, AREG induced activation, expansion and AREG expression in ST2$^+$ Tregs. Moreover, Tregs from *Areg*$^{-/-}$ mice were impaired in their capacity to suppress the activation of CD4$^+$ T cells in vitro. **Conclusion:** We here describe an immunosuppressive role of the IL-33/AREG axis in acute immune-mediated hepatitis, in which AREG suppresses the activation of ILC2s while maintaining ST2$^+$ Tregs and reinforcing their immunosuppressive function in liver inflammation.

Disclosures: The following people have nothing to disclose: Selina Wachtendorf, Fitriasari Jonin, Aaron Ochel, Fabian Heinrich, Gisa Tiegs, Katrin Neumann

2604-A | NON-ALCOHOLIC STEATOHEPATITIS (NASH) RESULTS IN ACCUMULATION OF CLONALLY EXPANDED CD8+ T CELLS IN THE LIVER

Abbigayl E.C. Burtis, Destiny M.C. DeNicola, Megan E. Ferguson, Beth A. Jiron Tamburini, Austin E. Gillen and Matthew A. Burchill, University of Colorado - Anschutz Medical Campus

Background: Chronic liver disease due to NASH is a rapidly increasing epidemic that is predicted to become the number one cause of liver transplantation worldwide. While many aspects of the pathogenesis of NASH have been studied, T cell function in NASH is still unresolved. In these studies, we aimed to determine if T cells are responding to antigens in the liver to modulate disease progression. **Methods:** To define the contribution of T cells in the progression of NASH, we utilized a combination of flow cytometry and single-cell RNA sequencing of T cells in the liver during the progression and resolution of NASH. Specifically, we interrogated T cells in the liver of mice fed a High-Fat, High Cholesterol (HFHC) diet for 25 or 31 weeks, mice fed HFHC diet for 26 weeks then control diet for 5 weeks, or caloric matched control diet. **Results:** In these studies, we found that NASH resulted in a dramatic accumulation of CD8+ T cells in the liver. Analysis of liver infiltrating CD8 T cells showed that T cells from the NASH and diet reversal model expressed markers of chronic antigenic stimulation including PD1, TIGIT, and Tox. Furthermore, T cell receptor (TCR) repertoire analysis demonstrated that T cells in the liver of mice with NASH had a significant reduction in TCR diversity. This reduction in diversity was driven by the expansion of T cell clones that represented up to 60% of the total T cell population in the liver. Diet reversal led to recovery of a higher TCR diversity and a correlative reduction in liver injury, providing evidence of an active role of T cell expansion in the progression of NASH-induced liver disease. Surprisingly, there was little overlap found in the TCR sequences of the clonally expanded T cells between individual mice fed the same NASH-inducing diet. This suggests that multiple antigens may be driving the expansion of T cells during NASH. **Conclusion:** Together our studies demonstrate that antigenic stimulation is driving the expansion and accumulation of CD8+ T cells in the liver during NASH and points to an active role for T cells in the progression of NASH-induced liver disease. Thus, current studies are aimed at identifying the antigenic driver(s) of expansion and if specific depletion of clonally expanded T cells alters the progression of NASH. Thus, investigation into the cause of the clonal expansion and what role the expanded T cells play in the progression of NASH has the potentiation to transform the treatment of this pervasive disease.

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2605-A | THE ROLES AND MECHANISM OF DHX34 ABLATION IN ENHANCING TUMOR IMMUNOGENICITY IN HEPATOCELLULAR CARCINOMA

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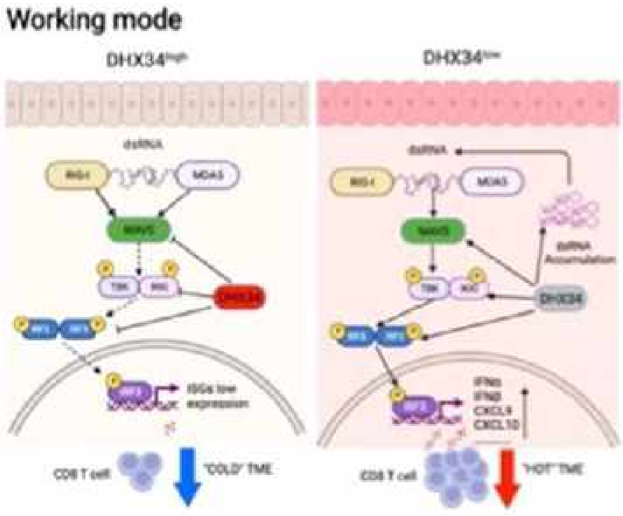
Background: Tumor immunotherapy has achieved significant clinical efficacy in recent years, but only some patients respond to immunotherapy, mainly because the tumor microenvironment inhibits the anti-tumor immune response. DHX34 is one of the RNA helicases, and its role in the regulation of tumor immune microenvironment has not been studied. Analysis of the clinical database of liver cancer in the early stage showed that DHX34 was highly expressed in liver cancer, and was negatively correlated with patient survival, T cell infiltration, and inflammatory cytokines expression. **Methods:** We knocked out DHX34 expression in HepG2, which significantly promoted the expression of inflammatory factors in vitro, enhanced T cell activation and effector function, and significantly enhanced the anti-tumor effect in vivo. **Results:** Mechanistic studies have shown that DHX34 knockout differential gene enrichment is in validating relevant pathways, mainly affecting type I interferon pathways. DHX34 knockout enhances the expression of ISGs genes such as RIG-I, MDA-5, MAVS and IFN-a, IFN-b, and overexpression of DHX34 partially inhibits or does not affect ISGs gene expression. At the same time, knocking out DHX34 also enhanced the expression of chemokines such as CXCL9 and CXCL10, which contributed to immune cell infiltration into the tumor microenvironment. We also found that DHX34 knockout leads to the accumulation of endogenous dsRNA in cells, and excess dsRNA can induce the activation of type I interferon pathway, leading to the expression of downstream effector factors, promoting the infiltration of inflammatory cells in the tumor microenvironment, and enhancing the anti-tumor immunity effect. **Conclusion:** Overall, this study elucidates the molecular mechanism by which DHX34 promotes tumor growth by reducing endogenous dsRNA accumulation and inhibiting type I interferon pathway activation. Inhibition or knockout of DHX34 significantly enhances the anti-tumor immune response. This study provides a theoretical basis for the development of DHX34 inhibitors to regulate the tumor immune microenvironment.



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2606-A | EXPERIMENTAL MODEL OF SEVERE ALCOHOL-ASSOCIATED HEPATITIS IN MICE INDUCED BY DUAL INJURY OF CHRONIC ALCOHOL AND NASH DIET RECAPITULATES KEY FEATURES OF HUMAN DISEASE

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Background: The prevalence of alcohol-associated hepatitis (AH) is increasing in the USA and this coincides with the obesity epidemic. However, current experimental models in mice cannot fully replicate the severe alcohol-associated steatohepatitis (AH) and significant fibrosis found in human disease or mimic the potentially combined insult of obesity, NASH and alcohol. The aim of this study was to develop a new alcohol feeding model that recapitulates the robust inflammatory and fibrotic phenotype characteristic of human AH. **Methods:** 8-10 weeks old male C57BL/6 mice received either chow or high fat-cholesterol-sugar diet (NASH diet) for 3 months. Some of the chow and NASH diet fed mice received alcohol in drinking water (*ad libitum*) plus weekly alcohol binges for 3 months. Liver tissue was analyzed for fibrosis, inflammation and regeneration markers by immunohistochemistry, qPCR, ELISA and western blotting. **Results:** Chronic alcohol plus NASH diet resulted in increased liver damage indicated by highly elevated ALT and bilirubin levels, compared to all other groups. Liver steatosis was significantly greater in the alcohol plus NASH diet compared to all other experimental groups based on oil-o-red staining, liver triglyceride levels and a dramatic increase in gene expression in fatty acid metabolism including adipose differentiation related protein, diglyceride acyltransferase, and fatty acid binding protein. The inflammatory phenotype of human AH was also recapitulated in the liver of chronic alcohol plus NASH diet fed mice, including increased monocyte chemoattractant protein-1, interleukin 6 and interleukin-1B protein levels as well as increased $CD68^+$ macrophages and $Ly6G^+$ neutrophils in the liver. Sirius red staining and expression of collagen 1, alpha-smooth muscle actin indicated advanced fibrosis in livers of alcohol plus NASH fed mice. In addition, indicators of epithelial to mesenchymal transition including higher snail and decreased expression of occludin, claudin and hepatocyte nuclear factor were present in chronic alcohol plus NASH diet fed mice compared to any of the other groups. Furthermore, chronic alcohol plus NASH diet led to hepatocyte dedifferentiation as marked by increase in albumin, hepatocyte growth factor and $Ki67^+$ cells. We also found enhanced ductular reaction and dysregulated hedgehog signaling consistent with advanced alcoholic hepatitis. **Conclusion**: We show that chronic alcohol administration with a NASH diet recapitulates key characteristics of human AH including liver damage, steatosis, systemic inflammation and liver immune cell infiltration. This model results in advanced liver fibrosis, ductular reaction and hepatocyte dedifferentiation suggesting a feasible model of human severe alcoholic hepatitis.

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The following people have nothing to disclose: Mrigya Babuta
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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

2607-A | GLYCINE PREVENTS MURINE AUTOIMMUNE CHOLANGITIS AND PANCREATITIS INDUCED BY DOUBLE-STRANDED RNA THROUGH MODULATION OF INNATE IMMUNE RESPONSES

Akira Uchiyama, Kazuyoshi Kon, Satoshi Sakuma, Kumiko Arai, Toshifumi Sato, Hiroo Fukada, Reiko Yaginuma, Kyoko Fukuhara, Shunhei Yamashina and Kenichi Ikejima, Juntendo University School of Medicine

Background: Autoimmunity is postulated to play a pivotal role in the pathogenesis of a variety of hepatobiliary and pancreatic diseases, including primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and autoimmune pancreatitis (AIP). Glycine, a non-essential amino acid, has been shown to prevent experimental liver injuries by attenuating hepatic innate immune responses to gut-derived endotoxin. In this study, we evaluated the effect of glycine on double-stranded RNA-induced innate and auto-immune responses in the liver and pancreas. **Methods:** Female, 8-week-old C57Bl6 mice were fed a diet containing 5% glycine or casein as controls, and given repeated, intraperitoneal injections of poly I:C (5 µg/g BW, twice/week) for up to 24 weeks. Some mice were euthanized following a single injection of poly I:C in combination with one-week pre-feeding with glycine-diet. Serum alkaline phosphatase (ALP) and amylase (AMY) levels were measured, and histopathological features of the liver and pancreas were assessed. Expression of immune cells were evaluated by immunohistochemical staining for F4/80, CD3, and CD20. Serum anti-mitochondria antibody (AMA)-M2 and anti-lactoferrin (LF) antibody were detected by ELISA. Hepatic mRNA levels for TNFα, IL-1β, IL-6, IFNα and IFNβ were quantified by real time RT-PCR. **Results:** Repeated injection of poly I:C induced overt inflammatory infiltration in the portal area, predominantly lymphocytes surrounding bile ducts, and massive distraction of pancreatic acinar cells with infiltration of inflammatory cell and mild fibrosis after 16 weeks and later. Indeed, the number of F4/80-, CD3- and CD20-positive cells were significantly increased with repeated injection of poly I:C in both liver and pancreas. These pathological changes of cholangitis and pancreatitis were largely ameliorated in mice fed a glycine-containing diet for 8 weeks starting from 16 weeks of poly I:C treatments; poly I:C-induced increases in ALP and AMY levels were markedly blunted in mice given glycine-containing diet. Repeated injections of poly I:C also elicited increases in serum AMA-M2 and LF levels, which were also blunted significantly in mice fed a glycine-containing diet. On the other hand, a single injection of poly I:C elicited transient, swift elevations in hepatic mRNA levels for TNFα, IL-1β, and IL-6, as well as IFNα and IFNβ; however, all of these parameters were blunted significantly in mice fed a glycine-diet. **Conclusion:** These findings clearly indicated that dietary glycine prevents development of autoimmune-related cholangitis and pancreatitis induced by repeated injections of poly I:C, most likely through attenuating innate immune responses. It is postulated that glycine is a promising immuno-nutrient for the treatment of autoimmune hepato-pancreatic diseases.

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2608-A | NANOPARTICLE-BASED ANTIFIBROTIC THERAPY FOR TREATMENT OF LIVER FIBROSIS

Sufeng Zhang[1,2,3], Rachel Zhang[1], Bruna Santos[1], Katrina Garrow[1], Adam Mohamed[1], Keiko Ishida[3], Wiam Madani[3], Alison Hayward[3], Niora Fabian[3], Joshua R. Korzenik[1,2] and Carlo Giovanni Traverso[1,2,3], (1)Brigham and Women's Hospital, (2)Harvard Medical School, (3)Massachusetts Institute of Technology

Background: Primary Sclerosing Cholangitis (PSC), an inflammatory disease of the liver without any therapy, leads to fibrosis and cirrhosis. Liver fibrosis results from abnormal wound repair during chronic liver injury, representing a clinical challenge. Inflammatory response accompanies fibrosis development, during which excessive inflammatory cytokines and molecules promote the activation and proliferation of hepatic satellite cells (HSCs) and lead to hepatocyte necrosis and apoptosis. Sulfasalazine (SSZ) was shown in retrospective studies to be beneficial for treating PSC. A prospective clinical trial is currently in process. SSZ was also found to be anti-fibrotic by increasing HSCs apoptosis. Hence, SSZ may reduce inflammation and reverse fibrosis in PSC and other liver diseases. However, the possible side effects on liver or kidney damage limit further studies on SSZ as anti-fibrotics. **Methods:** We aim to assess whether a nanoparticle (NP) delivery system can target SSZ to the liver for effective treatment. To this end, we encapsulated SSZ in albumin-based NPs, characterized the formulated NPs, investigated SSZ release from NPs, and evaluated the SSZ-loaded NPs in rodent models of liver fibrosis. When establishing the liver fibrosis models, we used $n = 5$ mice per group and $n = 4$ rats per group in the treated and control groups. NPs were administered intravenously to animals. The severity of liver fibrosis was determined by H&E histology and Sirius Red staining. **Results:** The characterization showed that NP sizing was tuned by the concentration of albumin used for NP formulation. The encapsulation efficiency (EE) of SSZ in NPs indicated that a higher albumin concentration led to a higher EE of SSZ. Next, we investigated the SSZ release from NPs and found that the supernatant from lipopolysaccharide-activated macrophages triggered SSZ release from NPs much faster than simulated intestinal fluids. Further, we established two rodent models of liver fibrosis, including thioacetamide (TAA) in mice and carbon tetrachloride (CCl4) in rats. With dye-conjugated NPs, the *in vivo* biodistribution study demonstrated that the SSZ-loaded NPs accumulated in the liver compared to other organs in CCl4-induced fibrosis in rats (Fig. 1). **Conclusion:** Our work revealed the potential of liver-targeting SSZ-loaded NPs for effective fibrosis treatment. Our next step is to fine-tune the SSZ delivered to the liver to maximize efficacy and minimize side effects.

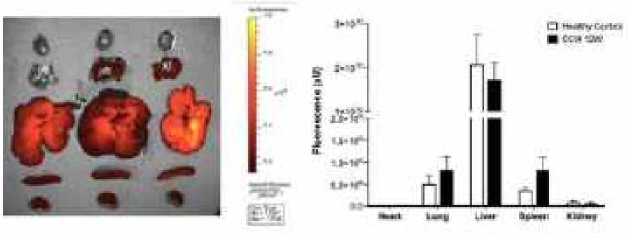

Fig. 1. *In vivo* biodistribution study demonstrated that the SSZ-loaded NPs accumulated in the liver compared to other organs in CCl4-induced fibrosis in rats.

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Disclosure information not available at the time of publication: Rachel Zhang, Bruna Santos, Katrina Garrow, Adam Mohamed, Keiko Ishida, Wiam Madani, Alison Hayward, Niora Fabian, Carlo Giovanni Traverso

2609-A | SINGLE NUCLEUS RNA-SEQUENCING REVEALS REGENERATIVE PROPERTIES OF EXOGENOUS IL-4 ON HEPATOCYTES IN MURINE PRECISION-CUT LIVER SLICES

Damra Camat[1,2], Diana Nakib[1,2], Sai Chung[1,2], Yijia Liu[1], Catia Perciani[2], Agata Bartczak[2], Michael Liyaw Cheng[1], Olivia Ivana Pezzutti[1], Sadaf Mazhab Jafari[1], Xue-Zhong Ma[2], Ian McGilvray[2] and Sonya A MacParland[1,2], (1)University of Toronto, (2)University Health Network

Background: The precision-cut liver slice (PCLS) model is a unique platform because it allows for the culturing and modulating of parenchymal and non-parenchymal cell types in intact liver tissue. Objectives: To extend the use of PCLS beyond drug assays, it is critical to standardise a protocol that allows slices to remain viable in culture for extended periods of time. We have established a reproducible workflow with a fixed end point that would allow for assessment of the effects of introduced interventions such as treatment with the pro-regenerative cytokine, interleukin 4 (IL-4). **Methods:** Liver slices were cultured for 5 days in the presence or absence of IL-4 to assess the impact on hepatocyte viability and regeneration. In cultured slices, we assessed morphology and apoptosis (H&E and TUNEL staining), proliferation (Ki-67 staining) and viability (ATP assay). To examine cellular pathways impacted by IL-4 treatment, single-nucleus RNA-sequencing (snRNA-seq) was performed on 4 slices per condition on Day 1 and Day 3. **Results**: IL-4 treated slices generated higher levels of ATP and displayed decreased apoptotic nuclei with an increased number of viable nuclei through the culture period. Ki-67 staining revealed that on Day 3 of culture, slices treated with IL-4 showed significantly more proliferating cells compared to untreated slices. SnRNA-seq revealed the presence of viable hepatic populations previously atlased in the murine liver in both IL-4 treated and untreated slices with transcripts associated with regenerative pathways (i.e., *Egr1*, *Rela*, *Gabpb1* and *Ets2*) enhanced in the IL-4 treated slices. **Conclusion:** We identified IL-4 as a potential promoter of regeneration and viability of hepatocyte-like and cholangiocyte-like cells. This renders IL-4 as a potential therapeutic modifier of hepatic disease and avenue of continued investigation.
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2610-A | SPLENIC MYELOID CELLS ENTER LIVER TO PROMOTE THE PRO-METASTATIC NICHE FORMATION

Xurui Zhang[1,2,3], Zhang Shaoying[1,2,3], Haiyan Chen[1,2], Mengchen Zhu[1,2,3], Na Huang[1,2,3], Guihu Wang[1,2,3], Nanbin Liu[1,2,3], Kang Zhang[1,2,3], Shemin Lu[1,4] and Zongfang Li[1,2,3,4], (1)National & Local Joint Engineering Research Center of Biodiagnositics and Biotherapy, the

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

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Background: The liver is the most common site for organ metastasis. The spleen and liver are connected anatomically and physiologically. All splenic blood perfuses to the liver through the portal vein. But it is unclear whether splenic myeloid cells are involved in the pro-metastatic niche formation and thus promote liver metastasis. Therefore, the aim of this research is to explore the function of splenocytes in liver metastasis **Methods:** Male or female C57BL/6 mice or KikGR mice aged 6-10 weeks were used in animal experiments. Experimental liver metastasis in mice was performed by implanting melanoma B16-GFP cells into the portal vein of mice using a 32 G syringe. Then the C57BL/6 mice were randomly divided into two groups, and mice in group A were adoptive transfer of spleen-derived cells of KikGR mice through the tail vein, followed by B16-GFP cells inoculated; mice in Group B were transplanted with KikGR mouse spleen to C57BL/6 mice, followed by B16-GFP cells inoculated through the portal vein. Additionally, KikGR mice were surgically exposed the spleen, and irradiated the spleen under a 405nm laser. The cells in the spleen were photoconverted by irradiation, so that the splenic cells emit red fluorescence, and then B16-GFP cells were inoculated through the portal vein, labeled as group C. When B16-GFP cells were seeded for 24 hours, the distribution of KikGR-positive cells in the liver were observed by intravital imaging through an image window in the abdomen of the mice. By which we determined whether spleen-derived myeloid cells participated in the pro-metastatic niche formation in liver. **Results:** GFP-positive B16 cells were detected in the livers of all three groups of mice by liver intravital imaging. In the livers of mice in groups A and B, a large number of KikGR-positive cells were detected; In group C mice, a large number of photoconverted KikRed-positive cells were detected in the liver. In these three groups of mice, spleen-derived myeloid cells (KikGR$^+$ cells) tended to be distributed around GFP-expressing tumor cells. **Conclusion:** As tumor cells enter the liver niche, splenic myeloid cells also rapidly recruited to the liver to facilitate the pro-metastatic niche formation.

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Disclosure information not available at the time of publication: Xurui Zhang, Haiyan Chen, Na Huang, Nanbin Liu, Kang Zhang

f 2611-A | CROSS-COMPARTMENT SINGLE-CELL TRANSCRIPTOMICS OF HUMAN IMMUNE CELLS REVEALS DYNAMIC PERTURBATIONS IN MONOCYTES AND MACROPHAGES IN NAFLD/ NASH

Michael S. Wallace[1], Hailey Patel[1], Michael Butler[1], Christopher Oetheimer[2], Joshua Elbaz[1], Charlotte Laurent Costentin[1], Owen Martin[1], Lai Ping Wong[1], Ulandt Kim[1], Edgar D. Charles[3], Ruslan Sadreyev[1], Raymond T. Chung[2] and Nadia Alatrakchi[2], (1) Massachusetts General Hospital, Harvard Medical School, (2)Massachusetts General Hospital and Harvard Medical School, (3)Bristol Myers Squibb

Background: Nonalcoholic fatty liver disease (NAFLD)/ nonalcoholic steatohepatitis (NASH) is the most common cause of liver disease worldwide. Of those with NASH, a significant portion will progress to cirrhosis/ fibrosis or liver failure, for which no approved therapies exist. Monocytes and macrophages (Mo/Ma) play a critical role in liver pathogenesis. However, their extreme complexity and often opposing functions are poorly understood and access to liver tissue is limited in humans, hampering the development of targeted therapies. We sought to characterize the single-cell transcriptome of Mo/Ma in human NAFLD using the less invasive fine needle aspirate (FNA) approach, which enriches immune cell populations. **Methods:** We analyzed single-cell RNA-sequencing data corresponding to paired liver FNAs and peripheral blood mononuclear cells (PBMCs) from 25 participants with histologically confirmed NAFLD, including 4 with simple steatosis, 10 with early NASH (F0-F1), 9 with advanced NASH (F2-F4), and 2 controls without steatosis. **Results:** The expected immune cell populations were captured, as well as small numbers of hepatocytes and hepatic stellate cells, in the liver compartment from each patient. We observed differences in gene expression across immune cell types between the two compartments. Mo/Ma showed a significant increase with the advancement of NASH; this increase was confined to the liver. This shift was accompanied by increased interferon-stimulated gene (ISG) expression in monocytes in both tissue compartments and in macrophages in the liver. Monocyte gene signatures were associated with NAFLD/NASH progression, with distinct features in each compartment. In CD14+ monocytes, we detected multiple inflammatory and feedback anti-inflammatory patterns as early as simple steatosis, specific to the liver compartment, which fluctuated throughout the course of NAFLD/NASH progression. CD14+ monocytes were heterogeneous and showed segregation of distinct programs (S100, MHC-II, and ISG), which were validated by tissue staining. We delineated macrophage populations and potentially profibrotic gene expression associated with advanced NASH and suggest potential developmental trajectories for these populations based on CD14+ monocyte subpopulations. **Conclusion:** We identified dynamic inflammatory perturbations in NAFLD monocytes in the liver as early as steatosis, prior to histological confirmation of inflammation, and identified genes associated with NASH progression to fibrosis.

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f 2612-A | MACROPHAGE NUCLEOTIDE CATABOLISM INHIBITS THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA

Chuanli Zhou, Shuang Liang and Zhenyu Zhong,
University of Texas Southwestern Medical Center

Background: Hepatocellular carcinoma (HCC), the dominant form of primary liver cancer, has emerged as the second leading cause of cancer-related deaths. The development of HCC is closely linked to chronic liver inflammation and impaired macrophage function. However, the precise molecular mechanism responsible for this dysregulation has remained elusive, posing a significant obstacle in the development of effective anti-HCC therapies. **Methods:** Experimental HCC models in *Samhd1*$^{F/F}$ and *Samhd1*$^{\Delta Mye}$ mice, and *in vitro* studies with BMDMs stimulated with conditioned medium released from DEN-treated hepatocytes were conducted. SAMHD1 oxidation and enzymatic activity were analysed in tumor associated macrophages and compared with liver macrophages from non-tumor regions. **Results:** In this study, we demonstrate a crucial role of SAMHD1 as a gatekeeper in macrophages, curbing uncontrolled liver inflammation and inhibiting HCC development in mice. By functioning as a dNTPase, SAMHD1 effectively restricts the abnormal accumulation of cytosolic dNTPs, averting uncontrolled neosynthesis of mitochondrial DNA (mtDNA) and the subsequent overproduction of mtROS. Consequently, this regulatory process effectively limits the production of chemokines CXCL1/2, thereby preventing excessive neutrophil infiltration into the liver, which is known to promote HCC progression. Interestingly, our findings also unveil extensive oxidation and functional impairment of SAMHD1 in HCC-associated liver macrophages, implying that the liver microenvironment actively inhibits SAMHD1 to facilitate tumorigenesis. **Conclusion:** Collectively, our results establish macrophage nucleotide catabolism as a pivotal factor in preventing liver inflammation and HCC, shedding light on the previously unrecognized role of SAMHD1 dysregulation as a pathogenic mechanism underlying HCC development.

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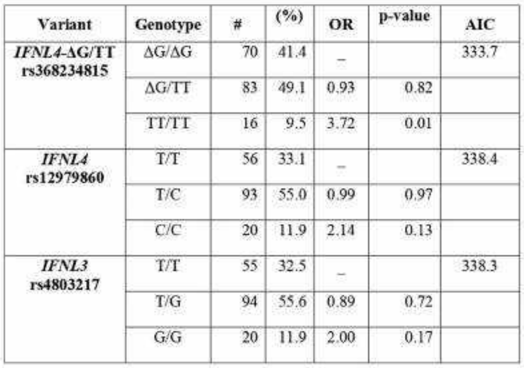
Disclosure information not available at the time of publication: Shuang Liang

2613-A | ROLE OF IFNL4 GENOTYPE IN HEPATIC INFLAMMATION AMONG BLACK INDIVIDUALS WITH CHRONIC HEPATITIS C

Harish Gopalakrishna[1], Ruth Pfeiffer[2], Sabrina C Ramelli[2], Ludmila Prokunina-Olsson[2], Stephen M Hewitt[2], David E Kleiner[3], Marc G. Ghany[1] and Thomas O'Brien[2], (1)National Institute of Diabetes and Digestive and Kidney Diseases, Nih, (2)National Cancer Institute, Bethesda, MD, United States, (3)Laboratory of Pathology, National Cancer Institute, Bethesda, MD

Background: Genetic variants in the interferon lambda region have been linked to hepatic inflammation and fibrosis progression in liver disease of several etiologies, including chronic hepatitis B, chronic hepatitis C and nonalcoholic steatohepatitis. The *IFNL4* rs368234815-TT allele abrogates expression of the IFNL4 protein and *IFNL3* rs4803217-G stabilizes *IFNL3* mRNA. Previous efforts to determine the causal variant for hepatic inflammation were hampered by strong linkage disequilibrium (LD) between these variants in populations of European ancestry; LD is weaker in populations of African ancestry. We examined associations of *IFNL4* and *IFNL3* variants with hepatic inflammation in Black patients with chronic hepatitis C virus (HCV) infection. **Methods:** The VIRAHEP-C trial compared response to peginterferon-α among Black and White patients who were infected with HCV genotype 1; this analysis is limited to Black patients. Pre-treatment liver biopsies were scored for inflammation using the modified Histology Activity Index (HAI) scoring system (portal 0-4, peri-portal 0-10, lobular 0-4) and for fibrosis using the Ishak scoring system (0-6). DNA specimens were genotyped for *IFNL4* rs368234815, *IFNL4* rs12979860 (previously known as 'IL28B') and *IFNL3* rs4803217 using TaqMan assays. Associations of the variants with hepatic inflammation and fibrosis were examined using logistic regression models in which the score was treated as an ordinal variable. We used the Akaike information criterion to assess model fit. **Results:** Among 169 Black participants, 65% were male with median age of 49 years. Total HAI scores were mild (0-6) in 25%, moderate (7-12) in 70% and severe (13-18) in 5%; 66% of patients had mild (Ishak 0-2), 29% had moderate (3-4) and 5% had severe fibrosis (5-6). *IFNL4*-ΔG and *IFNL3* rs4803217-T allele frequencies were 66% and 61%, respectively. *IFNL4*-TT/TT genotype was associated with 3.72-fold (p = 0.01) greater portal and 3.23-fold (p = 0.02) greater periportal inflammation compared to *IFNL4*-ΔG/ΔG (Table 1). Genotype analyses for the *IFNL3* rs4803217 and *IFNL4* rs12979860 variants revealed weaker, non-statistically significant associations with inflammation; the model based on genotype for *IFNL4* rs368234815 fit the data best (Table 1). In these patients with predominately mild fibrosis, we saw no association between any of the variants and increased fibrosis. **Conclusion:** *IFNL4*-TT/TT genotype, which eliminates IFNL4 protein expression within hepatocytes, was associated with greater hepatic inflammation; the weaker associations observed for *IFNL3* rs4803217 and *IFNL4* rs12979860 likely reflect LD. These results suggest that therapeutic administration of IFNL4 protein could ameliorate inflammation in patients with chronic liver diseases lacking curative therapies, such as chronic hepatitis B and nonalcoholic steatohepatitis.

Table 1. Associations for genotypes of *IFNL4* rs368234815, *IFNL4* rs12979860 and *IFNL3* rs4803217 with hepatic inflammation scores for the portal region - Black participants, Virahep-C.



Variant	Genotype	#	(%)	OR	p-value	AIC
***IFNL4*-ΔG/TT rs368234815**	ΔG/ΔG	70	41.4	–		333.7
	ΔG/TT	83	49.1	0.93	0.82	
	TT/TT	16	9.5	3.72	0.01	
***IFNL4* rs12979860**	T/T	56	33.1	–		338.4
	T/C	93	55.0	0.99	0.97	
	C/C	20	11.9	2.14	0.13	
***IFNL3* rs4803217**	T/T	55	32.5	–		338.3
	T/G	94	55.6	0.89	0.72	
	G/G	20	11.9	2.00	0.17	

AIC, Akaike information criterion - a lower score indicates better model fit.

Disclosures: The following people have nothing to disclose: Harish Gopalakrishna, Ruth Pfeiffer, Sabrina C Ramelli, Ludmila Prokunina-Olsson, Stephen M Hewitt, David E Kleiner, Marc G. Ghany, Thomas O'Brien

2614-A | A NOVEL SENOLYTIC NANOFORMULATION TARGETING THE HEPATIC SINUSOID IMPROVES HEPATIC FUNCTION AND FIBROSIS IN EXPERIMENTAL MODELS OF AGING

David Sanfeliu-Redondo[1], Vitor Francisco[2], Ines Tome[2,3], Andreia Marques[2,4], Peio Aristu[1,5], Joao Pitrez[2,6], Susana Rosa[2], Lino Ferreira[2,4] and Jordi Gracia-Sancho[1,7], (1)Idibaps - Hospital Clínic Barcelona - Ciberehd, Barcelona, Spain, (2)Cnc- Center for Neurosciences and Cell Biology, University of Coimbra, (3)Faculty of Pharmacy of the University of

Coimbra, (4)Faculty of Medicine of the University of Coimbra, (5)Barcelona Liver Bioservices (BLB), (6) Instituto Superior De Engenharia De Coimbra, (7) Inselspital - University of Bern, Bern, Switzerland

Background: Cell senescence characterized by a permanent cell cycle arrest and a senescence associated secretory phenotype, plays a key role in multiple pathologies associated with advanced age. Indeed, the aged liver exhibits hepatic microcirculatory dysfunction and sinusoidal fibrosis, which may be partly due to cell senescence. Senolytic drugs, such as navitoclax, able to interfere with the pro-survival pathways of senescent cells, can ameliorate pathological effects of senescence. However, translation of these compounds to the clinic is still limited due to low cell specificity and toxic effects. Here, we aimed at developing a nanoformulation containing navitoclax as an efficient strategy to target the hepatic sinusoid in preclinical models of healthy aging. **Methods:** Nanoformulation: A library of ~40 nanoparticles containing navitoclax was designed to be disassembled only in cells exhibiting high levels of SA-B-galactosidase activity. The bioactivity of the nanoformulations was screened to identify the best one targeting senescent endothelial cells. Hepatic effects: 20 months old Wistar rats were treated with either vehicle, soluble navitoclax (50mg/kg/day) or navitoclax-containing nanoparticles (NPs; 0.2mg/kg/day) ($n = 8$ per group). After a four-week resting period, *in vivo* hepatic and systemic hemodynamic, biochemical parameters, as well as molecular markers of liver fibrosis, senescence, and hepatic phenotype were assessed. **Results:** The NP library screening showed a nanoformulation with an optimized senolytic index of over 40x when compared with soluble navitoclax. Upon *in vivo* administration, selected NPs were mostly accumulated in the liver. Aged animals treated with NPs exhibited a reduction in portal pressure compared to vehicle (8.6 ± 0.2 vs. 9.3 ± 0.3, $p = 0.059$), with no changes in portal blood flow, suggesting decreased intrahepatic vascular resistance. Interestingly, hemodynamic improvement was not observed with the oral navitoclax treatment. Beneficial effects of novel NPs were associated with reduction in senescence markers (IL6 -72% and MMP13 -57%), improvement in hepatocyte phenotype (+52% hnf4; +51% slc22a, +5% albumin production) and, importantly, amelioration of hepatic fibrosis (-21% in Sirius red staining). **Conclusion:** Specifically targeting liver senescent cells in aging is possible using a novel formulation of senolytic nanoparticles. This technology rejuvenates liver function & architecture, thus representing a unique therapeutic opportunity for diseases coursing with cellular senescence.

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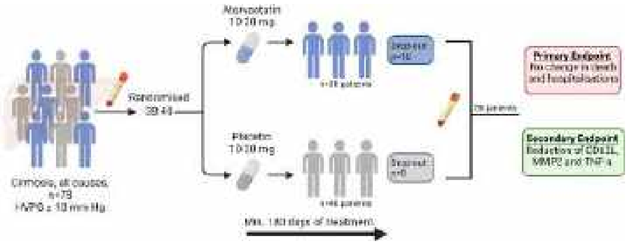
The following people have nothing to disclose: David Sanfeliu-Redondo, Peio Aristu

Disclosure information not available at the time of publication: Vitor Francisco, Ines Tome, Andreia Marques, Joao Pitrez, Susana Rosa, Lino Ferreira

2615-A | ATORVASTATIN REDUCES INFLAMMATORY BIOMARKERS TNF-Α, CD62L AND MMP-2 IN CIRRHOSIS. RESULTS FROM A RANDOMIZED PLACEBO-CONTROLLED TRIAL

Thit Mynster Kronborg, Hvidovre University Hospital

Background: Patients with cirrhosis and portal hypertension endure a high risk of complications. Besides anti-inflammatory and anti-fibrotic effects, statins may reduce portal pressure and thus the risk of complications and mortality. We aimed to investigate the effects of atorvastatin treatment on hospital admissions, mortality, inflammation and lipidomics in cirrhosis with portal hypertension. **Methods:** We performed a double-blinded, randomized, placebo-controlled clinical trial in patients with cirrhosis and portal hypertension. Atorvastatin (10-20 mg/day) was administered for six months. We measured splanchnic hemodynamics and analyzed cellular biomarkers and lipidomics at baseline and after six months. **Results:** Seventy-eight patients were randomized with 38 patients allocated to atorvastatin and 40 patients to placebo. Fifty-nine patients completed six months of intervention. Liver-related complications and mortality were similar between the groups. The hepatic venous pressure was unchanged after six months of atorvastatin (change -0.4 mmHg (16.1 vs. 15.5, $p = 0.6$)) and placebo (change -0.4 mmHg (15.1 vs. 14.7, $p = 0.6$)). The MELD score was unchanged in both groups. Atorvastatin decreased the cellular biomarkers TNF-α, CD62L and MMP-2 (*p*-values; 0.005, 0.011, and 0.023, respectively). **Conclusion:** In patients with cirrhosis, atorvastatin was safe to use, and induced anti-inflammatory effects with minor effects on lipids during a six-month treatment period. Atorvastatin did not reduce mortality, risk of liver-related complications, or hepatic venous pressure within six months of treatment. Future studies focusing on intervention in earlier stages of cirrhosis are desired.


Atorvastatin 10/20 mg
Placebo 10/20 mg
Cirrhosis, all causes, n=79
Min. 180 days of treatment
Primary Endpoint
Secondary Endpoint
Reduction of CD62L, MMP2 and TNF-α

Disclosures: The following people have nothing to disclose: Thit Mynster Kronborg

2616-A | EXERCISE REDUCES INFLAMMAGING IN SARCOPENIC CIRRHOTICS BY MODULATING NEUTROPHILS, MEMORY B CELLS AND IL-6 DYNAMICS

Preeti Negi, Nidhi Nautiyal, Swati Thangariyal, Ashmit Mittal, Rakesh Kumar, Shiv Kumar Sarin and Sukriti Sukriti, Institute of Liver and Biliary Sciences

Background: Sarcopenia is a multifactorial, progressive and generalized loss of skeletal muscle mass associated with inflammation, untimely immune ageing. The muscle regenerative capacity relies on the interplay between skeletal muscle and immune cells, as the later removes damaged cells and secretes growth factors for satellite cell proliferation and differentiation. However, moderate exercise enhances rejuvenation of immune cells and improves muscle growth. The aim of the study was to investigate effect of exercise in reprogramming the immune cells, reducing inflammation and improving muscle strength. **Methods:** Altogether 64 cirrhosis patients were included [78.1 % male, age 50 ± 12yr; MELD 14.5 (IQR 9.7-20.2], 42 with sarcopenia (SP) and 22 non-sarcopenic (NSP). Appendicular skeletal muscle index [ASMI {<5.5 kg/m^2 for women, <7.0 kg/m^2 for men}], dual-energy X-ray absorptiometry (DXA), gait speed, liver frailty index were measured to assess sarcopenia. High-dimensional immune profiling for monocytes, neutrophils, T and B cell subsets in peripheral blood [by flow cytometry], plasma levels of IL-6, TNFα, Myostatin and Follistatin [by ELISA] and gene expression for senescence associated secretory proteins [SASP; {IL-1b, MAPK3, CXCL10, TNFα, p21, p53] and IL-10, IL-22, IL-17A, Caspases [by q-Real time PCR] were performed. All parameters were measured before and immediately post-exercise. The exercise involved cycling on a half bicycle, sitting on a chair for 20 minutes with maximum safe effort. **Results:** Absolute counts of neutrophils (77.2 ± 12.9 vs 64.7 ± 13.6; $p = 0.03$) found high, while low lymphocytes ($p < 0.001$; 17.5 ± 5.6 vs 26.3 ± 9.4) and neutrophil/lymphocyte ratio (NLR)(4.23 ± 1.1 vs 2.9 ± 0.8; $p = 0.03$) was observed at baseline in SP. The frequency of memory B cells (12.2 ± 5.9 vs 4.5 ± 2.9; $p = 0.038$) significantly increased with low naïve B cells in SP than NSP, (taking the immunological space). Post- exercise, neutrophils and memory B cells significantly decline in SP patients ($p = 0.05$;$p = 0.015$). In plasma, IL-6 ($p = 0.04$), TNFα levels ($p = 0.03$) were high in SP than NSP at baseline. The myostatin (MYST) and follistatin were comparable in both groups. The MYST levels were inversely proportional to MELD-Na($r = -0.289$; $p = 0.002$). NLR and IL-6 was found to be independent predictors of sarcopenia (AUROC-0.75, $p = 0.004$ and 0.72, $p = 0.014$). The mRNA levels of SASP were > 3 fold up-regulated ($p < 0.05$) and IL-10 and IL-22 was > 4 fold down-regulated in SP than NSP. Interestingly, post-exercise, IL-6 levels significantly decline in SP patients ($p = 0.015$) but no changes were observed in MYST or follistatin in SP group. The SASP mRNA levels decline post exercise in both SP and NSP patients ($p < 0.001$). **Conclusion:** Exercise induces immune cells reprogramming by removing memory B cells, reducing inflammation and immune-senescence. The beneficial and immediate effect of exercise potentiates, better management of sarcopenia in liver disease condition.

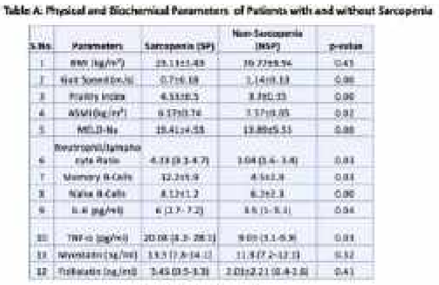
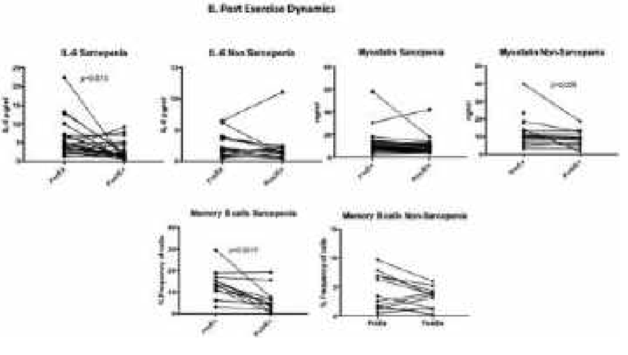


Table A: Physical and Biochemical Parameters of Patients with and without Sarcopenia



B. Post Exercise Dynamics

Disclosures: The following people have nothing to disclose: Preeti Negi, Nidhi Nautiyal, Swati Thangariyal, Ashmit Mittal, Rakesh Kumar, Shiv Kumar Sarin, Sukriti Sukriti

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

2617-A | FERROPTOSIS INDUCES TLR9-DEPENDENT ACTIVATION OF HEPATIC INFLAMMATORY RESPONSES

Mo Wang, Nanjing Drum Tower Hospital Affiliated to Nanjing University and Suzhen Yang, Gulou Hospital Associated with Nanjing University

Background: Hepatocyte death is an important cause of liver inflammation that ultimately leads to liver fibrosis, cirrhosis, and cancer. Ferroptosis is an emerging type of hepatic death associated with non-alcoholic fatty liver disease (NAFLD), but the mechanisms by which ferroptosis triggers inflammatory responses remain poorly understood. **Methods**: We utilized mouse model of NAFLD that was induced by feeding a Western diet (WD) for 16 weeks, and primary cultured mouse hepatocytes and Kupffer cells (KCs). Ferroptosis was induced by pharmacological inducer RSL3 and determined by propidium iodide (PI) staining in cultured cells and by TUNEL staining in mouse livers. The expression of inflammatory cytokines was determined by ELISA and qRT-PCR, and the number of myeloid cells in the liver was determined by staining of CD45. **Results**: We showed that 200 nM RSL3 induced robust ferroptosis of primary hepatocytes as determined by the number of PI-positive cells. RSL3 treatment (5 mg/kg) induced a significantly higher number of TUNEL-positive cells in mice with NAFLD than the control group. Compared to RSL3-treated chow-fed mice and untreated WD-fed mice, RSL3-treated WD-fed mice showed markedly higher production of inflammatory cytokines including the TNF-a and IL-1b as determined by ELISA and qRT-PCR. Increased inflammation in RSL3-treated NAFLD mice was further confirmed by the higher number of cells positive for CD45 staining. To assess the mechanisms of ferroptosis induced inflammatory response, we isolated extracellular vesicles (EVs) from both the culture media of RSL3-treated cells and the sera of RSL3-treated mice. EVs of RSL3-treated hepatocytes and mice both induced significant increases in the expression of cytokines including TNF-a and IL-1b. Intriguingly, the mRNA expression of TLR9 was also induced in EV-treated KCs and in the liver of RSL3-treated mice. Inhibition of TLR9 by its antagonist ODN 2088 mitigated EV-induced cytokine expression in KCs. The loss of TLR9 significantly attenuated RSL3-induced production of TNF-a and IL-1b in both chow and WD-fed mice. Moreover, by qPCR analysis we have identified a higher abundance of mitochondrial DNA (mtDNA) and less genomic DNA (gDNA) in the harvested EVs. Pretreatment of the isolated EVs by sonication and DNase I reduced the induction of TNF-a and IL-1b by cultured KCs. **Conclusion**: Ferroptosis induces the secretion of mtDNA-enriched EVs that induce TLR9-dependent inflammatory responses by the macrophages in NAFLD.

Disclosures: The following people have nothing to disclose: Mo Wang, Suzhen Yang

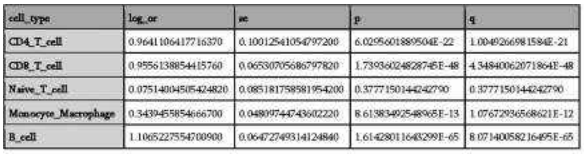
2618-A | IMAGING MASS CYTOMETRY ANALYSIS REVEALS CXCL9-DEPENDENT PRESERVATION OF INTRA-HEPATIC MACROPHAGE POPULATIONS IN CONGESTIVE HEPATOPATHY

Moira Hilscher, Hospital of the University of Pennsylvania, Siyuan Ma, Vanderbilt University Medical Center, Hongzhe Li, University of Pennsylvania, Nawras Habash, Mayo Clinic and Vijay Shah, Mayo Clinic Rochester, Rochester, MN

Background: Congestive hepatopathy (CH) has traditionally been described as a bland, non-inflammatory hepatopathy. As a result, an in-depth analysis of the intra-hepatic immune landscape has not been completed in CH. Our studies show that the sub-population of liver sinusoidal endothelial cells proximal to the central veins express CXCL9. In order to investigate the impact of CXCL9 on the immune microenvironment in CH, we performed imaging mass cytometry (IMC) on liver tissue obtained from patients with CH, Fontan-associated liver disease (FALD), and healthy controls (HC). As CXCL9 has been implicated in macrophage chemotaxis, we hypothesized that macrophages mediate congestive fibrosis. **Methods:** We stained tissue sections with 27 antibodies specific for structural and immune cell types. Multiplexed images were processed for cell segmentation. Per-cell mean signal intensity was then exported for normalization and analysis. Self-organizing map clustering was used for cell clustering and cell type phenotyping. **Results:** In order to address our hypothesis, we initially assessed changes in immune cell density in fibrotic regions. With the exception of naive T cells, we found that all immune cell subsets displayed highly significant enrichment patterns in fibrotic regions (Table 1). We then assessed changes in the intrahepatic innate and adaptive immune responses. Our analysis revealed that cell density, including immune cells, is decreased in diseased versus control tissues. A notable exception are intra-hepatic macrophages which are preserved in the setting of FALD and CH. In contrast, CH and FALD demonstrate a significant decrease in the intra-hepatic adaptive immune response compared to HCs (FALD versus HC median difference -81.904 cells/mm^2, p-value 3.36x10^{-4}; CH versus HC median difference -90.136 cells/mm^2, p-value 2.62x10^{-4}). To determine the impact of this change in the intra-hepatic adaptive

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

immune response, we tested if interaction frequency of immune cell populations correlated with clinical covariates. Post multiple-testing correction, the interaction between CD4 and CD8 T-cells correlated negatively with both fibrosis stage and with MELD-Na score (coefficient -0.911, p-value 0.048), suggesting that the decline in intra-hepatic adaptive immune cell populations is associated with more severe disease. **Conclusion:** FALD and CH are characterized by preservation of intra-hepatic macrophages which we hypothesize accelerate congestive fibrosis. Decreases in the adaptive immune cell populations, including CD4 and CD8 T-cells, may be associated with a more severe clinical phenotype.



cell_type	log_or	se	p	q
CD4_T_cell	0.9641106417716370	0.10012541054797200	6.0295601889504E-22	1.0049266981584E-21
CD8_T_cell	0.9556138854415760	0.06530705686797820	1.73936024828745E-48	4.34840062071864E-48
Naive_T_cell	0.07514004505424820	0.085181758581954200	0.3777150144242790	0.3777150144242790
Monocyte_Macrophage	0.3439455854666700	0.04809744743602220	8.61383492548965E-13	1.07672936568621E-12
B_cell	1.1065227554700900	0.06472749314124840	1.61428011643299E-65	8.07140058216495E-65

Table 1. Enrichment of immune cell populations in fibrotic regions. With the exception of naïve T cells, all immune cell subsets demonstrate highly significant enrichment patterns in fibrotic regions, which were defined as locations within a 20 micron neighborhood of a defined fibrotic area (per-cell average collagen marker greater than the 90% within image quantile).

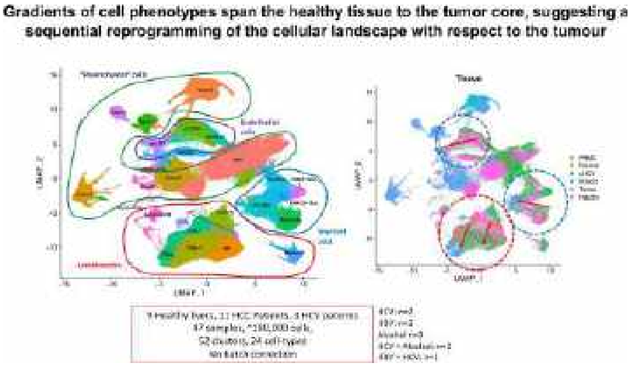
Disclosures: The following people have nothing to disclose: Moira Hilscher, Vijay Shah

Disclosure information not available at the time of publication: Siyuan Ma, Hongzhe Li, Nawras Habash

2619-A | REDUCED INFLAMMATORY POTENTIAL OF TUMOR ASSOCIATED MACROPHAGES PROMOTES T CELL TOLERANCE AND EXHAUSTION IN HUMAN HEPATOCELLULAR CARCINOMA

Jawairia Atif[1,2], Lawrence Wood[1,2], Lewis Liu[2], Catia Perciani[2], Xue-Zhong Ma[2], Justin Manuel[2], Tommy Ivanics[2], Marco Claasen[3], Roxana Bucur[2], Tallulah Andrews[4], Anand Ghanekar[5], Trevor J. Pugh[1,6,7], Gary Bader[1,8], Ian McGilvray[2], Gonzalo Sapisochin[2] and Sonya A MacParland[1,2], (1)University of Toronto, (2) University Health Network, (3)Toronto General Hospital, (4)University of Western Ontario, (5)The Hospital for Sick Children, (6)Princess Margaret Cancer Centre, (7) Ontario Institute for Cancer Research, (8)Donnelly Centre for Cellular and Biomolecular Research

Background: While hepatocellular carcinoma (HCC) is the seventh most common cancer worldwide, it is the third most lethal, reflecting the inadequacy of its current treatments. Despite recent advances in immunotherapy, response rates in HCC are still relatively low. HCC commonly occurs on a background of chronic liver disease (CLD) due to hepatitis C virus (HCV) or hepatitis B virus infection, or alcohol use disorder. The sequential changes to the immune microenvironment in the liver from health to CLD to HCC tumors are not well characterized. Immunoregulatory tumor-associated macrophages (TAMs) are enriched in the tumor microenvironment (TME) and have been linked to T cell tolerance and dysfunction in an HCC setting and represent potential targets for the treatment of HCC. **Methods:** Using single-cell RNA and TCR sequencing, we generated a transcriptomic atlas of 185,000 cells from healthy human livers (n = 11), chronic HCV infection (n = 5), and treatment-naive HCC resection samples from the tumour core (n = 11), the tumour-margin (n = 11), and adjacent-normal livers (n = 11) of varying aetiologies. Intracellular cytokine staining and *in vitro* assays were employed to determine the functional state of primary tumor-associated macrophages (TAM). Flow cytometry was used to validate T cell and TAM phenotypes. **Results:** All major non-parenchymal cell types display gradients of cell phenotypes spanning the healthy tissue to the tumour core, suggesting a sequential reprogramming of the cellular landscape with respect to the tumour. An enrichment of exhausted and clonally expanded CD8 + T cells (*TOX, PDCD1*), regulatory T cells (*FOXP3*) (Tregs), and immune-regulating macrophages (*MRC1, TREM2, CD9*) defines the tumor-core relative to the healthy and the adjacent-normal liver. We note the presence of a conserved TAM population in all patients, regardless of aetiology. With increased proximity to the tumor, macrophages secrete less TNF-α following *in vitro* LPS and IFN-γ stimulation and interact with T cells through more immunoregulatory pathways. Furthermore, TAMs exhibit reduced expression of pro-inflammatory genes, such as those in the cGAS-STING pathway. **Conclusion:** We present a geographically resolved single-cell transcriptional examination of the immune landscape in human HCC. Etiology-conserved pathways driving an immunoregulatory TAM phenotype are enriched in the TME and present opportunities for generating unified approaches to targeting all types of HCC.


Gradients of cell phenotypes span the healthy tissue to the tumor core, suggesting a sequential reprogramming of the cellular landscape with respect to the tumour

Disclosures: The following people have nothing to disclose: Jawairia Atif, Lawrence Wood, Lewis Liu, Catia Perciani, Xue-Zhong Ma, Justin Manuel, Anand

Ghanekar, Ian McGilvray, Gonzalo Sapisochin, Sonya A MacParland

Disclosure information not available at the time of publication: Tommy Ivanics, Marco Claasen, Roxana Bucur, Tallulah Andrews, Trevor J. Pugh, Gary Bader

2620-A | SINGLE CELL DISSECTION OF HUMAN CHECKPOINT INHIBITOR AND AUTOIMMUNE HEPATITIS REVEALS INSIGHTS INTO LIVER IMMUNE TOLERANCE

Molly Thomas[1], Tos Chan[1], Neal Smith[1], Shreyash Sonthalia[1], Marc S. Sherman[1], Swetha Ramesh[2], Alice Tirard[1], John McGuire[1], Mazen Nasrallah[3], Kasidet Manakongtreecheep[4], Jessica Tantivit[5], Leyre Zubiri[1], Dejan Juric[1], Ryan Sullivan[1], Nir Hacohen[6], Genevieve Boland[1], Georg M. Lauer[7], Kerry Reynolds[1] and Alexandra-Chloé Villani[1], (1)Massachusetts General Hospital, (2)UCLA, (3)Mass General Brigham, (4) Harvard University, (5)UCSD, (6)Broad Institute of MIT and Harvard, (7)Massachusetts General Hospital and Harvard Medical School

Background: Immune checkpoint blockade (ICB) targeting PD-1 and CTLA-4 to treat cancer has revolutionized immuno-oncology. However, therapy is limited by frequent immune-related adverse events, including hepatitis (irHepatitis), which occurs in ~1-17% of patients. While irHepatitis is often mild, it can cause severe hepatic dysfunction, lead to delays in cancer therapy, and is often treated with immunosuppressive agents that may compromise anti-tumor immune responses. irHepatitis shares clinical and histologic features with autoimmune hepatitis (AIH). The study of irHepatitis and AIH is therefore important for understanding how immune tolerance is lost across a spectrum of inflammatory liver diseases. **Methods**: To characterize the cellular and molecular underpinnings of irHepatitis, we used single-cell and single-nuclei RNA sequencing with paired T-cell receptor and B-cell receptor sequencing to characterize ~300,000 cells from the liver and blood of 23 patients (9 irHepatitis, 4 AIH, 3 controls on ICB, 7 controls not on ICB). irHepatitis was defined by a hepatocellular or cholestatic rise in liver function tests and centrilobular or panlobular histiocytic liver injury requiring steroids. Controls had drug-induced liver injury, hepatic steatosis, non-alcoholic steatohepatitis, primary biliary cirrhosis, or venous outflow obstruction not requiring immunosuppression. **Results**: In irHepatitis, we detected clonally-related, liver T cells expressing *CXCL13* and expanded cycling and cytotoxic CD8 T cells that spanned effector to exhausted phenotypes. Parallel analysis of tissue immune cells from patients with AIH or irHepatitis enabled the identification of cell types and states both common and unique to each type of immune-mediated liver injury. Analysis of matched blood samples from the same patient cohort revealed how cellular and transcriptional signatures in the liver were mirrored in circulating immune cells. Lastly, analysis of hepatocytes, cholangiocytes, and mesenchymal cells revealed inflammatory signatures suggesting liver parenchymal dysfunction. **Conclusion**: In defining the cellular and transcriptional programs that are altered in irHepatitis and AIH, we have identified novel pathways that could be therapeutically targeted to treat liver inflammation and have determined how PD-1 and CTLA-4 signaling may contribute to immune tolerance in the liver.

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f 2621-A | TARGETING CXCL9/CXCL10/CXCL11 USING NOVEL EPIGENOMIC CONTROLLERS FOR THE TREATMENT OF INFLAMMATORY LIVER DISEASE

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

Background: Hepatitis is a broad pathophysiological feature common to acute and chronic liver diseases characterized by activation of inflammatory mechanisms, including increased interferon gamma (IFNG) expression. IFNG is a pleotropic proinflammatory cytokine released by immune cells that contributes to liver injury by stimulating the release of chemokines CXCL9, CXCL10 and CXCL11 from hepatocytes. CXCL9-10-11 bind CXCR3 on T cells and promote their recruitment to the site of inflammation. Through our OMEGA platform, we are able to rapidly develop programmable mRNA medicines called Omega Epigenomic Controllers (OECs) to precisely tune gene expression at the pre-transcriptional level. OECs are mRNA therapeutics currently delivered in tissue-specific lipid nanoparticles (LNPs) that site-specifically modulate epigenetic states. Using OECs to simultaneously target all three *CXCL9-10-11* genes in a liver-specific manner represents a novel and promising strategy for treatment of inflammatory liver disease. **Methods:** The multigenic Insulated Genomic Domain (IGD) and component sequences driving epigenetic control of the *CXCL9-10-*

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

11 gene cluster were interrogated and OECs were designed to modulate expression of *CXCL9-10-11* in mouse and human cells. AML-12, Hepa1-6 mouse liver cell lines and primary human hepatocytes were stimulated with IFNG, and chemokine expression was analyzed by qPCR and/or Luminex. To determine the relative contribution of CXLC9, CXCL10, and CXCL11, cells were transfected with LNP-encapsulated OECs and conditioned media was used in a Boyden Chamber assay to evaluate effects on T-cell migration. **Results:** IFNG stimulation of primary human hepatocytes, as well as murine hepatic AML12 and Hepa1-6 cells, resulted in significant increases in *CXCL9*, *CXCL10* and *CXCL11* mRNA expression, simulating the pathophysiology seen in liver inflammation. Treatment with combinations of OECs targeting *CXCL9-10-11* potently downregulated *CXLC9-10-11* mRNA expression and corresponding protein levels relative to the IFNG-treated control. Further development led to a single bicistronic OEC that epigenetically targeted the *CXCL9-10-11* IGD, resulting in the simultaneous reduction of *CXLC9-10-11* mRNA expression. Exposure of primary human T-cells to conditioned hepatocyte media following IFNG stimulation and OEC treatment, resulted in a significant reduction in T-cell mediated migration, compared to IFNG-stimulated control. **Conclusion:** Here we demonstrate the development of a rationally and prospectively designed OEC which potently inhibits *CXCL9-10-11* expression in hepatocytes. Liver-specific multiplexed targeting of *CXCL9-10-11* with a programmable epigenomic mRNA therapy offers a novel approach to the treatment of inflammatory liver diseases.

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2622-A | THE CYTOTOXIC MOLECULES GRANZYME B AND TRAIL DIFFERENTIALLY AFFECT THE IMMUNOPATHOGENESIS OF MURINE SCLEROSING CHOLANGITIS

Katrin Neumann[1], Mareike Kellerer[1], Sana Javed[1], Laura K Berkhout[1], Christian Casar[1], Nico Will[1], Dorothee Schwinge[1], Christoph Schramm[2] and Gisa Tiegs[1], (1)University Medical Center Hamburg-Eppendorf, (2)University Medical Centre Hamburg-Eppendorf

Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by biliary inflammation and fibrosis. We observed an increased interferon (IFN)γ response in PSC patients and in a mouse model of sclerosing cholangitis. IFNγ induced expression of the cytotoxic effector molecules granzyme B (GzmB) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in intrahepatic NK and CD8^{+} T cells and mediated liver fibrosis in $Mdr2^{-/-}$ mice. Here, we analyzed the appearance of cytotoxic lymphocytes in PSC patients and investigated the significance of GzmB and TRAIL for PSC progression in $Mdr2^{-/-}$ mice. **Methods:** Single-cell RNA-seq and CITE-seq analysis was combined with multi-parameter flow cytometry. $Mdr2^{-/-}$ x $GzmB^{-/-}$ and $Mdr2^{-/-}$ x $Tnfs10^{-/-}$ mice were used for functional analyses. Cholangiocytes were visualized by immunohistochemistry. Liver injury and fibrosis were determined by standard assays. **Results:** We identified CD8^{+} T cell clusters with a cytotoxic gene expression profile in the livers of PSC patients. GzmB and TRAIL expression was increased in hepatic CD8^{+} T cells and NK cells in $Mdr2^{-/-}$ mice compared to wild type controls. Lack of GzmB did not affect the phenotype of these cytotoxic lymphocyte subsets but resulted in less severe liver injury and fibrosis. In contrast, disease severity of sclerosing cholangitis was aggravated in the absence of TRAIL. This was associated with increased expression of IFNγ and GzmB by NK and T cells, enhanced survival of hepatic T cells and expansion of cholangiocytes and stellate cells. **Conclusion:** While GzmB induces hepatic cell death and fibrosis in sclerosing cholangitis, TRAIL suppresses inflammatory and cytotoxic immune responses subsequently leading to reduced stellate cell activation and fibrosis.

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f 2623-A | TWO TRANSCRIPTIONALLY AND FUNCTIONALLY DISTINCT WAVES OF PRO-INFLAMMATORY VERSUS PRO-REPAIR NEUTROPHILS DURING ACUTE LIVER INJURY

Yousef Maali[1], Manuel Flores Molina[1,2], Omar Khedr[1], Mohamed Abdelnabi[1,2] and Naglaa H. Shoukry[1,2], (1) Centre De Recherche Du Centre Hospitalier De L'université De Montréal (CRCHUM), (2)Université De Montréal

Background: Neutrophils are key inflammatory players during acute liver injury (ALI) where they infiltrate necrotic areas. Emerging evidence suggests that neutrophils also contribute to inflammation resolution and tissue repair. However, the different neutrophil subsets involved in this process are not well defined. Herein, we sought to characterize neutrophils recruited at different stages following ALI, hypothesizing that each recruitment event corresponds to a different neutrophil subset with distinct functions. **Methods:** We used the CCl_4-induced ALI model and employed flow cytometry, multiplex-immunofluorescence (mIF), and qRT-PCR to examine intrahepatic neutrophil populations during the inflammatory (24 hrs), early repair (48 hrs) and late repair phases (72-96 hrs) post-CCl_4. We also sorted intrahepatic neutrophils and analyzed their transcriptional profiles using RNA-seq. Finally, we performed *ex-vivo* assays on sorted neutrophil to examine protein translation by puromycin incorporation assay, mitochondrial function using Mitotracker® Green and Red, and cell metabolism by Seahorse XF Cell Mito Stress Test. **Results:** We detected two temporarily distinct waves of neutrophils: (i) during necroinflammation (at 24 hrs) and (ii) during late repair (at 72 hrs). The early wave of neutrophils was preceded by and overlapped with an increase in gene expression of the major neutrophil chemoattractant *Cxcl1* while the second wave was associated with increased *Cxcl5.* Using RNA-seq analysis and validation by *ex-vivo* approaches, we identified distinct transcriptomic and functional profiles of early and late neutrophils. Early neutrophils were characterized by: (i) up-regulation of inflammatory cytokines (e.g., *Il12a*) and of the chemokine receptor *Cxcr5*, (ii) activation of the non-canonical NF-κB pathway, (iii) reduction of protein translation and (iv) decreased oxidative phosphorylation. In contrast, the late wave neutrophils exhibited an angiogenic profile with up-regulation of several genes and pathways associated with tissue repair and angiogenesis (e.g., *Cxcr4, Fgg, Cox-2)*. **Conclusion:** We report two waves of intrahepatic neutrophils with distinct transcriptomic and functional profiles during ALI. The first wave presents a pro-inflammatory profile, whereas the second wave exhibits an angiogenic and pro-repair profile. This study underscores the heterogeneity in neutrophils and their emerging role in tissue repair during ALI.

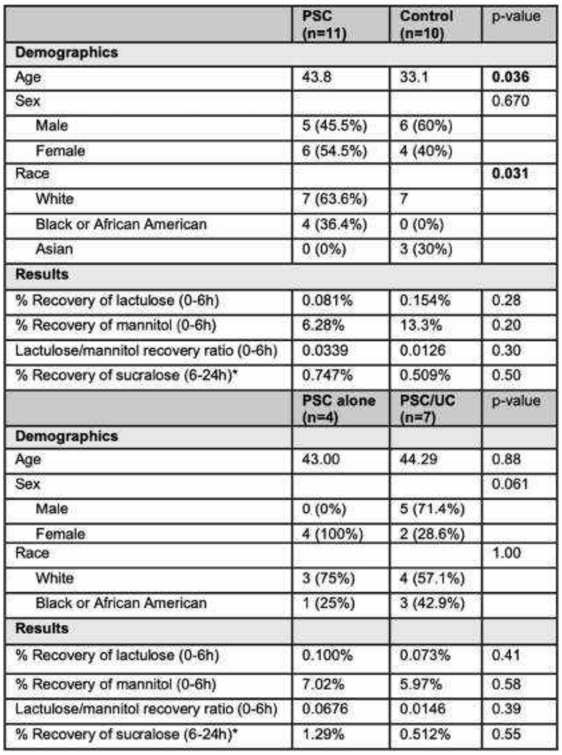
Disclosures: The following people have nothing to disclose: Yousef Maali, Manuel Flores Molina, Omar Khedr, Mohamed Abdelnabi, Naglaa H. Shoukry

2700-A | ASSESSING INTESTINAL PERMEABILITY IN PRIMARY SCLEROSING CHOLANGITIS USING A TRIPLE SUGAR TEST

Emma Rosenbluth[1], Imran Nizamuddin[2], Daina Ringus[1], Gregory Dean[3], Stephen Hanauer[1] and Josh Levitsky[1], (1)Northwestern University Feinberg School of Medicine, (2)Washington University School of Medicine in St. Louis, (3)University of Michigan

Background: While the pathogenesis of primary sclerosing cholangitis (PSC) remains enigmatic, the potential role of intestinal permeability has been postulated to account for the recognized association with ulcerative colitis (UC). The gut microbiome has been an attributable risk factor in both PSC and UC and either pre-existing increased gut permeability or active mucosal inflammation could account for translocation of bacteria, toxins, and pathogen-associated proteins to the liver via the portal system. However, few studies have been done to support this theory. We aimed to measure small and large intestinal permeability among patients with PSC and PSC/UC to evaluate this potential causative association. **Methods:** Subjects 18 years and older with a diagnosis of PSC, PSC and UC, and healthy controls were recruited from General Medicine and Gastroenterology clinics at Northwestern Memorial Hospital. To assess intestinal permeability, we used a 'triple sugar test', which measures urinary excretion of orally administered oligosaccharides (mannitol, lactulose, and sucralose). Subjects were asked to drink a 100 mL solution of 5g lactulose, 2g mannitol, and 2g sucralose and collect a 24-hour urine sample in two parts: 0-6 hours and 6-24 hours. Urine concentrations of each sugar were measured via mass spectrometry. The 0-6 hour lactulose/mannitol recovery ratio (LMR) was used to assess small intestinal permeability and the 6-24 hour percent recovery of sucralose assessed colonic permeability. Groups were compared using t-test for continuous variables and Fisher's exact for categorical variables. **Results:** There were 11 subjects with PSC (4 with PSC alone, 7 with PSC/UC) and 10 controls. Those with PSC were older (43 vs 33, $p = 0.036$) and less likely white (63.6% vs 70%, $p = 0.03$) compared to controls (Table 1). There were no significant demographic differences between the PSC and PSC/UC groups. There was no significant difference in the 0-6 hour LMR in PSC vs control (0.0339 vs 0.0126, $p = 0.3$) or PSC alone vs PSC/UC (0.0676 vs 0.0146, $p = 0.4$). There was no significant difference in the 6-24 hour percent recovery of sucralose in PSC vs control (0.75% vs 0.51%, $p = 0.5$) or PSC alone vs PSC/UC (1.3% vs 0.51%, $p = 0.5$). **Conclusion:** We found no significant difference in either small intestinal or colonic permeability between the PSC and control groups or between those with PSC alone and those with PSC and UC. While our sample size is limited, these preliminary data do not support the association of increased intestinal permeability compared to healthy controls. Further studies are warranted to explore the potential role of the intestine in the pathogenesis of PSC.

Table 1. Demographics and results.



	PSC (n=11)	Control (n=10)	p-value
Demographics			
Age	43.8	33.1	**0.036**
Sex			0.670
Male	5 (45.5%)	6 (60%)	
Female	6 (54.5%)	4 (40%)	
Race			**0.031**
White	7 (63.6%)	7	
Black or African American	4 (36.4%)	0 (0%)	
Asian	0 (0%)	3 (30%)	
Results			
% Recovery of lactulose (0-6h)	0.081%	0.154%	0.28
% Recovery of mannitol (0-6h)	6.28%	13.3%	0.20
Lactulose/mannitol recovery ratio (0-6h)	0.0339	0.0126	0.30
% Recovery of sucralose (6-24h)*	0.747%	0.509%	0.50
	PSC alone (n=4)	**PSC/UC (n=7)**	p-value
Demographics			
Age	43.00	44.29	0.88
Sex			0.061
Male	0 (0%)	5 (71.4%)	
Female	4 (100%)	2 (28.6%)	
Race			1.00
White	3 (75%)	4 (57.1%)	
Black or African American	1 (25%)	3 (42.9%)	
Results			
% Recovery of lactulose (0-6h)	0.100%	0.073%	0.41
% Recovery of mannitol (0-6h)	7.02%	5.97%	0.58
Lactulose/mannitol recovery ratio (0-6h)	0.0676	0.0146	0.39
% Recovery of sucralose (6-24h)*	1.29%	0.512%	0.55

Categorical values compared using Fisher's exact, continuous variables compared using t-test.
**PSC alone n=3, PSC/UC n=7.*

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2701-A | BACTEROIDES VULGATUS AMELIORATE NAFLD BY MODULATING GUT MICROBIOME AND JAK-STAT PATHWAY

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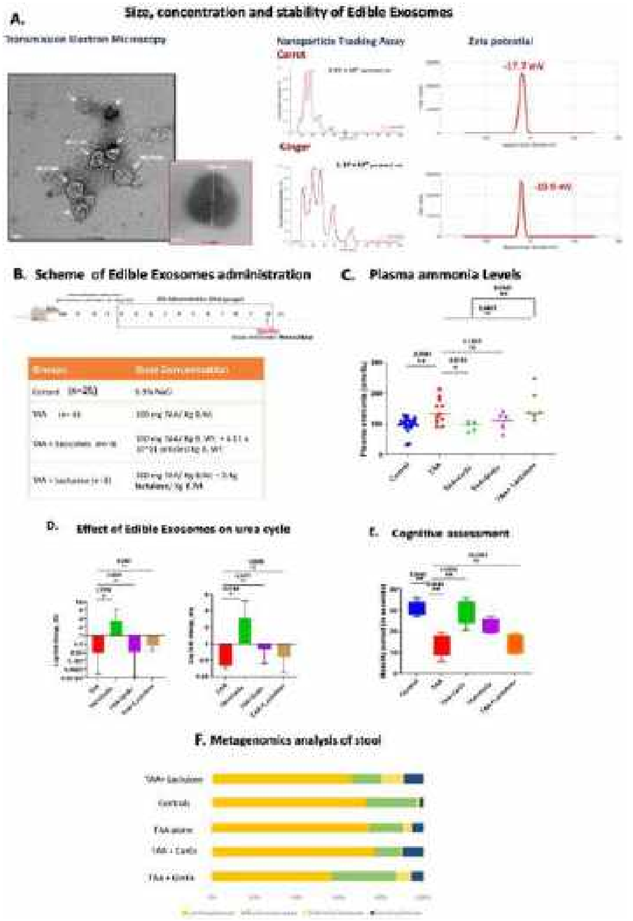
Background: Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent forms of liver disease worldwide. However, definitive medical treatments have not been. Recently, the gut microbiome has been linked to a number of diseases. This study aimed to elucidate the underlying mechanisms of western diet-induced NAFLD associated with the gut microbiome by gut-liver axis and explore the effects of *Bacteroides vulgatus* from the gut metagenomic and liver tissue analysis perspective. **Methods:** Six weeks old C57BL/6J mice were fed the Western diet with/without strains for 12 weeks. *B. vulgatus* and *V. dispar* were administered at a concentration of 2×10^9 CFU/day. We compared NAFLD activity score (NAS), histopathological analysis of liver tissue, fecal microbiome analysis, gut permeability analysis, liver tissue microarray and check markers level for inflammation and lipogenesis in the liver. **Results:** Western diet induces NAFLD through dysbiosis caused by reduction in *Bacteroidetes* and an increase in *Proteobacteria* phyla. But treat strain groups shows increase *Bacteroidetes* and decrease *Proteobacteria* phyla, and *Helicobacter* genus. Treat *B. vulgatus* shows significant results in serum total cholesterol level (153.29 ± 13.75, $P < 0.001$), L/B ratio (4.41 ± 0.32, $P < 0.0001$), CD68 (11.81 ± 5.58, $P < 0.01$) and improved NAS (2.57 ± 1.13, $P < 0.01$) compared with the western diet group (total cholesterol 213.5 ± 27.07; L/B ratio 5.45 ± 0.26; CD68 30.26 ± 8.79; NAS 4.7 ± 1.57). To determine the mechanism of the gut-liver axis, checked the gut permeability and found that the gut tight junction genes and proteins were higher in the *B. vulgatus* group than in the western diet group. Moreover, *B. vulgatus* downregulated the inflammation (TNF-α, 10.36 ± 3.01/1.66 ± 1.08, $P < 0.001$; IL-6, 5.61 ± 4.06/1.58 ± 0.41, $P < 0.05$) by regulating the fatty acid uptake (CD36, 10.37 ± 2.51/2.84 ± 2.03, $P < 0.05$), synthesis (FAS, 15.54 ± 7.64/5.23 ± 3.52, $P < 0.05$; SREBP-1c, 24.26 ± 6.96/10.54 ± 4.67, $P < 0.05$), and oxidation (PPARα, 6.09 ± 1.29/12.29 ± 1.76, $P < 0.001$) level. Microassay and geneset enrichment analysis were performed with RNA from liver tissue to identify differences in the Jak-STAT pathway. As a results, *B. vulgatus* ameliorates NAFLD through modulation of gut microbiota and Jak-STAT pathway resulting in reduced steatosis. **Conclusion:** Our study highlighted the association between gut microbiota and NAFLD and the importance of the gut-liver axis and confirmed the potential of *B. vulgatus* to improve NAFLD. Studying the mechanisms between probiotics and NAFLD will help design novel therapies.

Disclosures: Ki Tae Suk – Institute for Liver and Digestive Diseases, College of Medicine, Hallym University, Chuncheon 24252, Republic of Korea: Employee, No, No;
The following people have nothing to disclose: Sang Jun Yoon, Jung A Eom, Sang youn Lee
Disclosure information not available at the time of publication: Kyeong Jin Lee

f 2702-A | CARROT AND GINGER EDIBLE EXOSOMES RESTORE GUT MICROBIOME AND AMELIORATE HEPATIC INJURY BY REDUCING SYSTEMIC AMMONIA LEVELS: A COMPARATIVE STUDY

P. Debishree Subudhi, Jitendra Kumar, Anupama Parasar, Shivani Gautam, Varun Suroliya, Chhagan Bihari, Shiv Kumar Sarin and Sukriti Baweja, Institute of Liver and Biliary Sciences

Background: Elevated plasma ammonia is attributed to hepatic dysfunction and increased gut permeability and systemic inflammation. There is an urgent need of candidates which can reinstate the gut commensals, reduce ammonia levels and prevent hepatic injury. Hence, we investigated the effects of edible exosomes from carrot (CarEx) and ginger (GinEx) in reducing ammonia, changes in gut microbiome in acute hepatic encephalopathy model. **Methods:** Edible exosomes fractioned from black carrots (*Pusa Asita*) and Ginger (*Gingiber officinale*) by differential ultracentrifugation and characterized by transmission electron microscopy and nanoparticle tracking assay. Proteomics was performed to evaluate cargoes. Prophylactic administration of CarEx and GinEx was orally administered daily for 10 days with vehicle and lactulose in thioacetamide(TAA) induced acute hyperammonemia rat model. Ammonia, liver functionality was quantified with behavioral functions and gut microbiota assessment by 16s metagenomics. **Results:** The concentration of CarEx, $2.65 \times 10^9 \pm 0.65$ and GinEx, 1.17 x 109 particles/ mL with zeta potential -17.7 ± 2.4mV and -20.0 ± 2.0mV. Cargo proteins identified as bactericidal zeta toxin proteins, superoxide dismutase (anti-oxidant) and ferritin (cellular homeostasis) in CarEx. However, zingipain (anti-fungal,anti-inflammatory), Geranyol dehydrogenase(ant-microbial) in GinEx. After stomach like invitro digestion, no changes in concentration were found but particle size reduced (35-200nm) with intact zeta potential. Oral administration of CarEx in TAA animals reduced the plasma ammonia levels 92.2 ± 13.6mmol/L($p = 0.0151$), AST($p = 0.0043$) and increased albumin ($p = 0.0079$), whereas found comparable after GinEx,105.1 ± 25.9mmol/L and lactulose,157.9 ± 46.6mmol/L than vehicle. Both CarEx and GinEx improved cognition but CarEx have shown resurgence($p = 0.043$) by increasing the cellular antioxidant defence (Gsr,$p = 0.0357$) .In CarEx group, >5 fold upregulation of urea cycle enzymes (ornithin; $p = 0.0159$, arginase; $p = 0.0159$) than GinEx. The expression of occludin was also higher in CarEx than GinEx, lactulose or vehicle ($p < 0.001$). 16s metagenomics showed both CarEx and GinEx enhanced the colonisation of Firmicutes. CarEx enhanced abundance of Lachnospiraceae ($p = 0.0303$), Lactobacillaceae ($p = 0.0286$) than vehicle, which provide energy to maintain gut epithelia and short chain fatty acid production. Also, CarEx decreased growth of urease producing family *Enterobacteriaceae*($p = 0.0043$) which is not found after GinEx intervention. **Conclusion:** Carrot edible exosomes demonstrated superior effects in reducing plasma ammonia levels, improving liver function, cognition, enhancing the gut barrier integrity and attenuates the colonisation of urease producing bacteria in the gut.



Disclosures: The following people have nothing to disclose: P. Debishree Subudhi, Jitendra Kumar, Anupama Parasar, Shivani Gautam, Varun Suroliya, Chhagan Bihari, Shiv Kumar Sarin, Sukriti Baweja

2703-A | CHARACTERISTICS OF THE INTESTINAL ENVIRONMENT AND ITS RELATIONSHIP TO DISEASE PROGRESSION BASED ON THE FECAL BILE ACIDS COMPOSITION BEFORE AND AFTER HEPATITIS C VIRUS ELIMINATION

Takako Inoue[1], Hisayoshi Watanabe[2], Etsuko Iio[3], Masaya Onishi[4], Kei Moriya[5], Hideto Kawaratani[5], Yutaka Suzuki[4], Kentaro Matsuura[6], Hitoshi Yoshiji[7] and Yasuhito Tanaka[3], (1)Nagoya City University

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Background: Metabolites and gut microbiome, which form the gut-liver axis, interact and maintain homeostasis. We analyzed and reported that gut microbiome is altered in chronic hepatitis C (CHC) patients from the early stage and dysbiosis worsens with disease progression (Clin Infect Dis. 2018). In this study, we evaluated the characteristics of intestinal environment before and after hepatitis C virus (HCV) elimination and its relationship to the disease progression based on fecal bile acids composition. **Methods:** Thirty-eight CHC patients (20 chronic hepatitis [CH] and 18 cirrhosis [LC]) were enrolled in this study. The main exclusion criterion was prescription of ursodeoxycholic acid (UDCA). The enrolled patients provided their feces three times: before HCV elimination, 24 weeks after achieving virological remarkable response (SVR), and 48 weeks after SVR. Additionally, 23 healthy individual's were enrolled as the control group. Fecal bile acids were measured by a triple quadrupole mass spectrometer. The samples were classified into three clusters (deoxycholic acid [DCA] type, lithocholic acid [LCA] type, and UDCA type), according to the bile acids with high relative proportions and based on the enterotyping method (Nature, 2011). This study was approved by the ethical review committee of our institute. **Results:** Regarding the fecal bile acid composition before HCV elimination, 40% were LCA type (8/20), 35% were UDCA type (7/20), 25% were DCA type (5/20) in CH, and 44.4% were LCA type (8/18), 33.3% were UDCA type (6/18), 22.2% were DCA type (4/18) in LC, indicating that LCA and UDCA types were predominant under HCV infection. In contrast, in healthy individual's, 4.3% (1/23) were LCA type, 17.3% (4/23) were UDCA type, and 78.3% (18/23) were DCA type. Regarding the fecal bile acid composition at 48 weeks after achieving SVR, 15% (3/20) were LCA type, 25% (5/20) were UDCA type, 60% (12/20) were DCA type in CH. That is, in CH, HCV elimination significantly increased DCA type ($p = 0.025$). Meanwhile, in LC, 38.9% (7/18) were LCA type, 33.3% (6/18) were UDCA type, and 27.8% (5/18) were DCA type, showing no remarkable change from that under HCV infection ($p = 0.70$). **Conclusion:** The intestinal environment in terms of enterotypes is dominated by DCA types in healthy individual's, and LCA or UDCA types in CHC before HCV elimination. After achieving SVR, in CH, the frequency of DCA types approached that of healthy individual's. On the other hand, in LC, the frequency of DCA type did not change before and after HCV elimination. Generally, HCV elimination corrects BA imbalance. However, the degree of recovery depends on the disease progression.

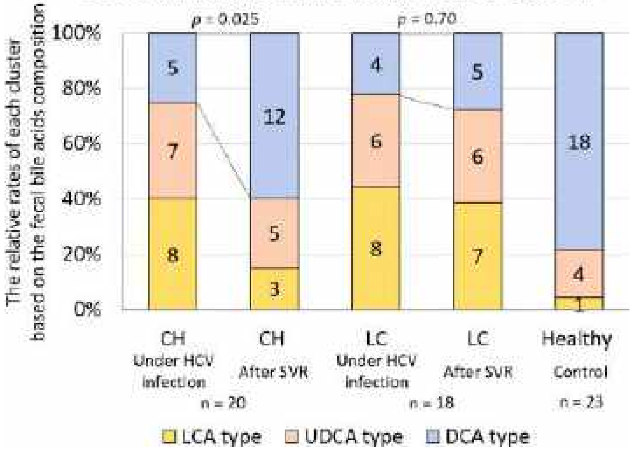
Figure Comparison of fecal bile acid composition before and after HCV elimination by disease progression

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Disclosure information not available at the time of publication: Hisayoshi Watanabe, Masaya Onishi, Kei Moriya, Hideto Kawaratani, Yutaka Suzuki, Kentaro Matsuura, Hitoshi Yoshiji

f 2704-A | CLUSTER ANALYSIS OF THE CHARACTERISTICS OF FECAL BILE ACID COMPOSITION AND CAUSES OF DYSBIOSIS IN CHRONIC HEPATITIS C

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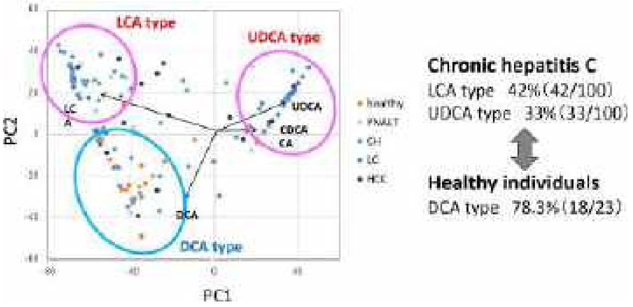
Background: Bile acids and gut microbiota, which form the gut-liver axis, interact and help to maintain homeostasis. In this study, we investigated the causes of dysbiosis in chronic hepatitis C (CHC), based on cluster analysis of the fecal bile acid composition (cluster analysis). **Methods:** One hundred CHC patients (9 with persistently normal ALT, 60 chronic hepatitis, 18 cirrhosis and 13 hepatocellular carcinoma), whose gut microbiota were analyzed in a previous study (Clin Infect Dis, 2018), and 23 healthy individual's were enrolled. The main exclusion criterion was prescription of ursodeoxycholic acid (UDCA). Fecal bile acids were measured by a triple quadrupole mass spectrometer. For cluster analysis, the samples were classified into three clusters (deoxycholic acid [DCA] type, lithocholic acid [LCA] type, and UDCA type), according to the bile acids with high relative proportions and based on the enterotyping method (Nature, 2011). Correlations between clusters and bacteria were analyzed using the envfit function and displayed as vectors in principal component analysis scatter plots. This study was approved by the ethical review committee of our institute. **Results:** Cluster analysis showed that 42% (42/100) of CHC patients were classified as the LCA type and 33% (33/100) as the UDCA type. In contrast, 78.3% (18/23) of healthy individual's were classified as the DCA type (Figure). Regarding the correlation between clusters and bacteria, most decreases of Clostridiales and Bacteroidales in CHC correlated with the DCA and LCA types, while *Streptococci* and *Lactobacilli,* which increased in CHC, correlated with the UDCA type. At the family level, Lachnospiraceae, Ruminococcaceae, and Rikenellaceae were most frequently correlated with the DCA, LCA, and UDCA types, in that order, while Streptococcaceae and Lactobacillaceae were correlated with the UDCA and LCA types, in that order. Streptococcaceae and Lactobacillaceae were most abundant in the order of the UDCA, LCA and UDCA types. At the species level, *Streptococci* and *Lactobacilli*, which increase in the gut of CHC patients, were inversely correlated with the relative amount of DCA in stool samples. **Conclusion:** By cluster analysis, CHC was classified as LCA or UDCA types, while healthy individual's were classified as the DCA type. DCA is hydrophobic and highly toxic to bacteria. In CHC, *Streptococci* and *Lactobacilli* may have escaped growth control due to decreased DCA in the intestinal environment, resulting in dysbiosis.

Figure The result of cluster analysis of the fecal bile acid composition in chronic hepatitis C patients



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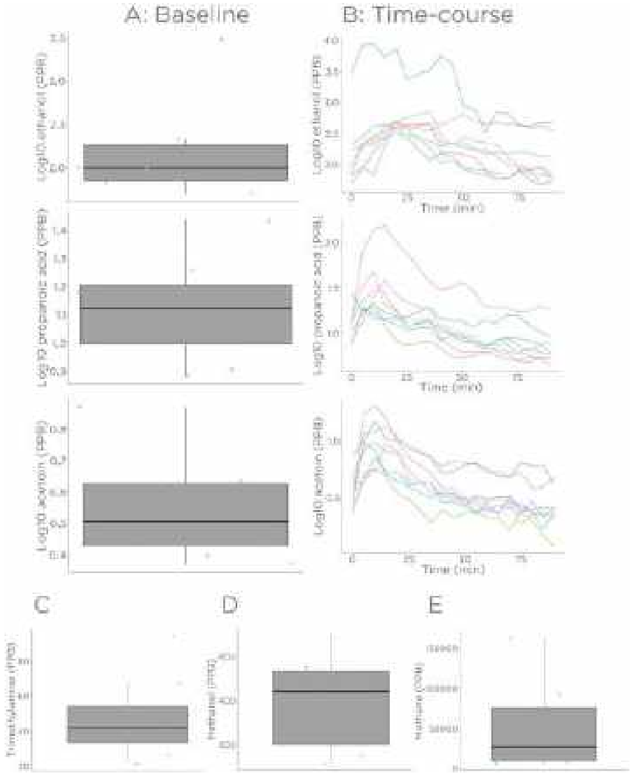
2705-A | GUT BACTERIA PHENOTYPING USING DYNAMIC BREATH ANALYSIS

Ahmed Tawfike, Antonio Murgia, Iris Banda, Yusuf Ahmed, Menisha Manhota, Federico Ricciardi, Kelly Sweeney, Louise Nicholson-Scott, Lucinda McConville, Olga Gandelman, Max Allsworth, Billy Boyle and Giuseppe Ferrandino, Owlstone Medical

Background: Gut microbiota dysbiosis results in overproduction of metabolites that exacerbate certain chronic diseases. For example, ethanol and 2-3-butanediol, produced by carbohydrate fermentation, were found associated with non-alcoholic steatohepatitis (NASH). Similarly, trimethylamine, produced from choline, is further metabolized in the liver to trimethylamine-N-oxide, a metabolite found associated with NASH severity and that exacerbate cardiovascular diseases. We explored the feasibility of a novel approach to measure gut bacteria metabolites, which can be applied to assess the extent of gut bacteria metabolism in diseases populations. **Methods:** A total of

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

8 healthy subjects were recruited with age e 18 years and body weight e 50 Kg. Subjects were instructed to fast overnight and to not drink alcoholic beverages the day before the experiments. Breath samples were collected before, and up to 90 minutes after ingestion of 75g of glucose with a time resolution of 5 minutes. Compounds of interest were measured using SIFT-MS with direct sampling. Results were expressed as part per billion (PPB v/v) as function of time post glucose ingestion. **Results:** Ambient measurements showed that all the investigated compounds were absent before and after conducting the experiment. Median (M) and interquartile range (IQR) baselines levels (before glucose administration) of ethanol, propanoic acid, and acetoin (an intermediate of the 2-3-butanediol fermentation), were respectively 99.4 [71.6-182.4], 13.3 [10-16.2], 3.2 [2.7, 4.2] PPB (Fig.1A). Post glucose ingestion we observed spikes of these compounds in breath of up to respectively 8629, 153, and 20 PPB (Fig. 1B). Additional diseases associated compounds, unrelated to glucose ingestion, were also detected, such as trimethylamine (M: 42.3, IQR: 33.6-54.3 PPB) (Fig.1C), methanol (M: 443, IQR: 199-531.4 PPB) (Fig.1D), and methane (M: 26988, IQR: 10100-76213 PPB) (Fig.1E). **Conclusion:** Dynamic breath analysis can be used for the clinical characterization of gut bacteria metabolism in healthy and disease populations to establish correlations between metabolites and disease severity and progression, as well as interaction of gut microbiota with response to therapeutic interventions. This non-invasive method can replace the current need for blood collection allowing scaling to large cohort populations.



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2706-A | GUT MICROBIOTA AS MEDIATOR AND MODERATOR BETWEEN HEPATITIS B VIRUS AND HEPATOCELLULAR CARCINOMA

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Background: Emerging evidence has demonstrated an intrinsic linkage between the gut microbiome and hepatitis B virus (HBV) induced liver diseases for its cross-talk with the gastrointestinal tract, termed the “gut-liver” axis. But the impact of gut microbiome on HBV-related hepatocellular carcinoma (HCC) remains unclear. Herein, we comprehensively signified the microbial as mediator and moderator between HBV and HCC and introduced a machine learning (ML) approach to predict the risk of HCC. **Methods:** Patients with chronic liver diseases or HCC were prospectively recruited between 2019 and 2022. Fecal samples were collected and subjected to 16S rRNA gene sequencing to determine differential taxa. The mediation/regulation effect of gut microbiome were explored between HBV and HCC using Bootstrap and Johnson-Neyman techniques. Univariate and multivariate logistic regression was applied to identify risk clinical characteristics. Several ML methods were employed to construct gut microbe-based models. The predictive performance was assessed using receiver operating characteristic curves, decision curves and calibration curve analyses. **Results:** A total of 571 patients were involved in the study, including 374 patients with HCC and 197 patients with chronic liver diseases. After propensity score matching to adjust confounding variables, 147 pairs of participants were enrolled in subsequent analysis. *Bacteroidia* and *Bacteroidales* were demonstrated to exert mediating effects between HBV and HCC, and the moderating effects varied across *Bacilli*, *Lactobacillales*, *Erysipelotrichaceae*, *Actinomyces* and *Roseburia*. HBV, alpha-fetoprotein, alanine transaminase, triglyceride and Child-Pugh were identified as independent risk factors for HCC occurrence. Seven ML-based HBV-gut microbe classifiers were established to predict HCC, with AUCs ranging from 0.802 to 0.910 that outperformed the clinical features-based model (AUC of 0.661). Furthermore, the merged clinical-HBV-gut microbe models exhibited a comparable performance to HBV-gut microbe models (AUCs from 0.833 to 0.913). **Conclusion:** Gut microbes are important factors between HBV and HCC through its potential mediating and moderating effects, which can be used as valuable biomarkers for the pathogenesis of HBV-related HCC.

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2707-A | GUT MICROBIOTA OF PATIENTS WITH HEPATITIS B VIRUS-RELATED CIRRHOSIS PROMOTES CIRRHOSIS DEVELOPMENT BY INJURING INTESTINAL BARRIER FUNCTION IN MICE

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Background: The gut microbiota is critical in maintaining intestinal barrier function. Microbiome dysbiosis and intestinal barrier dysfunctions are closely related to cirrhosis development and further complications. The present study investigated the effects of gut microbiota in patients with hepatitis B virus (HBV)-related cirrhosis on intestinal barrier function and hepatic fibrosis through fecal microbiota transplantation (FMT) experiments. **Methods:** This study recruited 12 cirrhotic patients and 12 healthy individual's from the Second Affiliated Hospital of Xi'an Jiaotong University. The fecal samples with obvious differences in microbiota structure were selected (5 cases in each group), and the bacterial suspension was prepared. Male C57BL/6 mice were randomly divided into four groups: healthy control group (HC), liver cirrhosis model group (LC), model group + bacterial suspension of healthy individual's (FMT-HI), model group + bacterial suspension of cirrhotic patients (FMT-CP). Carbon tetrachloride-induced cirrhosis model was established and mice were gavaged with bacterial suspension, lasting for 12 weeks. Colon and liver pathological morphology were observed by hematoxylin-eosin and sirius red staining, intestinal barrier function was detected using enzyme-linked immunosorbent assay and fluorescent probe, expressions of intestinal mucosal barrier and hepatic fibrosis related factors were detected by real-time quantitative polymerase chain reaction and immunofluorescence. **Results:** Compared with the intestinal bacterial suspension of healthy individual's, the cirrhotic mice treated with bacterial suspension of patients showed reduced expression of MUC2 and Claudin-2 in the colon, and increased concentrations of FITC-dextran and endotoxin in peripheral blood. The expression levels of various profibrotic cytokines (such as TGF-β1, IL-6, IL-17A) and α-smooth muscle actin in the liver were increased, and the hepatic fibrosis was aggravated **Conclusion:** The gut microbiota of HBV-related cirrhotic patients can reduce the intestinal barrier function and promote cirrhosis development in mice.

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2708-A | HOW PLANT BASED FOOD AND CULINARY MEDICINE IS TRANSFORMING HEPATOLOGISTS INTO CHEFS AND EDUCATORS

Thusha Nathan, None

Background: Physicians are challenged with their patients exposure to unhealthy food. Low income populations especially do not have access to healthy produce and/ or come from generational models that do not give them the tools on how to cook healthy meals. With the crisis of NAFLD and progression to cirrhosis , I propose that physicians practicing hepatology become versed in culinary medicine, that is, teaching their patients healthy meals and how to cook them. The physician , becomes an educator and a chef, in partnership with their patient. **Methods:** While working at a hepatology clinic, in the low income area of Fort Smith Arkansas, I implemented plant based diets into patients daily lives. I used recipe variations I learned while attending Brightwater Culinary School and those I learned while training to be a raw food chef in Bali, Indonesia. Culinary medicine is a growing field where physicians learn culinary skills to then pass those onto their patients. These programs are already taking shape in medical and culinary schools across the country. I implemented these diets using mostly plant based meals, in 500 patients over two years. Most of these low income patients had no access to plant based food nor basic knowledge of how to cook healthy meals. I instructed them on how to make tasty, healthy, low fat meals with the resources available to them. The key to culinary medicine is the breadth of variety and cooking techniques that the physician learns , that they then pass onto their patients. When the patients were given gourmet inspired recipes, presented to them by their physician, that were simple to prepare, they were compliant with these dietary changes.

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

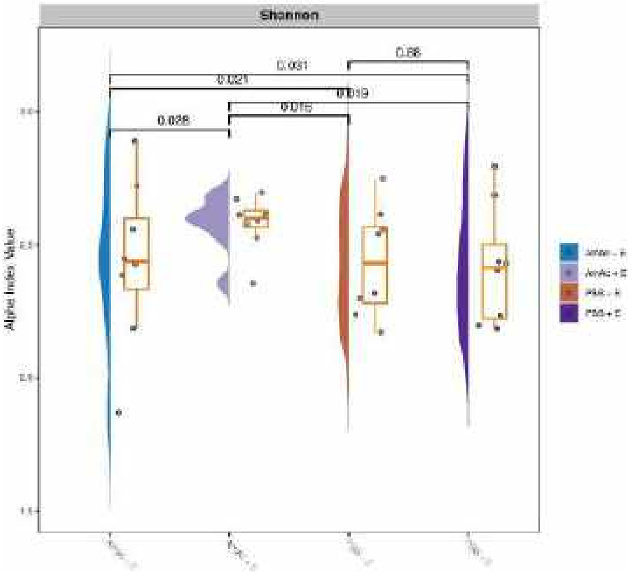
After two years- I saw marked emotional, physical, physiologic and lab improvement in their outcomes. **Results:** 100% of my patients agreed that few, if any, physicians discussed actual recipe preparation with them. 100% of my patients agreed that they felt a stronger connection to implement these changes because they were coming directly from the physician. 93% of my patients had weight loss of 10 pounds or greater, and 75% of my patients had improvement in their liver function tests and Hemoglobin A1C measured over 2 years. **Conclusion:** I propose that hepatologists engage in culinary medicine, and promote healthy, mostly plant based meals to their patients . This creates a deep bond of education and improved outcome between the physician and patient. Furthermore, in low income populations, patients do not have access to healthy food and rely on their physician to be an educator and break generational gaps in healthy food choice lifestyles. My results show that culinary medicine is an exciting and engaging field where the physician becomes a chef . These classes are already being implemented in medical schools across the country- including the University of Arkansas Medical Health Sciences Center.

Disclosures: The following people have nothing to disclose: Thusha Nathan

2709-A | HYPERAMMONEMIA IN CIRRHOSIS ALTERS EXERCISE INDUCED ALTERATIONS IN THE GUT MICROBIOME

Annette Bellar[1], Naseer Sangwan[1], Avinash Kumar[1,2], Saurabh Mishra[1], Nicole M. Welch[1] and Srinivasan Dasarathy[1], (1)Cleveland Clinic, (2)All India Institutes of Medical Sciences

Background: Patients with cirrhosis have loss of muscle mass and increased fatigue that are mediated by hyperammonemia. The gut microbiome (GMB) is believed to be a major contributor to hyperammonemia of liver disease. Even though ammonia causes perturbations in gut function, it is not known if the GMB Is altered during hyperammonemia. Skeletal muscle ammoniagenesis is increased during endurance exercise (EE) in healthy subjects. It is however not known if EE alters the GMB either in normal or hyperammonemic states. We aimed to identify whether: 1. 4 weeks of EE by voluntary wheel running (VWR) alters the GMB in vehicle-(phosphate buffered saline,PBS) treated mice; 2. Hyperammonemia alters the GMB either in the basal state or in response to EE. **Methods:** Hyperammonemia was induced in wild type, C57BL6 male mice at 8 weeks of age by surgical placement of osmotic pumps that delivered 2.5mmol/kg/day ammonium acetate (AmAc) or vehicle (PBS) for 6-weeks. After 2 weeks of pump placement, the PBS or AmAc treated mice were assigned to either 4 weeks of VWR or usual activity (UA). Mice were housed individually and a stool sample was collected prior to hyperammonemia at baseline (BL), 2 weeks after hyperammonemia, and after 4 weeks of exercise. Samples were stored in Zymo's DNA solution and batch processed for 16S sequencing, Shannon Alpha and beta diversity, and species prevalence were measured and analyzed using R. **Results:** At BL there was no difference in Shannon diversity between the mice groups (PBS-UA, PBS-VWR, AmAc-UA, AmAc-VWR) . At 2 weeks of pump placement before exercise, AmAc mice had a lower Shannon diversity (P = 0.041) compared to PBS. After 4 weeks of VWR or UA, Shannon diversity was similar in the PBS-UA and PBS-VWR (P = 0.88). In the post VWR/UA groups, AmAc-UA differed from either PBS-UA or PBS-VWR (P = 0.031 and 0.021 respectively). AmAc-VWR had the lowest Shannon diversity compared to the other groups. (PBS-UA P = 0.019, PBS-VWR P = 0.016, AmAc-UA P = 0.028). (Fig. 1) These results suggest that with AmAc treatment, 4 weeks of VWR resulted in lower Shannon Diversity of the GMB. Beta diversity, or diversity between the groups at BL was similar in the 4 mice groups. At 2 weeks after pump placement , AmAc mice clustered distinctly compared to PBS. After 4 weeks of UA/VWR, PCA plots showed distinct clustering of the PBS-VWR mice compared to the other groups. AmAc-UA and AmAc-VWR were clustered closely and were also near the PBS-UA. **Conclusion:** These data show that hyperammonemia alters Shannon diversity and beta diversity of the GMB. Exercise induced changes in beta diversity were most prominent in the PBS group with less changes during hyperammonemia. These data suggest that hyperammonemia can alter the alpha and beta diversity in response to exercise. Microbiome dependent responses to exercise may be different in hyperammonemic patients including those with liver disease and have implications for defining exercise programs in liver disease.



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2710-A | IDENTIFICATION AND CHARACTERIZATION OF THE GUT MICROBIAL SPECIES INVOLVED IN HEPATIC ENCEPHALOPATHY FROM THE ANALYSIS OF PATIENTS ADMINISTERED RIFAXIMIN★

Yoshimi Yukawa-Muto, Tomonori Kamiya, Norifumi Kawada and Naoko Ohtani, Osaka Metropolitan University Graduate School of Medicine

Background: Hepatic encephalopathy (HE) is one of the complications of liver cirrhosis (LC), and is partly caused by elevated blood ammonia (NH_3) levels due to NH_3-producing bacteria. However, the causative bacteria and corresponding mechanisms remain unclear. Therefore, we aimed to identify gut bacteria involved in the pathophysiology of HE, based on the analysis of the gut microbial profiles before and after rifaximin (RFX) administration in both effective cases and non-effective cases. **Methods**: From April 2017 to March 2020, fecal samples were collected from 24 decompensated LC patients who developed HE, 27 compensated LC patients, and 26 healthy controls. We compared the gut microbial profiles using sequence analysis of the 16S rRNA gene. 1) We identified candidate gut bacteria by Lefse analysis, and assessed whether the oral administration of the identified gut bacterial species enhances blood NH_3 levels and changes brain amino acid metabolites levels in a CCl_4-treated cirrhosis mouse model. 2) After 4 weeks of oral RFX administration, patients whose plasma NH_3 levels were reduced by RFX were defined as "responders," and patients whose plasma NH_3 levels showed no decrease were considered as "non-responders." We screened for the bacterial species associated with hyperammonemia in the non-responder group, and their functions were analyzed in vitro. 3) Metabolomic analysis of plasma and metagenomic analysis of fecal DNA were performed to investigate the pathophysiology of the non-responders. **Results**: 1) *Streptococcus salivarius* (*S. salivarius*), which harbors the urease gene, was the most abundant species in the decompensated LC (HE) group. The plasma NH_3 levels were increased in the mice treated with the urease-positive *S. salivarius* compared to the control mice. Moreover, significantly higher glutamine levels were detected in the mouse brains treated with the urease-positive *S. salivarius*. 2) *Ruminococcus gnavus* (*R.gnavus*) was significantly more abundant in RFX non-responders than responder patients after 4 weeks of RFX administration. *R.gnavus* itself had no NH_3-producing ability but was found to enhance the recombinant urease activity. 3) In RFX non-responders, conjugated secondary bile acid concentration in plasma was significantly lower than those of responders and bile acid-inducible (bai)-operon was not detected in their feces. In culture, the minimal inhibitory concentration of RFX against *S.salivarius* and *R.gnavus* was significantly decreased by the combination of conjugated secondary bile acids and RFX. **Conclusion**: *S.salivarius* and *R.gnavus* were identified as the specific gut bacterial species abundant in patients with HE. *R. gnavus* can enhance the urease activity of the co-existing urease-positive bacteria, that could contribute to NH_3 production. Conjugated secondary bile acids enhance the efficacy of RFX, suggesting the possibility of combination therapy with conjugated secondary bile acids and RFX.

Disclosures: The following people have nothing to disclose: Yoshimi Yukawa-Muto, Tomonori Kamiya, Norifumi Kawada, Naoko Ohtani

2711-A | INTESTINAL ACYL-CoA THIOESTERASE 12 PROMOTES HISTONE H3 AND PPARΓ ACETYLATION TO PRESERVE BARRIER FUNCTION AND PROTECT AGAINST NON-ALCOHOLIC STEATOHEPATITIS

Akiko Sugiyama[1], Susan J Hagen[2] and David E Cohen[1], (1)Brigham and Women's Hospital, Harvard Medical School, (2)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background: Acyl-CoA thioesterase 12 (Acot12), which hydrolyzes acetyl-CoA into acetate plus CoA, is robustly expressed in cytosol of small intestinal epithelial cells (IECs) and is markedly induced by high fat diet (HFD) feeding. We have shown that intestinal Acot12 promotes lipid absorption through the upregulation of PPARγ target genes and protects against non-alcoholic steatohepatitis (NASH) by suppressing HFD-induced IEC necroptosis, which preserves barrier function. Because acetyl-CoA is the substrate for protein acetylation, this study explored an association between nuclear protein acetylation in IECs and Acot12-mediated control of barrier function. **Methods:** Intestinal-specific *Acot12*$^{-/-}$ (*I-Acot12*$^{-/-}$) and control mice were fed a HFD for 12 w. Small intestine and liver were harvested for gene expression by quantitative real-time PCR and protein expression by immunoblot analysis. Necroptotic cell death was determined by immunohistochemistry (IHC) for mixed lineage kinase domain-like pseudokinase (MLKL). Lipopolysaccharide (LPS) concentrations in the portal blood and collagen deposition in liver were quantified. Acot12 localization was determined by IHC and by immunoblotting of nuclear and cytoplasmic

IEC proteins. Acetylation of total nuclear proteins, as well as histone H3 were evaluated by immunoblotting. PPARγ acetylation was determined following immunoprecipitation. **Results:** As we previously reported for lipid regulatory genes, jejunal expression of the anti-inflammatory PPARγ target gene *Il10* was downregulated in *I-Acot12*$^{-/-}$ mice. This occurred in concert with MLKL translocation to the plasma membrane of jejunal villus IECs, indicative of the activation of necroptosis, as well as with an increase in portal vein LPS concentrations and the induction of hepatic collagen deposition. Acot12 was present in the cytoplasm but not in the nucleus of IECs. In the absence of Acot12, we observed reduced acetylation of a subset of nuclear proteins, including H3 (H3K9, H3K14, H3K27) and PPARγ. **Conclusion:** Acot12 in the IEC cytoplasm promotes nuclear protein acetylation, most likely by generating acetate that becomes a key source of nuclear acetyl-CoA. We speculate that intestinal Acot12-mediated acetylation of histone H3 and PPARγ protects against NASH through the transcriptional upregulation of anti-inflammatory and the transrepression of inflammatory target genes, which collectively repress IEC necroptosis and preserve gut barrier function.

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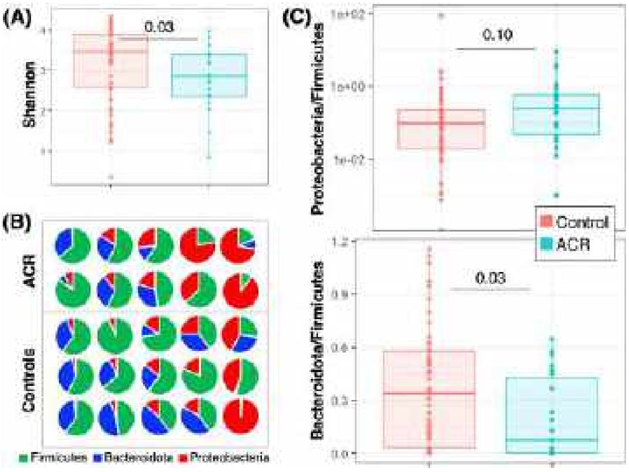
f 2712-A | INTESTINAL DYSBIOSIS IS ASSOCIATED WITH RISK OF ACUTE CELLULAR REJECTION AFTER LIVER TRANSPLANT IN PATIENTS WITH AUTOIMMUNE LIVER DISEASE

Yael R. Nobel, Heekuk Park, Medini K. Annavajhala, Alice M. Tillman, Dwayne Seeram, Dalia H. Moallem, Angela Gomez-Simmonds, Elizabeth Verna and Anne-Catrin Uhlemann, Columbia University Irving Medical Center, New York, NY

Background: Patients with autoimmune liver disease (AILD) – including autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and primary biliary cirrhosis (PBC) – are at increased risk for acute cellular rejection (ACR) after liver transplant (LT). The gut microbiota influence adaptive immunity and could contribute to ACR risk. We investigated the potential of the gut microbiota as a biomarker of ACR risk in patients with AILD. **Methods:** This was a nested case-control study of all LT recipients with AILD within a prospective cohort. Cases had biopsy-proven ACR (Banff score > = 4) within 1-year post-LT, and controls had no ACR within 1 year. Serial pre- and post-LT stool samples, until time of ACR (cases) or 1-year post-LT (controls), underwent DNA extraction and 16S rRNA sequencing. Taxonomic differences were assessed using DADA2. **Results:** Of 39 patients with AILD (49% AIH, 26% PSC, 8% AIH-PSC, 18% PBC), we identified 14 cases who developed ACR and 25 controls. ACR occurred at median 84 days post-LT. Disease severity, pre-LT medication exposures, rates of living donor LT, and use of post-LT immunosuppression induction did not differ between groups. Cases were younger than controls (median 31 vs. 61 years, $p < 0.01$) and trended toward higher rates of IBD (29% vs. 4%, $p = 0.09$) and use of broadened peri-LT antibiotic regimens (57% vs. 24%, $p = 0.09$). Gut microbiota composition was ascertained in 85 stool samples (84% post-LT) and differed significantly between groups. Post-LT, cases had significantly lower alpha diversity ($p = 0.03$; Fig. 1A), altered beta diversity (weighted Unifrac $p < 0.01$), and differential abundance of multiple taxa. Cases had higher Proteobacteria/Firmicutes ratio ($p = 0.10$) and lower Bacteroidota/Firmicutes ratio ($p = 0.03$) (Fig. 1B-C). Using Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt), several projected bacterial functional pathways differed between groups. Cases had reduced abundance of multiple pathways of branched-chain essential amino acid (BCAA) biosynthesis. **Conclusion:** Among patients with AILD undergoing LT, risk of ACR was associated with significantly altered gut microbiota composition. Patients who developed ACR had increased abundance of Proteobacteria, which produce pro-inflammatory bacterial lipopolysaccharide, and reduced abundance of BCAA biosynthesis pathways. These findings may provide a foundation for development of a novel microbial biomarker of ACR risk in LT recipients with AILD.



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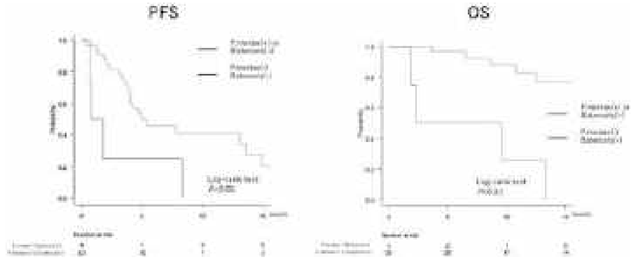
Disclosure information not available at the time of publication: Heekuk Park, Medini K. Annavajhala, Alice M. Tillman, Dwayne Seeram, Dalia H. Moallem, Angela Gomez-Simmonds, Elizabeth Verna, Anne-Catrin Uhlemann

2713-A | INTESTINAL MICROBIOME ASSOCIATED WITH EFFICACY OF ATEZOLIZUMAB AND BEVACIZUMAB THERAPY FOR HEPATOCELLULAR CARCINOMA

Yosuke Inukai, Kenta Yamamoto, Takashi Honda, Shinya Yokoyama, Takanori Ito, Norihiro Imai, Yoji Ishizu, Masanao Nakamura, Masatoshi Ishigami and Hiroki Kawashima, Nagoya University Graduate School of Medicine

Background: The treatment of hepatocellular carcinoma (HCC) has advanced in recent years with the introduction of several new agents. Atezolizumab, an immune checkpoint inhibitor (ICI), has been used in combination with Bevacizumab, an angiogenesis inhibitor, as a first-line treatment for unresectable HCC. Some studies have reported on the relationship between ICIs and the intestinal microbiome, with intestinal bacteria-mediated mechanisms thought to be involved in their efficacy and in adverse events. However, no studies have reported on specific intestinal microbiome associated with the efficacy of Atezolizumab and Bevacizumab. We analyzed fecal samples collected before treatment to investigate the relationship between the intestinal microbiome and the efficacy of Atezolizumab and Bevacizumab. **Methods:** We enrolled a total of 37 patients with advanced HCC who received treatment with Atezolizumab and Bevacizumab. Prior to the treatment, we collected fecal samples from the patients. Based on their best response to RECIST during the treatment period, we divided them into two groups: responders (complete response, partial response or stable disease) and non-responders (progressive disease). Using QIIME2, we analyzed the gut microbiome and compared the patient characteristics and gut microbiome composition between the two groups. Additionally, we conducted further analysis to investigate the relationship between the intestinal microbiome and prognosis. **Results:** Of these 37 patients, 28 were categorized as responders and 9 were categorized as non-responders. The median age of the two groups was 74 years, and liver function was significantly better in the responder group. When comparing the alpha and beta diversities, there were no significant differences between the two groups, and the proportions of microbiota were similar as well. In a comparison of the relative abundance of intestinal microbiome in the two groups, *Bacteroides stercoris* and *Parabacteroides merdae,* which have been reported to be associated with ICI effects, was higher in the responder group than in the non-responder group. When patients were divided into groups based on the presence or absence of these bacteria, the group lacking both *Bacteroides stercoris* and *Parabacteroides merdae* was significantly older, had higher levels of AFP, and showed worse progression-free survival and overall survival. **Conclusion:** Our study suggests that specific intestinal microbiome may play a crucial role in determining the treatment response of HCC patients receiving Atezolizumab and Bevacizumab therapy. These findings may pave the way for the development of novel microbiome-based therapeutic strategies for enhancing the efficacy of immunotherapy in HCC patients.



Disclosures: Takanori Ito – Chugai Pharmaceutical Co., Ltd: Speaking and Teaching, No, No; Chugai Pharmaceutical Co., Ltd: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AstraZeneca: Speaking and Teaching, No, No;
The following people have nothing to disclose: Yosuke Inukai, Kenta Yamamoto, Takashi Honda, Shinya Yokoyama, Norihiro Imai, Yoji Ishizu, Masanao Nakamura, Masatoshi Ishigami, Hiroki Kawashima

f 2714-A | ISOLATION OF MYENTERIC AND SUBMUCOSAL PLEXUS FROM MOUSE GASTROINTESTINAL TRACT AND SUBSEQUENT CO-CULTURE WITH SMALL INTESTINAL ORGANOIDS

Cristina Llorente, UC San Diego

Background: Liver disease is a major global health issue, causing millions of deaths annually.

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

Understanding its contributing factors, including alterations in intestinal homeostasis, is essential for effective prevention and treatment. Intestinal homeostasis is regulated by the interplay between the epithelium, the Enteric Nervous System (ENS), and immune cells, which influence the intestinal microbiota. In vitro models using neuronal cultures or organoids are needed to study the complex cellular interactions between the ENS and intestinal epithelium. **Methods:** We have pioneered an innovative 3D in vitro technique for coculturing small intestinal organoids with myenteric and submucosal neurons. The method entails a meticulous three-tiered process of cell isolation. Notably, we have made advancements in: (1) refining the isolation technique for cultivating the myenteric plexus, resulting in a mixed culture comprising enteric neurons and glial cells; (2) enhancing the isolation of the submucosal plexus, yielding a mixed culture of submucosal enteric neurons and glial cells; and (3) subsequently co-culturing myenteric and submucosal neurons with small intestinal organoids generated from pluripotent stem cells. **Results**: This co-culture system enables the establishment of neural connections with various cell types derived from the intestinal epithelium of the organoids. Through this cutting-edge technique, we can investigate the regulatory interactions among crucial intestinal cell populations and their alterations in the context of liver disease. Furthermore, we have developed a method for microinjecting the luminal space of small intestinal organoids with fluorescently-labeled dextran or ovalbumin. **Conclusion**: This technique provides a valuable platform for studying the role of the ENS and intestinal epithelium in liver disease. By establishing neural connections with various cell types derived from the organoids, we can investigate the regulatory interactions and their alterations in the context of liver disease. The technique could be useful in understanding the role of the ENS in maintaining cellular integrity, intestinal permeability, cellular physiology, and nutrient absorption. It also provides insights into intestinal stem cell behavior, proliferative-to-differentiation dynamics, and the role of the ENS in stimulating the secretion of intestinal epithelium-derived molecules involved in microbiota regulation and immune system modulation. Additionally, this technique offers the opportunity to explore signaling transduction pathways involved in these processes. This platform can be studied using a wide array of molecular and biochemical applications. The broad applicability of this technique can be extended to other experimental setups, incorporating alternative microinjections, including the introduction of specific bacterial species relevant to liver diseases.

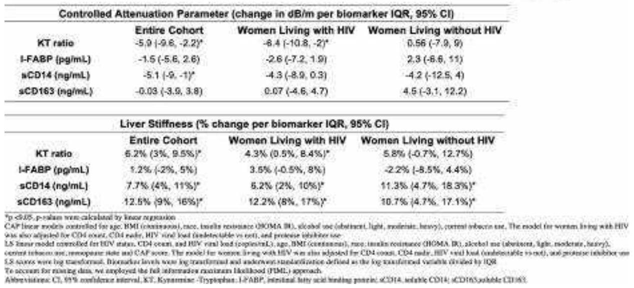
Disclosures: The following people have nothing to disclose: Cristina Llorente

f 2715-A | MICROBIAL TRANSLOCATION IS ASSOCIATED WITH HEPATIC FIBROSIS BUT NOT STEATOSIS IN WOMEN WITH AND WITHOUT HIV

Maria J. Duarte[1], Phyllis C. Tien[1], Ani Kardashian[2], Yifei Ma[1], Mark H. Kuniholm[3], Adaora A Adimora[4], Margaret Fischl[5], Audrey L. French[6], Elizabeth T. Topper[7], Deborah Konkle-Parker[8], Howard Minkoff[9], Ighovwerha Ofotokun[10], Michael Plankey[11], Anjali Sharma[12] and Jennifer C. Price[1], (1)University of California, San Francisco, (2)University of Southern California, Los Angeles, CA, (3)University at Albany, State University of New York, (4)University of North Carolina at Chapel Hill, (5)University of Miami Miller School of Medicine, (6) CORE Center/Stroger Hospital of Cook County, (7) Johns Hopkins Bloomberg School of Public Health, (8) University of Mississippi Medical Center, (9)State University of New York Downstate Health Sciences University, (10)Emory University School of Medicine, (11)Georgetown University Hospital, (12)Albert Einstein College of Medicine

Background: Non-alcoholic fatty liver disease (NAFLD), a leading cause of liver-related morbidity and mortality, is highly prevalent in people living with HIV (PLWH). Gut microbial translocation (MT) may play a role in NAFLD pathogenesis. Although HIV is associated with gut permeability, few studies have evaluated the interaction of the gut-liver axis on NAFLD in PLWH. We determined associations of HIV and circulating biomarkers of MT with hepatic steatosis and fibrosis in a large US cohort of women living with HIV (WLWH) and women living without HIV (WLWOH). **Methods:** Vibration controlled transient elastography (VCTE) was conducted from 2013-2018 among 1203 women without viral hepatitis (854 WLWH, 349 WLWOH). Serum biomarkers of MT were measured within 6 months of the VCTE visit: kynurenine to tryptophan (KT) ratio, intestinal fatty acid binding protein (I-FABP, a marker of gut epithelial integrity), and immune activation markers soluble CD14 (sCD14) and soluble CD163 (sCD163). We used multivariable linear regression to evaluate independent associations of each biomarker, HIV, and demographic, metabolic, and HIV-specific covariates with hepatic steatosis (controlled attenuation parameter [CAP]) and fibrosis (liver stiffness [LS]). **Results:** Median age was 49 years, 74% were non-Hispanic Black and over half were obese. Among WLWH, median CD4 count was 685 cells/mm^3. MT biomarker levels were higher in WLWH ($p < 0.001$ for each). There was no statistically significant difference in CAP and liver stiffness values amongst WLWH vs WLWOH (median CAP 248 dB/m for both and median LS 5.1 vs 4.9 kPa, respectively). In multivariable regression, greater BMI and insulin resistance (HOMA-IR) were associated with higher CAP whereas age and greater BMI were associated with higher LS. Higher KT ratio and sCD14 were associated with lower CAP values, whereas higher levels of MT biomarkers were significantly associated with higher LS ($p < 0.001$ for 3 of 4 biomarkers, Table 1). **Conclusion:** Compared to WLWOH, WLWH have higher circulating biomarkers of MT. Interestingly, KT ratio and sCD14 were positively associated with hepatic fibrosis but had inverse associations with steatosis. This suggests that MT may be a mechanism by which HIV increases the risk of hepatic fibrosis but not steatosis. This study lays the groundwork for future efforts evaluating the relationship between MT, microbial composition, and liver disease in PLWH.

Table1: Association between biomarkers of MT and Liver Vibration Controlled Transient Elastography Measures



Controlled Attenuation Parameter (change in dB/m per biomarker IQR, 95% CI)			
	Entire Cohort	Women Living with HIV	Women Living without HIV
KT ratio	-5.9 (-9.6, -2.2)*	-6.4 (-10.8, -2)*	0.56 (-7.9, 9)
I-FABP (pg/mL)	-1.5 (-5.6, 2.6)	-2.6 (-7.2, 1.9)	2.3 (-6.6, 11)
sCD14 (ng/mL)	-5.1 (-9, -1)*	-4.3 (-8.9, 0.3)	-4.2 (-12.5, 4)
sCD163 (ng/mL)	-0.03 (-3.9, 3.8)	0.07 (-4.6, 4.7)	4.5 (-3.1, 12.2)

Liver Stiffness (% change per biomarker IQR, 95% CI)			
	Entire Cohort	Women Living with HIV	Women Living without HIV
KT ratio	6.2% (3%, 9.5%)*	4.3% (0.5%, 8.4%)*	5.8% (-0.7%, 12.7%)
I-FABP (pg/mL)	1.2% (-2%, 5%)	3.5% (-0.5%, 8%)	-2.2% (-8.5%, 4.4%)
sCD14 (ng/mL)	7.7% (4%, 11%)*	6.2% (2%, 10%)*	11.3% (4.7%, 18.3%)*
sCD163 (ng/mL)	12.5% (9%, 16%)*	12.2% (8%, 17%)*	10.7% (4.7%, 17.1%)*

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2716-A | MULTI-OMICS ANALYSIS OF SEX-SPECIFIC HEPATOTOXICITY WITH TOXICANT EXPOSURES: ROLE OF THE GUT-LIVER AXIS

Zayna Qaissi[1], Richa Singhal[1], Shikshita Singh[2], Tyler C Gripshover[1], Eric C Rouchka[1], Jianmin Pan[3], Michael Merchant[1], Shesh N Rai[3] and Banrida Wahlang[1], (1) University of Louisville, Louisville, KY, (2)University of Ottawa, (3)University of Cincinnati

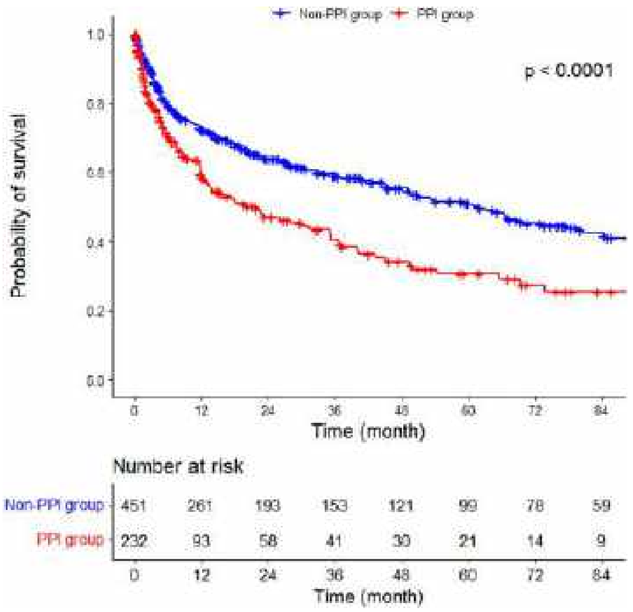
Background: Toxicants such as polychlorinated biphenyls (PCBs) have been associated with sex-dependent liver outcomes, with female mice exhibiting greater susceptibility for toxicant-associated steatohepatitis (TASH). While mechanisms such as metabolic/endocrine disruption have been identified, they do not sufficiently explain these sex-specific outcomes. Alternative mechanisms including PCB effects on gut microbiome warrant investigation. Therefore, this study's objective is to identify PCB-induced changes in the hepatic proteome and gut microbiome to determine disruption of physiological gut-liver interactions. **Methods:** Male and female C57BL/6 mice were exposed to Aroclor1260 (commercial PCB mixture, 20 mg/kg) and PCB126 (20 μg/kg) *p.o* for 2 weeks. Hepatic tissue was collected at euthanasia for peptide measurements (LC/MS). Cecal and ileal samples were isolated for 16S sequencing (analyzed using QIIME2) and gene expression analysis (RT-PCR) respectively. **Results:** Distinct hepatic proteomes were observed dependent on sex and exposure with 297 proteins modified in PCB-exposed male *vs.* female mice. While both PCB-exposed sexes showed hepatic aryl hydrocarbon receptor (AHR) activation, females also exhibited increased protein abundance for other AHR targets including flavin-monooxygenases and CD36. Computational analysis using MetaCore identified enriched "fatty acid metabolic process" in PCB-exposed females. Notably, PCB-exposed females had decreased activation (z-score) for hepatocyte nuclear factor (HNF4a), which is crucial for normal hepatocyte function. With regards to metagenomics, PCB-exposed females exhibited the lowest alpha diversity (OTUs). Beta diversity (UniFrac) was also significantly different with both sex and PCB exposures. PCB-exposed females but not males showed decreased abundance for the beneficial, gut health-promoting bacterial family, *Bifidobacteriaceae*. Ileal gene expression assessment demonstrated decreased mRNA levels for genes encoding gut barrier and antimicrobial proteins (*Cldn2*, *Muc2*, *Tff3*) and AHR target (*Cyp1a2*) in PCB-exposed females, implicating an unhealthy mucosal environment. **Conclusion:** Females were more responsive to altered lipid processes coupled with modified gut microbiota and compromised, intestinal environment, thus providing evidence for gut microbiome as an additional player in sex-specific PCB toxicity. Future studies include designing intervention strategies such as probiotics to attenuate PCB-mediated TASH.

Disclosures: The following people have nothing to disclose: Zayna Qaissi, Richa Singhal, Shikshita Singh, Tyler C Gripshover, Eric C Rouchka, Jianmin Pan, Michael Merchant, Shesh N Rai, Banrida Wahlang

f 2717-A | PROTON PUMP INHIBITOR TREATMENT IS ASSOCIATED WITH A HIGHER MORTALITY IN CIRRHOTIC PATIENTS: A MULTICENTER STUDY

Junsik Yoon[1], Ji Hoon Hong[2], Soo Young Park[3], Seung Up Kim[4], Hwi Young Kim[5], Ju Yeon Kim[2], Moon Haeng Hur[6], Min Kyung Park[2], Yun Bin Lee[6], Han Ah Lee[5], Gi-Ae Kim[7], Dong Hyun Sinn[8], Sung Jae Park[1], Youn-Jae Lee[1], Yoon Jun Kim[9], Jung-Hwan Yoon[2] and Jeong-Hoon Lee[10], (1)Inje University College of Medicine, (2)Seoul National University College of Medicine, (3)School of Medicine, Kyungpook National University, (4)Yonsei University College of Medicine, Seoul, Republic of Korea, (5) Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, South Korea, (6)Seoul National University Hospital, (7)Kyung Hee University School of Medicine, Seoul, South Korea, (8)Samsung Medical Center, (9)Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, South Korea, (10)Seoul National University College of Medicine, Seoul, South Korea

Background: Proton pump inhibitors (PPI) are frequently used in patients with cirrhosis. This study aimed to determine whether PPI use is associated with the prognosis of patients with cirrhosis. **Methods:** We conducted a multicenter retrospective cohort study involving 1,485 patients who had experienced hepatic encephalopathy (HE) from 7 referral centers in South Korea. The primary outcome was overall survival and secondary outcomes included the development of cirrhotic complications, including recurrent HE, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), and gastrointestinal bleeding. Patients treated with PPI with a mean defined daily dose (mDDD) e 0.5 (in the PPI group) were compared to those treated with PPI of an mDDD < 0.5 (non-PPI group) for each outcome. **Results:** Among 1,485 patients (median age, 61 y; male, 61%), 232 were assigned to the PPI group and 1,253 were assigned to the non-PPI group. PPI use was independently associated with a higher risk of death (adjusted HR [aHR] = 1.72, 95% confidence interval [CI] = 1.40–2.12, P < 0.001). This result was reproducible after propensity score-matching (PSM) (aHR = 1.61, 95% CI = 1.28–2.04, P < 0.001; Figure 1). PPI use was an independent risk factor of recurrent HE (before PSM: aHR = 1.89, 95% CI = 1.50–2.38, P < 0.01; after PSM: aHR = 1.62, 95% CI = 1.24–2.12, P < 0.001), SBP (before PSM: aHR = 1.57, 95% CI = 1.17–2.10, P = 0.003; after PSM: aHR = 1.94, 95% CI = 1.43–2.64, P = 0.02), HRS (before PSM: aHR = 1.66, 95% CI = 1.10–2.49, P = 0.01; after PSM: aHR = 1.76, 95% CI = 1.10–2.83, P = 0.008), and gastrointestinal bleeding (before PSM: aHR = 1.46, 95% CI = 1.11–1.93, P = 0.008; after PSM: aHR = 1.53, 95% CI = 1.10–2.11, P < 0.001). **Conclusion:** The use of PPI was independently associated with increased risks of mortality and cirrhotic complications.



Disclosures: The following people have nothing to disclose: Junsik Yoon, Ji Hoon Hong, Soo Young Park, Seung Up Kim, Hwi Young Kim, Ju Yeon Kim, Moon Haeng Hur, Min Kyung Park, Yun Bin Lee, Han Ah Lee, Gi-Ae Kim, Dong Hyun Sinn, Sung Jae Park, Youn-Jae Lee, Yoon Jun Kim, Jung-Hwan Yoon, Jeong-Hoon Lee

2718-A | RECOGNIZE SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO), WITH BREATH TEST CHARTS, DUE TO SULPHATE-REDUCING BACTERIA

Clara Peña Cañaveras[1], Silvia Miro Canís[1], Anna Puiggros-Font[1], Sonia Albertos Rubio[2], Clara Maria Aubo Delgado[1], Veronica Campos Garrido[1] and Miguel Angel Benitez Merelo[1], (1)Clilabdiagnostic, (2)Consorci Sanitari De L'alt Penedés-Garraf

Background: The intestinal microbiota has a remarkable role in our health since it influences not only the intestinal transit, but also is related to the immune, endocrine system, urinary system, etc. It may even be involved in the development of cancer. An increased number of bacteria colonizing the small intestine can produce a form of dysbiosis called small intestinal bacterial overgrowth (SIBO). It is estimated that up to 35% of the general population may suffer from SIBO. Breath testing is the noninvasive test widely used to diagnose SIBO. It is based on the fact that human body cells do not produce the gases that are being detected. The measured gases are: Hydrogen when there was mainly excessive proliferation of bacteria and Methane when there was an overgrowth of methanogenic archaea. Hydrogen sulfide is also produced by sulphate-reducing bacteria invasion, but the breath test charts can't detect it. Determine the number of SIBO that is due to sulphate-reducing bacteria and be aware of its incidence in the curve interpretation to classify patients correctly. **Methods:** Sibo-kit test (Isomed®) is used to measure the concentration of hydrogen and methane in exhaled air, after oral administration of lactulose, in 132 patients, using CO2 concentration as an internal control. Gases elevation greater than 20 ppm in H2 and/or greater than 10 ppm in CH4, respect to basal values, indicates the presence of the microbiota in the small intestine and therefore a positive SIBO. The graphs of patients with SIBO due to sulphate-reducing bacteria does not detect gaseous HS, so the curve is totally flat. 132 patients conducted in the Departament of Gastroenterology, were recluted during one year: 108 female and 24 male pacients, aged 15-80 years (mean:45 y). **Results:** 48 were negative (36.4%), 58 were SIBO positive (43.9%) and 26 were suggestive of SIBO due to sulphate-reducing bacteria (19.7%). **Conclusion:** As our results showed, the 19.7% of patients have a flat curve, which may make you think that the patient did not take the product. However, patients with SIBO from sulfate-producing bacteria also have flat curves because it does not detect gaseous HS. It must be considered to avoid false negative results. A misinterpretation of the graph will result in patients not being treated for SIBO.

Disclosures: The following people have nothing to disclose: Clara Peña Cañaveras, Silvia Miro Canís, Anna Puiggros-Font, Sonia Albertos Rubio, Clara Maria Aubo Delgado, Veronica Campos Garrido, Miguel Angel Benitez Merelo

2719-A | REGULATION OF SPLENIC-DERIVED REGULATORY T CELLS BY BACTEROIDES PROMOTES HEPATIC FIBROSIS PROGRESSION

Aiyu Zhang[1,2,3], Yang Zhao[1,2,3], Xi Chen[1,2,3], Zhang Shaoying[1,2,3], Qian Wang[1,2,3], Guangyao Kong[1,2,3] and Zongfang Li[1,2,3], (1)Shaanxi Provincial Clinical Research Center for Liver and Spleen Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China., (2)National & Local Joint Engineering Research Center of Biodiagnositics and Biotherapy, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China., (3)Shaanxi International Cooperation Base for Inflammation and Immunity, Xi'an, China

Background: To investigate the predominant bacterial species involved in promoting liver cirrhosis progression through gut dysbiosis and provide experimental evidence for understanding the role of dysbiotic gut microbiota in promoting liver fibrosis and finding new strategies for liver fibrosis prevention and treatment by regulating the gut microbiota. **Methods:** (1) A mouse model of liver fibrosis was established by intraperitoneal injection of carbon tetrachloride in SPF-grade C57BF/6 mice. Flow cytometry was used to assess the changes in $Foxp3^+$ regulatory T cells (Tregs) in the liver of model and control group mice. The changes in Treg cells in the liver were also evaluated after splenectomy in the model group mice. (2) Stool samples were collected from 25 patients with liver cirrhosis, portal hypertension, and hypersplenism before and six months after splenectomy. The collected stool samples were subjected to 16S rDNA sequencing, and bioinformatics analysis was performed to compare the abundance changes of bacterial species in the gut microbiota before and after surgery in the patients. **Results:** (1) Flow cytometry analysis revealed a significant increase in $Foxp3^+$ Tregs in the liver of the liver fibrosis model mice compared to the control group. The proportion of Treg cells in the liver of the splenectomy group mice was significantly reduced compared to the mice with intact spleens, but similar to that of the control group mice. (2) Before splenectomy, the abundance of *Bacteroides* was significantly higher than other bacterial species in the stool samples of clinical patients. Six months after splenectomy, the relative abundance of

Bacteroides decreased, and the microbial diversity in the patients' feces increased, indicating recovery of the patients' health. **Conclusion:** *Bacteroides* in the gut microbiota of liver cirrhosis patients may promote the recruitment of Treg cells in the liver by their metabolite polysaccharide A, which regulates the migration of Foxp3$^+$ Tregs through CD39. The increased Treg cells in the liver alter the liver's immune microenvironment, thereby promoting liver fibrosis progression. The significant decrease in liver Treg cell proportion after splenectomy suggests that the spleen may be a major source of Treg cell recruitment in fibrotic liver.

Disclosures: The following people have nothing to disclose: Aiyu Zhang, Zhang Shaoying, Guangyao Kong, Zongfang Li

Disclosure information not available at the time of publication: Yang Zhao, Xi Chen, Qian Wang

2720-A | RETOXIFICATION OF GLUCURONIDATED BILE ACIDS BY BETA-GLUCURONIDASE ENZYMES FROM INTESTINAL MICROBIOTA: A NOVEL TARGET FOR THE TREATMENT OF BILE ACIDS-RELATED DISEASES OF THE GUT-LIVER AXIS

Salma Dzanouni, William Gagnon, Mélanie Verreault, Jocelyn Trottier and Olivier Barbier, Université Laval, Faculty of Pharmacy, Québec, Canada

Background: The hepatic accumulation of toxic bile acids (BAs) is a major outcome of cholestatic liver diseases. Glucuronidation is an efficient and inducible detoxification reaction for BAs. Our lab has recently observed that glucuronidated BAs (BA-G) are efficiently deconjugated to toxic BAs by microbial β-glucuronidase (GUS) enzymes from the large intestine. This study aimed at elucidating how the GUS activity is regulated enzymatically, pharmacologically and by the diet. **Methods:** GUS assays were performed with 50μM BA-G in the presence of human or murine fecal proteins (5μg) at 37°C for 30min. The formation of unconjugated BAs was resolved using LC-MS/MS. For enzymatic screening, 11 BA-G species were assayed with feces from human (5♀: 5**B**) or CD1 mice (2♀:2**B**). For inhibition assays, the enzymatic reaction was performed with a pool of human (5**B**: 5♀) or murine (4**B**:4♀) feces in the presence of 200μM amoxapine. Finally, GUS assays were also performed using feces from human donors harvested before and after consumption of either 280g/day of frozen raspberries (16♀:7**B**) or 50g/day of freeze-dried blueberry powder (13♀:11**B**) for 8 weeks. **Results:** All BA-G assayed were reactive with human and murine feces, with percentage of deconjugation varying from 0.4 ± 0.1% with HDCA-6G and female mice samples to 47.1 ± 12.4% with LCA-24G and male mice feces. The inhibition rate of GUS activity caused by amoxapine was higher in women than in men (68.3 ± 2.9% versus 49.6 ± 1.9% reduction of LCA-3G to LCA conversion, for example). Assay with β-MCA-24G and murine feces also revealed sexual dimorphism with amoxapine being more efficient in female samples. Interestingly, in human volunteers, the consumption of blueberry extracts caused a significant ($p < 0.01$) reduction of LCA-3G deconjugation in men, while the GCDCA-3G to GCDCA conversion remained unaffected in the 2 sexes after a 8-week period of a diet enriched in raspberries. **Conclusion:** This study illustrates for the first time, the role of intestinal microbial GUS enzymes in the reactivation of nontoxic BAs into toxic acids. The sex-, enzymatic- pharmacological- and diet-dependent modulation of this activity is also revealed. Overall, our results identify these enzymes as novel pharmacological targets for the treatment of BA-related diseases of the gut-liver axis.

Disclosures: The following people have nothing to disclose: Salma Dzanouni, Mélanie Verreault, Jocelyn Trottier, Olivier Barbier

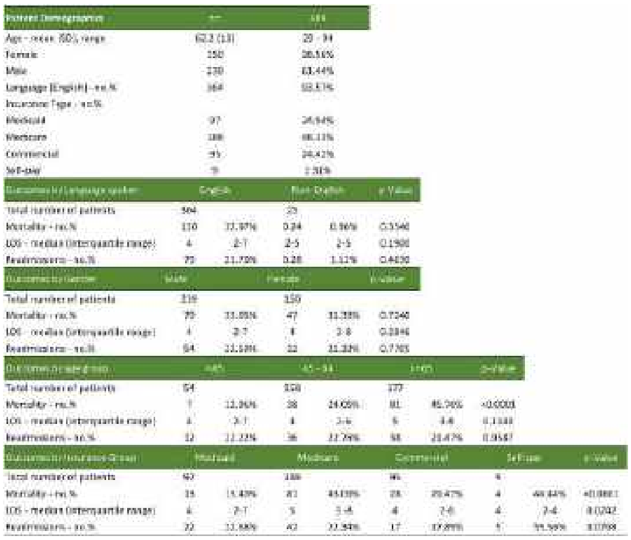
Disclosure information not available at the time of publication: William Gagnon

2800-C | "BREAKING BARRIERS, BRIDGING GAPS: UNVEILING THE IMPACT OF HEALTH DISPARITIES IN PATIENTS WITH LIVER CIRRHOSIS AT A COMMUNITY HOSPITAL"

Adalberto Guzman[1], Evelyn Calderon Martinez[1], Wern Lynn Ng[1], Samanta Landazuri[2], Anas Atrash[1] and Douglas M. Levin[3], (1)UPMC, (2)University of the Americas, (3)Ohio State University, Columbus, OH, United States

Background: Liver cirrhosis represents a critical global public health challenge, with its prevalence and impact on morbidity and mortality escalating in the United States. Disparities in liver disease prevalence, complications, outcomes, mortality, and treatment accessibility are closely intertwined with social determinants. **Methods:** Using Epic's SlicerDicer function, patients admitted to any hospital of UPMC Central PA between January and December of 2022 with a diagnosis of cirrhosis of any type were identified using ICD-10 codes. A total of 389 patients were enrolled. We reported continuous variables as mean, standard deviation and range for the normal distribution, and median and interquartile range for the abnormal distribution. The categorical variables were reported as number (percent). We used chi-square test to analyze between group differences for mortality and readmission analysis. The Fisher exact test was employed when any of the expected frequencies was five or less. We used the Wilcoxon rank-sum test to analyze the differences in length of stay, as appropriate. A p value less than 0.05

was considered statistically significant. All the analyses were done by SAS 9.4 (SAS Institute, Cary NC). **Results:** Among the patient population analyzed, 239 (61.4%) were male, with a mean age of 62.2 ± 9. Approximately 73% had Medicaid or Medicare as their primary insurance. Interestingly, there were no notable differences in mortality, length of stay, or readmission rates between English-speaking and non-English-speaking patients, suggesting that the extensive utilization of interpreter services in our hospitals may contribute to equitable outcomes. Notably, patients lacking insurance exhibited higher mortality rates and longer lengths of stay compared to those with Medicaid and Commercial insurances ($p < 0.0001$). Moreover, mortality rates were notably elevated among patients aged above 65 (45.7%, $p < 0.0001$). However, no statistically significant disparities in mortality, length of stay, or readmission were observed when comparing between genders. **Conclusion:** Our analysis demonstrated that language barriers were effectively addressed through the extensive use of interpreter services, resulting in comparable mortality, length of stay, and readmission rates between English-speaking and non-English-speaking patients. However, patients lacking insurance faced higher mortality rates and longer hospital stays compared to those with Medicaid and Commercial insurances, emphasizing the significance of adequate insurance coverage in improving outcomes. The mortality rate was notably higher among patients aged above 65, underscoring the need for tailored interventions for this age group. Gender did not show statistically significant differences in mortality, length of stay, or readmission. These findings highlight the importance of comprehensive care strategies for individual's affected by liver cirrhosis.



Patient Demographics	n=	n%							
Age – mean (SD), range	62.2 (13)	20 - 94							
Female	150	38.56%							
Male	239	61.44%							
Language (English) – n, %	364	93.57%							
Insurance Type – n, %									
Medicaid	97	24.94%							
Medicare	188	48.33%							
Commercial	95	24.42%							
Self-pay	9	2.31%							
Outcomes by Language spoken	**English**		**Non English**		**p Value**				
Total number of patients	364		25						
Mortality – no.%	110	[illegible]	0.24	0.96%	0.3540				
LOS – median (interquartile range)	4	2-7	2-5	2-5	0.1900				
Readmissions – no.%	79	21.70%	0.28	1.12%	0.4030				
Outcomes by Gender	**Male**		**Female**		**p Value**				
Total number of patients	239		150						
Mortality – no.%	79	33.05%	47	31.33%	0.7240				
LOS – median (interquartile range)	4	2-7	4	2-8	0.2846				
Readmissions – no.%	54	[illegible]	[illegible]	[illegible]	0.7305				
Outcomes by age group	**<45**		**45 - 64**		**≥65**		**p-Value**		
Total number of patients	54		158		177				
Mortality – no.%	7	12.96%	38	24.05%	81	45.76%	<0.0001		
LOS – median (interquartile range)	4	3-7	4	3-6	5	3-8	[illegible]		
Readmissions – no.%	12	22.22%	36	22.78%	38	21.47%	0.9587		
Outcomes by Insurance Group	**Medicaid**		**Medicare**		**Commercial**		**Self-pay**		**p Value**
Total number of patients	97		188		95		9		
Mortality – no.%	15	15.46%	[illegible]	[illegible]	28	29.47%	4	44.44%	<0.0001
LOS – median (interquartile range)	4	2-7	5	3-8	4	2-6	4	2-4	[illegible]
Readmissions – no.%	22	[illegible]	42	22.34%	17	17.89%	5	55.56%	[illegible]

Disclosures: The following people have nothing to disclose: Adalberto Guzman, Evelyn Calderon Martinez, Wern Lynn Ng, Samanta Landazuri, Anas Atrash, Douglas M. Levin

2801-C | A NOVEL CASE FINDING DATABASE CAN BE UTILISED TO IDENTIFY AND TARGET INDIVIDUALS IN AREAS OF DEPRIVATION AT RISK OF ADVANCED LIVER DISEASE

Christina Owen, Timothy Jobson, John Creamer, Emma Wesley and Almuthana Mohamed, Somerset NHS Foundation Trust

Background: Chronic liver disease often presents late, despite guidelines for diagnosis and staging. This may be worse in areas of deprivation. In the NHS in England the 'Core20Plus5' programme provides a mandate for tackling inequalities. 'Core20' refers to individual's in the 20% most deprived geographical areas defined by the Index of Multiple Deprivation (IMD). This ranks the population by decile; IMD deciles 1 & 2 represent the target population. In Somerset, England we created a novel case finding database using existing blood test results on 0.6m individual's to identify patients at risk of chronic liver disease. We tested the hypothesis that this database could be used effectively to target individual's in deprived areas. **Methods:** The database was used to identify adults aged 30-65 and risk stratify for chronic liver disease using persistent elevation of ALT ($\geq$90 d), FIB-4, and our recently developed Cumulative Liver Damage Index (CLDI - integral of ALT over time). Analyses were performed by IMD-decile, comparing IMD 1&2 (most deprived 20%) with the rest of the population. Additional searches were performed using low platelet (plt) count as a marker of possible portal hypertension, and elevation of bilirubin (bili). **Results:** 9.9% of the Somerset population live in areas of IMD 1&2; (i.e. Somerset is less deprived than the English average). These individual's had on average 19.5% more blood tests than those in less deprived areas. There was no significant difference between IMD deciles for persistently abnormal ALT, investigation with second line tests (liver screen), and distribution of CLDI. For those with persistently elevated ALT, a Fib 4 was calculated if possible; 13.6% in deprived areas (IMD 1 & 2) had FIB-4 > 2.67 compared to 8.9% of control (IMD 3-10); $p = 0.015$. For patients with a CLDI > 100k unit.days, 3.9% of deprived had low plts, c.f. 2.7% of control; 0.9% of deprived had a bili > 50umol/l (2.92mg/l) c.f. 0.6% control, and 0.6% of deprived had both elevated bili and low plts c.f. 0.3% control (all $p < 0.001$) (Fig 1). **Conclusion:** A case finding approach is applicable to the most deprived individual's in the population. We identified likely chronic liver disease in deprived areas at similar rates to the general population, but those in deprived areas had more indicators of fibrosis and decompensated disease. These data show that this

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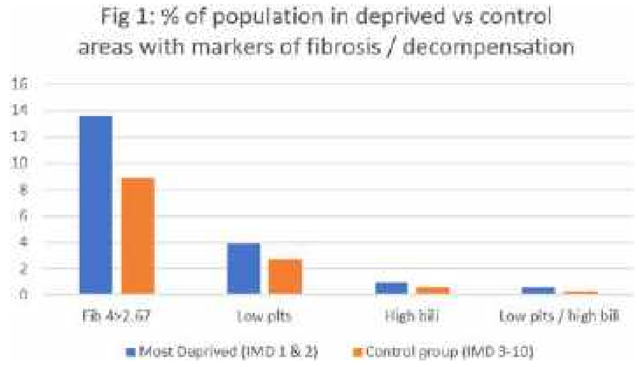
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

novel tool has potential to identify patients from areas of deprivation at risk of advanced liver disease.

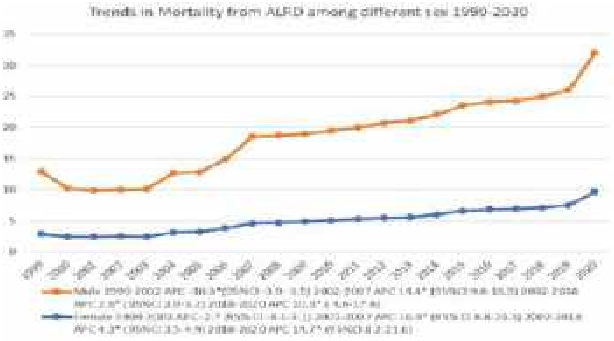


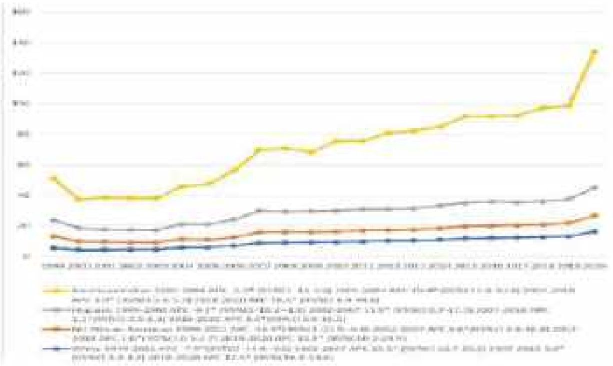
Disclosures: The following people have nothing to disclose: Christina Owen, Timothy Jobson, John Creamer, Emma Wesley, Almuthana Mohamed

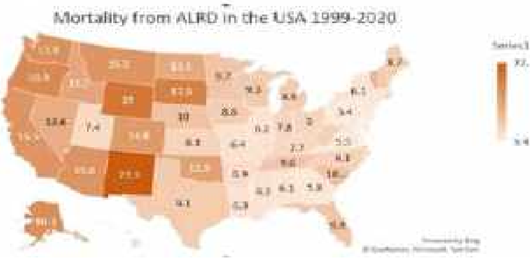
f 2802-C | ALARMING MORTALITY TRENDS IN ALCOHOLIC LIVER DISEASE RELATED MORTALITY AMONG ADULTS IN THE UNITED STATES FROM 1999-2020

Yousaf Zafar[1], *Melanie Baker*[1], *Arsalan Zafar Iqbal*[1], *Laila Manzoor*[1], *Isaac Dodd*[1] *and Jan Petrasek*[2], *(1) University of Mississippi Medical Center, (2)Texas Liver Institite*

Background: Alcohol-related Liver Disease (ARLD) refers to Liver damage caused by excess alcohol intake. In the United States, between 2010 and 2016, alcohol-related liver disease was the primary cause of nearly 1 in 3 liver transplants, surpassing hepatitis C. In this descriptive study we compared trends in US mortality rates from ARLD from 1999 and 2020. **Methods:** We sought to identify temporal, geographic, age and sex-based mortality trends of ARLD related deaths in the US over the past 2 decades. This population-based study utilized the CDC WONDER database to identify ARLD-related deaths occurring within the US between 1999 and 2020. ARLD-related crude and age-adjusted mortality rates (CMRs and AAMRs, respectively) were determined. Join point regression was used to determine trends in CMR/AAMR using annual percent change (APC) in the overall sample in addition to demographic (sex, race/ethnicity, age) and geographic (rural/urban, statewide) subgroups. **Results:** Between 1999 and 2020, a total of 447,676 deaths related to ARLD were reported. The overall AAMR increased significantly from 5.1/100,000 in 1999 to 13/100,000 in 2020. Men had a higher mortality than women (In 2020 alone AAMR was 22.6 Vs 9.6). APC continues to be higher in both sexes with APC increasing significantly in 2018 to 2020 (In males APC was 10.9 (95CI% 4.6-17.6) Vs females 14.7 (95%CI 8.2-21.6). ARLD related mortality was disproportionately seen to affect American Indians dispropotionately with AAMR in 2020 alone was 88.4 (95%CI 83.9-93) compared to other races- AAMR in Whites were 16.5 (95%CI 16.3-16.7), African American was 10.3 (95%CI was 9.9-10.7). Although trends in Metro and Nonmetro areas have increased over the past 2 decades, patients in the rural areas tend to be more affected. Overall, the trends for all groups assessed worsened from 2018-2020. New Mexico, South Dakota, and Wyoming seem to be states that have the highest AAMR from ARLD. **Conclusion:** ALRD -related AAMR were observed more among men, Americans Indians, and individual's living in rural areas. American Indians seem to be dispropotionately affected by ALRD with trends suggesting mortality increasing at an alarming rate. Discerning the reasons for the increase in ALRD-related mortality among these groups and examining the impact of the social determinants of heath may represent important opportunities to enhance care.







Disclosures: The following people have nothing to disclose: Yousaf Zafar, Melanie Baker, Arsalan Zafar Iqbal, Laila Manzoor, Isaac Dodd, Jan Petrasek

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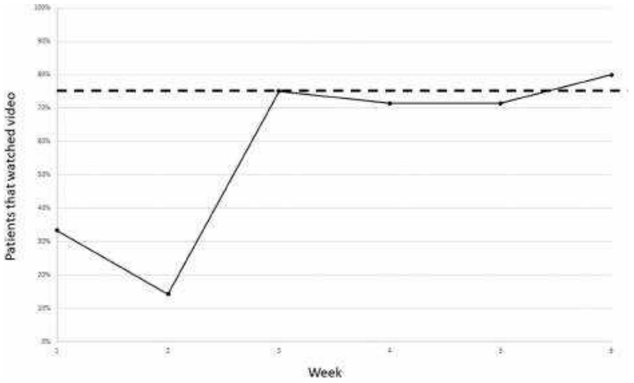
Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

2803-C | DESIGN AND IMPLEMENTATION OF EQUITY-FOCUSED VIDEO-BASED PATIENT EDUCATION FOR LIVER TRANSPLANT EVALUATION

Alexandra Strauss, Mary Rudolfi, Alexander Ginietis, Ahmet Gürakar, Neha Rajpal and Tanjala S. Purnell, Johns Hopkins University

Background: Patients undergoing liver transplant (LT) evaluation are faced with an arduous process that can be difficult to navigate. Social determinants of health, such as health literacy and patient-provider trust, may contribute to racial/ethnic disparities in evaluation completion. Generally, video-based patient education (VBPE) has been shown to improve patient outcomes, but there is no broadly available VBPE tailored to LT evaluation from a health equity perspective. Our aim was to create equity focused VBPE and within 6 weeks of implementation to achieve a 75% view rate by our LT clinic patients. **Methods:** In this quality improvement study, we reviewed the literature about VBPE and cultural sensitivity (e.g., Suitability Assessment of Materials, Patient Education Materials Assessment Tool) to develop a short video that is 1) racially/gender diverse, 2) simple verbiage without written words (i.e., accessible to all health literacy levels), 3) available audio/visually in 5 languages. We uploaded the video to a VBPE system within our electronic health record, so we could send/track it via the patient portal. From 4/3/23-5/22/23, we sent VBPE to patients undergoing outpatient evaluation. We performed typical process improvement techniques, such as Plan-Do-Study-Act cycles, tracers and Cause-Effect analysis to identify barriers. **Results:** The final video is publicly available online (https://www.youtube.com/watch?v=ezBg1vX0Ozg). Of the 43 patients undergoing evaluation, 24 (56%) watched the VBPE and 8 (19%) watched more than once. We identified barriers related to people (e.g., too sick/encephalopathy, overwhelmed, perceived as unnecessary, not tech-savvy), equipment (e.g., no patient portal access, difficulty navigating to video, instructions to video in English), methods (e.g., timing when to send video, sending is cumbersome/burdensome), environment (e.g., hospitalized after sending, rehabilitation center, lack of support system to encourage. By addressing several issues, we increased view rate from 33% and 16% in weeks 1-2 to 80% by week 6 (Figure). **Conclusion:** Through a health equity lens, we created a culturally-sensitive and broadly accessible VBPE for patients undergoing LT evaluation. We showed implementation in a busy clinic is feasible. This video can be adopted by other transplant centers as it describes widely standard procedures for evaluation. Further work is needed to assess the impact of the video on outcomes and to explore patient feedback.



Disclosures: Ahmet Gürakar – Orphalan: Advisor, No, Yes;

The following people have nothing to disclose: Alexandra Strauss

Disclosure information not available at the time of publication: Mary Rudolfi, Alexander Ginietis, Neha Rajpal, Tanjala S. Purnell

2804-C | DISTRESSED COMMUNITIES INDEX IN PATIENTS UNDERGOING LIVER TRANSPLANTATION IN A TERTIARY CARE CENTER IN MISSISSIPPI

Yousaf Zafar[1], David Landon Zepponi[1], Jonathan Parke[1], Laila Manzoor[1], Arsalan Zafar Iqbal[1], Chad Blackshear[1] and Jan Petrasek[2], (1)University of Mississippi Medical Center, (2)Texas Liver Institite

Background: Earlier research has revealed inequalities in transplantation rates among certain groups such as women, non-Caucasians, individual's without insurance or with public insurance, and those residing in rural areas. The Distressed Communities Index (DCI) serves as a mechanism to gauge the relative economic welfare of communities in the United States and sheds light on disparities at a local level throughout the country Our objective was to establish if there is correlation between patient that are evaluated and not listed for transplant and their respective DCI. We hypothesized that there would be significant correlation among patients with liver disease who are not listed and their DCI score. **Methods:**

A retrospective center-specific study with 1,509 adults that were undergoing liver transplant evaluation at the University of Mississippi Medical center from 2013 to 2023 were assessed for demographic data and DCI using their house zip code. This was correlated with whether they were evaluated, declined for Liver transplant, waitlisted, and eventually transplanted. **Results:** The cohort included 56% males and was 71% white. The mean age at evaluation was 55 years. 52% of patients evaluated had public insurance, 33% had private, 6% supplemented public insurance with private policies, 9% were uninsured. Patients were grouped by follow-up status: 220 were declined transplant, 857 were referred or lost to follow-up post-evaluation, 89 were placed on the waitlist, and 343 received transplantation. Among the patients declined for transplant, black patients had a 15.6-unit higher DCI than whites (95% CI 11.4,19.9; $p < 0.001$) and publicly insured patients had a 7.7-unit higher DCI than those with private insurance (95% CI 3.5,11.9; $p < 0.001$). Among the transplanted patients, black participants had a 14.2-unit higher DCI that whites (95% CI 7.4,12.1; $p < 0.001$). Results are based on the interaction effects of transplant group by hypothesized disparity from serial OLS regression models. **Conclusion**: Although formal testing indicates that DCI was not broadly associated with transplantation status, the data suggests some racial and insurance disparities could exist. Specifically, the results support an association with higher DCI in African Americans, although the variability was higher among those awaiting transplantation. Similarly, albeit less pronounced, was an association with higher DCI in patients with public insurance. Alternatively, our data did not suggest disparities based on sex, age at the time of evaluation or any effect modification based on the year of enrollment.

Disclosures: The following people have nothing to disclose: Yousaf Zafar, David Landon Zepponi, Jonathan Parke, Laila Manzoor, Arsalan Zafar Iqbal, Chad Blackshear, Jan Petrasek

2805-C | EXAMINING THE IMPACT OF DEMOGRAPHICS ON OUTCOMES AND TRANSPLANT EVALUATION IN INFECTED PATIENTS IN THE MEDICAL INTENSIVE LIVER UNIT: EXPERIENCE FROM A QUATERNARY CENTER

Sarah Khan[1], Hanna Hong[2], Sofia Molina Garcia[1], Stephanie Bass[1], Christine Koval[1], Aanchal Kapoor[1], Omar T. Sims[1] and Christina C. Lindenmeyer[1], (1) Cleveland Clinic, (2)Cleveland Clinic Lerner College of Medicine

Background: Prior studies have shown disparities in evaluation, listing and transplant rates on the basis of sex, race and socioeceonomic status. Few studies have examined disparities in transplant and outcomes in the critical care setting, which may further be impacted by infections and illness severity (i.e., acute-on-chronic liver failure, ACLF). We aimed to determine if age, sex, and race are independently associated with mortality, length of stay (LOS), and transplant evaluation among infected patients in the medical intensive liver unit (MILU). **Methods:** We conducted a study utilizing our prospective, longitudinal MILU registry of culture-positive patients admitted from August 2018- September 2022. A total of 211 patients with infections were included in the analysis. Univariate modeling was used to examine associations between demographics and outcomes of interest. **Results:** Of patients, 27 had fungal and 183 had bacterial infections. Median age was 58 years, and the majority were male (59.5%) and white (74.3%). Of non-white patients, 15.7% were Black, 3.8% were multiracial, and 0.5% were American Indian and Asian. Most patients had cirrhosis (77.9%), followed by severe acute liver injury (16.3%) and acute liver failure (5.8%). Altogether, 105 patients were evaluated for LT, 61 were listed, and 26 patients subsequently underwent transplant. Age, sex, and race were not associated with overall survival, hospital LOS, and ICU LOS (Table 1). However, age decreased the odds of transplant evaluation ($HR = 0.98$, 95% CI 0.95-0.99, $p = 0.039$), and white patients had increased odds of transplant evaluation (HR 2.46, 95% CI 1.31-4.63, $p = 0.005$). White patients had more favorable odds of listing and LT, but these were not statistically significant ($HR = 2.02$, 95% CI 0.78-5.24, $p = 0.15$; HR 2.27, 95% CI 0.75-6.88, $p = 0.146$ respectively). **Conclusion:** Among critically-ill patients with infections, white patients were significantly more likely to be evaluated for transplant. This disparity likely also translated to lower odds of listing and transplantation in non-white patients, but our study was likely underpowered in LT listing and transplantation modeling to detect statistical significance. Our work supports further investigation of disparities in transplantation among critically ill infected patients with liver disease, who may also be vulnerable to bias against transplant due to organ failures and associated ACLF. Our study was limited in accounting for non-demographic factors impacting transplantation evaluation.

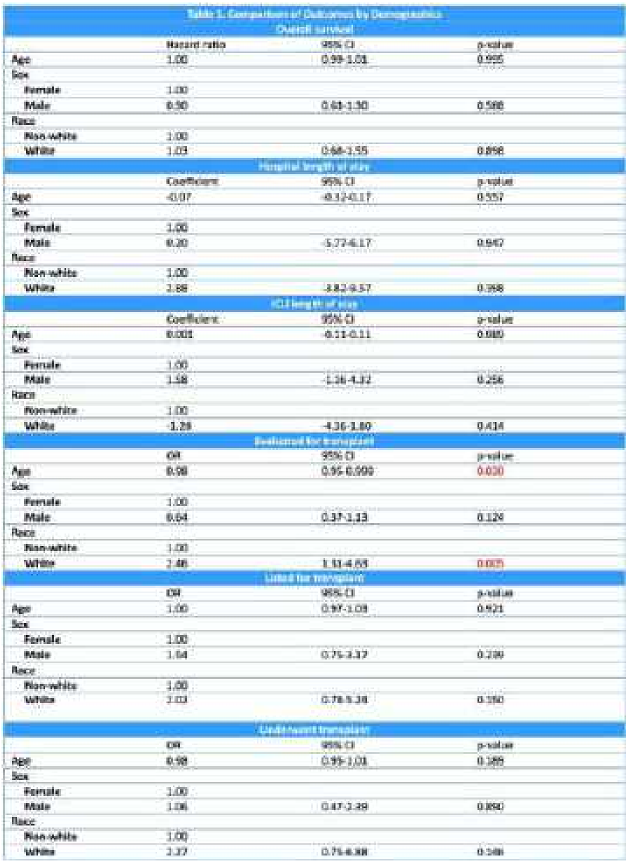


Table 1. Comparison of Outcomes by Demographics

Overall survival			
	Hazard ratio	95% CI	p-value
Age	1.00	0.99-1.01	0.995
Sex			
Female	1.00		
Male	0.90	0.61-1.30	0.588
Race			
Non-white	1.00		
White	1.03	0.68-1.55	0.898
Hospital length of stay			
	Coefficient	95% CI	p-value
Age	-0.07	-0.32-0.17	0.557
Sex			
Female	1.00		
Male	0.20	-5.77-6.17	0.947
Race			
Non-white	1.00		
White	2.88	-3.82-9.57	0.398
ICU length of stay			
	Coefficient	95% CI	p-value
Age	0.001	-0.11-0.11	0.980
Sex			
Female	1.00		
Male	1.58	-1.16-4.32	0.256
Race			
Non-white	1.00		
White	-1.28	-4.36-1.80	0.414
Evaluated for transplant			
	OR	95% CI	p-value
Age	0.98	0.95-0.999	0.030
Sex			
Female	1.00		
Male	0.64	0.37-1.13	0.124
Race			
Non-white	1.00		
White	2.48	1.31-4.69	0.005
Listed for transplant			
	OR	95% CI	p-value
Age	1.00	0.97-1.03	0.921
Sex			
Female	1.00		
Male	1.64	0.75-3.37	0.209
Race			
Non-white	1.00		
White	2.03	0.78-5.28	0.150
Underwent transplant			
	OR	95% CI	p-value
Age	0.98	0.95-1.01	0.189
Sex			
Female	1.00		
Male	1.06	0.47-2.39	0.890
Race			
Non-white	1.00		
White	2.27	0.75-6.88	0.148

Disclosures: Christina C. Lindenmeyer – Merck & Co. Author for Merck Manuals: Independent contractor (including contracted research), No, Yes;

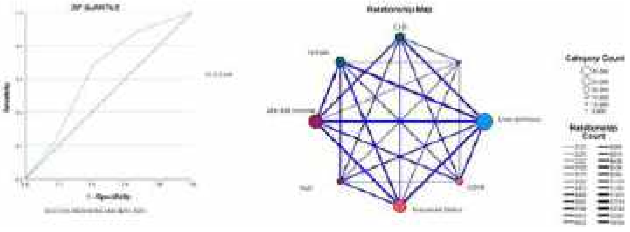
The following people have nothing to disclose: Sarah Khan, Stephanie Bass, Aanchal Kapoor

Disclosure information not available at the time of publication: Hanna Hong, Sofia Molina Garcia, Christine Koval, Omar T. Sims

2806-C | EXPLORING THE LINK BETWEEN LIVER CIRRHOSIS SEVERITY AND 30-DAY READMISSION RATES IN HIGH-RISK PATIENTS

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

Background: Early hospital readmissions among cirrhotic patients present a challenge for inpatient hospital facilities. Cirrhosis patients experience 1-month readmission rates ranging from 20-35%. Timely identification of high-risk patients could enable targeted interventions to minimize readmissions. Our study aimed to develop an automated risk model for 30-day readmissions in cirrhotic patients, leveraging electronic medical record (EMR) data obtained during initial hospitalization. Key factors assessed in this study include socioeconomic status (Medicare/Medicaid), gender, number of previous admissions within the past year, ascites, thrombocytopenia, low alanine aminotransferase levels, hyponatremia, anemia, and Model for End-stage Liver Disease (MELD) scores. **Methods:** We analyzed the Nationwide Readmission Database (HCUP) from 2019 to 2022 and collected data on 1,748,576 adult patients readmitted within 30 days. Our study initially employed standard logistic regression and decision tree methodologies to identify influential variables and establish significant decision rules. Subsequently, we divided the original dataset into strata and applied logistic regression to each stratum. Lastly, we examined the risk and accuracy of interacting variables in the logistic regression models through the use of Area under the Curve (AUC) and Odds Ratio assessments. **Results:** Between 2019 and 2022, a total of 1,748,576 patients were readmitted. After propensity score matching, 24,988 patients (mean age 57.4 ± 12.4, 54% women) were included in the study. We compared 11,444 (45%) liver cirrhosis patients to 13,544 (54%) patients without liver cirrhosis. Multiple logistic regression of the independent variables revealed a 7.2% readmission probability in the insurance group ($p < 0.01$), 4.2% for CAD ($p = 0.01$), and 4.8% for HLD ($p < 0.01$). The lower median income quartile (25k-35k) showed a 7.2% increase in readmissions ($p = 0.02$). Increased odds of readmission were observed in patients with a history of HLD requiring medication (2.4, $p < 0.01$), median household income (OR 2.19, $p < 0.01$), and insurance status ($OR = 1.53$, $p < 0.01$). Furthermore, female patients demonstrated higher odds of readmission (OR 1.21, $p < 0.01$). The accuracy of gender and insurance status was also significant, with gender AU ROC at 0.550 ($p < 0.01$) and insurance status AU ROC at 0.641 ($p < 0.01$), compared to logistic regression. **Conclusion:** Our findings indicate that patients with comorbid medical conditions, insurance status, gender, and those in the second income quartile exhibit a heightened risk for readmission. Further studies are required to assess whether implementing targeted interventions for high-risk patients can effectively reduce readmissions.



Disclosures: The following people have nothing to disclose: Rajmohan Rammohan, Melvin Joy, Dilman

Natt, Sai Greeshma Magam, Achal Patel, Abhishek Tadikonda, Jiten Desai, Sandra Gomez, Rucha Jiyani, Saher Sheikh, Susan Bunting, Paul Mustacchia

2807-C | GENDER AND RACIAL DISPARITIES IN OUTCOMES OF ACUTE LIVER FAILURE: A NATIONAL POPULATION BASED STUDY

Chidiebele Omaliko, One Brooklyn Health - Brookdale University Hospital Medical Center, Ayobami Olafimihan, John H Stroger Jr. Hospital of Cook County, Chukwunonso Ezeani, Baton Rouge General Medical Center, Baton Rouge, LA, Oghenefejiro Ogwor, St Peter University Hospital, New Brunswick, NJ, Chidiebube Jeremiah Ugwu, East Tennessee State University, Favour Markson, Lincoln Medical Center and Nzubechukwu Ugochukwu, Nnamdi Azikiwe University Teaching Hospital

Background: Acute Liver Failure (ALF) is associated with significant health care burden as well as mortality, morbidity and need for liver transplantation in the USA. There is a paucity of data that describe the sociodemographic differences in the outcomes of hospitalized patients admitted with acute liver failure. In this retrospective cohort study, we evaluated the racial and gender differences in the outcomes of patients hospitalized for acute liver failure. **Methods:** Using the National Inpatient Sample (NIS) database, we identified patients with a principal diagnosis of acute liver failure between 2016 - 2020 and divided them based on the different races and gender. Patients aged less than 18 years were excluded from the analysis. Using a multivariate analysis, we assessed for differences in the primary outcome of inpatient mortality while the secondary outcomes were hospital length of stay (LOS) and total hospital charges (THC). **Results:** There were 135,520 hospitalizations with a principal diagnosis of acute liver failure, with the majority (66.6%) being White, while Native Americans with 2,174 patients (1.7%) had the fewest hospitalizations. There was a significant difference in inpatient mortality among the different races ($p = < 0.01$), with Blacks having the highest mortality rate (12.2%) and Hispanics with the least mortality (7.1%). We also found a significant difference in mortality between females and males ($p = 0.03$). When secondary outcomes were analyzed, there was a significant difference in LOS between the races ($p = 0.002$), with Blacks having the longest length of stay (7.4 d) and Native Americans with the least (5.0 d). Regarding total hospitalization charges, Asians had the highest ($127,365), whereas Native Americans had the lowest ($46,530). This difference in hospitalization charges among the races was found to be statistically significant ($p = 0.000$). Between females and males, total hospitalization charges were also significantly different ($p = 0.042$), however length of hospital stay was not ($p = 0.429$). **Conclusion:** Our study found a significant difference in in-hospital mortality, length of stay and total hospitalization charges among the different races when admitted with a principal diagnosis of acute liver failure. There was also a significant difference between females and males as regards mortality and total hospitalization charges but no difference in length of stay. The reasons for these disparities are varied and not fully defined, hence there is a need to further understand and mitigate factors which can contribute to health disparity in acute liver failure.

Disclosures: The following people have nothing to disclose: Chidiebele Omaliko, Ayobami Olafimihan, Chukwunonso Ezeani, Oghenefejiro Ogwor, Chidiebube Jeremiah Ugwu, Favour Markson, Nzubechukwu Ugochukwu

f 2808-C | GENDER DISPARITIES IN ALCOHOLIC LIVER DISEASE RELATED MORTALITY IN UNITED STATES FROM 1999-2020

Fariha Ilyas[1], Hassam Ali[1], Maheen Ilyas[2], Mahnoor Khalid[3], Pratik Patel[4], Alexa Giammarino[5] and Sanjaya Kumar Satapathy[6], (1)East Carolina University, (2) New York Institute of Technology, (3)Foundation University Medical College, (4)Northwell Health, Forest Hills, NY, (5)Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, (6)Zucker School of Medicine - Hofstra University

Background: Alcohol Liver Disease (ALD) remains one of the leading causes of cirrhosis and nearly half of cirrhosis-related deaths in the United States. Previously, men were more affected by ALD compared to women. However, mounting evidence suggests increasing prevalence of alcohol abuse amongst women. Women are more sensitive to adverse health effects with lesser exposure than males. Our study aims to further illustrate the gender disparity in mortality of ALD. **Methods:** We used CDC Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) to access National Vital Statistics System data from 1999-2020. ALD related deaths in adults with age 25-85+ years were identified. Deaths were shown as age adjusted mortality rates (AAMR) per 100,000 population. Joinpoint regression was used to examine changes in trend, average annual percent change (AAPC) and annual percentage change (APC) in ALD related deaths, stratified by gender. **Results:** Between 1999 and 2020, 372,900 deaths related to ALD. AAMR increased from 6.7/100,000 in 1999 to 12.1/100,000 in 2020, showing a significant average annual percentage change (AAPC) of 2.7% (95% CI: 2.2%-3.2%, P < 0.001) (Figure 1A). For females, AAMR increased from 2.7/100,000 in 1999 to 6.4/100,000 in 2020 (Figure 1B). The overall trend showed a significant 3.9% AAPC (95% CI: 3.2%-4.7%, P < 0.001). For males, AAMR increased from 8.8/100,000 in 1999 to 13.9/100,000 in 2020, with an AAPC of 2.1% (95% CI: 1.4%-2.8%, P < 0.001). Comparing the cohorts revealed a significant 1.9% AAPC difference (95% CI: 0.8%-2.9%, P < 0.001), indicating a more pronounced mortality increase in females. **Conclusion:** Our study examined trends in ALD related mortality from 1999 to 2020, revealing a significant increase in mortality rates, with a more substantial rise amongst females. An increasing predominance of ALD in women may prognosticate future significant increase in morbidity and mortality related to liver cirrhosis, breast cancer, cardiovascular disease, and fetal alcohol spectrum. Our study highlights the importance of understanding the changing epidemiology and addressing individual, societal, and environmental factors influencing alcohol abuse and ALD.

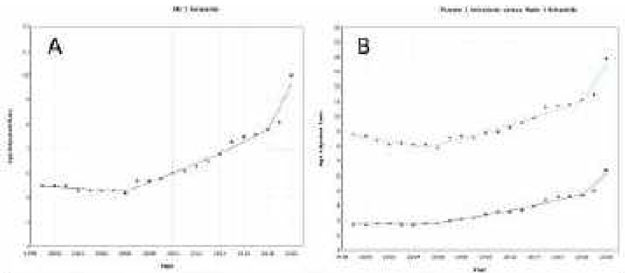


Figure 1: Overall (A) and gender based (B) mortality rates in Alcoholic Liver Disease.

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2809-C | HIGHER HOUSEHOLD DYSFUNCTION IN ADVERSE CHILDHOOD EXPERIENCES SCORE (ACES) ASSOCIATES WITH AN INCREASED RISK OF CIRRHOSIS IN ADULTHOOD

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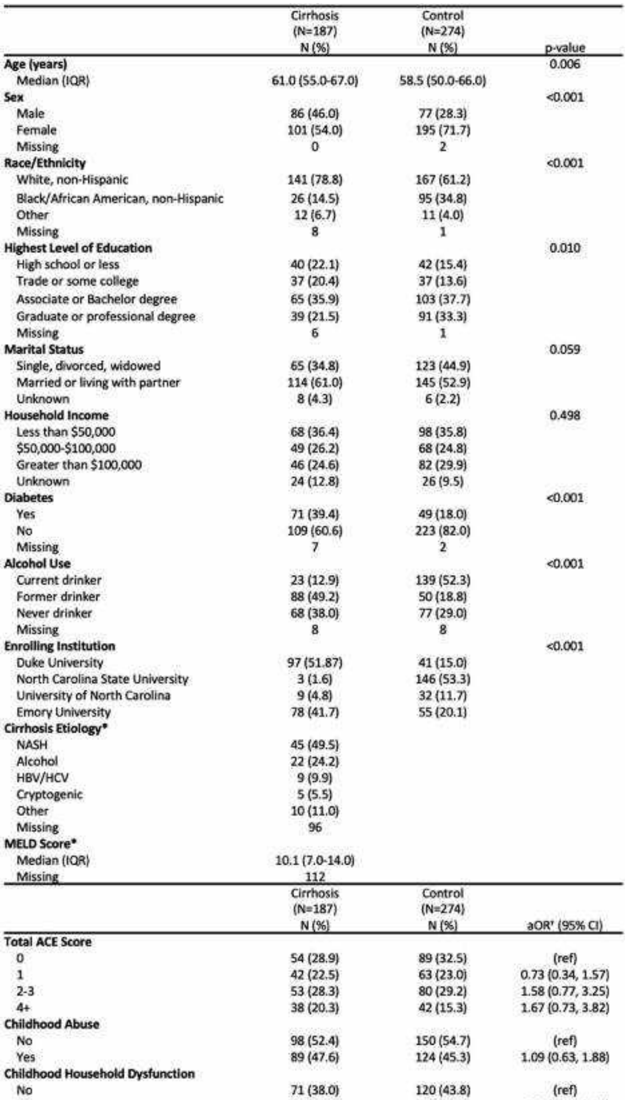
Background: Adverse childhood experiences (ACEs) have been linked to the development of chronic liver disease later in life. Historically, this link was driven by increased risk behaviors for viral and alcohol-related liver disease (ALD). With the rise of non-alcoholic steatohepatitis (NASH) in recent decades and its different underlying risks, we aimed to characterize the current association between ACEs and cirrhosis. **Methods:** We conducted a cross-sectional analysis of participants (pts) enrolled in the Southern Liver Health Study, a multi-site study investigating the association between environmental contaminants and liver cancer. We included two cohorts: pts with cirrhosis and healthy controls without cirrhosis aged 40-75 years enrolled between 1/1/2022 and 1/31/23. History of ACEs was collected using a validated survey with a score ranging from 0-8. Demographic information was obtained for all pts and additional medical history was obtained via chart review for pts with cirrhosis enrolled at Duke. Pt characteristics were summarized and adjusted multivariable logistic regression models were used to test the association between ACEs and cirrhosis. **Results:** 461 pts were included in the final analyses (cirrhosis, n = 187; healthy control, n = 274). Pts with cirrhosis were more likely to be older than controls (median: 61 vs. 58.5 yrs), male (46% vs. 28%), and non-Hispanic White (79% vs. 61%) (Table 1). Both cohorts reported a median of 1 ACE while more pts with cirrhosis reported e 4 ACEs than healthy controls (20% vs. 15%). NASH was the most common etiology of cirrhosis (49%), followed by ALD (24%). Cirrhosis was significantly associated with history of at least one ACE in the household dysfunction domain but not total ACE score or history of ACEs in the childhood abuse domain. Pts with cirrhosis reporting an annual household income of less than $50,000 was significantly associated with a total ACE score of e 4 (OR 3.07; 95% CI 1.35-6.97). **Conclusion:** Reporting at least one ACE relating to household dysfunction associated with a 78% higher odds of cirrhosis in adulthood. High total ACE score along with a low household income also significantly associated with cirrhosis. While we did not find an association between total ACE score and cirrhosis, we found that certain ACEs impact risk for cirrhosis more than others and that this may be impacted by other factors such as income. The high prevalence of NASH cirrhosis and different risk behaviors may explain these findings, but larger studies are needed. Future efforts should investigate whether and how ACEs differently impact the likelihood of cirrhosis and its various etiologies.



	Cirrhosis (N=187) N (%)	Control (N=274) N (%)	p-value
Age (years)			0.006
Median (IQR)	61.0 (55.0-67.0)	58.5 (50.0-66.0)	
Sex			<0.001
Male	86 (46.0)	77 (28.3)	
Female	101 (54.0)	195 (71.7)	
Missing	0	2	
Race/Ethnicity			<0.001
White, non-Hispanic	141 (78.8)	167 (61.2)	
Black/African American, non-Hispanic	26 (14.5)	95 (34.8)	
Other	12 (6.7)	11 (4.0)	
Missing	8	1	
Highest Level of Education			0.010
High school or less	40 (22.1)	42 (15.4)	
Trade or some college	37 (20.4)	37 (13.6)	
Associate or Bachelor degree	65 (35.9)	103 (37.7)	
Graduate or professional degree	39 (21.5)	91 (33.3)	
Missing	6	1	
Marital Status			0.059
Single, divorced, widowed	65 (34.8)	123 (44.9)	
Married or living with partner	114 (61.0)	145 (52.9)	
Unknown	8 (4.3)	6 (2.2)	
Household Income			0.498
Less than $50,000	68 (36.4)	98 (35.8)	
$50,000-$100,000	49 (26.2)	68 (24.8)	
Greater than $100,000	46 (24.6)	82 (29.9)	
Unknown	24 (12.8)	26 (9.5)	
Diabetes			<0.001
Yes	71 (39.4)	49 (18.0)	
No	109 (60.6)	223 (82.0)	
Missing	7	2	
Alcohol Use			<0.001
Current drinker	23 (12.9)	139 (52.3)	
Former drinker	88 (49.2)	50 (18.8)	
Never drinker	68 (38.0)	77 (29.0)	
Missing	8	8	
Enrolling Institution			<0.001
Duke University	97 (51.87)	41 (15.0)	
North Carolina State University	3 (1.6)	146 (53.3)	
University of North Carolina	9 (4.8)	32 (11.7)	
Emory University	78 (41.7)	55 (20.1)	
Cirrhosis Etiology*			
NASH	45 (49.5)		
Alcohol	22 (24.2)		
HBV/HCV	9 (9.9)		
Cryptogenic	5 (5.5)		
Other	10 (11.0)		
Missing	96		
MELD Score*			
Median (IQR)	10.1 (7.0-14.0)		
Missing	112		

	Cirrhosis (N=187) N (%)	Control (N=274) N (%)	aOR' (95% CI)
Total ACE Score			
0	54 (28.9)	89 (32.5)	(ref)
1	42 (22.5)	63 (23.0)	0.73 (0.34, 1.57)
2-3	53 (28.3)	80 (29.2)	1.58 (0.77, 3.25)
4+	38 (20.3)	42 (15.3)	1.67 (0.73, 3.82)
Childhood Abuse			
No	98 (52.4)	150 (54.7)	(ref)
Yes	89 (47.6)	124 (45.3)	1.09 (0.63, 1.88)
Childhood Household Dysfunction			
No	71 (38.0)	120 (43.8)	(ref)
Yes	116 (62.0)	154 (56.2)	1.78 (1.01, 3.12)

Table 1. Demographic information and ACE scores of participants with and without cirrhosis. * includes Duke data only. ' aOR was adjusted for age, sex, enrolling institution, diabetes, and alcohol use. Abbreviations: IQR = interquartile range; BMI = body mass index; NASH = non-alcoholic steatohepatitis; HBV = hepatitis B virus; HCV = hepatitis C virus; MELD = model for end-stage liver disease; ACE = adverse childhood experience; aOR = adjusted odds ratio; CI = confidence interval.

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f 2810-C | IMPACT OF FAMILY INCOME-TO-POVERTY RATIO ON LONG-TERM MORTALITY OF PERSONS WITH CHRONIC LIVER DISEASE IN THE UNITED STATES, 1999 – 2018

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Background: Chronic liver disease (CLD) is associated with increased morbidity and mortality. Understanding health disparity among those with CLD is imperative to develop appropriate interventions. We studied the demographics and mortality outcomes of those with CLD by socioeconomic (SES) level in the United States. **Methods**: In this retrospective study, data from NHANES from 1999-2018 linked with mortality files were used. All adults (20+ years) were included. CLD included viral hepatitis, defined by laboratory results, nonalcoholic fatty liver disease (NAFLD) by the US-FLI, and alcohol associated liver disease (ALD) by excessive alcohol consumption and liver enzymes. SES was defined as an income-to-poverty ratio of < 5 (low income) and e 5 (high income). The primary outcome was mortality. **Results**: We included a cohort of 59,204 individual's: 47,224 without CLD and 11,980 with CLD. Overall, the mean age was 49.59 ± 17.24, 57.06% male, 66.5% non-Hispanic White, 12.26% non-Hispanic Black, 17.57% Hispanic, and 3.67% Asian. Most (80.02%) CLD individual's did not have a college degree, and most were low-income (79.18%). Stratified by income-to-poverty ratio, the low-income cohort among those with CLD had a mean age of 49.09 ± 17.94, 55.17% male, 62.98% Non-Hispanic White, 13.61% Non-Hispanic Black: 13.61%, 10.59% Hispanic 10.59%, 3.37% Asian, P < 0.001), the majority did not have post-high school education (e bachelor's degree: 13.73%). In the overall cohort, 8.4% of individual's died during follow-up (n = 4,984 deaths; 4494 deaths in income-to-poverty ratio < 5 group and 490 deaths in e 5 income-to-poverty group). After adjusting for age, sex, and race and ethnicity, individual's in the low-income cohort compared to the high-income cohort were 2.01 (HR: 2.01; 95% CI: 1.79-2.26) times more likely to die, which was similar when analyzed by etiology- viral hepatitis (HR: 2.05; 95% CI: 1.31-3.24) and NAFLD (HR: 2.32; 95% CI: 1.69-3.18) but not by AFLD (HR: 1.17; 95% CI: 0.55-2.51). **Conclusion**: Individual's whose income-to-poverty ratio was < 5 were disproportionately represented among those with CLD. Outside of non-Hispanic Whites, Hispanics

carried the greater burden for NAFLD and AFLD, while non-Hispanic Blacks carried a greater burden for viral hepatitis, as did those with a lower education level and low-income women. Interventions must not only be culturally appropriate but also require attention to the potential lack of health literacy and be sex-specific.

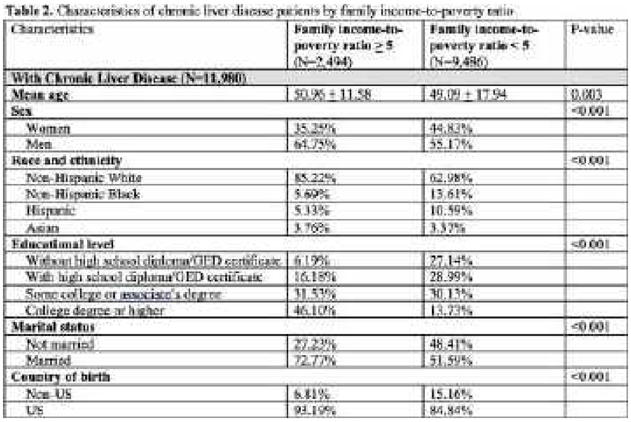
Table 2. Characteristics of chronic liver disease patients by family income-to-poverty ratio

Characteristics	Family income-to-poverty ratio ≥ 5 (N=2,494)	Family income-to-poverty ratio < 5 (N=9,486)	P-value
With Chronic Liver Disease (N=11,980)			
Mean age	50.96 ± 11.58	49.09 ± 17.94	0.003
Sex			<0.001
Women	35.25%	44.83%	
Men	64.75%	55.17%	
Race and ethnicity			<0.001
Non-Hispanic White	85.22%	62.98%	
Non-Hispanic Black	5.69%	13.61%	
Hispanic	5.33%	10.59%	
Asian	3.76%	3.37%	
Educational level			<0.001
Without high school diploma/GED certificate	6.19%	27.14%	
With high school diploma/GED certificate	16.18%	28.99%	
Some college or associate's degree	31.53%	30.13%	
College degree or higher	46.10%	13.73%	
Marital status			<0.001
Not married	27.23%	48.41%	
Married	72.77%	51.59%	
Country of birth			<0.001
Non-US	6.81%	15.16%	
US	93.19%	84.84%	

Disclosures: The following people have nothing to disclose: Brian Thanh Nguyen, Vy H. Nguyen, Michael H Le, Linda Henry, Ramsey Cheung
Disclosure information not available at the time of publication: Mindie H. Nguyen

2811-C | IMPACT OF SELF-REPORTED RACE AND ETHNICITY IN HOSPITALIZED PATIENTS WITH ACUTE KIDNEY INJURY AND CIRRHOSIS: RESULTS FROM THE HRS HARMONY CONSORTIUM

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Background: Race and ethnicity influence outcomes in patients with cirrhosis, though their impact on resource allocation and mortality in those hospitalized with acute kidney injury (AKI) is not well described. **Methods**: we performed a multicenter (15 hospitals, 11 transplant centers) retrospective cohort study of consecutive patients hospitalized with cirrhosis and AKI. Primary exposures were self-reported race and ethnicity. The primary outcome was 90-day mortality using an adjusted Fine and Grey model with competing risk of liver transplant. **Results**: 2063 patients were included. 81.1% (n = 1582) were non-Hispanic White (NHW), 8.6% (n = 178) were Hispanic, and 10.6% (n = 303) were Non-White, Non-Black (NWNB). Compared to NHW patients, Non-Hispanic Black (NHB) patients had more hypertension (69.9% vs. 57.7%) and chronic kidney disease (35.2% vs. 30.3%, p < 0.01 for both). Median MELD-Na score (26) was similar across racial and ethnic groups. Rates of HRS-AKI, peak AKI stage, intensive care unit admission, and length of stay did not differ significantly between groups. Compared to non-Hispanic patients, Hispanic patients required more dialysis (24.2% vs. 17%, p = 0.02) and had higher rates of liver transplant evaluation (12.4% vs. 5.2%, p = 0.001). Hispanic patients who died were less likely to receive palliative care consultation (23.9% vs. 42%, p < 0.001). Compared to NHW patients, NHB patients were less likely to be transferred to a liver transplant center from a community hospital (13.2% vs. 25%, p < 0.001) and less likely to be listed for liver transplantation (8.5% vs. 15.1%, p = 0.01). After adjusting for confounders, in multivariable analysis, neither ethnicity (non-Hispanic aHR 1.34 [95% CI 0.96, 1.88], p = 0.09), nor race (Black aHR 1.25 [95% CI 0.97, 1.62], p = 0.09) was associated with 90-day mortality. **Conclusion**: By race and ethnicity, there are no significant differences in 90-day mortality among hospitalized patients with AKI and cirrhosis. However, important differences in resource allocation, such as palliative care consultation rates and transfer to a liver transplant center, were identified that warrant further investigation.

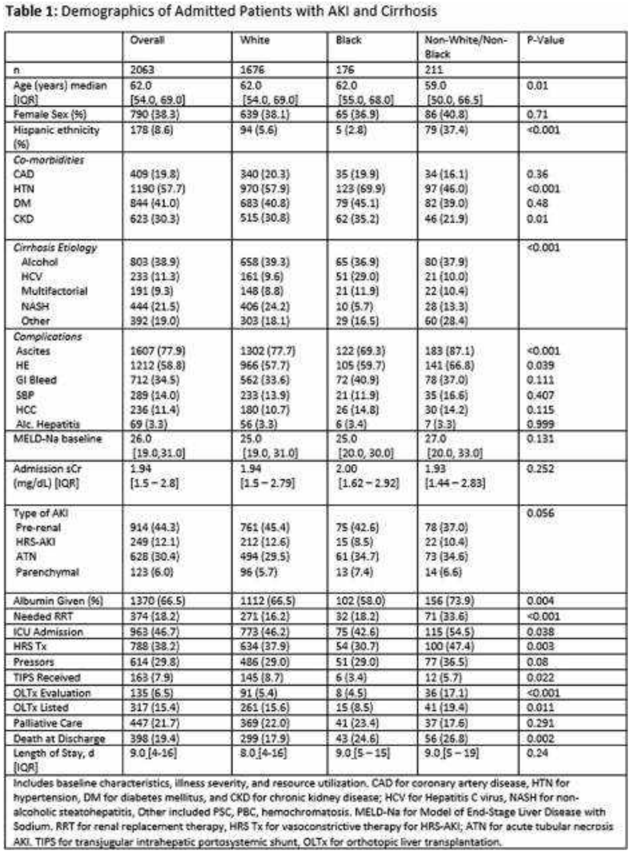
Table 1: Demographics of Admitted Patients with AKI and Cirrhosis

	Overall	White	Black	Non-White/Non-Black	P-Value
n	2063	1676	176	211	
Age (years) median [IQR]	62.0 [54.0, 69.0]	62.0 [54.0, 69.0]	62.0 [55.0, 68.0]	59.0 [50.0, 66.5]	0.01
Female Sex (%)	790 (38.3)	639 (38.1)	65 (36.9)	86 (40.8)	0.71
Hispanic ethnicity (%)	178 (8.6)	94 (5.6)	5 (2.8)	79 (37.4)	<0.001
Co-morbidities					
CAD	409 (19.8)	340 (20.3)	35 (19.9)	34 (16.1)	0.36
HTN	1190 (57.7)	970 (57.9)	123 (69.9)	97 (46.0)	<0.001
DM	844 (41.0)	683 (40.8)	79 (45.1)	82 (39.0)	0.48
CKD	623 (30.3)	515 (30.8)	62 (35.2)	46 (21.9)	0.01
Cirrhosis Etiology					<0.001
Alcohol	803 (38.9)	658 (39.3)	65 (36.9)	80 (37.9)	
HCV	233 (11.3)	161 (9.6)	51 (29.0)	21 (10.0)	
Multifactorial	191 (9.3)	148 (8.8)	21 (11.9)	22 (10.4)	
NASH	444 (21.5)	406 (24.2)	10 (5.7)	28 (13.3)	
Other	392 (19.0)	303 (18.1)	29 (16.5)	60 (28.4)	
Complications					
Ascites	1607 (77.9)	1302 (77.7)	122 (69.3)	183 (87.1)	<0.001
HE	1212 (58.8)	966 (57.7)	105 (59.7)	141 (66.8)	0.039
GI Bleed	712 (34.5)	562 (33.6)	72 (40.9)	78 (37.0)	0.111
SBP	289 (14.0)	233 (13.9)	21 (11.9)	35 (16.6)	0.407
HCC	236 (11.4)	180 (10.7)	26 (14.8)	30 (14.2)	0.115
Alc. Hepatitis	69 (3.3)	56 (3.3)	6 (3.4)	7 (3.3)	0.999
MELD-Na baseline	26.0 [19.0,31.0]	25.0 [19.0, 31.0]	25.0 [20.0, 30.0]	27.0 [20.0, 33.0]	0.131
Admission sCr (mg/dL) [IQR]	1.94 [1.5 – 2.8]	1.94 [1.5 – 2.79]	2.00 [1.62 – 2.92]	1.93 [1.44 – 2.83]	0.252
Type of AKI					0.056
Pre-renal	914 (44.3)	761 (45.4)	75 (42.6)	78 (37.0)	
HRS-AKI	249 (12.1)	212 (12.6)	15 (8.5)	22 (10.4)	
ATN	628 (30.4)	494 (29.5)	61 (34.7)	73 (34.6)	
Parenchymal	123 (6.0)	96 (5.7)	13 (7.4)	14 (6.6)	
Albumin Given (%)	1370 (66.5)	1112 (66.5)	102 (58.0)	156 (73.9)	0.004
Needed RRT	374 (18.2)	271 (16.2)	32 (18.2)	71 (33.6)	<0.001
ICU Admission	963 (46.7)	773 (46.2)	75 (42.6)	115 (54.5)	0.038
HRS Tx	788 (38.2)	634 (37.9)	54 (30.7)	100 (47.4)	0.003
Pressors	614 (29.8)	486 (29.0)	51 (29.0)	77 (36.5)	0.08
TIPS Received	163 (7.9)	145 (8.7)	6 (3.4)	12 (5.7)	0.022
OLTx Evaluation	135 (6.5)	91 (5.4)	8 (4.5)	36 (17.1)	<0.001
OLTx Listed	317 (15.4)	261 (15.6)	15 (8.5)	41 (19.4)	0.011
Palliative Care	447 (21.7)	369 (22.0)	41 (23.4)	37 (17.6)	0.291
Death at Discharge	398 (19.4)	299 (17.9)	43 (24.6)	56 (26.8)	0.002
Length of Stay, d [IQR]	9.0 [4-16]	8.0 [4-16]	9.0 [5 – 15]	9.0 [5 – 19]	0.24

Includes baseline characteristics, illness severity, and resource utilization. CAD for coronary artery disease, HTN for hypertension, DM for diabetes mellitus, and CKD for chronic kidney disease; HCV for Hepatitis C virus, NASH for non-alcoholic steatohepatitis, Other included PSC, PBC, hemochromatosis. MELD-Na for Model of End-Stage Liver Disease with Sodium. RRT for renal replacement therapy, HRS Tx for vasoconstrictive therapy for HRS-AKI; ATN for acute tubular necrosis AKI. TIPS for transjugular intrahepatic portosystemic shunt, OLTx for orthotopic liver transplantation.

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Disclosure information not available at the time of publication: Justin M. Belcher, Kevin R. Regner, Andrew Allegretti

2812-C | INTERACTION BETWEEN RACE AND HEALTH INSURANCE STATUS IS ASSOCIATED WITH CRITICAL HEALTH DISPARITIES IN HEPATOCELLULAR CARCINOMA OUTCOMES

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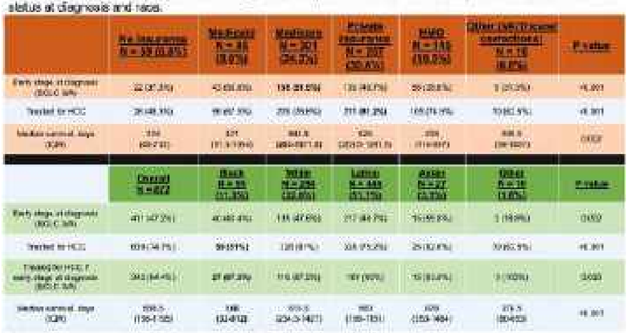
Background: Critical disparities exist in hepatocellular carcinoma (HCC) outcomes; Black race and insurance type are associated with differences in presentation, treatment, and survival. Inequities between private and government insurance may exacerbate racial disparities. Most studies examine insurance type *en bloc* despite differences between traditional Medicare (TM) and Medicare Advantage (MA). Our study explored the association of race/ethnicity and insurance on diagnosis, treatment, and survival in diverse patients with HCC. **Methods:** Since 2018, patients with HCC from the University of Miami and Jackson Memorial Hospitals have been enrolled into an observational longitudinal cohort. We performed chart review from electronic medical records to determine and categorize insurance type at diagnosis. We used descriptive statistics for demographics and disease-specific characteristics, and examined associations between race, insurance, and treatment outcomes using Pearson's chi-squared and Kruskal-Wallis rank sum tests. **Results:** The sample consisted of 872 patients and was 11.3% Black, 32.5% White, 51.5% Latino, 3.1% Asian, and 1.8% other. Median age at cancer diagnosis was 64 years and 74.9% were male. Individual's with private insurance or Medicare were significantly more likely to receive treatment compared to those with Medicaid or without insurance, $p < 0.001$. See Table 1. When stratified by Medicare type, 80.8% of TM patients were treated compared to 71.1% of MA patients, $p < 0.05$. Median survival was highest in Medicare patients (641.5 d) compared to all other insurance types, $p = 0.002$. Median survival was higher in TM patients (783 d) compared to MA patients (405 d), $p < 0.001$. Only 51% of Black patients received treatment compared to 81% of White, 75.2% of Latino, and 92.6% of Asian patients. Black patients were more likely to have Medicaid, especially managed-care Medicaid, and MA. Only 50% of Black patients with Medicare received treatment compared to 83.5% of White, 78.9% of Latino, and 100% of Asian patients with Medicare, $p < 0.001$. Even at early-stage diagnosis, Black patients were least likely to receive treatment, $p = 0.03$. **Conclusion:** Despite having insurance, Black patients have less access to HCC treatment compared to White, Latino and Asian patients. Insurance type is remarkably important to HCC outcomes. Efforts to educate communities on insurance coverage limitations, assess managed care Medicare and Medicaid plan quality, and advocate for coverage expansion are profoundly needed to improve HCC disparities.

Table 1: HCC outcomes (stage at time of diagnosis, receipt of treatment, and survival) based on health insurance status at diagnosis and race.



(BCLC = Barcelona Clinic Liver Cancer Staging System, 0 = Very Early Stage, A = Early Stage; IQR = Interquartile Range)

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f 2813-C | NEIGHBORHOOD DEPRIVATION INDEX IS ASSOCIATED WITH INCREASED MEDICATION LEVEL VARIABILITY INDEX AMONG ADULT LIVER TRANSPLANT RECIPIENTS AT A SINGLE CENTER

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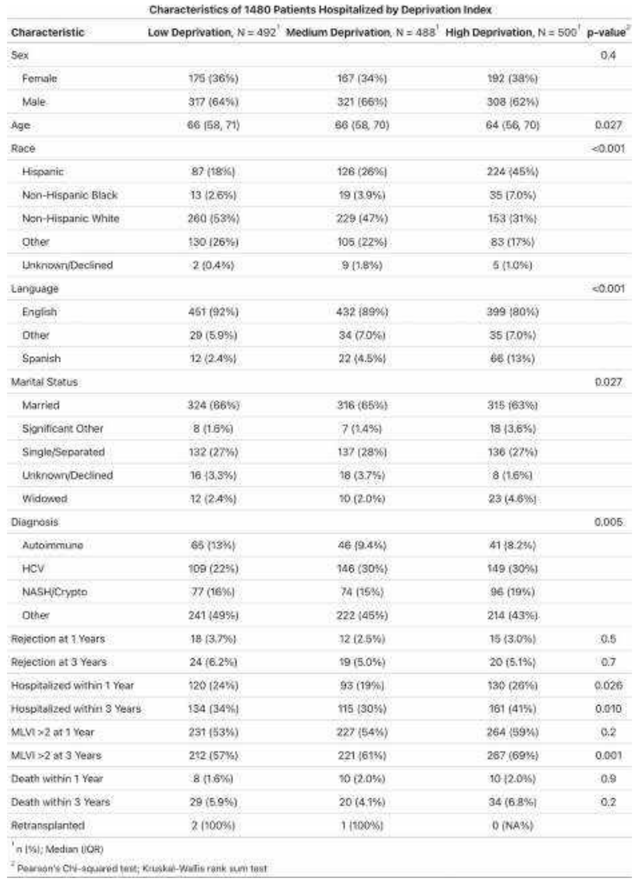
Background: The neighborhood deprivation index (NDI) measures one's neighborhood socioeconomic environment and predicts health outcomes among liver transplant recipients. Higher medication level variability index (MLVI), a biomarker of immunosuppression nonadherence, is associated with cellular rejection. We evaluated the relationship between neighborhood deprivation and MLVI. **Methods:** We included adult liver transplant (LT) recipients at a single center with > 1 year follow up. NDI was calculated using a validated composite measure, including 6 domains of deprivation. The NDI ranges from (0,1) and is available at the census tract level; patients' addresses were geocoded to identify their NDI. MLVI was defined as the standard deviation of e 3 sequential tacrolimus trough levels, dichotomized at MLVI > 2, based on prior studies. We used univariable and multivariable logistic regression to associate MVLI and NDI; NDI was transformed to a scale of 0-10 in regression models. **Results:** A total of 1480 LT recipients were included; 36% were female, median age was 65, and 27% had Hepatitis C. 28 participants experienced death within 1 year post-LT and 83 within 3 years; 3 participants required re-transplantation. When stratified by neighborhood deprivation (high, medium, and low), patients with high deprivation indexes were more likely to speak Spanish (13% vs 4.5% and 2.4%, $p < 0.001$), to be hospitalized at 1 year (26%, vs 19% and 24%, $p = 0.026$), and 3 years (41% vs 30% and 34%, $p = 0.009$) post-LT. Participants with high deprivation indexes were more likely to have high MLVI at 3 years (69% vs 61% and 57%, $p = 0.001$) post-LT. In univariable logistic regression, each 1 point increase in NDI was associated with a 1.2 times higher odds of MLVI > 2 at 3 years (95% CI 1.1 1.3). After adjusting for language, race, and relationship status, this association remained significant: aOR 1.2, 95%CI 1.1 - 1.3. **Conclusion:** After adjusting for language, race, and relationship status, neighborhood deprivation was significantly associated with increased MLVI at 3 years post LT—an effect that was independent of self-identified race. Future studies should investigate the factors of where patients live, eat, and work that drive poor medication adherence.



Characteristics of 1480 Patients Hospitalized by Deprivation Index

Characteristic	Low Deprivation, N = 492[1]	Medium Deprivation, N = 488[1]	High Deprivation, N = 500[1]	p-value[2]
Sex				0.4
Female	175 (36%)	167 (34%)	192 (38%)	
Male	317 (64%)	321 (66%)	308 (62%)	
Age	66 (58, 71)	66 (58, 70)	64 (56, 70)	0.027
Race				<0.001
Hispanic	87 (18%)	126 (26%)	224 (45%)	
Non-Hispanic Black	13 (2.6%)	19 (3.9%)	35 (7.0%)	
Non-Hispanic White	260 (53%)	229 (47%)	153 (31%)	
Other	130 (26%)	105 (22%)	83 (17%)	
Unknown/Declined	2 (0.4%)	9 (1.8%)	5 (1.0%)	
Language				<0.001
English	451 (92%)	432 (89%)	399 (80%)	
Other	29 (5.9%)	34 (7.0%)	35 (7.0%)	
Spanish	12 (2.4%)	22 (4.5%)	66 (13%)	
Marital Status				0.027
Married	324 (66%)	316 (65%)	315 (63%)	
Significant Other	8 (1.6%)	7 (1.4%)	18 (3.6%)	
Single/Separated	132 (27%)	137 (28%)	136 (27%)	
Unknown/Declined	16 (3.3%)	18 (3.7%)	8 (1.6%)	
Widowed	12 (2.4%)	10 (2.0%)	23 (4.6%)	
Diagnosis				0.005
Autoimmune	65 (13%)	46 (9.4%)	41 (8.2%)	
HCV	109 (22%)	146 (30%)	149 (30%)	
NASH/Crypto	77 (16%)	74 (15%)	96 (19%)	
Other	241 (49%)	222 (45%)	214 (43%)	
Rejection at 1 Years	18 (3.7%)	12 (2.5%)	15 (3.0%)	0.5
Rejection at 3 Years	24 (6.2%)	19 (5.0%)	20 (5.1%)	0.7
Hospitalized within 1 Year	120 (24%)	93 (19%)	130 (26%)	0.026
Hospitalized within 3 Years	134 (34%)	115 (30%)	161 (41%)	0.010
MLVI >2 at 1 Year	231 (53%)	227 (54%)	264 (59%)	0.2
MLVI >2 at 3 Years	212 (57%)	221 (61%)	267 (69%)	0.001
Death within 1 Year	8 (1.6%)	10 (2.0%)	10 (2.0%)	0.9
Death within 3 Years	29 (5.9%)	20 (4.1%)	34 (6.8%)	0.2
Retransplanted	2 (100%)	1 (100%)	0 (NA%)	

[1] n (%); Median (IQR)

[2] Pearson's Chi-squared test; Kruskal-Wallis rank sum test

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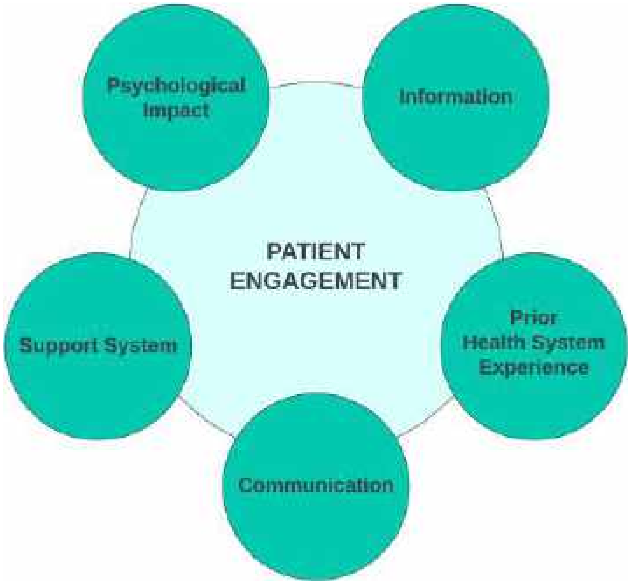
The following people have nothing to disclose: Laila Fozouni, Sharad Wadhwani

2814-C | PATIENT PERSPECTIVES ON LIVER TRANSPLANT EVALUATION: A QUALITATIVE STUDY

Alexandra Strauss[1], Janetta Brundage[1], Carolyn N. Sidoti[2], Vedant S. Jain[3], Ahmet Gürakar[1], Katlyn Mohr[1], Macey L. Levan[2], Dorry L. Segev[4], James P. Hamilton[5] and Hannah C. Sung[1], (1)Johns Hopkins University, (2) New York University, (3)Carle Illinois College of Medicine, (4)NYU Langone Health, (5)Johns Hopkins Medicine, Baltimore, MD

Background: Completing the liver transplant (LT) evaluation process requires patients to navigate logistical, financial, and other factors in a timely manner. This complexity is compounded by high-stakes interactions with many healthcare providers. We aimed to examine patients' perceptions and experiences during LT evaluation and characterize key supports and barriers for patients during evaluation. **Methods:** We performed a single center qualitative study with patients actively undergoing LT evaluation from 3/1/2021 and 5/26/2021. We thematically analyzed semi-structured interviews (n = 14). **Results:** We interviewed 7 (50%) women, and 3 (21%) participants that self-identified as either Black, Hispanic, or American Indian/Alaskan Native. Our analysis generated 8 themes within 5 thematic categories related to patient engagement (i.e., patient involvement/activation in their healthcare; Figure) in the LT evaluation process: 1) psychological impact of evaluation on participants' lives, such as feeling overwhelmed and making sense of needing a transplant; 2) information received during evaluation, including identifying relevant information and using different methods of finding information; 3) prior medical experience of the participant, specifically applying prior experiences to LT evaluation; 4) communication between participants and transplant providers, such as difficulty in understanding provider roles and appreciating provider demonstrations of empathy; and 5) support system of the participants, particularly relying on loved ones who take on multiple roles related to transportation, scheduling, or advocacy. **Conclusion:** Participants described psychological, informational, and interpersonal supports and barriers related to patient engagement in LT evaluation. Insights from this work can inform practice improvements and targeted interventions for reducing barriers and increasing patient engagement during the LT evaluation process to improve completion of evaluation and timeliness of listing.



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Disclosure information not available at the time of publication: Carolyn N. Sidoti, Vedant S. Jain, Katlyn Mohr, Macey L. Levan, Dorry L. Segev, James P. Hamilton, Hannah C. Sung

f 2815-C | PATIENT SATISFACTION WITH TELEHEALTH VISITS IN RURAL COMPARED TO URBAN COMMUNITIES

Corrin Hepburn[1], Jonah N. Rubin[1], Karolina Krawczyk[1], Scott J. Cotler[2], Steven J. Scaglione[3] and Cara Joyce[1], (1)Loyola University Medical Center, Chicago, IL, (2)

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

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Background: Recent studies performed in urban communities with access to technology suggest high patient satisfaction with telehealth. While virtual visits can increase the reach of clinical practice, technological barriers may reduce patient satisfaction in rural communities. Our aim was to compare preference for telehealth between hepatology patients living in urban and rural areas. **Methods:** A telephone survey was administered to hepatology patients who had a telehealth visit at our center from 3/20-3/21. Patient characteristics and survey responses were compared by urban and rural location as defined by the census tract based on zip code using Student's T-tests for continuous variables and Chi-Square or Fisher's exact test for nominal variables. Adjusted odds ratios were estimated from multivariable logistic regression models. **Results:** 164 out of 400 patients completed the survey (41%) with a mean age of 64 ± 10 years, 54% male and 75% non-Hispanic white. The most common etiologies of liver disease included alcohol (32%), non-alcoholic steatohepatitis (30%) and hepatitis C (22%). Compared to urban patients, rural patients had twice the transportation time to clinic (59 vs 30 minutes, $p < 0.001$), and were more likely to cancel due to transportation issues (46% vs 13%, $P < 0.001$). Rural patients also reported less proficiency with technology including more technical difficulties, such as less frequent daily computer use (29% vs 67%, $P < 0.001$), logging on to the portal or accessing the camera/microphone (75% vs 25%, $P < 0.001$) and less comfort with their devices (54% vs 9%, $P < 0.001$). (Table 1) Compared to patients who used computers for telehealth, smartphone use (aOR: 6.47, 95% CI: 2.40-19.3) and tablet use for telehealth (aOR: 5.23, 95% CI: 1.87-16.1) were associated with higher likelihood of telehealth visit preference. (Table 2). Overall, similar proportions of rural and urban patients were willing to have telehealth visits in the future (79% vs 86%, $p = 0.26$). However, rural patients were less likely to prefer telehealth compared to urban patients (aOR: 5.20, 95% CI: 2.15-13.7), and were more satisfied with in person visits than urban patients (79.2% vs. 37.9% $P < 0.001$). **Conclusion:** Rural patients reported more technical challenges to telehealth than urban patients. Rural patients favored in person hepatology visits despite having higher drive time and more transportation issues. Research is needed to improve telehealth delivery and satisfaction for rural patients.

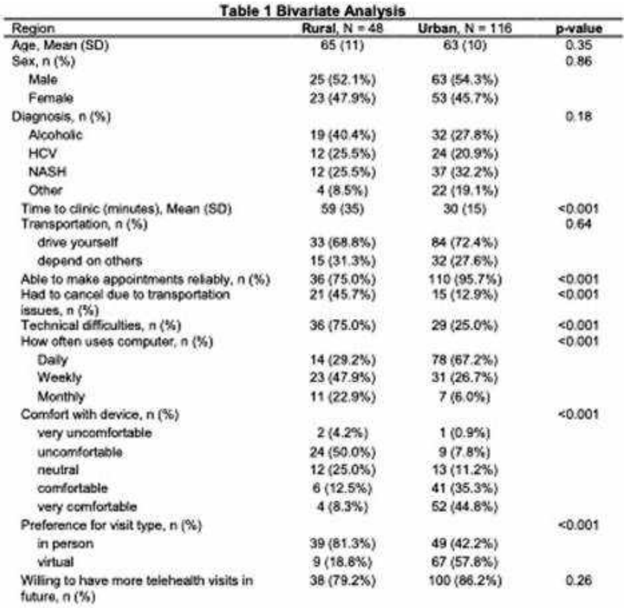

Table 1 Bivariate Analysis

Region	Rural, N = 48	Urban, N = 116	p-value
Age, Mean (SD)	65 (11)	63 (10)	0.35
Sex, n (%)			0.86
Male	25 (52.1%)	63 (54.3%)	
Female	23 (47.9%)	53 (45.7%)	
Diagnosis, n (%)			0.18
Alcoholic	19 (40.4%)	32 (27.8%)	
HCV	12 (25.5%)	24 (20.9%)	
NASH	12 (25.5%)	37 (32.2%)	
Other	4 (8.5%)	22 (19.1%)	
Time to clinic (minutes), Mean (SD)	59 (35)	30 (15)	<0.001
Transportation, n (%)			0.64
drive yourself	33 (68.8%)	84 (72.4%)	
depend on others	15 (31.3%)	32 (27.6%)	
Able to make appointments reliably, n (%)	36 (75.0%)	110 (95.7%)	<0.001
Had to cancel due to transportation issues, n (%)	21 (45.7%)	15 (12.9%)	<0.001
Technical difficulties, n (%)	36 (75.0%)	29 (25.0%)	<0.001
How often uses computer, n (%)			<0.001
Daily	14 (29.2%)	78 (67.2%)	
Weekly	23 (47.9%)	31 (26.7%)	
Monthly	11 (22.9%)	7 (6.0%)	
Comfort with device, n (%)			<0.001
very uncomfortable	2 (4.2%)	1 (0.9%)	
uncomfortable	24 (50.0%)	9 (7.8%)	
neutral	12 (25.0%)	13 (11.2%)	
comfortable	6 (12.5%)	41 (35.3%)	
very comfortable	4 (8.3%)	52 (44.8%)	
Preference for visit type, n (%)			<0.001
in person	39 (81.3%)	49 (42.2%)	
virtual	9 (18.8%)	67 (57.8%)	
Willing to have more telehealth visits in future, n (%)	38 (79.2%)	100 (86.2%)	0.26

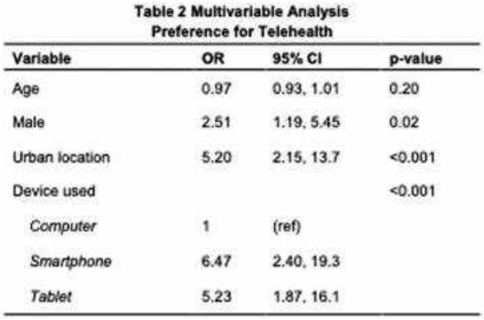

Table 2 Multivariable Analysis
Preference for Telehealth

Variable	OR	95% CI	p-value
Age	0.97	0.93, 1.01	0.20
Male	2.51	1.19, 5.45	0.02
Urban location	5.20	2.15, 13.7	<0.001
Device used			<0.001
Computer	1	(ref)	
Smartphone	6.47	2.40, 19.3	
Tablet	5.23	1.87, 16.1	

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Disclosure information not available at the time of publication: Jonah N. Rubin, Karolina Krawczyk, Cara Joyce

2816-C | PATIENTS WITH HEPATITIS B INFECTION ARE HIGHLY REPRESENTED IN DEPRIVED AREAS, LESS ENGAGED WITH HEALTHCARE AND CAN BE RAPIDLY IDENTIFIED USING A NOVEL CASE-FINDING DATABASE TO HELP ACHIEVE THE CHRONIC HEPATITIS B ELIMINATION 2030 GOAL

Almuthana Mohamed, Christina Owen, John Creamer, Sarah Gormley, Emma Wesley, Daniel Meron and Timothy Jobson, Somerset NHS Foundation Trust

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

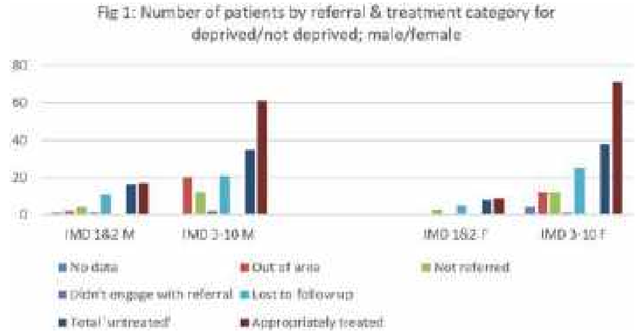
Fig 1: Number of patients by referral & treatment category for deprived/not deprived; male/female

Disclosures: The following people have nothing to disclose: Almuthana Mohamed, Christina Owen, John Creamer, Sarah Gormley, Emma Wesley, Daniel Meron, Timothy Jobson

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

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

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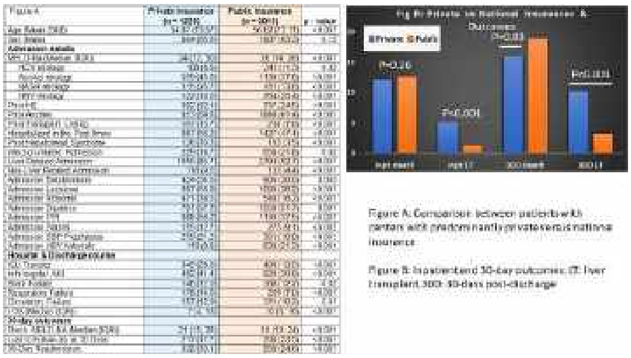
Background: Access to care in cirrhosis is based on insurance in most cases, which could be private (Pvt) or public based on individual centers/countries. However, the role of specific types of insurance on outcomes in a global cohort of cirrhosis inpts is unclear. **Methods**: The CLEARED Consortium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



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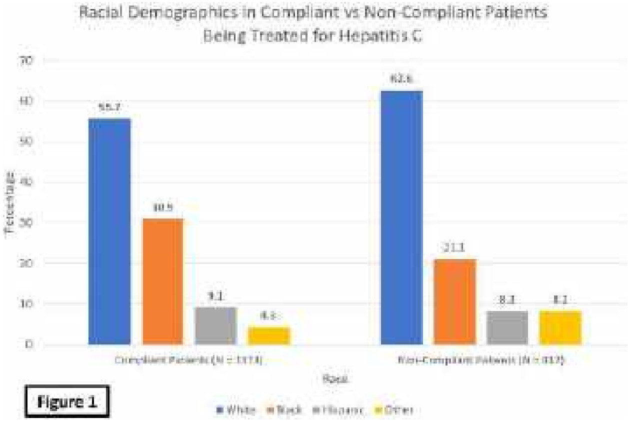
2818-C | RACIAL DISPARITIES IN ADHERENCE TO FOLLOW-UP AND ACHIEVEMENT OF SUSTAINED VIROLOGIC RESPONSE IN PATIENTS INFECTED WITH HEPATITIS C: A TERTIARY CENTER STUDY AND OPPORTUNITIES FOR FURTHER INVESTIGATION

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

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

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

socioeconomic status ($p < 0.001$) and further investigation revealed that many of them also missed several other healthcare appointments, had a history of medical noncompliance, and had difficulties with both transportation and telephone accessibility. Concurrent treatment for opiate use disorder and the presence of psychiatric disorders were also observed in this noncompliant patient population. This demographic was also 1.7 times more likely to have a psychiatric condition [95% CI 1.32-2.06, $p < 0.01$]. **Conclusion:** Race can play a role in follow-up and SVR achievement in HCV patients. However, factors such as psychiatric comorbidities, concurrent drug use, and socioeconomic status may actually act as effect modifiers or prove to be confounding variables. Further investigation is needed in order to pinpoint disparities in HCV treatment among different racial groups.



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2819-C | RACIAL DISPARITIES IN THE OUTCOMES OF HEPATORENAL SYNDROME HOSPITALIZATION: A NATIONAL POPULATION-BASED STUDY

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Background: There are scarce data describing the outcomes of hospitalized patients with hepatorenal syndrome (HRS) stratified by race. In this retrospective cohort study, we evaluated the differences in outcomes, stratified by race, among patients hospitalized with a diagnosis of HRS. **Methods:** Data was obtained from the 2016 to 2020 National Inpatient Sample (NIS) database. Our primary outcome was inpatient mortality while secondary outcomes were hospital length of stay (LOS), total hospital charges (TOTCHG). We conducted the analysis using the STATA software. Multivariate linear and logistic regression analysis was used to adjust for confounders. **Results:** There were 223,590 hospitalizations with a principal or secondary diagnosis of HRS, with blacks having the majority (67%) and the least being native Americans (1.9%). Among patients who were managed in the hospital for HRS, blacks had a 20% increase ($p = <0.01$), Asians had a 25% increase and natives had an 18% increase in the odds of mortality compared to whites, while adjusting for age, hospital bed size and region ($p = 0.01$). When secondary outcomes were assessed, there was significant difference in LOS between the races ($p = <0.01$) with blacks on average having 0.96 day increase in hospital stay, and Hispanics having a 0.6 day increase compared to white. The difference in length of stay in Asians and natives was not significant ($p = 0.055$ & 0.374 respectively). When total hospitalization charges were analyzed, blacks, Hispanics, and Asians had increased charges while natives had lower charges and the difference was significant ($p = 0.000$) **Conclusion:** Our study revealed a significant difference among different races who had HRS during hospitalization, with regards to inpatient mortality, length of stay and total hospital charges. While the reasons for the reasons for these differences are varied, and not fully defined, there is need for concerted effort to mitigate factors known to contribute to health inequality in liver diseases including socioeconomic status, access to health care, environmental and societal factors as well as implicit bias.

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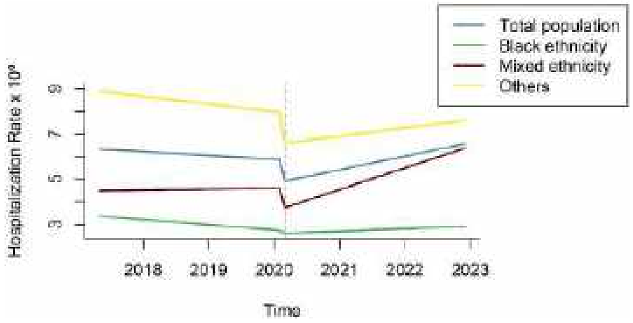
2820-C | RACIAL VARIATIONS IN ALCOHOL-RELATED LIVER DISEASE HOSPITALIZATIONS IN BRAZIL OVER THE COURSE OF COVID-19 PANDEMIC

Daniel Heringer[1], Gabriel Costa[2], Jeremy Weleff[3], Victor Rodrigues[4], Shreya Sengupta[5], Akhil Anand[5] and Srinivasan Dasarathy[6], (1)Universidade De São Paulo, (2)Universidade De Ribeirão Preto, (3)Yale University, (4)Universidade Do Estado Do Rio De Janeiro, (5)Cleveland Clinic, (6)Cleveland Clinic Foundation

Background: Globally, the COVID-19 pandemic increased the incidence and severity of alcohol-associated liver disease (ALD). Racial and social inequalities were magnified worldwide, including in Brazil, worsening health outcomes in minorities. We aim to determine the timely impact of the COVID-19 pandemic on ALD hospitalization rates for different ethnic groups in Brazil. **Methods:** We analyzed ALD related hospitalizations from Brazil's public health database from May 2017 to December 2022. Interrupted time series regression was used to model the association between the pandemic's emergence and monthly total ALD related hospitalizations and monthly total ALD related hospitalizations by four ethnic subgroups: Black, Mixed Ethnicity, Black and Mixed Ethnicity combined, and Others (White and Unknown Ethnicity). We obtained 34 data points before COVID-19 and 34 data points afterwards. **Results:** There were 84,787 ALD related hospitalizations during the study period. The mean age of hospitalized patients was 54 years, and 83.6% were male. The mean length of hospital stay was 8.6 days. After March 2020, at the start of the COVID-19 pandemic, there was a significant increase in ALD monthly hospitalization rates for the total population (0.065, 95% CI = 0.045 to 0.085, $p < 0.01$), Black population (0.0028, 95% CI = 0.006 to 0.050, $p < 0.05$), Mixed Ethnicity population (0.077, 95% CI = 0.063 to 0.090, $p < 0.01$), and for Mixed Ethnicity + Black population (0.066, 95% CI = 0.053 to 0.079, $p < 0.01$). The only subgroup that did not show a significant increase in hospitalizations was the Others subgroup population (0.059, 95% CI = -0,014 to 0.133, $p > 0.1$). The in-hospital mortality rate was 19.4% among the total population, which was evenly distributed among ethnicities, the rates for each being Black 19.49%, Mixed Ethnicity 18.80%, White 20.20% and Unknown Ethnicity 18.97%. **Conclusion:** The COVID-19 pandemic has led to increases in ALD hospitalizations. The rise in ALD hospitalizations was only significant in the Black and Mixed Ethnic, the poorest subpopulations in Brazil. This study aligns with existing literature suggesting the pandemic has accelerated health disparities and outcomes. Further studies are required to understand the impact of the pandemic on social, racial, and healthcare inequalities.



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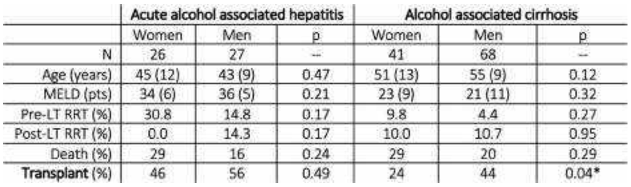
Disclosure information not available at the time of publication: Daniel Heringer, Gabriel Costa, Jeremy Weleff

2821-C | SEX OR INDICATION: DIFFERENCES IN LT ACCESS IN MEN AND WOMEN UNDERGOING LTE FOR ACUTE ALCOHOL ASSOCIATED HEPATITIS VS CHRONIC ALCOHOL LIVER DISEASE

Katherine M. Cooper[1], Alessandro Colletta[2] and Deepika Devuni[1], (1)UMass Chan Medical School, (2) UMass Chan Medical School, Worcester, MA

Background: Women have with liver disease often have poorer outcomes than men including increased death with acute on chronic liver failure and decreased access to liver transplant. However, few studies have compared outcomes in men versus women with acute alcohol associated hepatitis (AAH). We sought to evaluate sex differences in outcomes in patients with AAH compared to alcohol associated cirrhosis being evaluated with early sobriety (< 6 mos). We hypothesized that women would have worse outcomes than men and that the relative disparity in LT rate would persist in each group as the MELD scoring system is used for allocation in both sets of patients. **Methods:** Patients completing LTE with early sobriety between 2018 and 2021 were included. Patients were categorized by chronicity of ALD: cirrhosis from ALD (cALD) vs. alcohol associated hepatitis (aALD). To identify sex differences in outcomes of AAH, we compared variables in men (M) vs. women (W) with aALD and cALD, respectively. We also compared variables within sex to identify the effect of disease chronicity on outcomes in men and women. **Results:** 162 patients were identified (67 women, 95 men) of which 33% were being evaluated with AAH. A higher percentage of women were evaluated for AAH compared to men, though not to a significant degree (39% vs. 28%, $p = 0.16$). Use of steroids for aALD was similar in men and women (73% vs. 82%, $p = 0.47$). In the aALD cohort, there were no sex differences in MELD score (34 W vs. 36M), LT rate (46% W vs. 56% M, $p = 0.49$) or death at 1 year (29% W vs. 16% M, $p = 0.24$). In the cALD cohort, MELD score and 1 year death rate did not differ by sex (29% W vs. 20% M, $p = 0.29$) but women were transplanted less than men (24% W vs.44% M, $p = 0.04$). Renal replacement therapy (RRT) at the time of LTE was the most common in women with aALD, though this was not statistically more than men. There were no sex differences in post-LT renal replacement therapy for aALD at 6 months ($p = 0.17$) or 12 months ($p = 0.17$)) or for cALD at 6 months ($p = 0.95$) or 12 months ($p = 0.85$). In women, aALD did not affect risk of death but was associated with 250% increased odds of LT compared to cALD. On multivariable logistic regression controlling for age and MELD, sex was a statistically significant predictor of transplant the cALD group ($p = 0.03$) but not in the aALD group ($p = 0.74$). **Conclusion:** In contrast to our hypothesis, LT outcomes for men and women with AAH were similar. We also observed reduced sex-based disparity in LT in the aALD group relative to cALD despite similar MELD scores between sexes with aALD, though these MELD scores were notably higher than the cALD group. Efforts to understand sex-based disparities in LT and improve access for women may be augmented by evaluating the AAH LT pathway and studying nationwide trends in AAH may inform practices to improve outcomes in women.



	Acute alcohol associated hepatitis			Alcohol associated cirrhosis		
	Women	Men	p	Women	Men	p
N	26	27	--	41	68	--
Age (years)	45 (12)	43 (9)	0.47	51 (13)	55 (9)	0.12
MELD (pts)	34 (6)	36 (5)	0.21	23 (9)	21 (11)	0.32
Pre-LT RRT (%)	30.8	14.8	0.17	9.8	4.4	0.27
Post-LT RRT (%)	0.0	14.3	0.17	10.0	10.7	0.95
Death (%)	29	16	0.24	29	20	0.29
Transplant (%)	46	56	0.49	24	44	0.04*

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f 2822-C | SOCIODEMOGRAPHIC DISPARITIES AND LIVER DISEASE IN SARCOPENIC PATIENTS

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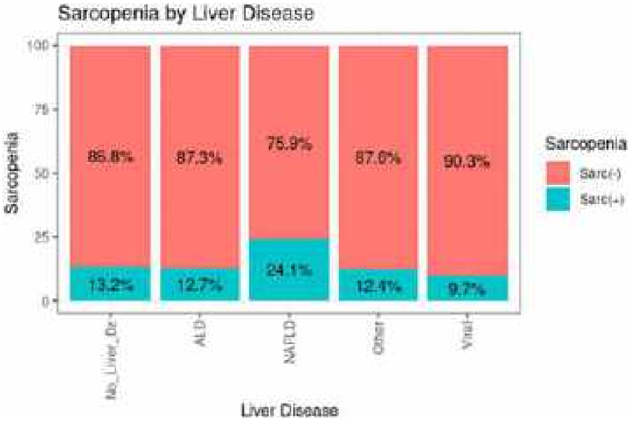
Background: Sarcopenia, a disease of low muscle mass, is common in patients with liver disease and is associated with poor outcomes. Treatment of sarcopenia involves a multi-disciplinary approach of nutrition and exercise. There are many sociodemographic, behavioral, and medical aspects that have been associated with sarcopenia, however these factors have not been fully investigated in patients with liver disease. Aim: To determine demographic and socioeconomic associations in the development of sarcopenia in patients with liver disease. **Methods:** A cohort of adults from the National Health and Nutrition Examination Survey (NHANES) 1999-2006 was analyzed. Subjects were classified as having liver disease based on aminotransferase levels as previously described. Sarcopenia was defined using appendicular lean mass (obtained by Dual-energy X-ray Absorptiometry, DEXA) adjusted for body mass index (BMI). Due to missing and invalid DEXA data, NHANES employed multiple-imputation methodology to provide complete and representative data. All analyses were conducted separately on each multiple imputation data set and combined via Rubin's rules. *P*-values for group comparisons were calculated by testing logistic regression parameter estimates. Cox proportional hazards regression was used for mortality analysis with mortality data available until 2015. **Results:** Of 16,072 subjects, 8,734 had liver disease and 807 subjects with liver disease had sarcopenia. Sarcopenia (HR 1.36), liver disease secondary to alcohol (HR 1.24) and viral hepatitis (HR 1.75), male sex (HR 1.54), age (HR 1.08), household income < 75 K (HR 1.63-1.99), and all levels of education less than a college degree (HR 1.60-2.13) were associated with increased mortality. Liver disease of other causes was associated with reduced mortality (HR 0.83). In a multivariate composite model, the following factors were associated with sarcopenia: Non-alcoholic fatty liver disease (NAFLD) (OR 1.68), male sex (OR 1.24), age (OR 1.05), Mexican American race (OR 3.03), other Hispanic race (OR 1.91), race other than White (OR 1.50), household income < 75 K (OR 1.57-1.72), and levels of education less than a college degree (OR 1.38-1.97). Black patients had less sarcopenia compared to non-Hispanic White patients (OR 0.25). **Conclusion:** There are multiple sociodemographic disparities in the development of sarcopenia. Patients with NAFLD are at higher risk of sarcopenia than patients with other etiologies of liver disease.



Disclosures: The following people have nothing to disclose: Camille A. Kezer, Vijay Shah, Douglas A. Simonetto

Disclosure information not available at the time of publication: Puru Rattan, Ryan Lennon, Blake Kassmeyer, Patrick S. Kamath

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

2823-C | THE COVID-19 PANDEMIC WORSENED DELAYS FOR HISPANIC PATIENTS REFERRED FOR LIVER TRANSPLANT

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Background: The pathway to liver transplant (LT) is a complex, stepwise process involving referral, evaluation, and waitlisting. Prior studies have identified disparities post-listing, but there is a paucity of data on inequities further upstream in the LT cascade. Our aim was to identify disparities underlying the LT referral and evaluation phases in relation to the COVID-19 pandemic. **Methods:** We performed a retrospective cohort study of adult patients referred for LT at a large transplant center during periods defined as pre-COVID (6/1/2018-5/31/2019) and COVID (6/1/2020-5/31/2021) eras. Referral phase (RP) was defined as time from LT referral to start of evaluation, and evaluation phase (EP) as time from evaluation start to waitlisting. Factors associated with delays in RP were identified using a Cox proportional hazard model; factors associated with delays in EP were identified using a Fine-Gray hazard model, with clinical recovery and drop out treated as competing risks. **Results:** In total, 712 patients were referred for LT during the study period (358 pre-COVID, 354 COVID). 61% were men, and the cohort was racially and ethnically diverse (52% White, 32% Hispanic, 10% Black). Of those referred, 544 (76%) started evaluation and 329 (46%) were ultimately waitlisted. Referral: Hispanic patients had longer RP compared to White patients (median 28.0 vs 22.5 d) after adjusting for covariates listed in Table 1 (HR 0.72, 95% CI 0.57–0.91). Presence of cardiometabolic risk factors was also associated with longer RP. Female sex, inpatient referral, MELD-Na > 25, and education level less than high school correlated with shorter RP (Table 1). Evaluation: Adjusting for covariates, Hispanic patients also had longer EP versus White patients (median 27.0 vs 21.0 d) in the COVID era (HR 0.58, 95% CI 0.36–0.93), but not in the pre-COVID era. Patients with college degrees and hepatocellular carcinoma had shorter EP in the COVID era only. Older age was associated with longer EP in both eras. **Conclusion:** Disparities in time to LT evaluation and waitlisting were exacerbated by the COVID-19 pandemic. Hispanic patients experienced longer wait time to start LT evaluation following referral compared to White counterparts, and also took longer to be waitlisted during COVID. Our data call for heightened monitoring of steps in the LT referral and evaluation process, and interventions are needed to ensure equitable and timely access to LT for underrepresented minority populations.

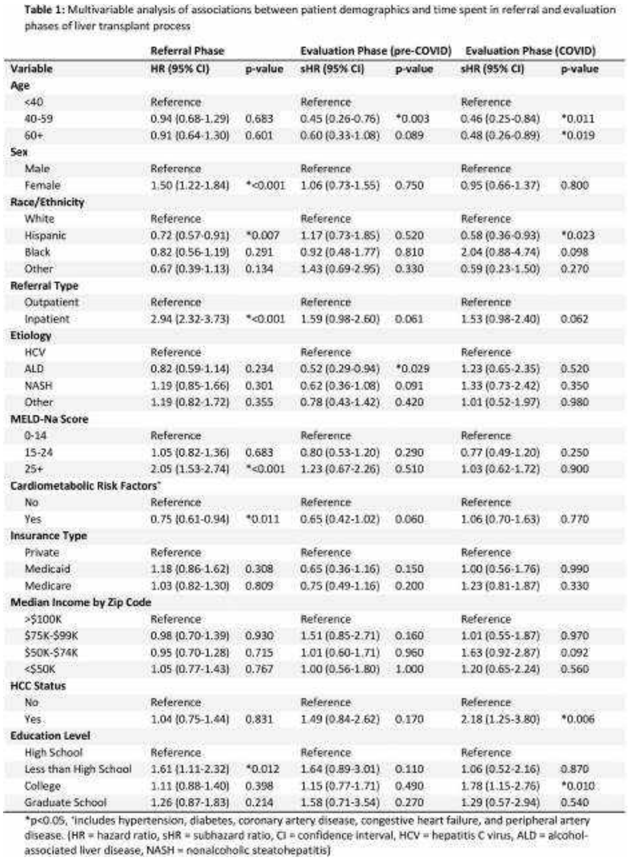

Table 1: Multivariable analysis of associations between patient demographics and time spent in referral and evaluation phases of liver transplant process

	Referral Phase		Evaluation Phase (pre-COVID)		Evaluation Phase (COVID)	
Variable	**HR (95% CI)**	**p-value**	**sHR (95% CI)**	**p-value**	**sHR (95% CI)**	**p-value**
Age						
<40	Reference		Reference		Reference	
40-59	0.94 (0.68-1.29)	0.683	0.45 (0.26-0.76)	*0.003	0.46 (0.25-0.84)	*0.011
60+	0.91 (0.64-1.30)	0.601	0.60 (0.33-1.08)	0.089	0.48 (0.26-0.89)	*0.019
Sex						
Male	Reference		Reference		Reference	
Female	1.50 (1.22-1.84)	*<0.001	1.06 (0.73-1.55)	0.750	0.95 (0.66-1.37)	0.800
Race/Ethnicity						
White	Reference		Reference		Reference	
Hispanic	0.72 (0.57-0.91)	*0.007	1.17 (0.73-1.85)	0.520	0.58 (0.36-0.93)	*0.023
Black	0.82 (0.56-1.19)	0.291	0.92 (0.48-1.77)	0.810	2.04 (0.88-4.74)	0.098
Other	0.67 (0.39-1.13)	0.134	1.43 (0.69-2.95)	0.330	0.59 (0.23-1.50)	0.270
Referral Type						
Outpatient	Reference		Reference		Reference	
Inpatient	2.94 (2.32-3.73)	*<0.001	1.59 (0.98-2.60)	0.061	1.53 (0.98-2.40)	0.062
Etiology						
HCV	Reference		Reference		Reference	
ALD	0.82 (0.59-1.14)	0.234	0.52 (0.29-0.94)	*0.029	1.23 (0.65-2.35)	0.520
NASH	1.19 (0.85-1.66)	0.301	0.62 (0.36-1.08)	0.091	1.33 (0.73-2.42)	0.350
Other	1.19 (0.82-1.72)	0.355	0.78 (0.43-1.42)	0.420	1.01 (0.52-1.97)	0.980
MELD-Na Score						
0-14	Reference		Reference		Reference	
15-24	1.05 (0.82-1.36)	0.683	0.80 (0.53-1.20)	0.290	0.77 (0.49-1.20)	0.250
25+	2.05 (1.53-2.74)	*<0.001	1.23 (0.67-2.26)	0.510	1.03 (0.62-1.72)	0.900
Cardiometabolic Risk Factors[†]						
No	Reference		Reference		Reference	
Yes	0.75 (0.61-0.94)	*0.011	0.65 (0.42-1.02)	0.060	1.06 (0.70-1.63)	0.770
Insurance Type						
Private	Reference		Reference		Reference	
Medicaid	1.18 (0.86-1.62)	0.308	0.65 (0.36-1.16)	0.150	1.00 (0.56-1.76)	0.990
Medicare	1.03 (0.82-1.30)	0.809	0.75 (0.49-1.16)	0.200	1.23 (0.81-1.87)	0.330
Median Income by Zip Code						
>$100K	Reference		Reference		Reference	
$75K-$99K	0.98 (0.70-1.39)	0.930	1.51 (0.85-2.71)	0.160	1.01 (0.55-1.87)	0.970
$50K-$74K	0.95 (0.70-1.28)	0.715	1.01 (0.60-1.71)	0.960	1.63 (0.92-2.87)	0.092
<$50K	1.05 (0.77-1.43)	0.767	1.00 (0.56-1.80)	1.000	1.20 (0.65-2.24)	0.560
HCC Status						
No	Reference		Reference		Reference	
Yes	1.04 (0.75-1.44)	0.831	1.49 (0.84-2.62)	0.170	2.18 (1.25-3.80)	*0.006
Education Level						
High School	Reference		Reference		Reference	
Less than High School	1.61 (1.11-2.32)	*0.012	1.64 (0.89-3.01)	0.110	1.06 (0.52-2.16)	0.870
College	1.11 (0.88-1.40)	0.398	1.15 (0.77-1.71)	0.490	1.78 (1.15-2.76)	*0.010
Graduate School	1.26 (0.87-1.83)	0.214	1.58 (0.71-3.54)	0.270	1.29 (0.57-2.94)	0.540

*p<0.05, [†]includes hypertension, diabetes, coronary artery disease, congestive heart failure, and peripheral artery disease. (HR = hazard ratio, sHR = subhazard ratio, CI = confidence interval, HCV = hepatitis C virus, ALD = alcohol-associated liver disease, NASH = nonalcoholic steatohepatitis)

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The following people have nothing to disclose: Ritodhi Chatterjee, Ruben Hernaez, Fasiha Kanwal, George Cholankeril, Tzu-Hao (Howard) Lee

Disclosure information not available at the time of publication: Karthik Goli, Jeong Woo Han, Chun-Sing Huang, John A. Goss

f 2824-C | TRANSPORTATION BARRIERS MAY IMPACT EVALUATION TIME AMONG LIVER TRANSPLANT CANDIDATES: A PROSPECTIVE STUDY

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Background: Access to transportation is a vital component of the transplantation process, yet transportation barriers are not well characterized in the adult liver transplant (LT) population. We examined sociodemographic qualities of LT candidates with transportation barriers and impact on time to completion of LT evaluation. **Methods:** Consecutive patients at Keck

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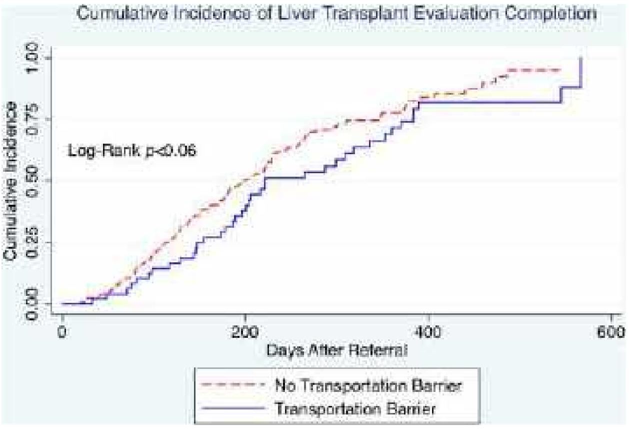
Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

USC Liver Transplant clinic at initial LT visit were approached to complete a survey between 11/1/2021-12/19/22. The 40-item multi-lingual survey assessed: 1) access to transportation, 2) transportation barriers, 3) technology access, and 4) social determinants of health (SDOH). We defined transportation barrier as reporting one of the following: unreliable transportation, some/a lot of trouble getting to clinic visits, or missing visit due to transportation. Sociodemographic differences between those with and without barriers were described. We then examined the relationship between presence of transportation barrier and time to completion of LT evaluation (=referral date to selection committee date) using Kaplan-Meier analysis. **Results:** Of 219 patients surveyed, 51 (23.3%) reported transportation barriers (41.7% surveyed in Spanish vs 14.7% in English). 92.7% owned a car with the vast majority either driving oneself or being driven to clinic visits. 5.9%, 4.1%, and 5.9% reported using public transport, rideshares/taxis, and medical transport, respectively. Few (<5%) reported the cost of gas or parking as significant barriers; 31.9% reported their usual driver sometimes not being available, 88.9% of the time due to work. Those with transportation barriers (vs none) had more negative SDOH indicators ($p < 0.05$): no car (13.7% vs 4.2%), unsteady living situation (28.0% vs 10.2%), food insecurity (54.9% vs 15.6%), financial stress (62.7% vs 41.7%), high school education (71.4% vs 53.2%), not employed (91.8% vs 75.6%), and non-private insurance (86.0% vs 66.5%). They were also more likely to be foreign-born (82.4% vs 53.6%), non-citizens (58.8% vs 27.3%), and not married (58.0% vs 39.2%) ($p < 0.05$). There was a trend towards longer time to LT evaluation completion among those with transportation barriers (median 151 d vs 134 d; see Figure). **Conclusion:** In this prospective cohort of LT candidates, nearly 1 in 4 reported experiencing transportation barriers, which may result in delays in completion of their evaluation. Providing transportation support may be one strategy to improve LT outcomes.



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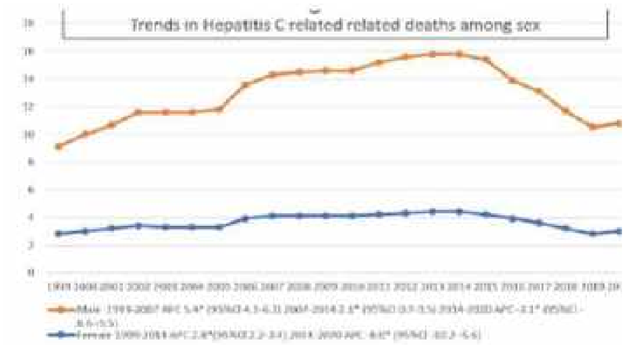
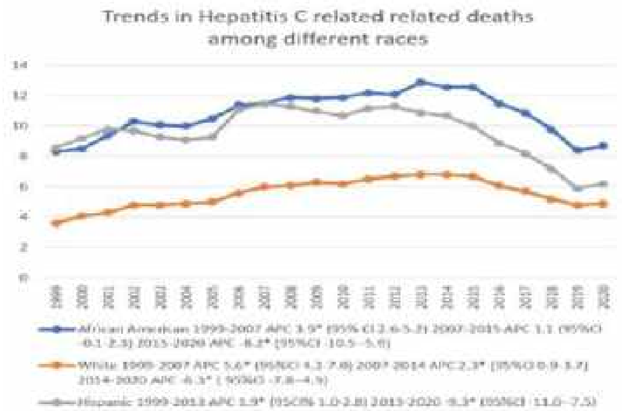
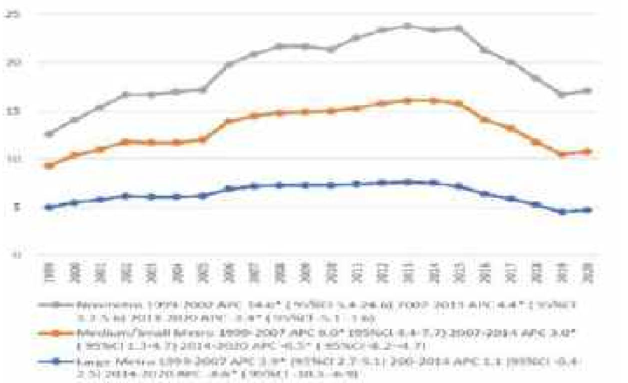
2825-C | TRENDS IN HEPATITIS C-RELATED MORTALITY AMONG ADULTS IN THE UNITED STATES FROM 1999-2020

Yousaf Zafar[1], *Omar Rizwan Sheikh*[1], *Adnan Zafar*[2], *Arsalan Zafar Iqbal*[1], *Isaac Dodd*[1], *Laila Manzoor*[1] *and Jan Petrasek*[3], *(1)University of Mississippi Medical Center, (2)Magnolia Regional Heath Center, (3)Texas Liver Institite*

Background: Hepatitis C Virus (HCV) is the most common blood-borne infection in the United States, and a leading cause of liver disease, transplant, and mortality. When curative direct-acting antiviral medications for hepatitis C became available in 2014, hepatitis C elimination became a realistic goal. The CDC goal is to reduce HCV-related mortality by 65% (from 2015) by 2030. **Methods:** We sought to identify temporal, geographic, age and sex-based mortality trends of HCV-related deaths in the US over the past 2 decades. This population-based study utilized the CDC WONDER database to identify hepatis C-related deaths occurring within the US between 1999 and 2020. HCV-related crude and age-adjusted mortality rates (CMRs and AAMRs, respectively) were determined. Join point regression was used to determine trends in CMR/AAMR using annual percent change (APC) in the overall sample in addition to demographic (sex, race/ethnicity, age) and geographic (rural/urban, statewide) subgroups. **Results:** Between 1999 and 2020, a total of 324,008 deaths related to HCV were reported. The overall AAMR increased from 2.9/100,000 in 1999 to 4.3/100,000 in 2020. Although the AAMR have declined since 2014, Men remain 2.5 times more predisposed to HCV related deaths compared to females. African Americans remain more predisposed than other ethnic groups and non-metro areas more than urban setting despite trends showing an overall improvement in the mortality rates from HCV related deaths. District of Colombia, Oregon, California, and Oklahoma largely affected. **Conclusion:** Hepatitis C-related CMR/AAMR were observed more among men, African Americans, and those from rural areas although trends have been decreasing in all groups likely due to HCV therapy. Discerning the reasons for the differences in Hepatitis C-related mortality among these groups and examining the impact of the social determinants of heath may represent important opportunities to enhance care.







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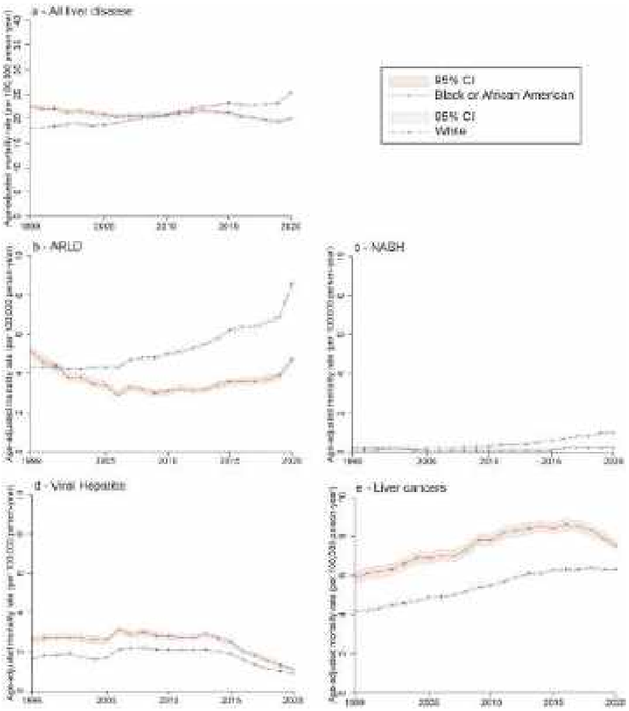
Disclosure information not available at the time of publication: Omar Rizwan Sheikh

2826-C | TRENDS IN LIVER DISEASE MORTALITY AMONG AFRICAN AMERICAN AND WHITE POPULATIONS IN THE UNITED STATES, 1999-2020

Yuting Huang[1], *Yichen Wang*[2] *and Liu Yang*[1], *(1)Mayo Clinic Florida, Ponte Vedra Beach, FL, (2)Trinity Health of New England*

Background: Liver disease is a significant public health concern in the United States, with notable disparities in mortality rates between different racial groups. This study aims to analyze the trends in liver disease mortality among African American and White populations between 1999 and 2020, and to explore the differences in mortality patterns by age, census region, and urbanization levels. **Methods:** We utilized the CDC WONDER database to ascertain age-adjusted liver-related mortality rates in Black and White Americans from 1999 to 2020. Liver-related mortality was defined as cases where the cause of death was liver disease. Linear regression analysis was employed to calculate the annual percent change (APC). Age-adjusted absolute rate difference and rate ratio were computed by subtracting and dividing the White population's rate from that of the Black population. The 95% confidence interval for these measures was estimated using the normal approximation method. **Results:** Between 1999 and 2020, liver diseases accounted for 171,627 Black and 1,314,903 White deaths. Age-adjusted mortality rates for African Americans decreased from 22.5 to 20.1 per 100,000 person-years (APC -0.4%, 95% CI -0.6% to -0.2%), whereas an increase was observed for Whites, from 17.9 to 25.3 per 100,000 person-years (APC 1.4%, 95% CI 1.4% to 1.7%). The absolute rate difference in 1999 was 4.6 (95% CI 4.2 to 5.0) and in 2020 it was -5.2 (95% CI -5.4 to -5.0). Correspondingly, the rate ratio decreased from 1.26 (95% CI 1.22 to 1.29) in 1999 to 0.79 (95% CI 0.78 to 0.81) in 2020. This pattern was evident in all census regions except the Midwest, more pronounced among younger (age 25-64) than older (age 65+) population, and observed across different urbanization levels. The pattern may be attributable to increasing alcohol-related liver disease and NASH-related deaths in Whites and tapering in viral hepatitis and liver cancer-related deaths in African Americans. **Conclusion:** Our findings reveal a concerning increase in liver disease mortality rates among White populations and a reassuring decline in African American populations from 1999 to 2020. This pattern is partially due to shifts in causes of liver-related deaths, with reductions in viral hepatitis and deceleration in liver cancer-related deaths in African Americans and increased alcohol-related liver disease and NASH in Whites. In light of these findings, targeted public health interventions and policies addressing racial group-specific needs are crucial.



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2827-C | TRENDS OF CHRONIC LIVER DISEASES BY INCOME LEVEL AND SOCIOECONOMIC FACTORS IN THE U.S. NATIONAL POPULATION

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Background: With polarizing income disparities between the top 20% and remaining 80% of the U.S. population, quality of healthcare may be prone to risk. By investigating the prevalence of chronic liver disease (CLD) based on income to poverty ratio and trends over time, we aimed to determine the impact of socioeconomic status on liver health risks. **Methods:** We combined data from 10 survey cycles (1999-2018) in NHANES. To model the existing 20-80 national divide observed in income groups, we divided participants into high- and lower-income groups by their income to poverty ratio using the cut-off point of 5 as it gave the closest proportion: 25-75. **Results:** Our study included 59,204 adult participants. 44,462 (75.1%) had an income to poverty ratio < 5 (lower-income) and 14,742 (24.9%) had ³5 (higher-income). The weighted prevalence of HCV, HBV, NAFLD, and ALD in lower-income groups were 2.2% (n = 876), 5.5% (n = 2,200), 33.8% (n = 4,345), and 4.7% (n = 2,086), respectively compared to lower rates in higher-income groups: 1.0% (n = 82), 3.2% (n = 263), 29.6% (n = 798), and 3.9% (n = 354). Lower-income groups had higher odds of having history of any CLD (odds ratio (OR), 1.22; 95% CI, 1.08—1.37; P = 0.001), when adjusted for age, sex, race and ethnicity, education, and country of birth. The same trend was observed for history of HCV infection (OR, 2.03; 95% CI, 1.46—2.81, P < 0.0001), HBV infection (OR, 1.47; 95% CI, 1.26—1.72; P < 0.0001), and NAFLD (OR, 1.17; 95% CI, 1.02—1.35; P = 0.030). From 1999 to 2018, lower-income groups had higher rates of viremic HCV infection (P < 0.0001), viremic HBV infection (P = 0.016), NAFLD (P < 0.0001), and AFLD (P < 0.0001) than higher-income groups. In terms of CLD prevalence trends over time, we found higher rates of viremic HCV infection (HCV antibodies positive and HCV-RNA present) in lower-income groups than higher-income groups (P < 0.0001). For current HBV infection (HBsAg positive), no clear trend over time was observed, but lower-income groups exhibited higher prevalence than higher-income groups (P = 0.016). However, prevalence of NAFLD and AFLD increased over time (NAFLD lower-income, P = 0.001; AFLD higher-income, P = 0.04) with similar disparities between income groups. (Figure 1) **Conclusion:** The prevalence of 4 major CLDs significantly differed between higher- and lower-income groups from 1999 to 2018. Recently in 2017-2018, higher median liver stiffness also highlighted the more advanced liver disease in lower-income groups, demonstrating the impact of poverty and socioeconomic factors on the prevalence and severity of liver diseases of various etiologies.

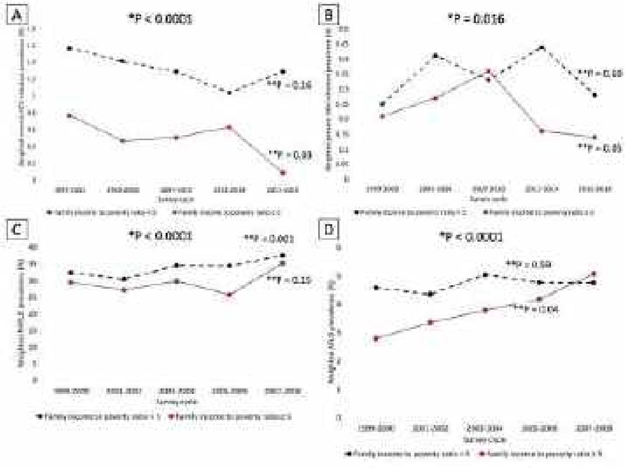

Figure 1. Trends in Prevalence of (A) viremic HCV infection, (B) present HBV infection, (C) NAFLD, and (D) ALD, by income group over time

*P for comparisons between the two income groups
**P for comparisons among time periods within each income group

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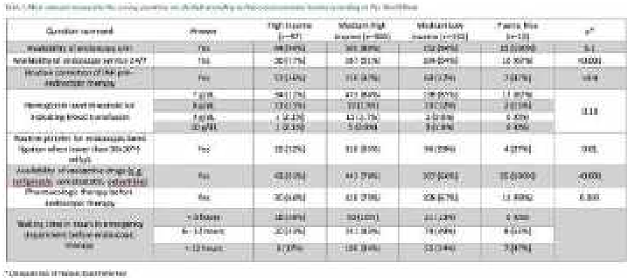
2828-C | UNCOVERING INSIGHTS ON ACUTE VARICEAL HEMORRHAGE: A CROSS-COUNTRY SURVEY STUDY ON THE MANAGEMENT OF UPPER GASTROINTESTINAL BLEEDING IN LATIN AMERICA

Josealberto Sebastiano Arenas-Martinez[1], Jesús Alejandro Ruiz Manríquez[2], Wagner Enrique Ramirez Quesada[3], Antonio Olivas Martinez[4], Luis C Chávez-García[2], Erick Jasso-Baltazar[5], Thamy Leidy Beltré-González[6], José Carlos Ticona-Pérez[7], Karla Avendano[8], Venny Alberto Venegas Gomez[2], Carlos Alonzo Garcia[9], Maria Fernanda Vasquez-Carit[10], Juanita Perez-Escobar[11], Godolfino Miranda Zazueta[12], Graciela Elia Castro-Narro[13] and Luis Eduardo Zamiora-Nava[2], (1)Instituto Nacional De Ciencias Medicas y Nutricion, (2)Instituto Nacional De Ciencias Medicas y Nutricion Salvador Zubirán, (3)Clínica Equilibrium, (4)University of Washington, (5)Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán, (6)Centro Médico Real Gastro-Metrics, (7) Hospital Regional Honorio Delgado, (8)Hospital Monte Sinaí, (9)Clínica Integra Medical Center, (10)Sistema De Estudios De Posgrado, Universidad De Costa Rica, (11)Hospital Juárez De México, (12)Instituto Nacional De Ciencias Médicas y Nutrición "Salvador Zubirán", (13)Medica Sur Clini

Background: Acute variceal hemorrhage (AVH) is a serious complication of portal hypertension and is associated with high mortality and high cost. Limited information exists regarding AVH management accessibility in Latin America (LATAM).This study aims to gather data on AVH management and resource availability across LATAM. The goal was to bridge the knowledge gap, enhance medical attention, and optimize specialized care for patients with AVH in the region. **Methods:** A survey was conducted using Microsoft Forms with recruitment via social media invitations and collaboration with local medical associations. It gathered data on demographics, clinical practices, and specialized resource availability. The LATAM countries were classified based on economic development (World Bank's classification system). Variables are described using percentages or medians and interquartile ranges and compared among socioeconomic regions using a X^2 test or analysis of variance as appropriate. **Results:** In total, 798 respondents from 20 LATAM countries completed the survey. The median age was 39 years, with 80% attending specialists, 14% residents, and 6% fellows. Countries were represented by 6% high-income, 72% upper-middle income, and 21% lower-middle income populations. Gastroenterology (62%) was the predominant specialty followed by internal medicine (23%), gastrointestinal endoscopy (18%), and hepatology (18%). Tertiary care centers accounted for 45% of the participants' primary activities, followed by second-level care (30%) and private practice (21%). As for the existence of endoscopy suites, there were no differences between surveyed countries but their availability 24/7 remains higher in high income countries. The availability of vasoactive drugs correlated with economic development. The detailed findings are presented in Table 1. **Conclusion:** In LATAM, the absence of standardized protocols, limited resources, and expertise pose challenges in AVH management. Enhancing access to specialized care and implementing standardized protocols is crucial to improve patient outcomes in the region.



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2829-C | ADVOCATING FOR ACTION IN HCC TO DELIVER IMPARTIAL AND PERSONALIZED CARE: AN OBSERVATIONAL HEALTH EQUITY TOOL PILOT STUDY

Jocelyn Timko, Linda Gracie-King, Marc Viens and Victor Ocana, AXIS Medical Education

Background: Hepatocellular carcinoma (HCC) incidence and mortality rates have risen among American Indian/ Alaska Native, Hispanic, and Black populations in the US, and are expected to increase in older populations due to hepatitis C, cirrhosis, obesity, diabetes, and non-alcoholic steatohepatitis. Screening and surveillance of these conditions occur less often in many Hispanic and Black populations, delaying HCC diagnosis. The project reviewed health disparities, inequities, and care variations with an aim to improve health equity using a customized Observational Health Equity Tool (OHET). The tool was designed to help identify a baseline of data that supports or refutes whether bias exists during HCC treatment encounters. Observations were scored from 0 = no effort to 4 = exemplary effort. **Methods:** The OHET Pilot Study was implemented at 3 US cancer centers. AXIS provided training and a customized manual for the observer on how to administer and score the observations. AXIS hypothesized that an OHET can assist clinicians in: (1) identifying baseline data that supports or refutes whether bias exists during treatment encounters, and (2) overcoming potential implicit bias and health disparities in HCC treatment planning. This activity was provided by AXIS and supported by education grants from Genentech and Exelixis. **Results:** Data from the 3 sites was collected from 30 patients with HCC, (minority cohort n = 10; non-minority n = 20). Observations proved inconclusive because the observers in all 3 sites failed to include the sensitive question asking whether the patient has experienced prior discrimination regardless of their race or ethnicity. This lack of data reinforces that a patient's race influences the patient/provider interaction. This is further compounded by the small sample size of minority patients. **Conclusion:** The OHET proved inconclusive in determining whether bias exists during treatment encounters, primarily due to poor survey administration and observer bias. The data suggested that the survey model failed to consider the likelihood that all survey questions would not be completed in one discrete encounter. The OHET may be better suited as a longitudinal study following a larger number of overall patients and more than one encounter. While this study proved inconclusive, it produced the insight that providers need to ask the difficult questions related to discrimination and bias.

Disclosures: The following people have nothing to disclose: Jocelyn Timko, Linda Gracie-King, Marc Viens, Victor Ocana

2830-C | ASSESSMENT OF THE METABOLIC HEALTH OF YOUNG INDIANS (18-25 YEARS) - AN INTERIM ANALYSIS OF PILOT PHASE I PROJECT ON STRONGER INDIA THROUGH A MILLION HEALTH EDUCATED STUDENTS (SMILES)

Kanica -[1], Priyanka Shenoy[1], Guresh Kumar[1] and Shiv Kumar Sarin[2], (1)Institute of Liver and Biliary Sciences, New Delhi, (2)Institute of Liver and Biliary Sciences

Background: Young adults are now known to be quite prone to develop fatty liver, NAFLD, heart attack or various Non Communicable Diseases (NCDs) like diabetes and hypertension. Much of the rise in such situations at young age is attributed to lifestyle changes like ultra-processed foods, reduced physical activity and increasing substance abuse in the Gen Z. SMilES (Stronger India through a Million Health Educated Students) initiative is designed to touch base with at least a million young adults in the age range of 18-25 years in India, to understand various risk factors for Fatty Liver and other NCDs amongst them. **Methods:** An online, pre tested, closed ended, self-assessment questionnaire under the mandate of 'Healthy Liver Healthy India' was administered to the young adults to screen for the most important risk factors for fatty liver and other NCDs with the help of trained epidemiologist through an on-line supervised survey. The initiative was started as a pilot study in New Delhi and is now planned for national implementation through various college networks. We aim to target one million college students of India between the age range of 18- 25 years to screen for the presence of risk of developing NCDs and fatty liver and to risk stratify them into Red (High risk), Yellow (Moderate risk) and Green (Low Risk) in Phase I. **Results:** Starting January 2023, we enrolled 4060 young adults across New Delhi. The grouping category was calculated using discriminant analysis and it was found that proportions in Red, Yellow and Green are 11%, 20.8% and 68.3% respectively. Further the cut offs for the score that we obtained from these variables using CART (Classification and Regression Tree) analysis came out be < 11 for green, 11-14 for yellow and > 14 for red. This was based on the scoring of factors as gender, BMI (17% obese, 12.2% overweight), waist circumference (39.2% action group II), presence of acanthosis nigricans (9.4%), personal and family history of thyroid (1.1%; 17.2%)/ Diabetes (7.9%; 26%)/ hypertension (2.4%; 30.6%)/ liver disease (1.7%; 8.7%)/ PCOS (3.1%; 2.1%)/ dyslipidaemia (10.5%)/ gallstones (7.7%)/ cancers (2.5%)/ cardiovascular diseases (5.7%), diet factors (non veg (52.2%)/ fast food (96.7%)/ sweets (92.4%)), smoking tobacco (3.9%), smokeless tobacco (1%), alcohol (5.6%) and physical activity of less than 150 minutes/week (54.3%). **Conclusion:** Our initial results show that nearly one in three young Indians has a moderate or high risk of metabolic diseases, with a predisposition to those with a positive family history of metabolic traits. Nearly all the interviewed subjects were consuming fast food and sweets with relatively less physical activity in half. A larger data set on the health stats of the young will help us to develop strategies for phase II, where interventions to reduce the proportion of red and yellow category of subjects will be undertaken.

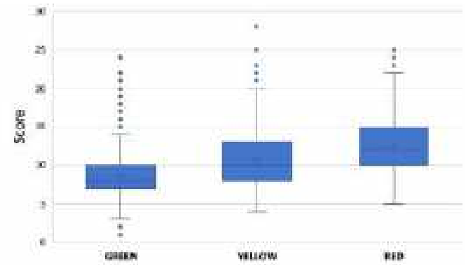

Figure 1.: Box and Whisker plot for risk stratification for fatty liver among Young Indians (18- 25 years) (n= 4060)

Disclosures: The following people have nothing to disclose: Kanica -, Priyanka Shenoy, Guresh Kumar, Shiv Kumar Sarin

f 2831-C | AWARENESS OF SIGNIFICANT LIVER FIBROSIS IN PATIENTS WITH NAFLD DIFFERS ACROSS ETHNICITIES

Fernando Bril and Meagan Gray, University of Alabama at Birmingham

Background: Non-alcoholic fatty liver disease (NAFLD) is a rapidly rising cause of liver fibrosis in the United States, however awareness amongst patients remains low. Previous reports suggest that the awareness of liver disease amongst Non-Hispanic Blacks is lower than other ethnicities, which may contribute to health disparities in this population. The purpose of this study is to evaluate the awareness of liver disease amongst patients with clinically significant or advanced fibrosis secondary to NAFLD across ethnic groups. **Methods:** Data were derived from the National Health and Nutrition Examination Surveys (NHANES) 2017-2020, which included a total of 7,767 adults with valid transient elastography (TE) measurements. Participants with excessive alcohol consumption, alternative etiologies of liver disease, and/or steatogenic medications were excluded. Patients of multiracial origin or without ethnic information were also excluded. Liver stiffness measurements e 8.2 and e 9.7 kPa were used to define the presence of significant (e F2) and advanced (e F3) fibrosis, as previously reported. Awareness of liver disease was assessed based on a positive response to "ever told you had any liver condition" on the Medical Conditions Questionnaire. **Results:** A total of 6,365 adults were included after secondary causes of liver disease were excluded; 50% male, 24.7% Hispanic, 35.2% Non-Hispanic White, 27.0% Non-Hispanic Black, and 13.1% Non-Hispanic Asian. The prevalence of clinically significant fibrosis was 8.7% (n = 555) and advanced fibrosis was 3.0% (n = 342) based on TE. The awareness of liver disease amongst patients with clinically significant fibrosis was highest in the Hispanic population and lowest in the Non-Hispanic Black population (p = 0.008) (Table 1). Amongst patients with advanced fibrosis, knowledge of liver disease was similar across ethnic groups, although numerically lower in Non-Hispanic Black patients (Table 1). **Conclusion:** In a large diverse national dataset, awareness of liver disease in patients with clinically significant or advanced fibrosis secondary to NAFLD was low across all ethnic groups. However, in subjects with clinically significant fibrosis, awareness was significantly lower among Non-Hispanic Black patients. Efforts to increase awareness of NAFLD and its risk to progress to fibrosis and cirrhosis are encouraged across all ethnic groups.

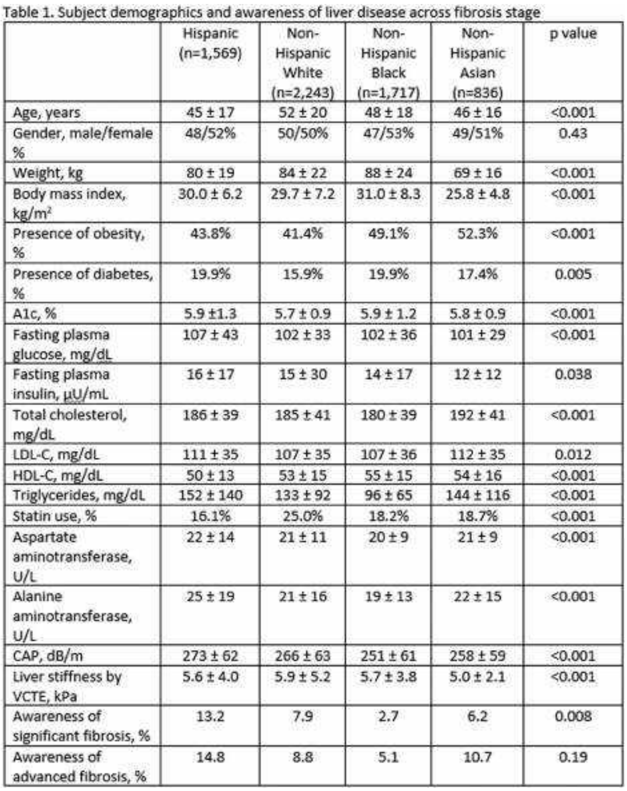

Table 1. Subject demographics and awareness of liver disease across fibrosis stage

	Hispanic (n=1,569)	Non-Hispanic White (n=2,243)	Non-Hispanic Black (n=1,717)	Non-Hispanic Asian (n=836)	p value
Age, years	45 ± 17	52 ± 20	48 ± 18	46 ± 16	<0.001
Gender, male/female %	48/52%	50/50%	47/53%	49/51%	0.43
Weight, kg	80 ± 19	84 ± 22	88 ± 24	69 ± 16	<0.001
Body mass index, kg/m²	30.0 ± 6.2	29.7 ± 7.2	31.0 ± 8.3	25.8 ± 4.8	<0.001
Presence of obesity, %	43.8%	41.4%	49.1%	52.3%	<0.001
Presence of diabetes, %	19.9%	15.9%	19.9%	17.4%	0.005
A1c, %	5.9 ±1.3	5.7 ± 0.9	5.9 ± 1.2	5.8 ± 0.9	<0.001
Fasting plasma glucose, mg/dL	107 ± 43	102 ± 33	102 ± 36	101 ± 29	<0.001
Fasting plasma insulin, µU/mL	16 ± 17	15 ± 30	14 ± 17	12 ± 12	0.038
Total cholesterol, mg/dL	186 ± 39	185 ± 41	180 ± 39	192 ± 41	<0.001
LDL-C, mg/dL	111 ± 35	107 ± 35	107 ± 36	112 ± 35	0.012
HDL-C, mg/dL	50 ± 13	53 ± 15	55 ± 15	54 ± 16	<0.001
Triglycerides, mg/dL	152 ± 140	133 ± 92	96 ± 65	144 ± 116	<0.001
Statin use, %	16.1%	25.0%	18.2%	18.7%	<0.001
Aspartate aminotransferase, U/L	22 ± 14	21 ± 11	20 ± 9	21 ± 9	<0.001
Alanine aminotransferase, U/L	25 ± 19	21 ± 16	19 ± 13	22 ± 15	<0.001
CAP, dB/m	273 ± 62	266 ± 63	251 ± 61	258 ± 59	<0.001
Liver stiffness by VCTE, kPa	5.6 ± 4.0	5.9 ± 5.2	5.7 ± 3.8	5.0 ± 2.1	<0.001
Awareness of significant fibrosis, %	13.2	7.9	2.7	6.2	0.008
Awareness of advanced fibrosis, %	14.8	8.8	5.1	10.7	0.19

Disclosures: Meagan Gray – NovoNordisk: Consultant, No, No; Theratechnologies, Inc: Consultant, No, Yes; Takeda Pharmaceuticals: Consultant, No, Yes;
Disclosure information not available at the time of publication: Fernando Bril

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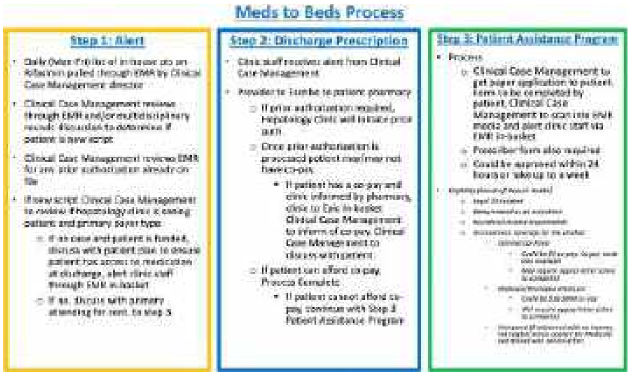
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

2832-C | CLEARING THE PATH: IMPROVING RIFAXIMIN ACCESS FOR LIVER PATIENTS AND EVALUATING IMPACT ON HOSPITAL READMISSION

Daniel Cain[1], Sommer Smith[2], Apurva A. Modi[3] and Shovendra Gautam[1], (1)TCU School of Medicine/ Baylor All Saints – Internal Medicine Residency Program, (2)Baylor Scott & White All Saints Medical Center, Forth Worth, TX, (3)Baylor Simmons Transplant Institute, Forth Worth, TX

Background: Hepatic Encephalopathy (HE) is a debilitating complication of chronic liver disease and accounts for roughly 55,000 hospitalizations each year. Rifaximin is known to decrease hospitalizations for patients with HE. Access to rifaximin has been a barrier to many due to the high cost associated with the medication. We describe a quality improvement project conducted in a real-world cohort which led to successful and timely access to rifaximin to patients with access barriers. **Methods:** This project is a prospective observational study on cohort of patients at an academic institution with a large transplant center with barriers in access to rifaximin. The method used was the classic Plan Do Check Act (PDCA) cycle. Data was collected from July 2021 through September 2022. This was accomplished by creating an EMR tool to identify patients who were prescribed rifaximin and then coordinating between the inpatient providers and outpatient hepatology clinic to ensure prior authorization (PA) or a prescription assistance program (PAP) was completed when required and that a follow-up was arranged. **Results:** A total of 258 patients were included in the current study after being identified as having inpatient prescriptions for rifaximin. 49 (18.9%) patients were identified as needing a referral to the hepatology outpatient clinic staff and potentially requiring a PA, 28 (10.85%) patients required a PA, 13 (5%) patients required a PAP, and 5 (1.9%) required a PAP after a PA was approved. All 28 (100%) patients in need of a PA and the 13 (100%) in need of a PAP received approval and were able to get a prescription for rifaximin filled, which was the primary goal of the project. Regarding the secondary goal of decreasing 30-day readmission rate, 9/28 (32%) of the PA patients were readmitted within 30 days of discharge. 3/28 (11%) of these patients were readmitted due to HE. 6/28 (21%) PA patients had a prior history of being readmitted within 30 days of discharge prior to the start of this project. Even after obtaining PAs, all 6/6 of these patients were readmitted within 30 days, 2/6 (33%) of them being for HE. **Conclusion:** The primary goal was to improve patients' access to rifaximin, which was achieved with 100% success for those requiring a PA or PAP. The secondary goal of reducing 30-day readmissions (all cause all conditions) was not successful, though further monitoring will continue. In conclusion, prioritizing PA processing prior to discharge is highly recommended to ensure patients with a history of HE with access to this morbidity-preventing medication.



Meds to Beds Process

Step 1: Alert

Step 2: Discharge Prescription

Step 3: Patient Assistance Program

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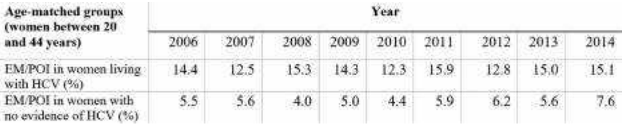
2833-C | EARLY MENOPAUSE AND PRIMARY OVARIAN INSUFFICIENCY IN WOMEN WITH AND WITHOUT CHRONIC HEPATITIS C: A RETROSPECTIVE OBSERVATIONAL STUDY OF WOMEN IN THE UNITED STATES

Harriet Dickinson, Sohul Shuvo, Laura E. Telep, Lauren Liu and Annalisa Rubino, Gilead Sciences, Inc.

Background: Women living with chronic hepatitis C (HCV) are believed to have an elevated risk of early menopause (EM, i.e. menopause before the age of 45) or primary ovarian insufficiency (POI, i.e. menopause between the ages of 20-39). EM and POI are associated with several deleterious effects including infertility and osteoporosis. It is also thought that women living with HCV may experience worse menopausal symptoms compared to their uninfected peers. In this study we aim to understand the proportion of women who experience EM/POI in cohorts of HCV infected and uninfected women, and whether women with HCV experience worse menopausal symptoms. **Methods**: This is a retrospective observational cohort study of administrative healthcare claims data for women aged 20-44 insured by commercial plans in the United States from 01 Jan 2006 to 31 Dec 2021. Two age-matched cohorts of women with and without evidence of HCV were created to estimate the proportion of EM/POI during 2006-2014 (i.e. during the ICD9 era). Later, among all available women with EM/POI, two unmatched cohorts of women with or without HCV between 2006 and 2020 were also formed. **Results**: The proportion of women with EM/POI was 14.2% in women living with HCV, and 5.5% in age-matched women without HCV between 2006-2014. Among women with HCV, the proportion with POI was 9.6% and EM 4.6%. Among women with no evidence of HCV, the proportion with POI was 3.7% and EM 1.8%. In the unmatched cohorts with EM/POI, those with HCV had higher levels of obesity before EM/POI diagnosis (11.9%), compared to women without evidence of HCV (7.7%). HCV-infected women had higher levels of vasomotor symptoms (13.5% versus 8.9%), osteoporosis (3.9% versus 0.7%) and incontinence (5.6% versus 2.6%) than uninfected women within 365 days of their initial EM/POI diagnosis. The use of hormone replacement therapy (HRT) was low in both cohorts, with $< 1.5\%$ of women receiving treatment within 365 days of EM/POI onset. **Conclusion**: Nearly one in seven women living with HCV aged 20-44 had a diagnosis for EM/POI, compared to one in 18 women without HCV. Women in the HCV cohort had higher prevalence of negative symptoms associated with EM/POI than in the non-HCV cohort. The treatment of women with EM/POI with HRT was found to be extremely low, highlighting opportunities for further treatment discussions. Such conclusions may inform treatment provisions for women living with HCV. Women with EM/POI should also be screened for HCV.



Age-matched groups (women between 20 and 44 years)	Year								
	2006	2007	2008	2009	2010	2011	2012	2013	2014
EM/POI in women living with HCV (%)	14.4	12.5	15.3	14.3	12.3	15.9	12.8	15.0	15.1
EM/POI in women with no evidence of HCV (%)	5.5	5.6	4.0	5.0	4.4	5.9	6.2	5.6	7.6

Disclosures: Harriet Dickinson – Gilead: Employee, Yes, No; Gilead: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;
Sohul Shuvo – Gilead: Employee, Yes, No;
Laura E. Telep – Gilead Sciences, Inc.: Employee, No, No; Gilead Sciences, Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
Lauren Liu – Gilead: Employee, Yes, No; Gilead: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;
Annalisa Rubino – Gilead: Employee, Yes, No; Gilead: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

2834-C | ELIMINATING HCV INFECTION FROM PRISONS IN SICILY: THE SINTESI PROJECT

Fabio Cartabellotta[1,2], Lorenza Di Marco[2,3], Fabio Santangelo[2], Fabrizio Scalici[4], Rosario Insinna[4], Tullio Prestileo[2,5], Maria Giovanna Minissale[1,2], Vincenza Calvaruso[2,6], Antonio Craxì[2] and Vito Di Marco[2,6], (1) Department of Medicine Buccheri -La Ferla Hospital, Palermo, Italy, (2)Sicilian Network for Therapy, Epidemiology and Screening in Hepatology (SINTESI), Italy, (3)Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Moderna, Italy, (4)Medical Area of the "Pagliarelli-Lorusso" Prison, Palermo, Italy, (5)Uosd Infectious Pathologies of Vulnerable Populations, Arnas-Civico Hospital, Palermo, Italy, (6)Gastroenterology & Hepatology Unit, Department of Health Promotion, Mother & Child Care, Internal Medicine & Medical Specialties (PROMISE), University of Palermo, Palermo, Italy

Background: In all countries HCV among prisoners has a higher prevalence than in the general population. Specific models of screening and linkage to care are needed to improve the care cascade. **Methods:** The SIcilian Network for Therapy, Epidemiology and Screening In Hepatology (SINTESI) run an HCV point-of-care project in all 23 prisons of Sicily. All prisoners received information on HCV screening and the possibility of receiving treatment with Direct Acting Antiviral (DAA) while incarcerated. HCV status was assessed by screening all subjects for anti-HCV by rapid oral test (OraQuick HCV) and immediate reflex testing for HCV-RNA (GeneXpert-HCV Viral Load, Cepheid). HCV RNA positive subjects received DAA therapy within 72 hours of screening. All prisoners signed an informed consent to use personal data. Chi-square test was used to analyze differences between groups **Results:** Among 5,912 prisoners (98% of entire prison population) informed of the screening project, 4,911 (83%) accepted to undergo HCV testing. The mean age was 42 years (range 18-86) and 95.8% was males. Non-Italian origin accounted for 12.2% of prisoners (3.7% other EU countries, 7.5% Africa, 0.6% Asia and 0.2% South America). Overall, 245 subjects (5%) testes anti HCV positive, with a prevalence of 4.9% among males and 6.7% among females ($p = 0.25$). We evaluated the risk of drug addiction in subjects with HCV infection in a prison. A prevalence of 25% (25/99) was found among PWUDs on opioid substitution, as compared to 2.9% (30/1,040) in non-PWUDs ($p < 0.0001$). Among 245 anti HCV positive prisoners, 20 refused to be tested for HCV-RNA, 100 tested negative (80 had a history of viral clearance under previous DAA treatment while 20 did not report previous therapy for HCV) and 125 were HCV-RNA positive. Twelve of the latter refused treatment, while 113 started a cycle of DAAs while incarcerated. Among 56 subjects assessable for SVR, 55 (98%) obtained HCV clearance. **Conclusion:** In Sicily, HCV infection is 4 times more common among people in prison than in the general population mostly due to parenteral drug use. Half of the prisoners with a positive screening were unaware of their HCV status and only 32% had received DAAs previously. A one shot HCV test-and-treat point-of-care approach is highly effective in this setting. The project was approved by the Regional Department of Health and the Regional Department of Prisons and was funded by HCV STAT (Simplification and Test and Treat Strategies toward HCV Elimination) program of Gilead Sciences

Disclosures: The following people have nothing to disclose: Fabio Cartabellotta, Lorenza Di Marco, Fabio Santangelo, Fabrizio Scalici, Rosario Insinna, Tullio Prestileo, Maria Giovanna Minissale, Vincenza Calvaruso, Antonio Craxì, Vito Di Marco

2835-C | ESTABLISHMENT OF A COMMUNITY-ACADEMIC PARTNERSHIP TO ENHANCE EQUITABLE RESEARCH PRACTICES WITH PEOPLE WHO INJECT DRUGS

Claire McDonell, Maia Scarpetta, Aanchal Narang, Ryan Assaf and Meghan Morris, UCSF

Background: People who inject drugs (PWID) are a socially marginalized population underrepresented in all levels of academic research. Establishing partnership between researchers and community members who work directly with PWID improves research rigor and equitable research and clinical approaches. However, outside of formal community-based participatory research (CBPR), there is limited literature discussing formation and evaluation strategies of community-research partnerships focused on PWID. **Methods:** Using principles from CBPR, we established a Community Academic Partnership group (CAP) to inform the development, implementation, interpretation, and dissemination of a randomized clinical study of hepatitis C virus (HCV) treatment initiation for young adult PWID (YPWID). An inductive member-guided approach informed CAP membership and group structure, norms and success indicators. **Results:** CAP members met monthly for the first 6-months and quarterly thereafter, indefinitely. Members represented academic institutions (n = 4), CBOs (n = 5) and YPWID (n = 2) and held roles including research assistance, outreach, case management, and senior leadership. The majority identified as cis-female (56%) and nonbinary (22%). A majority of members (56%) identified as white or Latino/a/x (33%). Results from the Measurement Approaches to Academic Partnership Success (MAPS) questionnaire indicated members prioritized four dimensions of success (in ranked order): valuing community knowledge, valuing opinions and experiences of individual members when working together, involving community partners throughout the research process, and addressing conflicts collaboratively. A history of positive collaboration among members and partners' commitment to group priorities were ranked as least important dimensions. Meetings were deemed worthwhile in the short-term due to food and honorarium provided, witnessing progress, and respectful engagement. Members viewed long-term CAP success as bringing the community's voice to the research process, demystifying research, and tailoring research to the needs of young PWID. **Conclusion:** Extending CBPR approaches to the process of forming and establishing a CAP requires willingness to share ownership of the CAP with all members and results in collaboration models that prioritize knowledge sharing and amplify historically marginalized voices.

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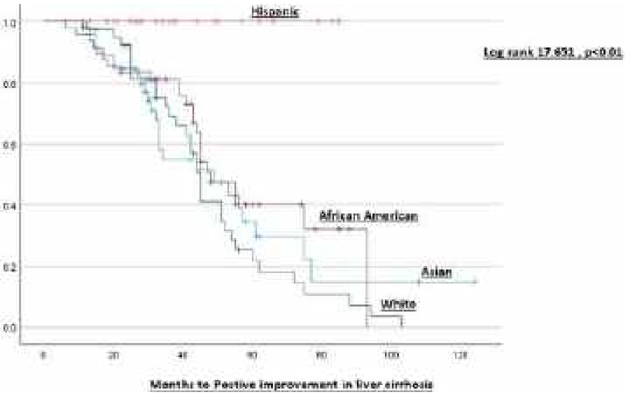
2836-C | ETHNICITY AND ITS EFFECT ON LIVER CIRRHOSIS REMISSION IN POST-BARIATRIC PATIENTS

Rajmohan Rammohan[1], Sai Greeshma Magam[1], Melvin Joy[2], Dilman Natt[1], Achal Patel[1], Abhishek Tadikonda[1] and Paul Mustacchia[3], (1)Nassau University Medical Center, (2)Nassau University Medical Center, East Meadow, NY, (3)Nassau Univeristy Medical Center

Background: The impact of race on fatty liver disease outcomes in post-bariatric surgery patients is a vital yet understudied area of research. Racial and ethnic differences in genetic, metabolic, and lifestyle factors have been observed to influence disease progression and response to treatment. Notably, certain racial groups may exhibit a higher propensity for developing fatty liver disease post-surgery, impacting prognosis and management strategies. Understanding these racial disparities can significantly enhance personalized care, improving liver health outcomes for all post-bariatric surgery patients **Methods:** Our study conducted a retrospective analysis of patients undergoing bariatric surgery at our institution from 2009-2022. We gathered extensive data, including comorbidities, insurance, pre-and post-surgery Fibrosis scores, pathology reports, and baseline characteristics using ICD and CPT codes. A 20% Fibrosis score improvement was marked as positive, with duration calculated from surgery day. Propensity score matching allowed baseline characteristic comparison. We used Kaplan Meier estimations to determine the improvement of liver cirrhosis among races and the Odds ratio to identify factors independently influencing the outcome **Results:** Our hospital conducted 960 bariatric surgeries from 2009-2022. Among these, 165 patients (17%) with pre and post-surgery fibrosis scores were studied. Fibrosis scores improved in 81 patients (8.1%), averaging 40.59 ± 20.76 months post-surgery. The average age was 50.29 ± 12.17, with females constituting 52%. The racially diverse cohort included 30.3% African American, 24.8% White, 48% Asian, and 17.5% Hispanic. Asians (29%) took the longest to show liver cirrhosis improvement (log-rank Mantel cox: 17.651, $p < 0.01$). Patients with higher education demonstrated faster cirrhosis improvement (OR:1.23, $P = 0.015$) **Conclusion:** Our study reveals racial disparities in post-bariatric surgery fatty liver disease outcomes. Among 165 analyzed patients, 8.1% saw improved fibrosis scores post-surgery, with Asians taking the longest to show cirrhosis improvement. Additionally, higher education patients improved more quickly, suggesting a socioeconomic influence on health outcomes. These insights call for further research on genetic, metabolic, and lifestyle influences to enhance personalized care strategies



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2837-C | FOOD INSECURITY POTENTIATES THE RISK OF NAFLD AMONG THOSE OF HISPANIC ANCESTRY: A NATIONALLY REPRESENTATIVE STUDY

Sebastian Niezen[1], Daniela Goyes[2], Aarshi Vipani[3], Ju Dong Yang[4], Walid S. Ayoub[4], Alexander Kuo[4], Michelle Long[5] and Hirsh Trivedi[4], (1)University of Pittsburgh Medical Center, (2)Yale University Medical Center, New Haven, CT, United States, (3)Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, CA, (4)Cedars-Sinai Medical Center, Los Angeles, CA, (5)Section of Gastroenterology, Evans Department of Medicine, Boston University School of Medicine

Background: Food insecurity, or inadequate access to nutritious food, is prevalent to Hispanic households that contributes to metabolic risk. A growing body of evidence has demonstrated an association between food insecurity and NAFLD. However, the association between these factors in individual's with Hispanic ancestry remains unknown. We aim to evaluate the influence of food insecurity on Hispanic ethnicities risk of NAFLD. **Methods:** We used data from the 2017-2020 pre-pandemic cycle of National Health and Nutrition Examination Survey (NHANES). Our analysis was restricted to participants aged 20 years and older who underwent VCTE. Food security status was assessed utilizing the US Food Security Survey Module. Data was obtained through questionnaire, physical examination, and laboratory tests. We constructed multivariable linear and ordinal logistic regression models to determine the association between Hispanic ethnicity and both LSM and CAP for fibrosis and steatosis, respectively. Covariates included age, sex, income, BMI, type 2 diabetes, food security, and education level. We posteriorly stratified our population based on reported food security status and re-constructed the models. As sensitivity analysis we excluded those who reported binge drinking (5+ drinks for men and 4+ drinks for women daily). **Results:** Among 6,945 eligible participants, individual's with Hispanic ancestry had higher CAP scores (275.4 ± 61.8 dB/m) compared to non-Hispanic individual's (261.4 ± 61.9 dB/m). Under multivariable analysis, those with Hispanic ancestry had significantly higher CAP scores (Beta-coefficient: 10.2 dB/m, 95% CI: 6.1 – 14.4 dB/m, $P = 0.001$). After stratifying based on food security status, both food-secure and food-insecure individual's of Hispanic ancestry demonstrated stronger association with steatosis compared to non-Hispanics. After stratifying based on food security status, the association in food insecure Hispanics was most pronounced (Beta-coefficient: 11.8 dB/m, 95% CI: 4.4- 19.3 dB/m, $P = 0.003$). The association remained significant after excluding binge drinkers (Beta-coefficient: 10.5 dB/m, 95% CI: 5.7 – 15.4, $P < 0.001$). No significant association was observed for LSM on either analysis. **Conclusion:** The prevalence of food insecurity is increasing nationally, particularly among Hispanic populations. Food insecurity potentiates the risk of NAFLD among those of Hispanic ancestry.

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2838-C | HEPATOCELLULAR CARCINOMA MANAGEMENT IN A MULTIDISCIPLINARY CLINIC IMPROVES CARE IN POPULATIONS IMPACTED BY HEALTH DISPARITIES

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Background: Health disparities affect morbidity and mortality due to Hepatocellular Carcinoma (HCC). The multidisciplinary model of HCC management has shown survival benefit but the effect on patients impacted by disparities is not well-established. This study compares outcomes among patients with HCC as differentiated by 1 – treatment in a multi-disciplinary clinic or standard of care; 2- socioeconomic factors associated with disparate care. **Methods:** A retrospective chart review assessed patients with HCC at the University of California, San Diego Medical Center from 2016 to 2022. Data were compared between patients seen in the multi-disciplinary (MDD) and control Hepatology clinics. Patients were summarized by demographic factors and metrics related to disease stage and medical care. Treatment and outcome measures were compared using the chi-square test for categorial variables or Fisher's exact test for groups with low proportions. **Results:** A total of 304 patients comprised the MDD ($n = 204$) and control ($n = 100$) cohorts of which 32.4% and 41.0% were of Hispanic origin, respectively. More Hispanic compared to non-Hispanic patients met metrics associated with disparate care, such as under-insurance (MDD cohort: 53.0% vs. 35.0%; $p = 0.022$). MDD compared to control patients had advanced disease (median T-stage: T2 vs. T1; $p < 0.0005$, BCLC stage: B vs. A; $p < 0.0005$). MDD patients had fewer missed appointments (27.0% vs. 60.0%; $p < 0.0005$), loss to follow up (7.8% vs. 22.0%; $p < 0.0005$) and shorter time to treatment after intake (median days 33.0 (IQR 15.0-55.0) vs. 68.5 (46.5-99.5); $p < 0.0005$). MDD Hispanic patients had fewer missed appointments (30.3% vs. 58.5%; $p < 0.001$), loss to follow-up (6.1% vs. 22.0%; $p < 0.05$) and time to treatment (median days 38.0 (IQR 21.25-61.5) vs. 68.5 (44.5-118.5); $p = 0.001$) compared to control Hispanic patients. Intervals from diagnosis to treatment (median days 63.0 (IQR 33.0-140.0) vs. 73.0 (51.0-112.0); $p = 0.234$) and referral to intake (median days 16.0 (IQR 11.5-27.0) vs. 18.0 (9.0-31.5); $p = 0.864$) were comparable. The latter was longer among MDD Hispanic patients (median days 21.0 vs. 15.0; $p < 0.05$). **Conclusion:** The MDD model facilitated timely initiation of therapies in patients with HCC, closer engagement in care, and was protective against loss to follow-up, including among Hispanic patients. Patients referred to the MDD clinic had advanced disease and were slow to establish care. Future efforts should encourage early primary provider referrals and address barriers to intake.

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Disclosure information not available at the time of publication: Kelli Liu, Kathryn Fowler, Zachary Berman, Tanya Wolfson, Jesse Nodora, Yuko Kono

2840-C | INNOVATIVE MODELS TO GUIDE EQUITABLE VIRAL HEPATITIS HEALTH DEPARTMENT PROGRAMS

Zakiya Grubbs and Jasmine West, Nastad

Background: The increasing burden of viral hepatitis, limited resources, and rapid turnover at health departments (HD) has highlighted the need to build HD capacity and strengthen collaborations grounded in health equity and harm reduction for people who inject drugs (PWID). Since 2019, NASTAD has implemented the Hepatitis Technical Assistance Center (HepTAC) for HD viral hepatitis prevention and surveillance staff by providing technical assistance (TA) and hosting the Virtual Learning Collaborative (VLC). TA requests range from epidemiology and surveillance to medication access to

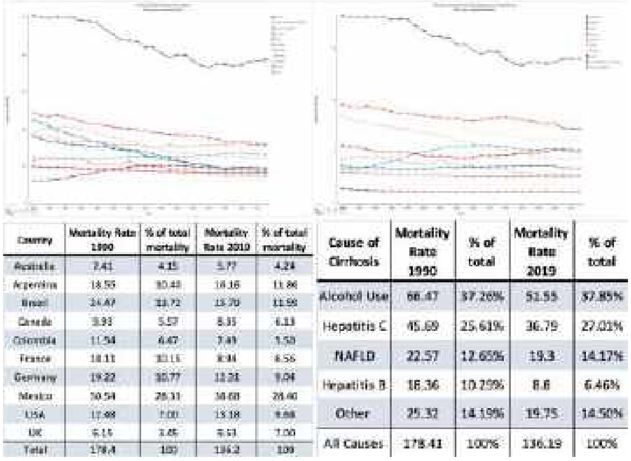
strategic planning. NASTAD hosts VLC didactic presentations, moderated discussions, and workshops led by HD staff i.e. equitable approaches to data collection; engaging non-traditional partners and people with lived experience (PWLE); removing restrictions to hepatitis treatment. NASTAD continues to address intersecting health inequities, and in 2022 established the Hepatitis Network for Education and Testing (HepNET), a network of HD government and community partners focused on addressing the unmet needs of PWIDs to improve access to viral hepatitis services. Through the monthly HepNET Learning Communities (LC), the Leading with Lived Experience Consultants provides TA to 3 jurisdictions to improve testing and linkage to care strategies for PWID with a commitment to racial justice and health equity. **Methods:** NASTAD uses a mixed methods approach to evaluate the effectiveness of these models to increase HD knowledge and capacity to implement a range of hepatitis services. Surveys and focus groups are utilized to garner feedback for improvement. **Results:** Between August 2019 and October 2022, HepTAC received 153 TA requests where 92% of survey respondents learned new information and 82% have already used this information in their work. From VLC sessions from August 2021 to July 2022, 94% of survey respondents found the sessions applicable to their work, 95% learned something new, and 85% are prepared to apply what they learned. Participants in VLC focus groups reiterated the usefulness of the sessions and opportunities to learn from peers. Similarly, the HepNET LC assessment demonstrated that 90% of participants are somewhat or very satisfied with the LC activities (February to April 2023), and awareness of intersectional identity and the multiple ways PWIDs are marginalized increased by 75%. **Conclusion:** Through engagement with HepNET and HepTAC models, HD staff have increased knowledge to implement key viral hepatitis strategies and develop tools to equitably engage PWLE. This multi-modal approach has proven responsive to the changing needs of HDs with limited resources and has advanced health equity in HD programming.

Disclosures: The following people have nothing to disclose: Zakiya Grubbs, Jasmine West

2841-C | MORTALITY RATES DUE TO CIRRHOSIS OF THE LIVER IN WESTERN COUNTRIES: 1990 TO 2019

Noel Balli[1], Connor Yost[1], Cathleen Kuo[2] and Kamalani Hanamaikai[1], (1)A. T. Still University School of Osteopathic Medicine in Arizona, (2)University of Buffalo

Background: Cirrhosis of the liver is a prevalent cause of death globally, with the most common contributors being Hepatitis B, Hepatitis C, alcohol consumption, and non-alcoholic fatty liver disease. The objective of this study is to examine the mortality rates associated with liver cirrhosis in ten major Western nations from 1990 to 2019. **Methods:** The Global Burden of Disease Database provided the data for this study, which investigated the age-standardized mortality rates linked to cirrhosis and other chronic liver ailments in ten Western countries (Australia, Argentina, Brazil, Canada, Colombia, France, Germany, Mexico, the United Kingdom, and the United States). **Results:** Of the ten countries examined in this study, eight have experienced a decline in mortality rates per 100,000 individual's linked to cirrhosis and other chronic liver conditions over the last three decades. Mexico had a disproportionately high mortality rate compared to the other nine countries included in the study, accounting for 28.33% of the ten-country total mortality rate in 1990, and 28.40% in 2019. Our analysis also investigated the various factors responsible for cirrhosis, including hepatitis B, hepatitis C, alcohol consumption, non-alcoholic fatty liver disease (NAFLD), and other causes. Among these, alcohol use had the highest proportion of deaths attributable to liver cirrhosis in 2019 at 37.85%, followed by hepatitis C (27.01%), NAFLD (14.17%), and hepatitis B (6.46%). **Conclusion:** While Western countries have witnessed a decline in the mortality rate associated with liver cirrhosis over the past three decades, Mexico and other Latin American nations still experience a disproportionate burden. To address this issue, more robust public health initiatives are necessary to raise awareness of the detrimental impact of chronic alcohol abuse. The findings of this study are particularly relevant to southern border states, where many Mexicans and other Latin Americans seek medical care.



Country	Mortality Rate 1990	% of total mortality	Mortality Rate 2019	% of total mortality
Australia	7.41	4.15	5.77	4.24
Argentina	18.55	10.40	16.16	11.86
Brazil	24.47	13.72	15.70	11.59
Canada	9.93	5.57	8.35	6.13
Colombia	11.54	6.47	7.49	5.50
France	18.11	10.15	8.94	6.56
Germany	19.22	10.77	12.28	9.04
Mexico	50.54	28.33	38.68	28.40
USA	17.98	7.00	13.18	9.68
UK	6.15	3.45	9.53	7.00
Total	178.4	100	136.2	100

Cause of Cirrhosis	Mortality Rate 1990	% of total	Mortality Rate 2019	% of total
Alcohol Use	66.47	37.26%	51.55	37.85%
Hepatitis C	45.69	25.61%	36.79	27.01%
NAFLD	22.57	12.65%	19.3	14.17%
Hepatitis B	18.36	10.29%	8.8	6.46%
Other	25.32	14.19%	19.75	14.50%
All Causes	178.41	100%	136.19	100%

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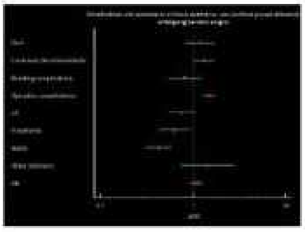
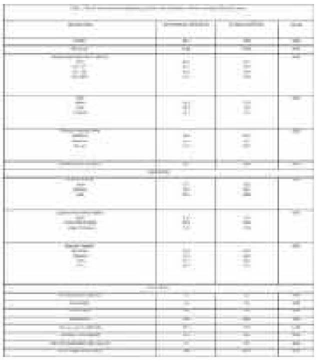
2842-C | POST BARIATRIC SURGERY OUTCOMES IN PATIENTS WITH CIRRHOSIS: A NATIONAL INPATIENT SAMPLE DATABASE STUDY

M'hamed Turki[1], Renuka Verma[2], Kamleshun Ramphul[3], Hemamalini Sakthivel[4] and Tejas Joshi[1], (1) Marshall University, (2)Guru Gobind Singh Medical School, (3)Independent Researcher, (4)One Brooklyn Health System/Interfaith Medical Center Program

Background: Bariatric surgery (BS) may improve the long-term prognosis in obese patients with cirrhosis. As these patients are prone to multiple infections and complications following surgeries, we sought to compare the postoperative course following bariatric surgery in obese individual's with and without a diagnosis of cirrhosis in the United States. **Methods:** We performed a retrospective study of obese adults (BMI e 30.0) that underwent a BS between 2016 and 2020 using the National Inpatient Sample. Comparisons between two cohorts of cirrhosis and non-cirrhosis patients via Chi-Square tests, t-tests, and logistic regressions were formed as appropriate. **Results:** Our sample consisted of 912999 cases of bariatric procedure (30.6% classified as Mixed Bariatric procedure), with 5470 (0.6%) patients with cirrhosis. Both groups included mostly females, whites, and private insurance coverages. In addition, most procedures were performed in the southern part of the United States, involving urban teaching hospitals and centers with large bed sizes. Patients with cirrhosis were older (mean age 53.22 vs. 44.49 y, $p < 0.01$). These patients also expressed a higher prevalence of multiple comorbidities (table 1). After careful adjustment of confounders, patients with cirrhosis showed higher odds of cardiovascular and thromboembolic events (aOR 1.331, $p = 0.03$), operative complications (aOR 1.491, $p < 0.01$), while reporting lower odds of pneumonia (aOR 0.634 , $p = 0.017$) and sepsis (aOR 0.428, $p < 0.01$). No differences in bleeding complications, urinary tract infections, other infections, acute kidney injury and mortality were observed between the two groups. **Conclusion:** As previously described in the literature, patients with cirrhosis are at an overall higher risk for cardiovascular and thromboembolic events throughout their lifetime. This study is demonstrating that the postoperative course following BS is no exemption. This study is suggesting that a diagnosis of cirrhosis in patients undergoing BS should probably warrant extra precautions for thromboembolic and cardiovascular events. As it has been reported in the past, patients with cirrhosis are comparatively receiving less chemical prophylaxis for deep venous thrombosis due to abnormalities in their INR; this might also partially explain our findings. We suggest proper screening and systemized post-operative protocols to help improve these outcomes.





Disclosures: The following people have nothing to disclose: M'hamed Turki, Renuka Verma, Kamleshun Ramphul, Hemamalini Sakthivel, Tejas Joshi

2843-C | POST LIVER TRANSPLANTATION OUTCOMES AMONGST HISPANIC PATIENTS TRANSPLANTED DUE TO FATTY LIVER DISEASE - SINGLE CENTER STUDY

Suaka Kagbo-Kue[1], David Chascsa[2], Jaclyn Tuck[1], Alyssa McGary[2] and Blanca Lizaola-Mayo[2], (1)Mayo Clinic, (2)Mayo Clinic Arizona, Phoenix, AZ

Background: Non-alcoholic steatohepatitis (NASH) is projected to become the leading indication for liver transplantation (LT) in the next decade in the United States due to the rising prevalence of obesity. The prevalence of non-alcoholic fatty liver disease (NAFLD) is higher and develops at a younger age in the Hispanic population, and is more frequently associated with hepatocellular carcinoma (HCC). Racial and ethnic disparities in liver transplantation are well-recognized but there remains limited data on survival outcomes among minorities. We investigated outcomes of mortality, graft survival and recurrence of hepatic steatosis among Hispanic patients. **Methods**: We retrospectively evaluated electronic medical records (EMR) of patients who underwent LT from January 2010 to June 2022 in our facility, were Hispanic and transplanted due to NASH cirrhosis with/without HCC and/or cholangiocarcinoma. Patients with other causes of chronic liver disease were excluded. Continuous variables were summarized using median and interquartile range (IQR), and categorical variables were summarized using frequency and percentage. Overall survival and graft survival were estimated using the Kaplan-Meier method. Univariate analyses were assessed with Cox-regression. **Results**: Out of 279 Hispanic patients transplanted during the study interval, 70 patients met selection criteria. The median age at transplant was 61, with similar distribution of males (48.6%) and females (51.4%). Majority of patients were high school level of education (54.3%), and 30% were working for income at listing. 32.9% had coexisting HCC. Mean MELD at transplant was 20.7%. All patients received donation after cardiac-death organs. Average BMI at transplant was 30.7%, pre-LT metabolic comorbidities included type 2 diabetes(DM2) (71.4%), hypertension (71.4%), hyperlipidemia (HLD) (25.7%), obesity (37.1%) and sleep apnea (7.1%). 11.4% had a simultaneous kidney transplantation (KT). Post LT, median follow-up IQR was 3 years; predominant new onset metabolic comorbidities were DM2 (10%) and HLD (21.4%); mean BMI at 1 year post LT was 29.7, and trended up to 33.1 at 3 years, peaking at 36.7 at 10 years. 2.9% had bariatric surgery(BS) post LT, while additional 11.9% were referred for BS but were yet to complete. Advanced NASH-related fibrosis evaluated by liver biopsy or non-invasive elastography was 2.4% at 1 year and stable (9.1%) at 2 and 5 years respectively. 8.6% of patients experienced graft failure; survival at 1, 2 and 5 years was stable at 91.4%. There was no significant association between BMI and mortality or graft failure. **Conclusion**: Our study highlights that Hispanic patients transplanted due to NASH have favorable post LT outcomes, however, there was limited sample size to determine the role of recurrent NASH and metabolic comorbidities in post LT outcomes. The importance of more research involving minority populations cannot be overemphasized.

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Disclosure information not available at the time of publication: Alyssa McGary, Blanca Lizaola-Mayo

2844-C | RACIAL DIFFERENCES IN LIVER FIBROSIS - ENVIRONMENT OR BIOLOGY?

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Background: Liver histology is the classic method for staging the severity of liver fibrosis, which in turn is one of the most important clinical predictors of outcome. Here, we have hypothesized that environmental or genetic factors may influence the propensity to develop fibrosis among racial groups, which in turn could impact the progression of liver disease. **Methods**: We examined the liver histology of all patients over 18 years of age who underwent liver biopsy at the Medical University of South Carolina (MUSC) from January 1, 2013 to July 1, 2021. Patients with malignancy, liver metastases, or missing data were excluded. Fibrosis was quantitated using the Metavir system (F0 = no fibrosis to F4 = histological cirrhosis). **Results**: Of 3,572 patients undergoing liver biopsy, approximately one-third had a biopsy to investigate chronic liver disease. This group included 850 (77%) White patients and 251 (23%) Black patients. Black patients had a higher prevalence of HBV (7% vs 2%), HCV (22% vs 14%), and autoimmune hepatitis (AIH) (14% vs 7%), while White patients had a higher prevalence of alcoholic liver disease (23% vs 14%) and non-alcoholic steatohepatitis (NASH) (16% vs 4%). Black patients had a higher prevalence of metabolic syndrome (36% vs 20%). White patients had an overall greater burden of fibrosis than Black patients (Table) and higher prevalence of cirrhosis (40% vs 30%, $p = 0.056$). However, overall, inflammation was significantly greater in Black patients (Table). Of note, patients with alcoholic liver disease had a greater prevalence of cirrhosis than those with other causes of cirrhosis; the prevalence of cirrhosis within each group was as follows: alcohol - 64%; HBV - 40%; HCV - 29%; HCV with alcohol - 47%; NASH - 36%; AIH - 29%; drug-induced liver injury - 8%; other - 30%; unknown - 27%; $p < 0.001$). In patients with NASH, the average steatosis grade was twice as high for Black as White patients (Table). White patients had higher prevalence of esophageal varices (41% vs 26%, $p < 0.01$), hepatic encephalopathy (22% vs 14%, $p < 0.01$), and splenomegaly (28% vs 9%, $p < 0.001$). Cumulative 5- year mortality was similar among White and Black patients (30% vs 28%). Patients with alcoholic liver disease had significantly higher cumulative 5-year mortality than other liver diseases (alcohol - 51%; HBV – 18%; HCV - 15%; HCV with alcohol - 29%; NASH - 30%; AIH – 20%; drug-induced liver injury – 17%; other - 43%; unknown - 25%; $p < 0.001$). **Conclusion**: White patients had a greater overall burden of fibrosis than Black patients, and a higher prevalence of NASH despite a lower prevalence of metabolic syndrome. Clinical complications of cirrhosis were more prominent in White than Black patients, although mortality was similar in both groups. The data suggest that there are inherent differences fibrosis in Black and White patients and suggest that fibrosis progression may be worse in White than Black patients.

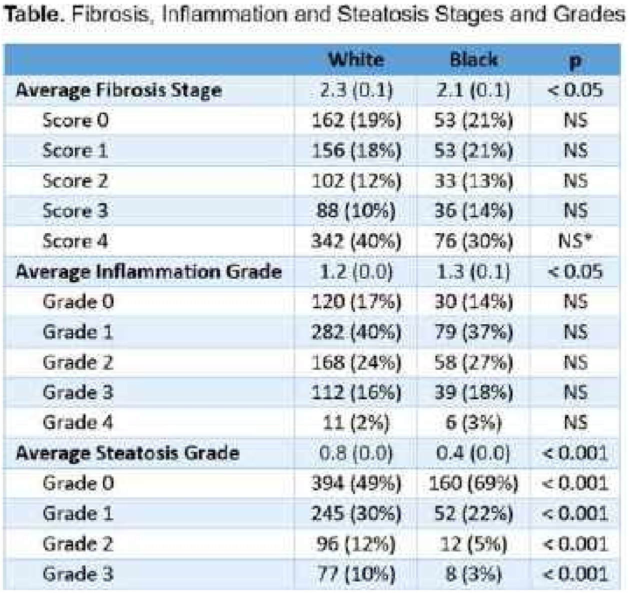

Table. Fibrosis, Inflammation and Steatosis Stages and Grades

	White	Black	p
Average Fibrosis Stage	2.3 (0.1)	2.1 (0.1)	< 0.05
Score 0	162 (19%)	53 (21%)	NS
Score 1	156 (18%)	53 (21%)	NS
Score 2	102 (12%)	33 (13%)	NS
Score 3	88 (10%)	36 (14%)	NS
Score 4	342 (40%)	76 (30%)	NS*
Average Inflammation Grade	1.2 (0.0)	1.3 (0.1)	< 0.05
Grade 0	120 (17%)	30 (14%)	NS
Grade 1	282 (40%)	79 (37%)	NS
Grade 2	168 (24%)	58 (27%)	NS
Grade 3	112 (16%)	39 (18%)	NS
Grade 4	11 (2%)	6 (3%)	NS
Average Steatosis Grade	0.8 (0.0)	0.4 (0.0)	< 0.001
Grade 0	394 (49%)	160 (69%)	< 0.001
Grade 1	245 (30%)	52 (22%)	< 0.001
Grade 2	96 (12%)	12 (5%)	< 0.001
Grade 3	77 (10%)	8 (3%)	< 0.001

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The following people have nothing to disclose: Michael L. Attanasi

f 2845-C | RACIAL, ETHNIC AND GENDER ENROLLMENT DISPARITIES IN NON-ALCOHOLIC FATTY LIVER DISEASE CLINICAL TRIALS IN THE UNITED STATES

Phillip Leff[1], Naim Alkhouri[2], Amit G. Singal[3], Karn Wijarnpreecha[4], Mazen Noureddin[5] and Nicole E. Rich[3], (1)Creighton University, (2)Arizona Liver Health, Phoenix, AZ, (3)University of Texas Southwestern Medical Center, (4)University of Arizona College of Medicine Phoenix, Phoenix, AZ, (5)Houston Research Institute, Houston, TX

Background: There are significant racial and ethnic disparities in NAFLD prevalence and severity in the U.S., with the highest burden in Hispanic men. Yet, disparities in enrollment in contemporary NAFLD trials (enrolling from 2017-present) have not been investigated. Thus, we aimed to characterize contemporary enrollment data from therapeutic NAFLD trials in adults aged > 18 years. **Methods:** We performed a systematic literature search in clinicaltrials.gov and PubMed for all NAFLD therapeutic trials in the U.S. from January 2011 to February 2023. Demographics of interest included: race, ethnicity (Hispanic vs. non-Hispanic) and reported gender. Enrollment fraction (EF), i.e., the number of trial enrollees divided by number of patients with NAFLD matched to the period of trial enrollment using estimates of the U.S. prevalence of NAFLD using NHANES 2017-2018 and 2020 U.S. Census data. **Results:** Among the 341 trials identified, 95 met inclusion criteria (n = 63 with US-only enrollment). Of these, 24 (25.3%) had not yet reported or published demographic enrollment data. Among the 71 trials (n = 9105 participants) reporting enrollment data, 8.5% were phase 1 and 74.6% were phase 2/3; 65.3% were sponsored by industry, 30.4% academia and 4.3% other. Women (n = 5137) comprised a higher proportion of trial participants compared to men (n = 3955; 56.4% vs 43.6%); this gender disparity was consistent across intervention type (drug vs. behavioral), time period (2011-2017 vs 2018-present), and US-only vs multinational trials, but not trial phase (phase 1 trials: 57.7% men vs 42.3% women). Men had a lower EF compared to women (0.002% vs 0.004%, p = 0.01) despite comprising an

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

estimated 57.2% of prevalent NAFLD cases. Race was reported in only 53/71 trials (n = 6984 participants; 86.2% White, 3.1% Black, 5.0% Asian, 0.5% AI/AN), while ethnicity was reported in only 36/71 trials (n = 5015 participants; 31.5% Hispanic, 68.5% Non-Hispanic). The proportion of studies reporting enrollment data on race increased significantly over time (62.8% in 2011-2017 vs. 89.3% in 2018-present, $p < 0.01$), whereas there was a slight decrease in the proportion reporting ethnicity over the same time period (41.9% vs 39.3%, $p = 0.10$). Among studies reporting ethnicity, Hispanic patients (comprising 20.1% of prevalent NAFLD cases) comprised 31.5% of trial participants. Overall, EF was highest among Asian (0.04%) and Hispanic participants (0.02%). Despite accounting for 8.8% of prevalent NAFLD cases, Black patients comprised only 3.1% of trial participants (EF 0.007%). This disparity remained consistent across trial phase, sponsor, and intervention type. **Conclusion:** There are persistent racial, ethnic and gender disparities in enrollment in NAFLD clinical trials and under-reporting of race and ethnicity of participants. Improving equitable access to NAFLD trials is not only morally imperative, but informs benefits across subgroups and improves generalizability of results.

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The following people have nothing to disclose: Phillip Leff, Karn Wijarnpreecha, Mazen Noureddin

2846-C | REPRODUCTIVE HEALTH CHARACTERISTICS IN PRE-MENOPAUSAL WOMEN WITH NAFLD

Grace Zhang, UCSF, San Francisco, CA, Yanin Srisengfa, UCSF and Monika Sarkar, University of California, San Francisco

Background: NAFLD is rising in reproductive-aged women, which has implications for pre-conception and pregnancy-related outcomes. Reproductive measures in young women with NAFLD are limited. **Methods:** We conducted a retrospective survey among reproductive-aged women (ages 18-45 y) with NAFLD and elevated liver tests at our center. Participants completed a one-time 80-question REDCap survey with branching logic from 2017-2023. NAFLD was diagnosed by imaging and/or biopsy in the absence of other causes of liver disease. Metabolic parameters were reported within 6 months of NAFLD imaging or biopsy. Prevalence of reproductive outcomes such as infertility, pregnancy events and complications were compared between our cohort and the general United States (U.S.) population using chi-square, with $p < 0.05$ considered statistically significant. **Results:** There were 79 reproductive-aged participants with NAFLD and elevated liver tests (median ALT U/L 72U/L, IQR 37-98). Median age was 34 years; 66% were White, and 34% Hispanic. Metabolic conditions included BMI > 30kg/m2 in 90% (median BMI 37.3, IQR 33.3- 42.4), diabetes mellitus in 23%, polycystic ovary syndrome in 53%, and dyslipidemia in 53%. Transient elastography-controlled attenuation parameter (TE-CAP) (n = 52), noted severe steatosis (CAP e 300 dB/m) in 70% and hepatic fibrosis (TE > 7kPa) in 29%. In those with liver biopsy (n = 56), 48% had NASH, 55% had > / = stage 1 fibrosis, and 7% had advanced fibrosis. For reproductive outcomes, 39% reported prolonged time to conception (> 12 mo). As compared to the general population, 21% in NAFLD vs 6% in the general population reported infertility, 48% vs 20% had prior miscarriage, and 54% vs 1% had recurrent miscarriages (all p values < 0.001) (Figure). Among those with pregnancies (n = 27), 37% reported gestational diabetes mellitus (vs 9% in the general population), 22% reported gestational hypertension (vs 8%), and 50% reported pre-term labor (vs 10%, all p values < 0.001). Prevalence of low birth weight was similar in our cohort at 9% vs 8% in the general population. **Conclusion:** In young women with NAFLD and elevated liver tests nearly half had histologically-confirmed NASH as well as fibrosis. These women with NAFLD also had higher rates of infertility, miscarriages, and higher rates of metabolic complications during pregnancy. Early collaboration with reproductive endocrinology and maternal-fetal medicine may help optimize reproductive outcomes in young women with NAFLD.

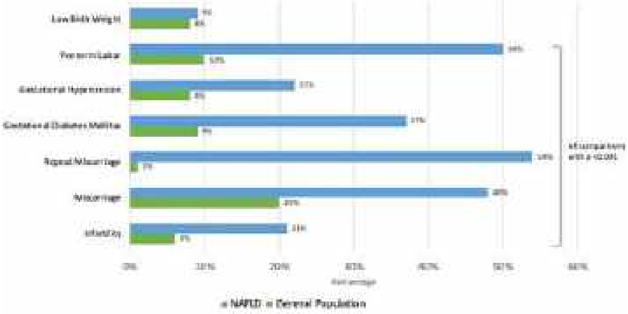

Figure. Prevalence of obstetric outcomes in women with NAFLD versus the general United States population (estimates from the Mayo Clinic 2020, and Centers for Disease Control 2020-2021).

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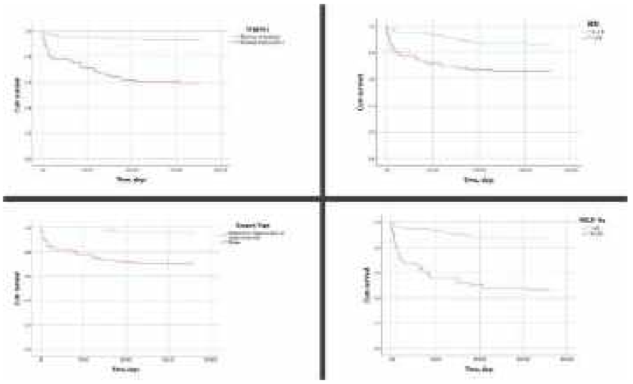
Disclosure information not available at the time of publication: Yanin Srisengfa, Monika Sarkar

2847-C | RISK FACTORS FOR MORTALITY AFTER SURGERY IN PATIENTS WITH CIRRHOSIS: A MULTICENTER COHORT

Martín Pacheco Serrano, Instituto Nacional De Ciencias Medicas Y Nutricion Salvador Zubiran, Ignacio García Juárez, Instituto Nacional De Ciencias Medicas y Nutricion, Jacqueline Cordova Gallardo, Hospital General Manuel Gea Gonz and David Medina-Julio, Hospital General Manuel Gea Gonzalez

Background: Patients with cirrhosis have a high risk of postoperative mortality compared with the average population. Because risk factors determined in different populations may not be generalizable to other ones, we conducted this retrospective study to evaluate the risk factors associated with mortality after surgery in a mexican cohort of patients with cirrhosis. **Methods:** We conducted an observational, retrospective study of patients with cirrhosis who underwent major surgery, at two centers located in Mexico City. Cox regression analysis was used to evaluate the impact of demographic, clinical, and biochemical characteristics on post-operative mortality. **Results:** We included data from 228 surgeries performed in 173 patients between January 2015 and September 2022. The median of age were 60 years (IQR 52-68) and 59.8% were women. The most frequent etiologies of cirrhosis corresponded to MAFLD (36.4%) and viral (21.4%). Most patients were Child-Pugh B/C (62.4%), with a median of MELD-Na of 15 (IQR 10-21). Most patients had already presented a decompensation event in the past (69.9%), mostly ascites (52%). Regarding other comorbidities, the most frequently found were diabetes mellitus (40.5%) and arterial hypertension (33-5%). The median of BMI were 25.6 (IQR 22.5-29.3). Regarding the ASA classification, 57.2% of patients were considered ASA 4. With respect to the type of surgery, the most frequently found were open abdominal (39.3%), chest/cardiac (16.8%) and abdominal wall (15.6%). A high proportion of procedures were considered emergent (43.4%). Mortality was calculated at 30(11.6%), 90(16.8%) and 180 days (18.5%) after surgery. A cox regression analysis was used to evaluate the impact of demographic, clinical, and biochemical characteristics on post-operative mortality. We found that a MELD-Na greater than 20 were associated with 30-day (HR = 6.33; 95%CI 2.7-14.84; p = 0.00), 90-day (HR = 3.62; 95%CI 1.9-6.7; p = 0.00) and 180-day mortality (HR = 4; 95%CI 2.2-7.2; p = 0.00). An emergent procedure and a type of surgery distinct from abdominal laparoscopic and abdominal wall, were associated with 90-day (HR = 2.44; 95%CI 1.1-5.8; p = 0.045 and HR = 10.96; 95%CI 2.6-46.4; p = 0.00, respectively) and 180-day mortality (HR = 2.35; 95%CI 1.1-5.3; p = 0.04 and 12.42; 95% CI 2.9-52; p = 0.00, respectively), but no 30-day mortality. By contrast, a blood urea nitrogen greater than 21 mg/dl were associated with 30-day (HR = 3.9; 95%CI 1.4-10.6; p = 0.00) and 90-day mortality (HR = 2.2; 95%CI 1.14-4.2; p = 0.02), but no 180-day mortality. **Conclusion:** A MELD-Na score greater than 20 points, were independently associated with early and long-term mortality after surgery. An emergent procedure and a type of surgery distinct from abdominal laparoscopic and abdominal wall, were associated with long-term mortality but no short-term mortality. By contrast, a BUN concentration greater than 21 mg/dl, was independently associated with early mortality.



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2848-C | SCREENING AND LINKAGE TO CARE FOR CHRONIC LIVER DISEASE AMONG REFUGEE PATIENTS PRESENTING FOR DOMESTIC MEDICAL EXAMINATION IN THE UNITED STATES

Sara Chapin[1], Julia Gasior[2], Vincent Lo Re III[2], Nadim Mahmud[1], Aba Barden-Maja[1] and Jessie Torgersen[2], (1)Hospital of the University of Pennsylvania, (2) University of Pennsylvania Perelman School of Medicine

Background: Chronic liver diseases (CLD), including hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcohol-related liver disease (ALD), and nonalcoholic fatty liver disease (NAFLD), are a major cause of global morbidity and mortality. Little is known regarding CLD screening and subsequent care among refugees, a vulnerable population with time-limited medical coverage. We sought to determine the prevalence of CLD and linkage to specialty care among refugees undergoing domestic medical examination (DME) in the United States (US). **Methods:** We conducted a single center, cross-sectional study of refugees e 18 years old presenting for DME in Philadelphia, PA between March 2017 and March 2021. Patient demographics, clinical and laboratory values were abstracted from the DME with follow up data collected through 9 months following DME. CLD screening was defined by collection of HCV antibody, HBV surface antigen, alcohol use history, and assessment of metabolic syndrome [MetS]. MetS was defined by US National Cholesterol Education Program Adult Treatment Panel III criteria. CLD etiology was defined as follows: chronic HBV (e 1 positive HBsAg), HCV (detectable HCV RNA), ALD (>7 drinks/week in women or >14 drinks/week in men with e 1 alanine aminotransferase [ALT] elevation >40 U/L in men or >30 U/L in women, excluding HBV and HCV), and NAFLD (MetS plus e 1 ALT elevation without HBV, HCV or ALD). Linkage to care for viral hepatitis was defined by e 1 office visit with Hepatology or Infectious Disease and treatment initiation was defined by e 1 prescription for antiviral therapy. Linkage to care for ALD and NAFLD was defined as e 1 office visit with counseling on alcohol cessation or weight loss, respectively. **Results:** 276 refugees were included (median age, 34 years [IQR: 26-42]; 56.2% male), from 34 countries (32.3% Southeast Asia, 27.9% Europe, 21.7% Africa, 15.2% Eastern Mediterranean, 2.9% Americas). HBV and HCV screening was performed in 96% and 34.7%, respectively. Chronic HBV was diagnosed in 4 (1.4%) refugees, of whom 3 were linked to care and 2 initiated antiviral therapy. HCV was identified in 2 (0.7%) refugees; both were linked to care and completed direct-acting antiviral therapy. Alcohol use history was recorded in 85.5%, identifying 2 (0.7%) refugees with ALD, both received counseling. MetS was identified in 10.1%; however, waist circumference was missing in 100% and body mass index was missing in 61.2% of DMEs. Five (1.8%) patients met criteria for NAFLD, with 2 receiving weight loss counseling. **Conclusion:** Near universal HBV screening (96%) was achieved among refugees completing DME, with much lower screening for HCV, ALD, and NAFLD. Improved CLD screening among refugees is needed to better understand disease burden. Successful linkage to specialist care and treatment initiation can be achieved in this vulnerable population.

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2849-C | SCREENING FOR HEPATITIS B IN THE BRONX WEST AFRICAN COMMUNITY WITH A BLOOD PRESSURE CUFF

Mandira Shashank[1], Julie Nguyen[1], Jessie Birnbaum[1], Fatima Omarufilo[1], Emmanuel U Emeasoba[1], Kwabena Boakye[1], Viktoriya Khaitova[1], Daniel Guttman[1], Mugdha Parulekar[1], Molly Fisher[1] and Samuel H. Sigal[2], (1)Montefiore Medical Center, (2)Montefiore Medical Center and Albert Einstein College of Medicine

Background: Hepatitis B (HBV) and hypertension (HTN) represent major health burdens in West Africa (WA). Underdiagnosis and inadequate control for both conditions are major public health concerns in WA, and the situation is further complicated in immigrants due to unfamiliarity with the US healthcare system. In contrast to HBV which is not well understood and associated with stigma, HTN is readily recognized as an important medical condition. We describe how HTN screening can facilitate HBV screening and enrollment into the US healthcare system. **Methods:** A 30-minute culturally sensitive educational program on HTN was delivered in collaboration with local faith-based organizations. A brief 5-minute presentation on HTN was also presented upon request at various community gatherings. Names and contact information were obtained after the events for those interested in attending a HTN screening clinic visit at which time a free blood pressure cuff was provided, HBV testing

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performed, and referrals of family and friends obtained. For those with HTN, participation in ongoing care was assessed. Insurance (ins) was arranged for eligible individual's, and linkage to ongoing care was provided for those without previous integration. **Results:** Seven 30-minute and five 5-minute presentations were conducted. After the 30-minute presentation, 207 of 396 attendees (52.3%) requested a clinic screening visit, and 69 (33.3%) returned for the appointment. Eighty-three individual's requested a clinic screening after the 5-minute presentation, and 52 (62.6%) returned for the appointment. Thirty-two individual's who were at a presentation but did not register subsequently contacted the Program for an appointment. A total of 94 referrals were made. 190 (69.6%) of the individual's evaluated had an elevated blood pressure or history of HTN, including 44 (16.1%) with newly diagnosed and 41 (15%) with severe HTN ($>160/90$) that required urgent intervention. All individual's except for 2 who reported previous testing agreed to HBV testing. 20 individual's (7.4%) were HBsAg positive. Among the 133 patients with HTN, 27 were not integrated into the US healthcare system. Arrangements for ins coverage and transition into ongoing care were made for all as indicated. **Conclusion:** HTN screening with the offer of a free blood pressure cuff can be effectively utilized to promote HBV screening and integration into the US healthcare system.

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2850-C | SIMILAR REJECTION AND RETRANSPLANT RATES BUT DECREASED SURVIVAL AMONG AFRICAN AMERICAN PATIENTS FOLLOWING LIVER TRANSPLANTATION

Mark Obri[1], Suhaib Alhaj Ali[2], Spandana Alluri[2], Momin Samad[2], Mohamed Ramzi Almajed[2], Yervant Ichkhanian[2] and Syed-Mohammed Jafri[3], (1)Henry Ford Health, (2)Henry Ford Hospital, (3)Henry Ford Health System

Background: There are known disparities in medicine in regards to sex and race. Investigation is important to evaluate these disparities and to aim to correct them, offering the best outcome for a diverse range of patients. The study aims to compare liver transplant outcomes based off of the race of the patient. **Methods:** A retrospective study was conducted at a single tertiary liver transplant center and was comprised of patients who underwent liver transplant from 2009 to 2019. The primary outcome was the rate of survival among different races. Secondary outcomes measured included the rate of rejection and re-transplant among different races in addition to the rate of survival among different sexes and donor types. **Results:** This study included 450 patients with race distribution of 83.6% white patients ($n = 376$), 10.4% black patients ($n = 47$), and 6.0% patients classified as "Other" races ($n = 27$). The primary outcome was the rate of survival compared amongst the three groups at 1 year, 3 years, and last known follow-up. Differences in survival rate among the three groups at 1 year was not statistically significant. At 3 years, the survival rate for white patients was 88.6%, black patients was 74.5%, and other patients was 92.6%; the chi-square statistics was 8.2 ($p = 0.016$) which is statistically significant at $p < 0.05$. At the last known follow-up, survival rate for white patients was 82.2%, black patients was 66.0%, and other patients was 88.9%; the chi-square statistic was 8.3 ($p = 0.016$) which is significant. Re-transplant rates did not significantly differ between races with re-transplant rates among white, black, and other patients at 4.3%, 1.2%, and 3.7% respectively. Rejection rates did not significantly differ between races with white, black, and other patients at 24.5%, 31.9%, and 18.5% respectively. Comparisons of survival among patients with difference sexes did not demonstrate a statistically significant difference. **Conclusion:** Correlation exists between different patients races and survival among liver transplant patients. Patients who are black have a statistically lower survival rate (66.0%) compared to those who are white (82.2%) or other (88.9%). Further investigation with larger population sizes including epidemiological studies and subgroup analyses is necessary to delineate the disparities which influence these outcomes. Published literature suggests that access to care, socioeconomic status, and racial biases are factors that influence healthcare access and affect outcomes.

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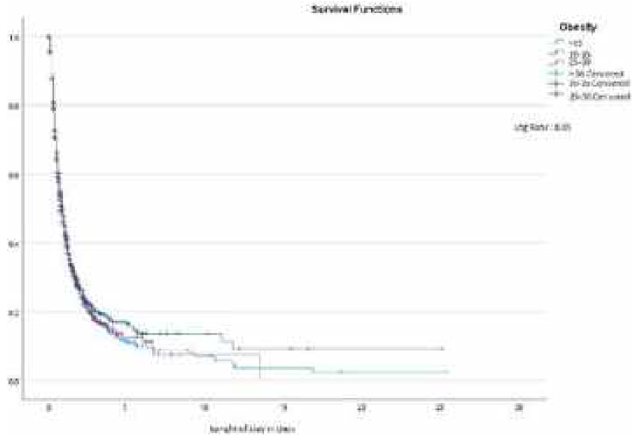
2851-C | THE TRIPLE BURDEN: HOW OBESITY AND LIVER CIRRHOSIS INFLUENCE PATIENT OUTCOMES, LENGTH OF STAY, AND HEALTHCARE COSTS"

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

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



Disclosures: The following people have nothing to disclose: Rajmohan Rammohan, Sai Greeshma Magam, Melvin Joy, Dilman Natt, Achal Patel, Abhishek Tadikonda, Jiten Desai, Sandra Gomez, Susan Bunting, Paul Mustacchia

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

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

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

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

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

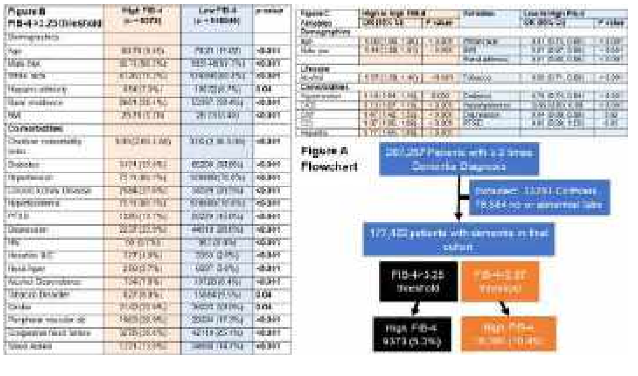


Figure B
Figure C
Figure A
Flowchart
High FIB-4
9373 (5.3%)

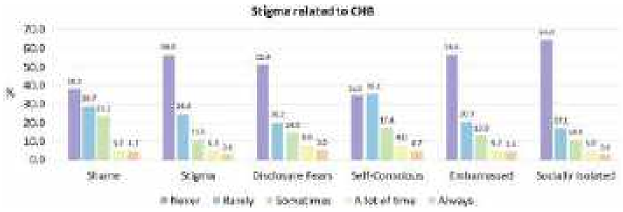
Disclosures: Jasmohan S. Bajaj – Bausch: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Grifols: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Sequana: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

Disclosure information not available at the time of publication: Scott Silvey, Nilang Patel

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

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

Background: Stigma regarding infectious diseases is known to cause emotional distress, isolate individual's from their social networks, impact adherence and health outcomes, and undermine societal support for affected groups. However, it is less well understood how stigma is experienced differently within specific patient groups, and which patient groups should be prioritized for support. **Methods:** Our NIDDK-funded longitudinal cohort study, Bio-Psycho-Social Drivers of Disparities in Liver Disease Progression among Korean Americans with Hepatitis B Infection (MPI: Juon/Klassen), follows 365 patients at two clinical sites, collecting retrospective and prospective medical data, as well as structured surveys, in-depth qualitative interviews, hair cortisol biomarkers of chronic stress, and GIS-based analyses of neighborhood resources. This analysis focuses on survey responses to the HBQOL-Stigma subscale, and associations with psychosocial characteristics, including depressive symptoms and acculturative stress. A purposively selected subset of 30 participants is participating in 60-minute audio-recorded in-depth interviews, to elaborate qualitatively on patterns observed in the structured data. Thematic coding uses MAXQDA qualitative software, facilitating integration of quantitative and qualitative patterns. **Results:** The six-item, 30-point stigma index had strong reliability (alpha = 0.92), with a mean score of 5.4, and a range of 0-24. In a multivariable regression model, older age was significantly associated with lower self-reported stigma. Women as well as those with higher depressive symptoms and acculturative stress reported greater hepatitis B-related stigma. In qualitative interviews, respondents elaborated that their CHB status was not internalized as part of their identity, but that they did feel CHB-related stigma, and were cautious about disclosure. Some viewed CHB stigma as higher among Korean-Americans than in Korea, due to the insular nature of U.S. immigrant communities. Others felt that older generations stigmatized CHB due to its potential threat to financial success and longevity. Younger patients felt that among their peers, CHB was mostly unknown and thus less stigmatized, but misperceptions about severity and contagiousness were common. **Conclusion:** Mixed methods approaches to understanding complex disease-related experiences can identify strategies for tailored education to reduce CHB-related stigma within cultural subgroups.



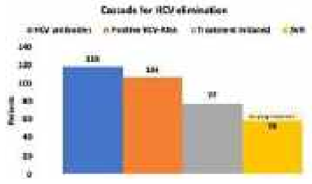
Disclosures: The following people have nothing to disclose: Ann Klassen, Hie-Won L. Hann, Mimi Chang, Ho Bae, Hee-Soon Juon

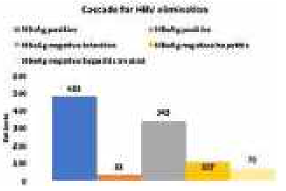
Disclosure information not available at the time of publication: Eunji Kim, Giyoung Lee, Katherine Clegg Smith, Kyunghee Koh

2854-C | VIRAL HEPATITIS B AND C IN A VULNERABLE POPULATION (MIGRANTS & HOMELESS). FIVE-YEAR RESULTS OF A PROSPECTIVE COHORT IN A LARGE ELIMINATION PROGRAM

Victor De Ledinghen[1], Anne-Laure De Araujo[2], Julie Dupuy[2], Rhizlane Houmadi[2], Adèle Delamarre[3], Paul Hermabessière[2] and Juliette Foucher[2], (1)Centre D'investigation De La Fibrose Hépatique, Bordeaux University Hospital, Pessac, France; Inserm U1053, Bordeaux University, Bordeaux, France., (2)CHU Bordeaux, Bordeaux, France, (3)Ordeaux

Background: Migrants and persons experiencing homelessness encounter many barriers to HBV/HCV care (from screening to treatment and follow-up). Therefore, it is necessary to provide easy and rapid access to diagnosis, treatment and follow-up, to these patients. In 2017, we started a program to promote more equitable link to care by bringing screening into the community and promoting easy access to care and follow-up in this population. The current study aimed assess this elimination strategy based on a community intervention and simplified access to care in our metropolis of about 800,000 inhabitants. **Methods:** From January 2017 to March 2023, all patients who attended our simplified access to care after a screening in any community center in our area were included. All patients had a clinical, biological, virological, morphological assessment, met a nurse and a physician, and another appointment was organized for their follow-up. In HCV patients, treatment was initiated as soon as possible and the follow-up was stopped after SVR, except in cirrhotic patients. In HBV/HDV patients, a follow-up at least once a year was organized. **Results:** A total of 728 patients were screened by 50 community centers and referred to our center. Among them, 83 (11.4%) never attended the first appointment. Characteristics of the 645 other patients were: male 499 (77.4%), mean age 30.7 yrs (148 patients (22.9%) were <18 y). Main countries of birth were Guinea (122), Georgia (69), Mali (57), and Ivory Coast (53). Viral infections were HBV 492 (76.3%), HCV 118 (18.3%), HDV 30 (4.7%) and coinfections 5 (0.7%). Median time between arrival in France and the first consultation was 158 days. 118 HCV monoinfected patients were included: 12 patients had spontaneous clearance of HCV infection. Among these 106 patients, 77 received a treatment. SVR was available in 58 patients (75.3%), treatment is on-going in 10 and 9 patients (11.7%) did not attend the visit to assess SVR. 492 HBV monoinfected patients were included. 9 patients had negative HBsAg. Median follow-up was 13.2 months (extremes: 0-74.3 mo). After exclusion of patients seen during the last year, this follow-up was 17.2 months. 33 patients were HBeAg+. Among them, 5 (15.2%) were lost to follow-up. 107 patients had HBeAg- hepatitis (HBV-DNA >2000 IU/ml) and 70 (65.4%) received a treatment. 21 patients (19.6%) were lost to follow-up. 343 had HBeAg- infection. Among them, 130 (37.9%) were lost to follow-up. Cascade of viral elimination is indicated in Figure. **Conclusion:** In this very difficult to manage population, the elimination of viral hepatitis is possible by working very closely with all community structures in the region. The care pathway was easy with very quick access to our expert center and 89% of patients attended the first appointment. Less than 20% of treated patients were lost to follow-up. This program is on-going with more community centers.





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The following people have nothing to disclose: Anne-Laure De Araujo, Julie Dupuy, Rhizlane Houmadi, Adèle Delamarre, Juliette Foucher
Disclosure information not available at the time of publication: Paul Hermabessière

3000-A | A NOVEL BEDSIDE METHOD TO QUANTIFY ASCITES SEVERITY VIA PARACENTESIS PRESSURE

Nikhilesh R Mazumder[1], Elliot B. Tapper[2], Sardar Ansari[1] and Anna Lok[2], (1)University of Michigan, (2) University of Michigan Medical Center

Background: High-pressure ‘tense’ ascites is the most debilitating form of ascites, requiring paracentesis to decompress. Tense ascites is thought to relate to more severe portal hypertension and more advanced liver disease. While thrombocytopenia is known to correlate with severity of portal hypertension and likelihood of variceal bleeding independent of MELD, its correlation with ascites pressure has not been studied. We describe a novel method to measure ascites pressure in outpatients undergoing paracentesis (“Paracentesis pressure”) and explore its relationship to known measures of liver disease severity. **Methods:** Adult outpatients undergoing therapeutic paracentesis were consented. An open-ended manometer and stopcock from a lumbar puncture kit was placed inline with the paracentesis tubing. The zero point was at the level of the xiphoid process at the mid-axillary line corresponding to the anatomical location of the right atrium with the patient lying at 30 degrees. Pressures were measured at end expiration during gentle breathing with suction disconnected. Pressure measurements were taken at the procedure start and repeated at 1.5L increments until the end of the procedure. Routine labs were obtained. Univariate and multivariate linear regression was performed after outlier analysis based on Cook’s distance to evaluate the relationship between ascites pressure, volume, thrombocytopenia, and lab measures of liver disease severity. **Results:** Eighty five procedures among 34 patients were included for analysis. Patients had a mean MELD-Na of 15.9 (SD 7), albumin of 3.3 (SD 0.5) g/L, and platelet count of 103 (SD 43)K/uL. At procedure start, paracentesis pressure was a mean of 11.2 (SD 3.8) cm H_2O, dropping to a mean of 2.9 (SD 3.9) cm H_2O after the removal of an average of 7.1L. MELD-Na was not associated with platelet count, opening pressure or volume drained ($p > 0.05$ for all). Thrombocytopenia was significantly associated with initial paracentesis pressure (Figure, 0.3 cmH_2O per 10K/uL drop, $p < 0.01$) but not with volume drained ($p = 0.06$). Serum albumin was not significantly associated with initial paracentesis pressure ($p = 0.06$) or volume drained (p = NS). **Conclusion:** In this preliminary study, we describe a bedside method using readily available materials to determine ascitic pressure in outpatients undergoing therapeutic paracentesis. The opening paracentesis pressure correlated with platelet count, but not MELD-Na, supporting its role as a MELD-independent marker of portal hypertension. Future studies should evaluate paracentesis pressure against HVPG in measuring portal hypertension in patients with ascites.

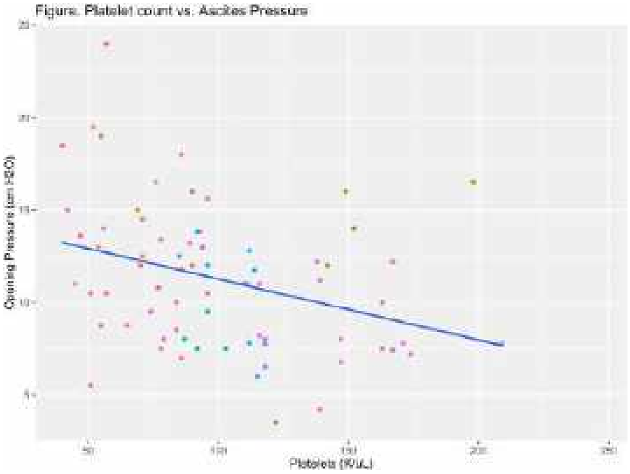


Figure: Platelet count vs. Ascites Pressure

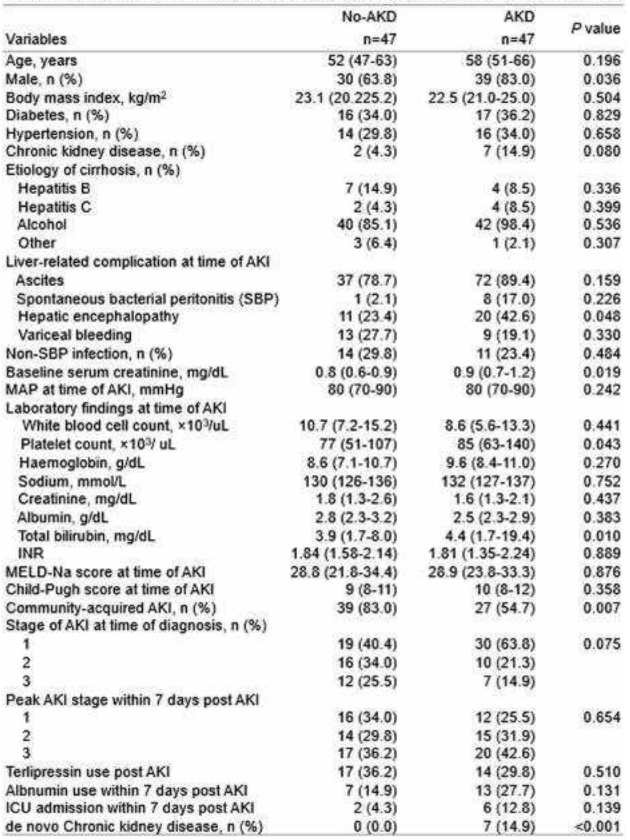
Disclosures: Anna Lok – Abbott: Consultant, Yes, No; Chroma: Consultant, No, No; Enochian: Advisor, No, Yes; GlaxoSmithKline: Consultant, No, No; Roche: Consultant, Yes, No; TARGET: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; TARGET: Advisor, No, No; Virion: Consultant, No, No;
The following people have nothing to disclose: Nikhilesh R Mazumder, Elliot B. Tapper
Disclosure information not available at the time of publication: Sardar Ansari

3001-A | ACUTE KIDNEY DISEASE IS COMMON AND ASSOCIATED WITH HIGH MORTALITY IN CIRRHOTIC PATIENTS WITH ACUTE KIDNEY INJURY

Jeongeun Song, Byung Seok Kim and Chang-Hyeong Lee, Daegu Catholic University School of Medicine

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

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



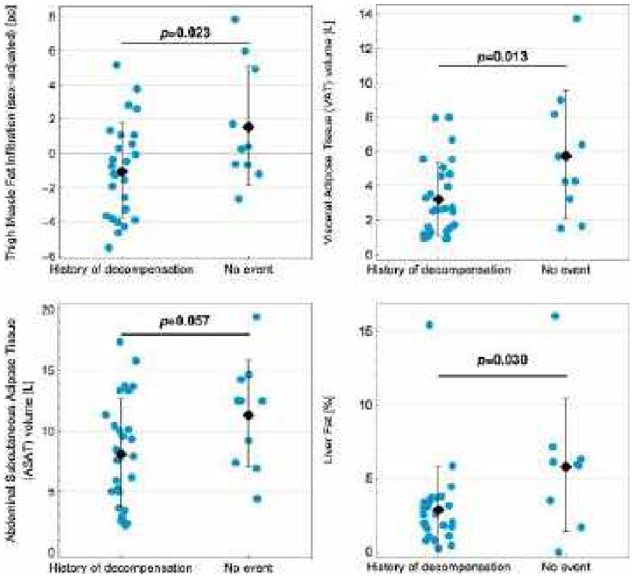
Variables	No-AKD n=47	AKD n=47	*P* value
Age, years	52 (47-63)	58 (51-66)	0.196
Male, n (%)	30 (63.8)	39 (83.0)	0.036
Body mass index, kg/m^2	23.1 (20.225.2)	22.5 (21.0-25.0)	0.504
Diabetes, n (%)	16 (34.0)	17 (36.2)	0.829
Hypertension, n (%)	14 (29.8)	16 (34.0)	0.658
Chronic kidney disease, n (%)	2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

Disclosures: The following people have nothing to disclose: Jeongeun Song, Byung Seok Kim, Chang-Hyeong Lee

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

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

Background: Recent studies highlight the limited prognostic value of MELD score in cirrhosis and underscore the importance of developing additional multi-modal biomarkers. While skeletal muscle mass is a robust predictor of clinical outcomes in patients with decompensated cirrhosis, there is little data evaluating the relationship between other body compartments, such as adipose tissue, and portal hypertension. Thus, the aim of the current study was to evaluate the association between adipose tissue compartments and portal hypertension among patients with cirrhosis. **Methods:** 37 patients (29 females) with cirrhosis underwent 8-min magnetic resonance imaging (MRI) and blood work after an overnight fast. The MRI based assessment was measured via AMRA® Researcher and quantified body fat compartments that included abdominal subcutaneous adipose tissue (ASAT), liver fat content (LF), muscle fat infiltration (MFI) and visceral adipose tissue (VAT). MFI was adjusted for sex differences. Complications of portal hypertension included history of ascites, esophageal varices, acute variceal hemorrhage, hepatic encephalopathy, and spontaneous bacterial peritonitis. Mixed model linear regressions was used for statistical testing between body fat compartments and history of portal hypertension complications, etiology of chronic liver disease and gender. **Results:** The average MELD score of the study cohort was 13 and the most common etiology of cirrhosis was alcoholic and nonalcoholic steatohepatitis (n = 20). There was less body fat in those patients with a history of decompensation events when compared to patients who did not have a decompensating events (Figure 1). The data from linear regression models with standardized β-coefficient is as follows: MFI -2.62 pp (p = 0.02), VAT -2.57 L (p = 0.01), ASAT -3.35 L (p = 0.06), and liver fat -2.94 percentage points (p = 0.03). In addition to aggregate endpoint of presence of any decompensating event, an association between lower fat compartments and individual portal hypertension complications was also noted. The association between body compartments and previous portal hypertension complications was independent of gender and etiology of chronic liver disease leading to cirrhosis. In multivariate models all the fat compartments, including ASAT ($p = 0.049$), were significantly associated with presence of portal hypertension. **Conclusion:** The current study provides data demonstrating the relationship between portal hypertension related complications and lower adipose tissue depots. These findings have the potential to provide additional risk stratification tools in patients in whom the MELD score may not be as robust of predictor of clinical events. However, this requires further validation in well-designed prospective studies.

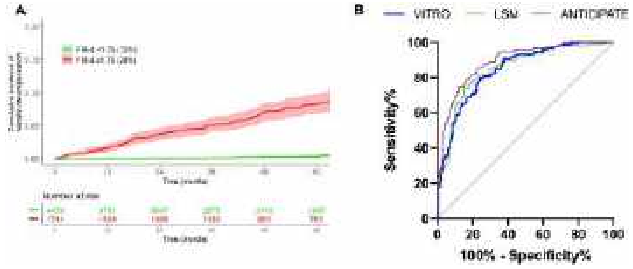


Disclosures: Jennifer Linge – AMRA Medical AB: Employee, Yes, No; Eli Lilly: Consultant, No, No; BioMarin: Speaking and Teaching, No, Yes;
Mikael Fredrik Forsgren – AMRA Medical AB: Employee, Yes, No;
The following people have nothing to disclose: Mohammad S. Siddiqui, Vaishali Patel, Seung Lee
Disclosure information not available at the time of publication: Danielle Kirkman, Geneva Roche, Hiba Kamal, Per Widholm, Olof Dahlqvist Leinhard

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

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

Background: The population at risk for liver-related complications is defined by compensated advanced chronic liver disease (cACLD), while presence of clinically significant portal hypertension (CSPH) identifies the target population for prevention of hepatic decompensation. Liver stiffness measurement (LSM) via vibration-controlled transient elastography enables non-invasive diagnosis of these conditions, but its availability is oftentimes limited to tertiary care, potentially impeding the identification of cACLD/CSPH in the community. Thus, we developed a routine laboratory-based algorithm to (i) identify patients with cACLD via fibrosis-4 index (FIB-4) and (ii) subsequently rule-in/rule-out CSPH using von Willebrand factor antigen/platelet count ratio (VITRO). **Methods:** FIB-4 cohort: To determine a FIB-4 cut-off for cACLD diagnosis, all patients with suspected cACLD undergoing LSM and FIB-4 assessment between 2007-2021 were characterized and followed-up for development of hepatic decompensation. VITRO cohort: cACLD patients (diagnosed by the FIB-4 cut-off) with hepatic venous pressure gradient (HVPG) measurement were analysed. **Results:** FIB-4 cohort: Among 6182 patients (median follow-up [FU] time: 54.6 mo) hepatic decompensation occurred in 3.4% ($n = 211$). Both LSM (AUC 0.90; 95%CI: 0.86-0.92) and FIB-4 (AUC 0.91; 95%CI: 0.88-0.94) exhibited excellent accuracy in predicting hepatic decompensation within 2 years of FU. FIB-4 e 1.75 (corresponding to LSM e 10kPa) was determined as cut-off for cACLD identification, ruling-out cACLD in 72% of patients. Patients with FIB-4 < 1.75 had negligible risk of of hepatic decompensation at 5 years of FU (cumulative incidence 0.03%). VITRO cohort: 317 cACLD patients (CSPH prevalence: 62.8%, $n = 199/317$) were included. Accuracy for diagnosing CSPG was similar for VITRO (AUC 0.85; 95%CI: 0.80-0.89), LSM (AUC 0.85; 95%CI: 0.81-0.89; DeLong-Test: $p = 0.903$) and the ANTICIPATE model (AUC 0.89; 95%CI: 0.86-0.93; p = 0.109). VITRO < 1.0 ruled-out (prevalence: 11.4%; sensitivity 97.5%) and VITRO e 2.5 ruled-in CSPH (prevalence: 41.6%; specificity 90.6%), with results comparable to the Baveno VII cut-offs LSM d 15kPa + PLT e 150G/L (prevalence: 10.1%; sensitivity: 99.0%) and LSM e 25kPa (prevalence: 44.2%; specificity: 89.0%). **Conclusion:** FIB-4 e 1.75 identifies cACLD and VITRO < 1.0 / e 2.5 rules-out/rules-in CSPH with a similar diagnostic accuracy as criteria based on LSM. Simple laboratory tests may broaden the access to risk stratification and facilitate early intervention to prevent first hepatic decompensation.



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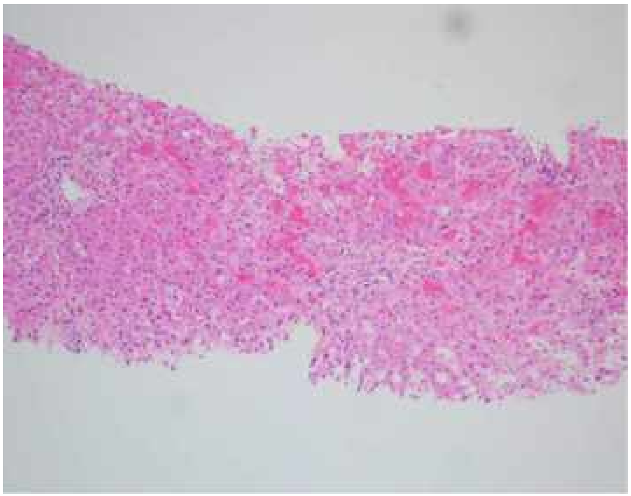
The following people have nothing to disclose: Lukas Hartl, Georg Semmler, Mathias Jachs, Benedikt Simbrunner, Benedikt Silvester Hofer, Lorenz Balcar, Michael Schwarz, Laurenz Fritz, Anna Schedlbauer, Katharina Stopfer, Daniela Neumayer, Jurij Maurer, Robin Szymanski, Bernhard Scheiner, Michael Trauner, Mattias Mandorfer

3004-A | ASCITES IN A SICKLE CELL PATIENT

Nilofar Najafian[1], Sammy Saab[2], Samuel W. French[1] and Akshay Shetty[2], (1)University of California-Los Angeles, (2)University of California, Los Angeles

Background: Sickle cell hepatopathy is an entity with a wide range of clinical presentations. Though sickling of red blood cells in hepatic sinusoids is commonly seen, no prior cases of associated portal hypertension have been reported in the absence of cirrhosis. **Methods:** Clinical data was extracted from the medical records and interpreted in this case report. **Results:** A post-liver transplant sickle cell patient was found to have acute sickle hepatic crisis and new onset ascites. Fluid analysis revealed a high SAAG, high protein ascites without evidence of a peritoneal infection. Transthoracic echocardiogram showed intact left ventricular function and normal right ventricular systolic pressure. Portal pressure measurements showed right atrial pressure of 8 mmHg, free hepatic vein pressure 12 mmHg, wedged hepatic vein pressure 21, and elevated hepatic venous pressure gradient (HVPG) of 9mm Hg. Trans-jugular liver biopsy showed pan-lobular vascular congestion and sinusoidal congestion in absence of rejection, steatosis, or fibrosis, suggesting sinusoidal obstruction syndrome in the setting of hepatic sickling as the cause of portal hypertension (Figure 1). **Conclusion:** Sinusoidal obstruction syndrome is an entity that may be seen in patients with sickle cell disease even after liver transplantation. Proactive practices post-transplant may help minimize recurrent sickle hepatopathy and development of portal hypertension.



Disclosures: The following people have nothing to disclose: Nilofar Najafian, Sammy Saab, Samuel W. French, Akshay Shetty

3005-A | BASELINE CORTISOL LEVELS DO NOT PREDICT ADRENAL DYSFUNCTION IN DECOMPENSATED CIRRHOSIS

Matthew Schliep, Brian Wentworth, Wendy M Novicoff, Zachary Henry and Helmy Siragy, University of Virginia

Background: Adrenal dysfunction (AD) is common in patients with decompensated cirrhosis. Data from the general population suggests that a low isolated morning total cortisol (TC) level may predict adrenal insufficiency, yet whether this can be extrapolated to patients with cirrhosis and hypoproteinemia is unknown. We aimed to assess whether an isolated morning cortisol level (both total and plasma free) predicted an impaired response to ACTH stimulation testing in non-critically ill patients with cirrhosis. **Methods:** We performed a single-center, retrospective cohort study including patients with decompensated cirrhosis admitted without critical illness or hemodynamic instability who underwent ACTH stimulation testing between Jan 1, 2017 and February 28, 2022. All patients had baseline TC and plasma free cortisol levels (PFC) drawn, then were administered standard-dose (250 μcg) synacthen stimulation test. An abnormal cortisol response (AD) was defined as an increase (delta) of TC < 9 μg/dL after 60 minutes. Between group variables were compared using the appropriate univariate test (mean ± SD, median (IQR), two-tailed independent t-test, or Mann-Whitney U test). Multivariate logistic regression models were constructed to investigate whether basal cortisol levels and/or other common clinical parameters (albumin level, HDL level, MELD score) predicted the presence of AD. A sensitivity analysis utilizing a TC < 5 μg/dL threshold was also performed. **Results:** One hundred and twenty-two patients were included for analysis; 58 met criteria for AD. Demographic variables, disease etiology, and electrolyte profile were similar between patients with and without AD. Patients with AD had more severe liver disease (Child-Pugh C classification: 76% vs. 37%, $p < 0.001$; MELD score: 20 vs. 17, $p = 0.008$) and hypoalbuminemia (2.6 vs. 2.9 mg/dL, $p = 0.019$). Basal TC (OR 1.000, 95% CI 0.912-1.096, 0.993) and PFC (OR 1.213, 95% CI 0.614-2.399, $p = 0.578$) were not predictive of AD on multivariate regression. A basal TC < 5 μg/dL also did not predict AD presence (OR 0.979, 95% CI 0.403-2.376, $p = 0.963$). MELD score and albumin level were significant independent predictors of AD in all models (Table 1). **Conclusion:** Baseline cortisol levels do not predict ACTH stimulation response in non-critically ill patients with decompensated cirrhosis. The presence of AD appears related to disease severity but formal adrenal axis testing is necessary for appropriate assessment.

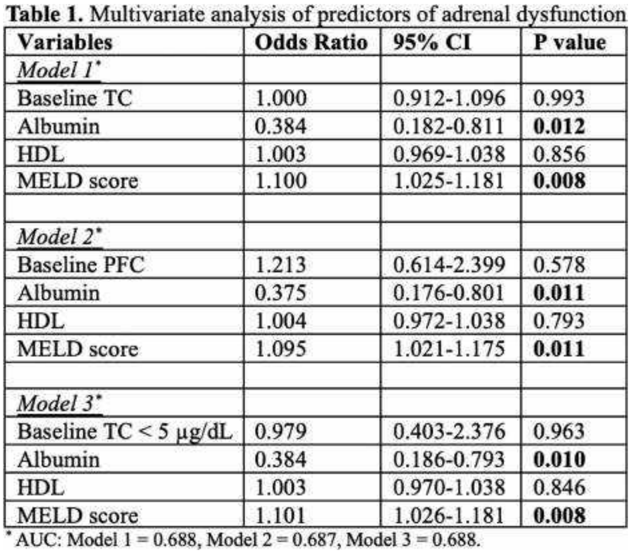


Table 1. Multivariate analysis of predictors of adrenal dysfunction

Variables	Odds Ratio	95% CI	P value
*Model 1**			
Baseline TC	1.000	0.912-1.096	0.993
Albumin	0.384	0.182-0.811	**0.012**
HDL	1.003	0.969-1.038	0.856
MELD score	1.100	1.025-1.181	**0.008**
*Model 2**			
Baseline PFC	1.213	0.614-2.399	0.578
Albumin	0.375	0.176-0.801	**0.011**
HDL	1.004	0.972-1.038	0.793
MELD score	1.095	1.021-1.175	**0.011**
*Model 3**			
Baseline TC < 5 μg/dL	0.979	0.403-2.376	0.963
Albumin	0.384	0.186-0.793	**0.010**
HDL	1.003	0.970-1.038	0.846
MELD score	1.101	1.026-1.181	**0.008**

* AUC: Model 1 = 0.688, Model 2 = 0.687, Model 3 = 0.688.

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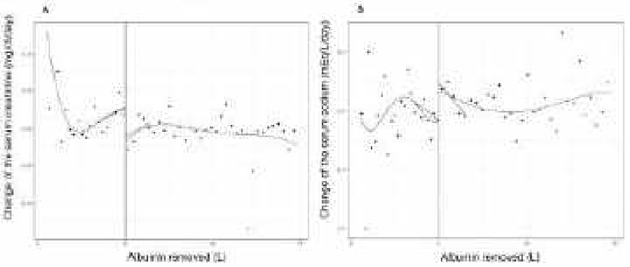
Disclosure information not available at the time of publication: Brian Wentworth, Wendy M Novicoff, Helmy Siragy

3006-A | CAUSAL EFFECT OF ALBUMIN INFUSION FOLLOWING LARGE-VOLUME PARACENTESIS: RE-EVALUATION OF THE AASLD PRACTICE GUIDANCE WITH REGRESSION DISCONTINUITY

Tomohiro Tanaka[1], Michael P Jones[2] and George Wehby[2,3], (1)University of Iowa Carver College of Medicine, (2)Center for Access and Delivery Research and Evaluation (CADRE), Iowa City VA Health Care System, (3)University of Iowa College of Public Health

Background: The 2021 AASLD Practice Guidance recommends using albumin infusion to prevent post-paracentesis circulatory dysfunction when > 5 liter of ascites are removed. However, the optimal cutoff for initiating albumin infusion following large-volume paracentesis (LVP) based on ascites removed remains understudied. **Methods:** We conducted a retrospective cohort study at a U.S. academic healthcare center on all patients who underwent outpatient LVP between 2019 and 2022. Patients with spontaneous bacterial peritonitis, post-LVP adjustment of diuretics, and/or hospitalization were excluded. The institution strictly followed the Guidance, which recommends albumin infusion for patients who had e 5 liters of ascites removed, making the cohort suitable for a Quasi-experimental, sharp regression discontinuity (RD) design to estimate the local average treatment effect of albumin infusion on the trajectory of serum creatinine and serum sodium levels. We also conducted sensitivity analyses using different kernel functions, bandwidths, and regression models that included both fixed effects (confounders) and random effects (unique patients). **Results:** Over the study period, a total of 1457 LVP procedures were performed on 236 unique patients, with a median of 2 procedures and an interquartile range (IQR) of 6 per patient. In our main RD models, we used a local polynomial and linear RD estimation. Results revealed that administering albumin infusion at threshold of 5 L of ascites removal led to a significant reduction in serum creatinine levels by 0.05 (95%CI: 0.01-0.097) and 0.048 (0.01-0.086) mg/dl/day, and an increase in serum sodium levels of 0.34 (95%CI: 0.12-0.6) and 0.39 (0.16-0.61) mEq/L/day, respectively, compared to those who did not receive albumin infusion (Figure). The RD plots also indicated elevated serum creatine and reduced serum sodium levels after draining 3-4 liters of fluid, approaching levels similar to or worse than with albumin infusion at 5 liters or more, suggesting potential benefits for albumin replacement at a lower cut-off. **Conclusion:** RD models provide strong evidence that administering albumin infusion just above 5L of ascites removal during LVP has significant benefits. The consistency of findings across sensitivity analyses underscores the robustness of the effect size estimation. Findings support the conduct of clinical trials to evaluate the efficacy of albumin infusion in patients who undergo LVP and have 3-5 or 4-5 liters of ascites removed.

Figure: Changes in serum creatinine (A) and serum sodium (B) levels per day following LVP. The solid curve represents the result of the polynomial regression model, and the dashed line represents the result of the local regression models within the optimal bandwidth based on the Imbens-Kalyanaraman (IK) method.

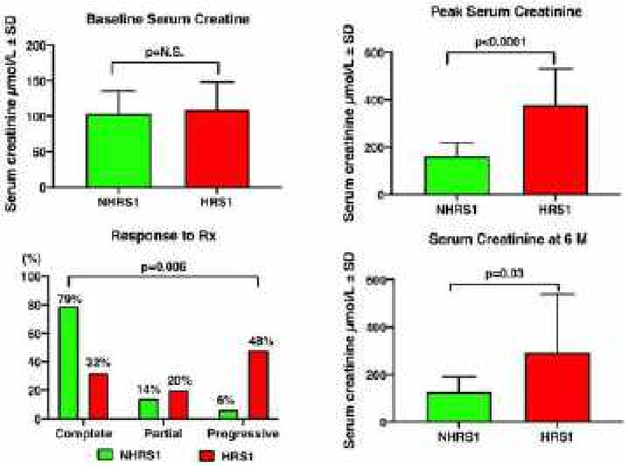


Disclosures: The following people have nothing to disclose: Tomohiro Tanaka, Michael P Jones, George Wehby

3007-A | CLINICAL FEATURES OF ACUTE KIDNEY INJURY-NON HEPATORENAL SYNDROME VERSUS TYPE 1 HEPATORENAL SYNDROME IN PATIENTS WITH CIRRHOSIS AND ASCITES FROM A SINGLE QUATERNARY REFERRAL ACADEMIC CENTRE

Neha Tiwari[1], Chinmay Bera[2], Cynthia Tsien[3], Audrey Kapelera[1], Nazia Selzner[3] and Florence Wong[1], (1) Division of Gastroenterology and Hepatology, Toronto General Hospital, Toronto, ON, Canada, (2)University Health Network, (3)Ajmera Transplant Center, University of Toronto, Toronto, ON, Canada

Background: The re-classification of renal dysfunction in cirrhosis to acute kidney injury (AKI), replacing type 1 hepatorenal (HRS1), is meant to lead to earlier diagnosis and treatment. The aim of this study was to identify clinical features that distinguish AKI-non-HRS1 (NHRS1) from HRS1 to facilitate earlier recognition of pending HRS1. **Methods:** Retrospective study of patients with cirrhosis and ascites from a single quaternary centre from Apr 2020 to Mar 2021 identified patients who fulfilled the 2015 International Ascites Club (IAC) diagnosis of AKI. They were then separated into those fulfilling the 2007 IAC diagnostic criteria of HRS1 vs. those who did not. Data were collected on demographics, clinical features, AKI characteristics, AKI and patient outcomes at 6 months. Multivariate analysis for factors predicting AKI severity was done. **Results:** 81 of 306 patients with ascites of various severities had 120 AKI episodes (stage 1: n = 84, stage 2 but not HRS1: n = 11, HRS1: n = 25). The 1st 2 groups formed the NHRS1 group. The HRS1 group were mostly alcoholics (93%) ($p = 0.03$ vs. NHRS1) with a shorter history of ascites (17M vs. 28M, $p = 0.04$), but a frequent history of SBP ($p = 0.05$). 55% of HRS1 patients presented as outpatients ($p = 0.01$ vs. NHRS1) with evidence of liver failure (INR: 2.1 vs. 1.6, $p = 0.02$, bilirubin: 175 vs. 45μmol/L, $p = 0.001$). The NHRS1 group was more likely to have dehydration as an AKI precipitant (34% vs. 8%, $p = 0.03$), whereas infection was the more frequent precipitant in HRS1 patients (32% vs. 6%, $p < 0.001$). 88% of HRS1 patients received midodrine and albumin, vs. 31% in the NHRS1 group ($p = 0.008$), whereas 8% of HRS1 and 41% NHRS1 patients received albumin only ($p < 0.001$). HRS1 patients received a mean of 321g of albumin vs. 107g in the NHRS1 group ($p < 0.001$). Response to treatment in HRS1 was inferior to that of NHRS1 ($p = 0.006$), as these patients had other organ failures (mean 2.3 organ failure vs. 1.3 in NHRS1 group, $p < 0.001$). Survival at 6 months was significant reduced ($p < 0.001$) in the HRS1 group due to recurrent stage 2 AKI ($p = 0.001$) and repeat hospital admissions ($p < 0.001$). For every 5-point increase in MELD, there is a 2.13 X the risk for the development of HRS1. **Conclusion:** This study identifies the profile of the patient likely to develop HRS1, with baseline MELD as a strong predictor. Every effort should be made to prevent MELD increase, as this may reduce the chance of HRS1 development, a condition with a potentially fatal outcome.



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Disclosure information not available at the time of publication: Cynthia Tsien, Audrey Kapelera

3008-A | COMPARISON OF MELD AND MELD-NA AS PROGNOSTIC SCORE FOR PATIENTS UNDERGOING TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT PLACEMENT

Akash Singh, Sagar Desai, Manisha Verma, Manish Thapar, Balasubramani Natarajan, Paul Brady and Richard S. Kalman, Einstein Healthcare Network

Background: The purpose of this study was to compare the ability of the model for end-stage liver disease (MELD) and sodium MELD (MELD-Na) scoring systems to predict outcomes after transjugular intrahepatic portosystemic shunt (TIPS) placement. MELD has traditionally been seen as the gold standard for post-TIPS mortality prediction. **Methods:** Eighty-five consecutive patients who underwent TIPS placement were retrospectively reviewed. The primary outcomes were death within 30 days and 90 days after TIPS placement (30- and 90- day mortality, respectively), and secondary outcome included death within 365 days after TIPS placement (365-day mortality). **Results:** Mortality rates within 30, 90, and 365 days after TIPS placement were 10.6% (9/85), 15.3% (13/85), and 21.2% (18/85). Simple logistic regression showed that MELD score predicted 30-day mortality (odds ratio [OR], 1.166; 95% CI, 1.059–1.285; $p = 0.002$) and 90-day mortality (OR, 1.154; 95% CI, 1.052–1.266; $p = 0.002$). MELD-Na score also predicted 30-day mortality (OR, 1.61; 95% CI, 1.059–1.273; $p = 0.001$) and 90-day mortality (OR, 1.144; 95% CI, 1.051–1.245; $p = 0.002$). In comparing the ROC AUCs for MELD with MELD-Na, they were similar in predicting 30-day mortality ($p = 0.367$) and 90-day mortality ($p = 0.218$). However, 365-day mortality prediction was significantly better with MELD as compared to MELD-Na while comparing both AUCs ($p = 0.041$). Overall, 30-day readmission rate after TIPS placement was 35% (30/85). The most common diagnosis at the time of readmission was decompensation of liver disease associated with hepatic encephalopathy (50%). There were five patients with high MELD-Na e 17, and low MELD < 15. There was no 90-day mortality in this

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

group, but the rate of readmission was 40%. **Conclusion:** MELD and MELD-Na are similar in predicting 30-day mortality and 90-day mortality. However, MELD seems to be more predictive of 365-day mortality than MELD Na. MELD should remain the gold standard for prediction of post-TIPS mortality at one year.

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Disclosure information not available at the time of publication: Sagar Desai, Manisha Verma, Balasubramani Natarajan, Paul Brady, Richard S. Kalman

3009-A | CONSULTATION TO HEPATOLOGY INCREASE RATES OF ANTIBIOTIC PRESCRIPTION FOR SPONTANEOUS BACTERIAL PERITONITIS PROPHYLAXIS AND REDUCED HOSPITAL MORTALITY FROM FUTURE SPONTANEOUS BACTERIAL PERITONITIS EPISODES

Parth Bhupendra Patel[1], Sujan Ravi[1], Ore Adekunle[1], Udita Gupta[1], Thomas Ruli[1], Mohamed Galal Shoreibah[2] and University of Alabama at Birmingham, (1)University of Alabama at Birmingham, (2)University of Alabama at Birmingham, Birmingham, AL

Background: Spontaneous bacterial peritonitis (SBP) is a common yet serious infection that occurs in cirrhotic patients with ascites. SBP has been shown to have a mortality rate of 80% with a delay in antibiotics being associated with an increased mortality. Many are familiar with the concept of initiating antibiotics due to elevated polymorphonuclear leukocytes or positive ascitic fluid cultures, but many are unaware of discharging patients with antibiotics for primary SBP prevention. In patients who meet criteria for low protein ascites (< 1.5 g/dL) and advanced liver failure (Child-Pugh > 9 and serum bilirubin > 3mg/dL) or renal impairment (serum creatinine of > 1.2 mg/dL, BUN levels > 25 mg/dL, or sodium of < 130 mEq/L) antibiotics such as Norfloxacin or Bactrim should be prescribed to prevent SBP episodes. We hypothesize that consultation to Hepatology in cirrhotic patients needing a paracentesis will lead to more antibiotic prescriptions, reduced in-hospital mortality, and increased prevention of future SBP episodes. **Methods:** We performed a retrospective cohort study and included cirrhotic patients admitted in 2021 that required a paracentesis. Data collected includes baseline characteristics, specific type of cirrhosis, whether Hepatology was consulted, total protein values collected during the admission, antibiotic prescriptions, the rate of future SBP episodes, and in-hospital mortality. Univariate and multivariate logistic regression analysis were performed for these outcomes. **Results:** Our cohort (n = 321) had an average age of 57.5 ± 11.11, an average BMI of 29.28 ± 14.01, and 193 (60%) of the cohort was male. Most of the cohort had either NASH (29.28%) or alcoholic (38.01%) cirrhosis. Out of 321 patients, 263 patients met criteria to check a total protein while 201 patients actually got a total protein check this admission or during a previous admission. Of these 201 patients, 100 (31.1%) patients met the requirements for initiation of antibiotics for SBP prevention. Out of these 100 patients, Hepatology was consulted on 24 patients and discharged with antibiotics while 5 patients were discharged on antibiotics without a Hepatology consult. When Hepatology was consulted, there were 2 episodes of future SBP events compared to 12 episodes occurring in the group without Hepatology consultation (p-value of 0.0001). When Hepatology was consulted hospital mortality due to SBP was 2 patients compared to 12 deaths in the no consult group (p-value of 0.0001). **Conclusion:** SBP is serious infection that has a high mortality rate of 80% with a delay in antibiotics being associated with an increased in-hospital mortality. Those patients that had a Hepatology consult were shown to have more antibiotics prescribed, less future SBP episodes, and an improvement in hospital mortality due to SBP. Our study shows that a timely consultation to Hepatology can be helpful in improving patient mortality and SBP prevention.

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Disclosure information not available at the time of publication: Sujan Ravi, Ore Adekunle, Udita Gupta, Thomas Ruli, Mohamed Galal Shoreibah

3010-A | COULD REAL TIME MONITORING OF URINE CONDUCTANCE IDENTIFY NATRIURESIS IN PATIENTS WITH CIRRHOSIS AND ACUTE KIDNEY INJURY?

Bill Zhang[1], Marlyn J. Mayo[2], Orson Moe[2] and Matthew Leveno[2], (1)University of Texas Southwestern Medical School, (2)University of Texas Southwestern Medical Center

Background: End-stage liver disease complicated by renal hypoperfusion and rapidly progressive acute kidney injury (AKI) carries high short-term mortality. Extrapolating from studies in patients with hepatorenal syndrome (HRS), it is possible that early treatment with vasopressors drives an increase in mean arterial pressure (MAP) sufficient to reverse the prerenal injury. Unfortunately, there is no clear guidance for the optimal prospective MAP target and it stands to reason that this will differ between patients. The onset of natriuresis may be a useful early marker of improved renal perfusion and could signal the arrival at the optimal MAP. However, it is impractical to measure serial urine electrolytes with the frequency required for titration of IV vasopressors. We hypothesized that changes in urinary conductance could serve as a practical surrogate for changes in urinary sodium concentrations. **Methods:** ICU patients with shock and AKI were prospectively enrolled. Serial urine samples were collected for spot urine sodium, potassium, chloride, and creatinine. In addition, each sample underwent conductivity testing using a benchtop meter. To assess whether changes in conductance predict changes in sodium, we compared each time point to the one immediately prior - a correct prediction was made if conductance and sodium both increased or both decreased at the next time point. If sodium was unchanged, the new time point was discarded as urine electrolytes were not sensitive to changes in sodium below 1 mEq/L. Results were analyzed using Fisher's Exact Test and Pearson correlation coefficient (*MATLAB ver. R2022a*). **Results:** A total of 97 paired urine sodium and conductance measurements were made in 10 patients, 8 of whom had cirrhosis. After excluding time points where sodium did not change from the previous time point, 56 paired measurements remained. Changes in conductance correctly predicted changes in sodium 36/56 times ($p = 0.029$). In five patients, conductance was significantly and positively correlated with sodium (representative patient in Figure 1). Two out of five patients whose conductance did not correlate with sodium had already developed acute renal failure and likely lacked the ability to manipulate renal sodium handling. **Conclusion:** Urine conductance appears to predict urine sodium, and thus natriuresis, in patients with cirrhosis and AKI. Serial monitoring of urine conductance may be a practical surrogate for detecting natriuresis and could inform clinical decision making when assessing hemodynamics.

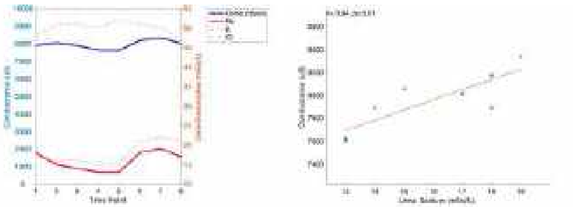

Figure 1. Representative urine electrolyte and conductance measurements from a patient. Left: urine conductance (solid blue) tracks urine sodium (solid red) over time. Right: urine conductance is significantly correlated with urine sodium measurements in this patient ($r = 0.84$, $p < 0.01$).

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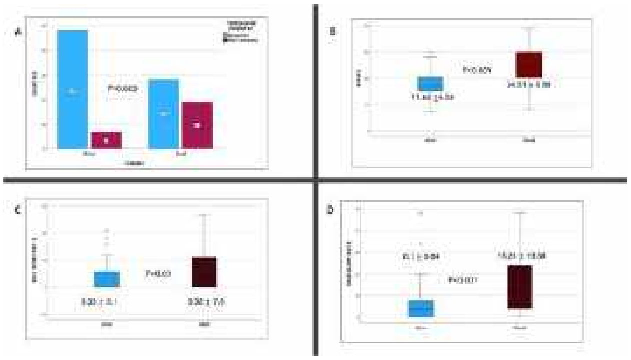
Disclosure information not available at the time of publication: Orson Moe, Matthew Leveno

3011-A | CRITICALLY ILL CIRRHOSIS PATIENTS RECEIVING TERLIPRESSIN + ALBUMIN FOR HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY (HRS-AKI) MUST BE MONITORED WITH POINT-OF-CARE ULTRASONOGRAPHY

Vedaghosh Amara, Pooja Karandikar, Anand Gupta, Sivakumar Reddy, Arun T.M Kumar, Sowmya T R, Manasa Alla, Shantan Venishetty, Mithun Sharma, Nageshwar D Reddy, Padaki Nagaraja Rao and Anand V. Kulkarni, Aig Hospitals, Hyderabad, India

Background: Terlipressin plus albumin (terli+alb) is recommended for patients with cirrhosis and hepatorenal syndrome-acute kidney injury (HRS-AKI). Pulmonary overload is a significant adverse event associated with the use of terli+alb. Therefore, we aimed to evaluate the role of Radiographic Assessment of Lung Edema (RALE) score and Lung UltraSonography (LUS) in critically ill cirrhosis (CIC) patients who receive terli+alb. **Methods:** Consecutive CIC patients with HRS-AKI who received terli+alb in the liver ICU from 28-04-2022 to 16-10-2022 were included in the study. Terlipressin was infused at a dose of 2 mg/day, increased every 48 hours in case of non-response, and albumin was infused at 20 g/day. The primary objective was to assess the RALES and LUS scores at baseline and day 3. The secondary objective was to determine the terlipressin response and predictors of in-hospital mortality. **Results:** 102 patients (alcohol-60.8%; age-50 ± 12.18 y; serum creat-2.55 mg/dl) received terli+alb for HRS-AKI. Of them, 55 survived (Gr. A), and 47 died (Gr. B) in hospital. Baseline serum creatinine (2.02 vs. 2.25 mg/dl), MELD NA score (26.4 vs. 25.3), SOFA score (12 vs. 11.63), and dose of terli+alb were similar among both groups. The proportion of patients with culture-proven infection was similar among both groups (21.8% vs. 30.4%). Thirteen percent in Gr. A compared to 55.3% in Gr. B were on mechanical ventilation ($P < 0.001$) at baseline. While on follow-up, only 11% in Gr. A and 95.7% in Gr. B required mechanical ventilation ($P < 0.001$). 12.7% in Gr. A and 40.4% n Gr. B were terlipressin non-responders ($P = 0.003$) (Fig. A). APACHE score was higher in Gr. B patients than in Gr. A (Fig. B). Rales score on days 1 (Gr. A: 3.34 ± 5.08 vs Gr. B:6.32 ± 7.57; $P = 0.01$) and 3 (Gr. A: 6.1 ± 8.64 vs. Gr. B: 15.26 ± 13.38;$P < 0.001$) were higher in Gr. B patients compared to Gr. A (Fig. C, D). 66% had worsening RALES scores on day 3 in Gr. B compared to 41.8% in Gr. A. ($P = 0.01$). LUS score worsened in 66% ($n = 31$) of patients in Gr. B compared to 40% ($n = 22$) in Gr. A ($P = 0.03$). The proportion of patients developing terlipressin adverse events (any grade) was more in Gr. B (23.4%) than in Gr. A (11%; $P = 0.07$). On multivariate logistic regression analysis, RALES score at day 3 (1.07 [1.02-1.13];$P = 0.003$), baseline APACHE score (OR, 1.18 [1.08-1.29];$P < 0.001$) and terlipressin non-response (OR, 4.91 [1.49-16.2];$P = 0.009$) predicted in-hospital mortality. **Conclusion:** Critically ill cirrhosis patients receiving terli+alb must be monitored with point-of-care ultrasonography. RALES score, APACHE score, and terlipressin non-response predict mortality in critically ill cirrhosis patients with HRS-AKI.



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3012-A | DESPITE A MINORITY BEING ELIGIBLE FOR CURATIVE OPTIONS, LINKAGE TO PALLIATIVE CARE REMAINS SUBOPTIMAL IN CIRRHOSIS-RELATED REFRACTORY ASCITES

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Background: Despite refractory ascites (RA) having a median transplant-free survival of six to twelve months, palliative care (PC) input in this cohort remains uncertain. We aimed to assess outcomes in cirrhosis-related RA with emphasis on the provision of PC. **Methods:** This single centre retrospective cohort study assessed patients admitted with RA (Jun 2012-Jun 2019) with last follow up on 31st Mar 2020. RA was defined as either diuretic intolerant or diuretic resistant ascites with three or more large volume paracentesis (LVP). **Results:** During the study period, 13% (89/667) of patients identified with cirrhosis-related ascites developed RA. The mean age was 59 ±13 years and 70% were male. The aetiologies of cirrhosis were alcohol (80%), metabolic associated fatty liver disease (18%) and viral hepatitis (10%). Median number of LVPs was 5 (IQR 3-8). Median CPS, MELD and UKELD scores were 9 (IQR 8-10), 13.8 ± 5.0 and 55.9 ± 5.3 respectively with 67% on diuretics at the time of RA diagnosis. Comorbidities included diabetes mellitus (33%), cardiovascular (33%) and psychiatric (24%) disorders. Overall, 37% had a prior history of spontaneous bacterial peritonitis. Though 38% were referred for a liver transplant/ trans-jugular intrahepatic porto-systemic shunt (TIPS), only 13% received one. Palliative long-term abdominal drains (LTAD) were inserted in 11 patients. Although 56% had documented end of life care discussions, only 33% were referred to PC. Time from RA diagnosis to PC referral was 15 weeks (IQR 4-32), time from PC referral to death being 9 weeks (IQR 4-16). Independent predictors of referral to PC were LTAD insertion (OR 11.0, CI 2.11-57.0, $p < 0.01$) and age (OR 1.57/ten years, CI 1.04-2.38, $p = 0.03$). There was a trend for PC referral to be a predictor of death outside hospital (OR 2.83, CI 0.89-9.04-0.89, $p = 0.078$). Compared to no intervention, receiving transplant/TIPS but not LTADs was associated with a significantly higher one-year survival (83% vs. 44% $p = 0.011$ and 36% vs 44% $p = 0.987$ respectively) (Fig 1). Independent predictors of mortality were undergoing transplant/TIPS (OR 0.15, CI 0.03-0.65, $p = 0.011$) and psychiatric co-morbidity (OR 0.32 CI 0.10-0.97 $p = 0.045$). **Conclusion:** One year survival of patients with cirrhosis-related RA who do not undergo TIPS/

transplant remains poor. Despite this, only a third are referred to PC and often too late. More research into the optimal timing and nature of PC interventions in RA is required.

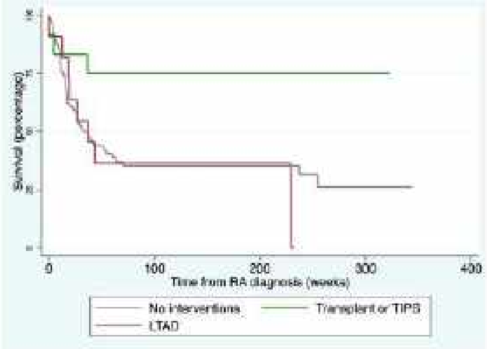

Fig 1 KM survival of patients with RA who underwent either TIPS/transplant or LTAD insertion compared to those who did not receive any intervention (p=0.011 and 0.987 respectively)

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3013-A | EFFICACY OF CONTINUOUS TERLIPRESSIN INFUSION IN HRS-AKI IN A TRANSPLANT-ENRICHED POPULATION: A COMPARATIVE PROSPECTIVE AND RETROSPECTIVE COHORT STUDY

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Background: Hepatorenal syndrome-acute kidney injury (HRS-AKI), a serious complication of decompensated cirrhosis with limited therapeutic options, is associated with significant morbidity and mortality. Liver transplant (LT) is the definitive treatment but access is limited. Continuous terlipressin infusion may provide HRS reversal and renal outcome benefits and as such was assessed in a population enriched with LT candidates. **Methods:** An open-label study of continuous terlipressin infusion (INFUSE; NCT04460560) was completed in a prospective cohort of 50 patients with cirrhosis, ascites, and HRS-AKI based on the 2015 revised diagnostic criteria. The cohort was enriched with patients listed/in evaluation/eligible for LT. ACLF grade 3, serum creatinine (SCr) $>$ 5.0 mg/dL, or MELD e 35 were exclusions. Following a 0.5 mg bolus, terlipressin was administered via continuous infusion at 2 - 8 mg/day based on SCr response and tolerability. A comparator cohort included 50 retrospective patients who received midodrine plus octreotide (M&O) or norepinephrine (NorEpi) for HRS-AKI and would have met INFUSE criteria. Complete response (CR) was defined as e 30% decrease in SCr with end of treatment (EOT) SCr d 1.5, partial response (PR) as e 30% decrease in SCr with EOT SCr $>$ 1.5, and nonresponse (NR) as $<$ 30% decrease in SCr. **Results:** (See table) CR was more often in the prospective continuous terlipressin infusion cohort compared to the retrospective M&O/NorEpi cohort (64% vs 16%, $p < 0.001$). Survival at days 30 and 90 of follow-up, while numerically higher in the prospective cohort, was statistically similar (Day 30: 94% vs 80%, $p = 0.07$; Day 90: 78% vs 68%, NS). RRT was uncommon among terlipressin CR or PR, while common among NR (3% vs 12.5% vs 70%, $p < 0.001$). LT alone was achieved in a higher proportion of terlipressin CR than PR or NR (63% vs 6% vs 31%, NS). One patient in the prospective cohort had hypoxic respiratory failure that responded to diuretics; one had a possibly drug-related rash. SAEs were not captured in the retrospective cohort. **Conclusion:** Response rates and SCr decline were greater in the prospective terlipressin infusion cohort compared with a retrospective M&O/NorEpi cohort. While continuous terlipressin infusion significantly decreased MELD and SCr at EOT, 90-day LT rates were high and similar between cohorts, and terlipressin CR had a higher rate of LT alone than PR or NR. RRT was required more often in the terlipressin NR group.

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

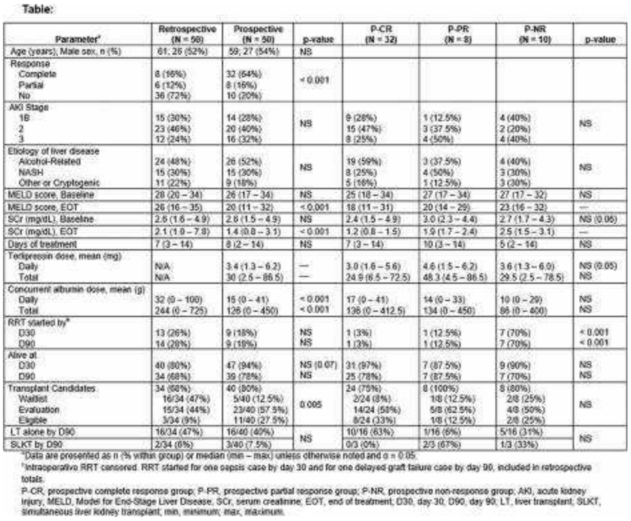

Table:

Parameter[*]	Retrospective (N = 50)	Prospective (N = 50)	p-value	P-CR (N = 32)	P-PR (N = 8)	P-NR (N = 10)	p-value
Age (years); Male sex, n (%)	61; 26 (52%)	59; 27 (54%)	NS				
Response Complete Partial No	 8 (16%) 6 (12%) 36 (72%)	 32 (64%) 8 (16%) 10 (20%)	< 0.001				
AKI Stage 1B 2 3	 15 (30%) 23 (46%) 12 (24%)	 14 (28%) 20 (40%) 16 (32%)	NS	 9 (28%) 15 (47%) 8 (25%)	 1 (12.5%) 3 (37.5%) 4 (50%)	 4 (40%) 2 (20%) 4 (40%)	NS
Etiology of liver disease Alcohol-Related NASH Other or Cryptogenic	 24 (48%) 15 (30%) 11 (22%)	 26 (52%) 15 (30%) 9 (18%)	NS	 19 (59%) 8 (25%) 5 (16%)	 3 (37.5%) 4 (50%) 1 (12.5%)	 4 (40%) 3 (30%) 3 (30%)	NS
MELD score, Baseline	28 (20 – 34)	26 (17 – 34)	NS	25 (18 – 34)	27 (17 – 34)	27 (17 – 32)	NS
MELD score, EOT	26 (16 – 35)	20 (11 – 32)	< 0.001	18 (11 – 31)	20 (14 – 29)	23 (16 – 32)	—
SCr (mg/dL), Baseline	2.6 (1.6 – 4.9)	2.6 (1.5 – 4.9)	NS	2.4 (1.5 – 4.9)	3.0 (2.3 – 4.4)	2.7 (1.7 – 4.3)	NS (0.06)
SCr (mg/dL), EOT	2.1 (1.0 – 7.8)	1.4 (0.8 – 3.1)	< 0.001	1.2 (0.8 – 1.5)	1.9 (1.7 – 2.4)	2.5 (1.5 – 3.1)	—
Days of treatment	7 (3 – 14)	8 (2 – 14)	NS	7 (3 – 14)	10 (3 – 14)	5 (2 – 14)	NS
Terlipressin dose, mean (mg) Daily Total	 N/A N/A	 3.4 (1.3 – 6.2) 30 (2.5 – 86.5)	 — —	 3.0 (1.6 – 5.6) 24.9 (6.5 – 72.5)	 4.6 (1.5 – 6.2) 48.3 (4.5 – 86.5)	 3.6 (1.3 – 6.0) 29.5 (2.5 – 78.5)	 NS (0.05) NS
Concurrent albumin dose, mean (g) Daily Total	 32 (0 – 100) 244 (0 – 725)	 15 (0 – 41) 126 (0 – 450)	 < 0.001 < 0.001	 17 (0 – 41) 136 (0 – 412.5)	 14 (0 – 33) 134 (0 – 450)	 10 (0 – 29) 86 (0 – 400)	 NS NS
RRT started by[†] D30 D90	 13 (26%) 14 (28%)	 9 (18%) 9 (18%)	 NS NS	 1 (3%) 1 (3%)	 1 (12.5%) 1 (12.5%)	 7 (70%) 7 (70%)	 < 0.001 < 0.001
Alive at D30 D90	 40 (80%) 34 (68%)	 47 (94%) 39 (78%)	 NS (0.07) NS	 31 (97%) 25 (78%)	 7 (87.5%) 7 (87.5%)	 9 (90%) 7 (70%)	 NS NS
Transplant Candidates Waitlist Evaluation Eligible	34 (68%) 16/34 (47%) 15/34 (44%) 3/34 (9%)	40 (80%) 5/40 (12.5%) 23/40 (57.5%) 11/40 (27.5%)	0.005	24 (75%) 2/24 (8%) 14/24 (58%) 8/24 (33%)	8 (100%) 1/8 (12.5%) 5/8 (62.5%) 1/8 (12.5%)	8 (80%) 2/8 (25%) 4/8 (50%) 2/8 (25%)	NS
LT alone by D90	16/34 (47%)	16/40 (40%)	NS	10/16 (63%)	1/16 (6%)	5/16 (31%)	NS
SLKT by D90	2/34 (6%)	3/40 (7.5%)		0/3 (0%)	2/3 (67%)	1/3 (33%)	

[*] Data are presented as n (% within group) or median (min – max) unless otherwise noted and α = 0.05.

[†] Intraoperative RRT censored. RRT started for one sepsis case by day 30 and for one delayed graft failure case by day 90, included in retrospective totals.

P-CR, prospective complete response group; P-PR, prospective partial response group; P-NR, prospective non-response group; AKI, acute kidney injury; MELD, Model for End-Stage Liver Disease; SCr, serum creatinine; EOT, end of treatment; D30, day 30; D90, day 90; LT, liver transplant; SLKT, simultaneous liver kidney transplant; min, minimum; max, maximum.

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f 3014-A | EFFICACY OF TARGETED AND RESPONSE-GUIDED ALBUMIN THERAPY VERSUS STANDARD MEDICAL TREATMENT IN OUTCOMES OF RECURRENT ASCITES IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

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Background: Long-term albumin administration improves outcomes in patients with uncomplicated ascites. Considering the cost and scarcity of albumin an individualized approach may be better for patients with recurrent ascites (RA). We aimed to compare a targeted and response-guided albumin strategy (Alb-Tr) in improving 6-month mortality compared to standard medical treatment (SMT). **Methods:** Single-center open-label randomized controlled trial. Patients in (Alb-Tr) arm received 20% albumin targeting serum albumin > 3 gm/dl at 60grams for 2 weeks followed by 20-40 grams/week until ascites control, or for a maximum of 12 months. Patients in both groups received SMT (salt restriction, diuretics +/- large volume paracentesis). Our primary endpoint was 6-month mortality. We also studied the impact of Alb-Tr vs. SMT on renal biomarkers, albumin modifications, C-reactive protein (CRP), monocyte function and mitochondrial respiration at 1-month. (Alb+SMT, n = 25, SMT- n = 25) **Results:** A total of 106 patients, mean age (48.8 ± 9.5 y, 84% males, 69% alcohol-related, with MELD 16 ± 5 were randomized [Alb-Tr; n = 52 versus SMT; n = 54). The two groups were comparable at baseline. A trend towards reduced mortality was noted in (Alb-Tr) [2(3.8%) vs. 8(15.4%); Log rank p = 0.06, HR 4.21, (0.89-19.8)]. The control of ascites was superior in (Alb-Tr) (52% vs.12%; p < 0.001), with reduction in therapeutic paracentesis (p < 0.001), lower incidence of acute kidney disease (AKD) (28% vs. 64%;p < 0.001), chronic kidney disease (CKD) (8% vs. 25%; p = 0.03) and hospitalizations (42%vs.72%;p = 0.004). The development of infections (25% vs. 37%; p = 0.39), hepatic encephalopathy (5.8% vs. 9.6%; p = 0.46) was not different. The dose of albumin was significantly higher in Alb-Tr [(224.4 ± 152.2) vs.(113.7 ± 137.4) gms; p < 0.001], with higher proportion of patients achieving the target albumin > 3 gm/dl (80.8% vs. 46.2%; p < 0.001) which was associated with higher ascites resolution (39.1%vs. 19.4%; p = 0.04), a trend towards lower AKD (20.3% vs. 36.1%; p = 0.08) and CKD development (11.1% vs. 25%; p = 0.07). A significant decrease in renal biomarkers, the HNA2 fraction, CRP, with improvement in monocyte and mitochondrial function was observed in Alb-Tr. At baseline, significantly higher levels of HMA, lower levels of HNA1 and on follow-up an improvement in mitochondrial respiration after albumin was observed in patients who achieved ascites resolution. (Figure) **Conclusion:** A targeted and response-guided albumin strategy reduces mortality, adverse renal outcomes and achieves better ascites control in patients with RA. Improvement in renal and innate immune function and a reduction in the irreversibly oxidized albumin fraction could explain the beneficial effects of long-term albumin. Albumin modifications and measurement of mitochondrial function could be potential biomarkers for identifying patients who would achieve ascites resolution after albumin therapy.

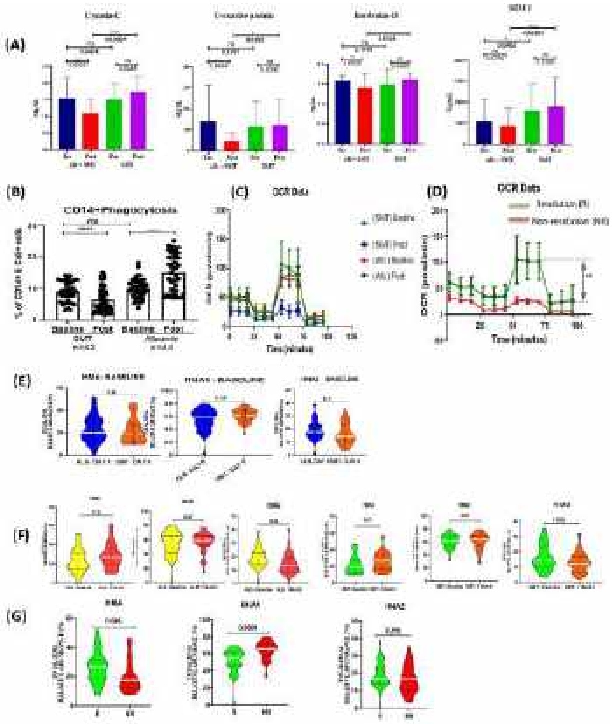

Fig. (A) Graph represents the levels of renal injury markers such as cystatin-C IL-18 and KIM-1 were significantly increased in follow up plasma samples of SMT groups while they significantly declined in ALB+SMT group . A decrease in CRP was observed in Alb+SMT vs. SMT (B and C) Improvement in monocyte function and mitochondrial function in Alb+SMT vs. SMT (C) showing real time changes OCR in response to oligomycin, FCCP and rotenone /antimycin in baseline and follow-up ALB+SMT and SMT groups. (D) Improvement in mitochondrial function in patients with ascites resolution(R) compared to no-resolution(NR) (E)&(F) shows comparable quantitative assessment of total humanmercaptoalbumin(HMA), human-nonmercaptoalbumin (HNA1), (HNA2) at baseline were not different with decrease in HNA2 in Alb+SMT (G) Patients with resolution of ascites (R) had higher HMA and lower HNA1 compared to those who did not resolve in Alb+SMT (NR)group.

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

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f 3015-A | EMPAGLIFLOZIN IN DIURETIC REFRACTORY ASCITES (DRAIN-EM): RESULTS OF A SINGLE-CENTER FEASIBILITY STUDY

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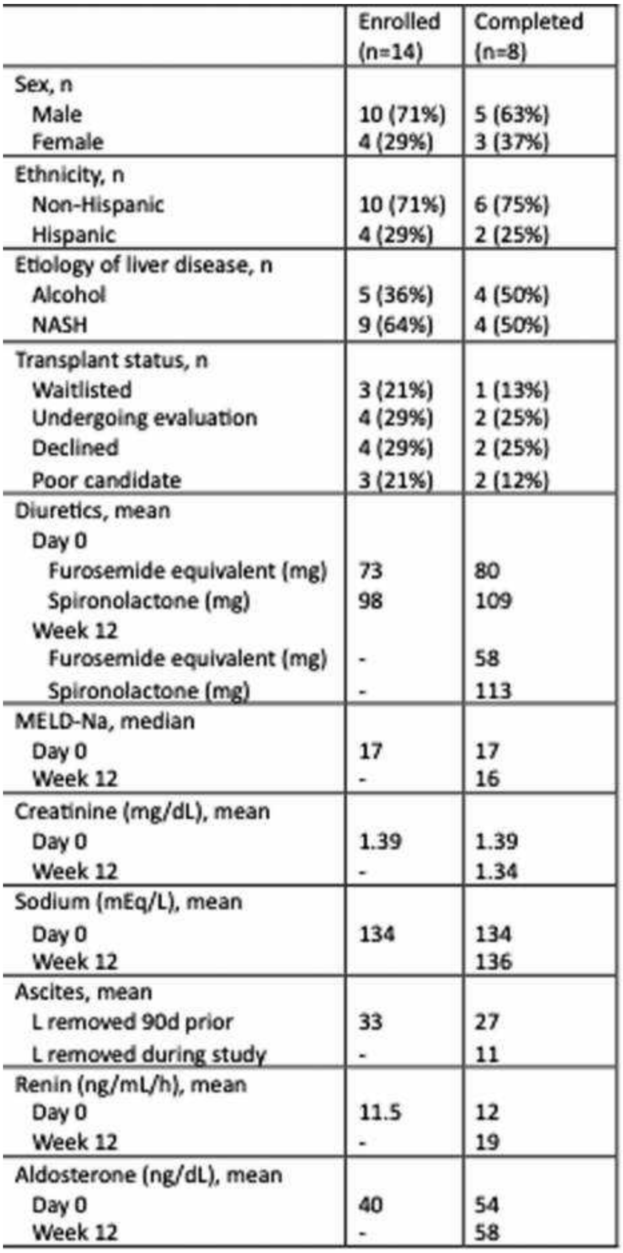
Background: Ascites is the most frequent complication of cirrhosis. Current pharmacologic therapy is limited to diuretics, but diuretic resistance develops in up to 10% of patients yearly. Sodium-glucose co-transporter-2 inhibitors (SGLT2-I) may be effective in this setting due to their nephroprotective effect from reducing renal hypoxia, in addition to causing glycosuria and increased sodium excretion. We conducted a pilot feasibility study to evaluate empagliflozin in managing diuretic-resistant ascites in patients with decompensated cirrhosis. **Methods:** Single-arm, single-center study at Stanford University from 12/2021-5/2023. Eligible patients were >18 years with decompensated cirrhosis complicated by diuretic-resistant ascites defined as 1) inability to mobilize ascites despite maximum tolerated dose of diuretics, 2) rapid re-accumulation of ascites requiring serial large volume paracentesis (LVP) or 3) development of diuretic-related complications such as azotemia, electrolyte disturbances or hepatic encephalopathy. Patients with eGFR <30 or hypotension requiring vasopressor therapy were ineligible. Enrolled patients received empagliflozin 10mg daily for 12 weeks, with regular study visits to assess drug side effects, renal function, ascites volume, overall health status and quality of life measured by SF-36 survey. Secondary endpoints included reduction in abdominal ascites, renal function, and hepatic encephalopathy. **Results:** Eighteen patients were screened, 14 (78%) enrolled and 8 (57%) completed the study. Reasons for early termination included liver transplant ($n=1$), TIPS ($n=2$), acute kidney injury ($n=1$) and patient preference due to ongoing volume retention within one month ($n=2$). All patients were able to comply with the study procedures. Most participants were male (71%), non-Hispanic (71%) with cirrhosis due to alcohol (36%) or NASH (64%) (Table 1). Median MELD-Na was 17 and stable during the study. There was a strong trend for reduction in volume of ascites removed by LVP during the study compared to the 12 weeks prior (mean change -16.7L, $p=0.07$, Wilcoxon signed rank test). Renin and aldosterone levels increased during the study without a significant change in serum creatinine (mean change -0.05, $p=0.48$), indicative of enhanced diuresis. Furosemide dosage was reduced in 4/8 (50%) by a mean of 40mg/day, while spironolactone dose was increased in one patient by 25mg. Four patients elected to continue empagliflozin off-label after study completion. **Conclusion:** In this 12-week feasibility study of patients with decompensated cirrhosis and diuretic-resistant ascites, empagliflozin seemed to improve diuresis and reduce need for LVP. These results are promising for potential clinical efficacy in patients with ascites due to decompensated cirrhosis and support larger clinical trials.



	Enrolled (n=14)	Completed (n=8)
Sex, n		
Male	10 (71%)	5 (63%)
Female	4 (29%)	3 (37%)
Ethnicity, n		
Non-Hispanic	10 (71%)	6 (75%)
Hispanic	4 (29%)	2 (25%)
Etiology of liver disease, n		
Alcohol	5 (36%)	4 (50%)
NASH	9 (64%)	4 (50%)
Transplant status, n		
Waitlisted	3 (21%)	1 (13%)
Undergoing evaluation	4 (29%)	2 (25%)
Declined	4 (29%)	2 (25%)
Poor candidate	3 (21%)	2 (12%)
Diuretics, mean		
Day 0		
Furosemide equivalent (mg)	73	80
Spironolactone (mg)	98	109
Week 12		
Furosemide equivalent (mg)	-	58
Spironolactone (mg)	-	113
MELD-Na, median		
Day 0	17	17
Week 12	-	16
Creatinine (mg/dL), mean		
Day 0	1.39	1.39
Week 12	-	1.34
Sodium (mEq/L), mean		
Day 0	134	134
Week 12	-	136
Ascites, mean		
L removed 90d prior	33	27
L removed during study	-	11
Renin (ng/mL/h), mean		
Day 0	11.5	12
Week 12	-	19
Aldosterone (ng/dL), mean		
Day 0	40	54
Week 12	-	58

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

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3016-A | EXTERNAL VALIDATION OF THE EXPECT TIPS SCORE IN A NORTH AMERICAN COHORT

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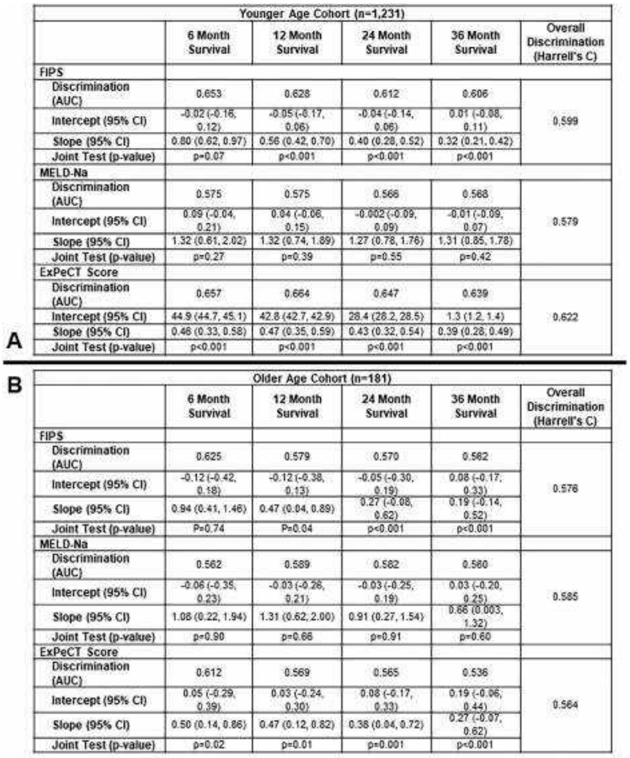
Background: Given the risks of transjugular intrahepatic portosystemic shunt (TIPS) implantation, prediction models are used for risk stratification. The Elderly Patients Calculator TIPS (ExPeCT) score is the most recent validated TIPS prediction model and was developed in an Italian cohort. We sought to validate the ExPeCT model in a large North American cohort. **Methods:** This was a retrospective study of patients with cirrhosis in the Veterans Health Administration who received TIPS from 2008-2022. Linear predictors of the ExPeCT model, Model for End-Stage Liver Disease Sodium (MELD-Na) score, and Freiberg index of post-TIPS survival (FIPS) score were calculated and incorporated into univariable Cox regression models for post-TIPS survival analysis. The cohort was divided into younger age (<70 y) and older age ($\geq$70) subcohorts to evaluate the overall and older-age versions of the ExPeCT prediction model. Discrimination through maximum follow up was evaluated using Harrell's C index. Discrimination at 6, 12, 24, and 36 months (mo) was calculated using time dependent area under the curve (AUC). Calibration of prediction models was evaluated by joint hypothesis testing of the intercept (null = 0) and slope (null = 1) at 6, 12, 24, and 36 mo, with $p < 0.05$ representing poor calibration. **Results:** The analytic cohort included 1,412 patients who received TIPS, with 1,231 patients < 70 years of age and 181 patients > 70 years of age. Older patients were more likely to have non-alcoholic fatty liver disease and had higher rates of diabetes, coronary artery disease, and heart failure. Older patients had higher post-TIPS mortality at 12 mo (38.7% vs 29.7%, p = 0.014), 24 mo (50.8% vs 41.6%, p = 0.019), and 36 mo (58.0% vs 49.5%, p = 0.032). In the younger age cohort, the overall ExPeCT model had the highest discrimination (Harrell's C: 0.622), while MELD-Na score had the lowest discrimination (Harrell's C: 0.579; Figure A). In contrast, MELD-Na score had the highest discrimination (Harrell's C: 0.585), while ExPeCT score had the lowest discrimination (Harrell's C: 0.564) in the older age cohort (Figure B). MELD-Na score had the best calibration across all time points in both cohorts (p > 0.05 for all). **Conclusion:** The ExPeCT score had the highest discrimination in the younger age cohort and the lowest in the older age cohort compared to FIPS and MELD-Na scores. The ExPeCT score represents a useful tool to assist in risk stratification of patients < 70 years of age undergoing TIPS procedure. Refitting and/or addition of model parameters to increase discrimination of the ExPeCT model for patients > 70 years of age is needed to improve performance in North American populations highly enriched in metabolic and cardiovascular disease.



A

Younger Age Cohort (n=1,231)	6 Month Survival	12 Month Survival	24 Month Survival	36 Month Survival	Overall Discrimination (Harrell's C)
FIPS					
Discrimination (AUC)	0.653	0.628	0.612	0.606	0.599
Intercept (95% CI)	-0.02 (-0.16, 0.12)	-0.05 (-0.17, 0.06)	-0.04 (-0.14, 0.06)	0.01 (-0.08, 0.11)	
Slope (95% CI)	0.80 (0.62, 0.97)	0.56 (0.42, 0.70)	0.40 (0.28, 0.52)	0.32 (0.21, 0.42)	
Joint Test (p-value)	p=0.07	p<0.001	p<0.001	p<0.001	
MELD-Na					
Discrimination (AUC)	0.575	0.575	0.566	0.568	0.579
Intercept (95% CI)	0.09 (-0.04, 0.21)	0.04 (-0.06, 0.15)	-0.002 (-0.09, 0.09)	-0.01 (-0.09, 0.07)	
Slope (95% CI)	1.32 (0.61, 2.02)	1.32 (0.74, 1.89)	1.27 (0.78, 1.76)	1.31 (0.85, 1.78)	
Joint Test (p-value)	p=0.27	p=0.39	p=0.55	p=0.42	
ExPeCT Score					
Discrimination (AUC)	0.657	0.664	0.647	0.639	0.622
Intercept (95% CI)	44.9 (44.7, 45.1)	42.8 (42.7, 42.9)	28.4 (28.2, 28.5)	1.3 (1.2, 1.4)	
Slope (95% CI)	0.46 (0.33, 0.58)	0.47 (0.35, 0.59)	0.43 (0.32, 0.54)	0.39 (0.28, 0.49)	
Joint Test (p-value)	p<0.001	p<0.001	p<0.001	p<0.001	

B

Older Age Cohort (n=181)	6 Month Survival	12 Month Survival	24 Month Survival	36 Month Survival	Overall Discrimination (Harrell's C)
FIPS					
Discrimination (AUC)	0.625	0.579	0.570	0.562	0.576
Intercept (95% CI)	-0.12 (-0.42, 0.18)	-0.12 (-0.38, 0.13)	-0.05 (-0.30, 0.19)	0.08 (-0.17, 0.33)	
Slope (95% CI)	0.94 (0.41, 1.46)	0.47 (0.04, 0.89)	0.27 (-0.08, 0.62)	0.19 (-0.14, 0.52)	
Joint Test (p-value)	P=0.74	P=0.04	p<0.001	p<0.001	
MELD-Na					
Discrimination (AUC)	0.562	0.589	0.582	0.560	0.585
Intercept (95% CI)	-0.06 (-0.35, 0.23)	-0.03 (-0.26, 0.21)	-0.03 (-0.25, 0.19)	0.03 (-0.20, 0.25)	
Slope (95% CI)	1.08 (0.22, 1.94)	1.31 (0.62, 2.00)	0.91 (0.27, 1.54)	0.66 (0.003, 1.32)	
Joint Test (p-value)	p=0.90	p=0.66	p=0.91	p=0.60	
ExPeCT Score					
Discrimination (AUC)	0.612	0.569	0.565	0.536	0.564
Intercept (95% CI)	0.05 (-0.29, 0.39)	0.03 (-0.24, 0.30)	0.08 (-0.17, 0.33)	0.19 (-0.06, 0.44)	
Slope (95% CI)	0.50 (0.14, 0.86)	0.47 (0.12, 0.82)	0.38 (0.04, 0.72)	0.27 (-0.07, 0.62)	
Joint Test (p-value)	p=0.02	p=0.01	p=0.001	p<0.001	

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3017-A | HEPATORENAL SYNDROME MORE SIGNIFICANTLY ASSOCIATED RISK OF DEATH IN WOMEN COMPARED TO MEN UNDERGOING INPATIENT LIVER TRANSPLANT EVALUATION

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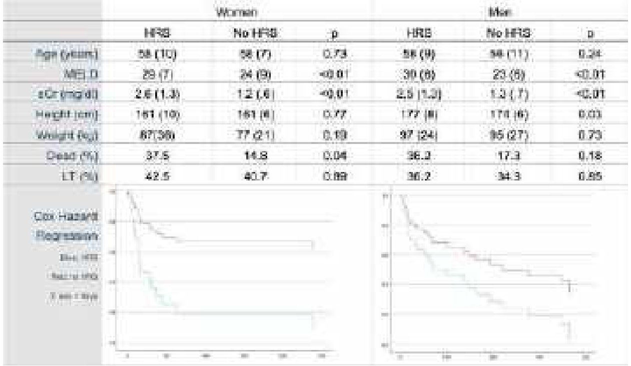
Background: Serum creatinine (sCr) has known limitations in diagnosing renal dysfunction in advanced liver disease (AdLD). Previous studies on hepatorenal syndrome (HRS) utilized sCr e 2.5 as a diagnostic criterion. This has resulted in reduced representation of women in the literature on the epidemiology and treatment of HRS. While this definition was updated in 2015, there is a lack of data on outcomes in men versus women since this time. We aimed to compare the impact of HRS on survival in patients undergoing inpatient liver transplant evaluation (LTE). **Methods:** Patients who completed urgent LTE for CLD over a 4-year period were retrospectively analyzed. We chose to compare inpatients who were approved to start LTE to limit the impact of access to an LT center or dialysis on outcomes. Presence of HRS was determined using ICD-10 codes and confirmed using clinical documentation (e.g., nephrology consultation, urine sediment assessment, urine electrolytes). Rate of HRS was compared between men and women. Mortality rate and transplant rate were compared by HRS status in men and women, in addition to age, MELD, height, and weight. The impact of HRS on mortality risk in the total cohort and in each sex was determined using univariate, multivariate, and Cox logistic regression. **Results:** 160 patients were analyzed (67 women, 93 men) of which 98 (61%) were diagnosed with HRS. Rate of HRS diagnosis did not differ between men and women (62% vs. 60%, p = 0.73). Age, sCr, MELD, transplant rate, mortality rates were similar in men and women with HRS [not shown]. Mortality rate was higher in women with HRS than without HRS (37.5% vs. 14.8%, OR: 3.5, p = 0.04), but morality rate did not differ by HRS status in men (36.2% vs. 17.3% OR 1.9, p = 0.18) (Table 1). This relationship persists on multivariate logistic regression controlling for age, ethnicity, MELD, and etiology of cirrhosis (data not shown). Cox hazard regression revealed a HRS to be associated with a HR 2.9 [p = 0.09] in women, compared to 1.4 [p = 0.44] in men (Table 1, bottom panel). **Conclusion:** Our results suggest the negative impact of HRS on survival may be more profound in women than in men being evaluated for LT. Women with HRS had a similar sCr than men in our analysis, which may be correlated with lower GFR and explain some differences in survival. While our study design did not allow for monitoring trends in sCr, we studied a high-risk population with access to LT services and renal replacement therapy. We highlight that women undergoing inpatient LTE are at increased risk of death due to renal failure. Alternate forms of GFR measurement may allow for early recognition and improve outcomes in women.



	Women			Men		
	HRS	No HRS	p	HRS	No HRS	p
Age (years)	58 (10)	58 (7)	0.73	58 (9)	58 (11)	0.24
MELD	29 (7)	24 (9)	<0.01	30 (8)	23 (6)	<0.01
sCr (mg/dl)	2.6 (1.3)	1.2 (.6)	<0.01	2.5 (1.3)	1.2 (.7)	<0.01
Height (cm)	161 (10)	161 (6)	0.77	177 (8)	174 (6)	0.03
Weight (kg)	67(38)	77 (21)	0.19	97 (24)	95 (27)	0.73
Dead (%)	37.5	14.8	0.04	36.2	17.3	0.18
LT (%)	42.5	40.7	0.89	36.2	34.3	0.95

Cox Hazard Regression

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3018-A | HUMAN ALBUMIN INFUSION IS SAFE AND EFFECTIVE EVEN IN PATIENTS WITHOUT ACUTE KIDNEY INJURY AND SPONTANEOUS BACTERIAL PERITONITIS

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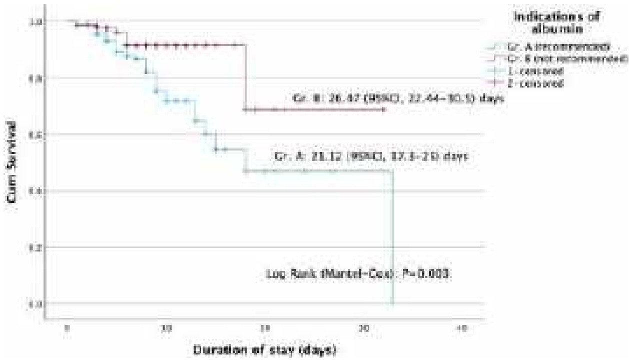
Sharma[1], Nageshwar D Reddy[1], Lakshmi P K[2], Rajesh Gupta[1], Padaki Nagaraja Rao[1] and Anand V. Kulkarni[1], (1)Aig Hospitals, Hyderabad, India, (2)Pulla Reddy College of Pharmacy

Background: Human albumin (HA) solution is currently recommended only for patients with spontaneous bacterial peritonitis (SBP) and acute kidney injury (AKI). However, its use in-hospitalized patients is quite frequent for various indications, including hypoalbuminemia, hyponatremia, and non-SBP infections. We aimed to compare the outcomes of patients receiving HA in recommended vs. not recommended indications. **Methods:** In this prospective study, consecutive hospitalized patients who received HA were included. The objectives were to compare the baseline characteristics, dose, and duration of HA administration, change in MELD NA score, resolution of infection and hyponatremia, and mortality among patients who received the HA for recommended (Gr. A) and not recommended indications (Gr. B). **Results:** 396 hospitalized patients received HA. Of them, 45.5% (n = 180) had AKI and/or SBP (Gr. A) at admission, and 54.5% (n = 216) of patients received albumin for non-recommended indications (Gr. B). The mean age (53 ± 13.46 y), sex (females-15%), and etiology distribution were similar among both groups. Indications in the Gr. B was cirrhosis with ascites and hypoalbuminemia-71.3% (n = 154); cirrhosis with overt hepatic encephalopathy and hypoalbuminemia-26.4% (n = 57); variceal bleed with hypoalbuminemia-2.3% (n = 5). The proportion of patients with concomitant hyponatremia (serum sodium < 130 meq/dl) was 47.8% in Gr. A and 44% in Gr. B ($P = 0.47$). MELD NA was significantly higher in Gr. A patients (27.32 ± 8.6 vs. 21.23 ± 7.3 in Gr B; $P < 0.001$) due to higher creatinine (2.5 ± 1.96 vs. 0.98 ± 0.33; $P < 0.001$), while the serum albumin levels were similar among both groups (2.71 ± 0.61 vs. 2.88 ± 2.13; $P = 0.31$). The total dose of HA was higher (88 ± 61.62 g vs. 71.31 ± 488.17 g; $P = 0.003$), and the duration was longer (4 ± 2.37 vs. 3.4 ± 1.82 d; $P = 0.005$) in Gr. A than Gr. B. At admission, 30% in Gr.A and 15.3% in Gr. B had a microbiologically proven infection ($P < 0.001$). Seventy-eight percent (141/180) had a resolution of AKI with albumin infusions in Gr. A while 5.5% (12/216) developed AKI (rise in sCr by > 0.3 mg/dl) in-hospital in Gr. B.On Kaplan-Meier analysis, mortality in Gr. A was higher than in Gr. B (21.1% vs. 6%; $P < 0.001$) (Figure). The proportion of patients achieving resolution of infection was similar among both groups (Gr. A: 79.6% vs. 94% in Gr. B; $P = 0.1$), while hyponatremia resolution was significantly higher in Gr. B (94.7%) than in Gr. A (75.6%; $P < 0.001$). The incidence of albumin-induced fluid overload was 2.8% in Gr. A compared to 1.4% in Gr. B ($P = 0.32$). **Conclusion:** Human albumin infusion is safe and effective even in patients without AKI and SBP and leads to the resolution of hyponatremia and infection.



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3019-A | INCREASED BASELINE INDICATORS OF INFLAMMATION IN PATIENTS WITH HEPATORENAL SYNDROME TYPE 1 AND GRADE 3 ACUTE-ON-CHRONIC LIVER FAILURE: IMPLICATIONS FOR TERLIPRESSIN THERAPY

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Background: Patients with hepatorenal syndrome type 1 (HRS1) and grade 3 acute-on-chronic liver failure (ACLF3) have an increased incidence of respiratory failure (RF) when treated with terlipressin. Patients with HRS1 with ACLF grade d 2 (ACLF d 2) do not have the same risk for RF. Concomitant albumin use has been excluded as a likely cause of increased risk for RF in patients with HRS1 and ACLF3 treated with terlipressin. This study aims to explore inflammation as a contributor to the development of RF in HRS1 patients with ACLF3 treated with terlipressin. **Methods:** Pooled data from the two largest terlipressin HRS1 trials were reviewed (CONFIRM-NCT02770716 and REVERSE-NCT01143246). Patients were separated into ACLF d 2 and ACLF3 groups baseline. Available clinic-biochemical parameters suggestive of inflammation were compared. **Results:** 292 patients received terlipressin:236 with ACLF d 2 group, 56 with ACLF3. Mean age 54.6 years, 58% male, mean MELD score

32.96. Patients with ACLF3 had more features of inflammation at baseline as suggested by tachycardia (82 ± 15 vs. 79 ± 15beats/min in ACLF d 2, p = 0.09), tachypnea (18.6 ± 2.9 vs. 17.8 ± 3.2 breaths/min, p = 0.007) without evidence of respiratory distress as indicated by similar SpO_2/FiO_2 ratios (400 ± 134 vs. 450 ± 56, p = 0.38) compared to the ACLF d 2 group. White cell count was significantly higher (10.9 ± 5.1 vs. 8.5 ± 5.7, p < 0.001) in subjects with ACLF3 despite similar incidence of prior infection (55.4% vs. 44.3%, p = 0.14) and similar percentage of patients on antibiotic just prior to receiving terlipressin (60.7% vs. 54.4%, p = 0.46). The ACLF3 group also had higher baseline MELD of 39.3 ± 1.7 (vs. 31.2 ± 6.2, p < 0.001) despite similar baseline serum creatinine levels (3.5 ± 0.9mg/dL vs. 3.9 ± 1.0mg/dL), suggesting marked liver dysfunction in the ACLF3 patients. Significantly more ACLF3 patients had alcoholic hepatitis at baseline (53.6% vs. 30.0%, p = 0.002) than ACLF d 2 patients. Similar differences in inflammatory parameters were also observed in 199 placebo ACLF3 vs ACLF d 2 patients. **Conclusion:** While placebo patients with ACLF3 also had increased baseline inflammatory features, our previous study showed the incidence of RF in the placebo ACLF3 group was low. (Wong F. et al. APT 2022; 56: 1284). Although not confirmed by inflammatory biomarkers, the current results suggest that the combination of terlipressin and intense inflammation may play a significant role leading to RF in HRS1 ACLF3 patients.

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3020-A | INCREASED MORTALITY AND GROWING CONCERN FOR EMERGENCE OF GRAM- POSITIVE BACTERIA AND MULTI-DRUG RESISTANT BACTERIA

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Background: Spontaneous bacterial peritonitis (SBP) is a serious infection that occurs in cirrhotic patients with ascites. SBP has been shown to have a mortality rate of 80% with a delay in antibiotics being associated with an increased mortality. The most prevalent bacterial organisms that are associated with SBP are typically gram- negative rods from the gastrointestinal track that can often be treated with fluoroquinolones or 3rd generation cephalosporins. However, there is a growing concern for an increased presence of gram-positive bacteria as well as multi-drug resistant organisms (MDRO) causing SBP. Those who have SBP or are prescribed antibiotics for primary SBP prevention are typically discharged with a fluoroquinolone or Bactrim. In this project we aim to evaluate the incidence of multi-drug resistant bacteria and gram-positive bacteria in cirrhotic patients with SBP and assess their impact on mortality. **Methods:** We performed a retrospective cohort study and included cirrhotic patients admitted in 2021 that required a paracentesis. Data collected includes baseline characteristics of the patients, specific type of cirrhosis, whether Hepatology was consulted, the rate of antibiotic prescriptions, the number of SBP episodes, the type of organism causing SBP, antibiotic resistance, the incidence of future SBP episodes, and the rate of in-hospital mortality. Univariate and multivariate logistic regression analysis were performed for these outcomes. **Results:** Our cohort (n = 321) had an average age of 57.5 ± 11.11, BMI of 29.28 ± 14.01, and 193 (60%) were male. Most of the cohort had either NASH (29.28%) or alcoholic (38.01%) cirrhosis. Out of 321 patients, 31 patients developed SBP during this admission and 34 patients developed SBP during future admissions. Of the 31 patients who had SBP this admission, 8 (25%) developed methicillin-resistant staphylococcus Aureus (MRSA) SBP and 16 (51%) developed GNR SBP. Of the 34 patients who developed future SBP episodes, 6 (17%) developed MRSA SBP and 11 (31%) developed

GNR SBP. Of the 16 GNR SBP, 9 demonstrated resistance to fluoroquinolones, 2 demonstrated resistance to 3 rd generation cephalosporins, and 3 demonstrated resistance to Bactrim. Of the 11 future GNR SBP episodes, 7 (64%) were resistant to fluoroquinolones, 2 (18%) were resistant to 3 rd generation cephalosporins, and 4 (36%) were resistant to Bactrim. Of the 14 antibiotic resistant GNR SBP patients, 12 patients expired while only 2 patients remained alive (P-value of 0.005). **Conclusion:** SBP is serious infection that has a high mortality rate of 80% with a delay in antibiotics being associated with an increased in-hospital mortality. It appears that the presence of MDRO is becoming more commonplace with many organisms being resistant to fluoroquinolones, Bactrim, and 3 rd generation cephalosporins. Our study also demonstrates higher mortality due to drug-resistant GNR and an increased prevalence of MRSA SBP.

Disclosures: The following people have nothing to disclose: Parth Bhupendra Patel

Disclosure information not available at the time of publication: Sujan Ravi, Udita Gupta, Ore Adekunle, Thomas Ruli, Mohamed Galal Shoreibah

3021-A | INTEGRATION OF POINT-OF-CARE ULTRASOUND (POCUS) IN AN INTERNAL MEDICINE RESIDENCY PRACTICE FOR DIAGNOSIS OF HEPATORENAL SYNDROME: A STANDARDIZED APPROACH

Adalberto Guzman[1], Evelyn Calderon Martinez[1], Wern Lynn Ng[1], Anas Atrash[1] and Douglas M. Levin[2], (1) UPMC, (2)Ohio State University, Columbus, OH, United States

Background: The current diagnostic criteria for HRS-1 rely on the absence of renal function improvement after two days of intravenous volume expansion or diuretic withdrawal. However, determining the need for volume expansion in suspected cases of HRS-1 lacks specific indicators. The hypothesis put forward is that point-of-care ultrasound (POCUS) can offer a more accurate assessment of volume status in cirrhosis patients with AKI, aiding in confirming or excluding the diagnosis of HRS-1. **Methods:** This study aimed to assess the intravascular volume status in cirrhosis patients with AKI and diagnosed with HRS-1, who were considered adequately repleted. Internal medicine residents participating in the pilot study performed point-of-care ultrasound on patients previously diagnosed with cirrhosis and meeting the AKI-HRS criteria upon admission. The study evaluated the clinical usefulness of point-of-care ultrasound (POCUS) in measuring the diameter of the inferior vena cava (IVCD) and the collapsibility index (IVCCI). Early improvement in kidney function was defined as a decrease of 20% or more in serum creatinine (sCr) levels within 48 to 72 hours. **Results:** The study enrolled a total of 33 patients. The evaluation of volume status revealed an average serum creatinine (sCr) level of 3.4 ± 1.7 mg/dL and a mean Model for End-Stage Liver Disease (MELD) score of 28 ± 9. Among the participants, 9 individual's (29%) were identified as having depleted fluid levels, indicated by an IVCD of less than 1.3 cm and an IVCCI greater than 40%. Additionally, 8 patients (25%) were classified as having expanded fluid levels due to an IVCD greater than 2 cm and an IVCCI less than 40%. Furthermore, 4 patients (11%) were diagnosed with intra-abdominal hypertension (IAH) based on an IVCD of less than 1.3 cm and an IVCCI less than 40%. Notably, a total of 12 patients (34%) demonstrated early improvement in kidney function following therapeutic interventions guided by POCE. These interventions included volume expansion, diuresis, or paracentesis, tailored to the specific fluid status classification of depletion, expansion, or IAH, respectively. **Conclusion:** This study examined the effectiveness of point-of-care echocardiography (POCUS) in assessing fluid status in cirrhosis patients with hepatorenal syndrome type 1 (HRS-1) and acute kidney injury (AKI). The findings suggest that POCUS, specifically measuring the inferior vena cava diameter (IVCD) and collapsibility index (IVCCI), can provide valuable information for determining fluid status in these patients. Therapeutic interventions guided by POCUS, such as volume expansion, diuresis, or paracentesis based on fluid status classification, resulted in early improvement in kidney function in 34% of patients. Early detection and targeted interventions addressing reversible causes of AKI, such as hypovolemia or hypervolemia, are essential for improving patient outcomes.

Disclosures: The following people have nothing to disclose: Adalberto Guzman, Evelyn Calderon Martinez, Wern Lynn Ng, Anas Atrash, Douglas M. Levin

3022-A | INTRAVENOUS N-ACETYLCYSTEINE AND ORAL MISOPROSTOL IN COMBINATION MAY BE EFFECTIVE IN TREATING HEPATORENAL SYNDROME

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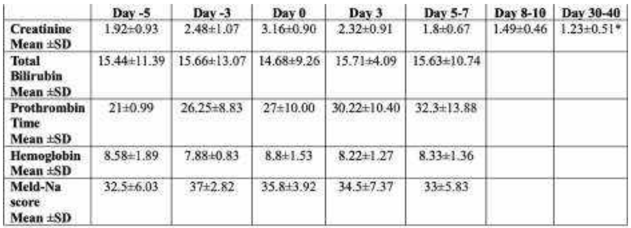
Background: Hepatorenal syndrome (HRS) is an ominous complication of de-compensated cirrhosis. We report here our experience in treating eight patients with de-compensated cirrhosis and acute kidney injury (AKI) 2-3 who did not respond to treatment with albumin and or octreotide/midodrine, with a combination of intravenous n-acetylcysteine infusion (NAC) and oral misoprostol. NAC infusion has previously been reported to reverse HRS in 12 patients with a three-month survival rate of 58% (Holt, Lancet, 1999). Oral misoprostol and albumin infusions have been used to temporarily reverse HRS in 4 patients (Fevery, J Hepatology, 1990). **Methods:** AKI was defined by the ICA-AKI criteria of 2015, six patients had AKI-3, two patients had AKI-2. One patient had preexisting chronic kidney disease stage 3a. All patients had de-compensated cirrhosis, alcoholic cirrhosis in seven patients and NASH-cardiac cirrhosis in one patient (BMI 50, EF 20%). Three patients had prior episodes of AKI that were treated successfully with NAC. Five patients were classified as acute on chronic liver failure type three. Five patients failed to respond to albumin infusions before NAC administration. Three patients failed octreotide and midodrine before NAC was given. NAC was used at a dose of 100 mgs/kg infused over 24 hours. Two patients received a loading dose of 150 mgs/kg over two hours. Seven of eight patients also received misoprostol 100 ugs 3-4 x a day. **Results:** Mean age of the patients was 48 ± 14. There were seven men and one woman in the study. Five patients responded to NAC without receiving albumin infusions during NAC treatment. All patients survived the hospitalization and were discharged home. One patient died 28 days after discharge and 40 days after starting NAC infusion. Another patient died eleven months after discharge. One patient received a liver transplant ten weeks after discharge. Five remaining patients were alive without liver transplantation six months to five years after discharge. Table 1 summarizes the findings of the present study. **Conclusion:** Intravenous NAC infusion and misoprostol in combination may be effective in treating hepatorenal syndrome that has not responded to albumin, octreotide, or midodrine. Further studies are warranted.



	Day -5	Day -3	Day 0	Day 3	Day 5-7	Day 8-10	Day 30-40
Creatinine Mean ±SD	1.92±0.93	2.48±1.07	3.16±0.90	2.32±0.91	1.8±0.67	1.49±0.46	1.23±0.51*
Total Bilirubin Mean ±SD	15.44±11.39	15.66±13.07	14.68±9.26	15.71±4.09	15.63±10.74		
Prothrombin Time Mean ±SD	21±0.99	26.25±8.83	27±10.00	30.22±10.40	32.3±13.88		
Hemoglobin Mean ±SD	8.58±1.89	7.88±0.83	8.8±1.53	8.22±1.27	8.33±1.36		
Meld-Na score Mean ±SD	32.5±6.03	37±2.82	35.8±3.92	34.5±7.37	33±5.83		

* (p ≤0.01)

Table 1. Response of kidney and liver function to N-acetylcysteine infusions.

Disclosures: The following people have nothing to disclose: Marko Kozyk, Kateryna Strubchevska, Jain Ritika, Tusar Desai

f 3023-A | MELD-SODIUM-CIRRHOTIC CARDIOMYOPATHY SCORE OUTPERFORMS MELD-SODIUM SCORE IN PREDICTING 90-DAY MORTALITY IN HOSPITALIZED PATIENTS WITH CIRRHOSIS

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Background: Cirrhotic cardiomyopathy (CCM) affects approximately 35% of patients with cirrhosis. An increased E/e’ ratio, reflective of increased left ventricular filling pressures, and decreased mitral septal e’ velocity, reflective of impaired relaxation, are two core components of the revised 2020 criteria of CCM. Data about the utility of bedside, point-of-care ultrasound (POCUS) and echocardiography (POC-Echo) with tissue Doppler imaging in patients with cirrhosis are limited. Conventional prognostic models in this patient population (e.g., Model for End-Stage Liver disease score) lack cardiac and hemodynamic variables which can be associated with adverse outcomes in patients with cirrhosis. **Methods:** This is a prospective study of two cohorts of critically ill patients who were admitted to the Liver intensive care unit in a single center between December 2019 and December 2022. The discovery cohort had ACLF and severe sepsis (with mean arterial pressure < 65mmHg) (NCT05059795; N = 120). Validation cohort had hepatorenal syndrome- acute kidney injury (HRS-AKI; NCT05434286; N = 140). Patients with coronary artery or valvular heart disease, those on dialysis, uncontrolled thyroid disease, porto-pulmonary hypertension, dilated cardiomyopathy, and hepatocellular carcinoma were excluded. CCM was defined per the CCM consortium 2020 criteria. We used a regression-based model to assess if CCM markers can predict mortality in critically ill patients with cirrhosis. The markers were integrated with MELD-Na to improve the predictive performance in the discovery cohort of ACLF with severe sepsis. We validated the derived score in the validation cohort of cirrhosis with HRS-AKI, based on the International Club of Ascites (ICA) criteria. **Results:** The discovery cohort of ACLF with severe sepsis had 120 patients [59% men, aged 49 ± 12 years, 56% alcohol-related disease, and median MELD-Na of 30(27 - 32)], of whom 68/120(56.6%) had circulatory failure, with overall mortality of 72/120(60%). CCM was present in 63/120(52.5%). The MELD-Na-CCM model was computed as MELDNa+1.815*E/e’(septal) +0.402*e’ (septal) based on multivariable logistic regression for prediction of 90-day mortality. In the discovery cohort, MELD-CCM outperformed MELD-Na

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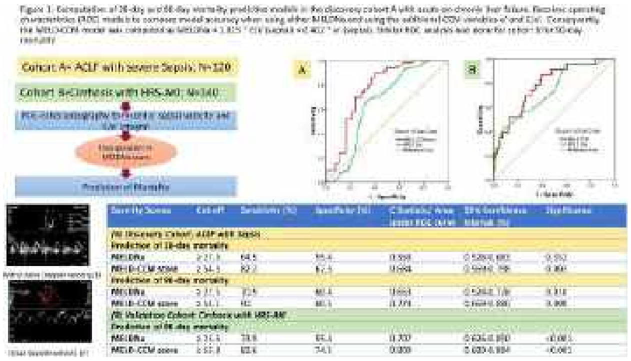
Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

(z-score = 2.07, $P = 0.038$) in predicting 90-day mortality. In the validation cohort of 140 patients with HRS-AKI, (84% men, aged 45.8 ± 12.9 years, 59% alcohol-associated, MELDNa 25 ± 5.6), thirty-four patients (24.3%) met criteria for CCM, with overall mortality at 90 days being 23(16.4%). Furthermore, in the validation cohort as well, MELD-CCM outperformed MELD-Na (z-score = 1.99, $P = 0.046$) in predicting 90-day mortality. **Conclusion:** POC-Echo measurements of CCM markers, namely, E/e' and e' significantly improve the predictive performance of MELD-Na for 90-day mortality. Further studies are needed to evaluate the implications of POCUS integration into modern hepatology practice.



Disclosures: The following people have nothing to disclose: Manhal Izzy, Madhumita Premkumar
Disclosure information not available at the time of publication: Kamal Kajal

3024-A | NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN PREDICTS THE EFFICACY OF TOLVAPTAN AND POST-TREATMENT ACUTE KIDNEY INJURY IN PATIENTS WITH LIVER CIRRHOSIS

Masato Nakai, Takashi Kitagataya, Masatsugu Ohara, Takuya Sho, Goki Suda, Koji Ogawa and Naoya Sakamoto, Hokkaido University Hospital

Background: Acute kidney injury (AKI) is associated with liver cirrhosis (LC), water retention, diuretics for treating water retention; it has a poor prognosis. Urinary neutrophil gelatinase-associated lipocalin (uNGAL) has attracted attention as an early diagnostic marker of AKI and reportedly predicts a poor prognosis in decompensated LC. This study investigated the usefulness of uNGAL in predicting the short- and long-term effects of tolvaptan (TVP) and the incidence of AKI post-TVP administration. **Methods**: Of the LC cases with water retention, 86 with available pre-treatment uNGAL were analyzed. A short-term response was defined as weight loss of e 1.5 kg within the first week according to the Japanese evidence-based clinical practice guidelines for LC; a long-term response was defined as a short-term response without early recurrence defined in the EASL practice guidlines. The uNGAL usefulness in predicting the short- and long-term effects of TVP and AKI incidence post-TVP administration was investigated. **Results**: The median pre-treatment uNGAL was 17.95 ng/ml. Short-term effects of TVP were observed in 52 patients. Of these, 15 patients had an early recurrence. Short-term responders had significantly lower uNGAL levels than non-responders. ROC analysis showed that the optimal cut-off value of uNGAL for predicting the short-term response was 50.2 ng/ml. In multivariate analysis, significant short-term predictive factors were C-reactive protein (CRP) < 1.4 mg/dl, uNa/K ratio e 3.51, and uNGAL < 50.2 ng/ml. Patients were classified according to these three cut-off values, with short-term response rates of 92.9%, 68.8%, 26.7%, and 0% for 0, 1, 2, and 3 points, respectively. In subanalyses of the cohorts excluding patients with pre-treatment AKI complications, uNGAL was also similarly predictive of short-term response to TVP. Long-term responders had better prognosis than non-responders and patients with early recurrence. CRP < 0.94 mg/dl and uNGAL < 50.2 ng/ml were significant factors for predicting the long-term response of TVP. Patients were classified according to these two cut-off values, with long-term response rates of 66.7%, 32.2%, and 0% for 0, 1, and 2 points, respectively.The AKI incidence post-TVP was 8.1% (n = 7). Patients with AKI after TVP administration had significantly higher NGAL values ($p < 0.01$). The best cutoff, which is predictive of the incidence of AKI post-TVP administration, was 38.1 ng/ml with an area under the receiver operating characteristic curve (AUCROC) of 0.898. This was a better value than other renal function-related factors, such as uL-FABP, sCr, sBUN, uUN, and uNa/K ratio or CRP. **Conclusion**: uNGAL is a useful predictor of the short- and long-term efficacy of TVP and can be useful in predicting AKI incidence post-TVP administration.

Disclosures: The following people have nothing to disclose: Masato Nakai, Takashi Kitagataya, Masatsugu Ohara
Disclosure information not available at the time of publication: Takuya Sho, Goki Suda, Koji Ogawa, Naoya Sakamoto

3025-A | NURSE LED CLINIC FOR PATIENTS WITH DECOMPENSATED LIVER DISEASE★

Pauline Dundas, Chirantha Premathilaka, Lorna Bailey, Theresa Milne, Shirley English, Lindsay McLeman,

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

Chaitra Chandra Shekar and Ashis Mukhopadhya, NHS Grampian

Background: Cirrhosis is an increasingly prevalent condition associated with significant morbidity and mortality. When these patients have unscheduled admissions following decompensation, lengths of stay, readmissions rates, and mortality can be very high. Ideally, factors leading to decompensation like diuretic dose or laxative treatment would be optimised to prevent admission in the first place but early detection can be challenging. In 2019, the nurse led close monitoring out-patient clinic was set up in Aberdeen Royal Infirmary to support patients with decompensated liver disease post-discharge. Patients are reviewed in 1-2 weeks, clinical examinations, routine tests, prescription modification and day case ascetic drains can be arranged. A multi-disciplinary team meeting for patient discussion occurs the following day. **Methods:** We performed a retrospective analysis of the case mix at our site between 2018 and 2022 to determine if there was a difference in lengths of stay, readmission rates, and mortality rates of the patients who attend the close monitoring clinic (CMC) compared to those who did not. Case identification was by using ICD-10 discharge codes encompassing decompensated liver disease **Results:** The mean number of admissions with decompensated liver disease each year was 136. On average, readmissions comprised 59% of total admissions. The close monitoring clinic had 560 appointments with 203 unique patients between 2019 and 2022, averaging 140 appointments and 59 unique patients per year. The average length of stay reduced significantly from 6.8 to 3.8 days (mean difference: 2.9 d, $p < 0.05$) if a patient attended CMC compared to if they had not. The 7 day readmission rate reduced significantly from 5.7% to 1.2% (mean difference: 4.5%, $p < 0.05$) if a patient attended CMC in the preceding year compared to if they had not. The 28 day readmission rate reduced from 21.7% to 3.1% (mean difference: 18.6%, $p < 0.05$). The 7 day mortality rate reduced significantly from 4.8% to 1.6% (mean difference 3.2%, $p < 0.05$) if a patient attended CMC compared to if they had not. The 28 day mortality rate reduced from 6.1% to 2.9% (mean difference 3.1%, $p < 0.05$). **Conclusion:** The close monitoring clinic is an effective intervention to reduce length of stay, readmission, and mortality. It also lowers the onus on hepatology consultant outpatient appointments. These improvements translate into fewer inpatient resources needed to care for this cohort and thus can be a cost-effective investment for healthcare systems.

Disclosures: The following people have nothing to disclose: Pauline Dundas

Disclosure information not available at the time of publication: Chirantha Premathilaka, Lorna Bailey, Theresa Milne, Shirley English, Lindsay McLeman, Chaitra Chandra Shekar, Ashis Mukhopadhya

3026-A | OBSTRUCTED UMBILICAL HERNIA OUTCOMES IN HOSPITALIZED DECOMPENSATED CIRRHOSIS SUBJECTS.; NATION WIDE TRENDS.

Mubeen Khan Mohammed Abdul[1], Waseem Amjad[2], Kamran Safdar[3], Ajay Sahajpal[1] and Sanjaya Kumar Satapathy[4], (1)Advocate Aurora St Lukes' Medical Center, (2)Harvard University Medical School, (3) University of Cincinnati, (4)Division of Hepatology, Northwell Health, and Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA.

Background: Obstructed ventral / umbilical hernia are associated with high morbidity and mortality in cirrhosis and surgery is often deferred in decompensated cirrhosis. Aim:Assess safety outcomes of obstructed ventral/umbilical hernia repair in cirrhosis. **Methods:** Study population consisted of national readmission database from last quarter of 2015 to 2017. Outcomes of obstructive ventral/umbilical hernia in relationship with surgical repair was computed in a multivariate model adjusted for age, gender, co morbid conditions and hepatic de compensatory events **Results:** There were 1946 subjects with obstructed umbilical/ventral hernia. Of them 446 subjects had surgical repair. Laparoscopic repair was done in 138 subjects. Mean age of those who underwent surgical repair was 60.50 ± 11.4 years and 60.5% were men. Ascites (70.9% vs. 54.8%, $p < 0.001$) and hepatic encephalopathy (10.8% vs. 6.1%, $p = 0.046$) was more prevalent in non-surgical repair group. Although multivariable adjusted hospital cost was higher in ventral hernia repair group (β: 28597, 95% CI: 5296 – 51897, $p = 0.02$), this was not associated with higher in-hospital mortality (OR: 0.43, 95% CI: 0.16-1.18, $p = 0.10$), 30-day readmission (HR: 1.26, 95% CI: 0.80 – 1.96, $p = 0.32$), and length of stay. Surgical repair in decompensated cirrhosis was associated with higher length of stay (β: 6.89, 95% CI: 1.59 – 12.19, $p = 0.01$) but similar mortality (OR: 0.47, 95% CI: 0.08 – 0.61, $p = 0.38$), 30-day readmission (HR: 0.63, 95% CI: 0.06 – 6.55, $p = 0.69$) and hospitalization cost was as compared to conservative group. Laparoscopic repair was associated with reduced hospital cost as compared to open repair (β: -31879, 95% CI: -64302 – 544, $p = 0.05$). **Conclusion:** Obstructed Umbilical/ventral hernia repair was safe in cirrhosis patients and did not increase mortality in decompensated cirrhosis. Laparoscopic repair improved hospital cost as compared to open repair. Future prospective studies are recommended to identify the role of surgical repair in decompensated cirrhosis.

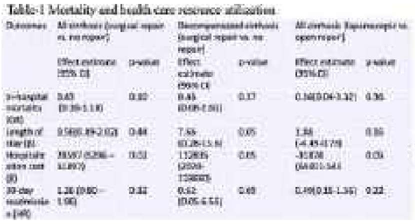
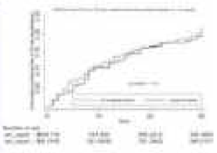


Table-1 Mortality and health care resource utilization



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

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

Ayusha Poudel[1], Taha Teaima[2], Sajana Poudel[1], Eman Elhamamsy[3] and Anurag Adhikari[4], (1)John H Stroger Jr. Hospital of Cook County, (2)Cook County Hospital, (3)Ain Shams University, (4)New York City Health and Hospitals/ Jacobi

Background: Hepatorenal syndrome (HRS) is a functional renal failure that develops as a consequence of decreased renal blood flow in patients with late-stage cirrhosis and ascites. The diagnosis requires combination of clinical observation and laboratory criteria. **Methods:** This is a retrospective study of the National Inpatient Survey (NIS) database of year 2020 including all adults age 18 and above with the discharge diagnosis of liver disease with and without hepatorenal syndrome. We identified the population with Chronic Liver disease with cirrhosis and Acute Kidney Disease with or without chronic kidney disease by searching the NIS database using the International Classification of Disease-10 (ICD-10). Inpatient mortality, morbidity, mean length of stay (LOS), mean total hospital charge (THC) and multivariate logistic regression, and linear regression analyses were used to analyze the data. **Results:** Out of 120,840 liver cirrhosis hospitalizations, 10,750 (8.9%) had developed hepatorenal syndrome. Patients with liver cirrhosis and hepatorenal syndrome had higher adjusted odds of inpatient mortality (Adjusted odds ratio [aOR]: 4.88, 95% confidence interval [CI]: 4.15-5.72, $p < 0.001$), longer mean LOS of 4.9 days (95% CI: 4.33-5.51, $p < 0.001$), and higher mean total hospital cost of $ 99255 (95% CI: 75731.6 - 122779.3, $p < 0.001$) than those without HRS. Out of all the patients admitted with cirrhosis, 5810 (4.8%) people died and in the subgroup with hepatorenal syndrome, 17.63% died ($P = 0.0000$). The OR for mortality in patients who develop hepatorenal syndrome is 5.8 [CI 5.06-6.64]. The mean length of stay in patients with HRS is 11.48 ± 0.36 days vs 5.34 ±0.5 days in patients without hepatorenal syndrome. The total cost of hospital stay was for patients with HRS was $192881 ± 15687 compared to those without which was $70293 ± 1796. The prevalence of sepsis in patients with HRS was 13.35% compared to those without which was 2.72% ($P = 0.000$), prevalence of mechanical ventilation was higher in the HRS subgroup at 6.98% vs 1.56% ($P = 0.0000$) and AKI prevalence in HRS was 89.58% vs 24.72% in HRS subgroup. ($P = 0.0000$) **Conclusion:** The patient with hepatorenal syndrome has in increased risk of mortality, longer days of hospital stay and higher hospital cost than those without. The risk of developing morbidities was also higher in the HRS subgroup.

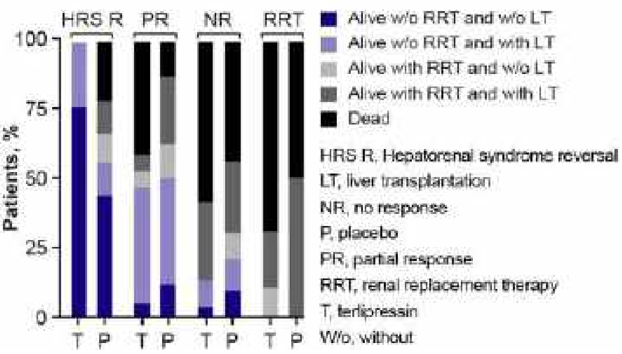
Disclosures: The following people have nothing to disclose: Ayusha Poudel, Taha Teaima, Sajana Poudel, Eman Elhamamsy, Anurag Adhikari

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

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

Background: Patients (pts) with untreated rapidly progressive hepatorenal syndrome (HRS) experience early mortality without liver transplantation (LT). Although HRS treatment can lower prioritization for LT due to a decrease in MELD score, a requirement for renal replacement therapy (RRT) is associated with poor survival. To determine the impact of terlipressin (terli) on LT and survival in pts with HRS, we analyzed data from the Phase III, randomized, placebo (pbo)-controlled REVERSE study. **Methods:** A subset of US pts from the REVERSE study (excluding those with hepatocellular carcinoma, alcoholic hepatitis, or aged > 70 y) were analyzed ($N = 125$) by treatment group (terli, $n = 66$; pbo, $n = 59$). Pts were divided into the following groups by treatment response: HRS reversal (serum creatinine [SCr] d 1.5 mg/dL), partial response (PR; SCr decreased > 0.3 mg/dL from baseline to end of treatment [EOT]), no response (NR), and those requiring RRT. The proportion of pts, (1) alive without RRT without LT, (2) alive with RRT with LT, (3) alive with RRT without LT, (4) alive with RRT with LT, or (5) dead, were assessed for each group at post-treatment Day 30, 60, and 90. Pts with HRS reversal were analyzed at the EOT for change in MELD score. **Results:** Reason for EOT: confirmed HRS reversal, 16.7% vs 15.3% (*P* = 0.830); RRT in 10.6% vs 11.9% (*P* = 0.824); EOT status: decrease in SCr, 31.8% vs 22.0% (*P* = 0.220); increase in SCr, 30.3% vs 37.3% (*P* = 0.409); for pts treated with terli and pbo, respectively. In pts with HRS reversal, survival without RRT at Day 90 was 100% for terli- and 55.6% for pbo-treated pts, respectively. Survival without RRT with/without LT progressively decreased in the PR and NR groups. Among those with RRT (n = 18), few pts were alive without LT at Day 90 (Figure). Baseline MELD scores were similar across treatment groups (mean [SD]: terli, 33.16 [6.16]; pbo, 32.67 [5.13]). HRS reversal was associated with decreased MELD scores (mean [SD]: terli, -4.4 [2.95] vs pbo, -5.6 [4.12]; *P* = 0.5032) from baseline to EOT. The incidence of LT at Day 30 was similar between the terli and pbo groups (30.3% vs 32.2%; *P* = 0.819). **Conclusion:** This post hoc subgroup analysis of pt data from REVERSE demonstrates clinical benefits among those who achieved HRS reversal and progressively worse outcomes for those with a PR or NR. Survival without LT is extremely limited for those who progress to RRT. Although MELD scores decreased with HRS reversal, overall LT rate was not adversely affected.

Figure. Clinical response at Day 90 by treatment response



Disclosures: Samuel H. Sigal – Mallinckrodt Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Mallinckrodt Pharmaceuticals: Consultant, Yes, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Consultant, No, No; Eli Lilly: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;

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Khurram Jamil – Mallinckrodt Pharmaceuticals: Employee, Yes, No;

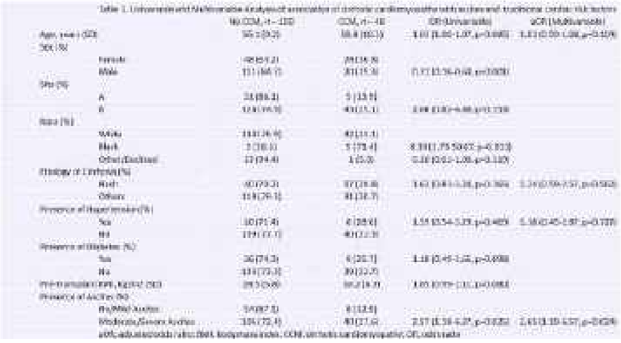
f 3029-A | Patients with Cirrhosis and Significant Ascites are At High Risk of Cirrhotic Cardiomyopathy

Xiaohan Ying[1], Anton Jordan De Witte[2], Adesola Oje[3], Ashley Spann[3], Christopher Slaughter[2], Jeffrey Annis[2], Yushan Pan[4], Catherine Ng[5], Evan Sholle[5], Russell Rosenblatt[6], Evan Brittain[2], Brett Fortune[7] and Manhal Izzy[3], (1)Weill Cornell Medicine, NY, (2)Vanderbilt University, (3)Vanderbilt University Medical Center, (4) Massachusetts General Hospital, (5)Cornell University, (6)Weill Cornell Medicine, Scarsdale, NY, (7)Montefiore Medical Center

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

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

patients who were evaluated for and received liver transplantation at two tertiary centers between January 1, 2015 and December 31, 2018. We excluded patients with primary cardiac disease, those without cirrhosis, and recipients of multi-organ transplant. Demographic, clinical, and echocardiographic data were collected. Univariable and multivariable logistic regression models were developed to determine associations between ascites and CCM, while controlling for traditional risk factors for cardiac dysfunction. We defined the severity of ascites based on Child Pugh classification as well as the International Ascites Club grading, where grade 2/3 ascites is equivalent to significant ascites. **Results:** Out of 348 patients, 207 (59.5%) had sufficient data to assess CCM, which was present in 48 patients (23%). The univariable analysis for CCM associations is depicted in Table 1. On multivariable analysis controlling for age, non-alcoholic steatohepatitis (NASH), and hypertension, significant ascites was strongly associated with CCM (aOR 2.65, 95% CI: 1.19 to 6.57, $p = 0.024$). Further multivariable analyses, controlling for the aforementioned covariates, were performed for individual markers of CCM and showed statistically significant associations with ascites: Ejection Fraction [EF] (β coefficient 2.02, 95% CI: 0.40 to 3.64, $p = 0.014$), left atrial volume index (LAVI) (β coefficient 5.96, 95% CI: 3.14 to 8.79, $p < 0.001$), E/e', which reflects left ventricular filling pressures (β coefficient 1.03, 95% CI 0.23 to 1.83, $p = 0.012$), and septal e', which reflects myocardial relaxation (β coefficient 0.70, 95% CI: 0.04 to 1.37, $p = 0.038$). **Conclusion:** Patients with cirrhosis and significant ascites were at increased risk for CCM. Furthermore, significant ascites was associated with hyperdynamic cardiac changes as demonstrated by increased EF and e', and with structural changes as demonstrated by increased LAVI. These findings elucidate potential implications of the interplay between CCM and decompensated cirrhosis and its clinical manifestations, such as refractory ascites and hepatorenal syndrome.



Disclosures: Brett Fortune – W L Gore and Associates: Consultant, No, No;

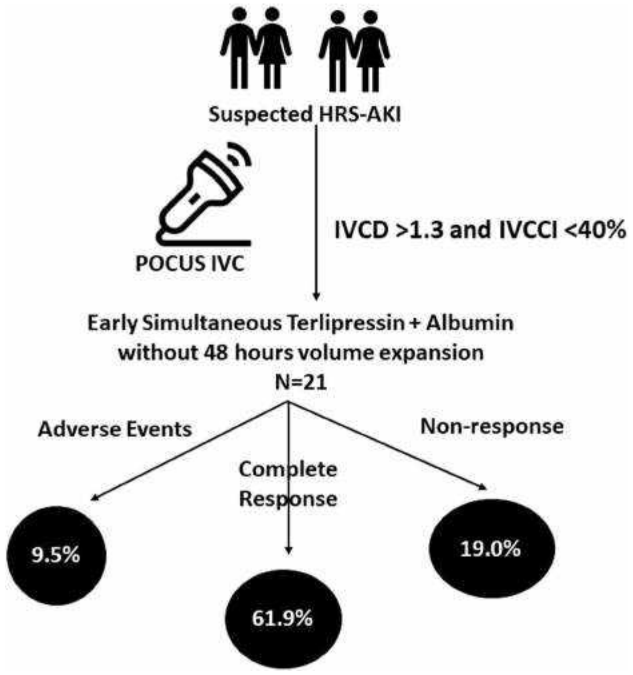
The following people have nothing to disclose: Xiaohan Ying, Ashley Spann, Russell Rosenblatt, Manhal Izzy

Disclosure information not available at the time of publication: Anton Jordan De Witte, Adesola Oje, Christopher Slaughter, Jeffrey Annis, Yushan Pan, Catherine Ng, Evan Sholle, Evan Brittain

3030-A | POINT OF CARE ULTRASOUND (POCUS) PERMITS EARLY INITIATION OF TERLIPRESSIN IN SUSPECTED HRS-AKI

Akash Roy[1], Indrajeet Tiwary[1], Subhash Tiwari[1], Madhumita Premkumar[2], Surender Singh[3] and Mahesh Goenka[1], (1)Apollo Hospitals, Kolkata, (2)Pgimer, Chandigarh, (3)Sgpgims, Lucknow

Background: The conventional definition of Hepatorenal Syndrome-Acute Kidney Injury (HRS-AKI) revolves around an initial strategy of volume expansion in suspected cases before initiating vasoconstrictor therapy. Early initiation of terlipressin has been shown to be feasible in HRS-AKI in ACLF. Volume status assessment using point of care ultrasound (POCUS) allows for early stratification of volume status and may allow for goal-directed early terlipressin initiation. We aimed to assess the use and safety of POCUS-assisted terlipressin initiation in HRS-AKI as a single-arm pilot study. **Methods:** Consecutive patients with suspected HRS-AKI (e Stage IB but excluding volume expansion criteria of ICA-HRS AKI criteria) were assessed with POCUS for inferior vena cava diameter (IVCD) and IVC collapsibility index (IVCCI). Patients were classified as volume replete if IVC at index assessment was > 1.3cm and IVCCI < 40%. Volume replete(VR) suspected HRS-AKI were initiated simultaneously on terlipressin 1mg every 6 hours along with the continuation of 20% intravenous albumin without awaiting the recommended 48 hours volume expansion criteria. Terlipressin response at day 7 was assessed using standard criteria. **Results:** 21 (40.3%) patients [age 51.23 ± 10.9 years, 80.9% males, 61.9% NASH cirrhosis, MELD 19(18-21)] were volume replete at index POCUS with mean IVCD 1.78 ± 0.18 cm. Baseline creatinine and creatinine at diagnosis of HRS-AKI were 1.02 ± 0.16mg/dl and 2.2 ± 0.49mg/dl, respectively. Overall, 17 (80.95%) responded to terlipressin with complete response in 13(61.9%) and partial response in 4(19.04%). At diagnosis, creatinine was higher in non-responders [2.75(2.2-2.3) vs 1.9 (1.9-2.1) $p = 0.01$]. Serious adverse events were noted in 2(9.5%) patients. **Conclusion:** POCUS-guided initiation of terlipressin in HRS-AKI is safe and feasible. Volume-replete patients at index diagnosis may be candidates for early initiation of terlipressin. However, further refinements in POCUS criteria and randomized allocation are required for the further validation of the hypothesis.



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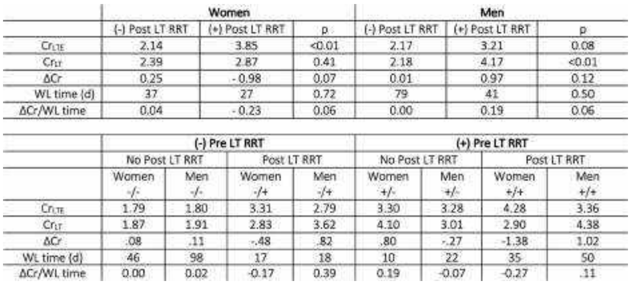
Disclosure information not available at the time of publication: Indrajeet Tiwary, Subhash Tiwari, Mahesh Goenka

3031-A | PRE LIVER TRANSPLANT SERUM CREATININE TRENDS DIFFER IN MEN AND WOMEN WHO REQUIRE POST LIVER TRANSPLANT RENAL REPLACEMENT THERAPY

Katherine M. Cooper[1], Alessandro Colletta[2] and Deepika Devuni[1], (1)UMass Chan Medical School, (2) UMass Chan Medical School, Worcester, MA

Background: Serum creatinine (sCr) is a poor marker of renal function in patients with advanced liver disease (AdLD). However, changes in sCr are still used to monitor the course of renal dysfunction in individual patients. We aimed to evaluate sex differences the relationship between sCr trends and post-liver transplant (LT) renal outcomes in patients with AdLD requiring inpatient LT evaluation (LTE). **Methods:** Urgent LTE's for AdLD over a 4-year period at our center were analyzed (n = 210); fulminant liver failure patients were excluded. MELD-Na labs from the time of LTE and the time of LT were collected. Metrics included “Delta -Cr”, “Cr slope” and “post-LT RRT”. “Delta Cr” was defined as the difference in sCr at the time of LTE (Cr_{LTE}) and sCr at the time of LT (Cr_{LT}). “Slope-Cr” was defined as “Delta Cr/waitlist days.” Post-LT-RRT_{30d} was defined was RRT requirement e 30 days post -LT. Patient's were dichotomized by whether or not their sCr reduced pre-LT (-Delta Cr vs. +Delta Cr). Data was compared between women and men (Top panel) and further by pre-LT RRT status (bottom panel). Data analysis included Fishers Exact test and T tests. **Results:** 210 patients were analyzed. Alcohol was the most common AdLD etiology (61%) with no differences by sex. 39% underwent LT (43 men, 39 women) of which 41.5% required e 1day of pre-LT RRT. Post-LT-RRT_{30d} occurred in 24.4% (23.1% women vs. 25.6% men, p = 0.79). Women with post-LT-RRT_{30d} had a larger reduction in sCr between LTE and LT compared to women without post-LT-RRT_{30d} (Delta Cr: -0.98 vs. +0.25, p = 0.07). When accounting for waitlist, this relationship persists(Slope-Cr: -0.23 vs. +0.04, p = 0.06). Men with post-LT-RRT_{30d} had a large increase in sCr between LT and LTE (Delta Cr 0.97 vs. 0.01, p = 0.12). These directionalities persists on subgroup analysis in patients with and without pre-LT RRT (bottom panel). A down-trending sCr (- Delta Cr) did not affect rate of post-LT-RRT_{30d} in women (61.1% vs. 57.1%, p = 0.80), but was associated lower rate of post-LT-RRT_{30d} in men (31.3% vs. 70.4%, p = 0.01**). Conclusion:** Predictors of post-LT renal function differ between men and women. Pre-LT renal function is considered a strong predictor of post-LT renal outcomes, but this may be less applicable to women with AdLD. In our analysis, a reduction in sCr between LT and LTE was observed in women requiring post-LT RRT while an increase sCr between LTE and LT was observed in men requiring post-LT RRT. These findings remained profound when accounting for waitlist days and when accounting for pre-LT renal replacement therapy. While this cohort is small, our results suggest a quick decline in sCr may portend a poor prognosis with post-LT for women. Potential causes of this phenomenon include increased muscle wasting between LTE and LT in women compared to men or more prevalence of critical illness myopathy in women compared to men at the time of LTE. Other methods of assessing GFR should be used routinely, particularly in women who present with AdLD.



	Women			Men		
	(-) Post LT RRT	(+) Post LT RRT	p	(-) Post LT RRT	(+) Post LT RRT	p
Cr_{LTE}	2.14	3.85	<0.01	2.17	3.21	0.08
Cr_{LT}	2.39	2.87	0.41	2.18	4.17	<0.01
ΔCr	0.25	- 0.98	0.07	0.01	0.97	0.12
WL time (d)	37	27	0.72	79	41	0.50
ΔCr/WL time	0.04	- 0.23	0.06	0.00	0.19	0.06

	(-) Pre LT RRT				(+) Pre LT RRT			
	No Post LT RRT		Post LT RRT		No Post LT RRT		Post LT RRT	
	Women -/-	Men -/-	Women -/+	Men -/+	Women +/-	Men +/-	Women +/+	Men +/+
Cr_{LTE}	1.79	1.80	3.31	2.79	3.30	3.28	4.28	3.36
Cr_{LT}	1.87	1.91	2.83	3.62	4.10	3.01	2.90	4.38
ΔCr	.08	.11	-.48	.82	.80	-.27	-1.38	1.02
WL time (d)	46	98	17	18	10	22	35	50
ΔCr/WL time	0.00	0.02	-0.17	0.39	0.19	-0.07	-0.27	.11

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3032-A | PREDICTING BIOMARKERS UNEARTHED USING URINARY PROTEOMICS FOR ACUTE KIDNEY INJURY (AKI) IN DECOMPENSATED CIRRHOSIS (DC)

Virendra Singh[1], *Inder Bhan Singh II*[2], *Arka De*[3], *Vivek Kumar*[3], *Jasvinder Nain*[3] *and Ashok Kumar*[4], *(1)Punjab Institute of Liver and Biliary Sciences, Mohali, India, Chandigarh, CH, India, (2)Postgraduate Institute of Medical Education and Research, (3)Post Graduate Institute of Medical Education and Research, (4)Post Graduate Institute of Medical Education & Research*

Background: AKI in decompensated cirrhosis adversely affects outcome before as well as after transplant in these patients. AKI occurs In around 20% of DC patients who are admitted. There is not much knowledge available about the prevalence of AKI in DC outpatients. Furthermore, there has not been much research done on the clinical indicators of AKI development in this situation. This ongoing longitudinal prospective study uses untargeted mass spectrometry-based urine proteomics to investigate the function of urinary biomarkers and assess the predictors of AKI among DC patients in the outpatient environment. **Methods:** Total 123 consecutive outpatients with DC were recruited. Patients with chronic kidney disease are excluded. All patients were followed up for a year at three-month intervals to observe the development of AKI, or more often if deemed clinically required. The International Club of Ascites (ICA) criteria was used to define AKI. Liquid chromatography-mass spectrometry (LC-MS) was used to do urine protein profiling, and Proteome Discoverer 3.0 was used to infer the results. **Results:** One hundred and twenty three patients (age: 50.94 ± 9.32 years, males: 104 (84.5%) were recruited and were included for analysis. The commonest etiologies included alcohol (n = 66, 53%), NAFLD (n = 25, 20.3%), and chronic viral hepatitis (n = 21, 17.07%). Median duration of follow-up was 6 (1-12) months. AKI developed in 21 (17.07%) patients on follow-up. At baseline around 1700 proteins in urinary samples were scanned. Baseline Beta 2 microglobulin, Uroplakin-1a, Cornifin-A and B, Urinary retinol binding protein 4, and Uromodulin (p = 1.1e-7, 6.6e-7, 1.7e-2, 2.3e-4, 2.3e-4, and 2.6e-2; respectively) were significantly higher in patients who developed AKI. NGAL at baseline was significantly higher in mortality group with Area under ROC value of 0.9903 and p-value of < 0.0001. **Conclusion:** The incidence of AKI in outpatients with decompensated cirrhosis was 17.07%. Beta 2 microglobulin, Uroplakin-1a, Cornifin-A and B, Urinary retinol binding protein 4, and Uromodulin may help in identification of patients who have a higher risk of AKI development and NGAL may act as mortality marker in DC patients with AKI.
Disclosures: The following people have nothing to disclose: Virendra Singh, Inder Bhan Singh, Arka De, Vivek Kumar, Jasvinder Nain, Ashok Kumar

3033-A | PREDICTING FUTURE DECOMPENSATION IN PATIENTS WITH CIRRHOSIS: A MACHINE LEARNING APPROACH TO RISK STRATIFICATION AT THE FIRST PATIENT VISIT

Micah Grubert Van Iderstine[1], *Braedon Griggs*[1], *Olivia Thorleifson*[1], *Gerald Y. Minuk*[2] *and Nabiha Faisal*[1], *(1) University of Manitoba, (2)Department of Internal Medicine, University of Manitoba, MB, Canada*

Background: Decompensation is a major turning point in the course of chronic liver disease. Determining which patients with cirrhosis will decompensate is challenging due to the complex non-linear relationships between lab values and patient outcomes. We aimed to develop and validate machine learning (ML) models to predict hepatic decompensation in a timely and accurate manner at the first patient visit. **Methods:** This study used a retrospective province-wide cohort of 3483 adult patients with cirrhosis or its complications seen in hepatology clinics between 1987 and 2023. Patients were identified to have cirrhosis and classified as either compensated or decompensated based on diagnostic and prescribing codes. We identified eleven potential biochemical and demographic predictors that can be evaluated at the first clinic visit. Patients were randomly selected for model development (80%, n = 2786) and validation (20%, n = 697). Twelve ML classification models including Support Vector Machine, Random Forest, XGBoost and AdaBoost were trained and tuned to differentiate between compensated and decompensated patients. Predictor inclusion and model selection were conducted with 10-fold cross-validation. Model performance was evaluated using precision, recall and f1 score. **Results:** Of the 3483 patients with cirrhosis, 992 patients were eventually diagnosed with decompensation and 2491 patients remained compensated. The mean age was 51.8 years, 50.5% were male, and mean length of follow-up was 7.5 years. Prediction on the validation dataset indicated that the AdaBoost classifier performed best with a compensated precision rate of 0.893 and decompensated recall of 0.791. The compensated recall was 0.616, and f1 score was 0.729. The decompensated patient precision was 0.421, and f1 score was 0.55 (Figure 1A, 1C). Ten-fold cross validation accuracy was 71.6% (SD = 2.5%). The AUC-ROC for the binary decision was 0.76 (Figure 1B). The features of highest predictive value were found to be INR, platelets, sodium, creatinine, albumin and bilirubin. **Conclusion:** The machine learning models developed using a province wide hepatology ambulatory database of cirrhosis patients can potentially define a high-risk group early in the course of disease. This, in turn, can lead to improved clinical outcomes and aid in treatment decision-making and prognostication. Additional external validation is needed to confirm the reliability and generalizability of these models.

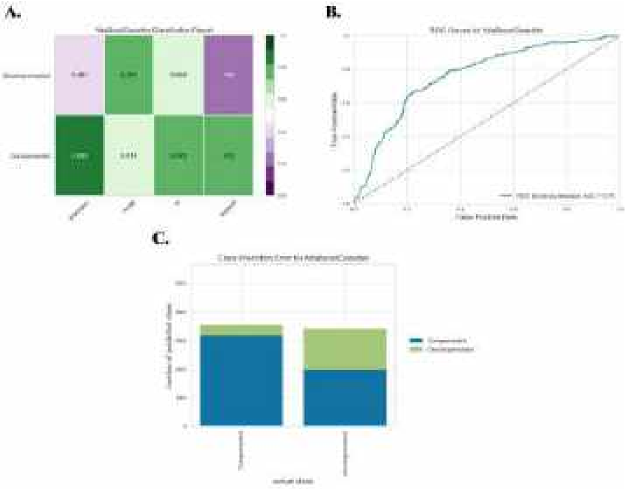

Figure 1. AdaBoost model performance metrics (A), receiver operator curve (B), and class prediction error chart (C). The columns of the class prediction chart illustrate the predicted distribution of patient outcomes compared to the actual outcomes shown in color.

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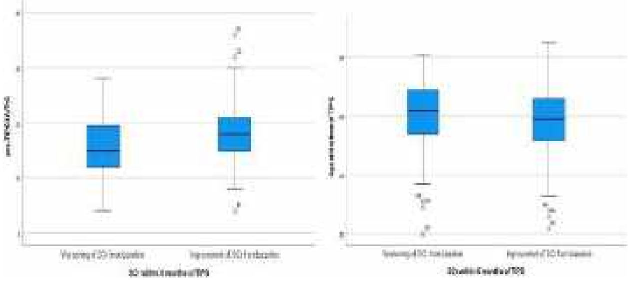
3034-A | PREDICTORS OF RENAL DYSFUNCTION IN PATIENTS UNDERGOING TIPS FOR DECOMPENSATED CIRRHOSIS

Shilpa Junna[1], Abhishek Shenoy[2], Sarah Uttal[2], Shantanu Warhadpande[2], Seth Waits[2], Robert J. Fontana[2] and Pratima Sharma[2], (1)Cleveland Clinic Foundation, (2)University of Michigan Medical Center

Background: Transjugular intrahepatic portosystemic shunts (TIPS) can improve hemodynamics in cirrhotic patients with complications of portal hypertension, however there are significant cardiac and renal implications associated with this procedure. While the cardiac effects are often instantaneous, changes in renal function may not be seen for up to several weeks. In this study, we examined the trajectory of serum creatinine (SCr) after TIPS placement and factors associated with worsening SCr post-TIPS. **Methods:** Data was collected retrospectively on all patients aged e 18 years who underwent TIPS for complications of decompensated cirrhosis at our institution from July 2017 to June 2022. Patients were followed until death or 12/31/2022. The primary outcome was change in SCr from baseline (within 30 d pre-TIPS) to post-TIPS (within 6 mo of TIPS), and was defined as a change of 0.01 mg/dL or higher. These patients were then divided into those with worsening or improving SCr post-TIPS. We subsequently used multivariate logistic regression to identify independent predictors of change in SCr post-TIPS. **Results:** The median age of the 165 patients was 59 years (20-85 y), 46% were female and 85% Caucasian. The leading etiologies of liver disease were NAFLD (39%) followed by alcohol associated disease (32%). The median MELD-Na score at the time of TIPS was 12 (6-30). The median SCr pre-TIPS was 0.97 mg/dL (0.39-4.7 mg/dL). Improvement in SCr post-TIPS was seen in 54% of patients (median 0.14 mg/dL) and an increase in SCr was noted in 46% (median 0.19 mg/dL). Only 4% of patients required renal replacement therapy post-TIPS. Median pre- and post-TIPS HVPG were 16.5 and 8 mm Hg, respectively (Figure 1). After adjusting for age at TIPS, sex, etiology of cirrhosis, pre-TIPS MELD Na, and pre-TIPS SCr, pre-TIPS HVPG was independently associated with worsening SCr post-TIPS. Every unit increase in pre-TIPS HVPG was found to worsen the SCr by 7% (OR: 1.074, $p < 0.025$) post-TIPS. Hospitalizations within 90 days of TIPS were more prevalent in those whose renal function had worsened compared to those with improvement (51% vs. 44%, $p = 0.05$). Interestingly, listing for liver transplantation and 1-year mortality were similar in both groups. **Conclusion:** Overall, worsening of SCr within 6 months of TIPS was seen in half of our cohort. Despite the significantly higher proportion of hospitalizations among those with renal dysfunction after TIPS, the survival and liver transplantation listing rates at 1-year post-TIPS were similar in both groups. Pre-TIPS HVPG appears to play an important role in predicting a patient's risk of renal dysfunction post-TIPS and may be useful in guiding post-TIPS management.



Disclosures: Pratima Sharma: Pratima Sharma, Abhishek Shenoy, Sarah Uttal, Shantanu Warhadpande, Seth Waits, Robert J. Fontana

3035-A | PREVALENCE OF HEART FAILURE AND HEPATIC CONGESTION IN NEPHROGENIC ASCITES: HISTOPATHOLOGIC AND ECHOCARDIOGRAPHIC CHARACTERIZATION

Areeba Khwaja[1], James Patton[2], Brian K. Carlile[3], James F. Trotter[4], Hussien Elsiesy[2], Bernard V. Fischbach[2], Mohanakrishnan Sathyamoorthy[5,6] and Stevan A. Gonzalez[2,6], (1)Mcgovern Medical School, University of Texas Health Science Center at Houston, Fort Worth, TX, (2)Baylor Simmons Transplant Institute, Forth Worth, TX, (3)Baylor Scott & White All Saints Medical Center, Fort Worth, TX, (4)Baylor Simmons Transplant Institute, Dallas, TX, (5)Baylor Scott & White Heart & Vascular Hospital Fort Worth, Fort Worth, TX, (6)Burnett School of Medicine at TCU, Fort Worth, TX

Background: Factors associated with development of nephrogenic ascites among patients with end-stage renal disease (ESRD) remain poorly characterized. Patients with ESRD are at increased risk of heart failure (HF). Comprehensive assessment of nephrogenic ascites vs cardiogenic ascites by transjugular (TJ) liver biopsy, echocardiography, and peritoneal fluid analysis could more accurately discriminate etiology, guide management, and ascertain clinical outcomes. **Methods:** Non-cirrhotic patients with ascites attributed to 1) ESRD maintained on hemodialysis or 2) HF were identified through a clinical hepatopathology database at a tertiary care hepatology program from 2011 to 2021. Liver histopathology and echocardiography data were reviewed on all patients. **Results:** 39 patients were identified: 24 with ESRD/nephrogenic and 15 with cardiogenic ascites. ESRD patients were younger ($p = 0.02$) and more commonly Hispanic or Black ($p = 0.03$). All cardiogenic ascites patients had established HF and no ESRD; common causes of HF included ischemic cardiomyopathy (CM, 27%), valvular heart disease (27%), and nonischemic CM (20%). Patients with ESRD had notably increased peritoneal fluid protein (median 4.5, range 3.0-5.8 g/dL) vs cardiogenic ascites (3.3, 2.0-4.6 g/dL; $p = 0.003$), while cardiogenic ascites was more frequently associated with a serum-ascites albumin gradient (SAAG) > 1.1 (82% vs 17%; $p = 0.001$). Liver biopsy included TJ hepatic venous pressure gradient (HVPG) in 35/39 (90%). Absence of cirrhosis was confirmed in all patients: 61.5% fibrosis stage 0-1, 25.6% stage 2. Bridging fibrosis was present in 4 patients, all with HVPG d 5. Sinusoidal dilation/congestion was associated with reduced right ventricular systolic function on echocardiogram ($p = 0.02$), elevated TJ free hepatic vein pressure (HVP) $>$ 10mmHg ($p = 0.001$), and was present in 14/15 (93%) of the cardiogenic cohort, yet was also observed in 15/24 (62.5%) with ESRD. The frequency of HVPG $>$ 5mmHg was similar in cardiogenic (20%) vs ESRD (15%, $p = 0.70$), and HVPG $>$ 9 was observed only in 2 patients with cardiogenic ascites. Elevated HVP $>$ 10mmHg was more common in cardiogenic ascites (93% vs 55%, $p = 0.01$), and was strongly associated with decreased survival among patients with ESRD (1-yr survival 0.38 vs 1.00, $p = 0.04$). **Conclusion:** Although peritoneal fluid characteristics differ between cohorts, histologic evidence of hepatic congestion is frequently observed in patients with ESRD and nephrogenic ascites, suggesting HF as an underlying cause. As right heart dysfunction with elevated HVP may have a greater impact on outcomes among patients with ESRD, further investigation identifying risk factors and early echocardiographic features of HF in this population is needed.

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3036-A | PREVENTION OF MORTALITY WITH LONG-TERM HUMAN ALBUMIN ADMINISTRATION IN PATIENTS WITH DECOMPENSATED CIRRHOSIS AND ASCITES: DESIGN AND STATUS OF THE PRECIOSA STUDY

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Background: Patients with decompensated cirrhosis develop ascites, variceal bleeding, hepatic encephalopathy, and bacterial infections, complications associated with worse survival compared to compensated cirrhosis. A pilot study suggested that long-term human albumin administration in decompensated cirrhotic patients may improve circulatory function and systemic inflammation. The aim of this pivotal study is to assess long-term

Albutein 20% (Grifols) treatment for patients with decompensated cirrhosis and ascites. **Methods:** A phase 3, multicenter, randomized (1:1), controlled, parallel-group, open-label study compares standard medical treatment (SMT) + Albutein 20% (1.5 g/Kg body weight, maximum 100 g/patient, every 10 ± 2 days up to 12 mo; treatment arm) versus SMT alone (control arm). Eligible patients are adult (>18 y old), diagnosed with liver cirrhosis and ascites, hospitalized for acute decompensation, with or without a history of acute-on-chronic liver failure (ACLF) at admission or during hospitalization but without ACLF at screening, and a CLIF-C AD score > 50 points. **Results:** As of May 2023, enrollment has been completed at 69 sites across North America and Europe, with 477 patients screened, and 410 patients randomized (the target enrollment). Primary efficacy endpoint is the time to liver transplantation or death through 1 year after randomization. Secondary efficacy endpoints include time to liver transplantation through 3 and 6 months, time to death through 3, 6, and 12 months, number of paracenteses and incidence of refractory ascites. Exploratory endpoints are incidence of ACLF through 3, 6 and 12 months, number and length of hospital and ICU admissions, incidence of cirrhosis-related complications, albumin concentration and albumin binding capacity, incidence of TIPS, CLIF-C OF, CLIF-C ACLF and CLIF-C AD, MELD, Child Pugh score and quality of life. Safety endpoints include adverse events, vital signs, physical and laboratory examinations. **Conclusion:** PRECIOSA should provide pivotal results on the efficacy and safety of long-term albumin therapy to potentially improve survival in decompensated cirrhosis and ascites (NCT03451292, EudraCT: 2016-001789-28).

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3037-A | PROGNOSTIC SIGNIFICANCE OF ACUTE KIDNEY INJURY STAGE 1B IN HOSPITALIZED PATIENTS WITH CIRRHOSIS: A U.S. NATIONWIDE STUDY

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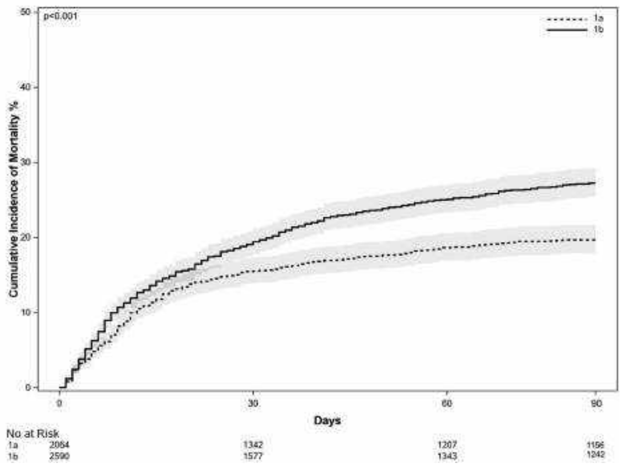
Background: Understanding the prognostic significance of acute kidney injury (AKI) stage 1B [serum creatinine (sCr) > 1.5mg/dL], compared to stage 1A (sCr < 1.5mg/dL) in an U.S. population is important as it can impact initial management decisions for AKI in hospitalized cirrhosis patients. Therefore, we aimed to define outcomes associated with stage 1B in a nationwide U.S. cohort of hospitalized cirrhosis patients with AKI. **Methods:** Hospitalized cirrhosis patients with AKI in the Cerner Health Facts database from 1/2009-09/2017 (n = 6,250) were assessed for AKI stage 1 (≥1.5-2-fold increase in sCr from baseline) and were followed for 90-days for outcomes. Primary outcome was 90-day mortality; secondary outcomes were in-hospital AKI progression and AKI recovery (return of sCr < 0.3 mg/dL of baseline). Competing risk multivariable analysis was performed to determine the independent association between AKI stage 1B, 90-day mortality (liver transplant as competing risk) and AKI recovery (death and liver transplant as competing risk). Multivariable logistic regression analysis was performed to determine the independent association between AKI stage 1B and

AKI progression. **Results:** 4,654 patients with stage 1 were analyzed: 1A (44%) and 1B (56%). Patients with stage 1B were older [median (interquartile range) 64 (56, 73) vs. 58 (50, 67) years, $p < 0.001$], more likely to be male [67% vs. 54%, $p < 0.001$), have non-alcoholic steatohepatitis [47% vs. 34%, $p < 0.001$], pre-existing chronic kidney disease (CKD) [60% vs. 9% ($p < 0.001$)], and ascites [66% vs. 60%, $p < 0.001$] compared to patients with stage 1A. Stage 1B patients had significantly higher cumulative incidence of 90-day mortality compared to stage 1A patients, 27% vs. 20% ($p < 0.001$) (Figure). On multivariable competing risk analysis adjusting for severity of liver disease and pre-existing CKD, patients with stage 1B (vs. 1A) had higher risk for mortality at 90 days [sHR 1.52 (95%CI 1.20-1.92), $p = 0.001$] and decreased probability for AKI recovery [sHR 0.76 (95%CI 0.69-0.83), $p < 0.001$]. Furthermore, on multivariable logistic regression analysis, AKI stage 1B (vs. 1A) was independently associated with AKI progression, OR 1.42 (95%CI 1.14-1.72) ($p < 0.001$). **Conclusion:** AKI stage 1B patients have significantly higher risk for 90-day mortality, AKI progression, and reduced probability of AKI recovery compared to AKI stage 1A patients. These results validate the prognostic significance of AKI stage 1B in an U.S. based population.

Figure: Comparisons of Cumulative Incidence of Mortality Between Patients with AKI Stage 1A and Stage 1B.



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3038-A | REGIONAL DIFFERENCES IN ACUTE KIDNEY INJURY PREVALENCE, CLINICAL CHARACTERISTICS AND PATIENT OUTCOMES IN A MULTI-NATIONAL CONSORTIUM OF INPATIENTS WITH CIRRHOSIS

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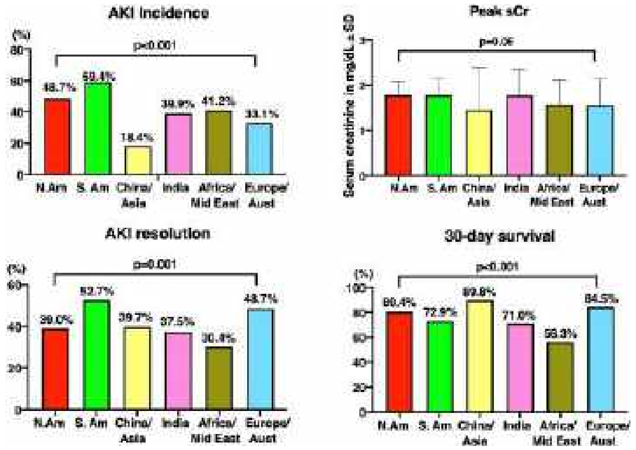
Background: Regional differences in cirrhosis etiologies, precipitating events, clinical practice may have an impact on AKI characteristics, AKI & patient outcomes across different parts of the world. We aim to assess these aspects of AKI amongst a global population of cirrhosis inpatients. **Methods:** The CLEARED Consortium prospectively enrolled cirrhotic inpatients from 6 continents. Baseline demographics, medications, admission & in-hospital details, AKI occurrence/severity, patient & AKI outcomes and survival at 1 month were collected. Multivariate analysis for AKI development using potential negative impact factors and patient's regional location was done. **Results:** 4161 patients were enrolled. Amongst the various regions, subcontinent India enrolled more men (81.6%) who were younger from than any other regions ($p < 0.001$ for both). Most common cirrhosis etiology was alcohol in Europe/Australia (74%), NASH in North (Nth) & South (Sth) Americas (26%) and hepatitis B in China & rest of Asia (45%) ($p < 0.001$ for all). Diuretics were the most commonly used drug ($> 50\%$ in all regions except India of 47.5%) followed by PPI (31% in China/Asia, 55% in India) ($p < 0.001$ for all). The admission MELD-Na varied (highest India: median = 28; lowest China/Asia: median = 17, $p < 0.001$). Common AKI precipitants were excess diuretics (Sth America 45% to Africa/Mid East 60%, $p < 0.001$), admission infection (China/Asia: 26% to Africa/Mid East 42%, $p < 0.001$). AKI distribution showed stage 1 H45% and stage 3 H30%. Most AKI were already present at admission (H70% India & Nth America, H60% in Africa/Middle East, and least in Europe/Australia = 23.6%) ($p < 0.001$). There were great variations in albumin (40% in China/Asia to 77% in India, $p < 0.001$) and vasoconstrictor use (24% in Sth America to 80% in India, $p < 0.001$) amongst AKI patients. Discharge MELD-Ma improved for patients without AKI or whose AKI resolved, but not for patients whose AKI only partially or not resolved. Multivariate analysis showed that diabetes, hypertension, prior LVP, admission parameters including NSBB use, MELD-Na and infection, as well as nosocomial infection all had a negative effect on AKI development. Using Nth Am. as an index, being in Sth Am. had 2X the risk, whereas all other regions had lower risk for AKI development ($p < 0.001$). AKI resolution & 30-day survival also varied across the continents (Figure). **Conclusion:** AKI incidence, precipitants, treatment and resolution in cirrhotic patients vary significantly around the world, which in turn may impact 30-day survival. Improved strategies for AKI prevention, diagnosis and management need to be devised to improve global outcomes.



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3039-A | ROLE OF PORTOSYSTEMIC SHUNT AND PORTAL VEIN STENT IN MANAGING PORTAL HYPERTENSION DUE TO HEMATOLOGICAL DISEASES

Jae-Sung Yoo[1], Jeong Won Jang[2], Jong Choi[2], Seung Kew Yoon[2] and Pil Soo Sung[3], (1)Seoul St Mary's Hospital, the Catholic University of Korea, Seoul, Republic of Korea, (2)The Catholic University of Korea, (3)The Catholic University Liver Research Center, Department of Biomedicine & Health Sciences, College of Medicine, the Catholic University of Korea

Background: Considerable patients with hematological malignancies experience complications related to portal hypertension. Many of these patients experience many complications of portal hypertension, including life-threatening complications such as varix bleeding. In our study, we sought to analyze the prognosis of patients of hematological malignancies with portal hypertension treated with transjugular intrahepatic portosystemic shunt and portal vein stents. **Methods:** We retrospectively assessed patients with hematological malignancies with portal hypertension who had complications including varix bleeding and ascites. We evaluated the prognosis of enrolled patients who were treated with portal vein stents and transjugular intrahepatic portosystemic shunts and also evaluated factors that seemed to be associated with their prognosis. **Results:** 11 patients were evaluated; the average age of the patients was 53.6 years old and 9 patients were female. The median total bilirubin of the 11 patients was 2.73; the median INR of the patients was 1.17; the average albumin of the 11 patients was 3.7. None of the patients tested positive for HBV or HCV infection. 3 patients had portal vein thrombosis. The average follow-up duration after TIPS or stent insertion procedure was 660 days and the median follow-up duration was 420 days. 4 patients were myelodysplastic syndrome patients; 3 patients were primary myelofibrosis (all positive for JAK2 V617F mutation) patients; 2 patients were multiple myeloma patients; 1 patient was essential thrombocytosis patient. Of the 11 patients, 1 patients experienced rebleeding. 2 patients also experienced rebleeding but this was because they went through TIPS closure or revision due to repetitive hepatic encephalopathy. 5 patients died during the follow-up, two of which were related to portal hypertension. 8 patients showed resolution of portal hypertension (HVPG 23 mmHg -> 5 mmHg) following TIPS and stent insertion. **Conclusion:** Portosystemic shunt and stent installation is an effective treatment option in managing portal hypertension due to hematological diseases.

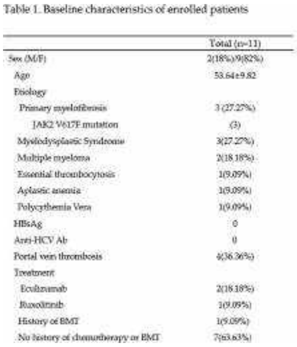

Table 1. Baseline characteristics of enrolled patients

	Total (n=11)
Sex (M/F)	2(18%)/9(82%)
Age	53.64±9.82
Etiology	
Primary myelofibrosis	3 (27.27%)
JAK2 V617F mutation	(3)
Myelodysplastic Syndrome	3(27.27%)
Multiple myeloma	2(18.18%)
Essential thrombocytosis	1(9.09%)
Aplastic anemia	1(9.09%)
Polycythemia Vera	1(9.09%)
HBsAg	0
Anti-HCV Ab	0
Portal vein thrombosis	4(36.36%)
Treatment	
Eculizumab	2(18.18%)
Ruxolitinib	1(9.09%)
History of BMT	1(9.09%)
No history of chemotherapy or BMT	7(63.63%)

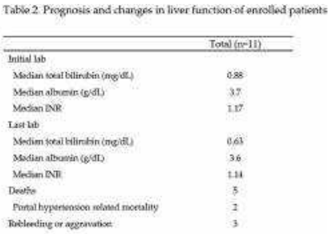

Table 2. Prognosis and changes in liver function of enrolled patients

	Total (n=11)
Initial lab	
Median total bilirubin (mg/dL)	0.88
Median albumin (g/dL)	3.7
Median INR	1.17
Last lab	
Median total bilirubin (mg/dL)	0.63
Madian albumin (g/dL)	3.6
Median INR	1.14
Deaths	5
Portal hypertension related mortality	2
Rebleeding or aggravation	3

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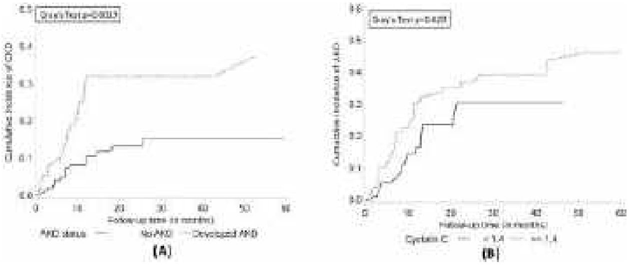
3040-A | SERUM CYSTATIN C PREDICTS THE DEVELOPMENT OF ACUTE KIDNEY DISEASE AND WORSE OUTCOMES IN PATIENTS WITH REFRACTORY ASCITES- A PROSPECTIVE COHORT STUDY

Rakhi Maiwall[1], Samba Siva Rao Pasupuleti[2], Neha Chauhan[1], Ashinikumar Kumar Hidam[1], Sherin Thomas[1] and Shiv Kumar Sarin[3], (1)Institute of Liver and Biliary Sciences, (2)Mizoram University (A Central University), Pachhunga University College Campus, (3)Ilbs

Background: Refractory ascites (RA) is one of the dreaded complications of cirrhosis. There are marked systemic and splanchnic hemodynamic alterations resulting in low mean arterial pressure (MAP) and decreased renal perfusion. There are no prospective studies evaluating the incidence, risk factors and role of Cystatin C (CysC) in predicting the development of acute kidney disease (AKD) in patients with cirrhosis and RA. **Methods:** Prospective cohort of RA were enrolled and serum CysC was performed for all patients. The primary outcome was development of AKD at 3-months. AKD and CKD were defined based on estimated glomerular filtration rate (eGFR) derived from the modification of-diet-in-renal-disease (MDRD6) on two consecutive occasions, 3 months apart. Binary logistic regression and competing risk-survival analysis was performed with TIPS, liver transplant and death as competing events to AKD or CKD. **Results:** A total of 297 patients with mean age 50.3 ± 10.0years, 86.9% males, 62% with alcohol-associated liver disease, 51% frail, with mean MELD 17 ± 7 and CTP 10.8 ± 1.9 were enrolled. These patients were followed for a median of 7.2 (2.8-17.7) months. The mean serum CysC was 1.6 ± 0.5 ng/ml. At follow up, 77 (26.2%) and 48 (16.3%) developed AKD and CKD respectively, 55 (18.7%) died, 14 (4.8%) underwent TIPS and 20(6.8%) liver transplantation. On multivariable logistic regression analysis, higher serum CysC (OR 2.58, 1.2-5.6), lower baseline eGFR (OR 0.10, 0.04-0.27), lower mean arterial pressure (OR 0.95, 0.91-0.99), presence of frailty (OR 4.78, 1.99-11.44) and the use of beta-blockers (OR 2.63, 1.23-5.65) significantly predicted the development of AKD at 3-months. On competing risk survival analysis, CysC (sHR 2.06, 1.15-3.67) and presence of frailty (sHR 1.85; 95% CI 1.03-3.31) independently predicted AKD. Higher CysC (sHR 2.80, 1.22-6.43), presence of frailty (sHR 2.67, 1.08-6.59) and AKD were significant risk factors for CKD (sHR 2.80, 1.47-5.34). Patients with AKD also had significant lower proportion of patients who achieved ascites control (47.1% vs. 27.3%; $p = 0.002$) and higher mean number of hospitalizations 0.27 ± 1.28 vs. 0.64 ± 0.98; $p < 0.001$). With each unit increase in CysC the instantaneous risk of AKD and CKD increased by 53 % and 138% respectively. A cut-off CysC of 1.4 ng/ml could predict the risk of AKD (HR 1.86, 1.06-3.26) and CKD (HR 5.52, 1.92-15.83). The development of AKD was also associated with higher mortality (HR 1.37, 1.01-2.36). **Conclusion:** Almost one-third of patients with refractory ascites develop AKD which is an independent predictor of CKD, lower ascites control, higher need of hospitalizations and mortality. Serum Cystatin C could guide risk stratification of patients with refractory ascites for adverse renal outcomes. Beta-blockers lead to higher risk of AKD development and should be carefully used in patients with refractory ascites who are frail, with lower mean arterial pressure and higher CysC.



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3041-A | SEX-BASED DISPARITIES IN BASELINE CHARACTERISTICS AND CLINICAL OUTCOMES OF PATIENTS WITH DECOMPENSATED CIRRHOSIS AND HEPATIC HYDROTHORAX

Mohamed Ismail, Rutgers New Jersey Medical School, Newark, NJ, Jennifer Asotibe, Rutgers New Jersey Medical School, Emmanuel Akuna, Albert Einstein Healthcare Network and Bubu A Banini, Yale University, New Haven, CT

Background: Although disparities in chronic liver disease by sex have been well described, sex-based disparities, specifically among patients with decompensated cirrhosis (DC) and concurrent hepatic hydrothorax (HHT), are lacking. We aimed to assess sex-based disparities in patient characteristics, etiologies of liver disease, and outcomes of patients with DC and HHT to determine if sex should be considered when approaching the early stages of the management of decompensated cirrhosis. **Methods:** Data from the 2016 -2019 National Inpatient Sample (NIS) database for patients admitted with cirrhosis were analyzed. By applying a stepwise and comprehensive set of inclusion and exclusion criteria, patients with decompensated cirrhosis with HHT were identified and analyzed. We further stratified the outcomes by gender. The primary outcome was inpatient

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

mortality. Secondary outcomes were hospital length of stay, total hospital charges, odds of development of respiratory failure, electrolyte derangements, sepsis, and need for paracenteses. Univariate and multivariate regression analyses were performed to adjust for confounders. **Results:** From 2016-2019, a total of 590,789 patients with a diagnosis of cirrhosis were admitted; 339,334 patients had decompensated cirrhosis, of which 15,397 patients (4.5%) had concurrent HHT. There were 8870 (57.6%) male patients with DC with HHT compared to 6524 (32.3%) female patients. The mean age was 59 years for male patients versus 62 years for females ($p < 0.0001$). Sex disparities seen among patients with HH were similar to disparities in the overall cohort of patients with DC. Compared to males, females had a higher prevalence of NASH (5.98% vs. 14.06%; $p < 0.0001$) and autoimmune hepatitis (0.74% vs. 2.88%; $p < 0.0001$) as an etiology for cirrhosis. On the other hand, males were more likely to have chronic hepatitis B (1.47% vs. 0.75%, $p < 0.0001$) and C (9.77% vs. 7.51%, $p < 0.0001$) as the etiology for cirrhosis compared to females. Male patients had lower odds of developing hypokalemia when compared to female patients (17.61% vs. 24.20%, $p < 0.0001$) but higher odds of developing hyponatremia compared to female patients (31.36% vs 28.34%, $p < 0.05$). There were no statistically significant differences in the odds of mortality, sepsis, respiratory failure, need for paracentesis, length of stay, or total hospital charges between males versus females. **Conclusion:** This study highlights sex-based disparities in baseline characteristics and etiologies of liver disease in patients with DC and concurrent HHT. These findings should be taken into consideration when approaching the early stages of the management of patients with decompensated cirrhosis.

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f 3042-A | SMALL FREQUENT PARACENTESIS USING AN INDWELLING CATHETER IS SAFE AND MORE EFFECTIVE AS COMPARED WITH REPEATED LARGE VOLUME PARACENTESIS IN CIRRHOTIC PATIENTS WITH REFRACTORY ASCITES (I-CARE)★

Manasa Alla[1], Saggere Muralikrishna Shasthry[2], Amar Mukund[1] and Shiv Kumar Sarin[3], (1)Institute of Liver and Biliary Sciences, (2)Instiyue of Liver and Biliary Sciences, (3)Ilbs

Background: Refractory ascites in cirrhosis carries a high mortality rate (up to 50 % in 6 mo). Repeated large volume paracentesis (LVP) has been associated with high morbidity, increased risk of acute kidney injury (AKI) & post paracentesis circulatory dysfunction (PPCD). We hypothesised that repeated small volume paracentesis through percutaneous indwelling drain (PCD) would decrease refilling, paracentesis related complications & requirement by over 50% over 3 months. **Methods:** We screened 187 consecutive patients with refractory ascites admitted at a tertiary care center from 2020-2022 and analysed a total of 121 patients (60 in LVP, 61 in the PCD). Clinical and hemodynamic parameters within study period were recorded. Primary end point was to assess the proportion of patients with 50% reduction in need for paracentesis over 3 months after enrolment in comparison to the pre enrolment 3 month data. Proportion of patients developing hepatic encephalopathy(HE), hyponatremia, AKI, PPCD, SBP at day 5 were also assessed. **Results:** Baseline demographics and clinical parameters, mean CTP and MELD scores were comparable{9.81 ± 1.31 vs. 9.5 ± 1.3, $P = 0.81$; 21.76 ± 3.9 vs 22.3 ± 3.03, $P = 0.55$} in LVP and PCD arms respectively. Mean amount of fluid removed was higher in LVP over 28 days{37 ± 13.04 vs. 30.7 ± 1.03, $P = 0.05$}. Proportion of patients needing reduction in paracentesis by 50% over 3-month was 68.8% (42/61) in PCD arm vs. 0% (0/60). Percentage decrease in paracentesis in the PCD group over 3-month follow up was 56.7 % vs. -21.6% in LVP arm ($P < 0.001$). Increased interval between paracentesis noted in PCD group (15.25 ± 6.05 d vs. 8.36 ± 2.18 d, $P < 0.05$). Between day 1 to day 5, a greater reduction in MAP was noted in the LVP arm compared to PCD arm (-10.1 ± 8mmHg vs. -2.7 ± 3 mmHg, $P = 0.03$). Incidence of PPCD was comparable between the two arms [31.6 % (19/60) vs. 29.5 % (18/60), $P = 0.98$]. Similarly, incidence of complications i.e, HE, infections, AKI episodes over 3 months were comparable between groups. Improved diuretic tolerability (mean dosage) was noted in PCD group at 3 month follow up with no difference in the 3 month mortality{10/60 (16.6%) vs.11/61 (18.03%), $P = 0.42$}. **Conclusion:** PCD guided gradual decompression of ascites is safe and superior to LVP and is aa better alternative in decreasing morbidity such as ascites refilling rates; reducing number of paracentesis and increasing the interval between paracentesis with improved quality of life.

Disclosures: The following people have nothing to disclose: Manasa Alla, Saggere Muralikrishna Shasthry, Amar Mukund, Shiv Kumar Sarin

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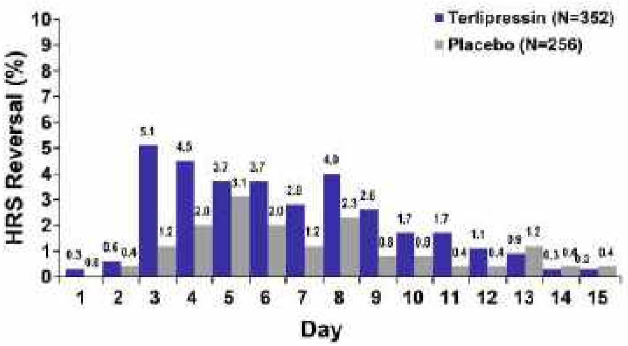
Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

3043-A | TERLIPRESSIN TREATMENT AND TIME TO CLINICAL RESPONSE: CHARACTERIZATION OF HEPATORENAL SYNDROME REVERSAL USING A POOLED DATABASE OF 3 PLACEBO-CONTROLLED PHASE III CLINICAL STUDIES

Brendan M. McGuire, University of Alabama at Birmingham, Birmingham, AL, Stevan A. Gonzalez, Baylor Simmons Transplant Institute, Prasun Jalal, Baylor College of Medicine and Khurram Jamil, Mallinckrodt Pharmaceuticals, Bridgewater, NJ

Background: Hepatorenal syndrome (HRS) is a potentially reversible form of acute kidney injury that can be treated with terlipressin (terli), an FDA-approved therapy for adult patients (pts) with HRS and rapidly worsening kidney function. Lower baseline serum creatinine (SCr) is positively associated with HRS reversal in pts randomized to terli (odds ratio [95% CI]: 0.483 [0.361–0.645], $P < 0.001$; Curry MP et al. *Hepatol Commun*. 2023;7(1): e1307). This study assessed the timing of HRS reversal using a pooled dataset from 3 North American-centric placebo (pbo)-controlled Phase III clinical studies. **Methods:** Pooled data from 3 clinical studies (OT-0401, REVERSE, and CONFIRM) that evaluated terli treatment of pts with HRS (N = 608), were assessed for time to HRS reversal and the proportion of pts achieving HRS reversal (numerically and cumulatively) per day. HRS reversal was defined as the proportion of pts with a SCr of d 1.5 mg/dL while on treatment, up to 24 hours after the last dose of study drug (days 1–15). Baseline renal function was assessed (via SCr levels) as a predictor of clinical response (HRS reversal) by multivariate logistic regression analysis. **Results:** HRS reversal was achieved by more pts in the terli group than the pbo group (33.2% [117/352] vs 16.4% [42/256], respectively; $P < 0.001$). Among pts who achieved HRS reversal, the mean (SD) time to HRS reversal was roughly 6 days across treatment groups (terli, 6.3d [3.02]; pbo, 6.7d [3.29]). Most (> 80%) pts had achieved a response by day 10 (Figure). The day that demarcated the greatest proportion of pts who achieved HRS reversal was day 3 (5.1%) in the terli group and day 5 (3.1%) in the pbo group. Similar to the previously reported data on terli, lower baseline SCr was also positively associated with HRS reversal for the pbo group (odds ratio [95% CI]: 0.437 [0.284–0.67], $P < 0.001$). Among patients in both treatment groups, lower baseline SCr was an independent predictor of HRS reversal. **Conclusion:** The greatest proportion of pts achieved HRS reversal as early as day 3 in the terli group, compared with day 5 for the pbo group. Most responses were achieved by day 10 with few additional pts achieving HRS reversal beyond day 10. While lower baseline SCr was a positive predictor of HRS reversal across treatment groups, overall, more pts treated with terli achieved HRS reversal than pbo. This analysis further supports the use of terli therapy, at a lower SCr, in pts with HRS to expedite time to clinical response.

Figure. Proportion of patients achieving hepatorenal syndrome (HRS) reversal by day (Pooled intent-to-treat population)



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Khurram Jamil – Mallinckrodt Pharmaceuticals: Employee, Yes, No;

3044-A | THE CIRCULATING PROTEIN MARKERS OF ASCITES IN ALCOHOL-ASSOCIATED LIVER DISEASE

Eric Przybyszewski[1], Caitlin A. Colling[1], Paige McLean Diaz[2], Raymond T. Chung[3], Esperance Schaefer[1], Jay Luther[4] and Russell P. Goodman[1], (1)Massachusetts General Hospital, (2)Massachusetts General Hospital, *Chicago, IL, (3)Massachusetts General Hospital and Harvard Medical School, (4)Massachusetts General Hospital, Anodover, MA*

Background: Alcohol-associated liver disease (ALD) represents a spectrum of liver pathology including decompensated cirrhosis and has a rising burden in the United States. Ascites is a common complication of progressive chronic liver disease including ALD and is associated with high morbidity and mortality. We tested the hypothesis that serum proteomics identifies biomarkers of ascites in adults with ALD. **Methods:** A prospective cohort of adult patients with alcohol use disorder and healthy controls was evaluated to determine serum proteomics biomarkers of ascites. Patients with other (non-alcohol) etiologies of liver disease were excluded. Proteomic analysis was performed on serum samples using the aptamer-based proteomic SomaScan platform to quantify 1305 proteins. **Results:** 87 adults with AUD and 6 controls were assessed including 29% women with median age 50.5 years, median BMI 25.2 kg/m2. Mean alcohol consumption was 65.9 +/- 62.6 drinks/week. Ascites status was determined from radiographic data (ultrasound or CT) and categorized as none (n = 62), trace (n = 5), small (n = 14), moderate (n = 8), or large (n = 4). Multivariable ordinal logistic regression models adjusting for age, sex, and BMI were used in analyses of ascites status to identify proteins associated with ascites severity (Figure 1A). Principal component analyses were used to demonstrate relative protein abundance grouped by ascites severity (none, trace/small, moderate/large) (Figure 1B). **Conclusion:** Large-scale serum proteomics identifies biomarkers that correlate with severity of ascites in patients with ALD. MRC1, EFEMP1, FLRT3, FLRT2, ALCAM represent potential proteomic biomarkers of ascites in ALD. Further evaluation of proteomic signatures of ascites and portal hypertension are warranted.

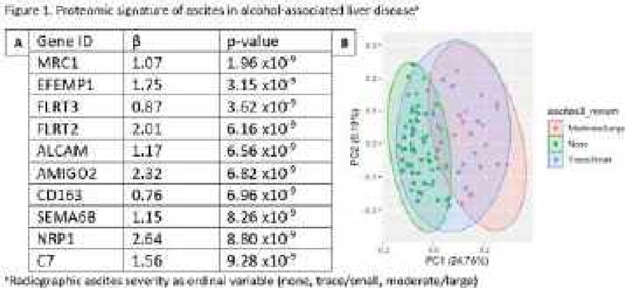


Figure 1. Proteomic signature of ascites in alcohol-associated liver disease*

Gene ID	β	p-value
MRC1	1.07	1.96 x10^{9}
EFEMP1	1.75	3.15 x10^{9}
FLRT3	0.87	3.62 x10^{9}
FLRT2	2.01	6.16 x10^{9}
ALCAM	1.17	6.56 x10^{9}
AMIGO2	2.32	6.82 x10^{9}
CD163	0.76	6.96 x10^{9}
SEMA6B	1.15	8.26 x10^{9}
NRP1	2.64	8.80 x10^{9}
C7	1.56	9.28 x10^{9}

*Radiographic ascites severity as ordinal variable (none, trace/small, moderate/large)

Disclosures: Raymond T. Chung – BMS: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boehringer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GSK: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Janssen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Salix: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Eric Przybyszewski, Paige McLean Diaz

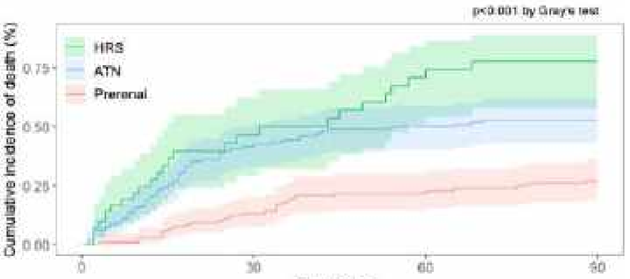
Disclosure information not available at the time of publication: Caitlin A. Colling, Esperance Schaefer, Jay Luther, Russell P. Goodman

3045-A | THE IMPACT OF ALCOHOL-ASSOCIATED HEPATITIS ON MORTALITY IN PATIENTS WITH CIRRHOSIS AND ACUTE KIDNEY INJURY

Ann T. Ma[1]*, Andrew S Allegretti*[2]*, Giuseppe Cullaro*[3]*, Tianqi Ouyang*[4]*, Sumeet Asrani*[5]*, Raymond T. Chung*[6]*, Eric Przybyszewski*[4]*, Robert M Wilechansky*[7]*, Jevon Robinson*[4]*, Pratima Sharma*[8]*, Douglas A. Simonetto*[9]*, Shelsea A. St. Hillien*[7]*, Nneka Ufere*[4]*, Kevin R. Regner*[10]*, Justin M. Belcher*[11]*, Kavish R. Patidar*[12] *and the HRS-HARMONY Consortium, (1)Toronto Centre for Liver Disease, University Health Network, (2)Division of Nephrology, Department of Medicine, Massachusetts General Hospital, (3)University of California San Francisco Medical Center, (4)Massachusetts General Hospital, (5)Baylor Simmons Transplant Institute, Dallas, TX, (6)Massachusetts General Hospital and Harvard Medical School, (7)Massachusetts General Hospital, Boston, MA, (8)University of Michigan, Ann Arbor, MI, (9)Mayo Clinic Rochester, Rochester, MN, (10)Medical College of Wisconsin, (11)Yale University, New Haven, CT, (12)Section of Gastroenterology,* *Department of Medicine, Baylor College of Medicine and Michael E. Debakey Veterans Affairs Medical Center*

Background: The development of acute kidney injury (AKI) in the setting of alcohol-associated hepatitis (AH) pertains a poor prognosis. However, whether the presence of AH itself drives worse outcomes in patients with cirrhosis and AKI is unknown. **Methods:** Retrospective cohort study of 11 hospital networks of consecutive adult patients admitted in 2019 with AKI and cirrhosis. Alcohol-associated hepatitis was defined as per NIAAA Alcoholic Hepatitis Consortia criteria. AKI phenotypes (prerenal, acute tubular necrosis [ATN], hepatorenal syndrome [HRS]) were determined by two adjudicators and a tiebreaker in case of disagreement. Cumulative incidence of death was calculated at 90 days from admission, with liver transplant (LT) as a competing risk for AH and AKI phenotypes. Competing risk multivariable analysis (LT as competing risk) was performed to determine the independent association between AH and 90-day mortality. **Results:** A total of 2,062 patients hospitalized with cirrhosis and AKI were included, of which 303 (15%) had AH. Most patients with AH had underlying alcohol-associated cirrhosis (87%), while few had hepatitis C or mixed etiology. Patients with AH, compared to those without, were younger (median age 53 vs 63, $p < 0.001$), had less chronic kidney disease (16% vs 33%, $p < 0.001$), more frequently had ascites (87% vs 76%, $p < 0.001$) and had higher Model for End-stage Liver Disease-Sodium (MELD-Na) scores on admission (median 32 vs 25, $p < 0.001$), driven mostly by bilirubin and INR. AKI phenotype significantly differed between patients with and without AH ($p < 0.001$), with ATN occurring more frequently in patients with AH (39% vs 29% in those without AH). Patients with AH fared worse overall, reaching more severe peak AKI stage, requiring more renal replacement therapy (RRT) and having a higher cumulative incidence of death at 90 days (45% vs 38%, $p = 0.026$). Using no AH as reference, the unadjusted sHR for 90-day mortality was higher for AH (sHR 1.24 [95%CI 1.03-1.50, $p = 0.024$]), but this was not significant when adjusting for MELD-Na. Interestingly, while HRS and ATN were associated with similar prognoses in the overall cohort, in patients with AH specifically, the 90-day cumulative incidence of death was significantly higher for HRS compared to ATN (78% vs 53%, Figure). Finally, amongst patients treated with RRT ($n = 373$), those with AH had similar 90-day mortality compared to those without (36% vs 41% respectively, p = NS). **Conclusion:** Hospitalized patients with cirrhosis and AKI presenting with AH have higher 90-day mortality than those without AH, but the worse outcomes may be driven by worse synthetic dysfunction rather than AH itself. Comparable survival of patients treated with RRT suggests that the presence of AH alone should not be a contraindication to starting RRT.

Figure Cumulative incidence of death in patients with alcohol-associated hepatitis, by AKI phenotype



At Risk *				
Prerenal	111	90	77	67
HRS	42	13	6	4
ATN	119	59	46	42
Events				
Prerenal	0	14	24	28
HRS	0	17	25	26
ATN	0	48	56	59

* Patients with AKI phenotypes other than those listed were excluded from this analysis.

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

Pratima Sharma: Pratima Sharma, Sumeet Asrani, Eric Przybyszewski, Robert M Wilechansky, Douglas A. Simonetto, Nneka Ufere, Kavish R. Patidar
Disclosure information not available at the time of publication: Tianqi Ouyang, Jevon Robinson, Shelsea A. St. Hillien, Kevin R. Regner, Justin M. Belcher

3046-A | THE IMPACT OF MELD SCORE AND ACLF GRADE ON OUTCOMES OF HEPATORENAL SYNDROME FOLLOWING TREATMENT WITH TERLIPRESSIN AND ALBUMIN IN PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS

Ethan M. Weinberg, Perelman School of Medicine, University of Pennsylvania, Khurram Jamil, Mallinckrodt Pharmaceuticals, Bridgewater, NJ, Richard Deng, Tech Data Corporation and K Rajender Rajender Reddy, University of Pennsylvania

Background: Hepatorenal syndrome with acute kidney Injury (HRS-AKI) is a devastating complication of end-stage liver disease (ESLD). Liver transplant (LT) is the best treatment for ESLD for patients who experience HRS-AKI; however, most patients with HRS-AKI are not candidates for LT, including many patients with acute alcohol-associated hepatitis (AH). Unlike decompensated cirrhosis, AH is characterized by an acute inflammatory syndrome, providing a unique reversible component in which LT may be avoided in those who recover. Reversal of HRS-AKI in AH is imperative to allow patients to recover clinically and seek treatments for alcohol use disorder. Terlipressin is the only FDA-approved treatment for HRS. The CONFIRM trial, the largest randomized control trial (RCT) for HRS treatment with terlipressin, suggested that those listed for transplant with Model for ESLD (MELD) scores ≥ 35, acute-on-chronic liver failure-grade 3 (ACLF-3), or serum creatinine (SCr) > 5.0 mg/dL may not benefit from terlipressin treatment. In this study, we sought to evaluate the interplay between renal and hepatic function in HRS reversal and survival among patients with AH who were enrolled in three large RCTs. **Methods:** Patients with a diagnosis of AH and cirrhosis from three Phase III double-blind, placebo-controlled studies of terlipressin plus albumin for the treatment of HRS type 1, were included (RCTs: NCT00089570, NCT01143246, NCT02770716). Patients were divided into two groups based on SCr at baseline: SCr ≤ 3.0 or SCr > 3.0. Each group was then further divided based on baseline MELD (< 35, ≥ 35) and ACLF grade (0–2, 3) and evaluated for HRS reversal and 90-day survival. **Results:** Across three RCTs, 205 patients with AH and cirrhosis were randomized to terlipressin plus albumin (SCr ≤ 3.0, n = 76; SCr > 3.0, n = 129). HRS reversal was most likely to occur among patients with SCr ≤ 3.0 with low MELD, although HRS reversal among those with SCr ≤ 3.0 and high MELD was more likely than in patients with SCr > 3.0 for either MELD group (Table). HRS reversal was more likely among patients with SCr ≤ 3.0; those with SCr ≤ 3.0 and ACLF-3 were more likely to experience HRS reversal than patients with SCr > 3.0, regardless of ACLF grade (Table). In the overall cohort, within subgroups (MELD < 35, MELD ≥ 35, ACLF-0–2, ACLF-3), 90-day survival did not differ between SCr ≤ 3.0 vs SCr > 3.0. However, HRS reversal among transplant-free terlipressin patients with AH, regardless of baseline SCr, did predict 90-day survival (17/39, 43.6% vs 11/62, 17.7%, *P* = 0.0047). **Conclusion:** Terlipressin plus albumin is an effective treatment for HRS-AKI in patients with AH. For such patients, early treatment (SCr ≤ 3.0) with terlipressin may increase the likelihood of HRS reversal, even among patients with MELD ≥ 35 or ACLF-3. HRS reversal with terlipressin plus albumin in patients with AH may increase 90-day survival, likely because of the potential for recovery from AH.

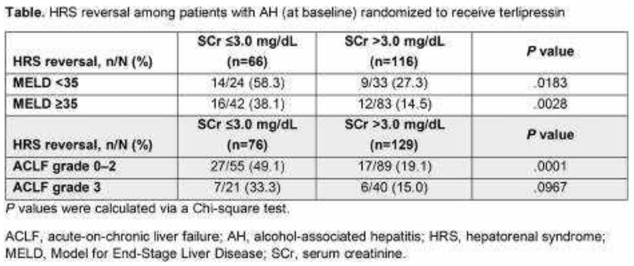

Table. HRS reversal among patients with AH (at baseline) randomized to receive terlipressin

HRS reversal, n/N (%)	SCr ≤3.0 mg/dL (n=66)	SCr >3.0 mg/dL (n=116)	*P* value
MELD <35	14/24 (58.3)	9/33 (27.3)	.0183
MELD ≥35	16/42 (38.1)	12/83 (14.5)	.0028
HRS reversal, n/N (%)	**SCr ≤3.0 mg/dL (n=76)**	**SCr >3.0 mg/dL (n=129)**	***P* value**
ACLF grade 0–2	27/55 (49.1)	17/89 (19.1)	.0001
ACLF grade 3	7/21 (33.3)	6/40 (15.0)	.0967

P values were calculated via a Chi-square test.

ACLF, acute-on-chronic liver failure; AH, alcohol-associated hepatitis; HRS, hepatorenal syndrome; MELD, Model for End-Stage Liver Disease; SCr, serum creatinine.

Disclosures: Ethan M. Weinberg – Mallinckrodt Pharmaceuticals: Consultant, Yes, No; Biovie: Consultant, No, No; PharmaIN: Consultant, No, No; Mallinckrodt Pharmaceuticals: Advisor, Yes, No;
Khurram Jamil – Mallinckrodt Pharmaceuticals: Employee, Yes, No;
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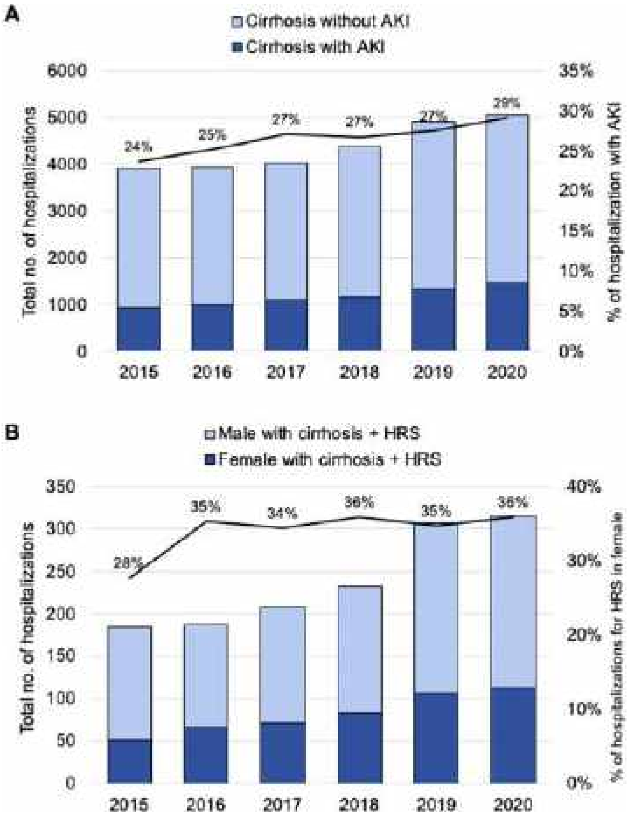
The following people have nothing to disclose: Richard Deng

3047-A | THE INCREASING BURDEN OF AKI AND HRS IN HOSPITALIZED PATIENT WITH CIRRHOSIS DIFFERENTIALLY AFFECTS FEMALE PATIENTS

Ann T. Ma[1], *Arshad Imrit*[2], *Marwa Ismail*[2], *Surain B Roberts*[3], *Fahad Razak*[2,4], *Amol A Verma*[2,5] *and Gideon Hirschfield*[6], *(1)Toronto Centre for Liver Disease, University Health Network, (2)St. Michael's Hospital, Unity Health Toronto, (3)Li Ka Shing Knowledge Institute, St Michael's Hospital, Unity Health Toronto, (4)University of Toronto, (5)Dept of Medicine and Ihpme, University of Toronto, (6)Toronto Centre for Liver Disease, University of Toronto, Toronto, Ontario, Canada*

Background: Acute kidney injury (AKI) is a frequent complication in hospitalized patients with cirrhosis and results in significant morbidity and mortality. Hepatorenal syndrome (HRS), a specific type of AKI, is particularly associated with poor outcomes in the absence of liver transplant. However, the burden and changing epidemiology of AKI and HRS are not well described in Canada. **Methods:** Data from 04/2015 to 03/2020 were obtained from 29 hospitals in Ontario, the most populated province in Canada, participating in the GEMINI collaborative. Using data from hospital information systems linked to administrative data, we included patients admitted with cirrhosis, as defined by having any discharge diagnosis from a previously validated approach using the international classification of diseases, 10th Revision—enhanced Canadian version (ICD-10-CA), and similarly identified admissions for AKI and HRS. We used logistic regression with cluster robust standard errors to estimate the trends over time. **Results:** A total of 26,221 admissions for 12,288 patients with cirrhosis were included (64% male, mean age 63). AKI was present in 6,997 (26.7%) episodes and HRS in 1,433 (5.4%). Patients who developed AKI were slightly older (mean age 65 vs 62 in those without AKI). AKI was associated with significantly worse outcomes, with higher need for ICU and mechanical ventilation, longer length of hospitalization and higher in-hospital mortality. The latter was 33.6% in those with AKI vs 8.4% in those without. Patients with AKI had 5-fold higher odds of dying in hospital (OR 4.97, 95%CI [4.61-5.35], $p < 0.001$). We found that the odds of having AKI rose over time among hospitalized patients with cirrhosis (OR 1.06, 95%CI [1.04-1.07], $p < 0.001$, Figure panel A), as did the odds of having HRS (OR 1.08, 95%CI [1.04-1.11], $p < 0.001$). Meanwhile, over the 6 years of observation, the mean age of patients admitted with AKI remained stable, as did their risk of in-hospital death. Finally, the odds of female patients being affected by HRS also increased over time (OR 1.07, 95%CI [1.00-1.15], $p = 0.042$, Figure panel B). **Conclusion:** The burden of AKI and HRS in patients admitted with cirrhosis in Ontario is increasing, and the proportion of female patients affected by HRS is as well. The temporal trends in this study may inform future considerations for therapies, such as terlipressin, which is becoming more widely available in North America.

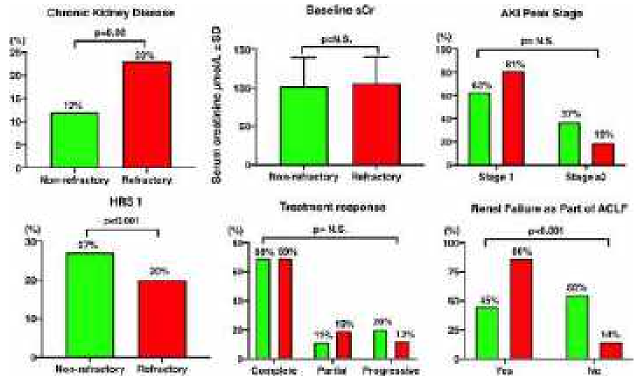


Disclosures: Gideon Hirschfield – Intercept: Consultant, No, No; GSK: Consultant, Yes, No; CymaBay: Consultant, No, No; Ipsen: Consultant, No, No; Falk: Consultant, No, No; Pliant: Consultant, No, No; Morphogen: Consultant, No, No; Roche: Consultant, No, No; Mirum: Consultant, No, No;
The following people have nothing to disclose: Ann T. Ma
Disclosure information not available at the time of publication: Arshad Imrit, Marwa Ismail, Surain B Roberts, Fahad Razak, Amol A Verma

3048-A | THE PREVALENCE AND CLINICAL FEATURES OF ACUTE KIDNEY INJURY ACROSS VARIOUS STAGES OF ASCITES IN PATIENTS WITH CIRRHOSIS FROM A SINGLE QUATERNARY REFERRAL ACADEMIC CENTRE

Neha Tiwari[1], Chinmay Bera[2], Cynthia Tsien[3], Audrey Kapelera[1], Nazia Selzner[3] and Florence Wong[1], (1) Division of Gastroenterology and Hepatology, Toronto General Hospital, Toronto, ON, Canada, (2)University Health Network, (3)Ajmera Transplant Center, University of Toronto, Toronto, ON, Canada

Background: Dynamic change in serum creatinine (sCr) is now used for the definition & severity staging of acute kidney injury (AKI). It is now recognized that many past patients with minor acute sCr changes, especially outpatients, could have been missed as having AKI. This study aims to assess the prevalence, clinical features of all stages of AKI amongst all patients with ascites at a quaternary academic centre. **Methods:** All patients with cirrhosis and ascites from Apr 2020-Mar 2021 were identified through patient records, and charts retrospectively assessed to collect demographics, clinical features, medications, ascites severity, AKI development, AKI and patient outcomes at 6 months. Multivariate analysis for factors predicting AKI development and resolution was done. **Results:** 306 patients were identified, 115 (38%) with refractory ascites (RA) as per International Club of Ascites criteria. 262 (86%) were outpatients. Patients with RA were compared to non-RA group (n-RA). RA patients were older (62yrs vs. 58 yrs, $p = 0.01$) with 70% men (vs. 61% n-RA, p = n.s.). There was no difference in cirrhosis etiology, or complications between the 2 groups. 70% of RA patients had tense ascites, with 98% requiring regular large volume paracenteses (LVP) ($p < 0.001$ vs. n-RA). Similar proportion of n-RA patients were on diuretics (79%) vs. the RA patients (68%), $p = 0.11$, but more RA patients were on meds for encephalopathy, and SBP prophylaxis (both $p < 0.001$), and less RA patients were on beta-blockers ($p = 0.004$). Baseline MELD-Na was higher in the RA group (18.1 ± 4.7 vs. 17.2 ± 6.8, $p = 0.01$), likely related to the presence of CKD in 23% of RA patients ($p = 0.02$). AKI occurred in 39% of RA and 19% of n-RA patients ($p < 0.001$). Most were stage 1 AKI, treated with albumin ± vasoconstrictor with similar response. LVP ($p = 0.002$) and baseline MELD-Na ($p = 0.01$) predicted AKI development, while lower peak sCr predicted AKI resolution ($p = 0008$). 11 (3.6%) n-RA and 22 (19%) RA patients developed ACLF, with 86% RA patients had their renal failure as part of the ACLF syndrome ($p < 0.001$ vs. n-RA patients). 6-month survival was similar between the 2 groups. **Conclusion:** AKI occurs not infrequently in n-RA patients who are mostly treated as outpatients. Although most are stage 1 AKI, 27% were severe and would be classified as type 1 HRS. ACLF in n-RA patients often involves organ failure other than renal failure. Therefore, patients with n-RA need to be monitored closely even when treated as outpatients.



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3049-A | TOTAL BILIRUBIN AT TIME OF ADMISSION PREDICTS RESPONSE TO TREATMENT FOR TYPE I HEPATORENAL SYNDROME

Steve Qian[1], Zohaib Ijaz[2], Andreas Zori[1], Giuseppe Joseph Morelli[2], Roberto J. Firpi[1], Roniel Cabrera[1] and Amir Y Kamel[1], (1)University of Florida, (2)University of Florida, Gainesville, FL

Background: Type 1 hepatorenal syndrome (HRS) is a manifestation of decompensated cirrhosis and is characterized by rapid onset of renal failure with doubling of serum creatinine (Cr) to >2.5 within a two-week period. Prognosis is poor with only 10% of patients surviving longer than 90 days[1]. Treatment of HRS in the United States is primarily with albumin, midodrine, and octreotide[2]. Data on response to therapy has remained mixed, with few studies on predictors of response. The aim of this study to assess the role of total bilirubin, albumin, and international normalized ratio (INR) as predictors for response to treatment in type 1 HRS. **Methods:** We performed a retrospective chart review on 371 adults with ICD-9/10 codes for decompensated cirrhosis and acute kidney injury. Patients were determined to have Type 1 vs 2 HRS as per the International Club of Ascites (ICA) guidelines. Patients had to meet the following criteria: cirrhosis with ascites, an acute increase in Cr to greater than 2.5 within a two-week span, absence of shock defined as systolic blood pressure (SBP) <90, no recent exposure to nephrotoxic agents, the absence of proteinuria (>500 g/dl) or pre-existing parenchymal disease, and no improvement in creatinine after discontinuation of diuretics and starting volume expansion. Other exclusion criteria included cardiac/respiratory failure, or prior beta-blocker use for variceal bleeding. All patients with treated with a combination of albumin, midodrine, and octreotide. Response to treatment was defined as the following within 3 days of initiation: Complete response – decrease in Cr to <1.5, partial response – decrease in Cr by $>50\%$ from baseline but not to <1.5, incomplete – decrease in serum Cr by $<50\%$ and not less than <1.5, no response – no decrease in Cr. Total bilirubin, albumin, and INR at admission were compared among the different responder groups. Two-tailed T-testing was used for statistical analysis. **Results:** Out of a total of 61 included patients, 25 (40.98%) achieved no response, 6 (9.84%) had partial response, 9 (14.75%) had incomplete response, and 21 had complete response (34.43%). The mean total bilirubin (mg/dL) in the respective groups were 12.4 ± 4.75, 12.25 ± 6.67, 11.13 ± 8.43, and 6.71 ± 1.97. The mean albumin (g/dL) in each respective group was 2.75 ± 0.24, 2.65 ± 0.60, 2.59 ± 0.34, 3.09 ± 0.12. Mean INRs were 1.94 ± 0.28, 2.32 ± 0.86, 2.47 ± 1.00, and 1.76 ± 0.06. When compared to the no response group, the complete response group had a lower mean total bilirubin ($p=0.038$), with no significant differences in their albumin ($p=0.068$) and INR ($p=0.37$). **Conclusion:** Patients that underwent with albumin, midodrine, and octreotide for type 1 HRS with a complete response had a lower mean total bilirubin at the time of admission when compared to their non-responder counterparts. There were no significant differences in mean albumin and INR between the two groups.

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Disclosure information not available at the time of publication: Giuseppe Joseph Morelli, Roberto J. Firpi, Roniel Cabrera, Amir Y Kamel

3050-A | TRANSIENT ELASTOGRAPHY PREDICTS THE PRESENCE OF SYSTEMIC VENOUS CONGESTION IN AMBULATORY PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

Paola Guerrero[1], Ignacio García Juárez[2], Hiram Noel Tadeo[3], Eduardo Rios Argaiz[3] and Alfonso Fernandez-Ramirez[1], (1)Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán, (2)Instituto Nacional De Ciencias Medicas y Nutricion, (3)Instituto Nacional De Ciencias Medicas y Nutrición Salvador Zubirán

Background: Development of Venous Excess Ultrasound Score (VExUS) as a non-invasive tool for venous congestion has allowed bedside patient assessment by abdominal doppler ultrasound imaging.

However, as venous congestion turns into hepatic congestion, we can try to apply these data to other non-invasive tools.

Although an increase in liver stiffness is related to an elevation of liver congestion in patients with heart failure, the relevance of transient elastography (Fibroscan) has not been studied in the context of venous congestion due to right heart failure, which could be a new easy, quickly and reliable non-invasive method to detect these alterations. Aim: To assess the relationship between venous congestion by VExUS and Fibroscan in outpatients with pulmonary hypertension or right heart failure. **Methods:** Patients with diagnosis or high probability of pulmonary arterial hypertension between january 2022 to january 2023 at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán were eligible. We excluded patients with a low-probability pulmonary arterial hypertension (TRV <2.8 m/s PASP <36 mmHg), acute heart failure, cirrhosis (Child Turcott Pugh B or C), chronic kidney disease or renal replacement therapy, solid organ transplantation or portal thrombosis.

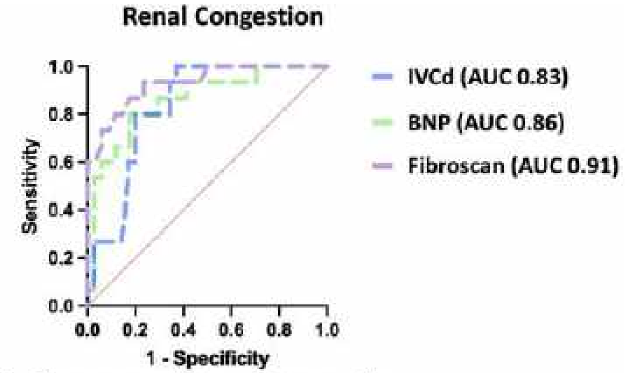
Fibroscan examinations with M or XL probe was performed by an echosens-certified gastroenterologist. VExUS was performed by 4 trained physicians (one nephrologist and three internists) with inter-observer Kappa Index 0.90 (0.86-0.97). Sociodemographic and clinical variables were collected and descriptive statistics using frequency and proportions for categorical variables were used. Correlation analysis was carried out using Pearson's coefficient individually between the kPa measurement by Fibroscan and the variables: PASP, IVCd, percentage of IVC collapsibility and portal vein pulsatity. Statistical significance was at p-value of < 0.05. **Results:** 58 patients were included, (82%) were women. The mean age was 57 yo.

A significant correlation was observed between liver stiffness measured in kPa and PASP, IVC diameter, and portal vein pulsatility.

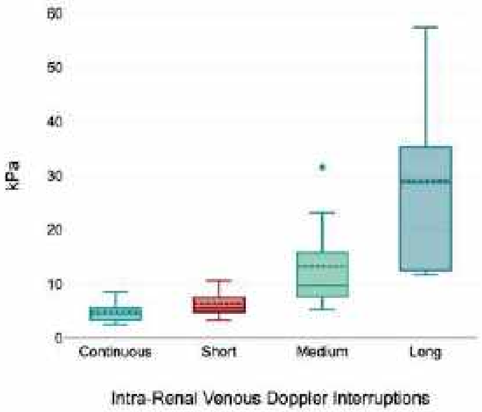
Liver stiffness was higher in patients with VExUS 2 or 3 (mean 14.5, RIC 9.1-30.2) than VExUS 0 or 1 (mean 5.2, RIC 3.9-6.9) and intra-renal venous Doppler interruptions.

When compared with BNP and IVCd; Fibroscan was a better predictor of renal congestion (AUC 0.91). **Conclusion:** Liver stiffness is greater in patients with VEXUS 2-3 vs VExUS 0-1 score, demonstrating that greater congestion means greater liver stiffness. Fibroscan is a better predictor than BNP and IVCd of renal congestion. In addition, transient elastography is a fast, safe and easy to perform non-dependent operator, that determines venous congestion in the same way that invasive tools.

Additional studies are needed to defined the fibroscan role in venous congestion assessment.



1a. Fibroscan predictor renal congestion



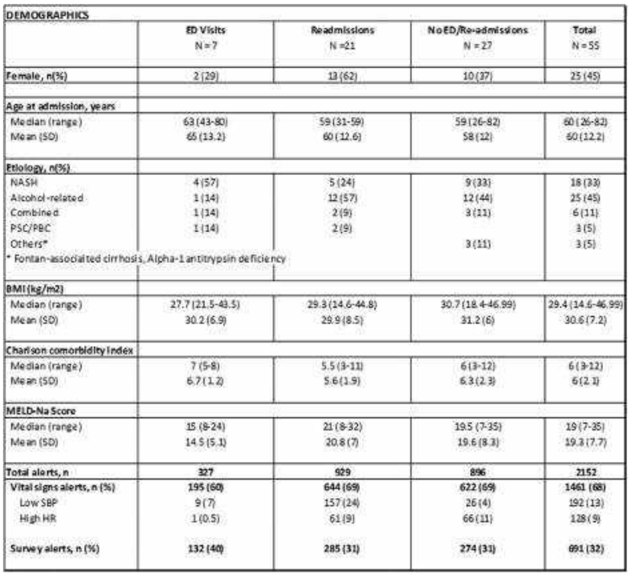
1b. correlation intra-Renal venous Doppler interruptions vs kPa

Disclosures: The following people have nothing to disclose: Paola Guerrero, Ignacio García Juárez, Hiram Noel Tadeo, Eduardo Rios Argaiz, Alfonso Fernandez-Ramirez

3051-A | TRENDS IN REMOTE PATIENT MONITORING ALERTS PRECEDING HOSPITAL READMISSION IN CIRRHOSIS PATIENTS WITH ASCITES

Kamalpreet S. Hara[1], Daniel Penrice[1], Beatriz Sordi Chara[1], Katherine Williams[1], Sara Kloft-Nelson[1], Vijay Shah[1], Patrick S. Kamath[2] and Douglas A. Simonetto[1], (1)Mayo Clinic Rochester, Rochester, MN, (2)Mayo Clinic, Rochester, MN

Background: Patients with decompensated cirrhosis are at high risk of hospitalizations and emergency department (ED) visits, with complications of volume overload being a common reason for readmission. Remote patient monitoring (RPM) programs may play an essential role in post-hospital care to potentially prevent hospital visits and reduce health care costs. This early analysis of our institutional experience with a cirrhosis-specific RPM program focuses on identifying potential signals preceding hospital visits. **Methods:** Hospitalized patients with decompensated cirrhosis were enrolled in a 90-day RPM program from April 2021 to October 2022. Daily vital signs (blood pressure, heart rate, oxygen saturation, temperature, weight) and symptom-based surveys were collected from home, and alerts were generated based on predefined thresholds. Retrospective analysis of RPM patients with current or diuretic-responsive ascites was performed to identify alert patterns that preceded hospital visits. **Results:** Of the 61 enrolled patients, 55 patients had ascites or a history of diuretic-responsive ascites. During the RPM monitoring period 21 patients were readmitted (38%) and 7 visited the ED (13%). In those who were readmitted, alerts for low systolic blood pressure (SBP < 90 mmHg) were triggered in 62% of patients and was the second-most frequent alert (24%) behind weight alerts. Those with high heart rate alerts (HR > 110 bpm) had increased rates of hospital readmission compared to those with no readmission or only ED visits (52% vs 14% vs 22%). To determine if vital sign monitoring alerts or survey alerts preceded first readmission, we analyzed frequency of alerts triggered in the days leading up to first readmission. Of the 21 patients who were readmitted during the study, median time to first readmission was 37 days (IQR 51). 7 patients had SBP alerts before their first readmission with median time from alert to readmission of 2 days (IQR 8). Similarly, 7 patients had HR alerts prior to readmission, with a median interval of 10 days (IQR 14.5) between alert and date of readmission. In the 2 weeks prior to readmission, 16 of 21 patients reported worsening symptoms on daily questionnaire generating a total of 80 alerts with a median of 4 alerts per patient (IQR 6). Most common symptomatic complaints prior to readmission were abdominal distension (30%), shortness of breath (28%) and ankle swelling (28%). **Conclusion:** These preliminary findings suggest a potential trend in vital signs and symptoms after hospital discharge that may precede impending hospital readmissions. Larger studies are needed to determine whether these patterns are independent predictors of hospitalizations and whether timely interventions may improve outcome.



DEMOGRAPHICS	ED Visits N = 7	Readmissions N = 21	No ED/Re-admissions N = 27	Total N = 55
Female, n(%)	2 (29)	13 (62)	10 (37)	25 (45)
Age at admission, years				
Median (range)	63 (43-80)	59 (31-59)	59 (26-82)	60 (26-82)
Mean (SD)	65 (13.2)	60 (12.6)	58 (12)	60 (12.2)
Etiology, n(%)				
NASH	4 (57)	5 (24)	9 (33)	18 (33)
Alcohol-related	1 (14)	12 (57)	12 (44)	25 (45)
Combined	1 (14)	2 (9)	3 (11)	6 (11)
PSC/PBC	1 (14)	2 (9)		3 (5)
Others*			3 (11)	3 (5)
* Fontan-associalted cirrhosis, Alpha-1 antitrypsin deficiency				
BMI (kg/m2)				
Median (range)	27.7 (21.5-43.5)	29.3 (14.6-44.8)	30.7 (18.4-46.99)	29.4 (14.6-46.99)
Mean (SD)	30.2 (6.9)	29.9 (8.5)	31.2 (6)	30.6 (7.2)
Charlson comorbidity index				
Median (range)	7 (5-8)	5.5 (3-11)	6 (3-12)	6 (3-12)
Mean (SD)	6.7 (1.2)	5.6 (1.9)	6.3 (2.3)	6 (2.1)
MELD-Na Score				
Median (range)	15 (8-24)	21 (8-32)	19.5 (7-35)	19 (7-35)
Mean (SD)	14.5 (5.1)	20.8 (7)	19.6 (8.3)	19.3 (7.7)
Total alerts, n	**327**	**929**	**896**	**2152**
Vital signs alerts, n (%)	**195 (60)**	**644 (69)**	**622 (69)**	**1461 (68)**
Low SBP	9 (7)	157 (24)	26 (4)	192 (13)
High HR	1 (0.5)	61 (9)	66 (11)	128 (9)
Survey alerts, n (%)	**132 (40)**	**285 (31)**	**274 (31)**	**691 (32)**

Disclosures: The following people have nothing to disclose: Kamalpreet S. Hara, Daniel Penrice, Beatriz Sordi Chara, Vijay Shah, Douglas A. Simonetto
Disclosure information not available at the time of publication: Katherine Williams, Sara Kloft-Nelson, Patrick S. Kamath

f 3052-A | UNDERSTANDING THE RELATIONSHIP BETWEEN MEAN ARTERIAL PRESSURE AND TERLIPRESSIN IN HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY REVERSAL: A POST HOC ANALYSIS OF THE CONFIRM, REVERSE, AND OT-0401 TRIALS

Giuseppe Cullaro, University of California San Francisco Medical Center, Kavish R. Patidar, Section of Gastroenterology, Department of Medicine, Baylor College of Medicine and Michael E. Debakey Veterans Affairs Medical Center, Andrew S Allegretti, Division of Nephrology, Department of Medicine, Massachusetts General Hospital and Khurram Jamil, Mallinckrodt Pharmaceuticals, Bridgewater, NJ

Background: Currently, only terlipressin is approved by the FDA for the treatment of hepatorenal syndrome-acute kidney injury (HRS-AKI). It is hypothesized that terlipressin reverses HRS-AKI by increasing mean arterial pressure (MAP). Here, we tested this hypothesis utilizing data from 3 large Phase III trials—CONFIRM, REVERSE, and OT-0401. **Methods:** To determine the impact of terlipressin on MAP: 1) We compared the daily median MAP between treatment and placebo and 2) completed a linear mixed-effects model with fixed effects for treatment and time and a random intercept for each subject. To determine the impact of MAP on HRS-AKI reversal: 1) We completed time-dependent Cox models and 2) determined target MAP cut-offs by comparing log-rank statistics. To determine the impact of the relationship between MAP and terlipressin on HRS-AKI reversal: 1) We tested the interaction between MAP and terlipressin in Cox models for HRS-AKI reversal and 2) completed a mediation analysis between terlipressin and time-weighted MAP on full HRS-AKI reversal. **Results:** A total of 477 patients were included in this analysis (61% received terlipressin). At baseline, MAP was similar in the terlipressin and placebo groups (median: 77 vs 76 mmHg, $P = 0.4$); however, after randomization, MAP was significantly higher in the terlipressin group (medians [mmHg]: Day 1: 85 vs 75; Day 2: 79 vs 75; Day 3: 81 vs 76; $P < 0.001$ each). In the mixed-effects model, terlipressin was associated with a 6.1 mmHg increase in MAP ($P < 0.001$) with no significant interaction between treatment and time ($P > 0.05$). In a time-dependent Cox model, each 5 mmHg increase in MAP was associated with a HR of 0.86 (95% CI 0.8–0.9) for HRS-AKI nonreversal. A MAP cut-off of 84.7 mmHg demonstrated the strongest association with HRS-AKI nonreversal (Figure). There was no significant interaction between MAP and terlipressin (HR 1.01, 95% CI 0.99–1.03). In the mediation analysis, MAP was a significant mediator of the impact of terlipressin on HRS-AKI reversal (average causal mediation effect: 35%, 95% CI 21%–50%). **Conclusion:** In this analysis, terlipressin led to an immediate, sustained increase in MAP, with a cut-off of 84.7 mmHg being a key pharmacodynamic target for HRS-AKI reversal. Our findings support that MAP is a significant mediator in the impact of terlipressin on HRS-AKI reversal.

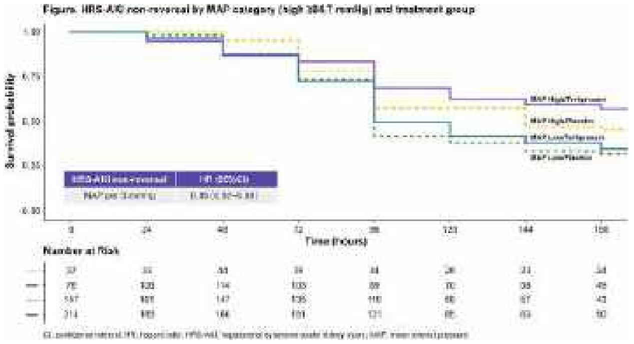


Figure. HRS-AKI non-reversal by MAP category (high ≥84.7 mmHg) and treatment group

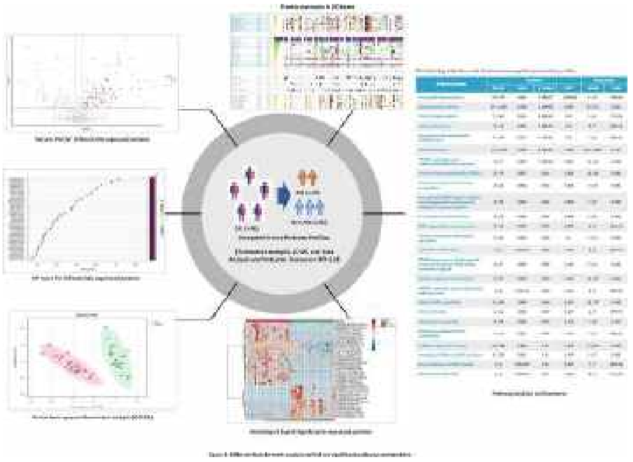
Disclosures: Giuseppe Cullaro – Ocelot Bio: Consultant, No, No; Novo Nordisk: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, Yes; Eli Lilly: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, Yes; Retro: Consultant, No, No;
Andrew S Allegretti – Mallinckrodt Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the

principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Mallinckrodt Pharmaceuticals: Consultant, Yes, No; Ocelot Bio: Consultant, No, No;
Khurram Jamil – Mallinckrodt Pharmaceuticals: Employee, Yes, No;
The following people have nothing to disclose: Kavish R. Patidar

f 3053-A | URINARY PROTEOMICS DIVULGES PREDICTIVE PROTEINS AND BIOLOGICAL PATHWAYS IN ACUTE KIDNEY INJURY WITH DECOMPENSATED CIRRHOSIS (AKID) STUDY

Inder Bhan Singh II[1], Arka De[1], Vivek Kumar[1], Surender Singh[1], Ashok Kumar Yadav[1] and Virendra Singh[2], (1) Post Graduate Institute of Medical Education and Research, (2)Punjab Institute of Liver and Biliary Sciences, Mohali, India, Chandigarh, CH, India

Background: Pre- and post-transplant outcomes are negatively impacted by the emergence of acute kidney injury (AKI) in decompensated cirrhosis (DC). It is challenging to do non-invasive research on the early development of AKI in DC. We anticipated that urinary proteomics would provide insight on the many processes underlying the development of AKI in DC. **Methods:** Patients with DC are included in our prospective longitudinal study, and we monitor them for the emergence of AKI in an outpatient setting. Out of 82 patients, 21 have so far gone on to develop AKI. These 21 AKI patients' baseline urine proteins were compared to those of 21 propensity-matched patients who did not develop AKI. The criteria of the International Club of Ascites were used to define AKI. Liquid chromatography-mass spectrometry (LC-MS) was used to do urine proteomics, and Proteome Discoverer 3.0 was used to infer the results. Several bioinformatic tools (gprofiler for gene ontology (GO), String and Cytoscape for networking, Reactome for pathway analysis) were used to identify the pathways that contributed to the development of AKI. To ascertain if Reactome pathways are enriched, the hypergeometric distribution test was applied. The Benjamani-Hochberg approach was used to adjust the derived probability score for the false discovery rate (FDR). **Results:** We discovered many pathways that were possibly implicated in the development of AKI and observed distress in AKI group using LC-MS. Reactome, included 66 of the 82 identities from the sample, and at least one of them hit 608 pathways. 75 proteins were significantly elevated in the AKI group and 137 had a log2 difference in comparison to patients without AKI, according to a proteomic study of more than 1700 proteins. Significant pathways identified included neutrophil degranulation, Innate Immune System, platelets degranulation, defects in vitamin and co-factor metabolism, activation of C3 and C5, attenuation phase and cellular response to heat stress (Figure 1). **Conclusion:** The development of AKI in outpatient DC patients could possibly be significantly impacted by immunity and inflammatory responses, according to urinary proteomics.



Disclosures: The following people have nothing to disclose: Inder Bhan Singh, Arka De, Vivek Kumar, Surender Singh, Ashok Kumar Yadav, Virendra Singh

3054-A | UTILITY OF CONCURRENT ADMINISTRATION OF ALBUMIN WITH TERLIPRESSIN FOR THE TREATMENT OF HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY: A POOLED ANALYSIS OF TWO RANDOMIZED CONTROLLED TRIALS

Manhal Izzy, Vanderbilt University, Florence Wong, University of Toronto, K Rajender Rajender Reddy, Perelman School of Medicine, University of Pennsylvania, Douglas A. Simonetto, Mayo Clinic Rochester, Rochester, MN, Ethan M. Weinberg, University of Pennsylvania, Kevin Moore, University College London, S. Chris Pappas, Orphan Therapeutics and Khurram Jamil, Mallinckrodt Pharmaceuticals, Bridgewater, NJ

Background: Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a serious complication of decompensated cirrhosis. The AASLD guidelines recommend co-administration of albumin with terlipressin for the treatment of HRS-AKI. This study aims to evaluate clinical outcomes in patients who received terlipressin with albumin compared to those receiving terlipressin alone. **Methods:** This is a post hoc analysis of pooled data from 2 randomized controlled trials (RCTs; REVERSE; NCT01143246 and CONFIRM; NCT02770716) studying terlipressin use in patients with HRS-AKI. While albumin was recommended to be co-administered with terlipressin, its use and

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

dosages were at the discretion of the investigators. Patients who received terlipressin with albumin were compared to those who received terlipressin only. All patients received albumin prior to terlipressin treatment. The outcomes were HRS-AKI reversal (primary) and respiratory adverse events (secondary). **Results:** Of the 296 patients in REVERSE and CONFIRM who received terlipressin, 172 were men, median age was 54 years, and mean MELD was 33; 46 patients received terlipressin alone. Potential predictors for HRS-AKI reversal were analyzed (Table); albumin use pre-terlipressin initiation in both groups was comparable and co-administration of albumin with terlipressin was not associated with a greater rate of HRS-AKI reversal compared with terlipressin alone ($P = 0.675$). In the overall cohort, the only factors that predicted reversal in multivariable analysis were duration of terlipressin treatment (OR 1.22, 95% CI 1.13-1.32, $P < 0.001$) and baseline MELD score (OR 0.95, 95% CI 0.91-0.99, $P < 0.001$). Respiratory events were associated, in the univariable analysis, with higher baseline MELD, ACLF grade 3, lower pre-event GFR, higher pre-event or day of event albumin level, lower dose of terlipressin on event date, and lower average daily dose of terlipressin. In the multivariable analysis, only baseline MELD (OR 1.06, 95% CI 1.001-1.11, $P = 0.027$) and terlipressin dose on the event date (OR 0.62, 95% CI 0.51-0.75, $P < 0.001$) were significant predictors. **Conclusion:** These results from 2 RCTs suggest that in select patients (e.g., with signs of fluid overload), using terlipressin without albumin does not compromise efficacy. Larger RCTs are needed to further support these findings. The comparable respiratory event rate, regardless of albumin use, emphasizes the need for careful selection and monitoring of patients even when using terlipressin without albumin.

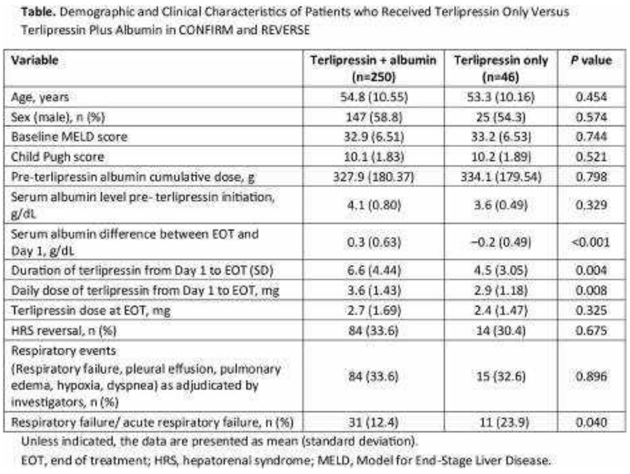

Table. Demographic and Clinical Characteristics of Patients who Received Terlipressin Only Versus Terlipressin Plus Albumin in CONFIRM and REVERSE

Variable	Terlipressin + albumin (n=250)	Terlipressin only (n=46)	*P* value
Age, years	54.8 (10.55)	53.3 (10.16)	0.454
Sex (male), n (%)	147 (58.8)	25 (54.3)	0.574
Baseline MELD score	32.9 (6.51)	33.2 (6.53)	0.744
Child Pugh score	10.1 (1.83)	10.2 (1.89)	0.521
Pre-terlipressin albumin cumulative dose, g	327.9 (180.37)	334.1 (179.54)	0.798
Serum albumin level pre- terlipressin initiation, g/dL	4.1 (0.80)	3.6 (0.49)	0.329
Serum albumin difference between EOT and Day 1, g/dL	0.3 (0.63)	−0.2 (0.49)	<0.001
Duration of terlipressin from Day 1 to EOT (SD)	6.6 (4.44)	4.5 (3.05)	0.004
Daily dose of terlipressin from Day 1 to EOT, mg	3.6 (1.43)	2.9 (1.18)	0.008
Terlipressin dose at EOT, mg	2.7 (1.69)	2.4 (1.47)	0.325
HRS reversal, n (%)	84 (33.6)	14 (30.4)	0.675
Respiratory events (Respiratory failure, pleural effusion, pulmonary edema, hypoxia, dyspnea) as adjudicated by investigators, n (%)	84 (33.6)	15 (32.6)	0.896
Respiratory failure/ acute respiratory failure, n (%)	31 (12.4)	11 (23.9)	0.040

Unless indicated, the data are presented as mean (standard deviation).

EOT, end of treatment; HRS, hepatorenal syndrome; MELD, Model for End-Stage Liver Disease.

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K Rajender Rajender Reddy – BMS: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Mallinckrodt Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Sequana: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Grifols: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Exact Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; HCC-TARGET: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; NASH-TARGET: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Spark Therapeutics: Consultant, No, No; Novo Nordisk: Consultant, No, No; Genfit: Consultant, No, No; BioVie: Consultant, No, No; Novartis: Advisor, No, No; Astra Zeneca: Advisor, No, No; Associate Editor Gastroenterology: Executive role , No, No; UptoDate: Royalties or patent beneficiary, No, No;

Ethan M. Weinberg – Mallinckrodt Pharmaceuticals: Consultant, Yes, No; Biovie: Consultant, No, No; PharmaIN: Consultant, No, No; Mallinckrodt Pharmaceuticals: Advisor, Yes, No;

S. Chris Pappas – Durect: Independent contractor (including contracted research), No, No; EMD Serono: Independent contractor (including contracted research), No, No; Exelixis: Independent contractor (including contracted research), No, No; HepQuant: Independent contractor (including contracted research), No, No; Mallinckrodt Pharmaceuticals: Independent contractor (including contracted research), Yes, No; Orphan Therapeutics LLC: Independent contractor (including contracted research), No, No; Sanofi: Independent contractor (including contracted research), No, No;
Khurram Jamil – Mallinckrodt Pharmaceuticals: Employee, Yes, No;
The following people have nothing to disclose: Manhal Izzy, Douglas A. Simonetto, Kevin Moore

3055-A | L-ORNITHINE L-ASPARTATE(LOLA) VERSUS STANDARD MEDICAL THERAPY (SMT) FOR IMPROVEMENT OF SARCOPENIA IN PATIENTS WITH CIRRHOSIS -A RANDOMIZED OPEN LABEL TRIAL

Rameez Raja Najar, Amrish Sahney, Manav Wadhavan, Prem Kumar Ganesan, Ajay Kumar, Jc Vij, Neha Berry, Reethesh S R, Pulkit Sondhi and Md Nuruddin Ansari, BLK MAX SS Hospital New Delhi

Background: Sarcopenia predisposes to hepatic encephalopathy due to reduced muscle capacity to scavenge ammonia. LOLA by reducing ammonia levels have a role in improving hepatic encephalopathy. Hyperammonaemia is one of the important mechanism for sarcopenia in cirrhosis. We thus aimed to assess the efficacy of LOLA in improving sarcopenia in liver cirrhosis. **Methods:** This study was conducted in a tertiary care hospital in India over a period of 2 years and all cirrhotic patients seen as outpatient were screened for sarcopenia(Anthropometry, CT L3 muscle area and index (Skeletal muscle index, SMI) by sliceOmatic application and Frailty by Liver frailty index(LFI)) at baseline and at follow up at 6 months. We excluded patients of child class C in our study. After exclusion, 48 patients had sarcopenia and were randomised through block randomization to receive either LOLA (5gm orally thrice daily) plus SMT((Protein 1.5 g/kg/day, Cal 35kcal/kg/day)-(LOLA Group, $n = 20$) or SMT alone (control group, $n = 17$). Patients were followed for 6 months. Patients were called fortnightly for adverse events related to treatment or any decompensation due to disease per se during 6 months follow up period. Standard statistical analysis was done. **Results:** In this open-label randomised trial, 37 cirrhotic patients with sarcopenia completed the study. All baseline characteristics were comparable between the two groups. The prevalence of sarcopenia was predominantly seen in age group > 50 years, Child Pugh class B and in MELD score in the range of 15-29. At 6months follow up, there was trend towards improvement in sarcopenia (SMI) in LOLA group compared to control group with delta SMI(SMI Δ0-6) of 0.155 vs 0.015 respectively(p value $= 0.09$). There was improvement in Liver frailty index (LFI Δ0-6) by 0.19 (15%) which was statistically significant (3.64 ± 0.28 in LOLA group vs. 3.98 ± 0.26 in control group, 95% confidence interval -0.06 to -0.318, p valve $= 0.005$). Also at follow up, patients in LOLA group showed significant improvement in PHES score (17% vs 5.9%, $p < 0.05$) compared to SMT group. **Conclusion:** Ours is the first study to compare the efficacy and safety of LOLA in improving sarcopenia in liver cirrhosis. Though there was statistically non-significant trend towards improvement in SMI in LOLA group compared to control group but there was statistically significant improvement in LFI and MHE in LOLA group compared to control group. Larger sample size is required to assess the significant improvement in muscle mass by adding ammonia lowering agent (LOLA) to standard medical therapy.

Disclosures: The following people have nothing to disclose: Rameez Raja Najar, Amrish Sahney, Manav Wadhavan, Prem Kumar Ganesan, Ajay Kumar, Jc Vij, Neha Berry, Reethesh S R, Pulkit Sondhi, Md Nuruddin Ansari

3056-A | A MULTICENTER, BLINDED, POSITIVE CONTROL, PHASE II/III, ADAPTIVE DESIGN AND SEAMLESS CONNECTION CLINICAL TRIAL OF RECOMBINANT HUMAN ALBUMIN INJECTION IN TREATMENT OF HYPOALBUMINEMIA IN CIRRHOTIC PATIENTS WITH ASCITES(PHASE II)

Xu Li[1], Yanhang Gao[1], Xinrui Wang[1], Wanyu Li[1], Yanjun Cai[1], Jinlin Hou[2], Runping Gao[1], Yu Pan[1], Qinglong Jin[1], Dachuan Cai[3], Bin Xu[4], Yulin Hu[1], Xiaofeng Wu[5], Xiaolin Guo[1], Xiaoping Wu[6], Xiangjun Jiang[7], Zhenjing Jin[8], Guangming Xiao[9], Jidong Jia[10], Wen Xie[11] and Junqi Niu[1], (1)The First Hospital of Jilin University, (2)Nanfang Hospital of Southern Medical University, (3)The Second Affiliated Hospital of Chongqing Medical University, (4)Beijing Youan Hospital Capital Medical University, Beijing, China, (5) The Sixth People's Hospital of Shenyang, (6)The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China, (7)Qingdao Municipal Hospital, (8) Second Hospital of Jilin University, (9)The Eighth Affiliated Hospital of Guangzhou Medical University, (10)Beijing Friendship Hospital, Capital Medical

University, Beijing, China, (11)Center of Liver Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, China

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

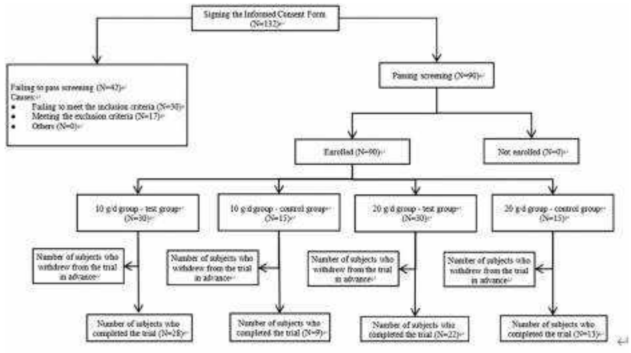
Signing the Informed Consent Form (N=132)
Failing to pass screening (N=42)
Causes:
Failing to meet the inclusion criteria (N=30)
Meeting the exclusion criteria (N=17)
Others (N=0)
Passing screening (N=90)
Enrolled (N=90)
Not enrolled (N=0)
10 g/d group - test group (N=30)
10 g/d group - control group (N=15)
20 g/d group - test group (N=30)
20 g/d group - control group (N=15)
Number of subjects who withdrew from the trial in advance
Number of subjects who withdrew from the trial in advance
Number of subjects who withdrew from the trial in advance
Number of subjects who withdrew from the trial in advance
Number of subjects who completed the trial (N=28)
Number of subjects who completed the trial (N=9)
Number of subjects who completed the trial (N=22)
Number of subjects who completed the trial (N=13)

Figure 1. Flow chart of subject disposition

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

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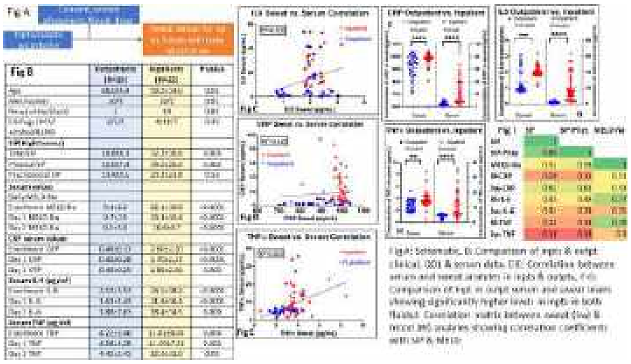
Background: Biomedical sensing, especially related to inflammatory markers, could increase insight into cirrhosis-related complications. Sweat sensing using the AWARE sensor could be used to monitor minute-by-minute changes in inpts/outpts with cirrhosis, which is a non-invasive monitoring modality. Aim: Define relationship of serum and sweat inflammatory markers in cirrhosis. **Methods**: Inpatients or outpatients with cirrhosis underwent AWARE sensor application daily for up to 3 days (Fig A). Daily blood CRP, IL-6 &TNF measurements were performed and compared with sweat values of these analytes. Serum value at each blood draw & sweat time-weighted average values of analytes were compared between inpts & outpts and correlated with each other. Blood IL-6/TNF were analyzed using ELISA while blood CRP was sent to our clinical lab. Quality of life using Sickness Impact Profile (SIP: high = worse with physical and psychological domains) was studied. Correlations between sweat & serum analytes with MELD-Na and SIP scores were performed. **Results**: 32 pts (10 outpt/22 inpts) were included. All outpts were seen for 3 days, while 13 inpts were seen for 2 days and 7 for 3 days with daily blood draws. Day 1 data, which was available on everyone, was analyzed and is presented. All inpts were admitted for cirrhosis-related complications (14 with infections, 8 with AKI/electrolyte issues, 8 with hepatic encephalopathy, 5 with ascites) and had mean Length of stay of 5.5 ± 0.81 days. 12 were on antibiotics. MELD score and all inflammatory markers were higher in inpts over several days (Fig B). SIP total/physical were higher in inpts. Correlation of sweat and serum IL-6, TNF & CRP were highly significant across groups, even though the values were higher in inpts (Fig C-E). This pattern was also seen in sweat and serum comparisons, which showed that regardless of the fluid tested, inpts had higher concentrations (Fig F-H). Correlations between MELD-Na, Total SIP, Physical SIP & the analytes showed that SIP & Physical SIP were only correlated with sweat CRP but not blood CRP, while the opposite pattern was seen with IL-6 and TNF, where blood values were more correlated. Both CRP in blood and serum were linked with MELD-Na but only blood TNF and IL-6 and not sweat levels were linked with MELD-Na (Fig I) **Conclusion**: We showed good correlation between sweat and serum values of CRP, IL-6 and TNF in outpatients and inpatients with cirrhosis. Values of both sweat and serum analytes were higher in inpatients compared to outpatients. Quality of life was significantly linked with sweat CRP but not serum CRP but the opposite pattern was seen with IL-6 and TNF. CRP values, regardless of serum or sweat, were linked with the MELD-Na. The differential linkage of sweat CRP to quality of life may be a novel pattern to evaluate for long-term management of these patients. The AWARE sensor is feasible in inpatients and outpatients with cirrhosis and show similar patterns to blood levels of CRP, IL-6 and TNF.



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

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

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

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

Mumbai. Depression, anxiety and stress were assessed using DASS-21 questionnaire at the time of diagnosis. Patients were followed up after 3 months and severity of psychiatric disorders were again measured and correlated with MELD-NA score using Chi square and t tests. **Results:** Most common psychiatric disorder was depression followed by anxiety and stress. The prevalence of mild, moderate and severe depression at enrolment was 45.2%, 28.1% ,15.6% respectively and on 3 months follow up was 39.3%, 31.1% and 21.5% respectively. The prevalence of mild, moderate and severe anxiety at enrolment was 30.4%, 25.2%, 17.2 % respectively and on 3 months follow up was 26.7%, 28.9% and 18.8% respectively. The prevalence of mild, moderate and severe stress at enrolment was 3.7%, 26.7%, 15.6% respectively and on 3 months follow up was 6.7%, 31.9% and18.5% respectively. There was a positive association between severity of depression and MELD-NA score (P = 0.022, C.I. = 95%), a positive association between severity of anxiety and MELD-NA score (P = 0.038, C.I. = 95%) and a positive association between severity of stress and MELD-NA score (P = 0.010, C.I. = 95%) at . These associations were found to be statistically significant. At 3 months also the severity of all 3 psychiatric disorders corelated positively with MELD Na scores. **Conclusion:** Liver cirrhosis is associated with increased prevalence of psychiatric disorders with more than 70 % percent patients having varying degrees of psychiatric diseases. Their severity increases with increase in MELD-NA score at presentation and at 3 months.

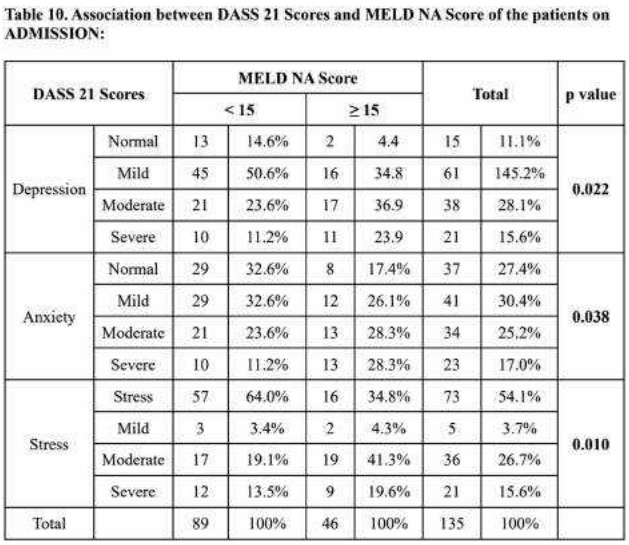

Table 10. Association between DASS 21 Scores and MELD NA Score of the patients on ADMISSION:

DASS 21 Scores		MELD NA Score				Total		p value
		< 15		≥ 15				
Depression	Normal	13	14.6%	2	4.4	15	11.1%	0.022
	Mild	45	50.6%	16	34.8	61	145.2%	
	Moderate	21	23.6%	17	36.9	38	28.1%	
	Severe	10	11.2%	11	23.9	21	15.6%	
Anxiety	Normal	29	32.6%	8	17.4%	37	27.4%	0.038
	Mild	29	32.6%	12	26.1%	41	30.4%	
	Moderate	21	23.6%	13	28.3%	34	25.2%	
	Severe	10	11.2%	13	28.3%	23	17.0%	
Stress	Stress	57	64.0%	16	34.8%	73	54.1%	0.010
	Mild	3	3.4%	2	4.3%	5	3.7%	
	Moderate	17	19.1%	19	41.3%	36	26.7%	
	Severe	12	13.5%	9	19.6%	21	15.6%	
Total		89	100%	46	100%	135	100%	

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3059-A | A QUICK AND ACCURATE TOOL COMBINED NUMBER CONNECTION TEST A WITH ANIMAL AND VEGETABLE NAMING TEST TO IDENTIFY MINIMAL HEPATIC ENCEPHALOPATHY IN HOSPITALIZED PATIENTS

Qiuyu Cheng[1], Yunhui Liu[2], Gege Wu[3], Hao Ye[4], Zhongyuan Yang[2], Zhongwei Zhang[2], Meng Zhang[2], Tingting Liu[2], Yuxin Niu[1], Deyan Tian[2], Xiaoyun Zhang[2], Xiaoping Luo[3], Xiaojing Wang[1], Tao Chen[1] and Qin Ning[1], (1)Tongji Medical College and State Key Laboratory for Diagnosis and Treatment of Severe Zoonostic Infectious Disease, Huazhong University of Science and Technology, (2)Department of Infectious Diseases, Tongji Hospital, Tongji Medical College and State Key Laboratory for Diagnosis and Treatment of Severe Zoonostic Infectious Disease, Huazhong University of Science and Technology, Wuhan, 430030, Hubei, China, (3)Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, (4)People's Hospital of Jingshan City

Background: Minimal hepatic encephalopathy (MHE) is easy to be ignored in hospitalized patients due to its inconspicuous symptoms and time-consuming diagnosis. We aimed to establish a quick and accurate diagnostic tool of MHE for inpatients. **Methods:** A total of 123 healthy volunteers and 252 inpatients with cirrhosis or acute-on-chronic liver failure (ACLF) without overt hepatic encephalopathy (OHE) were prospectively included and underwent the psychometric hepatic encephalopathy score (PHES), animal naming test (ANT), vegetable naming test (VNT), and animal and vegetable naming test (AVNT). Serum ammonia was measured among patients. Meanwhile, the newly occurred OHE during hospitalization was observed. **Results:** A diagnostic nomogram named AVNA via a combination of AVNT with number connection test A (NCT-A) was established, with an AUC of 0.98 (97.1% sensitivity, 93.2% specificity and 94.1% accuracy) for development cohort (n = 152) and 0.91 (87.9% sensitivity, 79.1% specificity and 82.0% accuracy) for validation cohort (n = 100), respectively. Patients with AVNA diagnosed MHE exhibited higher risk of 30-day OHE development in comparison with AVNA diagnosed none-MHE (P < 0.001). Moreover, the average time of AVNA test was significantly shorter than the PHES test (151 ± 77 sec to 398 ± 192 sec, P < 0.001). Decision curve analysis (DCA) demonstrated that serum ammonia did not have additional positive net benefits to AVNA for almost all of the threshold probabilities. **Conclusion:** A fast and accurate test AVNA with AVNT and NCT-A was established for inpatients with cirrhosis or ACLF, which enables appropriate diagnosis of MHE in daily clinical practice.

Disclosures: The following people have nothing to disclose: Qiuyu Cheng, Yunhui Liu, Gege Wu, Hao Ye, Zhongyuan Yang, Zhongwei Zhang, Meng Zhang, Tingting Liu, Yuxin Niu, Deyan Tian, Xiaoyun Zhang, Xiaoping Luo, Xiaojing Wang, Tao Chen, Qin Ning

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

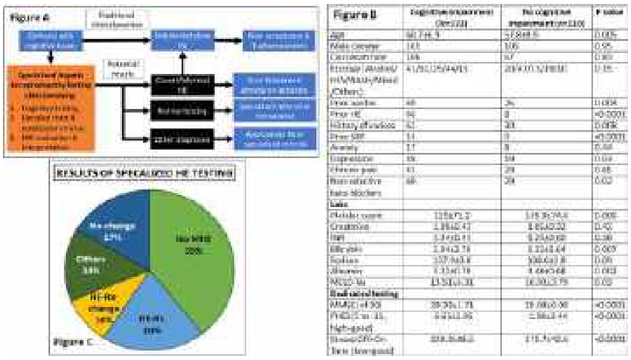
Asiya Tafader[1], Mahum Nadeem[1], Dan Park[1], Andrew Fagan[1], Brian C. Davis[1], Michael Fuchs[2], Puneet Puri[3], HoChong Gilles[4], Jennifer Miller[4], Felicia Tinsley[1] and Jasmohan S. Bajaj[5], (1)Virginia Commonwealth University and Richmond VA Medical Center, (2) Mcguire Veterans Affairs Medical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

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

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

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

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



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

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

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Disclosure information not available at the time of publication: Xiaoru Chen, Mariana M. Oliveira, Mélanie Tremblay

3062-A | ANALYSIS OF RELEVANT FACTORS OF PORTAL VEIN THROMBOSIS IN LIVER CIRRHOSIS

Jinglan Jin[1], Xiaotong Xu[1], Yuwei Liu[1], Hang Li[1] and Yaya Li[2], (1)First Hospital of Jilin University, (2)First Hospital of Jilin Hospital

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

The basic general information, past medical history, laboratory, and imaging examination data were collected and analyzed. **Results:** In univariate analysis, there was no signifcant diference between the two groups in IL-6, PC, reaction time(R), alpha angle (Angle), maximum amplitude, or coagulation index (CI) ($P > 0.05$). TNF-α in the PVT group was signifcantly lower than that in the non-PVT group ($P = 0.001$). K-time (K) in the PVT group was signifcantly higher than that in the non-PVT group($P = 0.031$). There was no signifcant diference in IL-6, TNF-α, PC, or TEG between diferent Child–Pugh classifcation groups ($P > 0.05$). There were no signifcant diferences in TEG between the plasma transfusion group and the non-plasma transfusion group. In Binary logistic regression analysis, TNF-α (OR = 0.9881, 95%CI = 0.971, 0.990, $P < 0.001$), K (OR = 1.28, 95% = 1.053, 1.569, $P = 0.014$), activate partial thromboplastin time(APTT) (OR = 0.753, 95% CI = 0.656, 0.865, $P < 0.001$), portal vein diameter(OR = 1.310, 95%CI = 1.108, 1.549, $P = 0.002$) and the history of splenectomy or embolism (OR = 7.565,95%CI = 1.514, 37.799, $P = 0.014$)were related to the formation of PVT. **Conclusion:** TNF-α, K, APTT, portal vein diameter, and splenectomy or embolism history were associated with PVT formation, but IL-6 was not.

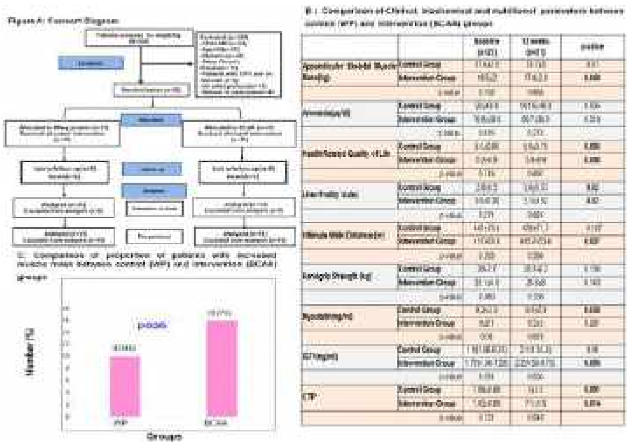
Disclosures: The following people have nothing to disclose: Jinglan Jin, Yuwei Liu

Disclosure information not available at the time of publication: Xiaotong Xu, Hang Li, Yaya Li

3064-A | BRANCHED CHAIN AMINO ACIDS SUPPLEMENTATION IMPROVES MUSCLE MASS, MUSCLE FUNCTION, AND FRAILTY IN PATIENTS WITH LIVER CIRRHOSIS: A RANDOMIZED CONTROLLED TRIAL

Puja Bhatia Kapoor[1], Jaya Benjamin[1], Rakhi Maiwall[1], Harsh Vardhan Tevethia[1], Rajan Vijayaraghavan[1], Guresh Kumar[1], Yogendra Kumar Joshi[1] and Shiv Kumar Sarin[2], (1)Institute of Liver and Biliary Sciences, New Delhi, (2)Institute of Liver and Biliary Sciences

Background: Progressive loss in muscle mass, strength and performance along with frailty are common complications in liver cirrhosis (LC). Within the realm of nutritional management, apart from a high calorie and high protein diet along with organized exercise, the role of myotropic nutrients like branched chain amino acids (BCAA) is promising, yet lacks corroboration from randomized controlled trials. Aim: Primary aim was to assess the effect of BCAA on muscle mass; secondary aims included effect on muscle strength and performance, frailty, health related quality of life (HRQoL), insulin like growth factor 1(IGF1) and myostatin. **Methods:** In this open label, randomized controlled trial, after screening 302 patients, 62 meeting the inclusion criteria (Fig 1A) were randomized to either intervention or control group, receiving 16gm/day of BCAA or whey protein (WP) respectively in addition to a diet providing 35 Kcal and 1.35 gm protein/kg wt and standard medical therapy, along with 30 minutes exercise for 12 weeks. Patients were followed-up to collect clinical, nutritional and biochemical details. Appendicular skeletal muscle mass (ASMM) was assessed by DEXA. Muscle strength by Hand Grip Dynamometer, muscle performance by 6 minute walk distance (6MWD), frailty by liver frailty index, and HRQoL by Chronic Liver Disease Questionnaire. IGF1 and myostatin levels were assessed by ELISA. **Results:** In all 62 patients [age: 47.3 ± 10.2 years, male (100%), etiology: (Alcohol: Cryptogenic: NASH: Others = 60%:22%:8%:10%), BMI: 20.8 ± 2.1 (kg/m2), CTP 7.9 ± 0.8] were randomized to BCAA (n = 31) and WP (n = 31) group. As per ITT analysis both the groups were comparable at baseline. 90 day mortality was comparable between the two groups [1(3.2) vs 2(6.5); p = 0.822).17 patients were lost to follow-up; 42 (Fig 1A) were analyzed as per-protocol. By the end of 12 weeks ASMM and 6MWD improved significantly in the BCAA group. Overall 26 patients (62%) had improved ASMM which was more frequent in the BCAA group (76 vs. 47.6%; 0.045) (Fig 1C). Anabolic marker-IGF1 improved significantly in the BCAA group only, whereas myostatin, the catabolic marker increased in the WP group, while remaining unchanged in the BCAA group (Table 1). CTP score, frailty and HRQoL improved significantly in both groups (Fig 1B); however, muscle strength remained unchanged. **Conclusion:** High calorie high protein diet along with exercise are imperative for improving frailty and HRQoL in cirrhosis, but only BCAA really spurs muscle mass, muscle performance and IGF1.



Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

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Disclosure information not available at the time of publication: Rajan Vijayaraghavan

3065-A | CHANGE IN FRAILTY STATUS WITH NUTRITIONAL THERAPY IN CIRRHOTIC PATIENT – A RANDOMIZED CONTROLLED TRIAL

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Background: Frailty is characterised by low physiologic reserve and decreased functional status and is associated with poor prognosis in patients with cirrhosis. There is limited data on nutritional intervention on frailty status in cirrhosis. Aim was to assess the effects of nutritional therapy on changes in frailty status in cirrhotic patients. **Methods:** A randomised controlled trial conducted in a tertiary care centre on patients with cirrhosis, who were randomised to assigned to nutritional therapy (group A: 30–35 kcal/kg/day, 1.0–1.5 g protein/kg/day;) and no nutritional therapy (group B: patients continued on their same diet) for 6 months. Frailty status was assessed by liver frailty index (LFI) and gait velocity(GV). Primary endpoints were improvement or worsening in frailty status. Secondary endpoints were improvement of other nutritional parameters and liver functions. **Results:** Till date 34 patients were randomised to group -A ($n = 18$, age 43.4 ± 9.8 yr, 14 men) and group-B ($n = 16$, age 42.7 ± 10.1 yr, 12 men). Alcohol was most common (64%) aetiology. Baseline characteristics including age, body mass index (BMI), haemoglobin, MELD score, mid arm circumference (MAC), hand grip (HG), GV and LFI were comparable in both the groups. Improvement in GV (ΔGV 0.99 ± 0.32 vs -0.82 ± 0.28, $p = 0.001$), LFI (ΔLFI -0.62 ± 0.24 vs 0.3 ± 0.32, $P = 0.001$) HG strength (ΔHG 4.2 ± 1.3 vs -2.9 ± 1.2, $p = 0.001$), MAC (ΔMAC 2.69 ± 0.28 vs -2.15 ± 0.26, $p = 0.01$) was observed in group A compared to group B at the end of study. Liver functions assessed by Child Turcotte Pugh and Model for end stage liver disease also significantly improved in group A compared to group B, $p < 0.001$. **Conclusion:** Nutritional therapy is effective in the improving the frailty status, nutritional parameters and liver functions in cirrhotic patients.

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Disclosure information not available at the time of publication: Shyam Sunder Sharma, Saksham Seth

3066-A | CLINICAL PREDICTORS AND OUTCOMES OF RAPID SKELETAL MUSCLE LOSS IN PATIENTS WITH CIRRHOSIS

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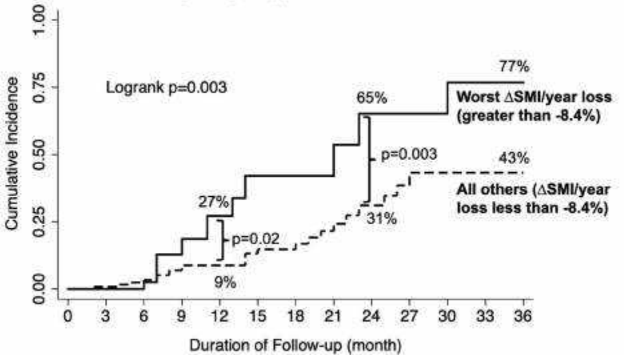
Background: Skeletal muscle mass is a strong predictor of morbidity and mortality in cirrhosis patients and therefore, represents a key potential interventional endpoint to improve outcomes. However, the average expected *rate of change* of skeletal muscle in this population has not been well characterized, hampering efforts to design adequately powered trials. In this study, we aimed to characterize the rate of change in skeletal muscle mass and evaluate its associations with clinical outcomes in cirrhosis patients. **Methods**: Included were prospectively enrolled ambulatory adults with cirrhosis awaiting liver transplant with at least 2 available abdominal CT scans within 6 months at enrollment and within 6 months of study endpoint from 2/2015-1/2018. Skeletal muscle index (SMI) was quantified by CT at the L3 vertebrae, normalized for height (cm^2/m^2). Percent change in SMI (ΔSMI/year) was calculated as (follow-up SMI - baseline SMI) / (baseline SMI) x 100 / interval between CT in years. The primary outcome was waitlist mortality, defined as death or delisting for being too sick for transplant. **Results**: Among 171 patients included: 32% were women, 56% were white with a median age 62 year. Median follow-up was 12 months (IQR 9-18). Median (IQR) ΔSMI/year was -1.1% (-8.4, 5.0) for the entire cohort, and similar for men with -1.1% (-7.3, 4.5) and women with -2.4% (-9.2, 8.2). "Rapid muscle loss" was defined by the worst 25th percentile value for ΔSMI/year at less than -8.4% ($n = 43$). Patients with rapid muscle loss had more ascites (63% vs. 44%), higher median MELD (14 vs 12), frailty (19% vs 13%), and higher baseline SMI (55 vs 51 cm^2/m^2 in men and 45 vs 39 cm^2/m^2 in women). Presence of ascites was a significant predictor of rapid muscle loss (OR 2.17, 95% CI 0.07-4.41), remaining significant after adjusting for age, sex, MELDNa, frailty, and baseline sarcopenia (OR 2.10, 95%CI 1.01-4.92). Cumulative incidence of waitlist mortality was significantly higher in patients with rapid muscle loss compared to all others at 12-month (27% vs 9%) and 36-month (77% vs 43%) (Figure). In univariable Cox regression, rapid muscle loss was associated with waitlist mortality (HR 2.62, 95%CI 1.33-5.15), which remained significant after adjusting for age, sex, ascites, encephalopathy, MELDNa, and baseline SMI (HR 2.71, 95%CI 1.30-5.66). **Conclusion**: Patients with cirrhosis experience ~1% muscle loss *per year*. For reference, natural age-related decline in muscle mass is ~2% *every 10 years* in the general population. In cirrhosis patients, rapid muscle loss was independently associated with higher waitlist mortality. Our data are essential for determining the effect size necessary to adequately power clinical trials targeting therapeutic interventions aimed at improving muscle mass in this population.

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



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

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Background: EncephalApp Stroop is a simple method to diagnose minimal hepatic encephalopathy & is linked with overt HE (OHE), & hospitalizations. Aim: (i) define Stroop OffTime+OnTime completion time test/retest variation and baseline differences in this completion time that would predict increased risk of OHE/hospitalizations over time & (ii) to validate this time difference in a second cohort. **Methods**: 3 prospective cohorts were enrolled: *Cohort 1:* Stroop at baseline then followed till OHE/hospitalization or last clinical outcome available from 2 centers (University+VA), *Cohort 2*: Test/retest cohort from University+VA & *Cohort 3:* Multi-center cohort followed for 3 mths. OffTime+OnTime was used as Stroop outcome (Fig A).

Cohort 1: Baseline cirrhosis details, co-morbidities & medications were collected. Stroop values were studied using Cox proportional hazards with OHE/hospitalization as primary outcomes. Baseline Stroop values between those who developed OHE/hospitalization sooner vs rest were compared unadjusted & adjusted for clinical variables.

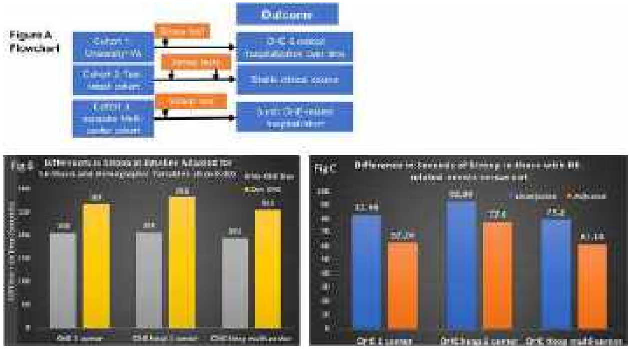
Cohort 2: A separate group underwent Stroop twice without underlying clinical change.

Cohort 3: Cirrhosis outpts from 10 N American sites underwent Stroop & were followed for 3 mths for OHE-related hospitalizations. Baseline adjusted/unadjusted Stroop differences were compared to cohort 1. **Results**: 2-center cohort: 278 pts (62 y, 96% men, MELD-Na 11, 33% prior OHE, 41% ascites) were followed for a median of 7 (3,24 IQR) mths. 16% developed OHE & 12% OHE hospitalization at a median of 6 & 3 mths post-testing respectively. On Cox Proportional hazards for OHE, Stroop time $p = 0.002$, MELD-Na $p < 0.0001$ & ascites $p = 0.003$, were significant; similar variables (Stroop $p < 0.001$, MELD-Na $p = 0.009$, Ascites $p = 0.03$ & beta-blockers $p = 0.04$) were significant for OHE hospitalization. Prior HE, meds & demographics were not linked. After adjusting, we found significant baseline Stroop differences between those that developed outcomes/not (Fig B).

Test-retest cohort: 44 pts (66 y, 42 men, MELD-Na 10, Prior OHE 25%, 34% ascites) received Stroop twice a median of 13 (4-24) mths apart without significant change in OffTime+OnTime (212.4 ± 65.1 vs 210.44 ± 79.9 sec, $p = 0.75$)

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

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



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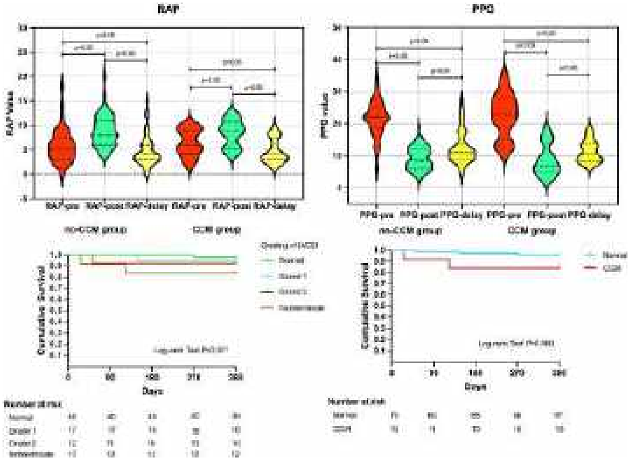
3068-A | DIASTOLIC DYSFUNCTION IN CIRRHOTIC CARDIOMYOPATHY: A PROSPECTIVE OBSERVATIONAL COHORT STUDY ON SHORT-TERM OUTCOMES IN CIRRHOTIC PATIENTS UNDERGOING TIPS

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

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



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3069-A | DISCHARGE SERUM POTASSIUM IN HOSPITALIZED CIRRHOSIS PATIENTS DOES NOT AFFECT CLINICAL OUTCOMES

Kimberline Chew[1], Katherine Ni[1], Zoe Verzani[2], Jang Hyun Kim[1], Lewis Paulino[1], Danielle Garfunkel[1], Max Schechter[3], Lital Aliasi-Sinai[4], Daniel Alvarez[1], Brett Fortune[1] and Clara Tow[1], (1)Montefiore Medical Center, (2)Weill Cornell Medical Center, (3)Albert Einstein College of Medicine, (4)Sackler School of Medicine

Background: Patients with advanced cirrhosis frequently have impaired potassium homeostasis. Potassium disturbances have been linked to unfavorable outcomes in patients with cirrhosis. Studies have looked at baseline potassium levels on admission, however there is limited investigation on the effects of discharge potassium levels towards outcomes in cirrhosis patients. **Methods:** We retrospectively developed a cohort of 253 hospitalized patients with cirrhosis between January to December 2021 at a major urban liver transplant health system. Potassium levels (K) were collected and verified through individual chart reviews. Serum potassium levels at discharge were classified into two categories: K < 4.0mEq/L and K e 4.0mEq/L. We analyzed the effects of discharge potassium on a primary outcome of all-cause 1-year mortality, while secondary outcomes were re-admission rates at 90 days and 1 year. Two-sample t-tests/Wilcoxon tests or Chi-square/Fisher's exact tests were used to compare the variables as appropriate. A multivariable logistic regression model was used to study the impact of discharge potassium on the outcomes adjusted for clinically relevant covariates, included based on prior literature. **Results:** Baseline characteristics between patients with K < 4.0mEq/L and K e 4.0mEq/L at discharge (n = 98 [39%] and 155 [61%], respectively) were similar in terms of age, gender, Model for End-Stage Liver Disease-Sodium (MELD-Na) score, MELD score, Child-Pugh score, diuretics use, presence of Hepatocellular Carcinoma (HCC), presence of Transjugular Intrahepatic Portosystemic Shunt (TIPS), lactulose usage, and type of cirrhosis. Median serum potassium and serum magnesium levels on admission were significantly lower in patients with K < 4.0mEq/L at discharge. There was no difference in all-cause death at 1 year between the two groups (p-value = 0.3). Having a potassium level of e 4.0mEq/L at discharge was associated with fewer 90-day readmissions (p-value = 0.044) and 1-year readmissions (p-value = 0.03) in the unadjusted model. After adjusting for relevant covariates, there was no difference for 90-day readmissions (aOR 0.75, 95% CI 0.38-1.48) or 1-year readmissions (aOR 0.75, 95% CI 0.38-1.48) (Table 1). **Conclusion:** Our study demonstrates that discharge potassium levels did not affect all-cause death at 1 year nor readmissions at 90 days and at 1 year. Our findings may also reflect study limitations due to type II error. Further elucidation into potassium homeostasis using larger cohorts is warranted to advance our understanding potassium's impact on clinical outcomes.

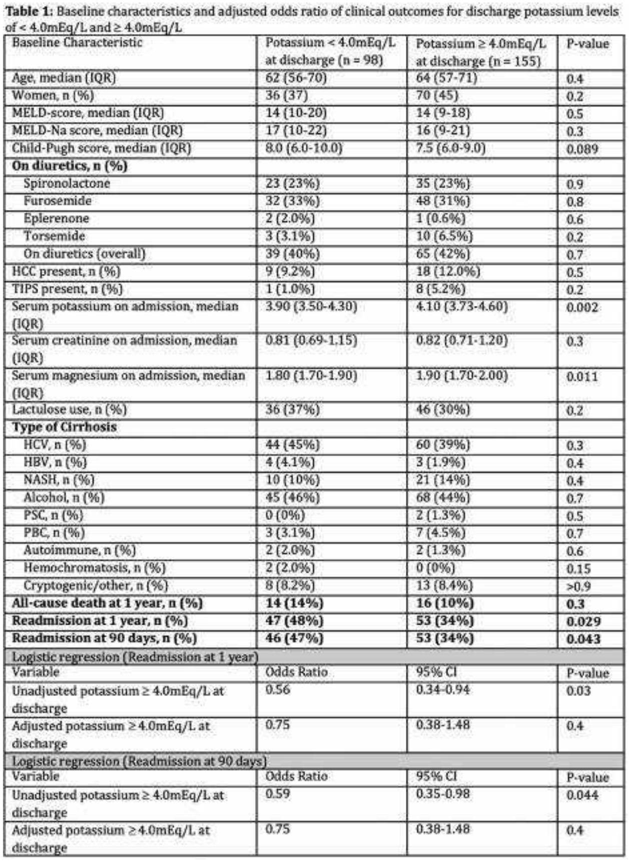

Table 1: Baseline characteristics and adjusted odds ratio of clinical outcomes for discharge potassium levels of < 4.0mEq/L and ≥ 4.0mEq/L

Baseline Characteristic	Potassium < 4.0mEq/L at discharge (n = 98)	Potassium ≥ 4.0mEq/L at discharge (n = 155)	P-value
Age, median (IQR)	62 (56-70)	64 (57-71)	0.4
Women, n (%)	36 (37)	70 (45)	0.2
MELD-score, median (IQR)	14 (10-20)	14 (9-18)	0.5
MELD-Na score, median (IQR)	17 (10-22)	16 (9-21)	0.3
Child-Pugh score, median (IQR)	8.0 (6.0-10.0)	7.5 (6.0-9.0)	0.089
On diuretics, n (%)			
Spironolactone	23 (23%)	35 (23%)	0.9
Furosemide	32 (33%)	48 (31%)	0.8
Eplerenone	2 (2.0%)	1 (0.6%)	0.6
Torsemide	3 (3.1%)	10 (6.5%)	0.2
On diuretics (overall)	39 (40%)	65 (42%)	0.7
HCC present, n (%)	9 (9.2%)	18 (12.0%)	0.5
TIPS present, n (%)	1 (1.0%)	8 (5.2%)	0.2
Serum potassium on admission, median (IQR)	3.90 (3.50-4.30)	4.10 (3.73-4.60)	0.002
Serum creatinine on admission, median (IQR)	0.81 (0.69-1.15)	0.82 (0.71-1.20)	0.3
Serum magnesium on admission, median (IQR)	1.80 (1.70-1.90)	1.90 (1.70-2.00)	0.011
Lactulose use, n (%)	36 (37%)	46 (30%)	0.2
Type of Cirrhosis			
HCV, n (%)	44 (45%)	60 (39%)	0.3
HBV, n (%)	4 (4.1%)	3 (1.9%)	0.4
NASH, n (%)	10 (10%)	21 (14%)	0.4
Alcohol, n (%)	45 (46%)	68 (44%)	0.7
PSC, n (%)	0 (0%)	2 (1.3%)	0.5
PBC, n (%)	3 (3.1%)	7 (4.5%)	0.7
Autoimmune, n (%)	2 (2.0%)	2 (1.3%)	0.6
Hemochromatosis, n (%)	2 (2.0%)	0 (0%)	0.15
Cryptogenic/other, n (%)	8 (8.2%)	13 (8.4%)	>0.9
All-cause death at 1 year, n (%)	**14 (14%)**	**16 (10%)**	**0.3**
Readmission at 1 year, n (%)	**47 (48%)**	**53 (34%)**	**0.029**
Readmission at 90 days, n (%)	**46 (47%)**	**53 (34%)**	**0.043**
Logistic regression (Readmission at 1 year)			
Variable	Odds Ratio	95% CI	P-value
Unadjusted potassium ≥ 4.0mEq/L at discharge	0.56	0.34-0.94	0.03
Adjusted potassium ≥ 4.0mEq/L at discharge	0.75	0.38-1.48	0.4
Logistic regression (Readmission at 90 days)			
Variable	Odds Ratio	95% CI	P-value
Unadjusted potassium ≥ 4.0mEq/L at discharge	0.59	0.35-0.98	0.044
Adjusted potassium ≥ 4.0mEq/L at discharge	0.75	0.38-1.48	0.4

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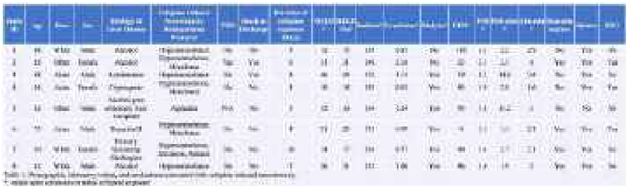
Disclosure information not available at the time of publication: Katherine Ni, Zoe Verzani, Jang Hyun Kim, Lewis Paulino, Max Schechter, Lital Aliasi-Sinai, Daniel Alvarez, Clara Tow

3070-A | DISTINGUISHING CEFEPIME INDUCED NEUROTOXICITY FROM HEPATIC ENCEPHALOPATHY: LESSONS FROM A CASE SERIES OF CEFEPIME NEUROTOXICITY IN HOSPITALIZED PATIENTS WITH CIRRHOSIS

Frances Lee, Vishwajit Kode and Todd Frederick, California Pacific Medical Center

Background: Cirrhosis can increase the risk of adverse side effects from medications, including those that are renally excreted due to portal hypertension, portosystemic shunts, and loss of protein binding capacity with hypoalbuminemia. Cefepime is a fourth-generation cephalosporin, known to induce cefepime induced neurotoxicity (CIN), defined as alterations in neurologic and psychologic function within 4-6 days of cefepime initiation that resolves with cefepime withdrawal. While described in patients with renal insufficiency, this phenomenon is increasingly described in patients with cirrhosis through case reports. **Methods:** This is a single center case series of hospitalized patients with cirrhosis exposed to cefepime in a tertiary care center in San Francisco between January 2018 to November 2022. These patients were reviewed from 430 charts gathered by data stewards using ICD-10 codes. Patients were selected for this case series if there was neurologic improvement with cefepime discontinuation, and diagnosis of CIN was made by transplant hepatologist or neurologist. **Results:** There were 8 patients with documented cefepime induced neurotoxicity during our study period. The average age was 58 years old, and 37% or 3 were female. 50% of the patients had a history of alcohol related liver disease, while one patient had received a liver transplant within 30 days of cefepime exposure. 87.5% or 7 patients had renal disease, of which 85.7% or 6 patients were on dialysis. 87.5% or 7 of the patients had hypersomnolence, 37.5% or 3 had myoclonus, 12.5% or 1 had agitation, and 12.5% or 1 had dizziness and aphasia. The patient with agitation was the only patient to not receive benzodiazepine and opiates during their cefepime exposure. The average MELD and MELD-Na score were 24 and 27, respectively. **Conclusion:** Distinguishing CIN from overt hepatic encephalopathy may be difficult to untangle for clinicians. This study demonstrates that while CIN may present with hypersomnolence, distinguishing features of CIN include myoclonus, agitation, aphasia, and dizziness. CIN is not limited to specific etiologies of liver disease and may occur shortly after orthotopic liver transplantation. Based on this series, cefepime use in patients with dual renal and decompensated cirrhosis should be reconsidered, particularly in those with higher MELD scores. This study can improve decision making for antibiotic administration and inform clinicians in their choice of antibiotic use.



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3071-A | EARLY ALBUMIN INFUSION MAY IMPROVE OUTCOMES IN MULTIDRUG-RESISTANT ORGANISM INFECTIONS AMONG PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS

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Background: Spontaneous bacterial peritonitis (SBP) due to multidrug-resistant organisms (MDROs) is a growing problem that portends higher rates of complications and mortality. Given that albumin infusion in conjunction with antibiotics is a guideline-recommended SBP treatment strategy, we aimed to determine the impact of albumin infusion timing on MDRO incidence and key clinical outcomes in patients with SBP. **Methods:** We used a nationwide Electronic Health Record (EHR) data set (Cerner Real World Data®) to extract real-world data on adult patients (e 18 y old) who received antibiotics and albumin while hospitalized with SBP between 01/01/2012–06/30/2022. ICD-9/10 codes, laboratory, and medication records were utilized to identify SBP cases and report patients' demographic and clinical characteristics at presentation (baseline). Albumin administration within 24 hours of hospital admission was defined as 'early albumin' while 'late albumin' comprised cases of albumin administration after 24 hours of admission. Descriptive analyses were performed to evaluate the overall antimicrobial administration pattern and to assess the impact of albumin infusion timing on various outcomes of interest, including MDRO incidence, in-hospital mortality, and hospital length of stay (LOS). MDROs were assessed based on EHR presence of ICD codes indicating resistance to antimicrobial drugs (ICD-9: V09; ICD-10: Z16) or administration of imipenem, meropenem, meropenemvaborbactam, polymyxin b, avibactam-ceftazidime, and tigecycline during the hospital encounter. **Results:** A total of 12,570 admissions were identified. The mean age was 56.7 years and 62% were men. The mean baseline MELD-Na was 24.4 and 18% of hospitalizations ended with the patient's death. Third-generation cephalosporins were the most administered antibiotic class (71.6%). Early albumin was administered in 8,180 (65.1%) cases. Compared to the late albumin group, the early group had a shorter LOS (median: 6.1 vs. 9.8 d) and a lower incidence of MDROs (13.6% vs. 17.7%) despite a higher baseline MELD-Na (mean: 25.5 vs. 22.3). Regardless of albumin use, cases of MDRO infections had longer LOS (median: 12.7 vs. 6.8 d) and higher in-hospital mortality (33.3% vs 15.0%) compared to non-MDRO cases. **Conclusion:** This real-world data shows that SBP treated with antimicrobials and early albumin had shorter LOS and lower rates of MDROs, despite a higher baseline MELD-Na. MDRO infections had a longer LOS and higher in-hospital mortality rate compared to non-MDRO cases overall. Further studies are warranted to evaluate additional interactions between albumin infusion timing and MDRO-related outcomes in SBP.

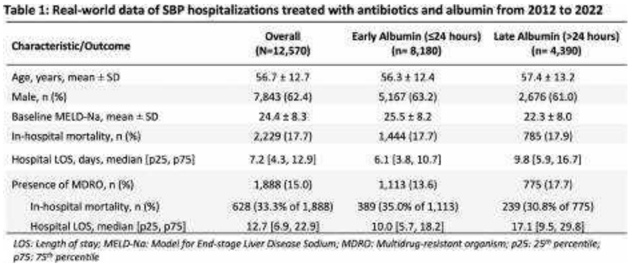

Table 1: Real-world data of SBP hospitalizations treated with antibiotics and albumin from 2012 to 2022

Characteristic/Outcome	Overall (N=12,570)	Early Albumin (≤24 hours) (n= 8,180)	Late Albumin (>24 hours) (n= 4,390)
Age, years, mean ± SD	56.7 ± 12.7	56.3 ± 12.4	57.4 ± 13.2
Male, n (%)	7,843 (62.4)	5,167 (63.2)	2,676 (61.0)
Baseline MELD-Na, mean ± SD	24.4 ± 8.3	25.5 ± 8.2	22.3 ± 8.0
In-hospital mortality, n (%)	2,229 (17.7)	1,444 (17.7)	785 (17.9)
Hospital LOS, days, median [p25, p75]	7.2 [4.3, 12.9]	6.1 [3.8, 10.7]	9.8 [5.9, 16.7]
Presence of MDRO, n (%)	1,888 (15.0)	1,113 (13.6)	775 (17.7)
In-hospital mortality, n (%)	628 (33.3% of 1,888)	389 (35.0% of 1,113)	239 (30.8% of 775)
Hospital LOS, median [p25, p75]	12.7 [6.9, 22.9]	10.0 [5.7, 18.2]	17.1 [9.5, 29.8]

LOS: Length of stay; MELD-Na: Model for End-stage Liver Disease Sodium; MDRO: Multidrug-resistant organism; p25: 25th percentile; p75: 75th percentile

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3072-A | ELEVATED PLASMA NEUROFILAMENT LIGHT CHAIN AND GLIAL FIBRILLARY ACIDIC PROTEIN LEVELS ASSOCIATED WITH PRESENCE OF MINIMAL HEPATIC ENCEPHALOPATHY

Qiuyu Cheng[1], Yunhui Liu[2], Gege Wu[3], Zhongyuan Yang[2], Zhongwei Zhang[2], Meng Zhang[2], Tingting Liu[2], Yuxin Niu[1], Deyan Tian[2], Xiaoyun Zhang[2], Xiaoping Luo[3], Xiaojing Wang[1], Tao Chen[1] and Qin Ning[1], (1) Tongji Medical College and State Key Laboratory for Diagnosis and Treatment of Severe Zoonostic Infectious Disease, Huazhong University of Science and Technology, (2)Department of Infectious Diseases, Tongji Hospital, Tongji Medical College and State Key Laboratory for Diagnosis and Treatment of Severe Zoonostic Infectious Disease, Huazhong University of Science and Technology, Wuhan, 430030, Hubei, China, (3)Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Astrocytes and neuronal dysfunction participate in the development of hepatic encephalopathy (HE). We aimed to investigate the association of plasma neurodegenerative biomarkers with minimal HE (MHE) and overt HE (OHE). **Methods:** This proof-of-concept study included 124 hospitalized patients with cirrhosis. The Psychometric Hepatic Encephalopathy Score was used to diagnose MHE. Plasma neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), tau, and ubiquitin carboxy-terminal hydrolase L1 (UCHL1) levels were measured using a single-molecule array. **Results:** A total of 46 patients without prior OHE (n = 109) were diagnosed with MHE. NfL and GFAP levels were significantly higher in patients with MHE than in those without MHE ($P < 0.05$). NfL levels were independently associated with the presence of MHE in multivariable logistic regression analysis (odds ratio 1.013, 95% confidence interval 1.001–1.025; $P < 0.05$). NfL, GFAP, tau, and UCHL1 levels did not differ in patients with and without virus hepatitis-related cirrhosis. NfL and GFAP levels correlated with IL-6 levels (Spearman's r = 0.3 and 0.255, $P < 0.05$, respectively). Tau levels were associated with the MELD score (Spearman's r = 0.236, $P < 0.05$), and plasma UCHL1 levels were correlated with serum albumin and ascites (Spearman's r = -0.219 and 0.281, $P < 0.05$, respectively). However, IL6 levels but not neurodegenerative biomarkers seem to have significant impact on the development of OHE. **Conclusion:** Plasma NfL and GFAP levels were significantly higher in patients with MHE as candidate blood biomarkers.

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3073-A | ESTABLISHMENT OF A NONINVASIVE DIAGNOSIS MODEL OF PORTOPULMONARY HYPERTENSION

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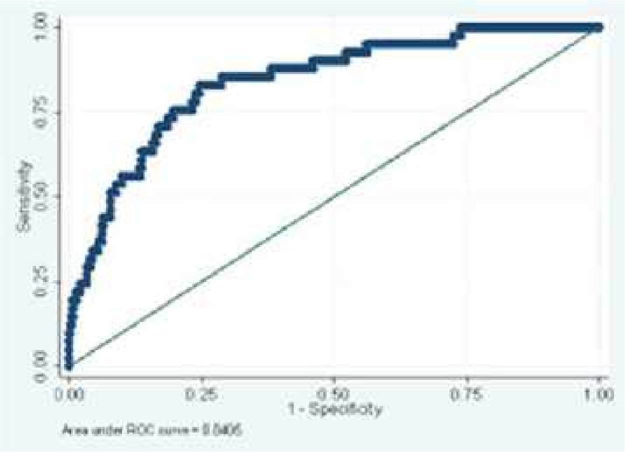
Department of Hepatology, the First Hospital of Jilin University, (2)The First Hospital of Jilin University

Background: Systolic pulmonary artery pressure calculated based on echocardiography provides an objective measure for the noninvasive detection of portopulmonary hypertension(POPH),while echocardiography is not routinely used to assess patients with portal hypertension, and computed tomography (CT)of the lungs is commonly used to judge complications of liver disease. The ESC guidelines recommend the use of the main pulmonary artery diameter (mPAD) measured by CT to help diagnose of pulmonary hypertension. The aim of this study was to develop a non-invasive diagnostic model for suspected POPH patients using mPAD measured by lung CT in combination with routine laboratory indices in hepatology to screen for suspected POPH patients requiring further assessment by cardiac ultrasound at low cost and high accessibility, to improve screening rates and subsequently facilitate early diagnosis and intervention, and to improve clinical prognosis. **Methods:** 493 patients with severe portal hypertension had their cardiac ultrasound and lung CT parameters measured during their hospitalization, and common laboratory parameters were measured. **Results:** A total of 493 patients with severe portal hypertension underwent echocardiography, including 41 patients with suspected POPH (sPAP > 40 mmHg). Age, albumin, mPAD, ascending aortic diameter (aAD), mPAD/aAD, and albumin-bilirubin score (ALBI) were statistically significant ($p < 0.05$) in univariate analysis. Multivariate backward stepwise regression analysis identified albumin, mPAD, splenorenal shunt, and ALBI as independent factors for sPAP > 40 mmHg ($P < 0.05$). The logical diagnostic equation predicting suspected POPH was equation $Y = -3.906 - 0.272$ albumin (g/l) + 0.221 mPAD (mm) + 2.225 (splenorenal shunt: yes = 1, no = 0)-1.929 ALBI. The AUC value for the diagnostic equation was 0.841 (95% CI: 0.779-0.902), indicating that the predicted probabilities from the logical equation were not significantly different from the actual probabilities and were well differentiated. The goodness-of-fit test (Hosmer-Lemeshow test $p = 0.978$) and the clinical decision analysis test performed well. Both the 5-fold and 10-fold cross-validation of the logistic equations showed good predictive performance of the model, with AUCs of 0.8258 and 0.8262 respectively, and good diagnostic performance of the diagnostic formula. **Conclusion:** This study developed a diagnostic model to identify patients with suspected POPH in patients with severe portal hypertension, and the model may assist in screening patients who require further evaluation with cardiac ultrasound or even right heart catheterisation.



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3074-A | ETIOLOGIC DIFFERENCES IN RISK OF HEPATIC DECOMPENSATION AND HEPATOCELLULAR CARCINOMA

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Background: There has been shifting epidemiology for cirrhosis over time, with an increasing proportion of cases due to non-viral etiologies including alcohol (ALD) and NAFLD. The anticipated impact of this change in epidemiology on cirrhosis prognosis is unknown. **Methods:** We included adult patients with cirrhosis at two large urban health systems in the United States. Patients with history of HCC or both ascites and hepatic encephalopathy at baseline were excluded. Our primary outcome was incident hepatic decompensation, defined as new onset hepatic encephalopathy or ascites after index visit, and secondary outcome was development of HCC. We used the Fine-Gray subdistribution hazards model to characterize time to both events, with liver transplantation and death as competing events and multivariable Fine-Gray regression models to identify associated factors. **Results:** We identified 201 patients with cirrhosis, with median age 62 years, 55.7% male. Cohort was diverse regarding race/ethnicity (54.7% White, 11.4% Black, 26.4% Hispanic) and liver disease etiology (24.4% HCV, 22.9% alcohol, and 31.3% NAFLD). During median follow-up of 28.1 months, 39.8% of patients had new hepatic decompensation and 14.4% developed HCC; 8.0% underwent transplant, and 17.9% died. The cumulative incidences of hepatic decompensation and HCC at 1, 2, and 3 years were 16.4% and 6.3%, 24.1% and 8.6%, and 31.6% and 9.2%, respectively. In multivariable analyses adjusted for age, sex, and Child Pugh components, liver disease etiology was significantly associated with both risk of hepatic decompensation and HCC. Compared to HCV infection, patients with NAFLD had higher hazards of hepatic decompensation (subdistribution HR [SHR] 2.01, 95%CI 1.02 – 3.97); ALD also had higher risk, but this did not reach statistical significance (SHR 1.69, 95%CI 0.82 – 3.47). The cumulative incidences of hepatic decompensation by etiology were as follows: HCV infection (30.7), NAFLD (76.2) and ALD (53.5) per 1000 person-years. Conversely, ALD (SHR 0.11, 95%CI 0.02 – 0.48) had lower hazards of HCC compared to HCV infection; HCC risk was lower with NAFLD, but this did not reach statistical significance (SHR 0.44, 95%CI 0.16 – 1.18). The cumulative incidences of HCC by etiology were as follows: HCV infection (36.4), NAFLD (22.9) and ALD (9) per 1000 person-years. **Conclusion:** The changing epidemiology of liver disease will likely result in notable changes in cirrhosis prognosis, with increased incidence of hepatic decompensation and reduced HCC.

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3075-A | FECAL CARRIAGE OF MULTIDRUG-RESISTANT ORGANISMS INCREASES THE RISK OF HEPATIC ENCEPHALOPATHY IN CIRRHOTIC PATIENTS: INSIGHTS FROM GUT MICROBIOTA AND METABOLITE ANALYSIS

Peishan Wu[1,2], Kuei-Chuan Lee[1,3], Pei-Chang Lee[1,3], Yun-Cheng Hsieh[1,3], Yi-Tsung Lin[1,4], Han-Chieh Lin[1,3] and Ming-Chih Hou[1,2,3], (1)Department of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, (2)Endoscopy Center for Diagnosis and Treatment, Taipei Veterans General Hospital, Taipei, Taiwan, (3)Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, (4)Division of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

Background: Multidrug-resistant bacterial infections negatively impact the prognosis in cirrhosis. We aimed to investigate the interaction among fecal carriage of multidrug-resistant organisms (MDROs), gut microbiota, associated metabolites, and clinical outcomes in cirrhosis. **Methods:** A prospective study enrolled 88 cirrhotic patients and 22 healthy adults. Patients were followed for at least one year and the cirrhosis related clinical outcomes were recorded. Cox proportional hazards regression models were used to identify predictors for clinical outcomes. Fecal microbiota were analyzed using 16S rRNA gene sequencing, and untargeted metabolomics analysis of plasma samples was performed on a UPLC-MS platform. **Results:** Cirrhotic patients had higher rates of fecal MDRO carriage compared to healthy population (33% vs. 9.1 %, $p = 0.026$), with ESBL-producing *Escherichia coli* predominance (59%). MDRO carriers had higher serum levels of lipopolysaccharide (LPS) (16.5vs. 12.2 ng/ml, $p = 0.006$) and higher rates of admission within 30 days (34.5% vs 13.6%, $p = 0.002$) than non-carriers. Within one year, 36 patients developed cirrhosis-related complications, and MDRO carriers had higher rates of hepatic encephalopathy (HE) than non-carriers (20.7 vs. 3.4%, $p = 0.008$). Cox-regression analysis identified lower serum levels of sodium (< 139 mmol/L), high levels of LPS (> 13.6 ng/mL) and fecal MDRO carriage as potential predictors for HE. Fecal microbiota analysis showed a marginal decrease in alpha diversity in cirrhotic patients with MDRO colonization, but no statistical significance was observed between MDRO carriers and non-carriers ($p = 0.159$). Nevertheless, a significant dissimilarity of beta diversity on fecal microbiota was observed between healthy control and

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

cirrhotic patients regardless of MDRO carriage ($p = 0.001$), as well as between cirrhotic patients with and without MDRO carriage ($p = 0.033$). LEfSe analysis showed a prominence of Bacilli, Lactobacillales, Lactobacillaceae and Lactobacillus in the feces of cirrhotic patients with MDRO carriage. Associations between differential bacterial metabolites, MDRO carriage, and the development of HE were further investigated, and 32 metabolites were found to be associated with MDROs and the occurrence of HE. Among them, lysine and PS(20:0/24:1(15Z)) were upregulated, while PI (18:1(11Z)/18:1(11Z)) was downregulated in MDRO carriers compared with non-carriers, independently of the severity of cirrhosis. **Conclusion:** Fecal carriage of MDROs may play a role in modifying the gut microbiota and associated metabolites in cirrhosis, potentially contributing to the development of HE in those with MDRO carriage. These findings provide valuable insights in identifying patients who would benefit from aggressive surveillance of fecal MDROs and developing targeted interventions to mitigate the risk of HE.

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3076-A | FIFTEEN-YEAR TRENDS IN THE PREVALENCE OF DECOMPENSATED CIRRHOSIS AND OVERT HEPATIC ENCEPHALOPATHY AMONG MEDICARE BENEFICIARIES IN THE UNITED STATES (2006-2020)

Robert J. Wong[1,2], Patrick Gagnon-Sanschagrin[3], Zeev Heimanson[4], Jessica Maitland[3], Remi Bellefleur[3], Annie Guérin[3], Ankur A Dashputre[5], Brock Bumpass[5], Olamide Olujohungbe[5], Danellys Borroto[5] and George J. Joseph[5], (1)VA Palo Alto Healthcare System, (2) Stanford University School of Medicine, (3)Analysis Group, Inc., (4)Salix Pharmaceuticals, (5)Bausch Health

Background: Development of hepatic decompensation, including overt hepatic encephalopathy (OHE), in patients with cirrhosis is associated with significant morbidity. Understanding the burden of cirrhosis and its complications over time is important to accurately assess healthcare utilization. This study describes the trends in decompensated cirrhosis among Medicare beneficiaries in the United States (US), with a focus on the prevalence of OHE and related hospitalizations and medication use. **Methods:** Medicare beneficiaries aged e 65 with cirrhosis (e 2 diagnoses of cirrhosis or its complications; ICD-9/10 codes) were identified using the 100% Medicare Research Identifiable Files (2006–2020). For each year, the prevalence of decompensated cirrhosis (defined as ascites, variceal bleeding, hepatorenal syndrome, OHE, or spontaneous bacterial peritonitis) and OHE were estimated among patients with cirrhosis who had Medicare enrolment for the entire calendar year. Prevalence of decompensated cirrhosis and OHE among patients with cirrhosis were reported overall and by age and sex. Annual prevalence of OHE medication use (lactulose and/or rifaximin) among patients with cirrhosis and OHE hospitalizations (e 1 inpatient stay with OHE as a primary diagnosis) among patients with OHE were estimated from 2006-2020. **Results:** Among patients with cirrhosis, the prevalence of decompensated cirrhosis grew by 0.9% year-over-year (YOY; $p < 0.001$) from 36.7% in 2006 to 42.7% in 2020; the prevalence of OHE grew by 2.7% YOY ($p < 0.001$) from 14.9% to 20.9%, respectively (Figure). Using multiple sensitivity analyses, the prevalence of OHE among patients with cirrhosis ranged from 20.9% to 31.7% in 2020. The prevalence of OHE appeared higher among males (2006: 15.5%; 2020: 22.2%) than females (2006: 14.5%; 2020: 19.7%) and higher among patients aged 65-74 (2006: 15.8%; 2020: 22.9%) than those e 75 (2006: 13.6%; 2020: 18.2%). Rifaximin utilization among patients with cirrhosis was 1.2% at its approval in 2010, 4.1% in 2014, and 3.1% in 2020. Among patients with OHE, the prevalence of OHE hospitalizations was 36.9% in 2006 and declined to 9.5% in 2020. **Conclusion:** Over the past 15 years, the prevalence of decompensated cirrhosis and OHE has notably increased among Medicare beneficiaries to over 40% and 20%, respectively in 2020. Over this same period, there were declines in OHE hospitalizations, which may reflect improvements in management of OHE. Future studies are warranted to explore the factors contributing to the observed trends.

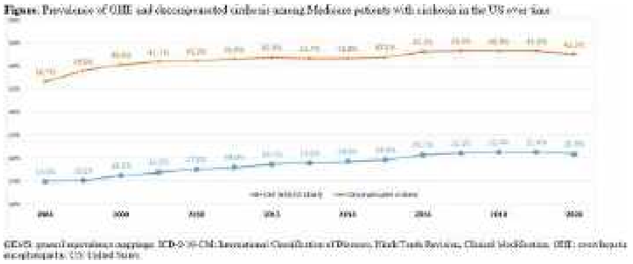

Figure: Prevalence of OHE and decompensated cirrhosis among Medicare patients with cirrhosis in the US over time

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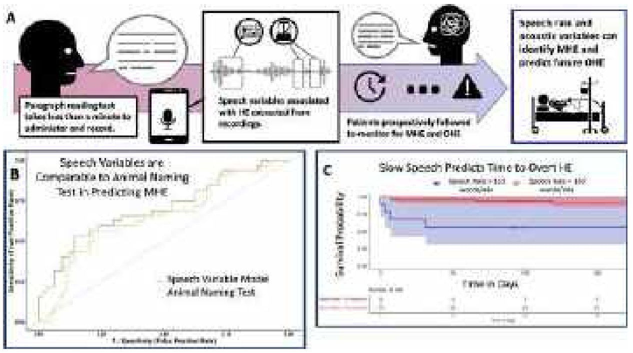
f 3077-A | HEAR-MHE: SPEECH IDENTIFIES MINIMAL HEPATIC ENCEPHALOPATHY AND PREDICTS FUTURE OVERT HEPATIC ENCEPHALOPATHY

Patricia Pringle Bloom[1], Caitlyn Fisher[1], Nazokat Otajonova[2], Luis Garrido-Treviño[3], Aran Farrell[2], Jessica Robin[4], Sumeet Asrani[3] and Anna Lok[5], (1) University of Michigan, (2)Baylor, (3)Baylor University Medical Center, Dallas, TX, (4)Winterlight Labs, (5) University of Michigan Medical Center

Background: There is high demand for a simple diagnostic test to identify minimal hepatic encephalopathy (MHE) or predict future overt HE (OHE). Current tools are burdensome, therefore rarely used in practice. If MHE is identified, treatment can improve quality of life and other outcomes. We aimed to evaluate if recorded speech: 1) correlates with validated HE tests, 2) can diagnose MHE in patients without prior HE, and 3) predicts future OHE. **Methods**: In a prospective study ("HE Audio Recording to Detect MHE" or HEAR-MHE), we enrolled 169 outpatients with cirrhosis from two geographically disparate centers. Patients underwent psychometric HE score (PHES; validated test to diagnose MHE), animal naming test, and audio recording while reading a paragraph. Speech variables (acoustic, lexical, and syntactic) were automatically extracted from the audio recordings via the Winterlight Labs Smartphone analysis platform, an app initially designed to characterize speech in dementia, and immediately transmitted data to the research team via a secure server. Patients were prospectively followed for 6 months to identify OHE episodes. Patients with cirrhosis were in 3 non-overlapping categories: (1) prior OHE + HE treatment, (2) MHE with no prior OHE (diagnosed by PHES d -4), (3) no MHE. Linear, logistic, and Cox regression predicted PHES, MHE, and time to OHE respectively. **Results**: Patients were median 63 years (IQR 55, 68), 52% male, median MELD 9 (IQR 7, 12), 39% had alcohol and 33% fatty liver-related cirrhosis. Audio recordings were median 36 seconds (IQR 33, 41). Speech correlates with PHES: 82 speech variables significantly associated with PHES in the overall cohort ($P < 0.05$ with false discovery rate [FDR] adjustment for multiple testing) – 5 speech tempo and 77 acoustic variables. A model of 5 speech variables (2 speech tempo and 3 acoustic) was strongly associated with PHES ($r^2 = 0.28$, $P < 0.0001$). Speech associates with MHE: 71 speech variables significantly differed between patients with and without MHE (i.e. groups 2 and 3; $P < 0.05$ with FDR adjustment) – 4 speech tempo and 67 acoustic variables. A model of 2 speech variables (1 speech tempo and 1 acoustic) was comparable to animal naming test to identify MHE (AUC 0.70 vs 0.66, $p = 0.19$). Speech predicts future OHE: There were 13 OHE events in 10 patients with cirrhosis (6 with prior OHE, 2 with MHE, 2 without OHE or MHE), median 33 days from enrollment. A model including speech rate and two acoustic variables predicted time to OHE ($P = 0.0001$). Specifically, a speech rate < 133 words/min had significantly shorter time to OHE than e 133 words/min ($HR = 0.11$, $P = 0.001$). **Conclusion**: Recorded speech while reading a paragraph – a quick and easy test – was associated with PHES, was able to identify MHE, and predicted future OHE. Speech is simple to record, provides immediate point-of-care data, and represents a promising biomarker in HE.


A
Paragraph reading task takes less than a minute to administer and record.
Speech variables associated with HE extracted from recordings.
Patients prospectively followed to monitor for MHE and OHE
Speech rate and acoustic variables can identify MHE and predict future OHE
B
Speech Variables are Comparable to Animal Naming Test in Predicting MHE
Speech Variable Model
Animal Naming Test
C
Slow Speech Predicts Time to Overt HE
Survival Probability
Time in Days

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3078-A | IMAGE ANALYSIS OF CARDIAC HEPATOPATHY SECONDARY TO CHRONIC HEART FAILURE: MACHINE LEARNING VERSUS GASTROENTEROLOGY AND RADIOLOGY SPECIALISTS

Suguru Miida[1], Hiroteru Kamimura[2], Hiroki Maruyama[1], Takafumi Tonouchi[1], Norihiro Sakai[2], Yusuke Watanabe[2], Naruhiro Kimura[2], Toru Setsu[2], Hiroyuki Abe[1], Takeshi Yokoo[2], Akira Sakamaki[2], Atsunori Tsuchiya[1], Kenya Kamimura[3] and Shuji Terai[2], (1) Niigata University, (2)Graduate School of Medical and Dental Sciences, Niigata University, (3)School of Medicine, Niigata University

Background: Liver damage secondary to chronic heart failure is called cardiac hepatopathy and is known as nutmeg liver, but its morphological characteristics in terms of medical imaging are not defined and are unclear. We aimed to analyze morphological features of Cardiac Hepatopathy from CT images of the liver using machine learning. Tricuspid regurgitation (TR) was used as an indicator of congestion. **Methods:** A total of 139 patients (90 males, mean age 73.1 ± 14.4 y) who had undergone echocardiography between April 2011 and April 2020 at our hospital and whose liver morphology was confirmed on liver CT images around 2 years were included. To exclude patients with liver damage due to non-cardiac causes, patients who were positive for hepatitis virus, heavy drinkers of alcohol, and autoimmune hepatitis, were excluded. Based on the ultrasonographic findings, patients were classified into three groups (53 patients with mild TR, 66 patients with severe TR, and 20 patients with severe TR). Among the various findings of congestive hepatopathy in CT images, we focused mainly on the dilation of the paraumbilical vein dilation caused by chronic congestion and hepatic right and left lobe diameter. We selected a single-slice CT image at the level where the paraumbilical vein is identifiable, as both lobes of the liver and the dilated findings of the inferior vena cava (IVC) could also be evaluated. We used SONY Neural Network Console to build the multilayer neural network algorithm to predict the severity of TR based on a single-slice CT image of the liver. The model was trained on 105 randomly selected cases as teacher data, and 34 cases were used as test data, and the accuracy was compared with that of four physicians specializing in gastroenterology and 3 physicians specializing in radiology. **Results:** Univariate analysis of blood test findings and echocardiographic data for each severity of TR in the three groups showed significant correlations in ALP, γ-GTP, TRPG (tricuspid regurgitant pressure gradient), and IVC diameter. The average accuracy rate of the specialists was 41.5%, whereas that of the machine learning was 63.9%, which was significantly better image discrimination. **Conclusion:** The results showed that machine learning can capture the morphological characteristics of liver damage associated with heart failure, and may contribute to the elucidation of the heart-liver interaction, which is a new background factor for liver disease in the future.
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3079-A | IMPACT OF OBESITY AND SARCOPENIA WHEN ESTIMATING GLOMERULAR FILTRATION RATE IN PATIENTS WITH COMPENSATED NASH CIRRHOSIS AND PORTAL HYPERTENSION. A NEED FOR POPULATION-SPECIFIC AND RACE-SPECIFIC VALIDATION

Pol Boudes, Galectin Therapeutics, Eric Lawitz, Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX, Don C. Rockey, Medical University of South Carolina, Stephen A Harrison, Pinnacle Clinical Research Center, San Antonio, TX and Naga P. Chalasani, Indiana University School of Medicine

Background: Serum creatinine (sCr) informs about renal function and drives the estimation of glomerular filtration rate (eGFR) by commonly used formulas. As a surrogate of muscle mass, sCr also informs about nutritional status (sarcopenia). In liver cirrhosis, particularly NASH cirrhosis where many patients are hypertensive and diabetics, both altered renal function and sarcopenia may have opposite influence on sCr and the best way to estimate GFR is uncertain. Furthermore, limited data is available in patients with portal hypertension (PH) due to NASH cirrhosis. Hence, we evaluated multiple creatinine-based eGFR equations in these patients. **Methods:** Patients (N = 161) enrolled in a prospective clinical study (NCT 02462967). NASH cirrhosis was confirmed by histology and other etiologies excluded. PH was established with a hepatic

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

venous pressure gradient of at least 6 mm Hg. Patients on non-selective beta-blockers, with previous cirrhosis decompensation, medium or large size varices, a MELD e 15, a Child-Pugh stage B or C, or an eGFR of less than 50 ml/minute estimated by Cockcroft-Gault (C-G) were not eligible. sCr was measured by a central laboratory. GFR was estimated by the C-G (includes age and weight), Modification of Diet in Renal Diseases (MDRD, includes age and sex, adjusted for black race) and Chronic Kidney Disease Epidemiologic collaboration (CKD-EPI 2009, includes age and sex, adjusted for black race), and CKD-EPI 2021 (not adjusted for black race) formulas. Descriptive summaries were provided (overall, by sex and diabetes status) and eGFRs results were compared between formulas. **Results:** The mean (SD) age was 58.4 (8.4) and weight was 98.2 (21) kg, 72% were females, 69% hypertensive, and 61.5% diabetics. All patients were of non-black race. sCr ranged from 27 to 124 μmol/L [normal range 62-124 μmol/L or 0.7-1.4 mg/dL], with a mean of 62.3 (18), 57.6 (17) and 74.6 (15), overall and for females and males, respectively; and 63.6 (16) and 61.5 (20) for non-diabetics and diabetics, respectively. 64.6% of patients had a sCr at or below the normal range for the central laboratory. The mean (SD) estimated GFR in ml/minute for the C-G, MDRD, CKD-EPI 2009 and 2021 were 150.3 (47), 102.3 (30), 95.7 (17), 98.6 (16), respectively. Compared to the MDRD, the C-G overestimated GFR by a mean of 52.8 mL/minute, frequently providing impossibly high values. Compared to CKD-EPI 2009 and 2021, the MDRD differed by more than 10 mL/minute in 40.4% and 50.9% of patients, respectively. **Conclusion:** In NASH cirrhosis with PH, obesity and low sCr confound the results of frequently used eGFR formulas. This could support the use of cystatin C-based formulas in this population. However, none of the eGFR equations, whether cystatin-based or not, have been validated in NASH cirrhosis, including various race/ethnic groups, and a reliable estimation of GFR is urgently needed.

Disclosures: Eric Lawitz – 89Bio Inc., AbbVie, Akero Therapeutics, Allergan, Alnylam Pharmaceuticals Inc., Amgen, Ascelia Pharma, AstraZeneca, Axcella Health, Boehringer Ingelheim, Bristol-Myers Squibb, Conatus Pharmaceuticals, Cymabay Therapeutics, CytoDyn, DSM, Durect Corporation: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Akero, Boehringer Ingelheim, BMS, Intercept, Novo Nordisk, Metacrine, Sagimet, Terns: Advisor, No, No; Abbvie, Gilead Sciences, Intercept: Speaking and Teaching, No, No;

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3080-A | INCREASED HYPERSENSITIVITY TO OXIDATIVE STRESS VIA IMPAIRED Keap1-Nrf2 FUNCTION IN C2C12 MYOTUBES EXPOSED TO AMMONIA

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Background: Sarcopenia exacerbates the prognosis of patients with liver cirrhosis. While hyperammonemia has been reported to impair skeletal muscle through myostatin, the association between skeletal muscle and oxidative stress responses under high levels of ammonia exposure has not been analyzed. This study aimed to investigate the relationship between hyperammonemia and oxidative stress responses in skeletal myotubes. **Methods:** Mouse C2C12 myoblasts were cultured in Dulbecco's Modified Eagle growth medium (DMEM) supplemented with 10% fetal bovine serum and high glucose. Upon reaching confluence, the myoblasts were differentiated into myotubes by replacing the medium with differentiation medium (DM) containing 2% horse serum for 7 days. On day 7 post differentiation, the medium was replaced with either DM or amino acid-modified medium (AMM) with varying concentrations of ammonia. The AMM consisted of the average concentration of plasma amino acids from patients with advanced cirrhosis (Kakazu E, et al. Hepatology. 2009 Dec; 50(6):1936-45), and L-glutamine in the medium was replaced with GlutaMAX™. Protein expression of myosin heavy chain (MYH) and nuclear factor erythroid-2-related factor 2 (Nrf2) was determined using western blotting. ROS levels in C2C12 myotubes and myoblasts were measured using fluorescent staining and flow cytometry. TCA cycle intermediates were measured through absorbance measurements. **Results:** Accurate measurements were challenging in DMEM of DM culture due to the spontaneous generation of ammonia mainly caused by L-glutamine metabolism. However, using AMM medium, in which L-glutamine was replaced with GlutaMAX™, effectively suppressed this phenomenon. The addition of ammonia to the medium decreased MYH protein expression in C2C12 myotubes. Furthermore, ammonia enhanced the accumulation of ROS induced by H_2O_2 in C2C12 cells. While H_2O_2 stimulation increased intranuclear Nrf2 protein expression in C2C12 myotubes, ammonia exposure suppressed this effect. Ammonia addition resulted in decreased levels of certain TCA cycle intermediates, including α-ketoglutarate and fumarate, in C2C12 myotubes. The Keap1-Nrf2 system serves as an important regulatory mechanism of the oxidative stress response. It has been reported that fumarate, a TCA cycle intermediate, alters the structure of the Nrf2 binding site of Keap1, promoting the nuclear translocation of Nrf2. The findings of this study suggest that the reduction of TCA cycle intermediates induced by ammonia in myotubes diminishes the nuclear translocation of Nrf2 and the response to oxidative stress. **Conclusion:** High levels of ammonia induce hypersensitivity to oxidative stress through impaired Keap1-Nrf2 function, resulting from imbalances in TCA cycle intermediates in C2C12 myotubes.

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3081-A | INFLUENCE OF MAFLD ON LONG-TERM OUTMES AFTER VIRAL ERADICATION IN HCV-RELATED CIRRHOSIS WITH PORTAL HYPERTENSION

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Background: The potential influence of co-factors on the course of cirrhosis after etiological therapy is poorly defined. Interferon-free antiviral therapies offer a unique possibility to study the impact of metabolic-dysfunction associated fatty liver disease (MAFLD) on the evolution of patients with HCV-related cirrhosis and portal-hypertension (PH) after achieving sustained virological response (SVR). This study investigates the influence of MAFLD on long-term outcomes after achieving SVR in patients with HCV-related cirrhosis and PH. **Methods:** We investigated a multicenter European cohort of patients previously included in a pooled IPD-analysis (https://doi.org/10.1016/j.jhep.2022.08.025). All had HCV-related cirrhosis with PH at baseline, demonstrated by an HVPG e 6mmHg, and all achieved SVR to antiviral therapy before 2018. Presence of MAFLD according to criteria defined by an international expert consensus (https://doi.org/10.1016/j.jhep.2020.03.039), was investigated at baseline. After SVR patients were followed until June-2022. We investigated whether MAFLD influences the risk of cirrhosis decompensation and mortality in a competing-risk framework. **Results:** 409 patients were included, 70 of them (17%) with MAFLD and 99 (24%). At baseline, metabolic derangements such as obesity, diabetes and arterial-hypertension were more frequent among patients with MAFLD. Baseline Child-Pugh, MELD, HVPG and presence of varices were similar in both groups. Patients with MAFLD less frequently had previous decompensation (13% vs 28%, $P = 0.007$) and NSBBs-therapy (20% vs 35%, $P = 0.017$). During a mean follow-up of 78 months (IQR, 64-85) after SVR, cirrhosis decompensation occurred in 27% MAFLD vs 11% without-MAFLD and death occurred in 29% vs 11%, respectively. The risk of developing decompensating events was higher in patients with MAFLD than in those without ($sHR = 2.49$, 95% $CI = 1.44\text{-}4.29$; $P = 0.001$). The risk of death was also higher in MAFLD-patients ($sHR = 2.64$, $95\%CI = 1.55\text{-}4.47$; $P < 0.001$). The 99 patients (24%) with history of alcohol-consumption had higher risk of decompensation ($sHR = 2.30$, $95\%CI = 1.35\text{-}3.92$; $P = 0.002$) and a non-significantly higher mortality risk ($sHR = 1.41$, $95\%CI = 0.79\text{-}2.50$; $P = 0.245$). Both MAFLD and alcohol consumption were independent predictors of decompensation by competing-risk multivariate regression, while MAFLD and previous decompensation were predictors of death. **Conclusion:** This study shows that, in patients with HCV-related cirrhosis and PH, the presence of MAFLD markedly increases the risks o decompensation and death during long-term follow-up after SVR. This suggests, that MAFLD may constitute a co-factor worsening prognosis in cirrhosis once the primary etiological factor has been removed/suppressed.

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Gallego Moya, Antonio Oliveira, Jose Luis Calleja, Rafael Bañares, Leire Pérez-Latorre, Agustin Albillos, Jose Ignacio Fortea, Xavier Torras Colell, Juan Carlos Garcia-Pagan, Mattias Mandorfer, Xavier Forns, Candido Villanueva Sanchez

3082-A | LONG-CHAIN ACYLCARNITINES PROMOTE MITOCHONDRIAL DYSFUNCTION IN IMMUNE CELLS: ROLE IN PATIENTS WITH ACUTELY DECOMPENSATED CIRRHOSIS

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Background: The hyperinflammatory state of patients with acute decompensation (AD) of cirrhosis is associated with mitochondrial dysfunction, which together represent important drivers of disease progression to acute-on-chronic liver failure. Elevated circulating levels of acylcarnitines predict mortality in these patients. Here, we hypothesize that they are not mere biomarkers of mitochondrial dysfunction but also exert detrimental effects on mitochondria of circulating immune cells. **Methods:** Plasma levels of acylcarnitines were measured in 20 patients with AD cirrhosis and 10 healthy subjects. The effects of selected medium- and long-chain acylcarnitines on mitochondrial function were screened in peripheral leukocytes from healthy donors. Changes in the mitochondrial membrane potential (MMP) and mitochondrial respiration were determined using the cationic dye JC-1 and the Agilent Seahorse XF technology. Mitochondrial ultrastructure was assessed by transmission electron microscopy. Gene expression at the mRNA and protein levels was measured by real-time PCR and Western blot, respectively. **Results:** Acylcarnitine levels were increased in blood of patients with AD cirrhosis in parallel with inflammatory cytokines and chemokines. Among the different acylcarnitines, the long-chain C16:0-carnitine impaired MMP and reduced spare respiration of peripheral mononuclear leukocytes without affecting mitochondria ultrastructure and cell viability. Importantly, C16:0-carnitine induced mitochondrial oxidative stress, suppressed the expression of the antioxidant *HMOX1* gene and increased *CXCL8* expression and IL-8 release in a concentration-dependent manner. The suppressive effect of C16:0-carnitine on *HMOX1* expression was reversed by etomoxir, which blocks the entrance of acylcarnitines into the mitochondrial matrix. Likewise, induction of *CXCL8* by C16:0-carnitine was prevented by the fatty acid beta-oxidation inhibitor trimetazidine. The impairment of mitochondrial membrane potential and mitochondrial oxidative stress associated with C16:0-carnitine was less severe when leukocytes were incubated in the presence of albumin. **Conclusion:** Our results indicate that elevated circulating long-chain acylcarnitines in patients with AD cirrhosis has the potential to actively promote mitochondrial dysfunction in immune cells, thereby contributing to systemic hyperinflammatory responses in these patients.

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3083-A | LONG-TERM EFFICACY AND OUTCOMES OF ORAL L-CARNITINE ADMINISTRATION IN PATIENTS WITH HYPERAMMONEMIA OR HEPATIC ENCEPHALOPATHY: A MULTICENTER RETROSPECTIVE STUDY

Joji Tani, Asahiro Morishita and Tsutomu Masaki, Kagawa University, Faculty of Medicine

Background: Hepatic encephalopathy (HE) is a neuropsychiatric manifestation that can occur in a number of conditions, including acute liver failure, advanced liver cirrhosis (LC) and portosystemic shunt (PSS) . Many patients with HE complain of lethargy, excessive daytime sleepiness, and sleep disturbances, which have a negative impact on their quality of life. There are few data on the long-term efficacy of L-carnitine administration in improving blood ammonia concentration (BAC) and preventing recurrence of HE. **Methods:** This study aimed to determine the effects of long-term L-carnitine administration on BAC and HE. Of 444 patients with L-carnitine administration from April 2012 to March 2021, we enrolled 242 patients with hyperammonemia or HE. A multicenter retrospective study was conducted to determine the long-term efficacy of L-carnitine administration. Using changes in BAC, recurrence rate of HE, number of hospitalizations, and prognosis at follow-up after L-carnitine therapy, we aimed to clarify the medium- and long-term therapeutic effects of L-carnitine on HE and hyperammonemia in a multicenter study. **Results:** Median BAC at the start and at 12, 24, 48, 96,144, and 192 weeks was 123, 95.5, 88, 83, 96, 82, and 86 µg/dL, respectively. BAC were significantly lower than those at the start ($p < 0.05$, respectively). The median improvement time to normalization of BAC was 100 days. The median BAC improvement time was significantly earlier in patients with an initial dose of more than 1500 mg (63 d with more than 1500 mg and 140 d with less than 1500 mg; $p = 0.0034$, log-rank test). The 113 patients with a history of hospitalization for HE followable for 2 years before and after L-carnitine therapy had a total of 183 hospitalizations for HE before treatment, compared with 62 hospitalizations after treatment ($p < 0.001$). The event incidence rate due to HE, such as emergency hospitalization, emergency transport, or additional medications, at 60, 180, 360, 720, and 1080 days after L-carnitine administration was 5.7%, 16.9%, 20.3%, 29.5% and 38.5%, respectively. The change in MELD scores before and after L-carnitine administration was statistically significant, while other variables did not show significant changes. The 180-, 360-, 720-, 1080-, and 1440-day OS rates after oral L-carnitine administration were 78.7%, 69.4%, 52.6%, 46.0%, and 32.8%, respectively. Finally, the median survival time was 880 days. Multivariate analysis revealed that the presence of ascites ($p = 0.0334$), ALBI score ($p = 0.0108$), and history of HCC ($p = 0.0098$) at baseline were significant factors associated with the OS rate. **Conclusion:** We found that oral L-carnitine administration was effective in patients with hyperammonemia or HE, reduced the number of hospital admissions due to HE in our multicenter study. Long-term L-carnitine administration is effective in hyperammonemic patients, and can reduce hospitalizations and events due to HE.

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3084-A | LOW SKELETAL MUSCLE INDEX IS A PREDICTOR OF LIVER-RELATED EVENTS AND MORTALITY IN PATIENTS WITH CIRRHOSIS INDEPENDENTLY OF PORTAL HYPERTENSION

Ikram Abow-Mohamed[1], Balqis Alabdulkarim[1], Xun Zhao[1], Dana Kablawi[1], Estelle Desgagne[1], Marc Deschenes[1], Philip Wong[2], Tianyan Chen[2], Giada Sebastiani[1], Benjamin Rehany[1], Mohamed Abu-Nada[1], David Valenti[1], Ali Bessissow[1] and Amine Benmassaoud[1], (1)Mcgill University Health Centre, (2) Department of Medicine, McGill University Health Centre, Montreal, QC, Canada

Background: Sarcopenia is prevalent in cirrhosis and is linked with mortality. However, its role in relation to portal hypertension is unclear. This study investigated the impact of muscle mass and portal hypertension on major liver events and mortality. **Methods:** This retrospective cohort study included adult patients with cirrhosis and available Hepatic Venous Pressure Gradient (HVPG) from 2012 to 2022. Total skeletal and psoas muscle indices (SMI, PMI) and subcutaneous adipose tissue index (SATI) at the 3rd lumbar vertebrae were measured at the time of HVPG using computed tomography images and *CoreSlicer*, a body composition analysis software. Sarcopenia was defined as SMI $< 39cm^2/m^2$ in females and $< 50cm^2/m^2$ in males and its predictors were assessed by logistic regression. Predictors of (i) new hepatic decompensation (ascites, hepatic encephalopathy, variceal bleeding), (ii) liver-related event (decompensation, hepatocellular carcinoma, liver transplantation, death), and (iii) mortality were assessed by Cox regression analysis. **Results:** Overall, 121 patients were included (46% with sarcopenia, 38% males, mean age 58.3 years, 34% with non-alcoholic fatty liver disease, median HVPG 10mmHg, median Model for end-stage liver disease (MELD) 13, 55% with prior decompensation). Sarcopenia was more likely in those with a prior decompensation (70% vs 43%, $p < 0.003$), lower ALT (21 vs 40, $p < 0.001$), lower PMI ($4.1cm^2/m^2$ vs $5.9cm^2/m^2$, $p < 0.001$), lower SATI ($37.4cm^2/m^2$ vs $76.4cm^2/m^2$, $p < 0.001$). After adjusting for age, prior decompensation, and ALT, SATI was the only independent predictor of sarcopenia (aOR 0.98, 95%CI 0.97-0.99). Over a median follow-up of 14.5 months, 32% of patients had a decompensation, 59% had a liver-related event, and 29% died. For new decompensation, after adjusting for HVPG and MELD, SMI (aHR 0.97, 95%CI 0.94-1.00) and sarcopenia (aHR 1.83, 95% CI 0.95-3.54) tended towards being independent predictors. For liver-related events, after adjusting for HVPG and MELD, SMI was an independent predictor (aHR 0.97, 95%CI 0.95-0.99), but not sarcopenia. For mortality, after adjusting for HVPG and MELD, SMI was significant predictor (aHR 0.96, 95% CI 0.92-0.99) while sarcopenia tended towards significance (aHR 1.95, 95%CI 0.98-3.89) (Table1). **Conclusion:** Our study demonstrates that low SMI is an important predictor of significant liver-related events and mortality, independently of portal hypertension in patients with cirrhosis.

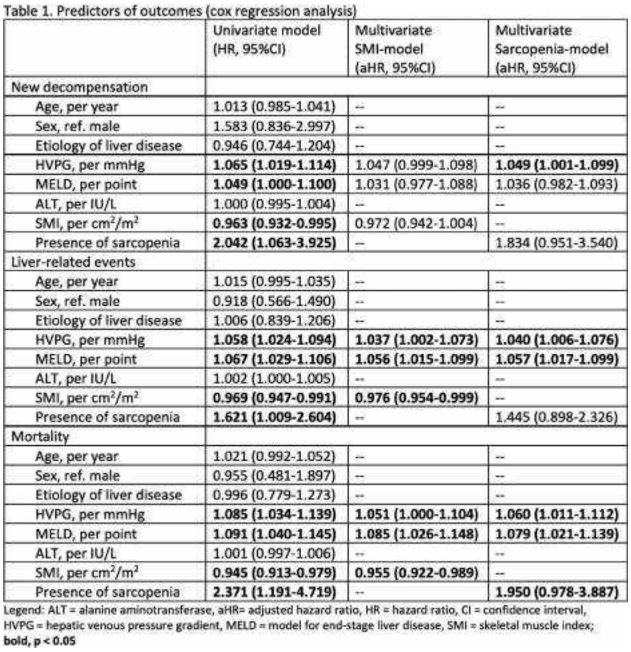

Table 1. Predictors of outcomes (cox regression analysis)

	Univariate model (HR, 95%CI)	Multivariate SMI-model (aHR, 95%CI)	Multivariate Sarcopenia-model (aHR, 95%CI)
New decompensation			
Age, per year	1.013 (0.985-1.041)	--	--
Sex, ref. male	1.583 (0.836-2.997)	--	--
Etiology of liver disease	0.946 (0.744-1.204)	--	--
HVPG, per mmHg	**1.065 (1.019-1.114)**	1.047 (0.999-1.098)	**1.049 (1.001-1.099)**
MELD, per point	**1.049 (1.000-1.100)**	1.031 (0.977-1.088)	1.036 (0.982-1.093)
ALT, per IU/L	1.000 (0.995-1.004)	--	--
SMI, per cm^2/m^2	**0.963 (0.932-0.995)**	0.972 (0.942-1.004)	--
Presence of sarcopenia	**2.042 (1.063-3.925)**	--	1.834 (0.951-3.540)
Liver-related events			
Age, per year	1.015 (0.995-1.035)	--	--
Sex, ref. male	0.918 (0.566-1.490)	--	--
Etiology of liver disease	1.006 (0.839-1.206)	--	--
HVPG, per mmHg	**1.058 (1.024-1.094)**	**1.037 (1.002-1.073)**	**1.040 (1.006-1.076)**
MELD, per point	**1.067 (1.029-1.106)**	**1.056 (1.015-1.099)**	**1.057 (1.017-1.099)**
ALT, per IU/L	1.002 (1.000-1.005)	--	--
SMI, per cm^2/m^2	**0.969 (0.947-0.991)**	**0.976 (0.954-0.999)**	--
Presence of sarcopenia	**1.621 (1.009-2.604)**	--	1.445 (0.898-2.326)
Mortality			
Age, per year	1.021 (0.992-1.052)	--	--
Sex, ref. male	0.955 (0.481-1.897)	--	--
Etiology of liver disease	0.996 (0.779-1.273)	--	--
HVPG, per mmHg	**1.085 (1.034-1.139)**	**1.051 (1.000-1.104)**	**1.060 (1.011-1.112)**
MELD, per point	**1.091 (1.040-1.145)**	**1.085 (1.026-1.148)**	**1.079 (1.021-1.139)**
ALT, per IU/L	1.001 (0.997-1.006)	--	--
SMI, per cm^2/m^2	**0.945 (0.913-0.979)**	**0.955 (0.922-0.989)**	--
Presence of sarcopenia	**2.371 (1.191-4.719)**	--	**1.950 (0.978-3.887)**

Legend: ALT = alanine aminotransferase, aHR= adjusted hazard ratio, HR = hazard ratio, CI = confidence interval, HVPG = hepatic venous pressure gradient, MELD = model for end-stage liver disease, SMI = skeletal muscle index; **bold, $p < 0.05$**

Disclosures: Giada Sebastiani – Merk: Speaking and Teaching, No, No; Gilead: Speaking and Teaching, No, No; Abbvie: Speaking and Teaching, No, No; Novonordisk: Speaking and Teaching, No, No; Pfizer: Speaking and Teaching, No, No; Pfizer: Advisor, No, No; Merk: Advisor, No, No; Novonordisk: Advisor, No, No; Gilead: Advisor, No, No; Theratec: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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3085-A | LOW SUBCUTANEOUS ADIPOSE TISSUE INDEX IS AN INDEPENDENT PREDICTOR OF MORTALITY IN FEMALE PATIENTS WITH CIRRHOSIS

Ikram Abow-Mohamed[1], Balqis Alabdulkarim[1], Xun Zhao[1], Dana Kablawi[1], Estelle Desgagne[1], Marc Deschenes[1], Philip Wong[2], Tianyan Chen[2], Giada Sebastiani[1], Benjamin Rehany[1], Mohamed Abu-Nada[1], David Valenti[1], Ali Bessissow[1] and Amine Benmassaoud[1], (1)Mcgill University Health Centre, (2) Department of Medicine, McGill University Health Centre, Montreal, QC, Canada

Background: Sarcopenia is an established predictor of worse outcomes in patients with cirrhosis. The clinical significance of low adipose tissue mass in this population is not well defined. This study investigated the impact of adipose tissue mass on mortality in patients with cirrhosis **Methods:** This retrospective cohort study included adult patients with cirrhosis and available Hepatic Venous Pressure Gradient (HVPG) from 2012 to 2022. Subcutaneous, visceral, and total adipose tissue indices (SATI, VATI, TATI) and total skeletal and psoas muscle indices (SMI, PMI) at the 3rd lumbar vertebrae were measured at the time of HVPG using computed tomography images and *CoreSlice*r, a body composition analysis software. Sarcopenia was defined as SMI $< 39 cm^2/m^2$ in females and $< 50 cm^2/m^2$ in males. Youden's Index (YI) cut-off was determined using the area under the receiver operating characteristics (AUROC) curves for SATI, VATI, TATI and mortality. Predictors of adipopenia and mortality were assessed by logistic and Cox regression analyses, respectively. **Results:** Overall, 121 patients were included (62% females, mean age 58.3 y, 34% with non-alcoholic fatty liver disease, median HVPG 10mmHg, median Model End-Stage Liver Disease (MELD) 13, 55% with prior decompensation). Over a median follow-up of 14.5 months, 35 (29%) patients died. SATI had highest AUROC (0.64, 95%CI 0.53-0.74) to predict death compared to VATI (ROC = 0.57) and TATI (ROC = 0.61). Based on YI, adipopenia^{SATI} was d $91.98 cm^2/m^2$ (sensitivity 94%, specificity 35%). Adipopenia^{SATI} was present in 89 (74%) patients. Predictors of adipopenia^{SATI} included male sex (OR 0.43, 95%CI 0.19-0.97), prior decompensation (OR 2.70, 95%CI 1.17-6.21), low SMI (OR 0.93, 95%CI 0.89-

0.97), and sarcopenia^{SMI} (OR 2.86, 95%CI 1.19-6.87). After adjustment, male sex (aOR 0.43, 95%CI 0.18-0.99) and sarcopenia^{SMI} (aOR 2.85, 95%CI 1.17-6.94) were independent predictors of adipopenia^{SATI}. For mortality, HVPG (aHR 1.06, 95%CI 1.01-1.11), MELD (aHR 1.09, 95%CI 1.03-1.15), and adipopenia^{SATI} (aHR 4.76, 95%CI 1.13-20.13) remained independent predictors (Table1). When stratified by sex, adipopenia^{SATI} was an independent predictor of mortality only in females (aHR 6.35, 95%CI 1.04-38.65). **Conclusion:** Our study reveals a significant association between low SATI and mortality in female patients with cirrhosis independently of HVPG and MELD. We propose a cut-off to identify adipopenia^{SATI} and allow risk stratification.

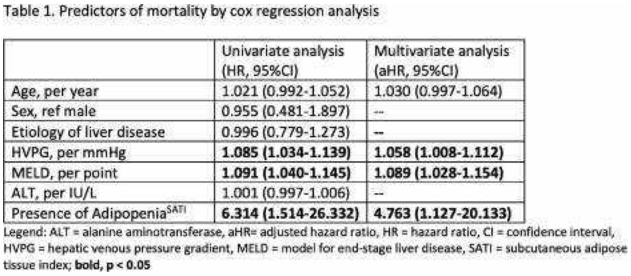

Table 1. Predictors of mortality by cox regression analysis

	Univariate analysis (HR, 95%CI)	Multivariate analysis (aHR, 95%CI)
Age, per year	1.021 (0.992-1.052)	1.030 (0.997-1.064)
Sex, ref male	0.955 (0.481-1.897)	--
Etiology of liver disease	0.996 (0.779-1.273)	--
HVPG, per mmHg	**1.085 (1.034-1.139)**	**1.058 (1.008-1.112)**
MELD, per point	**1.091 (1.040-1.145)**	**1.089 (1.028-1.154)**
ALT, per IU/L	1.001 (0.997-1.006)	--
Presence of Adipopenia^{SATI}	**6.314 (1.514-26.332)**	**4.763 (1.127-20.133)**

Legend: ALT = alanine aminotransferase, aHR= adjusted hazard ratio, HR = hazard ratio, CI = confidence interval, HVPG = hepatic venous pressure gradient, MELD = model for end-stage liver disease, SATI = subcutaneous adipose tissue index; **bold, p < 0.05**

Disclosures: Giada Sebastiani – Merk: Speaking and Teaching, No, No; Gilead: Speaking and Teaching, No, No; Abbvie: Speaking and Teaching, No, No; Novonordisk: Speaking and Teaching, No, No; Pfizer: Speaking and Teaching, No, No; Pfizer: Advisor, No, No; Merk: Advisor, No, No; Novonordisk: Advisor, No, No; Gilead: Advisor, No, No; Theratec: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Ikram Abow-Mohamed, Dana Kablawi, Marc Deschenes, Philip Wong, Tianyan Chen

Disclosure information not available at the time of publication: Balqis Alabdulkarim, Xun Zhao, Estelle Desgagne, Benjamin Rehany, Mohamed Abu-Nada, David Valenti, Ali Bessissow, Amine Benmassaoud

3086-A | LOWER LIVER STIFFNESS MEASUREMENT IN PATIENTS WITH CIRRHOSIS PREDICTS A LOWER RISK OF HEPATIC DECOMPENSATION

Gloria Horta[1], Iyiad Alabdul Razzak[1], Xinyuan Zhang[2], Xuehong Zhang[3], Christopher Danford[4] and Michelle Lai[1], (1)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (2)Brigham and Women's Hospital, Harvard Medical School, (3)Brigham and Women's Hospital, (4)Intermountain Health

Background: Cirrhosis from chronic liver disease is a global health burden with increasing incidence and mortality worldwide (Cheemerla et al., 2021). Once compensated cirrhosis progresses to decompensated disease, the median survival drops significantly from > 12 years to ~2 years, respectively (D'Amico et al., 2006). Vibration-controlled transient elastography (TE) is a commonly used non-invasive test measuring liver stiffness (LSM) used to diagnosis cirrhosis (Braude et al., 2023). In this study, we evaluated the role of TE in stratifying patients with cirrhosis in terms of their risk for developing decompensation. **Methods**: This is a retrospective-prospective cohort study of patients with cirrhosis conducted at the Liver Center of Beth Israel Deaconess Medical Center. A diagnosis of cirrhosis was based on liver biopsy, radiographic features of portal hypertension or nodular liver, prior LSM of > 12 kPa and thrombocytopenia, and/or endoscopic features of portal hypertension. Other historical clinical data relevant to cirrhosis (including comorbidities, prior decompensation events, prior TE results) were extracted. Subject enrollment began in August 2020 with an intended follow-up period of 8 years. Subjects were seen at 6 months intervals after enrollment. At the time of enrollment, all subjects underwent TE by FibroScan (Echosens), and LSMs were recorded in Kilopascals (kPa). We dichotomized subjects into TE < 10 kPa group and TE > = 10kPa group. We used multivariate logistic regression to evaluate whether TE > = 10kPa predicted liver decompensation events (defined as variceal hemorrhage, hepatic encephalopathy, and/or ascites), adjusting for covariates including age, sex, race, primary liver disease, and Child-Pugh score. **Results**: Two hundred sixty-five adult subjects with cirrhosis (mean age = 60; female = 40%) were included. The risk of at least one decompensation event was significantly lower in the TE < 10kPa group (OR: 0.31; 95% CI 0.16-0.60) (Table 1). Subgroup analysis of sixty-one subjects who had a prior TE showed a trend towards lower incidence of complications in subjects who had a decrease in their LSM, however, statistical significance was not reached (OR: 0.16; 95% CI 0.02-1.43). **Conclusion**: In patients with cirrhosis, a LSM < 10 kPa by TE predicts a significantly lower risk of liver decompensation.

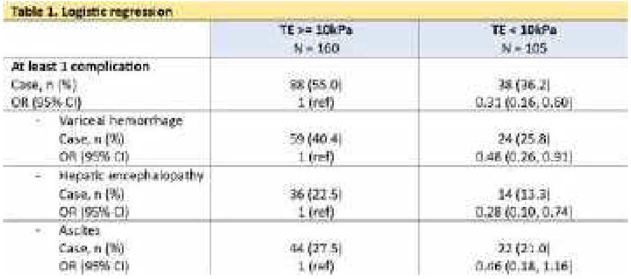

Table 1. Logistic regression

	TE >= 10kPa N = 160	TE < 10kPa N = 105
At least 1 complication		
Case, n (%)	88 (55.0)	38 (36.2)
OR (95% CI)	1 (ref)	0.31 (0.16, 0.60)
- Variceal hemorrhage		
Case, n (%)	59 (40.4)	24 (25.8)
OR (95% CI)	1 (ref)	0.48 (0.26, 0.91)
- Hepatic encephalopathy		
Case, n (%)	36 (22.5)	14 (13.3)
OR (95% CI)	1 (ref)	0.28 (0.10, 0.74)
- Ascites		
Case, n (%)	44 (27.5)	22 (21.0)
OR (95% CI)	1 (ref)	0.46 (0.18, 1.16)

Disclosures: The following people have nothing to disclose: Gloria Horta, Iyiad Alabdul Razzak, Xinyuan Zhang, Xuehong Zhang, Christopher Danford, Michelle Lai

3087-A | MENINGEAL LYMPHANGIOGENESIS IS AN IMPORTANT PHYSIOLOGICAL COMPENSATORY MECHANISM OF HEPATIC ENCEPHALOPATHY IN RATS WITH ADVANCED LIVER CIRRHOSIS

Shao-Jung Hsu[1,2], Hui-Chun Huang[1,2], Ming-Chih Hou[1,2] and Fa-Yauh Lee[1,2], (1)Taipei Veterans General Hospital, Taipei, Taiwan, (2)National Yang Ming Chiao Tung University, Taipei, Taiwan

Background: Hepatic encephalopathy (HE) is a lethal complication of liver cirrhosis and is derived from neuroinflammation and hyperammonemia. Meningeal lymphatics drain the waste and maintain the homeostasis of the brain. Previous study suggested that enhanced meningeal lymphangiogenesis in early cirrhosis ameliorated neuroinflammation and HE. However, meningeal lymphatic function in advanced liver cirrhosis has not been surveyed. This study aimed to evaluate the role of meningeal lymphatic system in advanced liver cirrhosis. **Methods:** Liver cirrhosis was induced in male Sprague-Dawley rats by common bile duct ligation. Early cirrhosis or late cirrhosis developed 4 or 6 weeks after operation, respectively. In addition, sham or deep cervical lymph node ligation was performed in parallel groups with advanced liver cirrhosis to block meningeal lymphatic drainage. **Results:** Rats with advanced liver cirrhosis had more severe portal hypertension, portosystemic collaterals, and hyperammonemia. However, there was no significant differences in the locomotor function and neuroinflammation between early and advanced cirrhotic rats. Interestingly, advanced liver cirrhosis group compared to early cirrhosis had meningeal lymphangiogenesis ($P = 0.047$), increased tracer uptake in brain ($P = 0.045$) and meningeal lymphatic drainage ($P = 0.001$). Blocking meningeal lymphatic drainage by deep cervical lymph nodes ligation inhibited meningeal lymphatic drainage and significantly deteriorated locomotor function and neuroinflammation in rats with advanced liver cirrhosis. **Conclusion:** Meningeal lymphangiogenesis developed in advanced liver cirrhosis and prevented the deterioration of neuroinflammation and hepatic encephalopathy. Meningeal lymphangiogenesis is an important physiological compensatory mechanism of hepatic encephalopathy in advanced liver cirrhosis.

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Disclosure information not available at the time of publication: Hui-Chun Huang, Fa-Yauh Lee

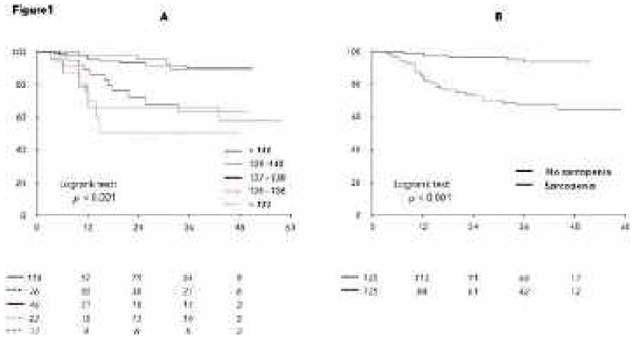
3088-A | MILDLY LOW SERUM LEVEL OF SODIUM IN CHRONIC LIVER DISEASE IS ASSOCIATED WITH SARCOPENIA AND IMPACTS POOR PROGNOSIS: A SINGLE-CENTER RETROSPECTIVE STUDY IN JAPAN

Atsushi Nakamura and Takeshi Ichikawa, Nipponkokan

Background: Recently, there has been growing interest in the association of mild chronic hyponatremia with sarcopenia and life span. Experiments in mouse models have shown that chronic hyponatremia induces hypogonadism and muscle atrophy (*Age 2013*). In chronic liver disease (CLD), hyponatremia is associated with portal hypertension (encephalopathy, ascites) and worse prognosis, and while sarcopenia is considered an independent associated factor with poor prognosis. In this study, we investigated the relationship between serum sodium levels and portal hypertension (PHT), sarcopenia in CLD by analyzing MR elastography (MRE) imaging data. **Methods:** This is a single-center, retrospective study of 741 patients (mean age 62 y, 60% male, 43% viral, 60 HCC) who underwent MRE. Serum sodium levels (mEq/L) were divided into 5 groups: < 135, 135-136, 137-138, 139-140, and > 140. PHT was evaluated by thrombocytopenia (< 150K), varices (any) and ascites (e Grade 1), and sarcopenia was diagnosed by PSMI (M/F: 12.62 / 9.77 cm^2/m^2), which is height-corrected paraspinal muscle area (PSMA) on MRI images (Cureus 2022). The ACLD was defined as F stage 3/4 on MRE. Albumin-bilirubin (ALBI) score was used to evaluate hepatic reserve function, and modified ALBI grade was used to classify severity. **Results:** 1) Serum level of sodium: The 5 groups were 19, 34, 95, 238, and 355 patients, respectively. Thrombocytopenia (%) was 63, 38, 29, 19, 17, varices (%) 57, 50, 30, 14, 12, ascites (%) 47, 32, 16, 5, 3, and sarcopenia (%) 74, 62, 43, 24, 23, all increased at < 139 mEq/L ($p < 0.01$ for each). Mean liver stiffness (LS) in the 5 groups: 6.6 ± 2.7, 5.7 ± 3.8, 4.2 ± 2.6, 3.2 ± 1.8, 3.2 ± 1.8 kPa, with a threshold for LS predicting low sodium (< 139) of e 3.4 kPa (AUC 0.68, $p < 0.01$). The LS thresholds predicting each event of PHT were then e 3.5 kPa for thrombocytopenia, e 4.7 kPa for varices, and e 5.5 kPa for ascites (AUC 0.82 - 0.95, $p < 0.01$ for each), while sarcopenia was e 3.4 kPa (0.67, $p < 0.01$). Multivariate analysis of risk factors for low sodium (< 139) in CLD revealed BUN, LS, ALBI score and sarcopenia ($p < 0.05$ for each). 2) Prognosis in ACLD: Liver-related deaths in 280 patients were 38 (mean follow-up: 27.1M). Kaplan-Meier curves for each serum level of sodium (Fig 1A) showed significantly poor survival at < 139 mEq/L (log-rank test $p < 0.01$). Prognostic analysis of the Cox proportional hazards model showed that mALBI grade

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

2b/3 (HR 6.05, 95%CI 2.42-15.99) and sarcopenia (HR 3.44, 95%CI 1.40-19.28) were poor prognostic factors ($p < 0.05$ both). **Conclusion:** Mild low sodium levels (< 139 mEq/L) in Japanese CLD were associated with PHT, suggesting that the coexistence of sarcopenia may impact poor prognosis.



Disclosures: The following people have nothing to disclose: Atsushi Nakamura, Takeshi Ichikawa

3089-A | MUSCLE FAT INFILTRATION, A POTENTIAL RISK MARKER, INCREASES RAPIDLY IN PATIENTS WITH COMPENSATED LIVER CIRRHOSIS – INTERIM RESULTS FROM THE PROSPECTIVE MULTI-CENTER CIRRHOSIS COHORT STUDY ACCESS-ESLD

Mikael Fredrik Forsgren[1,2], Wile Balkhed[2], Patrik Nasr[2], Daniel Sjögren[3], Jennifer Linge[1,2], Anna Cederborg[2], Markus Holmberg[2], Nils Dahlström[2], Henrik Stjernman[3], Martin Rejler[3], Stergios Kechagias[4], Olof Dahlqvist Leinhard[1,2] and Mattias Ekstedt[4], (1)Amra Medical AB, (2)Linköping University, (3)County Hospital Jönköping, (4)Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

Background: There is an unmet need for accurate and robust biomarkers identifying patients with compensated liver cirrhosis at risk of developing decompensation and other liver-related clinical events. Such biomarkers may also support the development of therapeutic options. A magnetic resonance imaging (MRI) based assessment (Muscle Assessment Score [MAsS]) combining sex-adjusted thigh muscle fat infiltration (MFI) and muscle volume z-score (MVZ), has been developed to describe muscle health. Large population studies have shown that MAsS better predicts physical function and hospitalization than its individual components. MAsS can be used to detect muscle composition (MC) phenotypes, of which the adverse MC (high MFI and low MVZ) independently predict all-cause mortality. The aim was to assess rate of change in MAsS and how MC phenotypes at baseline relates to clinical parameters at baseline and 6-months follow-up in ACCESS-ESLD – a prospective longitudinal multi-center cohort study of patients with liver cirrhosis. **Methods:** MAsS was measured using AMRA® Researcher based on an 8 min MRI acquired on the same day as blood samples and Child-Pugh score (CPT). MC phenotypes were defined according to literature. T-tests were used for statistical testing and mixed-effects modeling to asses the rate of change. **Results:** The first 34 patients (19 males; BMI 29.9 ± 6.6 kg/m^2, age 67 ± 8 yrs; mainly alcohol related cirrhosis and NAFLD, but also hepatitis B and/or C, and autoimmune diseases) with MRI and blood sample analysis at baseline and 6-months were included. MFI increased according to a rate of +0.329 pp/year ($p = 0.008$). There was a non-significant change in MVZ (-0.08 SD/year), see Fig. Compared to all other patients, subjects with the high MFI MC phenotype at baseline had: i) higher bilirubin at 6-months compared to baseline (+1.6 μmol/L, $p = 0.041$), and ii) similar CPT score at baseline (5.5 v. 5.3, $p = 0.432$), but iii) higher CPT score at 6-months (6.1 v. 5.5, $p = 0.034$). Interestingly, two patients had increased CRP of 29 mg/dL (+26 from baseline) and 86 (+84 from baseline) mg/dL at 6-months follow up – both had high MFI (11.8 and 14.6%) at baseline and no other patients had more than 5 mg/dL increase. **Conclusion:** In patients with compensated liver cirrhosis, MFI increased at a rate which is x2-3 higher than observed in general- and type-2 diabetes populations (see Fig), while muscle volume appeared stable in a 6-month time frame. Furthermore, patients with liver cirrhosis and high muscle fat MC phenotype had increased bilirubin levels 6 months later and a mild increase in CPT compared to the patients without the high muscle fat MC phenotype. The results suggest that MAsS, and in particular MFI, could be used for risk stratification of patients with compensated liver cirrhosis.

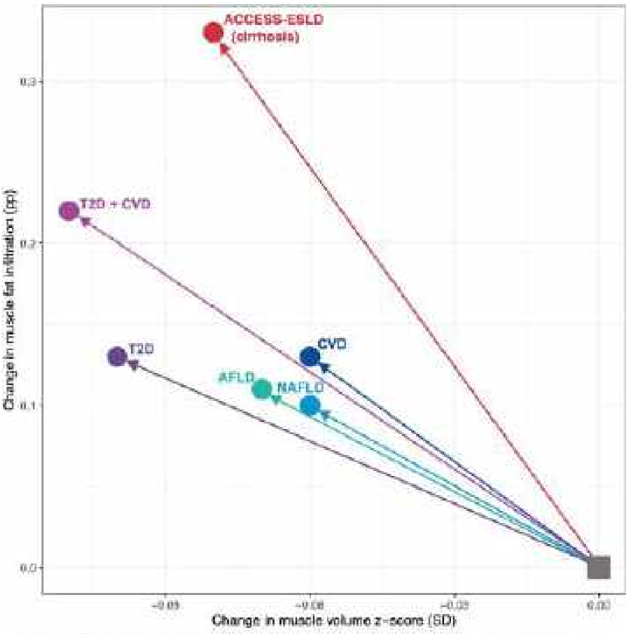


Figure 1 Average 1-year change in muscle composition in ACCESS-ESLD in the context of other disease groups stratified from the longitudinal UK Biobank: non-alcoholic fatty liver disease (NAFLD, N=353), alcoholic fatty liver disease (AFLD, N=350), cardiovascular disease (CVD, N=180), type 2 diabetes (T2D, N=135), and participants with both T2D and CVD (N=17).

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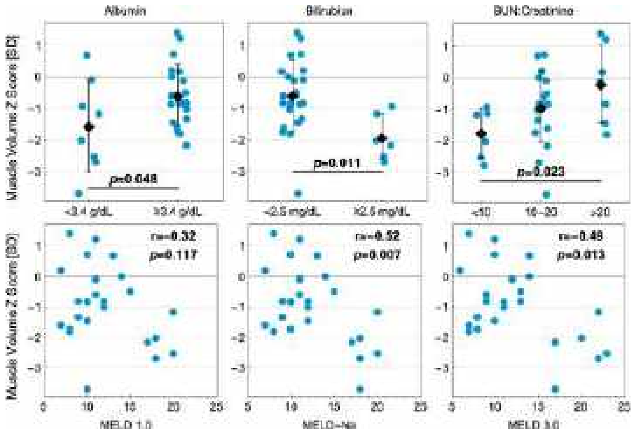
Jennifer Linge – AMRA Medical AB: Employee, Yes, No; Eli Lilly: Consultant, No, No; BioMarin: Speaking and Teaching, No, Yes;
Olof Dahlqvist Leinhard – AMRA Medical AB: Employee, Yes, No; Eli Lilly: Consultant, No, No; Fulcrum Therapeutics: Consultant, No, No; AMRA Medical AB: Stock – privately held company (individual stocks and stock options), Yes, No;
The following people have nothing to disclose: Wile Balkhed, Stergios Kechagias
Disclosure information not available at the time of publication: Patrik Nasr, Daniel Sjögren, Anna Cederborg, Markus Holmberg, Nils Dahlström, Henrik Stjernman, Martin Rejler, Mattias Ekstedt

3090-A | MUSCLE VOLUME Z-SCORE IS LOWER IN HIGH-RISK PATIENTS AWAITING LT – INTERIM RESULTS FROM A LIVER TRANSPLANT WAITLIST NATURAL HISTORY STUDY

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

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



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

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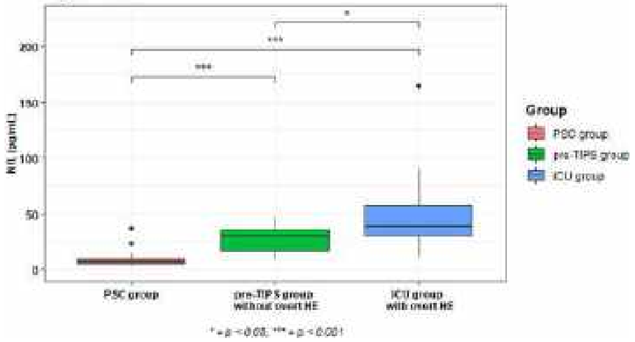
Background: Hepatic encephalopathy (HE) is one of the most frequent complications of cirrhosis. Hyperammonemia plays a key-role in its pathogenesis and is currently the only biomarker in blood supporting the clinical diagnosis. However, ammonia is less suitable for monitoring and predicting HE severity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

Figure 1: NfL



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

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Background: Hepatic encephalopathy (HE) is an important complication of end-stage of liver disease, portending poorer outcomes. The readmission rate of patients with cirrhosis was 20-30% in 30 and 90 days, and the most common reason was HE. Several factors were reported as predictors of readmission in HE patients. However, long-term studies are lacking and few new serological indicators beyond liver parameters have been found. Aiming to explore simple and effective predictors of short- and long-term readmission of HE patients, we performed this retrospective study. **Methods:** We performed a single-center retrospective study of adult patients who were admitted with HE. The primary endpoint was the first liver-related readmission in 30, 90 and 180 days. Logistic regression analysis and multiple linear regression analysis were performed to describe predictors associated with readmission and length of the first hospitalization. **Results:** 424 patients, who were admitted with HE, were included. 24 (5.7%), 63 (14.8%) and 92 (21.7%) patients were readmitted within 30, 90 and 180 days, respectively. 283 (66.7%) were males, and the mean age was 59.9 ± 11.5 years. 120 (28.3%) patients were with alcoholic liver disease (ALD). 40 (9.4%), 246 (58.0%) and 67 (15.8%) patients had hepatocellular carcinoma (HCC), ascites and variceal bleeding at baseline, respectively. Patients readmitted in 180 days were older (62.0 ± 9.6 & 59.3 ± 12.0, $p = 0.008$), with higher proportion of no insurance (27.2% & 15.7%, $p = 0.010$), ALD 37.0% & 25.9%, $p = 0.027$), chronic kidney disease (CKD) (22.8% & 11.7%. $p = 0.007$), HCC (16.3% & 7.5%, $p = 0.012$) and ascites (70.7% & 54.5%, $p = 0.004$) than those without readmission in 180 days. The most common reason of readmission was HE: 15 (62.5%), 30 (47.6%) and 48 (52.1%) patients were readmitted for HE in 30, 90 and 180 days, respectively. Besides, patients who were readmitted had higher level of neutrophil-to-lymphocyte ratio (NLR) at first discharge (8.17 ± 12,1 & 3.95 ± 4.96 ; 7.17 ± 9.72 & 3.67 ± 4.44; 6.80 ± 8.62 & 3.47 ± 4.28 , $p < 0.001$) than those without readmission in 30, 90 or 180 days. In logistic regression analysis, no insurance, ALD, ascites, model for end-stage liver disease (MELD) score and NLR at first discharge were significant predictors of readmission in 30, 90 and 180 days. Besides, age and HCC were also significantly associated with 90- and 180-day readmission (table 1). Variceal bleeding ($p = 0.006$), CKD ($p = 0.003$) and MELD score at discharge ($p = 0.024$) were significantly associated with the length of hospitalization at patients' first admission. **Conclusion:** NLR at discharge was the significant predictor of short- and long-term readmission of patients with HE. CKD was the significant factor affecting the length of hospitalization at the first admission in patients with HE.

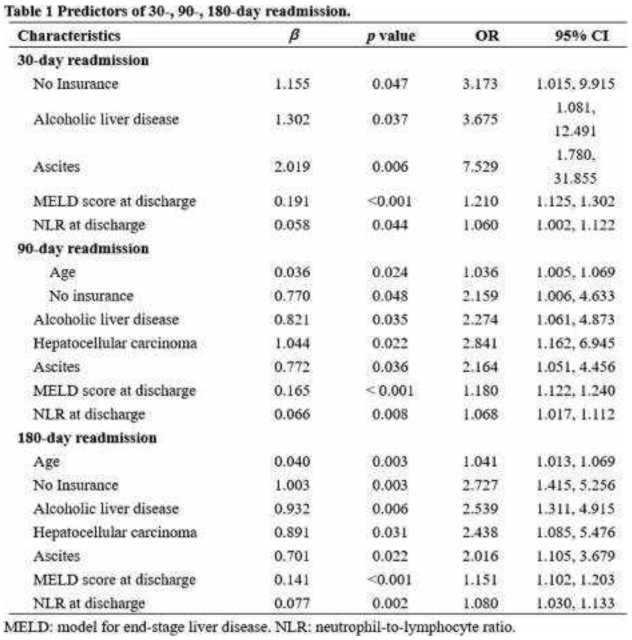

Table 1 Predictors of 30-, 90-, 180-day readmission.

Characteristics	β	*p* value	OR	95% CI
30-day readmission				
No Insurance	1.155	0.047	3.173	1.015, 9.915
Alcoholic liver disease	1.302	0.037	3.675	1.081, 12.491
Ascites	2.019	0.006	7.529	1.780, 31.855
MELD score at discharge	0.191	<0.001	1.210	1.125, 1.302
NLR at discharge	0.058	0.044	1.060	1.002, 1.122
90-day readmission				
Age	0.036	0.024	1.036	1.005, 1.069
No insurance	0.770	0.048	2.159	1.006, 4.633
Alcoholic liver disease	0.821	0.035	2.274	1.061, 4.873
Hepatocellular carcinoma	1.044	0.022	2.841	1.162, 6.945
Ascites	0.772	0.036	2.164	1.051, 4.456
MELD score at discharge	0.165	< 0.001	1.180	1.122, 1.240
NLR at discharge	0.066	0.008	1.068	1.017, 1.112
180-day readmission				
Age	0.040	0.003	1.041	1.013, 1.069
No Insurance	1.003	0.003	2.727	1.415, 5.256
Alcoholic liver disease	0.932	0.006	2.539	1.311, 4.915
Hepatocellular carcinoma	0.891	0.031	2.438	1.085, 5.476
Ascites	0.701	0.022	2.016	1.105, 3.679
MELD score at discharge	0.141	<0.001	1.151	1.102, 1.203
NLR at discharge	0.077	0.002	1.080	1.030, 1.133

MELD: model for end-stage liver disease. NLR: neutrophil-to-lymphocyte ratio.

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3093-A | NONALCOHOLIC FATTY LIVER DISEASE IS A SIGNIFICANT BURDEN AMONG OLDER ADULTS WITH CIRRHOSIS: STUDY OF AN ASIAN COHORT

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Background: As life expectancy is increasing worldwide, the rates of liver transplantation (LT) are also increasing among older adults. In Singapore, however, patients are ineligible for deceased donor liver transplantation beyond the age of 70. Without liver transplantation as a curative treatment option, the burden of liver disease will continue to increase in this cohort of patients. Therefore, it is important to understand the natural history of cirrhosis and decompensated liver disease in an older cohort of patients. The study aim was to describe the clinical outcomes of a cohort of older patients with cirrhosis aged e 70 years, including death. **Methods:** Patients admitted to a large tertiary public hospital in Singapore from January 1-December 31, 2018 with ICD-10 codes for cirrhosis (validated in a prior study) were captured. Various outcomes were tracked via manual chart abstraction by two independent investigators. Outcomes including decompensation were tracked until December 31, 2022. **Results:** Out of 924 distinct patients with cirrhosis, 233 were e 70 years old at the time of admission. Chart review revealed 57.1% patients had decompensated liver disease at time of diagnosis. The most common etiologies of cirrhosis were NAFLD/NASH (30%), Hepatitis B (25%), and cryptogenic cirrhosis (26.6%). During the study period, 174 (74.6%) had at least one decompensating event of which hepatocellular carcinoma was the most common (82 out of 174). Of the study cohort, 58 (27.3%) patients had no other comorbid illness, 99 (42.4%) had at least one comorbidity of which diabetes mellitus was the most common (59.6%), and 76 patients (32.6%) had > 1 comorbidity. Mortality data were also captured as follows: 1 year (17.2%), 3 year (33.9%), 5 year (46.8%). **Conclusion:** The burden of liver disease is significant among older adults, especially those without LT as a treatment option. These data highlight the significant role and burden of fatty liver disease and diabetes in this older cohort of cirrhosis patients and the need not only for care coordination amongst general practitioners and specialists to care for this population but also the need for greater preventive services to address risk factors for diabetes and NAFLD upstream.

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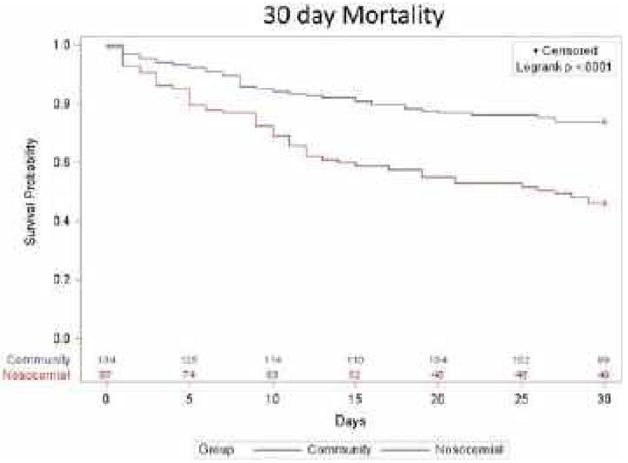
Disclosure information not available at the time of publication: Hiang Keat Tan

3094-A | NOSOCOMIAL SPONTANEOUS BACTERIAL PERITONITIS IS ASSOCIATED WITH INCREASED 30-DAY MORTALITY IN HOSPITALIZED PATIENTS WITH DECOMPENSATED CIRRHOSIS

Laura E. Lavette, Nicolas M. Intagliata and Zachary Henry, University of Virginia

Background: Spontaneous bacterial peritonitis (SBP) is one of the most common causes of infection in decompensated cirrhosis and is associated with high morbidity and mortality. Nosocomial infections have been associated with increased mortality in studies conducted in Europe and Asia; however, data are limited for patients in the United States. We aimed to examine the relative impact of nosocomial SBP (n-SBP) compared to community acquired SBP (ca-SBP) among patients hospitalized at a single center in the United States. **Methods:** Adult patients with cirrhosis and SBP were retrospectively enrolled over an 8-year period. SBP was defined as ascites fluid with $>$250 PMN/mm3 without an alternative explanation for peritonitis. Nosocomial infection was defined as SBP occurring greater than 48 hours after hospitalization. Patients with miscoded diagnoses, non-neutrocytic bacterascites, secondary peritonitis, or SBP diagnosed prior to hospital transfer were excluded. Significant predictors on univariate analysis ($p > 0.05$) were combined in a multivariate analysis. **Results:** Of 554 patients with cirrhosis and peritonitis, 222 met criteria for SBP, 87 cases with n-SBP and 135 cases with ca-SBP. Patients with n-SBP had significantly higher MELD scores at admission as compared to ca-SBP (26 vs 22, $p = 0.02$), longer length of stay (13 d vs 8 d, $p < 0.001$), and were more likely to be admitted to the ICU (49% vs 20%, $p < 0.001$). There was an increased rate of ascites culture positivity in the ca-SBP group as compared to the n-SBP (32% vs 17%, $p = 0.01$), but no significant difference in blood culture positivity or presence of multi-drug resistant organisms. The most common organisms cultured from ascites were Escherichia coli and Klebsiella pneumoniae with no significant differences between the two groups. There was no difference in use of proton pump inhibitors, non-selective beta blockers, or prophylactic antibiotics at admission between groups. Patients with n-SBP had a higher risk of 30-day mortality compared to patients with ca-SBP. On multivariate analysis, n-SBP (OR 2.1, 95% CI 1.1 – 4.0), MELD (OR 1.1, 95% CI 1.04 – 1.12), and admission to the ICU (OR 3.4, 95% CI 1.7 – 6.7) were independent predictors of mortality at 30 days. **Conclusion:** N-SBP is associated with an increased risk of death and is an independent predictor of 30-day mortality in patients with decompensated cirrhosis. Risk factors for the development of n-SBP may include factors such as prior history of SBP, multiple procedures and hospitalizations, and development of acute-on-chronic liver failure. Further study is needed to identify risk factors for n-SBP given the high risk of mortality identified in this cohort.



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3095-A | PARADOXICAL ASSOCIATION OF MELD-NA SCORE AND RATES OF BLOODSTREAM INFECTIONS IN PATIENTS WITH CIRRHOSIS AT AN URBAN INSTITUTION

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Background: The model for end-stage liver disease (MELD-Na) score is a prospectively developed and validated chronic liver disease severity scoring system that uses a patient's laboratory values for serum bilirubin, serum creatinine, and the international normalized ratio (INR), and Sodium level to predict three-month survival. Patients with cirrhosis are at higher risk for infections as compared to the general population. This study aims to determine whether the MELD-Na score can act as a predictor for bloodstream infections (BSI) in patients with cirrhosis. We hypothesize that higher MELD-Na scores will correlate with higher rates of BSI. **Methods:** In our retrospective chart review, patients with cirrhosis over eighteen years of age admitted from 2017 through 2018 were identified by query of the hepatology inpatient and consultation service database. Bloodstream infection (BSI) was defined as patients with microbiologic growth in blood cultures. Patients were excluded if pregnant or immunosuppressed from medication, malignancy, uncontrolled HIV infection, or were using beta-blocker medications. For all study patients, MELD-Na

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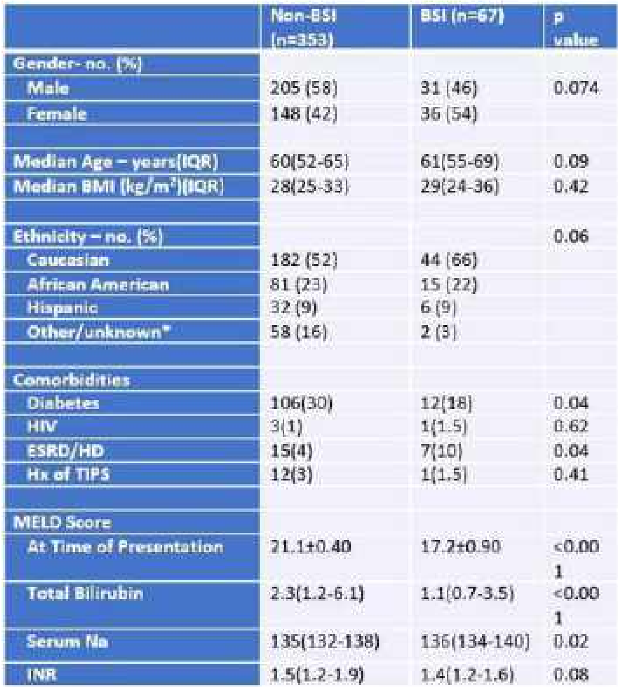
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

scores were collected, and association and comparison between patients with BSI and without were done. Skewed variables were presented as medians (Interquartile range) and compared using the Wilcoxon rank sum test. Multivariable logistic regression was used to assess the independent association of the MELD Score and BSI. **Results:** Of the 420 patients with cirrhosis, the mean age was 59.1 ± 10.9. 44% were female, 54% were Caucasian, 23% were African American and 9% were Hispanic, see the rest of the demographic and clinical parameters stratified by the presence of BSI in table 1. Out of all the patients, 67 (16%) had bloodstream infections. Patients with BSI had significantly lower baseline MELD scores 15 (12-22) vs 21 (15-26) $p < 0.001$. After multivariable logistic regression accounting for age, gender, race, and other potentially associated comorbidities, the baseline MELD score was significantly inversely associated with BSI OR 0.91 95%CI (0.87-0.95) $p < 0.001$. Both the Caucasian race and the presence of ESRD on dialysis were associated with higher odds of BSI (see table 2). Looking at the components of the MELD score aside from renal function, patients with BSI had significantly lower total bilirubin levels, higher sodium and a trend towards lower INR which is congruent with the inverse MELD score association. **Conclusion:** Patients in our cohort with BSI had significantly lower MELD scores compared to those without BSI, this seemingly paradoxical association should be further explored. Individual variables of the MELD-Na score are consistent with this inverse association as well which is perplexing, especially when serum sodium levels are considered.



	Non-BSI (n=353)	BSI (n=67)	p value
Gender- no. (%)			
Male	205 (58)	31 (46)	0.074
Female	148 (42)	36 (54)	
Median Age – years(IQR)	60(52-65)	61(55-69)	0.09
Median BMI (kg/m^2)(IQR)	28(25-33)	29(24-36)	0.42
Ethnicity – no. (%)			0.06
Caucasian	182 (52)	44 (66)	
African American	81 (23)	15 (22)	
Hispanic	32 (9)	6 (9)	
Other/unknown*	58 (16)	2 (3)	
Comorbidities			
Diabetes	106(30)	12(18)	0.04
HIV	3(1)	1(1.5)	0.62
ESRD/HD	15(4)	7(10)	0.04
Hx of TIPS	12(3)	1(1.5)	0.41
MELD Score			
At Time of Presentation	21.1±0.40	17.2±0.90	<0.001
Total Bilirubin	2.3(1.2-6.1)	1.1(0.7-3.5)	<0.001
Serum Na	135(132-138)	136(134-140)	0.02
INR	1.5(1.2-1.9)	1.4(1.2-1.6)	0.08

Disclosures: The following people have nothing to disclose: Nandakumar Mohan, Prutha Shah, Kevin B Lo

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3096-A | PLATELET ENHANCES THE ACCURACY OF SPLEEN STIFFNESS MEASUREMENT AND LIVER STIFFNESS MEASUREMENT TO PREDICT CLINICALLY SIGNIFICANT PORTAL HYPERTENSION IN CIRRHOSIS PATIENTS

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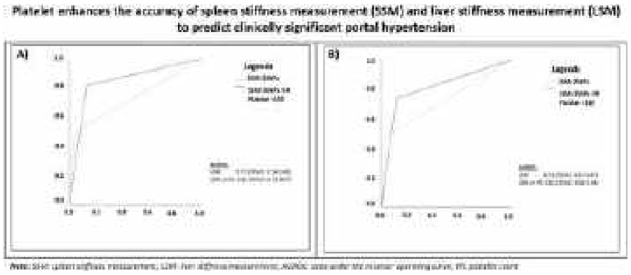
Background: Spleen stiffness measurement (SSM) and liver stiffness measurement (LSM) have been proposed to identify cirrhosis patients with clinically significant portal hypertension (CSPH). The wide adoption of SSM was limited by inconsistent cut-off values, high failure rate in inexperienced operator and obese patients. It was unclear if the combination of platelet could further improve the accuracy of SSM and LSM to predict CSPH in cirrhosis patients. We aim to compare the performance of LSM, SSM, with or without platelet to predict CSPH in cirrhosis patients. **Methods:** We prospectively included cirrhosis patients between May 2022 to January 2023. Both LSM and SSM were performed using 50-Hz vibration-controlled transient elastography (VCTE) after 4 hours of fasting. CSPH was defined as either the presence of gastroesophageal varices, collaterals, ascites, hepatic encephalopathy, or HVPG > 10mmHg. Performance of LSM and SSM were compared across various cirrhosis stages: compensated cirrhosis (CC) without CSPH, CC with CSPH, and decompensated cirrhosis (DC). **Results:** A total of 60 cirrhosis patients (95% Child-Turcotte-Pugh class A, 75% ALBI grade 1, 45% had CSPH) were included. The median (IQR) age was 63 (56-70) and 48% were male. Median (IQR) BMI was 26.9 (23.1-29.5), with 23% being obese. NASH (35%) was the commonest etiology, followed by HBV (32%) and autoimmune (17%). Median (IQR) LSM was 14.0kPa (10.4-22.9); median SSM was 28.9kPa (23.8-51.3). Technical success of LSM and SSM using 50Hz VCTE was 82% and 75%, respectively; 10% require XL probe. The median platelet count was 163x10^9/L (100-207), ALT was 28U/L (21-46), and bilirubin was 13umol/L (7-17), respectively. Both SSM and LSM correlate well with each other ($r = 0.704$, $p < 0.0001$), and increase with progressive cirrhosis stages ($p < 0.05$). Both SSM (AUC: 0.73, 95%CI: 0.58-0.88) and LSM (AUC: 0.72, 95%CI:

0.57-0.87) had comparable accuracy to predict CSPH. Youden index identified SSM > 50kPa and LSM > 25kPa as the optimal cut-off to rule in CSPH. Both SSM > 50kPa and LSM > 25kPa has similar accuracy to rule-in CSPH (specificity: 95.7%-96.2%, PPV: 91.7%). Combination of platelet count (< 140x10^9/L) significantly improves the prediction for CSPH using SSM > 50kPa (AUC: 0.85, 95%CI: 0.72-0.97) or LSM > 25kPa (AUC: 0.81, 95%CI: 0.68-0.94) (Figure 1). **Conclusion:** Both SSM > 50kPa and LSM > 25kPa have good accuracy to rule in CSPH in cirrhosis patients, which was further enhanced with the combination of platelet count.



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3097-A | POST-TIPS RIGHT ATRIAL PRESSURE AND LEFT ATRIAL VOLUME INDEX PREDICT HEART FAILURE AND MORTALITY: DUAL CENTER EXPERIENCE

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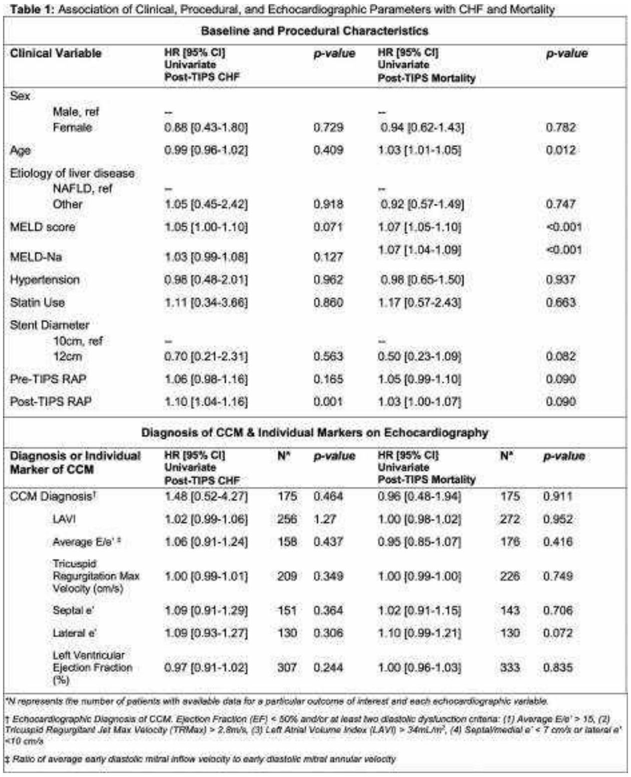
Background: Heart failure (HF) after Transjugular Intrahepatic Portosystemic Shunt (TIPS) occurs in up to 20% of patients within the first year. Understanding factors associated with development of HF among TIPS candidates is critical. We aim to evaluate the utility of hemodynamic measurements obtained immediately pre- and post-TIPS placement (intraprocedural) along with echocardiographic features of cirrhotic cardiomyopathy (CCM) in identifying patients at risk of post-TIPS HF and death. **Methods:** We performed a retrospective cohort study of adult patients seen at two tertiary care centers who underwent TIPS between 2010 and 2015 without pre-existing clinical coronary artery disease or significant valvular heart disease. Time-to-event and landmark analyses were used to assess associations of intraprocedural hemodynamics and pre-/post-TIPS echocardiographic parameters of CCM with HF hospitalization and mortality during 2 years of follow up. **Results:** A total of 360 patients (40% female, 67.5% Caucasian) met study criteria. Alcohol-associated liver disease was the most common etiology of cirrhosis (31.1%). Potential predictors of HF and mortality were analyzed (Table 1). Intraprocedural post-TIPS right atrial pressure (RAP) was associated with increased risk of HF hospitalization on univariate and multivariate analyses accounting for age and MELD (univariate HR 1.10 [1.04-1.16]; multivariate HR 1.10 [1.04-1.17]) per unit mmHg). An intraprocedural post-TIPS RAP cut off value of > 22 mmHg was associated with increased risk for HF (multivariate HR 2.71, p = 0.015, accounting for age and MELD). Pre-TIPS echocardiographic diagnosis of CCM was not associated with HF hospitalization or mortality. However, on landmark analysis of impact of echocardiographic changes within the first 180 days post-TIPS on subsequent mortality, increasing left atrial volume index (LAVI) was associated with increased mortality (HR 1.08 [1.01-1.15] per unit ml/m^2). **Conclusion:** Higher intraprocedural post-TIPS RAP and increase in LAVI after TIPS are associated with HF hospitalization and death, respectively. Echocardiographic features of CCM pre-TIPS were not associated with either outcome. These findings highlight the importance of intraprocedural hemodynamic measures and surveillance echocardiography in identifying patients at risk of HF hospitalization and death. Prospective evaluation of hemodynamic and CCM markers in relation to post-TIPS outcomes is warranted.

Table 1: Association of Clinical, Procedural, and Echocardiographic Parameters with CHF and Mortality



Baseline and Procedural Characteristics				
Clinical Variable	**HR [95% CI] Univariate Post-TIPS CHF**	***p-value***	**HR [95% CI] Univariate Post-TIPS Mortality**	***p-value***
Sex				
Male, ref	--		--	
Female	0.88 [0.43-1.80]	0.729	0.94 [0.62-1.43]	0.782
Age	0.99 [0.96-1.02]	0.409	1.03 [1.01-1.05]	0.012
Etiology of liver disease				
NAFLD, ref	--		--	
Other	1.05 [0.45-2.42]	0.918	0.92 [0.57-1.49]	0.747
MELD score	1.05 [1.00-1.10]	0.071	1.07 [1.05-1.10]	<0.001
MELD-Na	1.03 [0.99-1.08]	0.127	1.07 [1.04-1.09]	<0.001
Hypertension	0.98 [0.48-2.01]	0.962	0.98 [0.65-1.50]	0.937
Statin Use	1.11 [0.34-3.66]	0.860	1.17 [0.57-2.43]	0.663
Stent Diameter				
10cm, ref	--		--	
12cm	0.70 [0.21-2.31]	0.563	0.50 [0.23-1.09]	0.082
Pre-TIPS RAP	1.06 [0.98-1.16]	0.165	1.05 [0.99-1.10]	0.090
Post-TIPS RAP	1.10 [1.04-1.16]	0.001	1.03 [1.00-1.07]	0.090

Diagnosis of CCM & Individual Markers on Echocardiography						
Diagnosis or Individual Marker of CCM	**HR [95% CI] Univariate Post-TIPS CHF**	**N***	***p-value***	**HR [95% CI] Univariate Post-TIPS Mortality**	**N***	***p-value***
CCM Diagnosis†	1.48 [0.52-4.27]	175	0.464	0.96 [0.48-1.94]	175	0.911
LAVI	1.02 [0.99-1.06]	256	1.27	1.00 [0.98-1.02]	272	0.952
Average E/e' ‡	1.06 [0.91-1.24]	158	0.437	0.95 [0.85-1.07]	176	0.416
Tricuspid Regurgitation Max Velocity (cm/s)	1.00 [0.99-1.01]	209	0.349	1.00 [0.99-1.00]	226	0.749
Septal e'	1.09 [0.91-1.29]	151	0.364	1.02 [0.91-1.15]	143	0.706
Lateral e'	1.09 [0.93-1.27]	130	0.306	1.10 [0.99-1.21]	130	0.072
Left Ventricular Ejection Fraction (%)	0.97 [0.91-1.02]	307	0.244	1.00 [0.96-1.03]	333	0.835

**N represents the number of patients with available data for a particular outcome of interest and each echocardiographic variable.*

† Echocardiographic Diagnosis of CCM. Ejection Fraction (EF) < 50% and/or at least two diastolic dysfunction criteria: (1) Average E/e' > 15, (2) Tricuspid Regurgitant Jet Max Velocity (TRMax) > 2.8m/s, (3) Left Atrial Volume Index (LAVI) > 34mL/m², (4) Septal/medial e' < 7 cm/s or lateral e' <10 cm/s

‡ Ratio of average early diastolic mitral inflow velocity to early diastolic mitral annular velocity

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Disclosure information not available at the time of publication: John Laurenzano, Christopher Slaughter, Anthony Borgmann, Deepak Gupta, Nikhilesh Mazumder

3098-A | PREDICTION MODEL OF PORTAL HYPERTENSION USING MACHINE LEARNING ANALYSIS IN CIRRHOSIS PATIENTS

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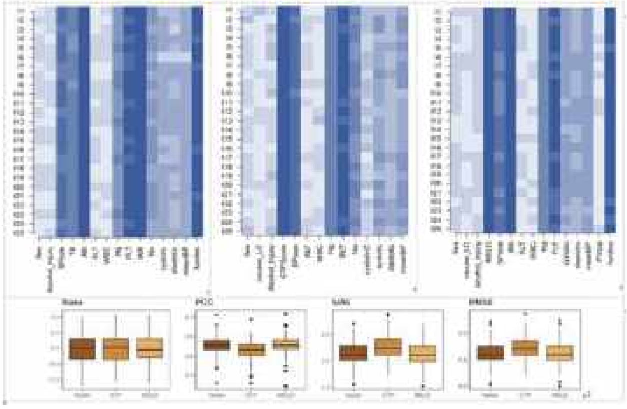
Background: Prediction of portal pressure has a crucial role in management of cirrhosis. Increased portal pressure drives poor outcomes in cirrhosis. Non-invasive methods for liver fibrosis for cirrhosis are widely investigated. However, measurement of hepatic venous pressure gradient is the gold standard for the presence of portal hypertension. Patients should undergo invasive measurement for pressure gradient measurement. We designed the model to predict portal pressure using the non-invasive parameters based on 670 pressure gradient data. **Methods:** We analyzed 670 patients' data who undergo hepatic vein pressure gradient (HVPG) measurement (2000. January – 2014. April). The procedure was performed in a stable state before the patients was planned to discharge. Unbiased manner of statistical was applied to select the HVPG-related predictors. The variable was categorized into continuous or categorical variables using class function in R Base package. Based on unbiased manner, HVPG and candidate features were entered into univariate linear regression (LiR) as independent and dependent variables. Next, specific cut-offs, including actual *p*-value or top ranking based on its ascending ordering, were applied to select the HVPG-related variables. Using the selected predictors and multivariate LiR, the HVPG prediction model was constructed. The multivariate LiR provided a value per a subject as the estimated value of HVPG, and the comparative analyses between the estimates and real HVPG values were conducted. To obtain the generalized finding, random sampling validation was used. The dataset was randomly divided into training and testing datasets with ratio of 0.7 to 0.3. The feature selection and establishment of HVPG estimation model was conducted exclusively using the training dataset. Performance measurement was conducted using the testing dataset. The tasks, including the random dataset split, feature selection, and establishment of HVPG prediction model were iterated at 50 times, yielding fifty lists of the candidate predictors and estimated HVPG values of testing dataset. **Results:** According to the rank-based manner, top 10 features provided the best performance among four cases (top 5, top 10, top 15, and top 20, Figure 1). We established three performance models using each factor, the CTP and MELD score. In factor model, the predictive function using simple factors is not inferior to others. Moreover, MAE (mean absolute error) shows a better result compared to CTP model. In predictive model of CSPH (HVPG e 10mmHg), the AUC was reported to 0.82. **Conclusion:** Increased portal pressure can be accessed by non-invasive parameters and machine learning analysis.



Disclosures: The following people have nothing to disclose: Han Seul Ki, Soon Koo Baik, Moon Young Kim

3099-A | PROGNOSTIC PREDICTABILITY OF SPONTANEOUS BACTERIAL PERITONITIS IN DECOMPENSATED CIRRHOSIS

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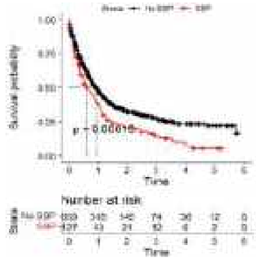
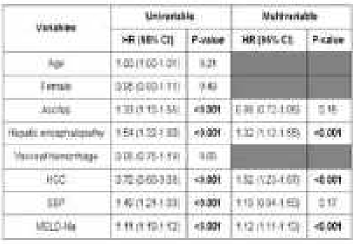
Background: Spontaneous Bacterial Peritonitis (SBP) remains a concerning complication associated with decompensated cirrhosis. Mortality rapidly increases with delayed intervention in the acute setting. Even despite acute resolution, SBP may serve as a predictor of worsened survival long term. Our retrospective analysis aims to investigate the prognostic predictive power of previously treated SBP and whether liver transplant (LT) impacts survival in this population. **Methods:** The study was approved by the Institutional Review Board. A prospectively maintained cohort of adult patients with cirrhosis, being evaluated for LT at our institution, was retrospectively reviewed from 2015-2020. SBP was diagnosed by an absolute neutrophil count (ANC) e 250/µL in ascitic fluid. Outcome of interest was LT or death. Patients were followed from baseline (date of LT evaluation) until last follow-up or death. Censoring occurred at the time of last follow-up. Cumulative incidence of outcomes was determined by the Kaplan-Meier method. Cox proportional hazard regression identified associations between covariates and outcomes. **Results:** 992 patients were evaluated for LT at our institution, of which 127 had SBP. SBP was associated with higher risk of mortality [1.49, 95%CI 1.21-1.83, P-value < 0.001]. The presence of ascites, hepatic encephalopathy (HE), hepatocellular carcinoma (HCC), and higher MELD-Na were also significantly associated with higher mortality (table 1). Survival probability at 1 and 5 years were significantly reduced in the SBP group when compared to the non-SBP group (Figure 1). Further, survival probability at 1- and 5-year time points were < 50% and < 25% respectively in the SBP group (Figure 1). **Conclusion:** Our analysis highlights the association between SBP and worsened survival probability. Given the complex physiology observed in decompensated cirrhosis, several factors may contribute to a worsened survival probability in subjects with known prior SBP. We acknowledge that variation in timing of intervention and non-uniform management of SBP may impact survival.





Variables	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.00 (1.00-1.01)	0.21		
Female	0.95 (0.80-1.11)	0.49		
Ascites	1.33 (1.13-1.56)	<0.001	0.88 (0.72-1.08)	0.18
Hepatic encephalopathy	1.54 (1.32-1.80)	<0.001	1.32 (1.12-1.55)	<0.001
Variceal hemorrhage	0.95 (0.75-1.19)	0.65		
HCC	2.72 (2.60-3.38)	<0.001	1.52 (1.23-1.88)	<0.001
SBP	1.49 (1.21-1.83)	<0.001	1.19 (0.94-1.50)	0.17
MELD-Na	1.11 (1.10-1.12)	<0.001	1.12 (1.11-1.13)	<0.001

Disclosures: The following people have nothing to disclose: Joseph Cappuccio, Karim Osman, Cristina Batarseh, Brenda Amuchi, Amir Ahmed Qamar

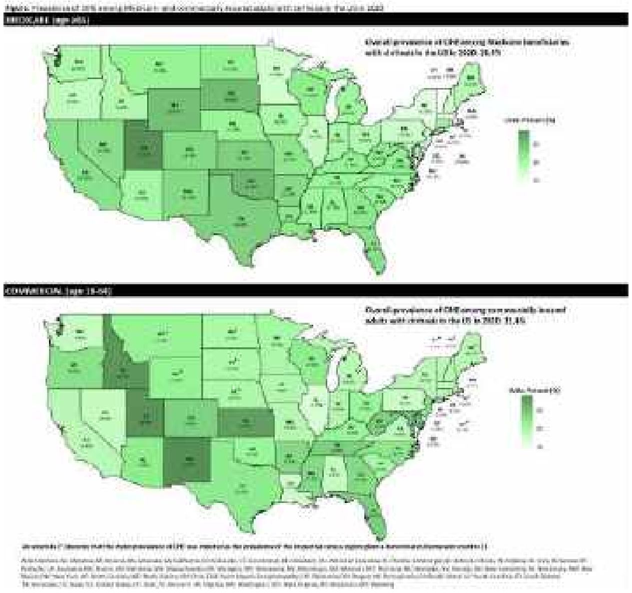
3100-A | REGIONAL VARIATIONS ACROSS THE UNITED STATES IN THE PREVALENCE OF OVERT HEPATIC ENCEPHALOPATHY AND RIFAXIMIN UTILIZATION AMONG COMMERCIALLY AND MEDICARE INSURED ADULTS

Robert J. Wong[1,2], Ankur A Dashputre[3], Patrick Gagnon-Sanschagrin[4], Zeev Heimanson[5], Jessica Maitland[4], Remi Bellefleur[4], Annie Guérin[4], Martha Sikes[3], Brock Bumpass[3], Olamide Olujohungbe[3], Danellys Borroto[3] and George J. Joseph[3], (1)VA Palo Alto Healthcare System, (2)Stanford University School of Medicine, (3)Bausch Health, (4)Analysis Group, Inc., (5)Salix Pharmaceuticals

Background: Overt hepatic encephalopathy (OHE) is a serious complication of liver cirrhosis and rifaximin 550mg is indicated to reduce the risk of OHE recurrence in adults. Regional variations in the prevalence of OHE and rifaximin prescription patterns—which may inform state-specific healthcare policies—are not well characterized. This study describes state-level prevalence of OHE and rifaximin prescriptions among patients with cirrhosis in the United States (US) in 2020. **Methods:** MarketScan Commercial Claims Database (age 18-64) and 100% Medicare Research Identifiable Files (age e 65) were used to identify patients with continuous health plan enrolment for the 2020 calendar year. Prevalent cases of OHE were identified in 2020 as the observed proportion of patients with e 1 diagnosis of OHE among patients with cirrhosis (e 2 diagnoses of cirrhosis or cirrhosis-related complications). Rifaximin utilization was calculated as the proportion of patients with e 1 rifaximin prescription fill in 2020 among patients with cirrhosis. The prevalence of OHE and rifaximin utilization were estimated separately for the commercial and Medicare populations. In states with denominator/

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

numerator counts < 11, the regional prevalence was imputed based on US Census regions. **Results:** In 2020, the overall prevalence of OHE among commercial and Medicare patients with cirrhosis were 21.4% and 20.9%, respectively. Prevalence of OHE ranged across states from 17.3% in Illinois to 28.9% in New Mexico for the commercial population and 14.0% in Vermont to 28.9% in Utah for the Medicare population (Figure). In 2020, the overall prevalence of rifaximin utilization among commercial and Medicare patients with cirrhosis were 6.3% and 3.1%, respectively. Prevalence of rifaximin utilization was generally higher among the commercial population (range: 4.5% in Michigan to 10.6% in Kansas) relative to the Medicare population (range: 2.2% in Arizona to 5.6% in North Dakota). **Conclusion:** One in five patients with cirrhosis in the US were estimated to have OHE in 2020 both in commercially insured and Medicare populations; commercially insured patients had greater utilization of rifaximin despite the similar rates of OHE. Further research is warranted to evaluate possible reasons for state-level variability observed in the prevalence of OHE and rifaximin use, which may reflect state-specific policies, access to healthcare, and patient demographics.



Disclosures: Robert J. Wong – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Exact Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Thera Technologies: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bausch Health: Consultant, No, No; Salix Pharmaceuticals: Consultant, No, No;
Ankur A Dashputre – Bausch Health: Employee, Yes, No;
Patrick Gagnon-Sanschagrin – Analysis Group: Employee, No, No;
Zeev Heimanson – Salix Pharmaceuticals: Employee, Yes, No;
Jessica Maitland – Analysis Group: Employee, No, No;
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Brock Bumpass – Bausch Health: Employee, Yes, No;
Olamide Olujohungbe – Bausch Health: Employee, Yes, No;
Danellys Borroto – Bausch Health: Employee, Yes, No;
George J. Joseph – Bausch Health: Employee, Yes, No;

3101-A | RELATIONSHIP BETWEEN SERUM ZINC LEVELS AND COMPLICATIONS IN PATIENTS WITH CIRRHOSIS COMPLICATED BY HEPATOCELLULAR CARCINOMA

Satoko Sawahashi[1], Akitoshi Sano[2], Jun Inoue[1], Masashi Ninomiya[3], Mio Tsuruoka[3], Kosuke Sato[4] and Atsushi Masamune[3], (1)Tohoku University Hospital, (2) Tohoku University Graduate School of Medicine, Sendai-shi, Japan, (3)Tohoku University Graduate School of Medicine, (4)Tohoku University Graduate School of Medicine, Sendai, Japan

Background: Zinc deficiency is common in patients with cirrhosis, and hypozincemia is known to be a factor influencing hepatic encephalopathy. This study investigated the factors associated with zinc deficiency and complications in patients with cirrhosis complicated by hepatocellular carcinoma (HCC) in our hospital. **Methods:** We studied 731 patients who were admitted to our department for treatment of HCC from July 2008 to June 2021. Fasting blood samples were collected in the early morning after admission. Skeletal muscle mass index (SMI) was calculated by measuring muscle mass at the level of the third lumbar vertebra using the manual trace method from CT scans taken before and after treatment. The cut-off value for zinc was set at 80 μg/dL, according to the Japanese Society of Clinical Nutrition's "Guidelines for the Treatment of Zinc Deficiency 2018". **Results:** Among all patients, zinc deficiency was present in 625 (85.5%). Zinc deficiency was significantly higher in patients taking diuretics ($p < 0.0001$) and in those with hypoalbuminemia ($p < 0.0001$). Serum zinc levels showed a significant negative correlation with plasma ammonia ratio ($R = -0.30$, $p < 0.001$) and a positive correlation with SMI ($R = 0.11$, $p = 0.0039$) and plasma BCAA levels ($R = 0.47$, $p < 0.0001$). Serum ammonia levels were significantly higher ($P < 0.0001$) in individual's with serum zinc levels below 80 µg/dL. In addition, SMI ($p = 0.008$) and plasma BCAA levels ($p = 0.0002$) were also significantly lower in these patients. **Conclusion:** Zinc deficiency was common in patients with cirrhosis complicated by HCC, especially in those taking diuretics and those with hypoalbuminemia. Zinc deficiency was associated with hyperammonemia, lower BCAA levels, and lower SMI. These findings highlight the importance of zinc deficiency in the management of complications in patients with cirrhosis complicated by HCC.

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The following people have nothing to disclose: Satoko Sawahashi, Akitoshi Sano, Masashi Ninomiya, Mio Tsuruoka, Kosuke Sato, Atsushi Masamune

3102-A | RIFAXIMIN REDUCES HEALTHCARE UTILIZATION IN PATIENTS WITH CIRRHOSIS AND RECURRENT EPISODES OF HEPATIC ENCEPHALOPATHY: A RETROSPECTIVE EFFICACY STUDY

Diederick van Doorn[1], Kirsi Van Eekhout[1], Koos De Wit[1], Lubburtus C. Baak[2], Michael Klemt-Kropp[3], Bart Verwer[4], Philip W Friederich[5], Gijs J. De Bruin[6], Xander Vos[7] and Bart Takkenberg[1], (1)Amsterdam University Medical Center, Amsterdam, Netherlands, (2)Olvg, (3) Noordwest Ziekenhuisgroep, Alkmaar, (4)Spaarne Gasthuis, (5)Meander Medical Center, Amersfoort, Netherlands, (6)Tergooi MC, Hilversum-Blaricum, (7) Dijklander Ziekenhuis

Background: Hepatic encephalopathy (HE) is a frequent complication of cirrhosis. Rifaximin has been approved and included in guidelines for secondary prevention of HE, but there are few real-world data on its efficacy and impact on healthcare utilization. In this study, we aimed to assess the efficacy of rifaximin as secondary prophylaxis for HE in Dutch patients. **Methods:** We conducted a retrospective cohort analysis from March 2010 to May 2023 in patients from 7 hospitals in the province of North Holland (The Netherlands) who received rifaximin as secondary prophylaxis for HE. Data were collected and compared six months before and six months after the prescription of rifaximin. The primary endpoint was overall survival (OS). Secondary endpoints were the effect of rifaximin on the number of admissions, admission days, and emergency department visits for complications of cirrhosis. Healthcare utilization was defined as any contact with the hospital. **Results:** We included 108 patients [65% male; median age 67.5 (IQR: 60.3-75.0)] with a median Model for End-stage Liver Disease (MELD) score of 15 (IQR 12-20). Most common etiology was alcoholic liver disease (52%). Median post-prescription follow-up for the entire cohort was 62 months (95%CI 51-73) with 63% being deceased. Median OS was 24 months (95%CI 8.9-39). The mean number of HE episodes after rifaximin was 0.96 and was lower than before rifaximin (2.2; $p < 0.001$). In addition, healthcare utilization decreased from 5.5 contacts in the six months before rifaximin to 3 contacts in the six months after rifaximin ($p < 0.001$). The mean number of hospital admissions decreased from 1.7 admissions per patient ($\pm$ 1.7) before to 1.0 admissions ($\pm$ 1.3; $p = 0.001$) after starting rifaximin, but mean length of hospital stay did not differ. The mean number of outpatient visits decreased from 2.4 visits per patient ($\pm$ 1.9) to 1.8 visits ($\pm$ 1.4; $p = 0.004$). The mean number emergency department presentations without admission decreased from 0.35 per patient ($\pm$ 0.6) to 0.17 ($\pm$ 0.5; $p = 0.039$). **Conclusion:** Prescribing rifaximin as secondary prophylaxis for HE significantly reduces the number of episodes of HE and, consequently, the healthcare utilization of patients.

Disclosures: The following people have nothing to disclose: Diederick van Doorn, Kirsi Van Eekhout, Koos De Wit, Lubburtus C. Baak, Michael Klemt-Kropp, Bart Verwer, Philip W Friederich, Gijs J. De Bruin, Xander Vos, Bart Takkenberg

3103-A | RISK FACTORS AND PROGNOSTIC SCORES ASSOCIATED WITH HEPATOCELLULAR CARCINOMA DEVELOPMENT IN PATIENTS WITH HEPATITIS B VIRUS

Ploutarchos Pastras, Evangelos Zazas, Maria Kalafateli, Ioanna Aggeletopoulou, Efthymios Tsounis, Stavros Kanaloupitis, Konstantinos Zisimopoulos, Eleni-Eirini-Konstantina Kottaridou, Aspasia Antonopoulou, Dimosthenis Drakopoulos, Georgia Diamantopoulou, Aggeliki Tsintoni, Konstantinos Thomopoulos and Christos Triantos, University Hospital of Patras

Background: Hepatitis B virus (HBV) infection constitutes a common cause of hepatocellular carcinoma (HCC) development. The identification of HCC risk factors and the comparison of prognostic scores are essential for early diagnosis and prognosis. The aim of this observational, retrospective study is to evaluate the clinical risk factors associated with HCC in HBV. **Methods:** Seven hundred seventy consecutive adults ($n = 770$) [mean age:48 (range:36-61)] with HBV, referred to our outpatients' Hepatology clinic between

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

01/1993 and 09/2020, were evaluated. Clinical data were examined as potential HCC risk factors and 5 prognostic scores were compared. **Results:** Forty-five patients (4.8%) presented HCC, whereas 725 did not. HCC patients were older ($p < 0.001$, 95%CI:1.071-1.178), were mainly male ($p = 0.001$, 95%CI:2.326-28.644), had increased cirrhosis rate at baseline ($p < 0.001$, 95%CI:4.448-33.017), and alcohol abuse ($p = 0.036$, 95%CI = 1.056-5.216), presented elevated platelets ($p < 0.001$, 95%CI:1.004-1.014), body mass index ($p < 0.711$, 95%CI:0.96-1.03) and HBV DNA ($p < 0.448$, 95%CI = 0.795-1.261) compared to non-HCC patients. The prognostic scores, GAG-HCC (Guide with age, gender, HBV DNA, core promoter mutations and cirrhosis-HCC) (Area = 0.911, 95% CI:0.856-0.967), PAGE-B (Area = 0.856, 95%CI:0.798-0.915), CU-HCC (Chinese University-HCC) (Area = 0.753, 95%CI:0.664-0.841), FIB-4 (fibrosis-4) (Area = 0.769, 95%CI:0.690-0.847), REACH-B (risk estimation for hepatocellular carcinoma in chronic hepatitis B) (Area = 0.804, 95%CI:0.736-0.871) were compared by ROC curve. Kaplan Meier Analysis was only used to GAG-HCC and PAGE-B scores (both $p < 0.001$ in high score for HCC occurrence). **Conclusion:** Most patients who developed HCC were older men, with liver cirrhosis, history of alcohol consumption and lower platelet values. GAG-HCC and PAGE-B scores appear to be reliable prognostic factors for the evaluation of HCC development risk in HBV patients.

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Disclosure information not available at the time of publication: Ploutarchos Pastras, Evangelos Zazas, Maria Kalafateli, Ioanna Aggeletopoulou, Efthymios Tsounis, Stavros Kanaloupitis, Konstantinos Zisimopoulos, Eleni-Eirini-Konstantina Kottaridou, Aspasia Antonopoulou, Dimosthenis Drakopoulos, Georgia Diamantopoulou, Aggeliki Tsintoni, Konstantinos Thomopoulos

3104-A | SLEEP DISTURBANCE IN PATIENTS WITH CIRRHOSIS AND TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

Ming Zhao, Xuefeng Luo, Xiaoze Wang and Yuling Yan, West China Hospital, Sichuan University

Background: Sleep disturbance (SD) is common in patients with cirrhosis and may lead to poor quality of life. Data regarding post-TIPS SD is scarce. The present study was designed to investigate the incidence and outcomes of post-TIPS SD. **Methods:** From August 2018 to November 2019, 73 patients treated with TIPS were prospectively enrolled. The Pittsburgh Sleep Quality Index (PSQI) used to assess sleep quality, and the presence of hepatic encephalopathy was evaluated using the West Haven criteria before and after TIPS. The primary outcome was the incidence of SD after TIPS. **Results:** 19 patients (26%) were the new onset of SD after TIPS and the median time from TIPS creation to the occurrence was 67 (40-98) days. Minimal hepatic encephalopathy (MHE) after TIPS (OR = 3;95% CI 1,8.78; $P = 0.046$) was demonstrated as an independent risk factor for SD. Five of six (83%) patients with SD improved after treatment with eszopiclone. Ten of thirteen (77%) patients with SD improved spontaneously without treatment. The incidence of MHE in patients with SD was higher than that in patients without SD (58% vs 31%, $P = 0.04$). **Conclusion:** The incidence of SD is not uncommon in patients who underwent TIPS. MHE is an independent risk factor associated with post-TIPS SD. Eszopiclone may be effective and safe for patients with SD after TIPS. ClincialTrials.gov number, NCT03685994.

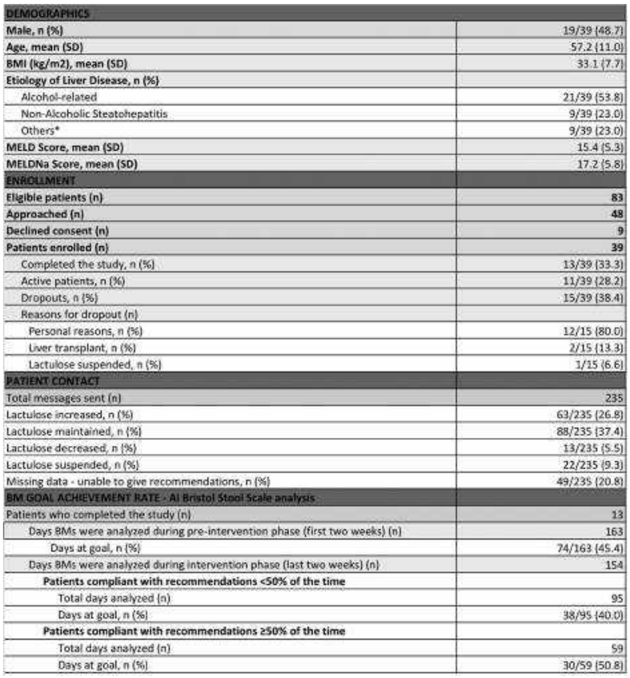
Disclosures: The following people have nothing to disclose: Ming Zhao, Xuefeng Luo, Yuling Yan

Disclosure information not available at the time of publication: Xiaoze Wang

3105-A | SMARTPHONE APPLICATION BASED LACTULOSE TITRATION FOR PREVENTION OF HEPATIC ENCEPHALOPATHY

Beatriz Sordi Chara[1], Kamalpreet S. Hara[2], Daniel Penrice[2], Kathryn A. Schmidt[1], Asaf Kraus[3], Jacob Anstey[3], David Tiede[3], Vijay Shah[2], Patrick S. Kamath[1] and Douglas A. Simonetto[2], (1)Mayo Clinic, Rochester, MN, (2)Mayo Clinic Rochester, Rochester, MN, (3)Dieta Health, Oak Park, CA

Background: Lactulose is the first line treatment for Hepatic Encephalopathy (HE). Patients are instructed to self-titrate to achieve 2 to 4 bowel movements (BM) per day. The mobile application “Dieta Health” is a digestive health tracking tool designed to analyze pictures of stools taken by users and provide an Artificial Intelligence (AI) derived interpretation of the stool characteristics, including the Bristol Stool Scale (BSS). In this pilot study, we enrolled subjects prescribed lactulose to determine if an AI enabled application could improve the rate at which patients met BM goals and the acceptance of such tool in this population. **Methods**: Our study included patients with cirrhosis receiving lactulose for prevention of HE, who were being followed at the Hepatobiliary Clinic at Mayo Clinic Rochester. The participants downloaded the Dieta app on their smartphones and were instructed to capture pictures of BM during the 4-week study period. Surveys were delivered to track daily intake of lactulose. During the first 14 days (lead-in phase), data was collected but no intervention was performed. For the last 2 weeks (intervention phase), patients received daily lactulose dose recommendations, according to a decision algorithm that considered the BM frequency and BSS from the previous 24 hours, with a goal range BM target of 2-4 per day in the BSS 3-5 range. Compliance with the recommendations was classified as low if followed $<$ 50% of the time, and high, e 50% of the time. **Results**: Currently, 39/50 patients have been enrolled, 24 (61.5%) completed/active in the study, and 15 (38.4%) dropouts. Two subjects received liver transplant during the period, and the rest dropped out due to individual reasons. Out of 235 recommendations sent, 63 (26.8%) suggested increasing dose, 88 (37.4%) maintaining current dose, and 35 (14.8%) had subjects decrease or stop lactulose for the day. Among the 13 patients who have completed the study, 74/163 (45.4%) represented days at goal for BM during the lead phase. During the intervention phase, patients with high compliance with the recommendations showed 30/59 (50.8%) days at goal. While low compliant patients were at goal for 38/95 (40.0%) days. Patients were compliant with image uploading, on average, 94% of the time. Average compliance with recommendations on the days image data was uploaded reached 43.6%. The End of Study Survey revealed that most patients (76.8%) found the app user-friendly, and (69.1%) found recommendations helpful. Nine (75%) subjects would always recommend the app, and 7 (53.7%) felt that symptoms were better controlled while using the application. **Conclusion**: This feasibility pilot study suggests that stool image assessment through a smartphone application may be a useful tool for accurate determination of BSS and personalized daily lactulose titration. Future iterations of the existing app interface, based on patient subject will likely improve patients` satisfaction and compliance.



DEMOGRAPHICS	
Male, n (%)	19/39 (48.7)
Age, mean (SD)	57.2 (11.0)
BMI (kg/m2), mean (SD)	33.1 (7.7)
Etiology of Liver Disease, n (%)	
Alcohol-related	21/39 (53.8)
Non-Alcoholic Steatohepatitis	9/39 (23.0)
Others*	9/39 (23.0)
MELD Score, mean (SD)	15.4 (5.3)
MELDNa Score, mean (SD)	17.2 (5.8)
ENROLLMENT	
Eligible patients (n)	83
Approached (n)	48
Declined consent (n)	9
Patients enrolled (n)	39
Completed the study, n (%)	13/39 (33.3)
Active patients, n (%)	11/39 (28.2)
Dropouts, n (%)	15/39 (38.4)
Reasons for dropout (n)	
Personal reasons, n (%)	12/15 (80.0)
Liver transplant, n (%)	2/15 (13.3)
Lactulose suspended, n (%)	1/15 (6.6)
PATIENT CONTACT	
Total messages sent (n)	235
Lactulose increased, n (%)	63/235 (26.8)
Lactulose maintained, n (%)	88/235 (37.4)
Lactulose decreased, n (%)	13/235 (5.5)
Lactulose suspended, n (%)	22/235 (9.3)
Missing data - unable to give recommendations, n (%)	49/235 (20.8)
BM GOAL ACHIEVEMENT RATE - AI Bristol Stool Scale analysis	
Patients who completed the study (n)	13
Days BMs were analyzed during pre-intervention phase (first two weeks) (n)	163
Days at goal, n (%)	74/163 (45.4)
Days BMs were analyzed during intervention phase (last two weeks) (n)	154
Patients compliant with recommendations <50% of the time	
Total days analyzed (n)	95
Days at goal, n (%)	38/95 (40.0)
Patients compliant with recommendations ≥50% of the time	
Total days analyzed (n)	59
Days at goal, n (%)	30/59 (50.8)

Disclosures: The following people have nothing to disclose: Beatriz Sordi Chara, Kamalpreet S. Hara, Daniel Penrice, Vijay Shah, Douglas A. Simonetto

Disclosure information not available at the time of publication: Kathryn A. Schmidt, Asaf Kraus, Jacob Anstey, David Tiede, Patrick S. Kamath

3106-A | SPONTANEOUS PORTOSYSTEMIC SHUNTS AS A THERAPEUTIC TARGET FOR PORTOPULMONARY HYPERTENSION

Tsuyoshi Ishikawa[1], Natsuko Nishiyama[1], Maho Egusa[1], Tsuyoshi Fujioka[1], Daiki Kawamoto[1], Ryo Sasaki[1], Tatsuro Nishimura[1], Norikazu Tanabe[1], Issei Saeki[1] and Taro Takami[2], (1)Yamaguchi University Graduate School of Medicine, (2)-

Background: Spontaneous portosystemic shunts (PSSs) have been reported to contribute to the onset of portopulmonary hypertension (PoPH) via pulmonary arterial pressure elevation by increasing pulmonary flow volume due to progressive hyperdynamic circulation and pulmonary vascular resistance following vasoactive factor-mediated pulmonary vasoconstriction. The present study aimed to investigate changes in pulmonary hemodynamics and vasoactive factors by PSS occlusion and to demonstrate the effects of balloon-occluded retrograde transvenous obliteration (BRTO) on cardiopulmonary circulation in portal hypertension. **Methods:** This retrospective study included 40 patients with portal hypertension and spontaneous PSSs (median PSS diameter: 13.56 mm) who underwent BRTO at our hospital. Blood examination, chest computed tomography (CT), and transthoracic echocardiography (TTE) were performed before and 1 month after the procedure. We statistically analyzed the changes in serological and hemodynamic parameters by BRTO. **Results:** PSS occlusion led to significantly decreased levels of brain natriuretic peptide (53.9 to 40.0 pg/mL, $p < 0.05$), endothelin-1 (ET-1: 1.62 to 1.31 pg/mL, $p < 0.01$), and 5-hydroxytryptamine (52.6 to 45.5 ng/mL, $p < 0.05$). BRTO resulted in a significant reduction in the main pulmonary artery diameter (mPA-D: 26.5 to 25.6 mm, $p < 0.01$), mPA-D to ascending aorta diameter ratio (mPA-D/aAo-D: 0.83 to 0.81, $p < 0.05$), and inferior vena cava diameter (IVC-D: 18.4 to 17.7 mm, $p < 0.01$), as observed on the chest CT. TTE showed a decrease in tricuspid regurgitation pressure gradient (TRPG: 27.5 to 24.9 mmHg, $p = 0.06$) by the occlusion of PSSs. Additionally, reductions in mPA-D, mPA-D/aAo-D, and TRPG following BRTO were equivalent in patients with PSS e 13.56 mm (large PSS group, $n = 20$) and those with PSS $<$ 13.56 mm (small PSS group, $n = 20$). However, postoperatively, a significant decrease in

IVC-D (18.1 to 17.4 mm, $p < 0.01$) was observed only in the large PSS group; conversely, a significant decrease in ET-1 levels (1.56 to 1.09 pg/mL, $p < 0.01$) was observed only in the small PSS group, suggesting a different mechanism for regulating pulmonary hemodynamics by the PSS diameter. **Conclusion:** Besides preventing vasoactive factors from entering the pulmonary circulation without being inactivated by hepatic metabolism, BRTO may also decrease pulmonary flow volume, thereby improving cardiopulmonary hemodynamics. Thus, PSS occlusion could be a potential therapy for PoPH through pulmonary flow control and vasoactive factor regulation regardless of the degree of portosystemic shunting.

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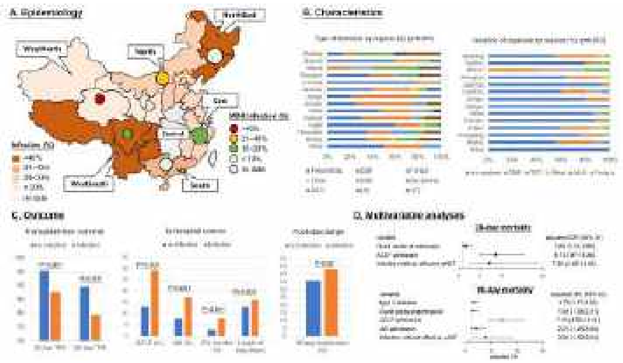
3107-A | STUDY OF INFECTIONS IN HOSPITALIZED PATIENTS WITH CIRRHOSIS IN CHINA: A PROSPECTIVE COHORT STUDY FOR THE SONIC CONSORTIUM

Zhujun Cao[1], Huadong Yan[2], Yingling Wang[3], Xiaoguang Dou[4], Yang Ding[4], Qinghua Meng[5], Wei Zhang[5], Minghua Lin[6], Haibin Gao[6], Yongchao Xian[7], Jin Guan[7], Xiaoping Wu[8], Lingling Lai[8], Yuerong Zhang[9], Ning Zhou[9], Caiyan Zhao[10], Ziyue Li[10], Honying Pan[11], Dujing Bao[11], Yongping Chen[12], Yi Chen[12], Chenghai Liu[13], Yongping Mu[13], Peng Hu[14], Huan Deng[14], Xiaorong Mao[15], Ni Jiang[15], Jiabin Li[16], Yufeng Gao[16], Xinsheng Xie[17], Min Deng[17], Lihua Huang[18], Yiguang Li[18], Minghua Su[19], Huan Liang[19], Yingren Zhao[20], Taotao Yan[20], Longgen Liu[21], Dongmei Zhu[21], Qin Zhang[22], Rongkun Yin[22], Lijuan Ouyang[23], Yuqian Hong[23], Chuanwu Zhu[24], Yaoren Hu[2], Qing Xie[25] and SONIC Consortium, (1)Department of Infectious Disease, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, (2)Department of Hepatology, Key Laboratory of Diagnosis and Treatment of Digestive System Tumors of Zhejiang Province, Hwamei Hospital, Ningbo No.2 Hospital, University of Chinese Academy of Sciences, (3) Department of Infectious Diseases, the Fifth People's Hospital of Suzhou, (4)Shengjing Hospital of China Medical University, Liaoning, China, (5)Department of Critical Care Medicine of Liver Disease, Beijing You'an Hospital, Capital Medical University, Beijing, China, (6) Department of Severe Liver Diseases, Fuzhou Municipal Infectious Disease Hospital, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fujian, China, (7)The Third People's Hospital of Guilin, Guilin, Guangxi, China, (8)The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China, (9)The First People's Hospital of Lanzhou City, Lanzhou, Gansu, China, (10)Department of Infectious Diseases, Third Affiliated Hospital of Hebei Medical University, Shijiazhuang, Hebei, China, (11)Department of Infectious Diseases, Zhejiang Provincial People's Hospital, Zhejiang, China, (12)First Affiliated Hospital, Wenzhou Medical University, Zhejiang, China, (13) Department of Cirrhosis, Institute of Liver Disease, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, (14)Second Affiliated Hospital of Chongqing Medical University, Chongqing, China, (15)Department of Infectious Disease, the First Hospital of Lanzhou University, Lanzhou, Gansu, China, (16)First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China, (17)The First Hospital of Jiaxing, Zhejiang, China, (18)The Fifth People's Hospital of Wuxi, Affiliated to Jiangnan University, Wuxi, Jiangsu, China, (19)Department of Infectious Disease, the First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China, (20)Department of Infectious Diseases, First Affiliated Hospital of Xi'an Jiaotong University, Shanxi, China, (21)Department of Liver Diseases, the Third People's Hospital of Changzhou, Changzhou, Jiangsu, China, (22)Department of Hepatology and Infection, Tongren Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, (23)Xiamen Hospital of Traditional Chinese Medicine, Xiamen, Fujian, China, (24)The Affiliated Infectious Diseases Hospital of Soochow University, Suzhou, Jiangsu, China., (25) Ruijin Hospital, Shanghai Jiao Tong University School of Medicine

Background: Bacterial infections in cirrhosis are linked to higher mortality. The global burden of multi-drug resistance (MDR) is on the rise but regional data in China remains unavailable. We aimed to investigate infection and impact of regional variations on outcome across a national population of inpts with cirrhosis. **Methods**: We collected data from pts non-electively admitted with cirrhosis at 23 centers in China from 2018 to 2019. Data were collected for demographics, comorbidities, etiology of cirrhosis, cause of admission, medical history and hospital course. All infections were confirmed with prespecified criteria and clinically suspected without evidence were excluded. Once infection was diagnosed, the characteristics, microbiology, antibiotic and outcome data were collected. Patients were followed until death, transplantation, or 90-day post-discharge. **Results**: Infection was confirmed in 342 of 1294 pts (26%) among from 6 administrative regions. Infection characteristics A total of 372 episodes (#) of infection were confirmed with balanced source of acquisition (31% community, 39% health-care, 30% nosocomial). No.1 type was pneumonia (45%) followed by SBP (23%) and spontaneous bacteremia (11%). Organisms were identified in 106 # (29%) with 62% GNB, 20% GPC and 9% fungi. MDR was confirmed in 14% of all # and 57% in # with isolated organisms. Regional variations EastNorth sites had the highest infection rate, yet lowest rate of organism isolation and MDR infection than other sites, whereas WestNorth sites were literally the opposite (Fig.1A). Despite of the highest rate of MDR infection in WestNorth sites, the resolution of infection was highest with the highest rate of eABT efficacy (44 vs 26% in WestSouth and < 20% in the rest regions).Infection type and pathogens varied significantly across regions (Fig.1B). Independent risk factors for MDR infection were infection in WestNorth China, prior infections before hospitalization, and UTI or bacteremia. Patient outcome Occurrence of infection significantly decreased 28-, 90-day transplant-free survival, leading to more ACLF, AKI and ICU transfer, longer hospital stay and more readmission after discharge. (Fig.1C). eABT were given promptly (within 24h of infection) in 76% and initiated with broad coverage in 67% of infections, leading to an overall 81% of resolution. Multivariable analysis demonstrated that infections with inefficient eABT are associated with 7- and 4-fold risk of 28- and 90-day mortality, respectively, independent of overt ascites, ACLF and AKI (Fig.1D). **Conclusion:** In this national cohort of inpatients with cirrhosis in China, bacterial infection is prevalent and MDR bacteria is emerging with regional variations and may be underestimated due to low identification of pathogens. Future work should focus on improving microbiology and antibiotic resistance data availability in guiding effective antibiotic treatment while suppressing MDR spread.



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3108-A | SYSTEMATIC UNDERCOUNTING OF OVERT HEPATIC ENCEPHALOPATHY HOSPITALIZATIONS IDENTIFIED BY USING HOSPITAL-ADMINISTERED MEDICATION DATA

Arun Jesudian[1], Patrick Gagnon-Sanschagrin[2], Jessica Maitland[2], Deborah Chan[2], Kana Yokoji[2], Annie Guérin[2], Zeev Heimanson[3], Ankur A Dashputre[4], Brock Bumpass[4], Olamide Olujohungbe[4], Danellys Borroto[4] and George J. Joseph[4], (1)Weill Cornell Medicine, NY, (2)Analysis Group, Inc., (3)Salix Pharmaceuticals, (4) Bausch Health

Background: Overt hepatic encephalopathy (OHE) is a serious neurological disorder, and OHE hospitalizations are burdensome for patients, caregivers, and the healthcare system. The absence of an OHE-specific diagnosis (dx) code may lead to an underestimation of the burden of OHE hospitalizations. This study used dx codes in conjunction with hospital-administered medications to identify OHE hospitalizations in the United States among insured adult patients. **Methods:** OHE hospitalizations were identified in the PINC AI™ Healthcare Database (PHD; 2015–2022). Hospitalizations with a dx for other rifaximin indications (traveler's diarrhea/irritable bowel syndrome with diarrhea) were excluded. OHE hospitalizations were defined as follows: OHE as a primary dx (definition 1), or in-hospital rifaximin/lactulose use combined with a dx for altered mental status, unspecified encephalopathy, or cirrhosis (definition 2). Hospitalization characteristics (treatments, diagnoses), hospital characteristics (urban/rural, bed size), and outcomes (billing charge [2022 USD], length of stay [LOS]) were descriptively reported. Outcomes were assessed separately for the two definitions of OHE hospitalizations and for Medicare and commercially insured patients. **Results:** There were 33,127 OHE hospitalizations identified based on definition 1 and 99,217 additional OHE hospitalizations identified based on definition 2. OHE hospitalizations based on definition 1 had a mean hospital billing charge of $56,648, a mean LOS of 5.2 days, and the majority received in-hospital lactulose (91.9%; average time to first dose: 0.2 d) and/or rifaximin (61.9%; average time to first dose: 0.7 d). OHE hospitalizations based on definition 2 had a mean hospital billing charge 2.5 times higher ($139,870) and a mean LOS 2.0 times longer (10.4 d) than those based on definition 1, and the majority received in-hospital lactulose (96.4%; average time to first dose: 1.9 d) and/or rifaximin (55.3%; average time to first dose: 2.6 d). OHE hospitalizations, irrespective of definition 1 or 2, had similar rates of OHE-related medication administration, comorbidities, and hospital characteristics. Results were consistent irrespective of insurance type. **Conclusion:** Identifying OHE hospitalizations solely based on the presence of a primary diagnosis for OHE significantly

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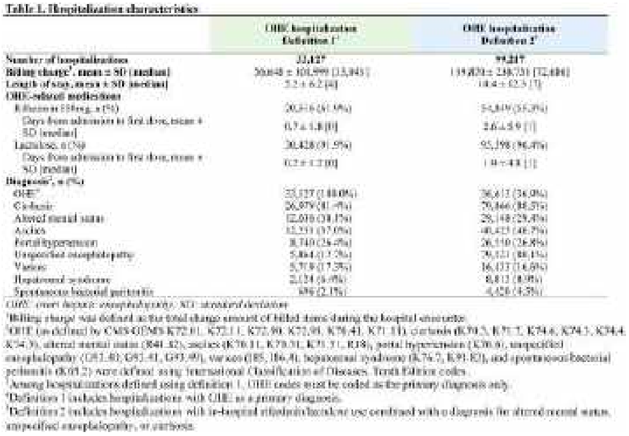
underestimates the rate, LOS, and costs of OHE hospitalizations.



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Patrick Gagnon-Sanschagrin – Analysis Group: Employee, No, No;
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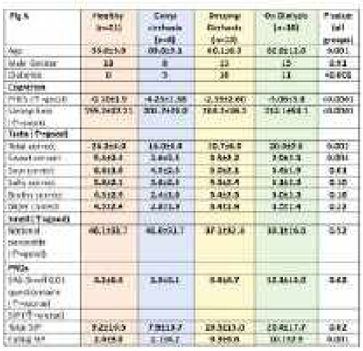
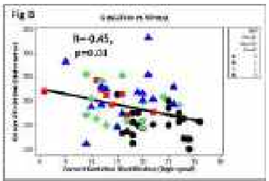
3109-A | TASTE AND SMELL CHANGES AFFECT EATING-RELATED QUALITY OF LIFE AND ARE LINKED WITH COGNITIVE IMPAIRMENT IN CIRRHOSIS AND RENAL FAILURE PATIENTS

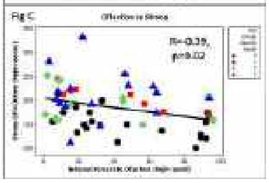
Andrew Fagan[1], Courtney Brown[2], Mary Leslie Gallagher[3], Travis Mousel[1], Michael Fuchs[4], Puneet Puri[5], Brian C. Davis[6], James Wade[5], Nilang Patel[1] and Jasmohan S. Bajaj[7], (1)Virginia Commonwealth University and Richmond VA Medical Center, (2) Richmond VAMC, (3)McGuire Veterans Affairs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

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

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient







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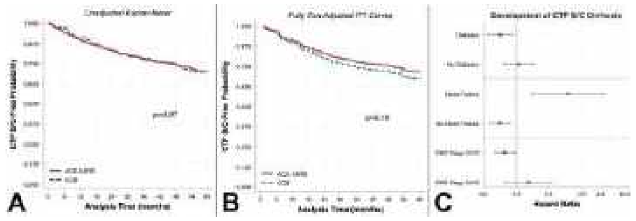
3110-A | THE ASSOCIATION BETWEEN ANGIOTENSIN CONVERTING ENZYME INHIBITOR OR ANGIOTENSIN RECEPTOR BLOCKER EXPOSURE AND PROGRESSION OF CIRRHOSIS

Roy X Wang, University of Pennsylvania, Marina Serper, University of Pennsylvania, Philadelphia, PA, United States, Tamar H. Taddei, Yale University, New Haven, CT, David E. Kaplan, Division of Gastroenterology and Hepatology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA and Nadim Mahmud, Hospital of the University of Pennsylvania

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



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3111-A | THE PREVALENCE OF CIRRHOTIC CARDIOMYOPATHY ACCORDING TO DIFFERENT DIAGNOSTIC CRITERIA

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Background: Cirrhotic cardiomyopathy (CCM) is cardiac dysfunction in patients with end-stage liver disease in the absence of prior heart disease. Recently published criteria by 2019 Cirrhotic Cardiomyopathy Consortium set a lower threshold for reduced ejection fraction to diagnose systolic dysfunction in cirrhotic patients. We aimed to assess the prevalence of cirrhotic cardiomyopathy according to different diagnostic criteria. **Methods:** The patients with liver cirrhosis in Beijing You'an Hospital affiliated to Capital Medical University were collected continuously from 2020 to 2022. They were divided into CCM group and CCM-free group.The diagnosis of CCM was based on the Montreal 2005 World Congress of Gastroenterology criteria or 2019 Cirrhotic Cardiomyopathy Consortium criteria. Echocardiography was performed by an experienced cardiologist (ID) on a iE33 ultrasonography. **Results:** A total of 186 patients with cirrhosis fulfilled the inclusion criteria. Overall CCM prevalence of 2005 criteria was significantly higher compared to for and 2019 criteria : 32.26% VS 25.81% ($P < 0.0001$). The concordance was observed between the 2005 criteria and 2019 criteria ($k = 0.403$).In 35/48 patients of CCM according to 2019 criteria,Systolic dysfunction was more frequently diagnosed compared to 3/60 patients according to 2005 criteria(75% vs 5%, $P < 0.0001$).On the contrary,diastolic dysfunction was fewer frequently diagnosed in CCM according to 2019 criteria compared to 2005 criteria(25% vs 95%, $P < 0.0001$). **Conclusion:** A considerably higher prevalence of systolic dysfunction according to the 2019 criteria was observed. Long-term follow-up studies are needed to establish the validity of these criteria to predict clinically relevant outcomes.

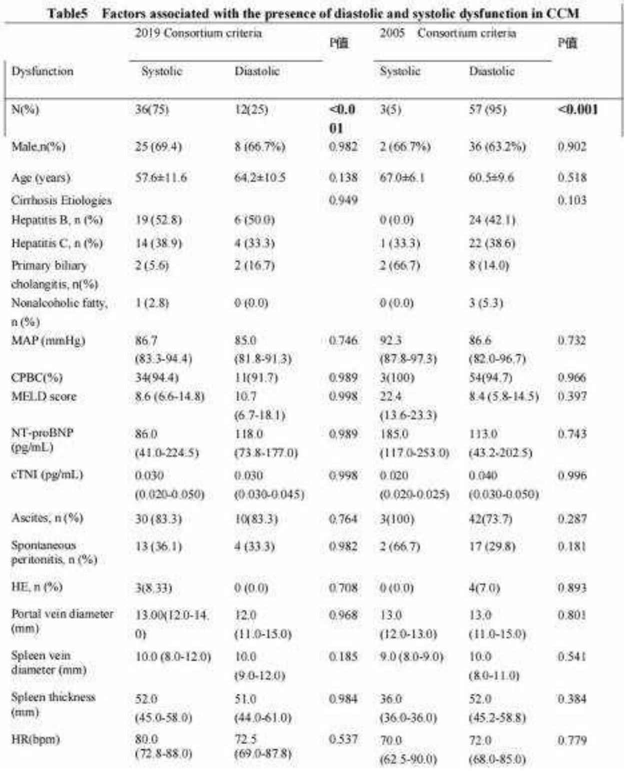


Table5 Factors associated with the presence of diastolic and systolic dysfunction in CCM

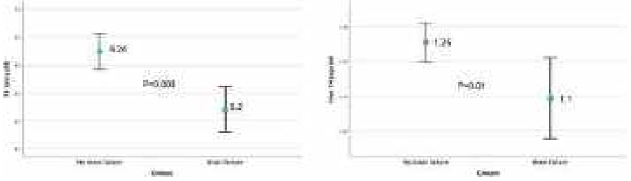
	2019 Consortium criteria		P值	2005 Consortium criteria		P值
Dysfunction	Systolic	Diastolic		Systolic	Diastolic	
N(%)	36(75)	12(25)	**<0.001**	3(5)	57 (95)	**<0.001**
Male,n(%)	25 (69.4)	8 (66.7%)	0.982	2 (66.7%)	36 (63.2%)	0.902
Age (years)	57.6±11.6	64.2±10.5	0.138	67.0±6.1	60.5±9.6	0.518
Cirrhosis Etiologies			0.949			0.103
Hepatitis B, n (%)	19 (52.8)	6 (50.0)		0 (0.0)	24 (42.1)	
Hepatitis C, n (%)	14 (38.9)	4 (33.3)		1 (33.3)	22 (38.6)	
Primary biliary cholangitis, n(%)	2 (5.6)	2 (16.7)		2 (66.7)	8 (14.0)	
Nonalcoholic fatty, n (%)	1 (2.8)	0 (0.0)		0 (0.0)	3 (5.3)	
MAP (mmHg)	86.7 (83.3-94.4)	85.0 (81.8-91.3)	0.746	92.3 (87.8-97.3)	86.6 (82.0-96.7)	0.732
CPBC(%)	34(94.4)	11(91.7)	0.989	3(100)	54(94.7)	0.966
MELD score	8.6 (6.6-14.8)	10.7 (6.7-18.1)	0.998	22.4 (13.6-23.3)	8.4 (5.8-14.5)	0.397
NT-proBNP (pg/mL)	86.0 (41.0-224.5)	118.0 (73.8-177.0)	0.989	185.0 (117.0-253.0)	113.0 (43.2-202.5)	0.743
cTNI (pg/mL)	0.030 (0.020-0.050)	0.030 (0.030-0.045)	0.998	0.020 (0.020-0.025)	0.040 (0.030-0.050)	0.996
Ascites, n (%)	30 (83.3)	10(83.3)	0.764	3(100)	42(73.7)	0.287
Spontaneous peritonitis, n (%)	13 (36.1)	4 (33.3)	0.982	2 (66.7)	17 (29.8)	0.181
HE, n (%)	3(8.33)	0 (0.0)	0.708	0 (0.0)	4(7.0)	0.893
Portal vein diameter (mm)	13.00(12.0-14.0)	12.0 (11.0-15.0)	0.968	13.0 (12.0-13.0)	13.0 (11.0-15.0)	0.801
Spleen vein diameter (mm)	10.0 (8.0-12.0)	10.0 (9.0-12.0)	0.185	9.0 (8.0-9.0)	10.0 (8.0-11.0)	0.541
Spleen thickness (mm)	52.0 (45.0-58.0)	51.0 (44.0-61.0)	0.984	36.0 (36.0-36.0)	52.0 (45.2-58.8)	0.384
HR(bpm)	80.0 (72.8-88.0)	72.5 (69.0-87.8)	0.537	70.0 (62.5-90.0)	72.0 (68.0-85.0)	0.779

Disclosures: The following people have nothing to disclose: Lixia Ma, Zhang Jing

3112-A | THYROXINE LEVELS PREDICT THE DEVELOPMENT OF BRAIN FAILURE IN PATIENTS WITH CIRRHOSIS

Anand V. Kulkarni, Moiz Vora, Ramyasri Ramagundam, Sowmya T R, Shantan Venishetty, Manasa Alla, Mithun Sharma, Nageshwar D Reddy and Padaki Nagaraja Rao, Aig Hospitals, Hyderabad, India

Background: In-hospital development of overt hepatic encephalopathy (HE) is not uncommon. Until recently, there were no simple biomarkers to predict the development of HE. A recent study reported that thyroxine levels predict the development of brain failure (grade 3-4 HE) in hospitalized patients. We aimed to validate the role of thyroid function tests in the prediction of brain failure. **Methods:** In this single-center prospective study, we enrolled consecutive patients with cirrhosis admitted to our hospital from September 10, 2022, to April 1, 2023. The primary objective was to assess the incidence of brain failure, and the secondary was to compare the characteristics of patients who developed brain failure, including baseline demographics, thyroid profile, duration of hospital stay, and in-hospital mortality. **Results:** A total of 164 patients (age-52.41 ± 11.03; NASH-36%; MELD NA-22.25 ± 6.95) without brain failure and acute-on-chronic liver failure were included in the study. Baseline characteristics, including age, sex distribution, comorbidities, the reason for admission, and MELD NA score, were similar among both groups. The most common indication for admission was infection (22%). The incidence of brain failure was 19.5% (95%CI, 13.35-27.6) during a mean hospital stay of 6.71 ± 4.25 days among 164 patients. Thirty-one percent of those who developed brain failure and 15% of those who did not develop brain failure were admitted for grade 1-2 HE. Total thyroxine (T4) levels were significantly lower in patients who developed brain failure compared to those who did not (5.2 ± 1.12 vs. 6.24 ± 1.88 mg/ml; $P = 0.003$). Free T4 levels were also lower in patients with brain failure (1.1 ± 0.31 vs. 1.25 ± 0.32 ng/ml; $P = 0.01$) (Figure). However, there was no difference in the T3, free T3, and TSH levels among the two groups. The duration of hospital stay was longer in patients who developed brain failure (8.56 ± 4.31 vs. 6.26 ± 4.13 d; $P = 0.006$). In-hospital mortality was higher in those who developed brain failure (28%) than those who did not (13%; $P = 0.05$). On univariate logistic regression analysis, grade 1-2 HE at admission (OR, 2.54 [1.05-6.17];$P = 0.04$), total thyroxine (0.64 [0.47-0.87];$P = 0.005$) and free T4 levels (OR, 0.17 [0.04-0.71];$P = 0.01$) predicted development of brain failure while on multivariate logistic regression analysis, only total thyroxine levels predicted the development of brain failure (odds ratio, 0.64 [0.47-0.88];$P = 0.005$). AUROC for T4 was 0.63% (95%CI, 0.53-0.72; $P = 0.02$) for the prediction of brain failure. **Conclusion:** Total thyroxine levels predict the development of brain failure in patients with cirrhosis admitted to the hospital. This simple economical biomarker is an excellent tool for the prediction of HE.



Disclosures: The following people have nothing to disclose: Anand V. Kulkarni, Moiz Vora, Ramyasri Ramagundam, Sowmya T R, Shantan Venishetty, Manasa Alla, Mithun Sharma, Nageshwar D Reddy, Padaki Nagaraja Rao

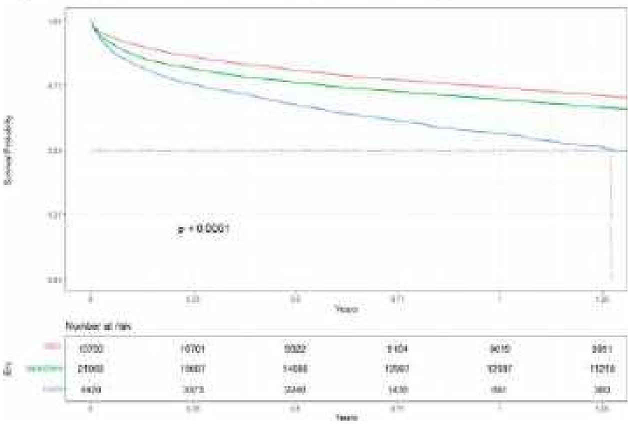
3113-A | TIME TICKS FASTER: TRENDS OF TIME TO DECOMPENSATION AMONG PATIENTS WITH CIRRHOSIS, 2011-2021

Bima J Hasjim[1], *Mitchell Paukner*[1], *Mohsen Mohammadi*[1], *Praneet Polineni*[2], *Therese Banea*[1], *Lisa B. VanWagner*[3], *Andres Duarte-Rojo*[4], *Lihui Zhao*[1], *Sanjay Mehrotra*[1] *and Daniela P. Ladner*[5], *(1) Northwestern University, (2)Northwestern University, Chicago, IL, (3)University of Texas Southwestern Medical Center, (4)Northwestern University Feinberg Scho, (5)Northwestern Memorial Hospital*

Background: The past decade has been marked by events that have effected cirrhosis management and its outcomes. We performed a population-based study in a large metropolitan area to investigate trends in time to decompensation over the past decade. **Methods:** We conducted a retrospective analysis of adult patients (> 17-years-old) with cirrhosis using the CAPriCORN database – a multicenter, electronic health record database in the Chicago metropolitan area from 2011-2021. Eras in the past decade were categorized into < 2014 (1/1/2011-12/31/2013), 2014-COVID (1/1/2014-1/19/2020), and COVID (1/20/2020-8/1/2021). Cirrhosis outcomes, frailty (defined by the Hospital Frailty Risk Score), and COVID-19 were defined by validated ICD and CPT codes. Time to decompensation were reported using the Kaplan Meier method. Cox proportional hazard models were used to identify the associated hazard of decompensation while controlling for clinical covariates. **Results:** Among 44,893 patients with cirrhosis, the mean (± SD) age was 59.4 (± 12.5) years; follow-up was 3.21 (± 3.28) years, 42.2% were women, 47.1% were Non-Hispanic White, 15.0% Black, 8.3% Hispanic and 44.5% were enrolled in Medicare/Medicaid. Patients who were diagnosed with cirrhosis more recently experienced faster times to decompensation compared to those who were diagnosed earlier in the decade ($p < 0.001$, *Figure*). Between eras, there were differences in frailty, age, and etiology at cirrhosis diagnosis ($p < 0.001$). Patients who had intermediate (HR:1.18, CI:1.13-1.24, $p < 0.001$) and high (HR:1.37, CI:1.30-1.45, $p < 0.001$) risk of frailty had an increased hazard of decompensation. When adjusting for frailty, there was no difference in hazard of decompensation between < 2014 and 2014-COVID era, although patients diagnosed in the COVID era had a higher hazard (HR:1.44, CI:1.33-1.56, $p < 0.001$). There was an interaction between HCV etiology and era of diagnosis – those diagnosed after 2014 had lower hazards of decompensation ($p < 0.010$).

Conclusion: In the last decade, patients experienced faster times to decompensation compared to those diagnosed earlier in the decade. In part, these differences may be associated with increasing frailty. Though this effect is seen across etiologies, patients with HCV had a lower hazard of experiencing a decompensation event among patients diagnosed with cirrhosis after 2014, which may reflect the effect of direct acting antivirals in these patients.

Figure 1. Kaplan Meier curve for time to decompensation stratified by era.



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3114-A | TIPS PLACEMENT TO REDUCE PORTAL HYPERTENSION PRIOR TO BARIATRIC SURGERY IN MORBIDLY OBESE PATIENTS WITH CIRRHOSIS

Raluca Pais[1], Yasmina Chouik[2], Lucile Moga[3], Louise Lebedel[4], Caroline Jezequel[5], Maud Robert[6], Emilie Malézieux[7], Christine C. Silvain[8], Hélène Larrue[9], Delphine Weil Verhoeven[10], Laurent Genser[11], Jerome Dumortier[12], Vlad Ratziu[13], Dominique Thabut Damais[14] and Rudler Marika[1], (1)Aphp, (2)Department of Hepatology, Croix Rousse Hospital, Hospices Civils De Lyon, France, (3)Hôpital Beaujon, (4)CHU Caen, (5) CHU Rennes, (6)Hôpital Herriot, (7)CHU Montpellier, Montpellier, France, (8)CHU Poitiers, (9)CHU Toulouse, (10)CHU Besançon, (11)Pitié-Salpêtrière Hospital, (12) CHU Lyon, (13)Assistance Publique-Hôpitaux De Paris, Paris, France, (14)Groupement Hospitalier Aphp-Sorbonne Université, Hôpital De La Pitié-Salpêtrière, Paris, France

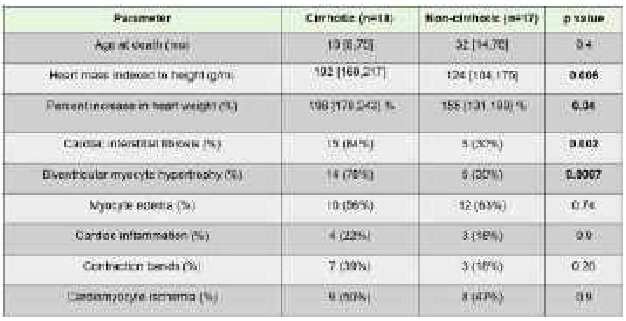
Background: Because of the increasing prevalence of non-alcoholic fatty liver disease (NAFLD), it is expected that more candidates to bariatric surgery (BarS) will have cirrhosis. In cirrhotic patients (pts), clinically significant portal hypertension (CSPH) increases mortality after abdominal surgery. We aimed to study the impact of pre-operative transjugular intrahepatic portosystemic shunt (TIPS) placement on the outcome of BarS in pts with cirrhosis. **Methods:** Multicentric retrospective cohort of pts with cirrhosis (histology or noninvasive methods) undergoing BarS. Hepatic venous pressure gradient (HVPG), and TIPS placement were performed before BarS according to centers' policy. The primary outcome was one-year decompensation-free survival in pts with TIPS (TIPS-g) or without pre-operative TIPS (no TIPS-g). Secondary outcomes were development of acute on chronic liver failure (ACLF) and acute decompensation (AD) at 28, 42, 90 days, 1 year after BarS. **Results:** Between 2010 and 2021, 50 pts were included (92% Child-Pugh A, MELD score 8 (6–13), male gender 46%, age 55 ± 12 yrs, BMI 38.3 ± 13 kg/m2, Roux-en-Y gastric bypass 56%, TIPS placement 18%). There were no significant differences at baseline between TIPS-g and no TIPS-g for age, gender, BMI, % of type-2 diabetes, or BarS procedure. At baseline, TIPS-g pts had more frequently previous decompensation (22% vs 0%, $p = 0.002$), more esophageal varices (EV) (large EV, 56% vs 0%, $p < 0.001$), a higher HVPG (14 (11-19.5) vs 7 (6.5-8) mmHg, $p < 0.001$), and a higher MELD score (10 (9.5-11) vs 7 (7-8), $p = 0.01$. After TIPS, mean HVPG decreased to 7 (IQR, 3-7) mmHg ($p = 0.027$), which was similar to mean HVPG in the no TIPS-g. The mean weight loss was 31 ± 12 kg at one year and similar between groups. Hospital stay after BarS was similar in the 2 groups ($p = 0.77$). The one-year decompensation-free survival was 80% (TIPS-g) and 90% (no TIPS-g), $p = 0.53$. All patients were alive one year after BarS. Two patients in the no TIPS-g developed transient grade 1 ACLF immediately after BarS, vs none in the TIPS-g. MELD score was higher in the TIPS-g at day 28, 42 and 90 after BaS ($p = 0.006$, $p = 0.008$, and $p = 0.004$), but one-year MELD score and AD were similar in the 2 groups ($p = 0.74$ and $p = 0.99$). **Conclusion:** In pts with cirrhosis and severe portal hypertension undergoing BarS, TIPS was successfully and safely performed and

reduced HVPG. This led to similar outcomes after BarS as in pts without TIPS placement.
Disclosures: Dominique Thabut Damais – gilead: Speaking and Teaching, No, No; Cellaion SA: Advisor, No, No; Abbie: Speaking and Teaching, No, No;
The following people have nothing to disclose: Raluca Pais, Yasmina Chouik, Lucile Moga, Louise Lebedel, Caroline Jezequel, Maud Robert, Emilie Malézieux, Christine C. Silvain, Hélène Larrue, Delphine Weil Verhoeven, Laurent Genser, Jerome Dumortier, Vlad Ratziu, Rudler Marika

3115-A | UNIQUE MORPHOMETRIC AND HISTOPATHOLOGIC FEATURES OF HEARTS IN PEDIATRIC CIRRHOSIS

Dalia A Bashir[1], Taylor Kaye Nack[1], Noelle Gorgis[1], Manpreet Virk[1], Kelby Fuller[1], N. Thao N. Galván[2], Kalyani Patel[1], Sanjiv Harpavat[3] and Moreshwar S Desai[1], (1)Baylor College of Medicine, (2)Baylor College of Medicine, Houston, TX, (3)Texas Children's Liver Center - Baylor College of Medicine, Bellaire, TX

Background: Cirrhotic cardiomyopathy (CCM) is a consequential co-morbidity in children with cirrhosis with adverse impact on perioperative outcomes. Despite the clinical relevance, little is known about the pathophysiology of pediatric CCM, as it has yet not been characterized beyond mere echocardiography (2DE). We aimed to review autopsy reports to identify morphometric and histopathologic features of the hearts in children with end stage cirrhosis to better define pediatric CCM. We hypothesized that *the hearts of children with end stage cirrhotic liver disease exhibit features on necropsy that are distinct from those without cirrhosis.* **Methods:** We retrospectively reviewed cardiac autopsy records of children with end stage liver disease listed/transplanted at our institution from 2004-2021. Those with incomplete autopsies, co-existing congenital heart defects and Alagille syndrome were excluded. Presence of hypertrophy, edema, inflammation, fibrosis, and other microscopic features were compared between those with and without cirrhosis of liver/graft at time of demise. Heart weights were documented at necropsy, and % increase in weights (from standard norms for age) were compared between groups. 2DEs done immediately prior (median days 7[IQR: 3,35]) to autopsy were correlated to cardiac necropsy findings. Statistics: Mann Whitney test for continuous variables and Fisher's exact test for categoric variables; Spearman (rho) for correlation. **Results**: Median [IQR] **Results:** Of 35 necropsies (median age 30 [10,68] months; 54% females), 18 (52%) had cirrhotic liver/graft confirmed on histology at necropsy. Compared to children with non-cirrhotic livers/grafts, those with cirrhosis had significantly higher heart mass indexed to height, % increases in heart weights from established norms, higher frequency of bi-ventricular myocyte hypertrophy, and endo-myocardial fibrosis (TABLE). Frequency of myocardial edema, inflammation, ischemia, and contraction band necrosis was comparable between groups (TABLE). Additionally, raw LV mass and LV mass indexed to height obtained on 2DE done prior to autopsy tightly correlated with raw heart mass (rho = 0.87; 95%CI (0.75-0.94); p < 0.001) and heart mass indexed to height (rho = 0.6; 95% CI (0.3-0.8); p = 0.007) obtained at time of autopsy. **Conclusion:** Cardiomegaly, interstitial myocardial fibrosis and bi-ventricular hypertrophy appear to be more prevalent in pediatric end stage cirrhotic liver disease. Discovery of bi-ventricular involvement and endo-myocardial fibrotic changes suggest a potential role for a systemic mediator in pathologic liver-heart interaction. Furthermore, a tight correlation of 2DE with cardiac necropsy findings support the use of 2DE as an effective non-invasive modality to detect CCM. Further studies are needed to identify the triggers/metabolites for CCM, so that treatments can be designed to halt/reverse the progression of this cardiomyopathy.



Parameter	Cirrhotic (n=18)	Non-cirrhotic (n=17)	p value
Age at death (mo)	10 [6,75]	32 [14,70]	0.4
Heart mass indexed to height (g/m)	192 [160,217]	124 [104,175]	0.006
Percent increase in heart weight (%)	198 [178,242] %	155 [131,199] %	0.04
Cardiac interstitial fibrosis (%)	15 (84%)	5 (30%)	0.002
Biventricular myocyte hypertrophy (%)	14 (78%)	5 (30%)	0.0007
Myocyte edema (%)	10 (56%)	12 (63%)	0.74
Cardiac inflammation (%)	4 (22%)	3 (18%)	0.9
Contraction bands (%)	7 (39%)	3 (18%)	0.26
Cardiomyocyte ischemia (%)	9 (50%)	8 (47%)	0.9

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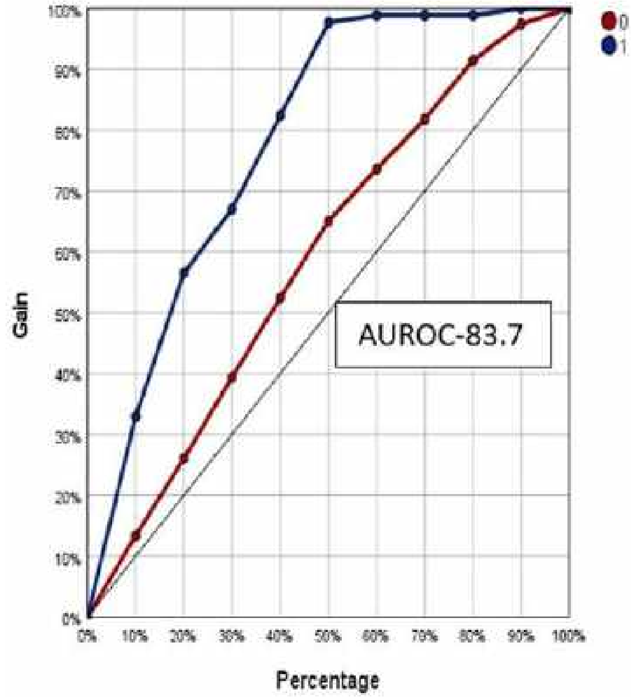
Disclosure information not available at the time of publication: Dalia A Bashir, Noelle Gorgis, Manpreet Virk, N. Thao N. Galván, Kalyani Patel, Sanjiv Harpavat

3116-A | USE OF MACHINE LEARNING MODEL TO PREDICT MORTALITY IN CIRRHOTIC PATIENTS PRESENTING TO EMERGENCY ROOM(ER)-REACH-ER STUDY

Harsh Vardhan Tevethia[1], Rakhi Maiwall[1], Mrudal Daga[2], Chandan Kumar[2], Rahul Khajuria[2], Tushar Madke[2], Akhil Deshmukh[2], Guresh Kumar[1] and Shiv Kumar Sarin[3], (1)Institute of Liver and Biliary Sciences, New Delhi, (2)Ilbs ,New Delhi, (3)Institute of Liver and Biliary Sciences

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



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Disclosure information not available at the time of publication: Akhil Deshmukh

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

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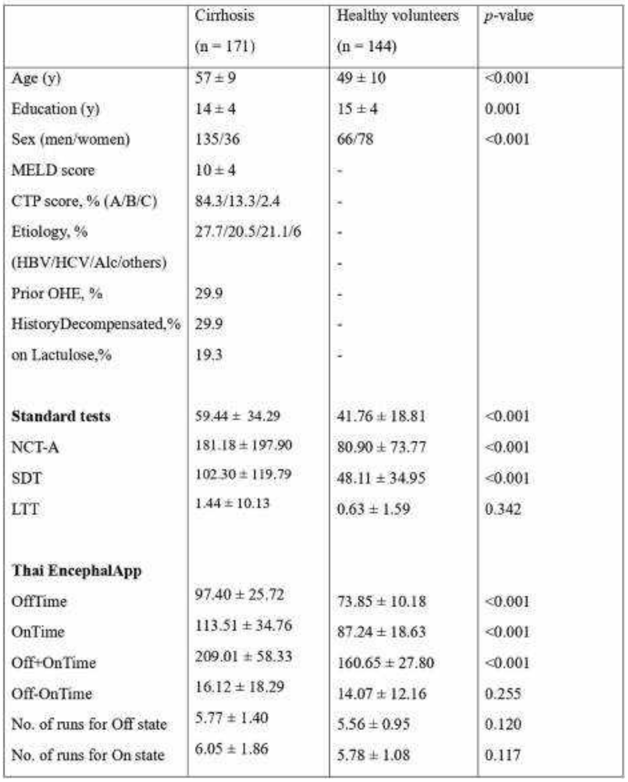
Background: The EncephalApp Stroop Test was developed to diagnose covert hepatic encephalopathy (CHE). However, information regarding the best cut-off (Ontime+OFFtime) is still scant in outside North America populations. We aim to analyze the usefulness of this diagnostic method and to describe a cut-off value of the Thai version EncephalApp (Thai EncephalApp) stroop test to screen CHE in Thailand. **Methods:** In this cross-sectional and single-center study, median and 95% higher from the expected Stroop value for every healthy controls defined the diagnosis of CHE. We evaluated gender, age, education, etiology of cirrhosis, Child-Pugh/MELD scores, and previous hepatic encephalopathy (HE). Healthy controls and patients without HE were compared for the task validation. The Chi-square and Mann-Whitney tests, and logistic regression analysis were used for statistical evaluation. **Results:** We included 171 patients with cirrhosis (79% male) and 144 controls (46% male) around 51y. Viral hepatitis (47%) was the major etiology of cirrhosis. The median MELD was 10 and Child-Pugh A was more frequent (84%). There was no significant difference in test results between controls and patients without HE. The regression formula in healthy people was made using age, gender, and education, of which only age and education were significant which a cut-off of > 175 sec defined the diagnosis of CHE (OffplusOn = 121 + 1.35 Age[year] – 1.77 Study[year]) which found 39% of CHE. Patients with CHE on Thai EncephalApp Stroop Test was additive to MELD score with p = 0.06 on multivariate analysis. **Conclusion:** Thai EncephalApp Stroop Test may be useful in a stepwise diagnosis algorithm or even as a stand-alone screening tool to detect CHE in Thai patients with cirrhosis.

Table 1: Data comparing hospitalized patients and healthy volunteer participants



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

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

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

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Background: Chronic hepatitis C virus (HCV) infection is a leading cause of chronic liver disease (CLD) worldwide. Its prevalence is of particular significance in developing countries. Generalized access to Direct Acting Antivirals (DAA) in public healthcare has greatly increased the rates of sustained virological response (SVR), but evidence that correlates it with clinically significant improvement is lacking. The Baveno VII consensus has recently proposed the term of cirrhosis recompensation as objective evidence of clinical improvement. In the present study, we aimed to validate this new definition in patients with HCV-related cirrhosis treated with DAA after SVR. **Methods:** This is a single center, prospective cohort study, which included all patients with decompensated ACLD (dACLD) due to HCV, older than 18 years, that had received DAA and achieved SVR, at our institution in Mexicali, Mexico, from January 1, 2018, to October 31, 2021. Baseline patient characteristics were collected, participants were followed up for clinical events, biochemical tests, and VCTE at the time of SVR, 12 weeks and 52 weeks after achieving virological cure, the primary endpoint was cirrhosis recompensation rate according to BVII definition, direct comparison of variables and outcomes was established between those who reached the PO. Secondary outcomes were improvement in CTP, MELD-Na, LS by VCTE, and absolute platelet count. Multivariate regression was used to identify predictors of recompensation. Patients with an additional etiology of CLD, severe extra-hepatic organ dysfunction or active malignancies were excluded. **Results:** A total of 108 patients that were treated with DAA and achieved SVR were studied, 67% were men with a median of 51 years in the whole cohort. The most frequent multimorbidity was T2DM (11.5%). At 52 weeks, 57 patients achieved resolution of ascites, EH, and absence of recurrent variceal bleeding for at least 12 months (52.7%). Compared to those that did not achieve recompensation, recompensated patients had a lower Median MELD-Na at 12 and 52 weeks (12 vs 15; 10 vs 14, respectively), were more often classified as CTP A at the same cutoffs (66% vs 39% week 12; 92% vs 43% week 52), had a higher number of patients with > 150,000 Plt (87% vs 37% at week 52), and more frequently had a LS < 12 kPa by VCTE at 52 weeks (47% vs 13%). As regards to predictors for reaching the primary outcome, a reduction in MELD-Na > 2 absolute points at week 12 or 52 (OR 1.06, 95% CI 1.03-1.10, p < 0.05), and an overall MELD-Na equal or < 11 (OR 1.10, 95% CI 1.05-1.15, p < 0.05) were the factors with the higher odds of cirrhosis recompensation. **Conclusion:** Our study showed that among patients with HCV infection and decompensated cirrhosis treated with DAA and SVR, achieving recompensation correlated to an improvement in clinical scores, a higher proportion of patients with normal platelets and overall, a lower LS by VCTE.

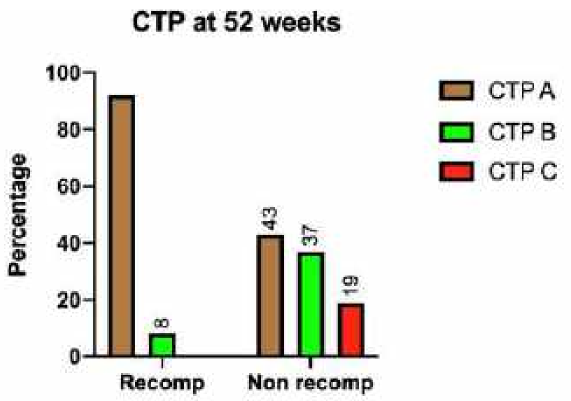

Figure 1. *CTP score at 52 weeks amongst patients that achieved recompensation vs those who did not*

At 52 weeks, 92% of patients with recompensation were classified as **CTP A**, compared to only 43% of patients without recompensation. 8% of recompensated patients were **CTP B**, but that number increased to 37% for non-recompensated. Finally, 19% patients without recompensation remained at **CTP C.**

Disclosures: The following people have nothing to disclose: Luis Alejandro Rosales Renteria, Diana Laura López Rubio, Nancy Midory Hirata Medina, Hiram Jaramillo, Jocelin Sandoval Briones, Laramie Tinoco, Diana Sandoval Gutierrez, David Prieto Nava, Araceli Bravo Cabrera, Rodolfo Ruiz Luján, Maria Sarai González Huezo, Jesús Alberto Camacho Escobedo

3119-A | VENOUS THROMBOEMBOLISM RISK IN PATIENTS WITH CIRRHOSIS INFECTED WITH COVID-19: A MULTI-CENTER PROPENSITY-MATCHED ANALYSIS.

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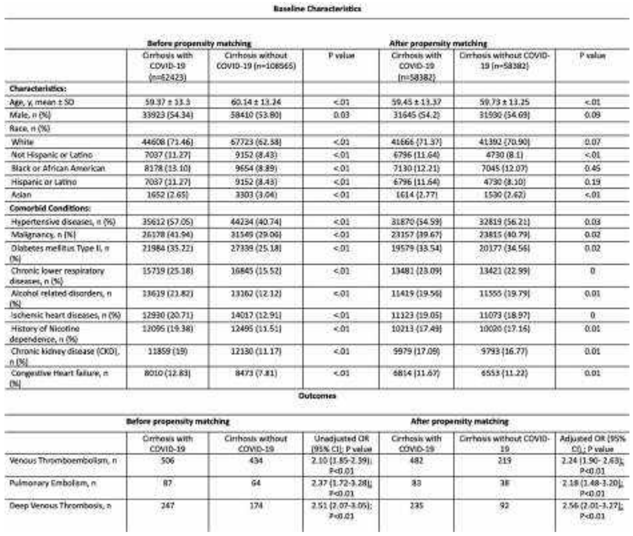
Background: Previous studies have demonstrated that COVID-19 infection predisposes to developing venous thromboembolic events (VTE), and the risk is substantially increased in patients with underlying coagulopathic disorders, including cirrhosis. Using a large research network, this study aimed to examine the incidence of VTE in patients with cirrhosis, both with and without concurrent COVID-19 infection. **Methods:** We queried the TriNetX electronic health records network (with over 100 million patients) between January 1, 2020, and December 31, 2022, to identify all the patients with cirrhosis. These patients were then stratified into two groups (COVID and non-COVID) based on the presence or absence of COVID-19. Two well-matched cohorts (with and without COVID) were created using a 1:1 propensity score matching model. Patients under 18 years old, with pre-existing VTE diagnoses, or already receiving therapeutic anticoagulation were excluded. We estimated the incidence of VTE, and using a Cox model, we compared incidences of VTE in propensity score-matched cohorts of cirrhosis patients with and without COVID-19. We also compared the incidence of pulmonary embolism (PE), portal vein thrombosis (PVT), and deep venous thrombosis (DVT). **Results:** We identified a total of 170,988 patients with cirrhosis, out of which 62,423 (36.50%) were in the COVID group and 108,565 (63.50%) were in the non-COVID group. The patients in the non-COVID group were older (60.14 ± 13.24 vs. 59.37 ± 13.3, $P < 0.01$) than the COVID group, and majority were male and Caucasian. The COVID group had substantially higher comorbidities, including hypertension, diabetes mellitus, and malignancy (Table 1). Before propensity score matching, the COVID group had a greater incidence of VTE compared to the non-COVID group (0.88% vs. 0.42%, odds ratio [OR] 2.10, 95% confidence interval [CI] 1.85-2.39). This difference persisted after propensity score matching (0.88% vs. 0.44%, OR 2.24, 95% CI 1.90-2.63). Additionally, on subgroup analysis, the COVID group had a higher incidence of PE, PVT, and DVT. **Conclusion:** Our findings indicate that patients with cirrhosis and concurrent COVID-19 infection have a twofold increased risk of developing VTE compared to those without COVID-19. However, further prospective studies are required to determine whether this patient population will benefit from a prophylactic full-dose anticoagulation approach compared to standard thromboprophylaxis for the prevention of these thromboembolic events.



Baseline Characteristics

	Before propensity matching			After propensity matching		
	Cirrhosis with COVID-19 (n=62423)	Cirrhosis without COVID-19 (n=108565)	P value	Cirrhosis with COVID-19 (n=58382)	Cirrhosis without COVID-19 (n=58382)	P value
Characteristics:						
Age, y, mean ± SD	59.37 ± 13.3	60.14 ± 13.24	<.01	59.45 ± 13.37	59.73 ± 13.25	<.01
Male, n (%)	33923 (54.34)	58410 (53.80)	0.03	31645 (54.2)	31930 (54.69)	0.09
Race, n (%)						
White	44608 (71.46)	67723 (62.38)	<.01	41666 (71.37)	41392 (70.90)	0.07
Not Hispanic or Latino	7037 (11.27)	9152 (8.43)	<.01	6796 (11.64)	4730 (8.1)	<.01
Black or African American	8178 (13.10)	9654 (8.89)	<.01	7130 (12.21)	7045 (12.07)	0.45
Hispanic or Latino	7037 (11.27)	9152 (8.43)	<.01	6796 (11.64)	4730 (8.10)	0.19
Asian	1652 (2.65)	3303 (3.04)	<.01	1614 (2.77)	1530 (2.62)	<.01
Comorbid Conditions:						
Hypertensive diseases, n (%)	35612 (57.05)	44234 (40.74)	<.01	31870 (54.59)	32819 (56.21)	0.03
Malignancy, n (%)	26178 (41.94)	31549 (29.06)	<.01	23157 (39.67)	23815 (40.79)	0.02
Diabetes mellitus Type II, n (%)	21984 (35.22)	27339 (25.18)	<.01	19579 (33.54)	20177 (34.56)	0.02
Chronic lower respiratory diseases, n (%)	15719 (25.18)	16845 (15.52)	<.01	13481 (23.09)	13421 (22.99)	0
Alcohol related disorders, n (%)	13619 (21.82)	13162 (12.12)	<.01	11419 (19.56)	11555 (19.79)	0.01
Ischemic heart diseases, n (%)	12930 (20.71)	14017 (12.91)	<.01	11123 (19.05)	11073 (18.97)	0
History of Nicotine dependence, n (%)	12096 (19.38)	12495 (11.51)	<.01	10213 (17.49)	10020 (17.16)	0.01
Chronic kidney disease (CKD), n (%)	11859 (19)	12130 (11.17)	<.01	9979 (17.09)	9793 (16.77)	0.01
Congestive Heart failure, n (%)	8010 (12.83)	8473 (7.81)	<.01	6814 (11.67)	6553 (11.22)	0.01

Outcomes

	Before propensity matching			After propensity matching		
	Cirrhosis with COVID-19	Cirrhosis without COVID-19	Unadjusted OR (95% CI); P value	Cirrhosis with COVID-19	Cirrhosis without COVID-19	Adjusted OR (95% CI); P value
Venous Thromboembolism, n	506	434	2.10 (1.85-2.39); P<0.01	482	219	2.24 (1.90- 2.63); P<0.01
Pulmonary Embolism, n	87	64	2.37 (1.72-3.28); P<0.01	83	38	2.18 (1.48-3.20); P<0.01
Deep Venous Thrombosis, n	247	174	2.51 (2.07-3.05); P<0.01	235	92	2.56 (2.01-3.27); P<0.01

Disclosures: The following people have nothing to disclose: Khadija Naseem, Abdullah Sohail, Ahmad Khan, Talal Adhami

3120-A | VIBES MNEMONIC: A SYSTEMATIC APPROACH TO MANAGING COMPLICATIONS OF CIRRHOSIS IMPROVES RESIDENT CONFIDENCE

Rachael Mahle, Marc S Sherman and Esperance AK Schaefer, Massachusetts General Hospital

Background: Management of patients with cirrhosis is challenging and complex, and important elements of clinical care may be overlooked. A systematic approach to patients with cirrhosis was developed at our institution in 2009 which is used widely by housestaff and medicine faculty. The framework, titled VIBES, highlights cirrhosis-specific complications including Volume (ascites, hepatic hydrothorax, renal function), Infection (spontaneous bacterial peritonitis (SBP)), Bleeding (varices, portal hypertensive gastropathy, portal vein thrombosis), Encephalopathy (hepatic encephalopathy (HE)), and Screening/Surveillance (hepatocellular carcinoma (HCC) screening, hepatitis vaccination). We evaluated if this structured approach improves trainee comfort with care of patients with cirrhosis. **Methods:** Internal medicine residents were surveyed prior to and 3 months into intern year. During the 3 month window, trainees were educated on the VIBES framework formally (faculty lecture) and informally (residents). The survey assessed the impact of incorporating the VIBES structure on their comfortability managing patients with cirrhosis using Likert scales. **Results:** 73 responses were received ($n = 43$ for the pre-survey and $n = 24$ for the post-survey). There was a statistically significant increase in reported intern comfort of the management of ascites ($p < 0.01$), SBP ($p < 0.01$), esophageal varices ($p < 0.01$), HE ($p < 0.01$), and HCC ($p = 0.047$). Management of hepatorenal syndrome trended towards but did not reach significance ($p = 0.12$). Among respondents, 75.0% felt the mnemonic broadened their differential for patients with cirrhosis, 95.6% felt it improved quality of care for patients with cirrhosis, and 87.5% felt it helped them more clearly communicate care for patients with cirrhosis with other providers. **Conclusion:** Use of the VIBES framework significantly improves trainee confidence in managing patients with cirrhosis in nearly all facets of management. In addition, trainees unanimously reported the approach broadened their differentials, improved inter-provider communication, and overall improved the quality of care for patients with cirrhosis. Early education and utilization of this framework in medical training has the promise of improving care of this complicated patient population. Widespread use of this simple conceptual framework and mnemonic has the potential to reduce provider-level contribution to the considerable variation in inpatient cirrhosis mortality.

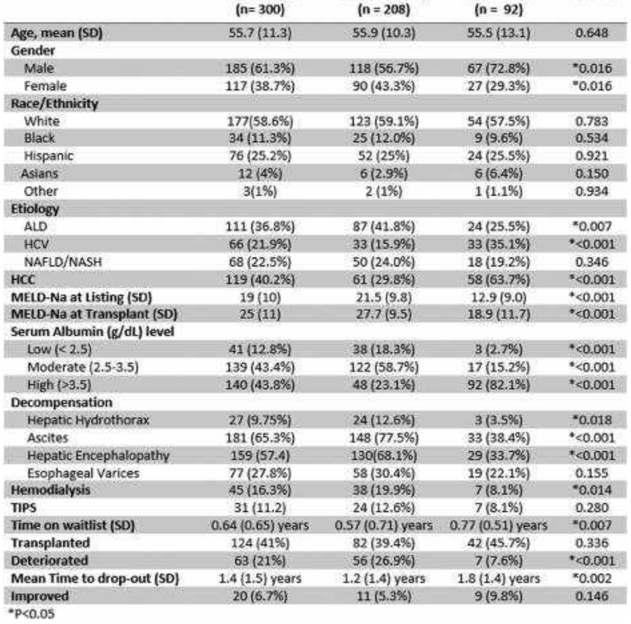
Disclosures: The following people have nothing to disclose: Rachael Mahle

Disclosure information not available at the time of publication: Marc S Sherman, Esperance AK Schaefer

3121-A | ZINC DEFICIENCY ASSOCIATED WITH INCREASED RISK OF MORTALITY IN PATIENTS WITH ADVANCED LIVER DISEASE

Ronald Samuel[1], Anjiya Shaikh[2], Tzu-Hao (Howard) Lee[1], Vinh Vincent Tran[1], Kadon Caskey[1], Scott Berger[1], Basim Ali[1], Cameron Goff[1], Christo Mathew[1], Marguerite Poche[1], Prisca Pungwe[1], Norvin Hernandez[1], Richard Bui[1], Ryan Ward[1], Ankur Patel[1], Seulgi Kim[1], Zahraa Al Lami[1], Ruben Hernaez[1], Abbas Rana[1], Rise Stribling[1], John A. Goss[1], Hashem B. El-Serag[1], Fasiha Kanwal[1] and George Cholankeril[1], (1) Baylor College of Medicine, (2)University of Connecticut

Background: Zinc deficiency has been associated with complications in patients with cirrhosis, such as hepatic encephalopathy. However, the impact of zinc deficiency on mortality in these patients is poorly understood. We aimed to assess the effect of zinc deficiency on liver transplant (LT) waitlist outcomes and the role of zinc supplementation. **Methods:** We performed a retrospective cohort study in all adult patients added to the LT waitlist at our institution from January 2017 to August 2018 with follow-up through April 2023. Serum zinc levels were collected in all patients prior to listing as part of LT evaluation protocol. Patients with zinc deficiency, defined as Zinc levels < 60 (mcg/dL), were prescribed parenteral zinc supplementation (50 mg daily). Repeat serum zinc levels were collected within 3-12 months after initiation of supplementation. Differences in repeat zinc level were compared using paired t-test. Multivariable Fine and Gray analyses were performed to assess the risk of waitlist dropout (death or deterioration) from baseline zinc level, accounting for competing risks of LT and delisting for improvement. **Results:** Of the 300 patients listed for LT, 69.3% (n = 208) had zinc deficiency. Compared to patients with normal zinc levels, patients with zinc deficiency had a higher proportion of female, alcohol-associated liver disease (ALD), and absence of hepatocellular carcinoma (HCC). Patients with zinc deficiency also had a significantly higher MELD-Na score at listing, and were more likely to have severe hypoalbuminemia (< 2.5 mg/dL), ascites, hepatic encephalopathy, and hepatic hydrothorax (Table 1). In our multivariable competing risks analysis, zinc deficiency was associated with 3.8 fold higher risk (sHR, 3.75, 95% CI, 1.32 – 10.61) of mortality accounting for age, gender, ALD, HCC, and MELD-Na at listing. 78 patients with zinc deficiency had repeat levels measured after at least 3 months of supplementation, of which 93.6% (n = 73) had persistently low zinc levels, and no significant difference in repeat measurements (P = 0.6). **Conclusion:** Zinc deficiency is common in patients with advanced liver disease and is a significant predictor for waitlist mortality. However, parenteral zinc supplementation did not significantly alter zinc levels. Further investigation into the complexity of zinc absorption and metabolism in advanced liver disease, better strategies for zinc supplementation, possible relation to frailty, and the potential impact on patient outcomes are needed.



	All Patients (n= 300)	Zinc Deficiency (n = 208)	Normal Zinc (n = 92)	P value
Age, mean (SD)	55.7 (11.3)	55.9 (10.3)	55.5 (13.1)	0.648
Gender				
Male	185 (61.3%)	118 (56.7%)	67 (72.8%)	*0.016
Female	117 (38.7%)	90 (43.3%)	27 (29.3%)	*0.016
Race/Ethnicity				
White	177(58.6%)	123 (59.1%)	54 (57.5%)	0.783
Black	34 (11.3%)	25 (12.0%)	9 (9.6%)	0.534
Hispanic	76 (25.2%)	52 (25%)	24 (25.5%)	0.921
Asians	12 (4%)	6 (2.9%)	6 (6.4%)	0.150
Other	3(1%)	2 (1%)	1 (1.1%)	0.934
Etiology				
ALD	111 (36.8%)	87 (41.8%)	24 (25.5%)	*0.007
HCV	66 (21.9%)	33 (15.9%)	33 (35.1%)	*<0.001
NAFLD/NASH	68 (22.5%)	50 (24.0%)	18 (19.2%)	0.346
HCC	119 (40.2%)	61 (29.8%)	58 (63.7%)	*<0.001
MELD-Na at Listing (SD)	19 (10)	21.5 (9.8)	12.9 (9.0)	*<0.001
MELD-Na at Transplant (SD)	25 (11)	27.7 (9.5)	18.9 (11.7)	*<0.001
Serum Albumin (g/dL) level				
Low (< 2.5)	41 (12.8%)	38 (18.3%)	3 (2.7%)	*<0.001
Moderate (2.5-3.5)	139 (43.4%)	122 (58.7%)	17 (15.2%)	*<0.001
High (>3.5)	140 (43.8%)	48 (23.1%)	92 (82.1%)	*<0.001
Decompensation				
Hepatic Hydrothorax	27 (9.75%)	24 (12.6%)	3 (3.5%)	*0.018
Ascites	181 (65.3%)	148 (77.5%)	33 (38.4%)	*<0.001
Hepatic Encephalopathy	159 (57.4)	130(68.1%)	29 (33.7%)	*<0.001
Esophageal Varices	77 (27.8%)	58 (30.4%)	19 (22.1%)	0.155
Hemodialysis	45 (16.3%)	38 (19.9%)	7 (8.1%)	*0.014
TIPS	31 (11.2)	24 (12.6%)	7 (8.1%)	0.280
Time on waitlist (SD)	0.64 (0.65) years	0.57 (0.71) years	0.77 (0.51) years	*0.007
Transplanted	124 (41%)	82 (39.4%)	42 (45.7%)	0.336
Deteriorated	63 (21%)	56 (26.9%)	7 (7.6%)	*<0.001
Mean Time to drop-out (SD)	1.4 (1.5) years	1.2 (1.4) years	1.8 (1.4) years	*0.002
Improved	20 (6.7%)	11 (5.3%)	9 (9.8%)	0.146

*P<0.05

Disclosures: The following people have nothing to disclose: Ronald Samuel, Tzu-Hao (Howard) Lee, Vinh Vincent Tran, Christo Mathew, Ankur Patel, Ruben Hernaez, Abbas Rana, Fasiha Kanwal, George Cholankeril

Disclosure information not available at the time of publication: Anjiya Shaikh, Kadon Caskey, Scott Berger, Basim Ali, Cameron Goff, Marguerite Poche, Prisca Pungwe, Norvin Hernandez, Richard Bui, Ryan Ward, Seulgi Kim, Zahraa Al Lami, Rise Stribling, John A. Goss, Hashem B. El-Serag

3122-A | DIFFERENCES IN METABOLITES AND PHYSIOLOGICAL MAKER BETWEEN HEPATIC VENOUS PRESSURE GRADIENTS BY PORTAL VEIN BLOOD IN PATIENTS WITH LIVER FIBROSIS

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Background: Liver fibrosis interferes with normal function by altering the structure of a particular organ and is one of the main causes of death. Liver cirrhosis (LC) is defined as an advanced stage of liver fibrosis with hepatic vasculature and structural distortion. The development of portal hypertension is characteristic of LC. We investigate the difference in metabolites in portal vein blood according to the degree of hepatic venous pressure gradient (HVPG) in patients with hepatic fibrosis. **Methods:** We used humanely collected portal vein blood (PVB). We mixed PVB with Acetonitrile:3'-distilledwater = 1:1 (v/v) and centrifuged at 13200 rpm and 4°C for 5 minutes after vortex for 1 min and sonicate for 5 min under ice. After transferring the supernatant to a new tube, Acetonitrile:Methanol = 1:3 (v/v) was added and then proceeded as described above. The supernatant was transferred to a new tube and concentrated with a speed vacuum concentrator. The HPLC conditions used were as follows: column temperature was set at 30 °C, injection volume was 10 μL, mobile phase A was water with 0.1% formic acid and mobile phase B was 5 acetonitrile. **Results:** We measured the biochemical indicators HVPG, ALT, AST and Albumin using humanely collected PVB. The group consisted of three stages according to the degree of HVPG. The average HVPG of each group was 6 ± 2.3, 14.1 ± 0.4, and 22.2 ± 4.2, showing differences between groups. The intergroup AST indices were 57 ± 14.5, 74 ± 37.6, and 103 ± 48.7, indicating a proportional increase with increasing HVPG values. However, ALT and Albumin indices did not show differences between groups. PVB was sampled in each group and metabolite was analyzed by HPLC to confirm differences between groups. At the peak of retention time 4, 14 minutes, it can be seen that the area value is 139.4, 45.4, 16.2 mAU and 21.2, 9.2, 7.1 mAU and low from the group with high HVPG. On the other hand, at the peak of Retention time 9 minutes, it can be seen that the group with high HVPG has a large area value of 0.3, 0.8, and 107.6 mAU. **Conclusion:** We investigated differences in biochemical indices and metabolites in PVB in patients with liver fibrosis according to the degree of HVPG. Differences in biochemical indices according to the stage of HVPG were confirmed. In addition, metabolites were confirmed through HPLC, and differences in patterns depending on the stage were confirmed. This suggests that hepatic fibrosis patients can be a maker of severity without measuring HVPG.

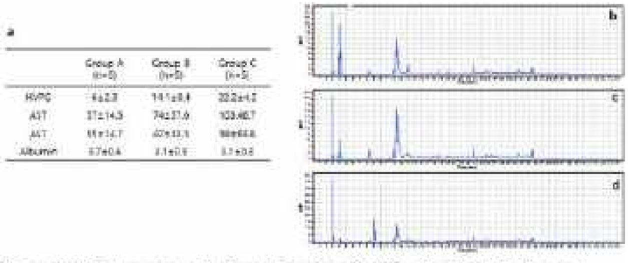


Figure: HPLC chromatography for confirmation of HPVG, physiological index and metabolite using portal vein blood. (a) HPVG and physiological index in each group, (b) HPLC chromatography of Group A, (c) HPLC chromatography of Group B, (d) HPLC chromatography of Group C.

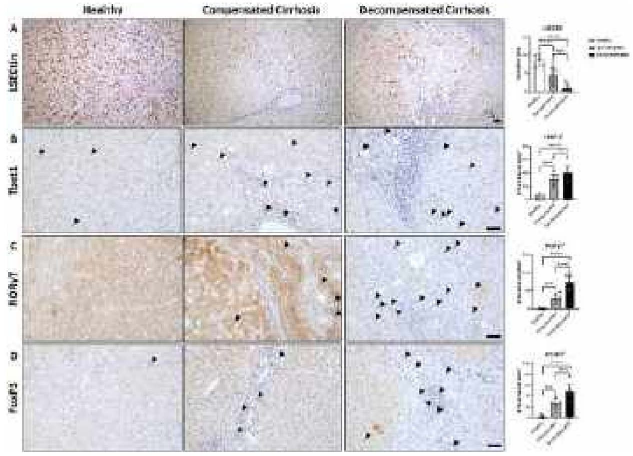
Disclosures: Dong Joon Kim – Institute for Liver and Digestive Diseases, College of Medicine, Hallym University, Chuncheon 24252, Republic of Korea: Employee, No, No; Ki Tae Suk – Institute for Liver and Digestive Diseases, College of Medicine, Hallym University, Chuncheon 24252, Republic of Korea: Employee, No, No;

The following people have nothing to disclose: Sang youn Lee, Su Been Lee, Kyeong Jin Lee, Jung A Eom, Sung- Min Won

3123-A | HEPATIC LSECTIN REDUCTION CONTRIBUTES TO T HELPER 17 CELL EXPANSION IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

Sebastian Martínez[1,2], Enrique Angel[1,2], Isabel Gómez-Hurtado[3], Anabel Fernandez Iglesias[4], Javier Morante[1,5], Jordi Gracia-Sancho[3,6], Esther Caparrós[1] and Ruben Frances[1,2,3], (1)Miguel Hernández University, Spain, (2)IIS Isabial, Alicante, Spain, (3) Ciberehd, Instituto De Salud Carlos III, Madrid, Madrid, Spain, (4)Idibaps, Barcelona, Spain, (5)Instituto De Neurociencias, Csic-Umh, San Juan De Alicante, Spain, (6)Idibaps - Hospital Clinic Barcelona, Barcelona, Spain

Background: Liver Sinusoidal Endothelial Cells (LSECs) are considered promoters of immune tolerance during hepatic homeostasis. We propose that the innate receptor C-type lectin LSECtin mediates this immunomodulatory function. During liver damage, LSECtin negatively regulates hepatic T-cell immune response through its interaction with different effector T-cell ligands. We have shown the negative transcriptional regulation of LSECtin in LSECs from experimental models of cirrhosis, resulting in a proinflammatory Th17 cell differentiation. Thus, our aim is to investigate LSECtin expression during liver disease progression in human hepatic tissue and its relationship with T cell expansion. **Methods:** Cirrhotic liver tissue was obtained from patients with alcohol or non-alcoholic steatohepatitis who underwent liver transplantation. Patients were grouped in compensated (n = 6) or decompensated (n = 7) based in their clinical characteristics. Non-lesioned non-tumorous liver tissues were used as healthy controls (n = 5). IHC staining was used to assess different proinflammatory and profibrogenic markers as well as LSECtin, TBET, RORγT and FOXP3 expression. Isolated RNA was subjected to RNAseq, performed in an Illumina platform HiSeq2500 and the transcriptomic profile of cirrhotic livers during disease progression was defined. LSECtin, RORγT and FOXP3 expression was correlated using this data. **Results:** LSECtin expression was progressively reduced in hepatic tissue from compensated and decompensated patients, as shown by IHC (Figure 1A). This was further confirmed by Western Blot and qPCR. The expression of transcription factors related to Th1, Th17 and Treg is shown in Figure 1B-1D. RORgT and FOXP3 were progressively increased in hepatic tissue from compensated to decompensated disease. TBET didn't show significant differences between groups. RNAseq analyses confirmed the significantly increased expression of RORgT and FOXP3 transcripts levels in patients compared to healthy livers. An inverse significant correlation was observed for LSECtin with RORgT (r = -0.573; p = 0.003) and FoxP3 (r = -0.438; p = 0.003), whereas no correlation could be established between LSECtin and Tbet (r = -0.007; p = 0.735). **Conclusion:** Th17 cell expansion is inversely associated with LSECtin expression in hepatic tissue of cirrhotic patients. The recovery of LSECtin could ameliorate the unbalanced inflammatory milieu and contribute to restore homeostasis in patients with cirrhosis.



Disclosures: The following people have nothing to disclose: Sebastian Martínez, Enrique Angel, Isabel Gómez-Hurtado, Anabel Fernandez Iglesias, Javier

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

Morante, Jordi Gracia-Sancho, Esther Caparrós, Ruben Frances

3124-A | IMPACT OF THROMBOCYTOPENIA IN CHRONIC LIVER DISEASE

Oyedotun Babajide[1], Elizabeth Soladoye[2], Oluwanifemi Balogun[3], Abayomi Oyenuga[4] and Kalpana Panigrahi[1], (1)One Brooklyn Health-Interfaith Medical Center, (2) Piedmont Athens Regional, Athens, GA, (3)Albert Einstein Medical Center, Philadelphia, PA, (4)University of Minnesota

Background: Chronic liver disease (CLD) is a leading cause of morbidity and mortality worldwide, with an estimated 1.5 billion cases and over 1.32 million deaths in 2017. Thrombocytopenia is a common complication of CLD-related portal hypertension with its severity and frequency directly related to the severity of CLD. There are multiple pathophysiologic mechanisms for thrombocytopenia including; decreased activity of thrombopoietin, hypersplenism in portal hypertension, medications, and suppressive effects of alcohol on the bone marrow from chronic alcoholism. This study aimed to investigate the relationship between thrombocytopenia and health outcomes of patients with chronic liver disease. **Methods**: This one-year retrospective study evaluated the effects of thrombocytopenia on patients with CLD using the 2017 Nationwide Inpatient Sample (NIS) database. We identified and categorized adults with a diagnosis of chronic liver disease into those with an additional diagnosis of thrombocytopenia and those without. We evaluated the association between thrombocytopenia and the following outcomes: mortality, hospitalization cost, and length of stay (LOS) while adjusting for age, sex, race, elective vs non-elective admissions using multivariate logistic regression. All statistical analysis was done using SAS.9.0 **Results**: Within the identified 299,104 records with a diagnosis of CLD without missing covariates, 16.04 % (n = 47,965) had an additional diagnosis of thrombocytopenia, while 83.96% (n = 251,139) did not. In our general sample of CLD patients, the average age was 58.4 years (SE = 0.08 y), 55.6% were men, 66.7% white, and 89.7% were non-elective admissions. Amongst patients with CLD and thrombocytopenia, the mean age was 59.3 years (SE = 0.09 y), 61.2% were men, 66.9% white and 93.2% were non-elective admissions. In patients with CLD without thrombocytopenia, the average age was 58.3 years (SE = 0.08 y), 54.6 % were men, 66.6% white, and 88.9% were non-elective admissions. Using multivariable models, patients with thrombocytopenia had higher odds of in-hospital mortality (OR: 1.30; 95% CI: 1.26-1.35) and higher hospital costs ($107,444 vs. $90,256, P < 0.0001) compared to those without thrombocytopenia. In addition, the LOS (5.86 d vs 5.14 d, p < 0.0001) was statistically significant **Conclusion:** Thrombocytopenia has a negative impact on patients with CLD, associated with increased mortality and hospitalization costs compared to CLD patients without thrombocytopenia lending credence to its use as a predictor of mortality and morbidity in these patients

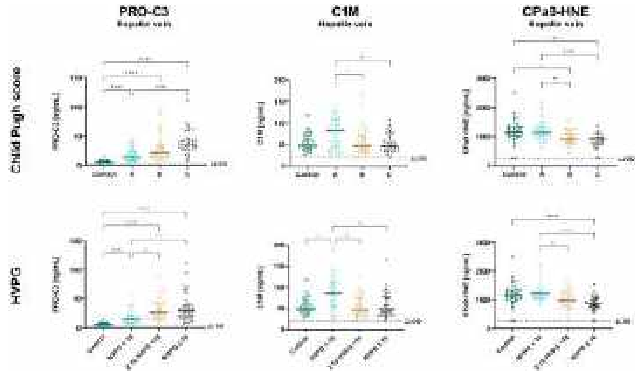
Disclosures: The following people have nothing to disclose: Oyedotun Babajide, Elizabeth Soladoye, Oluwanifemi Balogun, Abayomi Oyenuga, Kalpana Panigrahi

3125-A | INFLAMMATION BIOMARKERS REFLECT DISEASE SEVERITY AND DISCRIMINATE CLINICALLY SIGNIFICANT PORTAL HYPERTENSION IN CIRRHOSIS

Emilie Skovgaard, Nordic Bioscience a/S; University of Copenhagen, Nina Kimer, Bispebjerg University Hospital, Troels Malte Busk, Hvidovre Hospital, Morten Karsdal, Nordic Bioscience a/S, Denmark, Diana J. Leeming, Nordic Bioscience A/S and Søren Møller, Hvidovre Hospital, Hvidovre, Denmark

Background: Patients with cirrhosis and portal hypertension (PH) often develop complications that must be carefully monitored. The degree of PH is measured by the hepatic venous pressure gradient (HVPG), which however is an invasive procedure and search for noninvasive alternatives are warranted. This study aimed at investigating inflammation biomarkers for cirrhotic disease activity and to predict HVPG and clinically relevant HVPG cut-offs. **Methods:** The cohort included 105 patients with cirrhosis (Child Pugh classification A: n = 36, B: n = 34, C: n = 35) and 39 healthy controls. HVPG was assessed in patients with cirrhosis by liver vein catheterization. Inflammation biomarkers for type I collagen degradation (C1M) and a human neutrophil elastase fragment of calprotectin, a marker of neutrophil activity (CPa9-HNE), and the fibrogenesis biomarker of type III collagen (PRO-C3), were assessed in plasma EDTA samples from the hepatic vein. The performance of each marker to detect cirrhotic disease severity and clinically relevant HVPG cut-offs was determined as well as the correlation between each biomarker and HVPG. **Results:** PRO-C3 and CPa9-HNE correlated significantly with HVPG

($R_s = 0.34$ and $R_s = -0.31$ respectively, $p < 0.001$ for both). PRO-C3 significantly separated controls from all Child Pugh groups ($p < 0.0001$) and controls from HVPG cut-offs (HVPG < 10: $p < 0.001$, HVPG e 10: $p < 0.0001$), and furthermore separated patients with HVPG < 10 mmHg from patients with clinically significant PH (HVPG e 10 mmHg). Both inflammation markers, C1M and CPa9-HNE, decreased with cirrhotic disease severity and could significantly discriminate mild from moderate cirrhosis (C1M: $p < 0.05$, CPa9-HNE: $p < 0.01$) and mild from severe cirrhosis (C1M: $p < 0.05$, CPa9-HNE: $p < 0.0001$). Both markers could separate clinically significant PH from patients with HVPG < 10 mmHg. **Conclusion:** PH and increased disease severity in patients with cirrhosis were associated with a decrease in the inflammation related biomarkers, C1M and CPa9-HNE, whereas these were associated with an increase of the fibrogenesis biomarker PRO-C3. This might suggest that inflammation becomes less prominent in patients with moderate and severe cirrhosis and PH as compared to mild cirrhosis.



Disclosures: Morten Karsdal – Nordic Bioscience: Employee, No, No;

The following people have nothing to disclose: Emilie Skovgaard

Disclosure information not available at the time of publication: Nina Kimer, Troels Malte Busk, Diana J. Leeming, Søren Møller

3126-A | IT'S TIME TO REDEFINE CALORIE TARGETS IN CRITICALLY ILL VENTILATED PATIENTS WITH LIVER CIRRHOSIS – EVIDENCE FROM INDIRECT CALORIMETER BASED RANDOMIZED CONTROLLED TRIAL

Varsha Shasthry[1], Jaya Benjamin[2], Rakhi Maiwall[2], Guresh Kumar[3], Prashant Agarwal[1], Shiv Kumar Sarin[4] and Yogendra Kumar Joshi[2], (1)Ilbs, (2)Institute of Liver and Biliary Sciences, New Delhi, (3)Institute of Liver and Biliary Sciences, New Delhi, India, (4)Institute of Liver and Biliary Sciences

Background: Energy expenditure (EE) may not be augmented in all patients with liver cirrhosis (LC), critical illness and mechanical ventilation (MV) may influence it further. The energy requirement(ER) in critically ill ventilated patients with LC is not yet known. Over or underfeeding might influence clinical outcomes. Indirect calorimeter (IC) is the gold standard method to measure EE. Hence we aimed to study the effect of IC-guided energy delivery on the clinical outcome of mechanically ventilated patients with LC, primarily on the duration of MV and secondarily on changes in EE(Kcal/day), respiratory quotient (RQ), substrate oxidation(% of EE), nitrogen balance (NB) along with mortality at day 7 and day 28. **Methods:** In this single-center, non-blinded randomized, controlled trial conducted at an exclusive liver intensive care unit (ICU), MV patients with LC expected to stay for > 3 days (n = 252) were screened. Thereafter, 83 patients meeting inclusion and exclusion criteria were randomized to the intervention arm i.e. enteral nutrition (using polymeric formula) with ER measured by IC (MER; n = 42) and the control arm, ER estimated at 35-40 kcal/kg ideal body weight (IBW)/day as per recommendations (EER; n = 41). Intervention protocol was till weaning or death whichever was earlier. The protein target was 1.5g/Kg IBW in both groups. IC (Quark RMR) was performed under the steady state in all 83 patients on alternate days. NB was calculated using 24-hour urinary urea nitrogen. **Results:** The baseline characteristics of the patients are given in Table 1. The measured EE was significantly lower than the estimated (1689 ± 463 vs.2375 ± 295, $p < 0.001$). Energy and protein adequacy were comparable. There was no difference in the median duration of MV (days) between MER and EER groups [7 (IQR 5-10) vs. 8 (IQR 5-10); $p = 0.63$], however, the proportion of patients weaned off was significantly higher in the MER group compared to EER [13(31%) vs.5 (12.2%); $p = 0.038$; OR 3.2]. The measured EE, RQ, fat, and carbohydrate oxidation were comparable between the groups. Mean NB was positive in both groups. 7-day mortality was significantly lower in MER compared to the EER group [13/42(30.9) vs.21/41 (51.2); Log-rank $p = 0.025$]; 28-day mortality was comparable. **Conclusion:** The energy requirements in ventilated patients with liver cirrhosis are lower than recommended in the guidelines. Providing calories guided by IC, particularly in the initial 7 days of ICU admission increases the chances of weaning and survival in these patients.

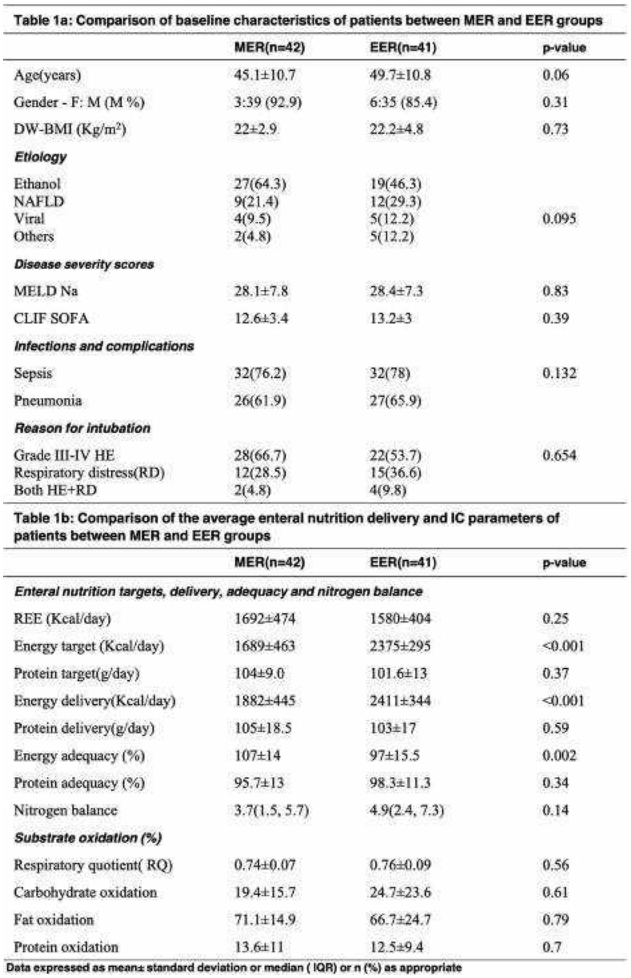


Table 1a: Comparison of baseline characteristics of patients between MER and EER groups

	MER(n=42)	EER(n=41)	p-value
Age(years)	45.1±10.7	49.7±10.8	0.06
Gender - F: M (M %)	3:39 (92.9)	6:35 (85.4)	0.31
DW-BMI (Kg/m²)	22±2.9	22.2±4.8	0.73
Etiology			
Ethanol	27(64.3)	19(46.3)	
NAFLD	9(21.4)	12(29.3)	
Viral	4(9.5)	5(12.2)	0.095
Others	2(4.8)	5(12.2)	
Disease severity scores			
MELD Na	28.1±7.8	28.4±7.3	0.83
CLIF SOFA	12.6±3.4	13.2±3	0.39
Infections and complications			
Sepsis	32(76.2)	32(78)	0.132
Pneumonia	26(61.9)	27(65.9)	
Reason for intubation			
Grade III-IV HE	28(66.7)	22(53.7)	0.654
Respiratory distress(RD)	12(28.5)	15(36.6)	
Both HE+RD	2(4.8)	4(9.8)	

Table 1b: Comparison of the average enteral nutrition delivery and IC parameters of patients between MER and EER groups

	MER(n=42)	EER(n=41)	p-value
Enteral nutrition targets, delivery, adequacy and nitrogen balance			
REE (Kcal/day)	1692±474	1580±404	0.25
Energy target (Kcal/day)	1689±463	2375±295	<0.001
Protein target(g/day)	104±9.0	101.6±13	0.37
Energy delivery(Kcal/day)	1882±445	2411±344	<0.001
Protein delivery(g/day)	105±18.5	103±17	0.59
Energy adequacy (%)	107±14	97±15.5	0.002
Protein adequacy (%)	95.7±13	98.3±11.3	0.34
Nitrogen balance	3.7(1.5, 5.7)	4.9(2.4, 7.3)	0.14
Substrate oxidation (%)			
Respiratory quotient(RQ)	0.74±0.07	0.76±0.09	0.56
Carbohydrate oxidation	19.4±15.7	24.7±23.6	0.61
Fat oxidation	71.1±14.9	66.7±24.7	0.79
Protein oxidation	13.6±11	12.5±9.4	0.7

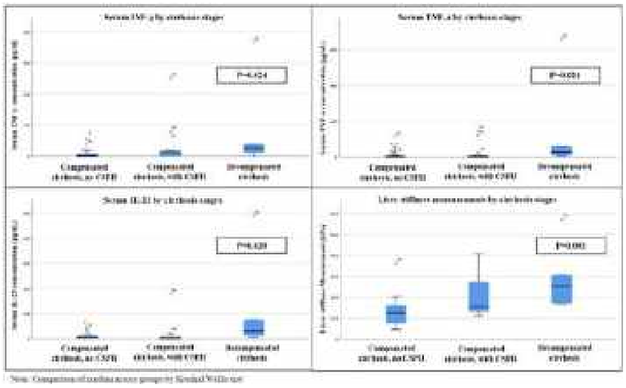
Data expressed as mean± standard deviation or median (IQR) or n (%) as appropriate

Disclosures: The following people have nothing to disclose: Varsha Shasthry, Jaya Benjamin, Rakhi Maiwall, Guresh Kumar, Prashant Agarwal, Shiv Kumar Sarin, Yogendra Kumar Joshi

3127-A | LIVER STIFFNESS MEASUREMENT STRONGLY CORRELATES WITH SYSTEMIC INFLAMMATION IN STABLE CIRRHOSIS PATIENTS

Yu JUN Wong[1,2], Heng Yi Tan[3], Geraldine Lim[4], Siew Yoon Yap[4], Seok Hwee Khoo[4], Jessica Tan[1], Rahul Kumar[1,2] and Paul Edward Hutchinson[3], (1)Department of Gastroenterology & Hepatology, Changi General Hospital, (2)Duke-Nus Medical School, Singhealth, (3) Flow Cytometry Laboratory, Life Sciences Institute, National University of Singapore, (4)Clinical Trial Research Unit, Changi General Hospital

Background: Liver stiffness measurement (LSM) is a non-invasive prognostic fibrosis marker which predicts liver-related events in liver cirrhosis patients (PMID: 36064306). While liver inflammation may influence LSM, the association between LSM and systemic inflammation in stable cirrhosis patients is unknown. We aim to evaluate the association between changes in LSM and systemic inflammation in stable cirrhosis patients. **Methods**:This single center prospective cohort study recruited stable cirrhosis patients between 1st May 2022 to 31st January 2023. Peripheral blood serum was collected on the same day of liver stiffness measurement (LSM). LSM was performed using vibration-controlled transient elastography (VCTE) as per manufacturer's instruction. Primary predictor was the changes in LSM. The primary outcomes were changes in serum cytokines measured using BioLegend LegendPlex Assay. Patients with signs of infection or on immunosuppressants within 2 weeks were excluded from the analysis. **Results:** A total of 46 stable cirrhosis patients (95.8% Child-Pugh Class A, 75% ALBI grade 1) were analyzed. The median (IQR) age was 63 (56-71), 54.2% were male; with NASH (43.8%) being the predominant cirrhosis etiology in this cohort, followed by HBV (39.6%) and HCV (12.5%). Median (IQR) FIB-4 was 2.2 (1.4-3.5); median LSM was 14.1kPa (11.1-19.6), with 100% having reliable LSM ($IQR/M < 0.3$). At baseline, the median (IQR) white cell count (WBC) was 6.4 (5.2-7.5), neutrophil/leukocyte ratio (NLR) was 1.8 (1.5-2.8), BMI was 27.1 (23.8-30.1), and ALT was 30 (22-46). LSM strongly correlates with multiple inflammatory cytokines: IFN-γ (0.68, $p < 0.001$), TNF-α ($r = 0.66$, $p < 0.001$), IL-1β ($r = 0.61$, $p < 0.001$), IL-8 ($r = 0.64$, $p = 0.001$), IL 18 ($r = 0.59$, $p < 0.001$), IL-10 ($r = 0.57$, $p < 0.001$), TGF-β1 ($r = 0.60$, $p < 0.001$). Among patients with normal ALT (< 35 IU/ml), these correlations remained strong: IFN-γ (0.70, $p < 0.001$), TNF-α ($r = 0.72$, $p < 0.001$), IL-1β ($r = 0.68$, $p < 0.001$), IL-8 ($r = 0.70$, $p < 0.001$), IL 18 ($r = 0.59$, $p = 0.001$), IL-10 ($r = 0.63$, $p = 0.002$), and TGF-β1 ($r = 0.65$, $p = 0.001$). IFN-γ, TNF-α, IL-23 and LSM increase as cirrhosis stages progress from compensated cirrhosis without clinically significant portal hypertension (CSPH), compensated cirrhosis with CSPH to decompensated cirrhosis (Figure 1). Neither the age, BMI, white cell count, neutrophil/leukocyte ratio, ALT, AST nor platelet correlates with any of these cytokines. **Conclusion:** LSM strongly correlates with systemic inflammation in stable cirrhosis patients. Our novel finding suggests LSM and measurement of serum inflammatory cytokines may aid in further phenotyping stable cirrhosis patients beyond fibrosis stage.



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Rahul Kumar – Gilead: Speaking and Teaching, No, No; Abbvie: Speaking and Teaching, No, No; Intercept Pharma: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; Verve Therapeutics: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; Crisper Therapeutics: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; Madrigal Therapeutics: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; ETNB: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
The following people have nothing to disclose: Heng Yi Tan, Geraldine Lim, Siew Yoon Yap, Seok Hwee Khoo, Jessica Tan
Disclosure information not available at the time of publication: Paul Edward Hutchinson

3128-A | MELD 3.0: AN UPDATED MODEL FOR PREDICTION OF MORTALITY AMONGST PATIENTS WITH CIRRHOSIS VALIDATED IN A LARGE TERTIARY HOSPITAL IN SINGAPORE

Hong-Yi Lin[1], Pooi Ling Loi[2], Jeanette Pei-Xuan Ng[3], Wei Quan Teo[4], Amber Chung[4], Prema Raj[4] and Jason Pik Eu Chang[3], (1)Yong Loo Lin School of Medicine, National University of Singapore, (2)Department of Gastroenterology & Hepatology, Singapore General Hospital, Singapore, (3)Singapore General Hospital, (4) Singhealth-Duke Nus Transplant Centre

Background: The original Model for End-Stage Liver Disease (MELD) was introduced to predict 3-month survival to prioritize organ allocation for liver transplantation and has been updated since its inception. A recent study in the USA optimized the current model (MELDNa) with new variables and updated coefficients to propose MELD 3.0, the latest model which could suggest better prediction of 3-month mortality. This study aims to validate the prognostic performance of MELD 3.0 in patients with cirrhosis admitted to Singapore's largest tertiary hospital. **Methods:** Demographical, clinical, biochemical and survival data of patients with cirrhosis admitted to Singapore General Hospital (SGH) from January 01, 2018, to December 31, 2018, were studied retrospectively. Area under the receiver operating characteristic curves (AUROC) was computed to determine the discriminative effects of three prognostic models (MELD 3.0, MELDNa, and MELD) to predict 1-month (30-day), 3-month (90-day) and 1-year (365-day) mortality and compared with the DeLong's test. Youden's index was used to determine the optimal MELD 3.0 cut-off for high-risk patients. Competing risk analysis was performed for patients at various risk levels. **Results:** 862 patients were included (median age 70.0 years [IQR 63.0–78.7], 65.4% males, 75.8% Chinese). The proportion of patients with Child-Turcotte-Pugh classes A/B/C at admission were 55.5%, 35.5% and 9.0% respectively. The median scores of MELD 3.0, MELDNa and MELD were 12.2 (IQR 8.7–18.3), 11.0 (IQR 8.0–17.5), 10.3 (IQR 7.8–15.0) respectively. The 30-day, 90-day, 365-day mortality were 5.7%, 13.2% and 26.9% respectively. MELD 3.0 performed significantly better compared to MELDNa and MELD in predicting 30-day, 90-day, 365-day mortality (AUROC of MELD3.0/MELDNa/MELD: 0.823/0.793/0.783, 0.754/0.724/0.707, 0.682/0.644/0.654, in predicting 30-day, 90-day, 365-day mortality respectively, all $p < 0.05$) (Table 1). Patients with a MELD 3.0 score > 17 had high risk of 90-day mortality. When compared to patients with MELD 3.0 score d 17, patients with MELD 3.0 score > 17 had significantly poorer survival ($p < 0.05$) and had higher 90-day mortality (46.8% vs 16.4%). **Conclusion:** MELD 3.0 performed better than its predecessors in predicting mortality in patients with cirrhosis admitted to SGH, consistent with the findings in the recent USA study. MELD 3.0 score > 17 predicts higher mortality.

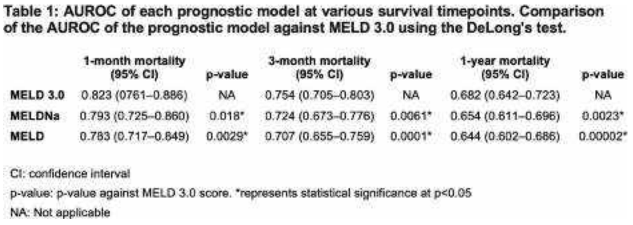


Table 1: AUROC of each prognostic model at various survival timepoints. Comparison of the AUROC of the prognostic model against MELD 3.0 using the DeLong's test.

	1-month mortality (95% CI)	p-value	3-month mortality (95% CI)	p-value	1-year mortality (95% CI)	p-value
MELD 3.0	0.823 (0761–0.886)	NA	0.754 (0.705–0.803)	NA	0.682 (0.642–0.723)	NA
MELDNa	0.793 (0.725–0.860)	0.018*	0.724 (0.673–0.776)	0.0061*	0.654 (0.611–0.696)	0.0023*
MELD	0.783 (0.717–0.849)	0.0029*	0.707 (0.655–0.759)	0.0001*	0.644 (0.602–0.686)	0.00002*

CI: confidence interval

p-value: p-value against MELD 3.0 score. *represents statistical significance at p<0.05

NA: Not applicable

Disclosures: The following people have nothing to disclose: Hong-Yi Lin, Pooi Ling Loi, Jeanette Pei-Xuan

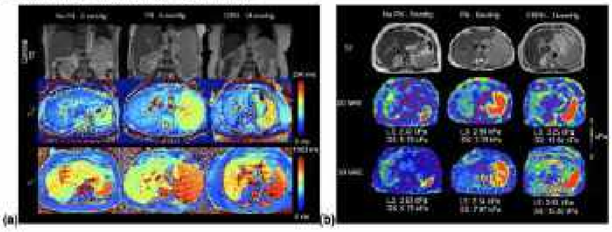
Ng, Wei Quan Teo, Amber Chung, Prema Raj, Jason Pik Eu Chang

3129-A | NONINVASIVE DIAGNOSIS OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION WITH MR ELASTOGRAPHY, T1, AND T1Á MAPPING OF THE LIVER AND SPLEEN

Efe Ozkaya[1], Octavia Bane[1], Amine Geahchan[1], Paul Kennedy[1], Stefanie Hectors[1], Aaron Fischman[1], Swan N. Thung[2] and Bachir Taouli[3], (1)Icahn School of Medicine at Mount Sinai, (2)Icahn School of Medicine at Mount Sinai (ISMMS), (3)Mount Sinai Hospital, New York, NY

Background: Portal hypertension (PH), a common complication of liver cirrhosis, is defined as an elevated portal venous pressure gradient across the liver due to increased intra-hepatic vascular resistance. PH is diagnosed via invasive measurement of hepatic venous pressure gradient (HVPG) > 5 mmHg, and clinically significant PH (CSPH) by HVPG e 10 mmHg. Quantitative magnetic resonance imaging (MRI) has shown promise for non-invasive diagnosis and characterization of liver disease and PH. The goal of our study is to evaluate the diagnostic value of MR elastography, T_1, and $T_{1\rho}$ mapping in patients with chronic liver disease. **Methods:** Our prospective IRB approved study included 67 patients (M/F = 35/32, mean age 52.5 y, range 19-79y) with chronic liver disease of mixed etiologies and suspected PH. All patients underwent abdominal MRI at 1.5T (Aera, Siemens) including MRE, $T_{1\rho}$, and T_1 mapping pre and post injection of gadoxetate disodium at the hepatobiliary phase (HBP) of the liver and spleen (Figure 1). Invasive HVPG measurements and transjugular liver biopsy were performed within 1 month of MRI. 2D MRE and 3D MRE were performed at 60 Hz using SE-EPI sequences and dual passive drivers enabling simultaneous liver and spleen acquisition. For T_1 mapping, an IR Look-Locker protocol with 32 inversion times, was used before and 20 minutes after injection of gadoxetate. T_1 maps were generated in MATLAB 2021 by fitting the signal to modified Look-Locker equation. $T_{1\rho}$ maps were obtained mid-liver and mid-spleen by mono-exponential fit of four images at 500Hz spin- lock frequency and 4 different spin-lock times. Association between liver/spleen MRI parameters with HVPG were assessed using Spearman correlation. Diagnostic models combining multiple parameters were constructed by logistic regression. The diagnostic performance of the parameters and models for prediction of CSPH was determined by ROC analysis. **Results:** Mean HVPG measurement was 6.3 ± 5.1 mmHg, and 13 (19%) patients had CSPH. 2D MRE of the liver ($r = 0.450$, $p < 0.001$), 2D MRE of the spleen ($r = 0.434$, $p < 0.001$), and 3D MRE of the liver ($r = 0.428$, $p = 0.002$) showed the strongest correlations with HVPG compared to other parameters (Figure 1). For prediction of CSPH, the best diagnostic performance was observed with 2D MRE spleen stiffness (AUC = 0.869; Figure 1, $p < 0.001$). This was followed by 2D MRE liver stiffness, T1-HBP and liver $T_{1\rho}$ with AUCs 0.817 (0.768 = 0.970), 0.806 (0.683-0.928), and 0.802 (0.671-0.934), respectively. A logistic regression model combining 2D MRE spleen stiffness with liver and spleen $T_{1\rho}$ diagnosed CSPH with AUC = 0.917 (0.807-1.00). **Conclusion:** 2D MRE spleen stiffness is a promising biomarker of CSPH. Our results show that hemodynamic changes associated with PH can be diagnosed non-invasively through splenic stiffness measurement, and through combinations of liver and spleen quantitative MRI parameters.

Figure 1: **(a)** Coronal T_2-weighted anatomical images (top row), $T_{1\rho}$ maps (middle row), and T_1 maps (bottom row) of a 59-year-old male with no PH (left), a 79-year-old female with PH (middle), and 63-year- old male with CSPH (right). From left to right, measured values for liver T_1 were 594.4, 540.9, 638.9 msec, for spleen T_1 values were 774.2, 777.1, 830.3 msec. Spleen showed a clear $T_{1\rho}$ elevation with increased PH severity (from left to right: 99.0, 109.6, and 131.4 msec), while liver $T_{1\rho}$ values measured were 7.9, 55.7, 53.1 msec. **(b)** Axial T_2-weighted anatomical images (top row), 2D MRE elastograms (middle row), and 3D MRE elastograms (bottom row) of a 60-year-old male with no PH (left), a 79-year-old female with PH (middle), and 65-year-old male with CSPH (right). HVPG, liver stiffness (LS), and spleen stiffness (SS) are also shown. **(c)** Correlation between significant imaging parameters of Liver and Spleen with HVPG. **(d)** Diagnostic performance of significant parameters of Liver and Spleen in patients without CSPH (<10 mmHg) vs. those with CSPH (≥10 mmHg).



(c)

Technique	Parameter	r	p-value
Elastography	Liver Stiffness 2D MRE	0.450**	<0.001
	Liver Stiffness 3D MRE	0.428**	0.002
	Liver Storage 3D MRE	0.436**	0.002
	Spleen Stiffness 2D MRE	0.434**	<.001
	Spleen Stiffness 3D MRE	0.389**	.004
T1	Liver T1pre	0.333**	0.008
	Liver T1 HBP	0.368*	0.013
	Spleen T1ρ	0.322**	.009
Serum test	Platelets	-0.303*	0.015
	FIB-4	0.569**	<0.001

**Correlation is significant at the 0.01 level; *Correlation is significant at the 0.05 level

(d)

Parameters	no-CSPH (<10mmHg)	CSPH (≥10mmHg)	p-value (MWU)	AUC [95% CI]	Sensitivity	Specificity	Cutoff
Liver Stiffness 2D MRE (kPa)	N=50 4.28±2.47	N=12 6.75±2.04	0.001	0.817 [0.667-0.967]	0.833	0.720	4.55
Liver Stiffness 3D MRE (kPa)	N=40 4.23±3.25	N=11 6.88±3.72	0.005	0.777 [0.620-0.935]	0.818	0.825	4.89
Liver Storage 3D MRE (kPa)	N=36 3.65±2.75	N=9 5.07±3.44	0.005	0.802 [0.660-0.945]	0.889	0.75	3.98
Spleen Stiffness 2D MRE (kPa)	N=46 7.38±2.30	N=11 11.25±2.55	<0.001	0.869 [0.768-0.970]	1.000	0.646	7.56
Spleen Stiffness 3D MRE (kPa)	N=41 8.46±3.42	N=11 11.29±4.51	0.023	0.725 [0.512-0.938]	0.818	0.756	9.70
Liver T1pre (msec)	N=47 540.31±77.88	N=13 597.37±41.05	0.004	0.764 [0.645-0.883]	0.923	0.660	564.40
Liver T1 HBP (msec)	N=36 252.24±166.50	N=9 400.62±94.66	0.005	0.806 [0.683-0.928]	0.889	0.750	327.29
Liver T1ρ	N=54 48.9±7.4	N=12 55.7±5.8	<0.001	0.802 [0.671-0.934]	0.846	0.745	52.5
Spleen T1ρ	N=54 96.7 ± 17.9	N=13 113.4 ± 19.1	0.016	0.718 [0.555-0.881]	0.692	0.706	106.2
FIB-4	N=46 2.73±2.48	N=13 5.93±4.60	0.004	0.760 [0.613-0.906]	0.692	0.771	0.483

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

Ezra Lowe[1], Steven Schoenfeld[1], Eric Lawitz[2], Stephen A Harrison[3], Zeid Kayali[4] and Pol Boudes[1], (1)Galectin Therapeutics, (2)Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX, (3) Pinnacle Clinical Research Center, San Antonio, TX, (4) Inland Empire Liver Foundation

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

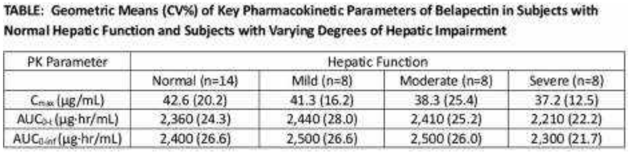

TABLE: Geometric Means (CV%) of Key Pharmacokinetic Parameters of Belapectin in Subjects with Normal Hepatic Function and Subjects with Varying Degrees of Hepatic Impairment

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

Disclosures: Ezra Lowe – Galectin Therapeutics: Employee, Yes, No;
Eric Lawitz – Abbvie, Gilead Sciences, Intercept: Speaking and Teaching, No, No; Akero, Boehringer Ingelheim, BMS, Intercept, Novo Nordisk, Metacrine, Sagimet, Terns: Advisor, No, No; 89Bio Inc., AbbVie, Akero Therapeutics, Allergan, Alnylam Pharmaceuticals Inc., Amgen, Ascelia Pharma, AstraZeneca, Axcella Health, Boehringer Ingelheim, Bristol-Myers Squibb, Conatus Pharmaceuticals, Cymabay Therapeutics, CytoDyn, DSM, Durect Corporation: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
Stephen A Harrison – Novo Nordisk: Speaking and Teaching, Yes, No;
The following people have nothing to disclose: Steven Schoenfeld
Disclosure information not available at the time of publication: Zeid Kayali, Pol Boudes

f 3131-A | SINGLE NUCLEAR RNA SEQUENCING OF TERMINAL ILEUM IN PATIENTS WITH CIRRHOSIS DEMONSTRATES MULTI-FACETED ALTERATIONS IN THE INTESTINAL BARRIER

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

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

early (on lactulose) & advanced (on rifaximin). snRNA-seq was performed and Seurat 4.0, an R package was employed to analyse the feature-barcode matrices. Cell-type-specific marker genes were used for the identification of cell types. QIAGEN Ingenuity Pathway Analysis (IPA) was used to identify the cell-type specific pathways dysregulated in cirrhosis. Specific genes related to inflammation (IL-1, IL-6, TNFa) and mucus production were compared across all cell types and within enterocytes, goblet, and Paneth cells. **Results**: Subjects: We performed snRNA-seq in 4 subjects who were age-matched (56 y); the highest MELD was in the advanced decomp group (14) vs early decomp (9) vs comp (6). SnRNAseq successfully identified all different cell types. There is a significant loss of stem cells in all cirrhosis pts (1.55-5.74% vs 21.5% controls). The relative proportion of Paneth cells was higher in advanced decomp (18% vs 4-8% in the rest).

Inflammatory genes: IL1, IL6 and TNF-related genes were significantly upregulated in the enterocytes in all decompensated subjects, especially those with advanced HE compared to healthy control (Fig 1C).

Paneth cells: The greatest expression of defensin-coding genes was in controls, compensated cirrhosis vs decomp pts (advanced or not).

Goblet cells: Lower expression of goblet cell markers (FcGBP,CLCA1, and SPDEF, involved in differentiation of goblet cells, improving mucus regeneration and suppressing inflammation) was seen in advanced decomp pts. However, MUC2 expression, involved in mucin production was higher in both decomp groups. IPA: We found higher IL6, IFN gamma and alpha activation, adhesion, cytotoxicity, and migration of polymorphs and lymphocytes and lower xenobiotics handling (PXR, RXR) and protein kinase signaling in advanced decomp vs remaining groups. **Conclusion**: Using snRNA-seq in the terminal ileum of patients with compensated and decompensated cirrhosis compared to controls, we found a higher inflammatory expression along with suppressed defensin and mucus stabilization gene expression in decompensated compared to other groups. All cirrhosis pts had lower stem cell population versus controls. These alterations may contribute to the many aspects of intestinal barrier dysfunction in advanced cirrhosis.

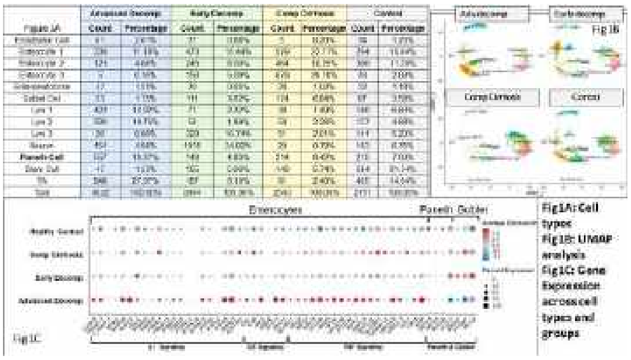

Fig1A: Cell types Fig1B: UMAP analysis Fig1C: Gene Expression across cell types and groups

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

Huiping Zhou:

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

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Background: Porto-sinusoidal vascular disease (PSVD), formerly referred to as idiopathic non-cirrhotic portal hypertension, encompasses a diverse group of disorders that primarily affects the porto-sinusoidal vascular system resulting in portal hypertension. Multiple etiologies including immunologic, hematologic, genetic disorders, infections, toxins, and drugs can cause PSVD. Variceal bleeding is the common initial manifestation of clinically significant portal hypertension (CSPH) in patients with PSVD. BAVENO VII criteria are a validated noninvasive model to identify CSPH and varices in cirrhotic patients. However, these criteria do not apply to PSVD. We aimed to develop a noninvasive diagnostic model for predicting varices and CSPH in PSVD. **Methods:** We included a single center cohort of biopsy proven PSVD patients who were part of a prospective natural history protocol (NCT02417740). All patients had liver stiffness (LSM) measured using transient elastography and upper endoscopy or imaging studies assessing for presence of CSPH. CSPH was defined by BAVENO VII specific criteria as the presence of any one of: varices on endoscopy, portal hypertensive bleeding, or porto-systemic collaterals on imaging. Univariate analysis was used to examine variables that can predict varices and CSPH. Multivariate model was constructed using a logistic regression analysis of statistically significant variables in univariate analysis. A sequential-testing algorithm was developed using the best performing model. **Results:** Of the 44 patients, 28 (64%) had varices and 35 (79.5%) had CSPH. LSM was higher in patients with varices (12.7 kPa vs 6 kPa, $p < 0.01$) and CSPH (12 kPa vs 5.4 kPa, $p < 0.01$). Platelet count was lower in patients with varices (71 vs 151, $p < 0.01$) and CSPH (84 vs 144, $p = 0.03$). Multivariate analysis combining LSM, and platelet count predicts varices (AUROC 0.82 ± 0.07, $p < 0.01$) and CSPH (AUROC 0.86 ± 0.07, $p < 0.01$). A step-wise algorithm combining LSM of 10 kPa and platelet of 80 x 10^9 /L was developed.(Figure) This algorithm performed with specificity of 81%, negative predictive value (NPV) of 81% and positive predictive value (PPV) of 89% to detect varices ($p < 0.001$). The same model performed with sensitivity of 77%, specificity of 89% and PPV of 96% to detect CSPH ($p < 0.001$). Accuracy of the model for predicting varices and CSPH was 93% and 80%, respectively. **Conclusion:** We developed a simple model by combining LSM with platelet count that can be used to identify CSPH in PSVD patients. This noninvasive model can predict the risk of varices and aid in deciding the need for endoscopic surveillance or initiating therapy for portal hypertension. However, this model requires further validation in a larger independent cohort.

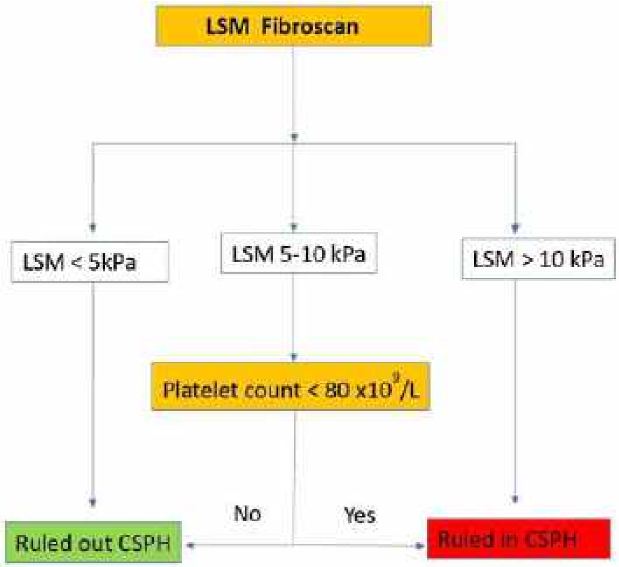

Figure: Step-wise decision algorithm

Disclosures: The following people have nothing to disclose: Harish Gopalakrishna, Maria Mironova, Nehna Abdul Majeed, Asif Ali Hitawala, Shani Scott, Jaha Norman-Wheeler, David E Kleiner, Christopher Koh, Theo Heller

3133-A | ACCURACY OF A DEDICATED 100 HZ VIBRATION-CONTROLLED SPLEEN STIFFNESS MEASUREMENT VERSUS BAVENO CRITERIA FOR THE DETECTION OF VARICES IN PATIENTS WITH COMPENSATED CIRRHOSIS

Angelo Armandi[1,2], Tiziana Sanavia[2], Emma Vanderschueren[3,4], Georg Semmler[5], Antonio Liguori[6], Salvatore Petta[7], Maurice Michel[1], Merle Marie Werner[1], Talal Merizian[1], Christian Labenz[1], Mathias Jachs[8], Mattias Mandorfer[5], Wim Laleman[3,9], Luca Miele[6], Thomas Reiberger[10] and Jörn M. Schattenberg[1], (1)University of Mainz, (2)University of Turin, (3)University Hospitals Leuven, (4)Catholic University of Leuven, Department of Chronic Diseases, Metabolism and Aging (CHROMETA), Leuven, Belgium, (5)Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria, (6)Università Cattolica Di Roma, Department of Internal Medicine, Fondazione Policlinico a. Gemelli, (7)Sezione Di Gastroenterologia, Dipartimento Promozione Della Salute, Materno-Infantile, Di Medicina Interna e Specialistica Di Eccellenza "G. D'alessandro", Università Di Palermo, Palermo, Italy, (8)Medical University of Vienna, (9)Catholic University of Leuven, Leuven, Belgium, (10)Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna

Background: Clinically significant portal hypertension (CSPH) marks a critical step in the natural history of compensated advanced chronic liver disease (cACLD) and may lead to esophageal varices (EV). The Baveno VI criteria suggest liver stiffness measurement (LSM) and platelet count (PLT) for non-invasive identification of cACLD patients not requiring screening gastroscopy. We investigated the accuracy of the novel 100 Hz vibration-controlled transient elastography-based spleen stiffness measurement (SSM) exam for the identification of EV in cACLD patients. **Methods:** Retrospective study of Mainz, Vienna, Leuven, Rome and Palermo. Patients with cACLD of any etiology (LSM ≥ 10kPa or histological F4 fibrosis), but without previous decompensation (bleeding, encephalopathy, ascites) were included. SSM and LSM were obtained using Fibroscan F630 ≤ 1 month within screening gastroscopy. Prediction performance between different SSM cut-offs with respect to the Baveno criteria (LSM > 20kPa and/or PLT < 150 G/L) were compared by logistic regression with 10-fold cross-validation, adjusted for age, gender, BMI, transaminases, INR, albumin, and bilirubin. Backward feature selection based on likelihood ratio test was applied to identify significant confounders. Performance was calculated by balanced accuracy (BA), specificity (SP) and sensitivity (SE). Wilcoxon test was used to evaluate significant performance improvement of SSM cut-offs with respect to Baveno criteria, or to signifcant confounders. **Results:** 343 cACLD patients with a median age of 59 years (60.3% male) and NAFLD as the main etiology (51.3%) were included. 137 had EV with 49 high-risk EV (HR-EV), while median SSM, LSM and PLT were 40.5kPa, 21kPa and 139 G/L, respectively. The figure shows BAs at different SSM cut-offs, compared to Baveno (red line). The best overall performance with all-type EV was at SSM = 60 kPa (BA = 0.72, SP = 0.86, SE = 0.58); Baveno: BA = 0.66, SP = 0.86, SE = 0.39. Comparing HR-EV vs. absence of EV, the best cut-off was at 50kPa (BA = 0.71, SP = 0.95, SE = 0.47; Baveno: BA = 0.56, SP = 0.92, SE = 0.29). These SSM thresholds significantly improved BA when significant confounders were considered. **Conclusion:** The novel spleen-dedicated 100 Hz SSM is associated with presence of EV in cACLD patients. In both all-type EV and HR-EV, SSM showed better accuracy than the Baveno LSM-PLT criteria, achieving a better trade-off between SP and SE.

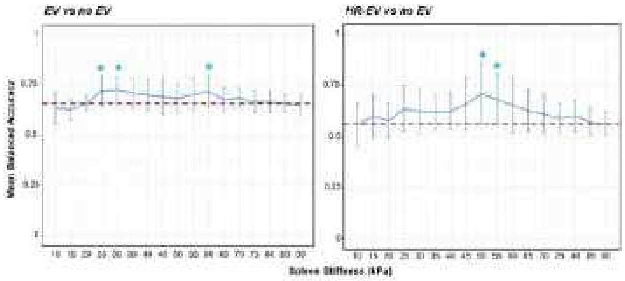

Figure 1. Mean Balanced Accuracy at different Spleen Stiffness cut-offs. Dashed red-line: Baveno performance. The asterisk indicates that the SSM models showed a balanced accuracy significantly higher (i.e. Wilcoxon test p-value <5%) with respect to both the same model including only the selected confounders and Baveno.

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The following people have nothing to disclose: Angelo Armandi, Tiziana Sanavia, Emma Vanderschueren, Georg Semmler, Antonio Liguori, Salvatore Petta, Maurice Michel, Merle Marie Werner, Talal Merizian, Christian Labenz, Mathias Jachs, Mattias Mandorfer, Luca Miele, Jörn M. Schattenberg

3134-A | AN INTERNATIONAL SURVEY ON PRACTICE PATTERNS FOR THE MANAGEMENT OF GASTRIC VARICES

Lolwa Al-Obaid[1], Mohammad Bilal[2], Katarzyna M. Pawlak[3], Nadeem Tehami[4], Diogo De Moura[5], Rashid Ns Lui[6], Jayanta Samanta[7], Aymen Almuhaidb[8], Andres Rodriguez Parra[9], Andres Cardenas[10], Marvin Ryou[11] and Ahmad Najdat Bazarbashi[1], (1)Washington University in St. Louis, (2)University of Minnesota, (3) Samodzielny Publiczny Zaklad Opieki Zdrowotnej Ministerstwa Spraw Wewnetrznych I Administracji w Szczecinie, (4)University Hospital Southampton NHS Foundation Trust, (5)Universidade De Sao Paulo Hospital Das Clinicas Da Faculdade De Medicina De Ribeirao Preto, (6)The Chinese University of Hong Kong, (7)Postgraduate Institute of Medical and Educational Research, (8)King Faisal Specialist Hospital and Research Center, (9)Hospital General Dr Manuel Gea Gonzaleza, (10)Barcelona Clinic, Barcelona, Spain, (11)Brigham and Women's Hospital

Background: Gastric varices (GV) account for 10-20% of all variceal bleeding and are associated with significant morbidity and mortality. Management of GV include medical, endoscopic and interventional radiology (IR) therapies, however, many of these therapies remain debated with few well-established societal guidelines. The aim of this study was to evaluate international practice patterns of providers managing GV. **Methods:** A 34 item online questionnaire assessing baseline demographics of survey respondents and practice patterns managing GV were sent to providers caring for patients with gastrointestinal disorders. Data was analysed based on survey responses. Mean with standard deviations were calculated for continuous data, while percentages were calculated for categorical data. **Results:** A total of 187 respondents from 6 continents were included. Demographics are summarized in table 1. More than half respondents were from North America and Asia. Advanced endoscopy was the most common subspecialty. Beta blockers were the most common primary prevention modality across all regions ($n = 128$, 68.7%). Respondents in North America were more likely to refer patients to IR for the management of bleeding isolated gastric varices (IGV-1) than physicians in all other regions (49.2% vs 10.6%, $p = 0.0001$). Compared with hepatologists, interventional endoscopists were more likely to recommend EUS-guided coil therapy for management of initial and recurrent bleeding IGV-1 (20% vs 3.3%, $p = 0.037$, 30.3% vs 3.2%, $p = 0.0011$). For bleeding gastroesophageal varices type-1 (GOV-1), endoscopic variceal ligation (EVL) was uniformly the most common treatment approach ($n = 108$, 57.8%). While glue injection was the most common method of endoscopic treatment for bleeding IGV-1/GOV-2 overall, physicians in Asia used it more frequently than all other regions (83% vs 50.1 % $p = 0.0001$). N-Butyl-2-Cyanoacrylate was the most commonly used glue ($n = 89$, 48.1%). Surveillance EGD was recommended one month following endoscopic glue injection by 72.5% of respondents. EUS-guided coil therapy for bleeding GV was used more frequently in North America than other regions combined (34% vs 5%, $p = 0.0001$) [Figure 1] with 83.7% of respondents preferring the use of coil with glue as opposed to coils alone, with 87.8% favoring 19g needles. Significant variability existed in recommended surveillance timeline post EUS-coil therapy. Respondents in North America and Europe were more likely to refer patients with recurrent GV bleeding to IR, compared with their counterparts in all other regions (67% vs 48%, $p = 0.0092$). **Conclusion:** This study highlights geographic variations in the management of GV, likely due to resources, expertise and historical practice patterns. EUS coil therapy is increasingly being utilised in North America, while traditional endoscopic glue injection continues to be the most common endoscopic approach.

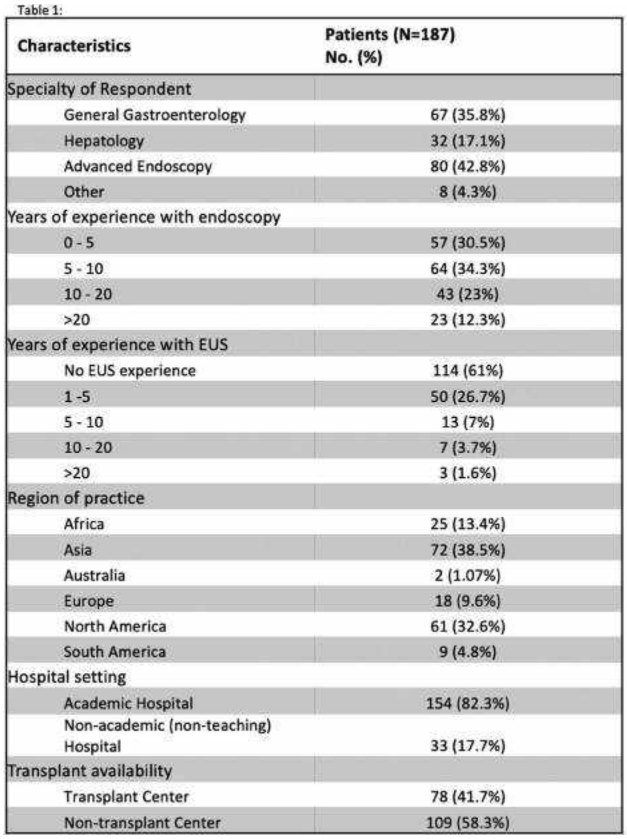

Table 1:

Characteristics	Patients (N=187) No. (%)
Specialty of Respondent	
General Gastroenterology	67 (35.8%)
Hepatology	32 (17.1%)
Advanced Endoscopy	80 (42.8%)
Other	8 (4.3%)
Years of experience with endoscopy	
0 - 5	57 (30.5%)
5 - 10	64 (34.3%)
10 - 20	43 (23%)
>20	23 (12.3%)
Years of experience with EUS	
No EUS experience	114 (61%)
1 -5	50 (26.7%)
5 - 10	13 (7%)
10 - 20	7 (3.7%)
>20	3 (1.6%)
Region of practice	
Africa	25 (13.4%)
Asia	72 (38.5%)
Australia	2 (1.07%)
Europe	18 (9.6%)
North America	61 (32.6%)
South America	9 (4.8%)
Hospital setting	
Academic Hospital	154 (82.3%)
Non-academic (non-teaching) Hospital	33 (17.7%)
Transplant availability	
Transplant Center	78 (41.7%)
Non-transplant Center	109 (58.3%)

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3135-A | ASPIRIN REDUCES RISK OF ASCITES AND ENCEPHALOPATHY IN CIRRHOTIC PATIENTS WITHOUT INCREASING THE RISK OF GASTROINTESTINAL BLEEDING

Roie Tzadok, Nir Bar, Ayelet Grupper, Eugene Feigin and Helena Katchman, Tel Aviv Sourasky Medical Center

Background: There is accumulating data regarding the beneficial effects of aspirin on the advancement of liver fibrosis, both in animal models and on laboratory indices of fibrosis. Aspirin was also shown to be associated with reduced HCC risk in cirrhotic patients. This study was aimed to evaluate clinical outcomes in cirrhotic patients treated with aspirin in comparison to non-treated cirrhotic patients.

Methods: In a retrospective study at Tel Aviv Sourasky Medical Center, we compared aspirin treated cirrhotic patients for various indications to non-treated patients. Patients were followed-up for composite clinical outcomes, including decompensations, thrombotic and vascular complications (portal vein thrombosis, DVT, TIA, CVA, acute coronary syndrome and myocardial infarction) and HCC. Cox regression multivariate models were used to compare clinical sequalae between the groups. **Results:** From 2009-2018, 2413 patients with cirrhosis were treated at our center. One thousand and sixty-nine patients were followed up for a minimum of three months (median 13 mo, IQR 33.1-57.67 mo). One hundred and thirty-six patients (12.7%) were treated with aspirin for various indications. Baseline clinical and laboratory characteristics of both groups were comparable. Aspirin use was associated with risk reduction for decompensations, including a composite risk of ascites and hepatic encephalopathy, in a multivariate Cox regression analysis ($p = 0.035$). Aspirin use showed a tendency toward encephalopathy risk reduction as a single variable ($p = 0.055$), but not for the development of ascites. Aspirin was not associated with an increased risk of gastrointestinal bleeding in both univariate ($p = 0.281$) and multivariate analyses models adjusted for gender, age, platelet count, MELD score, statin, beta blocker and PPI use ($p = 0.446$). **Conclusion:** Aspirin use may confer a protective effect against a composite outcome of hepatic encephalopathy and ascites, and is not associated with increased risk of gastrointestinal bleeding in patients with cirrhosis. Further prospective studies on larger cohorts are necessary to elucidate its mode of action and confirm our findings.

Disclosures: The following people have nothing to disclose: Roie Tzadok, Nir Bar, Ayelet Grupper, Eugene Feigin, Helena Katchman

3136-A | CLINICAL MALNUTRITION IS ASSOCIATED WITH WORSE OUTCOMES IN PATIENTS WITH PORTAL VEIN THROMBOSIS: A FIVE-YEAR NATIONWIDE ANALYSIS

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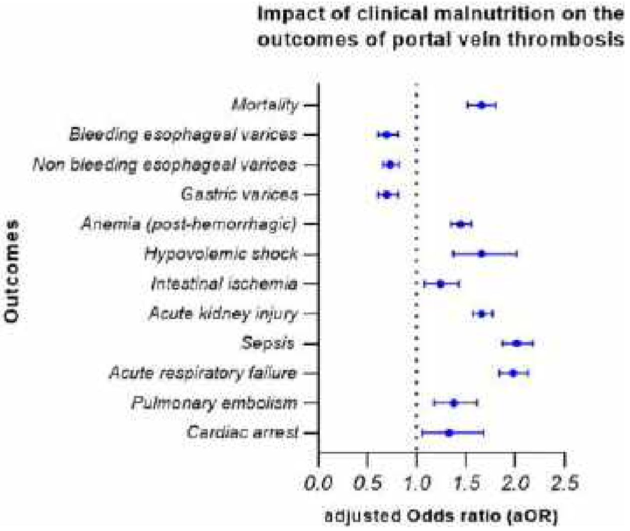
Background: Portal vein thrombosis (PVT) is most commonly associated with liver cirrhosis, but is also seen in prothrombotic conditions, including cancers. Chronic malnutrition is common in this population, however, there is no literature describing the effects of malnutrition on the outcomes of PVT. Therefore, the authors of this study aimed to update the literature. **Methods:** This is a retrospective longitudinal study of patients admitted with a diagnosis of PVT. Using weighted data from the Nationwide Inpatient Sample (NIS) database from 2016 to 2020, we assessed PVT outcomes (mortality, hospital utilization, total healthcare charges, complications) in patients with and without malnutrition. Baseline characteristics were analyzed using T-test and Chi-Square, and a multivariate regression analysis was used to estimate outcomes for patients with malnutrition. Data analysis was performed using STATA® Version 17.0 Software, with statistical significance set at $p < 0.05$. **Results:** Among a total of 252,455 hospital admissions with a diagnosis of PVT, 57,020 (22.6%) had a secondary diagnosis of clinical malnutrition. Malnutrition was associated with a 90,540 U.S. dollar increase in total healthcare charges (95%CI: 79,657 - 101,422), and a 6-day increase in the length of stay (95%CI: 5.63 - 6.47). Pertaining to complications, malnutrition was associated with higher risks of mortality (adjusted Odds ratio (aOR) = 1.66, 95%CI: 1.52 - 1.80), acute intestinal ischemia (aOR = 1.24, 95%CI: 1.08 - 1.43), post-hemorrhagic anemia (aOR = 1.45, 95%CI: 1.35 - 1.55), hypovolemic shock (aOR = 1.66, 95%CI: 1.37 - 2.02), acute kidney injury (aOR = 1.66, 95%CI: 1.57 - 1.77), sepsis (aOR = 2.02, 95%CI: 1.87 - 2.18), pulmonary embolism (aOR = 1.38, 95%CI: 1.18 - 1.61), acute respiratory failure (aOR = 1.98, 95%CI: 1.84 - 2.13), and cardiac arrest (aOR = 1.32, 95%CI: 1.05 - 1.68). Malnutrition was associated with a significant reduction of esophageal varices with bleeding (aOR = 0.91, 95%CI: 0.68 - 1.23), esophageal varices without bleeding (aOR = 0.73, 95%CI: 0.66 - 0.82), gastric varices (aOR = 0.70, 95%CI: 0.60 - 0.81) (figure 1). **Conclusion:** The prevalence of clinical malnutrition in patients admitted with PVT is high. Moreover, malnutrition seems to be associated with worse outcomes in patients admitted with PVT. Therefore, it is imperative that clinicians address malnutrition in order to improve survival, complications, and hospital utilization of patients with PVT.



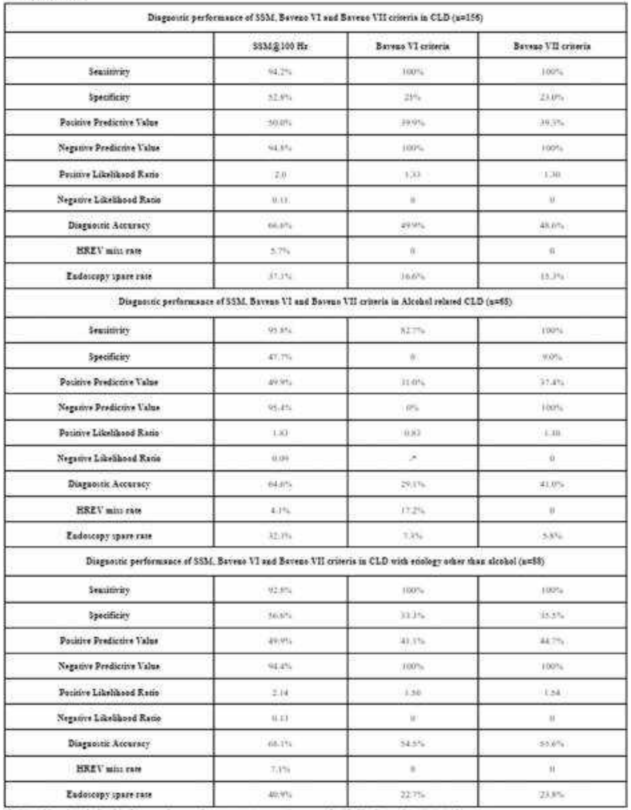
Disclosures: The following people have nothing to disclose: Yassine Kilani, Syeda Ashna Fatima Kamal, Priscila Castro Puello, Saqr Alsakarneh, Mohammad Aldiabat, Vikash Kumar, Fnu Vikash

3137-A | COMPARISION OF SPLENIC STIFFNESS MEASUREMENT BY TRANSIENT ELASTOGRAPHY USING 100Hz PROBE WITH BAVENO CONSENSUS CRITERIA TO PREDICT HIGH RISK ESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE

Harsh Prakash Jain, Manas Kumar Kumar Panigrahi, Prajna Anirvan, Mohd imran Chouhan Sr, Abhijeet Rai, Shubham Gupta, Mansi Choudhary, Hemanta Kumar Nayak and Subash Chandra Samal, All India Institute of Medical Sciences, Bhubanswar, India

Background: Clinically significant portal hypertension (CSPH) in patients with chronic liver disease (CLD) portends risk of variceal bleeding. Esophageal varices are classified into high and low risk based on endoscopic appearance. However, prevalence of High Risk Esophageal Varices (HREV) is low in early cirrhosis. Using non-invasive tools with high negative predictive value for HREV can avoid endoscopies in these patients. We evaluated the diagnostic performance of Splenic Stiffness Measurement (SSM) by Transient Elastography (TE) using a 100 Hz probe and compared it with Baveno Criteria to predict HREV. **Methods:** Consecutive individual's with cirrhosis were enrolled. Relevant blood investigations and endoscopy were performed to detect and grade esophageal varices. Liver Stiffness Measurement (LSM) and SSM were performed by TE . A dedicated 100 Hz probe was used for SSM. **Results:** From June 2021 to April 2023, 281 patients with cirrhosis were screened and 156 were enrolled. Etiology of cirrhosis in these patients was attributed to alcohol, chronic viral hepatitis and other etiologies in 68 (43.5%), 30 (19.2%) and 58 (37.1%) patients, respectively. HREV were detected by endoscopy in 52 (33.3%) patients. SSM using 100 Hz probe was successfully performed in 98% (n = 153) of the patients enrolled. On multivariate analysis, only SSM was significantly associated with HREV. AUROC of LSM and SSM and platelet count to predict HREV was 0.643 and 0.805, respectively . Sensitivity, specificity, negative predictive value and positive predictive value were 94.2%, 52.8%, 94.8% and 49.9%, respectively when SSM cut-off upto 35 kPa was used to rule out HREV. Using this cut-off, 5.7% HREV were missed and 37.1% endoscopies were spared which was more than twice the number of endoscopies spared using either Baveno VI (16.5%) or Baveno VII (16.6%) criteria in the same population. On subgroup analysis, SSM, Baveno VI and VII criteria performed worse for alcohol related CLD (n = 68) as compared to non-alcohol related etiologies (n = 88) with lower number of endoscopies spared (32.3% vs 40.9%, 7.3% vs 23.8% and 5.8% vs 22.7%, respectively) with rate of missed HREV < 5% for all three non-invasive tools. **Conclusion:** Our study highlighted few important lacunae in the literature. Firstly, the cut-offs used by non-invasive tools to predict HREV seem to be affected by ethnicity, etiology of CLD and method of SSM measurement (100 Hz vs 50 Hz). Secondly, the Baveno consensus criteria need validation before the same recommended cut-offs can be used with SSM@100Hz. Thirdly, despite SSM demonstrating acceptable performance in predicting HREV, need of the ideal noninvasive tool remains unmet.

Table: Comparison of diagnostic performance of Splenic Stiffness Measurement, Baveno VI and Baveno VII Criteria to predict High Risk Esophageal Varices in Chronic Liver Disease



Diagnostic performance of SSM, Baveno VI and Baveno VII criteria in CLD (n=156)			
	SSM@100 Hz	Baveno VI criteria	Baveno VII criteria
Sensitivity	94.2%	100%	100%
Specificity	52.8%	21%	23.0%
Positive Predictive Value	50.0%	39.9%	39.3%
Negative Predictive Value	94.8%	100%	100%
Positive Likelihood Ratio	2.0	1.33	1.30
Negative Likelihood Ratio	0.11	0	0
Diagnostic Accuracy	66.0%	49.9%	48.6%
HREV miss rate	5.7%	0	0
Endoscopy spare rate	37.1%	16.6%	15.3%
Diagnostic performance of SSM, Baveno VI and Baveno VII criteria in Alcohol related CLD (n=68)			
Sensitivity	95.8%	82.7%	100%
Specificity	47.7%	0	9.0%
Positive Predictive Value	49.9%	31.0%	37.4%
Negative Predictive Value	95.4%	0%	100%
Positive Likelihood Ratio	1.83	0.83	1.10
Negative Likelihood Ratio	0.09	-*	0
Diagnostic Accuracy	64.0%	29.1%	41.0%
HREV miss rate	4.1%	17.2%	0
Endoscopy spare rate	32.3%	7.3%	5.8%
Diagnostic performance of SSM, Baveno VI and Baveno VII criteria in CLD with etiology other than alcohol (n=88)			
Sensitivity	92.8%	100%	100%
Specificity	56.6%	33.3%	35.5%
Positive Predictive Value	49.9%	41.1%	44.7%
Negative Predictive Value	94.4%	100%	100%
Positive Likelihood Ratio	2.14	1.50	1.54
Negative Likelihood Ratio	0.13	0	0
Diagnostic Accuracy	68.1%	54.5%	55.6%
HREV miss rate	7.1%	0	0
Endoscopy spare rate	40.9%	22.7%	23.8%

*NPV could not be calculated in this group because there were no true negative cases identified by Baveno VI criteria in this group

CLD - Chronic Liver Disease, HREV - High Risk Esophageal Varices, SSM - Splenic Stiffness Measurement by Transient Elastography using 100 Hz probe.

Disclosures: The following people have nothing to disclose: Harsh Prakash Jain, Manas Kumar Kumar Panigrahi, Prajna Anirvan

Disclosure information not available at the time of publication: Mohd imran Chouhan, Abhijeet Rai, Shubham Gupta, Mansi Choudhary, Hemanta Kumar Nayak, Subash Chandra Samal

3138-A | DEVELOPMENT OF A SCORING SYSTEM FOR PREDICTING ESOPHAGEAL VARICES WORSENING AFTER BALLOON-OCCLUDED RETROGRADE TRANSVENOUS OBLITERATION

Tatsuro Nishimura[1], Tsuyoshi Ishikawa[1], Maho Egusa[1], Natsuko Nishiyama[1], Tsuyoshi Fujioka[1], Daiki Kawamoto[1], Ryo Sasaki[1], Norikazu Tanabe[1], Issei Saeki[1] and Taro Takami[2], (1)Yamaguchi University Graduate School of Medicine, (2)Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi, Japan

Background: Balloon-occluded retrograde transvenous obliteration (BRTO) is a safe and effective treatment for gastric varices (GV) and refractory hepatic encephalopathy (HE) associated with portosystemic shunts (PSSs). However, esophageal varices (EV) worsening after BRTO is the most concerning postoperative complication. The present study aimed to statistically identify predictive factors of EV worsening after BRTO and develop a new scoring system for EV worsening. **Methods:** Seventy-six patients with PSSs who had undergone BRTO for GV or HE [mean age = 67.6 years; female/male = 37/39; Child-Pugh class A/B/C = 37/32/7; mean Hepatic venous pressure gradient = 10.8 mmHg] at our hospital between April 2008 and March 2021 were enrolled in this retrospective study. Statistical analysis identified factors associated with the EV worsening after BRTO, and the Kaplan-Meier method determined the cumulative EV worsening rates. **Results:** BRTO was successfully performed in all 76 patients. During a median follow-up period of 18.0 months (range 0-120 mo), EV worsening was observed in 50 patients, of whom 42 showed worsening of the F category, 5 showed appearance of red color sign and 3 showed rapture of EV. The cumulative EV worsening rates at 12-, 24-, and 36 months were 35.5 %, 51.5 %, and 58.1 %, respectively. Univariate analysis using the Cox proportional hazards model revealed a significant association of EV worsening after BRTO with male, platelet count d 8.3x10^4 /μL, MELD-Na score > 11, and presence of EV before BRTO. Multivariate analysis showed that male (hazard ratio [HR] 2.27, 95%CI 1.17-4.39, P = 0.013), platelet count d 8.3x10^4 /μl (HR 2.11, 95%CI 1.06-4.19, P = 0.032) and presence of EV before BRTO (HR 2.36, 95%CI 1.06-5.27, P = 0.029) were significant independent risk factors of EV worsening. The rate of EV worsening was significantly higher patients in male, platelet count d 8.3x10^4 /μL and presence of EV before BRTO (P < 0.001). We developed a scoring system for predicting EV worsening after BRTO consisting of the above 3 factors, which ranged from 0 to 3 points (because the HR of each factor is almost equal, one point for each factor). Patients stratified into 4 groups according to this score showed significantly different cumulative EV worsening rates (0 vs 1 vs 2 vs 3 points: median time to EV worsening, not reached vs 19.2 vs 10.2 vs 6.5 mo; P < 0.001). **Conclusion:** EV worsening after BRTO can be predicted by 3 factors: "male", " platelet count d 8.3x10^4 /μL" and "presence of EV before BRTO". We have established a new scoring system for predicting EV worsening after BRTO. And we developed a risk stratification and postoperative strategy by this scoring system. This scoring system helps detect EV worsening as early as possible after BRTO and can make it possible to perform early endoscopic treatment in the event of worsening to risky varices.

Disclosures: The following people have nothing to disclose: Tatsuro Nishimura, Tsuyoshi Ishikawa, Maho Egusa, Natsuko Nishiyama, Tsuyoshi Fujioka, Daiki Kawamoto, Ryo Sasaki, Norikazu Tanabe, Issei Saeki, Taro Takami

3139-A | DOES STATUS MATTER? ANALYZING OUTCOMES BETWEEN TEACHING STATUS AND MORTALITY IN US HOSPITALS: A NATIONAL STUDY OF PATIENTS WITH COVID-19 AND VARICEAL BLEEDING

Marisa Pope[1], Brian Blair[1], Lucy Joo[1], C Jonathan Foster[1], Yaser Khalid[2] and Neethi Dasu[1], (1)Jefferson Health NJ, (2)Wright Center for Gme/Geisinger Health System

Background: Esophageal varices occur within the portal system in patients with liver cirrhosis. Variceal hemorrhage can be a fatal complication of liver cirrhosis. The COVID-19 pandemic posed a huge dilemma within gastroenterology due to limited endoscopic procedures given risk of exposure to respiratory droplets. In addition, larger teaching hospitals in urban areas had been associated with higher mortality rates during the COVID-19 pandemic. The aim of this study is to compare tertiary care centers versus teaching hospitals and identify differences in mortality rates during COVID -19 in patients with variceal bleeding. **Methods:** All patients aged 18 years and above with COVID-19 with a concomitant diagnosis of variceal bleed were identified from the year 2020 were identified from the US Nationwide Inpatient Sample (NIS), an extensive publicly available all-payer inpatient care database in the USA. Multivariate regression analysis was used to estimate the odds ratios of in-hospital mortality, the average length of hospital stay (LOS), and hospital charges (TOTHC), after adjusting for age, gender, race, primary insurance payer status, hospital type and size (number of beds), hospital region, hospital teaching status, and other demographic characteristics. In addition, the relationship between hospital teaching status and outcomes, including mortality, post-procedural bleeding, CVA (cerebrovascular accident), acute kidney injury (AKI), and sepsis, were analyzed. **Results:** Our study identified approximately 1,685,745 patients with COVID-19, of which 45,590 were diagnosed with variceal bleeding. The average age was noted to be 63. *The analysis revealed no difference in mortality or length of stay (LOS) between patients admitted to teaching and non-teaching hospitals*. Admission to the ICU, however, was higher in patients at teaching hospitals (OR 5.18, CI: 5.02-5.35), p = 0.00). Total hospital charges were higher in patients admitted to teaching hospitals ($16,805.71, CI: $14,511.44 - $19,099.98), p = 0.00). Independent positive predictors of increased mortality, LOS, and TOTHC are identified in Table 1. **Conclusion:** In patients with COVID-19 and concomitant variceal bleeding, although total hospital charges were higher in patients admitted to teaching hospitals, there was no noted difference in mortality or length of stay. We further identified complications (post-procedural bleeding, CVA, AKI) that increased mortality, LOS, and TOTHC in patients admitted to teaching hospitals. The presence of sepsis did lead to an increased LOS and TOTHC in patients admitted to teaching hospitals but did not affect mortality. This data suggests that a healthcare facility's teaching status does not necessarily worsens patient outcomes with regard to mortality and identifies crucial risk factors that, if identified early, can be beneficial in mitigating further risk in teaching hospitals.

Disclosures: The following people have nothing to disclose: Marisa Pope, Brian Blair, Lucy Joo, C Jonathan Foster, Yaser Khalid, Neethi Dasu

3140-A | EFFICACY AND SAFETY OF ENDOSCOPIC ULTRASOUND GUIDED EMBOLIZATION FOR PRIMARY PROPHYLAXIS OF LARGE CARDIO-FUNDAL GASTRIC VARICES -A SINGLE CENTER EXPERIENCE

Ahmed El Sabagh[1,2], Ronald Samuel[1], Islam Mohamed[1,2], Megha Bhongade[1], Prasun K. Jalal[1], Tara Keihanian[1] and Kalpesh Patel[1], (1)Baylor College of Medicine, (2)Faculty of Medicine, Ain Shams University

Background: Gastric variceal bleeding is a life-threatening condition with a high mortality rate. Bleeding risk from gastric varices is lower compared to esophageal varices, but usually is more severe with a higher mortality rate. Primary prophylaxis of gastric varices can potentially reduce the risk of hemorrhage and improve survival. Endoscopic ultrasound (EUS) guided embolization of gastric varices is an effective treatment modality for gastric varices. Limited data exists regarding the efficacy of this procedure in the primary prophylaxis against bleeding from large cardio-fundal gastric varies. The aim of our study is to show the efficacy and safety of EUS-guided gastric varices embolization for primary prophylaxis against gastric variceal bleeding. **Methods:** A single-center retrospective observational study evaluating patients with large cardio-fundal gastric varices without prior bleeding who underwent EUS-guided coiling and glue injection for primary prophylaxis against bleeding from gastric varices between January 2016 and September 2022, at Baylor College of Medicine. The primary outcome was EUS confirmed gastric varices obliteration. Secondary outcome was post-treatment gastric variceal bleeding rate within six months. **Results:** Twenty-one patients underwent primary prophylaxis for large cardio-fundal gastric varices during the study period (61.9% female). Mean age of patients was 60.2 ± 14.0. Concurrent liver cirrhosis was found in 90.5% (n = 19) of the patients. Only 57.1% (n = 12) of patients were on beta blocker before the endoscopic therapy. Technical success - defined as achieving complete embolization of the targeted gastric varices confirmed by EUS colored Doppler imaging - was achieved in 100% of patients. The mean number of coils was 4.0 ± 1.4 and mean glue volume of 1.5 ± 0.6 ml. Out of the 21 patient who received the procedure, 15 of them had a follow-up EUS in over 4.7 ± 2.3 months. EUS- confirmed gastric varices obliteration was noted in 13 patients (86.7%). The two patients with recurrent gastric varices were successfully treated with EUS-guided embolization with 2.5 ± 0.7 coils and 2.5 ± 0.7 ml glue. Post-treatment gastric variceal bleeding within 6 months occurred in one patient that required repeat EUS-guided embolization and glue with a good outcome. No patients required alternative treatment with TIPS or other modalities within 6 months. No serious adverse events including anesthesia complications, procedural bleeding, or embolic events were noted due to the procedure. **Conclusion:** EUS-guided embolization of large cardio-fundal gastric varices can be considered an effective and safe modality for primary prophylaxis against bleeding in cirrhotic patients. Larger prospective randomized trials are needed to highlight the efficacy and safety of this technique in larger population with cirrhosis, including patients with non-cirrhotic portal hypertension and extra-hepatic portal obstruction.

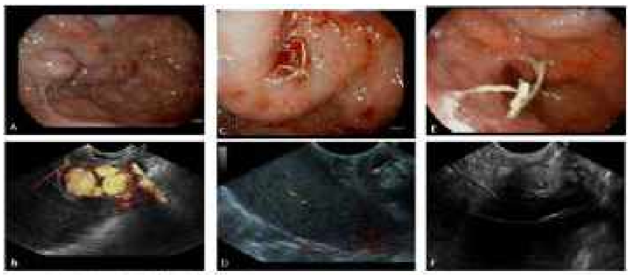


Figure 1. EUS-guided coil embolization.

A: Gastric varices noted in the gastric fundus seen endoscopically and under EUS with doppler (B). C: Gastric varices after glue and coiling in the gastric fundus endoscopically and with EUS with doppler showing obliteration (D). E: Follow-up after 4 months demonstrates extruding cyanoacrylate on EGD and obliteration of varices on EUS (F).

Disclosures: The following people have nothing to disclose: Ahmed El Sabagh, Ronald Samuel, Islam Mohamed, Megha Bhongade, Prasun K. Jalal, Tara Keihanian, Kalpesh Patel

3141-A | EFFICACY AND SAFETY OF PERCUTANEOUS TRANS-HEPATIC OR TRANS-SPLENIC VARICEAL OBLITERATION FOR GASTRIC VARICEAL BLEEDING

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Background: Gastric variceal bleeding (GVB) is a serious complication of liver cirrhosis that is associated with increased mortality. GVB can be managed by endoscopic variceal ligation (EVL) or radiological interventions, such as balloon-ccluded retrograde transvenous obliteration (BRTO) or transjugular intrahepatic portosystemic shunt (TIPS). Although many studies showed that BRTO has advantages over TIPS, BRTO requires a gastrorenal shunt. We evaluated the efficacy and safety of percutaneous trans-hepatic or trans-splenic variceal obliteration (PTVO) as an alternative for management of GVB when BRTO is impossible. **Methods:** Seventeen patients (mean age 59 y, 13 men) with liver cirrhosis who received PTVO for uncontrolled GVB from October 2017 to January 2023 were retrospectively examined. Efficacy was evaluated by the rate of successful prevention of rebleeding during follow-up, and improvement of liver function based on Child-Pugh (CP) class. Safety was evaluated by the rate of postprocedural complications. **Results:** The causes of cirrhosis were hepatitis B (n = 3), hepatitis C (n = 2), alcohol consumption (n = 4), autoimmune hepatitis (n = 2), and a combination of factors (n = 6). Before procedure, eight had CP class A, seven had CP B, and two had CP C. The PTVO was performed using a trans-splenic approach (n = 7) or a trans-hepatic approach (n = 10), and was successful in all patients. However, two experienced rebleeding during hospitalization; one was considered irrecoverable and expired and the other received embolization. CP class improved in 3 patients (33.3%) and remained the same in 6 patients (66.7%) at 1 to 3 months. CP class improved in 1 patient (14.3%), remained the same in 5 patients (71.4%), and worsened in 1 patient (14.3%) at 6 months. **Conclusion:** PTVO of patients with cirrhosis led to no significant deterioration in liver function or procedure-related complications. This procedure can be considered an effective and safe option for patients with GVB when a conventional approach is not possible.

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The following people have nothing to disclose: Hyun Young Woo, Ki Youn Yi, Young Joo Park, Chang Won Kim

3142-A | EFFICACY AND SAFETY OF THALIDOMIDE IN PREVENTING RECURRENT BLEED FROM GASTRIC ANTRAL VASCULAR ECTASIA IN PATIENTS WITH LIVER CIRRHOSIS

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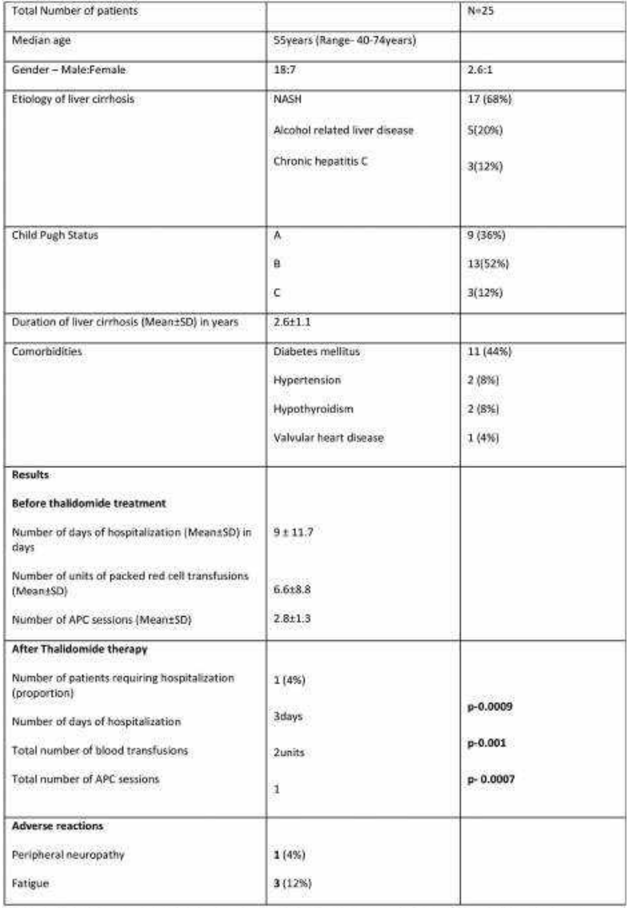
Background: Recurrent gastrointestinal bleed due to gastric antral vascular ectasia (GAVE) is an uncommon complication in patients with liver cirrhosis. Apart from variceal bleed, bleed from GAVE can add to significant morbidity in these patients causing anemia, recurrent blood transfusions and hospitalizations. GAVE does not respond to medical therapy with beta blockers. Endo therapy such as argon plasma coagulation (APC) can be useful for acute bleed however recurrence is not uncommon. Medical management to prevent recurrent bleeding episodes using oral thalidomide therapy, which is hypothesised to act on vascular endothelial growth factor receptors (VEGF) preventing angiogenesis has been observed in certain case reports of GAVE. However, the data about its efficacy and safety in larger group of cirrhotic patients is lacking. In this study, we aimed at comparing the efficacy of thalidomide in terms of number of days of hospitalizations, number of blood transfusions for anemia and number of endoscopic treatment sessions for GAVE before and after oral thalidomide treatment for a minimum period of 6 months. **Methods:** This is a pre - post intervention study where 25 patients of liver cirrhosis presenting with more than one episode of GI bleed from GAVE were included. Patients with acute variceal bleed were excluded. Acute episode of bleed from GAVE was managed by endotherapy in the form of APC and subsequently patients were started on oral thalidomide therapy at a dose of 50mg per day. Patients were followed for a total duration of 1 year with a follow up interval of 3 months. Recurrent episodes of bleed, hospitalizations and requirement of blood transfusions were recorded. Patients were enquired for adverse effects of thalidomide at every follow up visit. **Results:** A total of 25 patients with liver cirrhosis were included in the study. Median age of patients was 55 years. Majority of patients were males (n = 18). Most common etiology of cirrhosis in these patients was non- alcoholic steatohepatitis (NASH) which was observed in 17 (68%) patients. Diabetes mellitus was the most common co-morbidity among these patients observed in 11 (44%) patients. Mean dose of thalidomide administered was 50mg per day for a median duration of 6 months. Out of 25 patients, only one patient (4%) required hospitalization for a duration of 2 days and one session of APC for GAVE during a follow up period of 1 year. Only 2 patients required (1unit each) blood transfusions in view of anaemia after initiation of thalidomide therapy during a follow up period of 1 year. Table 1 describes the results of the study. No major adverse effects were observed in any of these patients except for 3 patients who reported mild fatigue. One patient had mild lower limb peripheral neuropathy which resolved with symptomatic therapy. **Conclusion:** Thalidomide is a safe and effective option for prevention of recurrent gastrointestinal bleed due to GAVE in patients with liver cirrhosis.



Total Number of patients		N=25
Median age	55years (Range- 40-74years)	
Gender – Male:Female	18:7	2.6:1
Etiology of liver cirrhosis	NASH	17 (68%)
	Alcohol related liver disease	5(20%)
	Chronic hepatitis C	3(12%)
Child Pugh Status	A	9 (36%)
	B	13(52%)
	C	3(12%)
Duration of liver cirrhosis (Mean±SD) in years	2.6±1.1	
Comorbidities	Diabetes mellitus	11 (44%)
	Hypertension	2 (8%)
	Hypothyroidism	2 (8%)
	Valvular heart disease	1 (4%)
Results		
Before thalidomide treatment		
Number of days of hospitalization (Mean±SD) in days	9 ± 11.7	
Number of units of packed red cell transfusions (Mean±SD)	6.6±8.8	
Number of APC sessions (Mean±SD)	2.8±1.3	
After Thalidomide therapy		
Number of patients requiring hospitalization (proportion)	1 (4%)	
Number of days of hospitalization	3days	**p-0.0009**
Total number of blood transfusions	2units	**p-0.001**
Total number of APC sessions	1	**p- 0.0007**
Adverse reactions		
Peripheral neuropathy	1 (4%)	
Fatigue	3 (12%)	

Table 1- Clinical characteristics of cirrhotic patients with GAVE and outcomes before and after thalidomide therapy

NASH- non-alcoholic steatohepatitis, APC-Argon plasma coagulation, GAVE-gastric antral vascular ectasia

Disclosures: The following people have nothing to disclose: Sowmya T R, Mithun Sharma, Padaki Nagaraja Rao

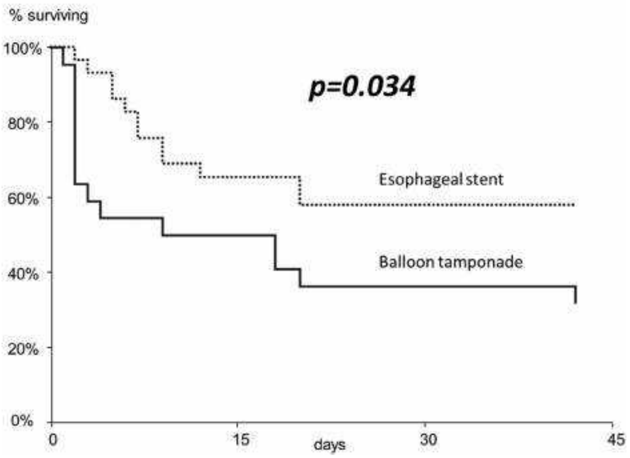
Disclosure information not available at the time of publication: Anand V. Kulkarni, Duvurr Nageshwar Reddy

3143-A | ESOPHAGEAL STENT (ES): A NEW DETERMINANT OF BETTER PROGNOSIS OF PATIENTS WITH REFRACTORY PORTAL HYPERTENTION RELATED BLEEDING (R-PHT-B): RESULTS OF A FRENCH NATIONWIDE RETROSPECTIVE COHORT STUDY

Delphine Weil Verhoeven[1,2], Jean-Paul Cervoni[1], Morgane Clément[1], Charlotte Bouzbib[3], Grégoire Boivineau[4], Guillaume Delaval[5], Isabelle Hourmand Ollivier[5], Noémie Reboux[6], Edouard Bardou-Jacquet[7], Cassandra Rayer[7], Marine Camus[8], Caroline Lemaitre[9], André-Jean Remy[10], Laure Ekrief[11], Guillaume Conroy[12], Faustine Wartel[13], Armand Garioud[14], Jean-Pierre Arpurt[15], Maeva Guillaume[16], Thierry Thévenot[1,2], Lucine Vuitton[2,17], Stéphane Koch[17], Marika Rudler[3], Vincent Di Martino[1,2] and ANGH, GRAPHE, CREGG, SFED and CFHTP Groups, (1)CHU Jean Minjoz, Service D'hépatologie Et Soins Intensifs Digestifs, (2)Université De Franche-Comté, (3) Hôpital Pitié-Salpêtrière, Aphp, Service D'hépato-Gastroentérologie, Unité De Soins Intensifs, (4)AP-HM, Hépato-Gastro-Entérologie Et Oncologie Digestive, (5) CHU De Caen, Service d'Hépato-Gastroentérologie, (6) CHU De Brest, Service D'hépato-Gastroentérologie, (7) Service Des Maladie Du Foie, CHU De Rennes, (8)Hôpital Saint-Antoine, Aphp, Service D'endoscopie Digestive, (9) Groupe Hospitalier Du Havre, Service D'hépato-Gastroentérologie, (10)Centre Hospitalier De Perpignan, Service D'hépato-Gastroentérologie, (11)CHU De Tours, Service D'hépato-Gastroentérologie, (12)Centre Hospitalier Régional De Metz-Thionville, Service D'hépato-Gastroentérologie, (13)Centre Hospitalier De Valenciennes, Maladies De L'appareil Digestif Et De La Nutrition, (14)Centre Hospitalier Intercommunal Villeneuve-St-Georges, (15)Centre Hospitalier D'avignon, Service D'hépato-Gastroentérologie, (16)Clinique Pasteur, (17)CHU Jean Minjoz, Service De Gastroentérologie

Background: Tamponade is used as a bridge therapy in patients with refractory portal hypertension related bleeding (R-PHT-B). The need for tamponade is rare, and the prognostic determinants of patients receiving tamponade are not well known. Esophageal stents (ES) have been introduced to replace balloon tamponade, but to date, there are few data comparing the effectiveness of these two procedures, and the use of ES has not demonstrated a survival benefit. **Methods:** We retrospectively analyzed a French nationwide cohort of patients treated with tamponade for R-PHT-B. Primary outcome measure was day(d)-42 survival. Multivariate analyses were conducted using a Cox model adjusted to a propensity score evaluating the probability of having received an ES. **Results:** 69 pts (65 cirrhotics, 87% males, 57yrs, 94% Child-Pugh B/C) admitted for R-PHT-B between 2002 and 2023 in University (N = 7) or General (N = 5) hospitals who underwent tamponade were included. Initial endoscopy and attempt to control bleeding had been performed in 88% and 70% of patients, respectively. Tamponade was performed using balloon or ES (Danis stent) in 40 and 29 patients, respectively. Our propensity score incorporated 21 variables and was able to predict the use of ES (rather than balloon tamponade) in 86% of patients with high accuracy (AUROC = 0.94). A rescue TIPS (rTIPS) was placed in 20 patients (29%), before d4. No difference was observed between the two procedures regarding the occurrence of complications. Overall mortality was 46% at d5 (due to refractory hemorrhagic shock for 75% of cases), and 65% at d42 (mainly due to persistent bleeding and multi-organ failure). In univariate analyses, d42-survival was higher in patients with ES *vs.* balloon tamponade (58% *vs.* 32%, $p = 0.034$), in those with rTIPS *vs.* others (63% *vs.* 38%, $p = 0.048$), and in patients with better liver function as indicated by a MELD score < 30 (75% vs. 30%, $p = 0.026$) or no history of hepatic encephalopathy (56% *vs.* 10%, $p = 0.046$). Multivariate Cox analysis adjusted for MELD score and propensity score ($R^2 = 0.29$) confirmed that the use of ES (HR = 4.32, 95%CI:1.34-13.99; $p = 0.014$) and of rTIPS (HR = 3.08, 95%CI:1.04-9.10; $p = 0.042$) were two independent predictors of d42-survival. **Conclusion:** In patients who undergo tamponade for refractory portal hypertention related bleeding, the use of esophageal stent, as well as rescue TIPS placement, are independent predictors of day 42 survival.

Figure 1. day 42 survival according to the device used for tamponade



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Disclosure information not available at the time of publication: Jean-Paul Cervoni, Morgane Clément, Grégoire Boivineau, Guillaume Delaval, Isabelle Hourmand Ollivier, Noémie Reboux, Cassandra Rayer, Marine Camus, Caroline Lemaitre, André-Jean Remy, Laure Ekrief, Guillaume Conroy, Faustine Wartel, Armand Garioud, Jean-Pierre Arpurt, Maeva Guillaume, Thierry Thévenot, Lucine Vuitton, Stéphane Koch, Vincent Di Martino

3144-A | HIGH CORRELATION OF HEPATIC SHEAR WAVE VELOCITY WITH ESOPHAGEAL VARICES COMPLICATION RATE IN PATIENTS WITH CHRONIC LIVER DISEASES

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Background: Histological evaluation by liver biopsy is considered the gold standard for assessing liver disease; however, it is highly invasive. Non-invasive liver stiffness measurement by shear wave elastography (SWE) is effective for evaluating the hepatic fibrosis stage and related diseases. In this study, we investigated the correlations of liver stiffness with hepatic inflammation/fibrosis, functional hepatic reserve, and related diseases in patients with chronic liver disease (CLD). **Methods:** Shear wave velocity (Vs) values were measured using point SWE in 71 patients with liver disease from 2017 to 2019. Liver biopsy specimens and serum biomarkers were collected at the same time, and splenic volume was measured using computed tomography images with the software Ziostation2. Esophageal varices (EV) were evaluated by upper gastrointestinal endoscopy. Youden's index (sensitivity + specificity - 1) was used to identify the optimal cutoff point. **Results:** Among CLD-related function and complications, Vs values were highly correlated with liver fibrosis and EV complication rates ($P < 0.05$). The median Vs values for liver fibrosis grades F0, F1, F2, F3, and F4 were 1.18, 1.34, 1.39, 1.80, and 2.12 m/s, respectively. Comparison of receiver operating characteristic (ROC) curves to predict cirrhosis showed that area under the ROC (AUROC) curve for Vs values was 0.902, which was not significantly different from the AUROCs for the FIB-4 index, platelet count, hyaluronic acid, or type IV collagen 7S, while it was significantly different from the AUROC for mac-2 binding protein glycosylation isomer (M2BPGi) ($P < 0.01$). Comparison of ROC curves to predict EV showed that the AUROC for Vs values was 0.901, which was significantly higher than the AUROCs for FIB-4 index ($P < 0.05$), platelet count

($P < 0.05$), M2BPGi ($P < 0.01$), hyaluronic acid ($P < 0.05$), and splenic volume ($P < 0.05$). The optimal cutoff value of Vs based on Youden index was 2.08 with a sensitivity of 80.0% and specificity of 85.4%. In patients with advanced liver fibrosis (F3+F4), there was no difference in blood markers and splenic volume, while Vs value was significantly higher in patients with EV ($P < 0.01$). **Conclusion:** Hepatic shear wave velocity was highly correlated with EV complication rates in chronic liver diseases as compared to blood markers and splenic volume. In advanced CLD patients, Vs values of SWE are suggested to be effective in predicting the appearance of EV noninvasively.

Disclosures: The following people have nothing to disclose: Shouichi Namikawa, Takuto Nosaka, Yu Akazawa, Tatsushi Naito, Kazuto Takahashi, Hidetaka Matsuda, Masahiro Ohtani, Yasunari Nakamoto

3145-A | IMPACT OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS AND NON-SELECTIVE BETA-BLOCKERS AS PRIMARY PROPHYLAXIS OF ESOPHAGEAL VARICEAL BLEEDING, ASCITES, HEPATIC ENCEPHALOPATHY, AND MORTALITY IN COMPENSATED CIRRHOTIC PATIENTS

Julton Tomanguillo Chumbe[1], Mark Ayoub[2], Lauren Searls[2], Hamid Ullah[2], Frank Annie[2], Ebubekir Daglilar[1] and Nadeem Anwar[1], (1)West Virginia University - Charleston Area Medical Center, Charleston, WV, (2) Charleston Area Medical Center/WVU Charleston Division

Background: Bench studies have shown that renin-angiotensin-aldosterone system (RAAS) inhibitors significantly reduce liver fibrogenesis and portal hypertension. Despite encouraging results in animal studies, replication of these benefits has been poorly reported in clinical studies. This study aimed to evaluate the impact of RAAS inhibitors and non-selective beta-blockers (NSBB) as primary prophylaxis in compensated cirrhotic patients for esophageal variceal bleeding (EVB), ascites, hepatic encephalopathy (HE), hepatorenal syndrome (AKI-HRS), and mortality. **Methods:** We queried the Trinetx-Research Network (92 health care organizations within the USA) between 2011 and 2020. Patients with compensated cirrhosis were divided into two cohorts; a first cohort of patients on NSBB (Propranolol or Nadolol) and Renin-angiotensin-aldosterone system (RAAS) inhibitors; and a second cohort of patients on NSBB alone. **Results:** 54,138 patients with compensated cirrhosis were included in this analysis. Of these 41.7% (n = 22,577) were on both NSBB and a RAAS inhibitor, and 58.3% (n = 31,560) were only on NSBB. The raw data showed that the patients in the NSBB and RAAS group were older (69.4 ± 10.6 vs 65.9 ± 12.2, $P < 0.001$), and had higher rates of key comorbidities such as chronic heart failure (8.3 vs 3.6, $P < 0.001$), chronic kidney disease (9.9 vs 4.4%), CAD (12.9% vs 5.5%, $P < 0.001$), and diabetes mellitus (47.6% vs 20.9%, $P < 0.001$). Subsequently, two well-matched cohorts were created using a 1:1 propensity-scored matching model (17,318/17,318). Patients on NSBB and a RAASS inhibitor had lower mortality rates at 6 months (4.2% vs 4.7%, $P = 0.01$), and 12 months (6.6% vs 8.2%, $P = 0.0002$); lower EVB at 6 months (1.7% vs 2.1%, $P = 0.004$), and12 months (2.3% vs 2.8, $p = 0.0009$); lower ascites at 6 months (1.1% vs 1.5%, $p = 0.003$), and 12 months (1.7% vs 2.1%, $p = 0.01$); lower HE at 6 months (0.5% vs 0.7%, $p = 0.01$), and at 12-months no significant decrease in HE (0.9% vs 1.1%, $P = 0.05$), No significance difference was found between cohorts on the rate of AKI-HRS and SBP. **Conclusion:** In a large nationwide study, the adjunctive therapy of a RAAS inhibitor in compensated cirrhotic patients on NSBB had a significantly lower rate of EVB, ascites, and mortality (up to 1-year) when compared with patients on NSBB alone.

Disclosures: The following people have nothing to disclose: Julton Tomanguillo Chumbe, Mark Ayoub, Lauren Searls, Hamid Ullah, Frank Annie, Ebubekir Daglilar, Nadeem Anwar

3146-A | IMPACT OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS AND NON-SELECTIVE BETA-BLOCKERS ON ESOPHAGEAL VARICEAL BLEEDING AND MORTALITY IN PATIENTS WITH DECOMPENSATED CIRRHOSIS: A NATIONWIDE ANALYSIS

Julton Tomanguillo Chumbe[1], Mark Ayoub[1], Lauren Searls[1], Hamid Ullah[1], Frank Annie[1], Ebubekir Daglilar[2] and Nadeem Anwar[2], (1)Charleston Area Medical Center/WVU Charleston Division, (2)West Virginia University - Charleston Area Medical Center, Charleston, WV

Background: Routinely, the use of renin-angiotensin-aldosterone system inhibitors (RAASi) in patients with decompensated cirrhosis is not recommended due to the increased risk of renal dysfunction. However, many of these patients have heart failure, hypertension, and chronic kidney disease, where the use of RAASi are indicated as guideline-directed medical therapy. Therefore, the use of RAASi in many of these patients cannot be avoided. The aim of this study is to assess the impact of combined RASSi use with NSBB versus

NSBB alone on rate of esophageal variceal bleed (EVB) and mortality. **Methods:** We queried the Trinetx-Research Network (92 health care organizations within the USA) between 2011 and 2019. Patients with decompensated cirrhosis were divided into two cohorts; a first cohort of patients who received NSBB (Propranolol or Nadolol) and RAASi; and a second cohort of patients on NSBB alone. We compared all-cause mortality, EVB, ICU length of stay (ICU LOS) at 6-months, and 1 year between propensity matched (PSM) pairs of patients. **Results:** A total of 85,015 subjects were included in this analysis. Of these, 31,693 (37%) were taking NSBB as well as a RASSi and 53,322 (63%) only NSBB. Raw data showed the NSBB and RAASi group were older (69.7 ± 10.5 vs 65.8 ± 11.6, $P < 0.001$), and had higher rates of key comorbidities such as chronic heart failure (20.5% vs 14.5%, $p < 0.001$), diabetes mellitus (58.1% vs 28.2%, $p < 0.001$), and hypertension (80.7% vs 46.0%, $p < 0.001$). Subsequently, two PSM cohorts were created using a 1:1 model (25,571/25,571). The NSBB and RASSi group had a lower rate of EVB compared to NSBB group at 6-months (4.6.% vs 5.1%, $P = 0.005$), and 1-year (6.0% vs 6.8%, $P = 0.0005$); lower mortality at 6-months (12.5% vs 13.2%, $P = 0.01$), and 1-year (18.5% vs 19.3%, $P = 0.01$); lower ICU LOS at 6-months (11.6% vs 12.4%, $P = 0.008$), and 1-year (15.3% vs 16.6%, $P < 0.0001$); although this benefit on the hospital LOS was not seen at 6-months (12 d vs 12 d, $P = 0.09$), or 1-year (7 d vs 7 d, $P = 0.14$). No increase rate of hepatorenal syndrome (HRS) was found between RAASi to NSSB versus NSSB only at 1 year (5.3% vs 5.6%, $p = 0.27$) **Conclusion:** In a large nationwide study, patients with decompensated cirrhosis on NSBB and a RAASi had a statistically significant lower rate of esophageal bleeding, mortality, and ICU-length of stay. The addition of RAASi to a NSSB was not significantly associated with increased rate of HRS.

Disclosures: The following people have nothing to disclose: Julton Tomanguillo Chumbe, Mark Ayoub, Lauren Searls, Hamid Ullah, Frank Annie, Ebubekir Daglilar, Nadeem Anwar

3147-A | INDEX PRESENTATION AND DECOMPENSATION OF CIRRHOSIS VARY ACCORDING TO THE UNDERLYING ETIOLOGY

Mithun Sharma[1], Anand V. Kulkarni[2], Sowmya T R[2], Manasa Alla[2], Shantan Venishetty[2], P. Nagaraja Rao[1] and Nageshwar D Reddy[2], (1)Asian Institute of Gastroenterology, Hyderabad, Telangana, India, (2)Aig Hospitals, Hyderabad, India

Background: Ascites have been reported as the initial most common decompensating event in patients with liver cirrhosis. However, data are scarce regarding the mode of initial diagnosis of cirrhosis and whether the initial decompensating event varies based on the underlying etiology. The current study was designed to evaluate these two important events in the natural history of liver cirrhosis. **Methods:** All consecutive patients presenting to the liver outpatient clinic of the institute and the emergency room were included in the study. A detailed history was taken to find out how the first diagnosis of liver cirrhosis was made, along with a note of the presenting features. The first decompensating event was defined as the development of ascites, variceal bleed, hepatic encephalopathy, or rise in serum bilirubin to greater than 2 mg/dl. The underlying etiology of liver disease was confirmed as per the standard definitions used for NASH, Alcohol associated cirrhosis(AAC), alcoholic hepatitis, autoimmune hepatitis, Wilson's disease, primary biliary cholangitis, primary sclerosing cholangitis etc. **Results:** A total of 1035 liver cirrhosis patients were included in the study. Of these, 710(68.89%) were alcohol-associated, while the remaining were hepatitis B 65(6.58%), hepatitis C (12(1.16%), Autoimmune hepatitis(15(1.45%), PBC (2 (0.19%) and the remaining NASH related (230 (22.23%). The most common reason why cirrhosis was detected was an episode of upper gastrointestinal bleeding in AAC (42%). In comparison, in all other etiologies of cirrhosis, the initial reason for cirrhosis detection was the development of edema and or ascites (48.2%). Incidental detection of cirrhosis during a routine evaluation was significantly higher in NASH-related cirrhosis (23.6%) than in other etiologies. In our cohort, the most common decompensating event in cirrhosis was ascites (overall 72.4%) across all etiologies, while alcoholic patients had a significantly more proportion of bleeding episodes as initial decompensating events (26.4%) versus 12.2% in other etiologies ($p < 0.002$). In addition, a significantly more number of hepatocellular carcinoma as the index presentation was found in hepatitis B-related CLD (11.4%) vs non viral etiologies (2.8%). **Conclusion:** Alcohol-associated cirrhosis has a different mode of initial presentation of cirrhosis leading to the first diagnosis and is associated with significantly more bleeding episodes as the index decompensating event. HCC are more common at the first diagnosis in patients with hepatitis B.

Disclosures: The following people have nothing to disclose: Mithun Sharma, Anand V. Kulkarni, Sowmya T R, Manasa Alla, Shantan Venishetty, P. Nagaraja Rao, Nageshwar D Reddy

3148-A | LOW PLATELET COUNT, HIGH ASPARTATE AMINOTRANSFERASE-TO-PLATELET RATIO (APRI), AND HIGH FIBROSIS-4 SCORE ARE ASSOCIATED WITH DECOMPENSATION IN PATIENTS WITH LIVER CIRRHOSIS

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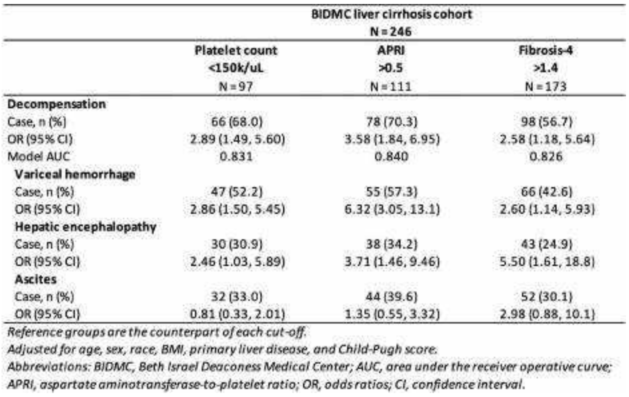
Background: There are a few studies suggesting aspartate aminotransferase (AST)-to-platelet ratio (APRI) and Fibrosis-4 (FIB-4) score's utility in predicting liver-related complications in patients with non-alcoholic fatty liver disease (NAFLD). However, to our knowledge, their performances have not been studied in patients with liver cirrhosis. This study aims to examine if such clinical noninvasive markers could predict the risk of liver decompensation in patients with liver cirrhosis. **Methods:** Beginning August 2020, we developed a prospective cohort of patients with liver cirrhosis at the Liver Center of Beth Israel Deaconess Medical Center, with intended follow-up visits every 6 months. Cirrhosis diagnosis was based on liver biopsy, imaging, vibration-controlled transient elastography, and/or endoscopic features. This study included 246 patients who received lab tests at enrollment, e.g., platelet count, AST, and alanine transaminase (ALT). We further calculated APRI and FIB-4 as the main predictors, and classified them based on clinically meaningful cutoffs. Outcome was liver decompensation events, including variceal hemorrhage, hepatic encephalopathy, and ascites. Demographics and clinical data, e.g., age, sex, race, primary liver disease, and body mass index (BMI), were recorded. Multivariable logistic regression models were fitted to estimate odds ratios (OR) and area under the receiver operative curve (AUC). **Results:** By up to four follow-up visits, 119 patients had at least one liver-related complications. Low platelet count (<150k/uL to ≥ 150k/uL; OR = 2.89; 95% confidence interval (CI): 1.49, 5.60; model AUC = 0.831), high APRI (>0.5 to ≤ 0.5; OR = 3.58; 95% CI: 1.84, 6.95; model AUC = 0.840), and FIB-4 (>1.4 to ≤ 1.4; OR = 2.58; 95% CI: 1.18, 5.64; model AUC = 0.826) were strongly associated with higher risk of decompensation, after adjusting for age, sex, race, primary liver disease, BMI, and Child-Pugh score. Significant associations persisted when adjusting for Model for End-Stage Liver Disease (MELD) score. Specifically, high APRI was strongly associated with higher risk of variceal hemorrhage (OR = 6.32; 95% CI: 3.05, 13.1) and FIB-4 was strongly associated with hepatic encephalopathy (OR = 5.50; 95% CI: 1.61, 18.8). **Conclusion:** Platelet count, APRI, and FIB-4 are inexpensive, readily available tools to identify patients with liver cirrhosis who are at higher risk for liver decompensation. Of note, APRI > 0.5 and FIB-4 > 1.4 showed strongest associations in our liver cirrhosis cohort, independent of Child-Pugh and MELD scores. Future studies are warranted to replicate their clinical application.



	BIDMC liver cirrhosis cohort N = 246		
	Platelet count <150k/uL N = 97	APRI >0.5 N = 111	Fibrosis-4 >1.4 N = 173
Decompensation			
Case, n (%)	66 (68.0)	78 (70.3)	98 (56.7)
OR (95% CI)	2.89 (1.49, 5.60)	3.58 (1.84, 6.95)	2.58 (1.18, 5.64)
Model AUC	0.831	0.840	0.826
Variceal hemorrhage			
Case, n (%)	47 (52.2)	55 (57.3)	66 (42.6)
OR (95% CI)	2.86 (1.50, 5.45)	6.32 (3.05, 13.1)	2.60 (1.14, 5.93)
Hepatic encephalopathy			
Case, n (%)	30 (30.9)	38 (34.2)	43 (24.9)
OR (95% CI)	2.46 (1.03, 5.89)	3.71 (1.46, 9.46)	5.50 (1.61, 18.8)
Ascites			
Case, n (%)	32 (33.0)	44 (39.6)	52 (30.1)
OR (95% CI)	0.81 (0.33, 2.01)	1.35 (0.55, 3.32)	2.98 (0.88, 10.1)

Reference groups are the counterpart of each cut-off.
Adjusted for age, sex, race, BMI, primary liver disease, and Child-Pugh score.
Abbreviations: BIDMC, Beth Israel Deaconess Medical Center; AUC, area under the receiver operative curve; APRI, aspartate aminotransferase-to-platelet ratio; OR, odds ratios; CI, confidence interval.

Disclosures: The following people have nothing to disclose: Xinyuan Zhang, Gloria Horta, Christopher Danford, Michelle Lai, Xuehong Zhang
Disclosure information not available at the time of publication: Iyiad Alabdul Razzak, Longgang Zhao

3149-A | LYMPHOCYTE-RELATED NUTRITIONAL MARKERS AND MUSCLE VOLUME ASSESSMENT ARE USEFUL FOR PREDICTING PROGNOSIS IN LIVER CIRRHOSIS COMPLICATED WITH PORTAL HYPERTENSION

Arisa Yamamoto, Takuto Nosaka, Yu Akazawa, Kazuto Takahashi, Tatsushi Naito, Hidetaka Matsuda, Masahiro Ohtani and Yasunari Nakamoto, University of Fukui

Background: Malnutrition and metabolic abnormalities with liver disease induce sarcopenia and affect pathogenesis, therefore, their clinical importance has been increasingly recognized. Lymphocyte-related nutritional markers are simple immunotrophic markers, although the association with muscle volume or long-term prognosis in cirrhosis has not been fully evaluated. In this study, we examined the association between lymphocyte-related nutritional markers, muscle volume and long-term prognosis in cirrhosis patients with portal hypertension. **Methods:** The

Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

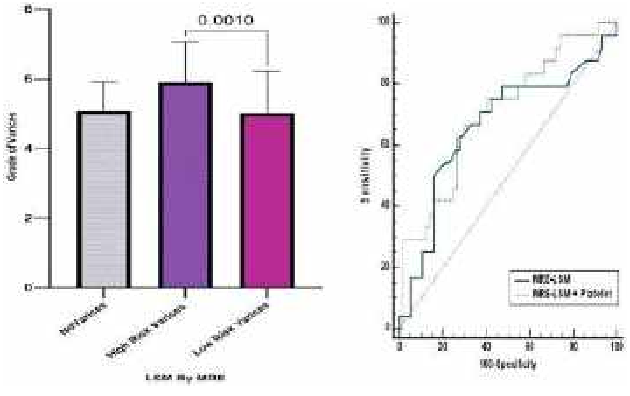
subjects were 96 cirrhotic patients with non-ruptured esophageal and gastric varices who underwent initial endoscopic treatment or B-RTO from April 2006 to March 2023. Median age 69 (40-88) years, male/female ratio 63/33, median observation period 1075 (11-5831) days, background liver diseases: HBV 3/HCV 33/ Alcohol 35/ Others 25, pre-treatment Child-Pugh classification: A 44/ B 43/ C 9. Lymphocyte-related nutritional markers were examined by Neutrophil-to-lymphocyte ratio (NLR), Prognostic Nutritional Index (PNI), and Controlling Nutritional Status (CONUT). Muscle volume was measured using a 3D medical imaging workstation ziostation2 and evaluated by Psoas Volume Index (PVI) (cm3/m2), which is the volume of the psoas major muscle divided by the square of the height. Sarcopenia was defined using the psoas major index (PMI) (cutoff values: male 6.36 cm2/m2, female 3.92 cm2/m2). **Results:** Cumulative survival rates were 87.1% at 1 year, 63.7% at 3 years, and 41.2% at 5 years. The mean/median values of each marker before treatment were NLR 2.37 ± 1.68/2.12, PNI 40.1 ± 6.30/40.1, CONUT 4.57 ± 2.62/4.00, PVI male: 128.9 ± 39.8/124.2 cm3/m2, female: 90.0 ± 20.3/91.2 cm3/m2, 28 patients (29.2%) were classified as sarcopenia group. When the cut-off values were set to NLR 3.0, PNI 40, and CONUT 5 according to previous reports, NLR e 3.0, PNI d 40, CONUT e 5, and sarcopenia groups had significantly worse prognosis ($p < 0.05$). PVI showed a very strong correlation with PMI ($r = 0.827$, $p < 0.001$), but there was no significant correlation between each lymphocyte-related nutritional marker and PVI. In multivariate analysis of survival, age e 65 years, NLR e 3.0, and albumin level < 3.5 g/dL were independent prognostic factors ($p < 0.05$). **Conclusion:** In liver cirrhosis patients with portal hypertension, lymphocyte-related nutritional markers NLR, PNI, and CONUT were all associated with life prognosis, suggesting that these may be useful as prognostic indicators and nutritional intervention markers. Objective quantification of psoas muscle volume by 3D-CT can more accurately assess muscle mass and sarcopenia, and may help predict prognosis in liver cirrhosis patients.

Disclosures: The following people have nothing to disclose: Arisa Yamamoto, Takuto Nosaka, Yu Akazawa, Kazuto Takahashi, Tatsushi Naito, Hidetaka Matsuda, Masahiro Ohtani, Yasunari Nakamoto

3150-A | MAGNETIC RESONANCE ELASTOGRAPHY (MRE) NON-INVASIVELY PREDICTS HIGH-RISK ESOPHAGEAL VARICES IN OBESE NAFLD CIRRHOSIS

Akash Roy[1], Awanish Tewari[1], Nipun Verma[2], Usha Goenka[1], Surabhi Jajodia[1], Swayambhu Banerjee[1], Vikram Patil[1] and Mahesh Goenka[1], (1)Apollo Hospitals, Kolkata, (2)Post Graduate Institute of Medical Education and Research, Chandigarh, India

Background: Liver stiffness measurement (LSM) by magnetic resonance elastography (MRE) is helpful in the prediction of esophageal varices (EVs) and high-risk varices (HRVs) in cirrhosis. Conventional transient elastography has been shown to underperform in high-risk varices (HRVs) prediction in obese non-alcoholic fatty liver disease (NAFLD) cirrhosis. MRE-LSM for predicting EVs and HRVs, specifically in obese NAFLD cirrhosis, remains relatively unexplored. **Methods:** In a prospective study, consecutive patients with NAFLD compensated cirrhosis who were obese (Body mass index e 25kg/m2) and underwent MRE (Philips Ingenia 3.0T with mDixon quant software) for LSM and endoscopy for screening of varices were enrolled. Diagnosis of cirrhosis was based on clinical parameters and imaging (ultrasonography and computed tomography). The diagnostic performance of MRE for predicting the presence of EVs and HRVs was evaluated using the area under receiver-operating characteristics curves ((AUROC), and regression analyses were performed for multiple variables related to the presence of EVs or HRVs. **Results:** 82 obese patients (mean age 53.85 ± 9.62, 29.6% females, mean BMI 29.1 ± 3.39) with compensated NAFLD cirrhosis (70.3% Diabetes, 49.3% Hypertension, 19.7% Dyslipidemia) were enrolled. 47 (58.0%) had EVs, 20 (24.6%) had HRVs. Median [95% confidence interval (CI)] MRE-LSM was 4.9(4.6-5.1), 4.9(4.6-5.3) and 5.6(5.0-6.10) for no varices, low risk varices (LRVs) and HRVs respectively, with differences being significant between LRVs and HRVs ($p < 0.01$). AUROC for MRE-LSM for any varices, LRVs, and HRVs were 0.55(0.43-0.66, $p = 0.45$), 0.57(0.46-0.68, $p = 0.25$) and 0.66(0.55-0.76, $p = 0.02$, cut-off > 5.2) respectively. Odds ratio (95%CI) for MRE-LSM and platelet count (PLC) for HRVs were 1.57(1.01-2.4) and 0.98 (0.97-0.99), respectively. Logistic regression model with MRE-LSM and PLC had an AUC of 0.70(0.59-0.80, $p = < 0.01$). **Conclusion:** MRE-LSM is significantly higher in obese NAFLD compensated cirrhosis with HRVs than those without EVs or LRVs. MRE-LSM, in combination with PLC, identifies HRVs in obese NAFLD cirrhosis.



Disclosures: The following people have nothing to disclose: Akash Roy, Nipun Verma

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

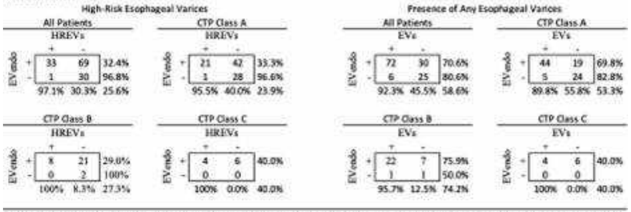
Disclosure information not available at the time of publication: Awanish Tewari, Usha Goenka, Surabhi Jajodia, Swayambhu Banerjee, Vikram Patil, Mahesh Goenka

3151-A | MULTICENTER VALIDATION OF THE EVENDO SCORE TO NONINVASIVELY RISK STRATIFY PATIENTS WITH CIRRHOSIS UNDERGOING INITIAL VARICEAL SCREENING

Andrew Richard Roney[1], Pauline Yasmeh[2], Tien S. Dong[1], Harry Trieu[3] and James Tabibian[2], (1)University of California, Los Angeles, (2)Olive View-UCLA, Burbank, CA, (3)University of Southern California

Background: Many patients with cirrhosis have either no esophageal varices (EVs) or only low-risk EVs (LREVs) on initial screening esophagogastroduodenoscopy (EGD) and do not directly benefit from a screening EGD, yet still face the associated hazards of sedation and procedure-related complications. Non-invasive methods are thus needed to identify patients who may defer initial screening EGD and thereby avoid the associated risks and costs. The EVendo score, a machine learning-based tool, predicts the presence of EVs and high-risk EVs (HREVs) using readily available clinical data. We aimed to further validate the EVendo score in patients undergoing initial screening EGD. **Methods:** We conducted a multicenter retrospective study of screening EGDs performed from January 2019 through May 2020 at the Veterans Affairs West Los Angeles Medical Center, Olive View-UCLA Medical Center, and Ronald Reagan UCLA Medical Center. Patient demographic, biochemical, clinical, and endoscopic data prior to EGD were abstracted from electronic medical records. Patients with a prior EGD or prior episode of variceal bleeding were excluded. The EVendo score was calculated for each patient, and its ability to predict any EVs and HREVs was assessed. **Results:** A total of 133 patients were included in the study. Ninety-two patients were classified as CTP Class A, 31 as Class B, and 10 as CTP Class C. The etiologies of cirrhosis were as follows: alcohol (n = 46), HCV (n = 29), NASH (n = 31), HBV (n = 5), autoimmune hepatitis (n = 5), and multifactorial (n = 17). There were no statistically significant differences in patient demographics or biochemical data, except for platelet count, between those with and without HREVs. The EVendo score had a sensitivity of 97.1% and a negative predictive value of 96.8% for detecting HREVs. For detecting the presence of any EVs the EVendo score had sensitivity of 92.3% and a negative predictive value of 80.6%. Using the EVendo score would have reduced initial screening EGD by 22.6% (30/133), missing 2.9% of HREVs (1/34). The number of initial screening EGDs avoided in CTP class A patients increased to 30.4% (28/92), missing 4.5% of HREVs (1/22). **Conclusion:** This study validates the high sensitivity and negative predictive value of the EVendo score and its potential for non-invasively identifying patients who can avoid initial screening EGD on the basis of low probability of HREVs. Furthermore, in CTP class A patients an even higher percentage of EGDs can be spared, potentially due to the lower probability of these patients having portal pressures significant enough to cause HREVs compared to CTP class B and C patients.

Figure 1. Standard 2x2 diagnostic tests table between HREVs and EVendo > 3.9, and presence of any EVs and EVendo > 3.9 in all patients and those across CTP class



High-Risk Esophageal Varices

All Patients

EVendo	HREVs +	HREVs -	
+	33	69	32.4%
-	1	30	96.8%
	97.1%	30.3%	25.6%

CTP Class A

EVendo	HREVs +	HREVs -	
+	21	42	33.3%
-	1	28	96.6%
	95.5%	40.0%	23.9%

CTP Class B

EVendo	HREVs +	HREVs -	
+	8	21	29.0%
-	0	2	100%
	100%	8.3%	27.3%

CTP Class C

EVendo	HREVs +	HREVs -	
+	4	6	40.0%
-	0	0	
	100%	0.0%	40.0%

Presence of Any Esophageal Varices

All Patients

EVendo	EVs +	EVs -	
+	72	30	70.6%
-	6	25	80.6%
	92.3%	45.5%	58.6%

CTP Class A

EVendo	EVs +	EVs -	
+	44	19	69.8%
-	5	24	82.8%
	89.8%	55.8%	53.3%

CTP Class B

EVendo	EVs +	EVs -	
+	22	7	75.9%
-	1	1	50.0%
	95.7%	12.5%	74.2%

CTP Class C

EVendo	EVs +	EVs -	
+	4	6	40.0%
-	0	0	
	100%	0.0%	40.0%

Values from left to right for each diagnostic table: true positive, false positive, positive predictive value, false negative, true negative, negative predictive value, sensitivity, specificity, prevelance; VNT, varices needing treatment; CTP, Child-Turcotte-Pugh

Disclosures: James Tabibian – Guidepoint Global Advisors: Consultant, No, No; Gerson Lehman Group, Inc.: Consultant, No, No; Techspert: Consultant, No, No; AlphaSights: Consultant, No, No; DeciBio: Consultant, No, No; Olympus: Consultant, No, No; Ipsen: Consultant, No, Yes; Atheneum: Consultant, No, No; ClearView Healthcare Partners: Consultant, No, No; iota Biosciences: Consultant, No, No; Pure Healthcare Strategy: Consultant, No, No; KeyQuest Health: Consultant, No, No; Ambu: Consultant, No, No;
The following people have nothing to disclose: Andrew Richard Roney, Tien S. Dong
Disclosure information not available at the time of publication: Pauline Yasmeh, Harry Trieu

3152-A | NON-VARICEAL UPPER GASTROINTESTINAL BLEEDING CARRIES THE SAME SHORT-TERM PROGNOSIS AS VARICEAL BLEEDING IN PATIENTS WITH CIRRHOSIS AND SHOULD BE CONSIDERED A DECOMPENSATING EVENT

Rajiv Kurup, Deloshaan Subhaharan, Tehara Wickremeratne, Andrew Sloss, Jonathan Mitchell, Rohit Gupta and James Patrick O'Beirne, Sunshine Coast University Hospital

Background: According to the Baveno consensus recommendations, upper gastrointestinal bleeding (UGIB) that occurs secondary to portal hypertension in patients with cirrhosis is considered a decompensation event and is associated with a high mortality rate. Nevertheless, it remains uncertain whether non-portal hypertension-related bleeding carries the same level of prognostic significance. This study aimed to compare the survival rates between portal hypertension-related and non-portal hypertension-related bleeding in patients with cirrhosis. **Methods:** This retrospective study included patients with cirrhosis admitted to Sunshine Coast University Hospital with UGIB, hepatic encephalopathy, ascites, and jaundice between November 2016 and October 2020. Patients were divided into portal hypertension-related bleeding, non-portal hypertension-related bleeding and outcomes were compared to other causes of decompensation. UGIB from portal hypertension-related bleeding was classified as either secondary to gastro-oesophageal varices or portal hypertensive gastropathy. Gastroscopy reports were analysed, and variceal bleeding was defined in accordance with the Baveno criteria. **Results:** 243 patients were included. The majority of patients were male (65.8%) and the median age was 59 years (IQR 50-67). The main aetiology of cirrhosis was alcohol in 63%. 106 patients were Child-Pugh (CP) class C and 81.1% were admitted with other causes of decompensation. The median CP score was 7 for both portal hypertension-related bleeding (IQR 5-9.5) and non-portal hypertension-related bleeding (IQR 5-9) with no significant difference between these groups (p 0.66). In comparison, patients with other causes of decompensation had a median CP score of 10 (IQR 8-11) which was significantly higher than the UGIB group ($p < 0.001$). 84 patients presented with UGIB with 45 (53.6%) being portal hypertension-related and 39 from other causes including Mallory Weiss tears and oesophageal and gastric ulcers. There was no significant difference in 30-day, 90-day and 1-year survival between portal hypertension-related and non-portal hypertension-related bleeding. There was a significant difference in overall survival between the UGIB group and patients with other causes of decompensation (p 0.002). However, there was no significant difference in overall survival between portal hypertension-related and non-portal hypertension-related bleeding. **Conclusion:** This data suggests that early outcomes in patients admitted with portal hypertension-related and non-portal hypertension-related bleeding are similar. Therefore, even non-portal hypertension-related bleeding can be considered as a decompensating event and could influence mortality possibly by serving as a trigger for acute-on-chronic liver failure. The diversion of survival curves on prolonged follow up confirms the impact of portal hypertension on long-term prognosis.

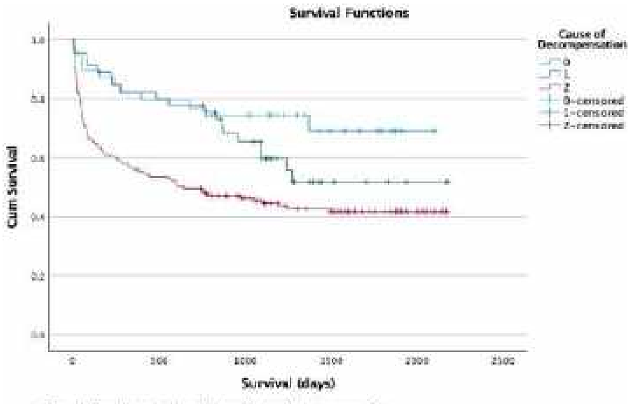


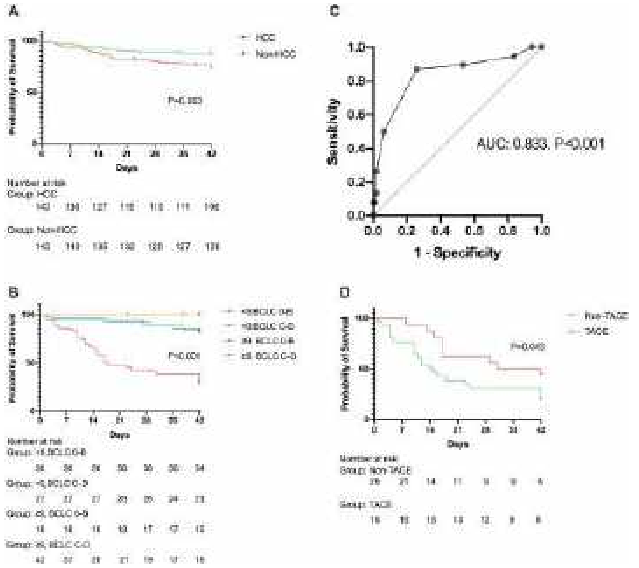
Figure 1: Overall survival in patients with hepatic decompensation.
0 = non-portal hypertension bleeding, 1 = portal hypertension bleeding, 2 = other causes of decompensation.

Disclosures: The following people have nothing to disclose: Rajiv Kurup, Deloshaan Subhaharan, Tehara Wickremeratne, Andrew Sloss, Jonathan Mitchell, Rohit Gupta, James Patrick O'Beirne

3153-A | OUTCOMES AND PROGNOSTIC FACTORS OF CIRRHOTIC PATIENTS WITH ACUTE VARICEAL BLEEDING AND CONCURRENT HEPATOCELLULAR CARCINOMA

Guofeng Liu[1], Xuefeng Luo[2], Xiaoze Wang[1] and Tong Xiang[1], (1)West China Hospital, (2)West China Hospital, Sichuan University

Background: The treatment outcomes and risk factors for poor prognosis of acute variceal bleeding (AVB) in hepatocellular carcinoma (HCC) patients remain unclear. Hence, we assessed the clinical outcomes and prognostic factors of these patients. **Methods:** This is a retrospective case-control study. AVB patients with HCC admitted between 2016 and 2019 were included. For each patient with HCC, a patient without HCC was matched by age, sex, and Child-Pugh class. Follow-up was continued until death and transplantation. **Results:** A total of 286 patients were included. The five-day treatment failure, 6-week mortality, and 1-year mortality rates of all enrolled AVB patients were 26.6%, 19.6%, and 36.1%, respectively. HCC patients had higher 6-week and 1-year mortality (26.6% vs. 12.6, $P = 0.003$; 53.3% vs. 18.9%, $P < 0.001$, respectively). Among AVB patients with HCC, alpha-fetoprotein (AFP) levels (HR, 1.001;95% CI, 1.000-1.002; $P = 0.001$), BCLC stage (C-D vs. 0-B) (HR, 7.752; 95% CI, 1.688-35.592; $P = 0.008$), transcatheter arterial chemoembolization (TACE) treatment (HR, 0.293; 95%CI, 0.102-0.842; $P = 0.023$), and Child-Pugh score (HR, 1.496, 95% CI, 1.210-1.849; $P < 0.001$) were independent risk factors of 6-week mortality in multivariate analysis. Furthermore, the risk of 6-week mortality was significantly higher among patients with a Child-Pugh score e 9 and BCLC stage C–D ($P < 0.0001$). **Conclusion:** AVB patients with HCC had a worse prognosis than patients without. The Child-Pugh score and the presence and stage of HCC are strong predictors of 6-week mortality.



Disclosures: The following people have nothing to disclose: Guofeng Liu, Xuefeng Luo, Xiaoze Wang, Tong Xiang

3154-A | OUTCOMES OF OUTPATIENT ELECTIVE ESOPHAGEAL VARICES BAND LIGATION IN CIRRHOTIC PATIENTS WITH SIGNIFICANT THROMBOCYTOPENIA

Julton Tomanguillo Chumbe[1], Mark Ayoub[2], Lauren Searls[2], Frank Annie[2], Harleen Chela[2], Nadeem Anwar[1] and Ebubekir Daglilar[1], (1)West Virginia University - Charleston Area Medical Center, Charleston, WV, (2)Charleston Area Medical Center/ WVU Charleston Division

Background: Current guidelines recommend against platelets transfusion prior to emergent esophageal varices band ligation (EVL) in cirrhotic with a platelet count less than $50*10^3$/uL. However, recommendations for elective esophageal varices ligation less clear. This study aims to assess the outcomes of cirrhotic patients who underwent EVL as an outpatient. **Methods:** Adult patients 18 years and older with the diagnosis of cirrhosis with and without significant thrombocytopenia, as defined by the cut-off of $50*10^3$/uL, were identified using TriNetX database between 2007 and 2020. Patients who received platelets transfusion on the day of band ligation were excluded. TriNetx includes clinical data from a total of 106 different healthcare organizations in 14 countries. Patients with cirrhosis with significant thrombocytopenia who underwent outpatient elective EVL were divided into two cohorts; the first cohort comprised patients with significant thrombocytopenia (platelet count between 30 and $49*10^3$/uL); and a second cohort of patients with platelet greater and equal than $50*10^3$/uL. We compared the rate of mortality and esophageal variceal bleeding propensity score matched (PSM) pairs of patients. **Results:** A total of 7,392 cirrhotic patients that underwent outpatient EVL were included in this analysis. Of these 8.9% ($n = 664$) had significant thrombocytopenia, and 91.1% ($n = 6{,}726$) had platelets greater and equal than $50*10^3$/uL. The raw data showed that patients with significant thrombocytopenia were younger (59.7 ± 13 vs 62.4 ± 12.7, $P < 0.0001$), and there was no significant difference in key comorbidities. Subsequently, two well-matched cohorts were created using a 1:1 PSM based model (664/664). No significant difference was noted between cirrhotic patients with and without significant thrombocytopenia in the rate of post-EVL esophageal variceal bleeding, mortality at 14 days and 1-month. The end-point were not statistically different in both group in terms of 14-days esophageal varices bleeding (10.54% vs 12.50%, $P = 0.26$), 14-days mortality (2.86%% vs 3.31%%, $P = 0.63$), and 1-month mortality (4.51% vs 6.17%, $P = 0.17$). **Conclusion:** Elective endoscopic bad ligation is safe with platelet count greater and equal than 30 $*10^3$/uL comparing to threshold of $50*10^3$/uL. This lower threshold may prevent unnecessary use of platelet transfusions.

Disclosures: The following people have nothing to disclose: Julton Tomanguillo Chumbe, Mark Ayoub, Lauren Searls, Frank Annie, Harleen Chela, Nadeem Anwar, Ebubekir Daglilar

3155-A | PORTAL HYPERTENSION MANIFESTATIONS OF CROHN'S DISEASE

Keiya Watakabe, Shun Kaneko, Yasuhiro Asahina, Miyako Murakawa, Tatsuya Suzuki, Yuka Hayakawa, Kento Inada, Tomohiro Mochida, Taro Shimizu, Jun Tsuchiya, Masato Miyoshi, Fukiko Kawai-Kitahata, Kento Takenaka, Toshimitsu Fujii, Sei Kakinuma, Mina Nakagawa and Ryuichi Okamoto, Tokyo Medical and Dental University

Background: The screening and diagnosis of portal hypertension (PH) have been difficult especially in non-liver chronic disease, despite severe complications. Inflammatory bowel diseases (IBD) are associated with a variety of extraintestinal manifestations, including hepatobiliary disorders. The hepatobiliary manifestations are reported in both ulcerative colitis (UC) and Crohn's disease (CD) but are more commonly reported about UC. The aims of this study were to reveal the prevalence of advanced liver

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

disease and PH in CD which was less reported, and to identify risk factors. **Methods:** CD patients receiving MRI test (n = 459) were recruited prospectively form Tokyo Medical and Dental University Hospital between April 2017 and September 2021. Fatty Liver and spleen index were diagnosed by MRI. The risk factors and prevalence of PH were analyzed. **Results:** A total of 459 CD patients were median age 33 (18-85) years, majority male (70.0%). 79 cases (17.2%) had fatty liver. During a median follow-up of 3.2 years, we identified 5 (1.1%) cases of PH. Underlying liver disease of PH included non-alcoholic steatohepatitis (NASH, n = 2), granulomatous hepatitis (n = 1), drug induced liver injury (n = 1), and primary sclerosing cholangitis (PSC, n = 1). Median FIB-4 (3.34 vs 0.622) and spleen index (63.75 cm^2 vs 27.03 cm^2) were significantly higher in patients with PH than other CD patients, respectively ($p < 0.001$). Case 1; A 40-year-old man who had a history of three times intestine resections due to bleeding and perforation required liver transplantation due to liver failure caused by progression of NASH decompensated cirrhosis. Case 2; A 45-year-old man was maintained clinical remission of CD with anti-integrin therapy. During follow-up, esophagogastric varices, aggravated splenomegaly and thrombocytopenia were found. He was finally diagnosed granulomatous hepatitis from liver biopsy. The endoscopic injection sclerotherapy for varices, and anti-TNFα for granuloma hepatitis and CD were administered. **Conclusion:** CD patients found to be included some advanced liver disease and PH cases, despite their younger age. PH was not caused only by NASH. FIB-4 and spleen index are also useful in liver surveillance in regular MRI follow up of CD patients.

Disclosures: The following people have nothing to disclose: Keiya Watakabe, Shun Kaneko, Yasuhiro Asahina, Miyako Murakawa, Tatsuya Suzuki, Yuka Hayakawa, Kento Inada, Tomohiro Mochida, Taro Shimizu, Jun Tsuchiya, Masato Miyoshi, Fukiko Kawai-Kitahata, Kento Takenaka, Toshimitsu Fujii, Sei Kakinuma, Mina Nakagawa, Ryuichi Okamoto

3156-A | PORTAL VEIN THROMBOSIS PREDICTS HIGHER MORTALITY IN CIRRHOSIS PATIENTS WITH ACUTE VARICEAL BLEEDING: A SINGAPORE NATIONWIDE AVB AUDIT

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Background: Portal vein thrombosis (PVT) was associated with a higher risk of acute variceal bleeding (AVB) and rebleeding in cirrhosis patients. However, it's impact on the mortality risk beyond the setting of liver transplantation remained debatable (eg: in the setting of AVB). Using the Singapore nationwide AVB audit registry, we sought to determine the prognostic impact of PVT in cirrhosis patients presented with AVB. **Methods:** Medical records of AVB patients hospitalized in all public hospitals in Singapore from January 2015 to December 2020 were individually reviewed by investigators. Primary predictor was the presence of PVT, identified based on imaging within 6 months of the AVB episode. Primary outcome was 6-week mortality, secondary outcomes included rebleeding at 5 days and mortality at 1 year. Baseline differences between PVT and non-PVT groups were balanced using propensity score matching (PSM), adjusting for gender, cirrhosis etiology, Child-Turcotte-Pugh (CTP) class, ascites, presence of hepatocellular carcinoma (HCC), AST and platelet count. Sensitivity analysis was performed in (1) AVB patients without HCC, (2) MELD d 10 and (3) MELD > 10, to account for tumour thrombus and severity of cirrhosis. **Results:** Among 888 cirrhosis patients (mean age 62, 75% male) with AVB from seven hospitals in Singapore studied, 15% had PVT. AVB patients with PVT were more likely to be female with HBV-related cirrhosis and had more advanced liver disease ie: ascites, higher CTP score, higher AST, and more likely to have HCC (*67% vs 17%, p < 0.0001*). In the PSM cohort (n = 262) with balanced distribution in gender, cirrhosis etiology, cirrhosis severity (ie: CTP score, MELD score, liver decompensating events), and HCC between the PVT and non-PVT group, AVB patients with PVT had similar 5-days rebleeding rate, but were more likely to be hypotensive upon presentation (*28% vs 13%, p = 0.003*), and had higher mortality at 6-week (*30% vs 16%, p = 0.009*) and 1-year (*64% vs 36%, p < 0.001*). In multivariate analysis, PVT predicted a higher 1-year mortality after adjusting for HCC, gender, CTP and MELD score (*OR: 2.9, 95%CI: 1.6-5.3*). Sensitivity analysis showed PVT was associated with a higher 1-year mortality, regardless of low or high MELD score, (MELD≤10: *64.5% vs 12.1%, p < 0.0001;* MELD > 10: *63% vs 44%, p = 0.013*); and also in patients without HCC (*37% vs 18%, p = 0.004*). **Conclusion:** The presence of PVT predicts a poorer prognosis in cirrhotic patients with AVB even after adjusting for the severity of cirrhosis and HCC. PVT commonly co-exist with HCC, which is an important consideration when individualizing treatment decision for PVT in patients with AVB.

Disclosures: Yu JUN Wong – Gilead: Speaking and Teaching, No, Yes; AbbVie: Speaking and Teaching, No, Yes;

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3157-A | POST EVL BLEED IS DEPENDENT ON BOTH OPERATOR AND PATIENT RELATED FACTORS

Mithun Sharma[1], Harsh Vardhan Tevethia[2], Anand V. Kulkarni[3], Manasa Alla[3], Shantan Venishetty[3], Sowmya T R[3], Padaki Nagaraja Rao[3] and Nageshwar D Reddy[3], (1)Asian Institute of Gastroenterology, Hyderabad, Telangana, India, (2)Institute of Liver and Biliary Sciences, New Delhi, (3)Aig Hospitals, Hyderabad, India

Background: Early post endoscopic variceal (EVL) bleeding, particularly in patients with prophylactic variceal ligation, is a major concern. Studies have shown that it is associated with higher MELD score, a higher number of bands used, the presence of gastric varices, and lower hemoglobin at admission. There has always been a need to evaluate if the risk is increased due to other causes like the experience of the operator, the type of underlying liver disease, or the level at which these bands are applied **Methods:** This was a prospective study to evaluate the incidence and identify the risk factors for early posy EVL bleeding in patients with liver cirrhosis. All adult patients above 18 years who underwent EVL at the Institute were included in the study. The etiology of underlying liver disease, the indication of EVL, the experience of the endoscopist [residents in final year training or junior consult defined as less than 2 years of completing GI training or consultant (> 2 yrs)], number of bands applied, the highest level at which it was applied, use of proton-pump inhibitors post procedure etc were noted in pre-designed sheets. These patients were followed up for the next 3 weeks either physically or by telephonic interview. Any patient who had a hemoglobin drop > 1 g/dl or had episodes of hematemesis or melena had a relook endoscopy to identify the cause of the bleed. **Results:** During the study period from January 2021 to January 2023, 687 EVL patients were included, of which 108 were for acute bleeding, 204 underwent prophylactic EVL, and the remaining patients had repeat EVL for variceal eradication. The incidence of a bleed within 3 weeks was 26/687 (3.87), and 90% of bleed occurred within 2 weeks. The most common bleed was melena 21/26 (80.7), followed by hematemesis in 3/26(11.5%) and the remaining had hemoglobin drop. Possible band slippage and active spurting bleed were found in 2/3 of patients with hematemesis, which was controlled by repeat ligation, and one patient underwent rescue TIPS. There was a significant bleed in EVL done by residents (10/26 post-EVL bleeders, OR 4.6). The other risk factors were patients with CHILD B/C (OR 6.8), patients who had scarred tissue at the banding site as assessed by the endoscopist OR 3.75), using more than 5 bands (OR 2.4) and if bands were applied at the perforating zone(OR 3.5). There was no association with the level of platelet count or the INR value. **Conclusion:** Early post EVL bleeding is dependent on both the operator and patient-related factors. Advanced liver disease, repeated banding sessions, and application of more bands coupled with a relatively inexperienced operator could lead to more complications, though this needs to be further evaluated in a study powered specifically to meet this end point.

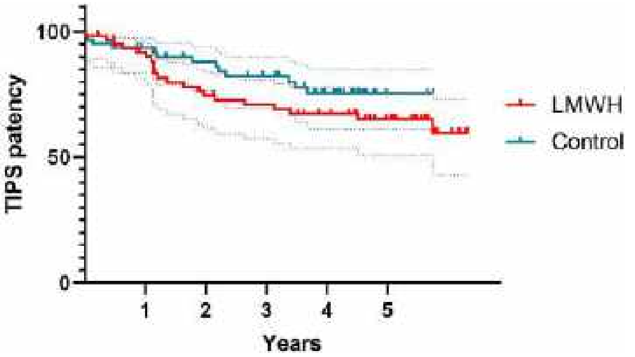
Disclosures: The following people have nothing to disclose: Mithun Sharma, Harsh Vardhan Tevethia, Anand V. Kulkarni, Manasa Alla, Shantan Venishetty, Sowmya T R, Padaki Nagaraja Rao, Nageshwar D Reddy

f 3158-A | POST-TIPS SHORT-TERM LOW MOLECULAR WEIGHT HEPARIN FOR THE PREVENTION OF EARLY TIPS DYSFUNCTION: A RANDOMISED CONTROLLED TRIAL

Xiaoze Wang[1], Xuefeng Luo[2] and Guofeng Liu[1], (1) West China Hospital, (2)West China Hospital, Sichuan University

Background: Transjugular intrahepatic portosystemic shunt (TIPS) dysfunction is defined as a loss of decompression of the portal venous system due to occlusion or stenosis of the TIPS. Whether post-TIPS LMWH was necessary when polytetrafluoroethylene-covered stent was used during TIPS creation was not answered. The present study was designed to evaluate the effect of short-term use of LMWH on early TIPS dysfunction. **Methods:** Between September 2015 and

October 2017, consecutive eligible patients with cirrhosis and portal hypertension were randomly assigned to receive LMWH for three days after TIPS procedure (n = 62) or not (n = 62), respectively. All patients were followed up over a twelve-month period. The primary endpoint was TIPS patency rate at one year. Secondary endpoints were overall survival and LMWH-related complication. This trial was registered in ClinicalTrials.gov (NCT03171727). **Results:** During a median follow-up of 54.6 months, the TIPS patency rate at one year was 91.7% in the LMWH group and 93.5% in the control group (HR 1.52, 95% CI 0.78-2.99, P = 0.22). In multivariable logistic regression, stent shortening in the hepatic vein (HR 4.54; 95% CI 1.02-21.42; P = 0.041) was demonstrated as an independent significant risk factor for shunt dysfunction. There were no statistically significant differences in survival (93.5% vs. 95.1% at 1 year; HR = 1.05, 95% CI 0.48-2.31, P = 0.90) or adverse events between the two groups. **Conclusion:** Short-term use of LMWH after TIPS creation may not be necessary as it does not result in a distinct patency and survival benefit in covered TIPS.



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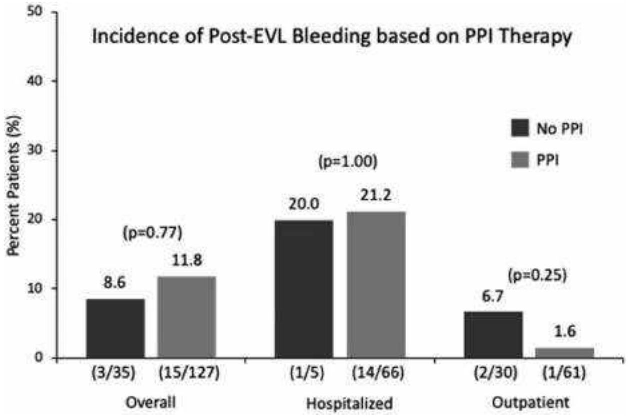
Disclosure information not available at the time of publication: Xiaoze Wang

3159-A | PREVENTION OF BLEEDING EVENTS AFTER ENDOSCOPIC VARICEAL LIGATION WITH PROTON PUMP INHIBITORS: BENEFIT OR RISK

Ricardo Albarran-Anguiano[1], Shivang S. Mehta[2], Apurva A. Modi[2], Themistoklis Kourkoumpetis[2], Saleh Elwir[3], James F. Trotter[3] and Stevan A. Gonzalez[2], (1) Baylor Scott & White All Saints Medical Center, Fort Worth, TX, (2)Baylor Simmons Transplant Institute, Forth Worth, TX, (3)Baylor Simmons Transplant Institute, Dallas, TX

Background: Proton pump inhibitors (PPI) are frequently used following endoscopic variceal ligation (EVL) in both acute hemorrhage or elective procedures; although PPI therapy may decrease postbanding ulcer size, its impact on bleeding risk is not well defined. **Methods:** Retrospective cohort study of consecutive patients with cirrhosis who underwent elective or emergent esophagogastroduodenoscopy (EGD) between January 2021 and October of 2022 were evaluated for bleeding outcomes following EVL based on PPI use in a large tertiary care hepatology practice affiliated with a liver transplant program. **Results:** 197 patients were included in the cohort: 39% alcohol-related cirrhosis, median MELD-Na 14 (range 6-40), 34% Child's Classification C, 65% ascites, 46% encephalopathy. Overall, 162 (82%) required EVL and 100 (51%) underwent EGD while hospitalized. Hospitalized patients were less likely to undergo EVL (71% vs. 94%, p < 0.001) and more frequently had non-variceal sources of bleeding (p = 0.002). Among those requiring EVL, 18/162 (11%) experienced a bleeding episode within 30 days following the procedure, which occurred more frequently in those who underwent EVL while hospitalized (21% vs. 3%, p < 0.001). In those with post-EVL bleeding, a post-banding ulcer was identified in 11/18 (61%) and active bleeding was seen in 9/18 (50%) on follow up EGD. Overall, PPI therapy given at the time of EVL had no impact on incidence of post-EVL bleeding events (Figure). Among hospitalized patients who underwent EVL, 66/71 (93%) received PPI therapy, which was given by oral administration (26%), IV push (41%), or continuous infusion (33%), and 70% received at least 72 hrs of therapy. Formulation, dose, or duration of PPI had no association with incidence of post-EVL bleeding among hospitalized patients (p = NS). Among outpatients who underwent elective EVL, PPI therapy was given less frequently in 61/91 (67%, p < 0.001) and administered orally as once daily (57%) or twice daily (43%). In the outpatient setting, PPI dose or duration also had no association with incidence of post-EVL bleeding (p = NS). **Conclusion:** PPI therapy at the time of EVL may not decrease the risk of post-EVL bleeding regardless of hospitalization status or PPI formulation, dose, and duration. Risk-benefit of PPI use should be assessed prior to decisions on initiating therapy.



Disclosures: Apurva A. Modi – Salix Pharmaceuticals: Speaking and Teaching, Yes, No; Abbvie: Speaking and Teaching, Yes, No; Gilead Pharmaceutical: Speaking and Teaching, Yes, No; Intercept Pharmaceuticals: Speaking and Teaching, Yes, No;
James F. Trotter – hepquant: Advisor, No, No;
Stevan A. Gonzalez – Mallinckrodt Pharmaceuticals: Consultant, No, Yes; Mallinckrodt Pharmaceuticals: Speaking and Teaching, No, No; Salix Pharmaceuticals: Speaking and Teaching, No, Yes;
The following people have nothing to disclose: Ricardo Albarran-Anguiano
Disclosure information not available at the time of publication: Shivang S. Mehta, Themistoklis Kourkoumpetis, Saleh Elwir

3160-A | PROSPECTIVE EVALUATION OF PATIENTS WITH NON-CIRRHOTIC PORTAL HYPERTENSION: A SINGLE CENTER STUDY

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Background: Non-cirrhotic portal hypertension (NCPH) is a spectrum of liver diseases, including porto-sinusoidal vascular disorder (PSVD), that is associated with elevated portal pressures in absence of cirrhosis. Unlike cirrhosis, patients with NCPH have preserved liver synthetic function, however, develop similar complications of portal hypertension (PH). The mechanisms, natural history, and diagnostics approach to NCPH are not fully explored. We aimed to study disease progression and outcomes in NCPH. **Methods:** Patients with NCPH or known to be at risk for NCPH by the virtue of underlying disease were enrolled into single center prospective study NCT02417740. Patients with evidence of other liver diseases, including cirrhosis were excluded. Clinically significant portal hypertension (CSPH) was diagnosed by presence of varices, including esophageal (EV), portal hypertensive gastropathy or portosystemic collaterals. All participants had an initial liver biopsy. Blood work, liver stiffness measurement (LSM) and abdominal imaging was repeated every 6 to 12 months. Patients with CSPH underwent esophagogastroduodenoscopy for EV screening. **Results:** 47 patients were enrolled, 36 (77%) had CSPH and 11 (23%) had absence of CSPH despite having biopsy features suggestive of PSVD or predisposition due to underlying disease. Median follow-up time was 43 months. Patients with CSPH were mostly White, (97.2%), older, mean age 50.9 ± 13.8 years, had higher spleen-height ratios, and lower platelet counts than patients without CSPH. Most frequent underlying disorders in both groups were primary immunodeficiencies (47%), and autoimmune disorders (13%). 25% patients with CSPH had no underlying diagnosis identified. Most common features in liver biopsies were nodular regenerative hyperplasia (51% of all biopsies), perisinusoidal fibrosis (47%), obliterative portal venopathy (23%), and sinusoidal dilation (21%). Patients with CSPH had significantly higher LSM by transient elastography, median 9.7 kPa vs 5.0 kPa. No patient without CSPH died or had any liver-related complications during the follow-up period (Fig. 1). 7 (19%) of patients with CSPH died, 1 received a liver transplant and 5 (14%) had decompensation (new-onset variceal bleeding (VB), ascites and/or spontaneous bacterial peritonitis). 6/7 of deaths were related to PH or liver disease, 1 died from recurrence of acute lymphoblastic leukemia. **Conclusion:** We observed significant rates of decompensation events in the group with CSPH. The rates of VB were lower than reported previously, although this may be due to inadequate follow up, alternatively regular follow-up allowed for early intervention, initiation of beta blockers and prevention of complications. NCPH has potential for significant morbidity and mortality and close follow-up of patients is crucial.

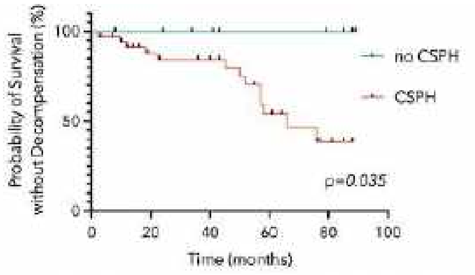

Figure 1. Probability of being alive without decompensation in presence of clinically significant portal hypertension (CSPH) in NCPH cohort was 91% at 1 year, 84% at 2 years, and 54% at 5 years.

Disclosures: The following people have nothing to disclose: Maria Mironova, Harish Gopalakrishna, Asif Ali Hitawala, Shani Scott, David E Kleiner, Christopher Koh, Theo Heller
Disclosure information not available at the time of publication: Nehna Abdul Majeed

f 3161-A | RECALIBRATED MELD 3.0 PERFORMS BEST TO PREDICT 6-WEEK MORTALITY AFTER ACUTE VARICEAL BLEEDING: EXTERNAL VALIDATION IN A LARGE MULTINATIONAL COHORT

Adam Buckholz[1], Yu JUN Wong[2], Rochelle Wong[3], Michael P. Curry[4], Gyorgy Baffy[5], Erik Chak[6], Tarun Rustagi[7], Le Shaun Ang[8], Wen Hui Leia Teo[8], Arpan Mohanty[9] and Brett Fortune[10], (1)New York Presbyterian Hospital Program, (2)Department of Gastroenterology & Hepatology, Changi General Hospital, Singapore, (3)Weill Cornell Medicine, NY, (4) Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (5)VA Boston Healthcare System, (6)Univ of California Davis School of Medicine, (7)California Pacific Medical Center, (8)Changi General Hospital, (9)Boston University School of Medicine, (10) Montefiore Medical Center

Background: Acute variceal bleeding (AVB) due to cirrhosis results in 15-20% mortality within 6 weeks, but accurate risk stratification remains elusive. We aim to externally validate the recalibrated Child-Turcotte-Pugh (CTP) and MELD/MELD 3.0 model for the prediction of 6-week mortality using a large multinational cohort of cirrhosis patients with AVB. **Methods:** The development cohort (DC) consists of consecutive cirrhosis patients presenting with AVB identified retrospectively from 2 hospitals in New York. The primary predictors included liver disease indices such as CTP Score, MELD, or MELD 3.0. These indices were recalibrated using logistic recalibration and internally validated using bootstrapping with replacement. The primary outcome was 6-week mortality according to Baveno 6 consensus. Predictive value was quantified as a combination of discrimination by AUROC, and calibration by Hosmer-Lemeshow (HL) test by splitting the cohort into quintiles ($p > 0.05$ means statistically calibrated) and furthermore by the Brier Score, which measures disagreement between observed and forecasted outcome (lower # = better agreement). External validation of the recalibrated models was performed using a multinational AVB cohort (2012-2020) from four US Centers (UC) and one Singapore Center (SC). **Results:** There were 126 patients in the DC, 229 in the UC, and 143 in the SC (total n = 498) with overall 6-week mortality 16%, similar among sites. Patients in the SC had a significantly lower baseline MELD (11.9 vs 16.3, $p < 0.01$) and CTP Score (7.3 vs 8.9, $p < 0.01$) with higher mean age (60.6 vs 58.4, $p < 0.01$) compared to the DC, while the DC and UC had similar baseline characteristics. Each liver index had similar discrimination ($p > 0.05$) for 6-week mortality [Fig 1A]. The performance of all indices were suboptimal in DC and overall cohort before recalibration. Upon logistic recalibration with bootstrapping, the equation obtained for CTP was logit = -6.44 + 0.503*CTP, for MELD was logit = -4.54 +0.159*MELD and for MELD 3.0 was logit = -4.76 + 0.152*MELD 3.0, all of which were internally valid for 6-week mortality prediction after AVB. In external validation, only MELD 3.0 remained calibrated at $p > 0.05$ in both the UC and SC [Fig 1B-D], and had the lowest, albeit similar, Brier Score (MELD 0.120, CTP 0.113, MELD 3.0 0.112). In a LOWESS smoothing model [Fig 1E], observed 6-week mortality was consistently below 5% among those with MELD 3.0 < 12 and > 20% among those with MELD 3.0 > 20. **Conclusion:** In a large diverse multinational cohort of patients with AVB, we recalibrated and externally validated MELD 3.0 as the best liver index in predicting 6-week mortality after AVB. Use of simple predicted mortality thresholds may aide clinicians in the management of these patients and provide important measures for future therapeutic trial design.

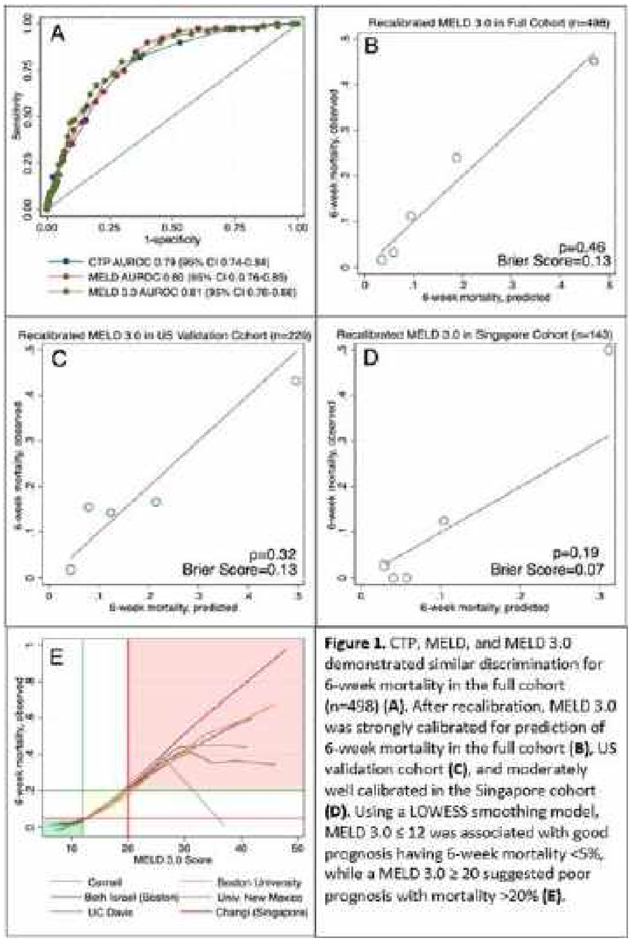

Figure 1. CTP, MELD, and MELD 3.0 demonstrated similar discrimination for 6-week mortality in the full cohort (n=498) **(A)**. After recalibration, MELD 3.0 was strongly calibrated for prediction of 6-week mortality in the full cohort **(B)**, US validation cohort **(C)**, and moderately well calibrated in the Singapore cohort **(D)**. Using a LOWESS smoothing model, MELD 3.0 ≤ 12 was associated with good prognosis having 6-week mortality <5%, while a MELD 3.0 ≥ 20 suggested poor prognosis with mortality >20% **(E)**.

Disclosures: Yu JUN Wong – Gilead: Speaking and Teaching, No, Yes; AbbVie: Speaking and Teaching, No, Yes;

Michael P. Curry – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Mallinckrodt Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Sonic Incytes: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Albireo: Consultant, No, No; Alexion: Consultant, No, No;

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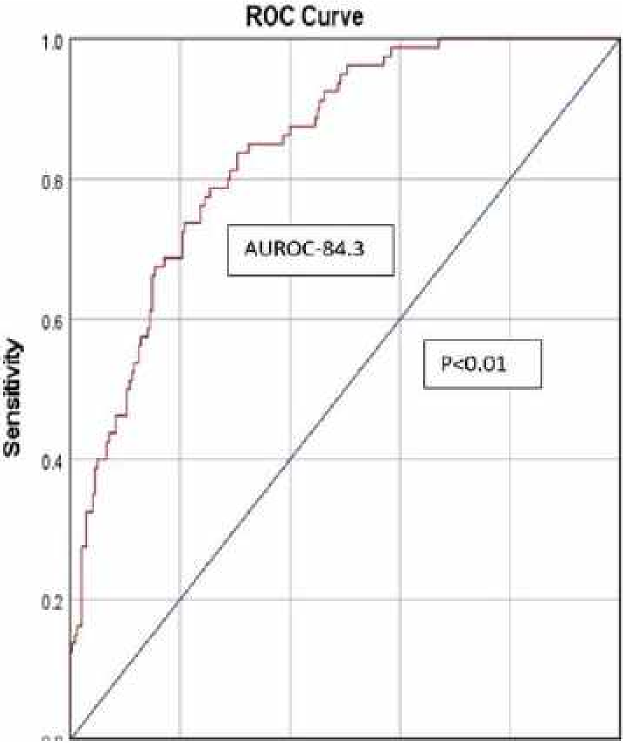
Disclosure information not available at the time of publication: Rochelle Wong, Gyorgy Baffy, Tarun Rustagi, Le Shaun Ang, Wen Hui Leia Teo, Arpan Mohanty

3162-A | ROLE OF SPLENIC STIFFNESS IN THE PREDICTION OF VARICEAL BLEED(VB) IN PATIENTS WITH CIRRHOSIS- SAVIOR STUDY

Harsh Vardhan Tevethia[1]*, Anirban De*[1]*, Ankur Jindal*[1]*, Vinod Arora*[2]*, Guresh Kumar*[3] *and Shiv Kumar Sarin*[4]*, (1)Ilbs ,New Delhi, (2)Institute of Liver and Biliary Sciences, New Delhi, India, (3)Institute of Liver and Biliary Sciences, New Delhi, (4)Institute of Liver and Biliary Sciences*

Background: Hepatic venous pressure gradient(HVPG) and Liver stiffness(LS) have been shown to be correlated with with variceal bleed in cirrhosis patients. Splenic stiffness(SS) has been shown to correlate with HVPG. We investigated the role of splenic stiffness in the prediction of variceal bleed(VB) in patients with cirrhosis **Methods:** Patients presenting with AVB(Group 1) were prospectively enrolled between April 2021 to May 2022 admitted in the GI Bleed unit at ILBS New Delhi. Patients seen during the same period without AVB who had undergone HVPG (Group 2) were included as controls. Baseline data at admission including HVPG, LS, SS were included. Associations were determined using logistic regression analysis. The primary objective of the study was to assess the role of SS in the prediction of AVB and Liver Related Events(LRE) in comparison to LS and HVPG **Results:** Altogether 320 patients were analysed, 80 with AVB (Group 1) and 240 without bleed (group 2), [males(56.8%),MELD score 15 ± 2.1,predominant etiology ethanol(46.3%) followed by NASH(32.3%)]. The baseline HVPG was higher in AVB than non-AVB group (18.91 mmHg vs 15.78 mmHg $p < 0.01$) along with higher LS(48.2kPa vs 33.kPa, $P < 0.01$). The SS was higher in the AVB group(74.3kPa vs 56kPa $P < 0.01$).Development of LRE was also higher in the AVB group (46.3% vs 21.7% $P < 0.01$). Baseline SS e 69.7kPa along with LS e 45.9kPa and HVPG > 17.5mmHg predicted LRE ($P < 0.01$). Corelation with HVPG was significant with both LS and SS respectively ($P < 0.01$).The AUROC for SS was 87.8(95%C.I-80.2-94.2) as compared to HVPG which was 76.1(95%C.I-66-86.1) and for LS 72.3(95%C.I-61.5-83.1).SAVIOR score for the prediction of AVB using significant non-invasive parameters on multivariate analysis;SS(O.R-1.07 95%C.I-1.0-1.1),LS(O.R-1.03 95% C.I-1.01-1.05),bilirubin(O.R-0.94 95%C.I-0.88-0.99), ethanol etiology (O.R-2.02 95%C.I-1.07-3.71) was created, and gave an AUROC of 84.3($P < 0.01$) with high sensitivity 76% ,specificity 75% and negative predictive value 77%. **Conclusion:** Splenic stiffness closely correlates with the degree of portal hypertension, more so compared to HVPG and LS. A baseline SS of more than 69.8kPa as well as SAVIOR Score > 30 could help stratify patients who need aggressive surveillance as well as better preventive strategies including dosing of beta-blockers and endoscopy prophylaxis

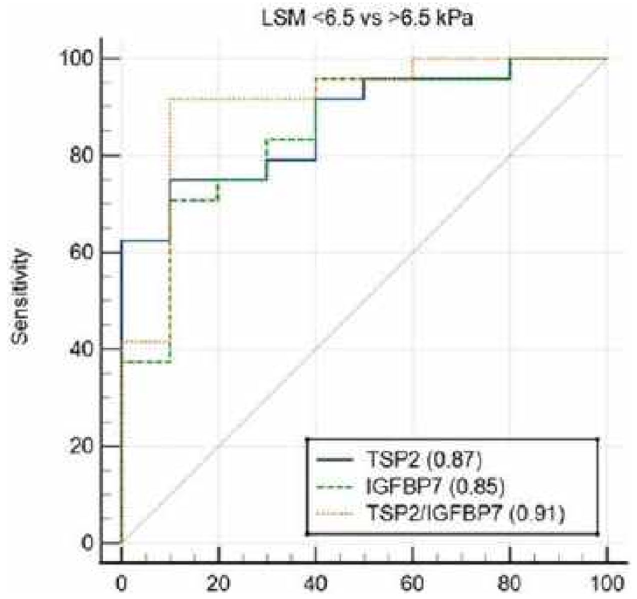


Disclosures: The following people have nothing to disclose: Harsh Vardhan Tevethia, Anirban De, Ankur Jindal, Vinod Arora, Guresh Kumar, Shiv Kumar Sarin

f 3163-A | SERUM THROMBOSPONDIN 2 AND INSULIN-LIKE GROWTH FACTOR PREDICT ADVANCED LIVER FIBROSIS WITH COMMON VARIABLE IMMUNODEFICIENCY

Rambabu Surabattula[1], Valentina Strohmeier[2], Anna-Maria Globig[2], Sudharani Myneni[1], Maximilian Heeg[2], Gerhard Kindle[2], Sigune Goldacker[2], Caroline Von Spee-Mayer[2], Michele Proietti[2,3], Birke Bausch[2], Dominik Bettinger[2], Michael Schultheiss[2], Robert Thimme[4], Klaus Warnatz[2] and Detlef Schuppan[1,5], (1) University Medical Center Mainz, (2)University Medical Center Freiburg, (3)Hannover Medical School, (4) University of Freiburg, (5)Harvard Medical School

Background: Timely detection of segmental fibrosis and portal hypertension as a manifestation in a significant subgroup of patients with common variable immunodeficiency (CVID) represents a challenge, since it is usually not associated with classical liver cirrhosis. So far there are no standard biomarkers to diagnose portal hypertension in patients with CVID. To identify relevant markers, we assessed elastography and novel serum markers of liver fibrogenesis and metabolism/inflammation in well-defined cohort of patients with CVID. **Methods:** Sandwich ELISAs measuring the matricellular fibrosis markers thrombospondin-2 (TSP2) and thrombospondin-4 (TSP4) and the metabolism/inflammation/fibrosis-related markers insulin-like growth factor binding protein-7 (IGFBP7), CD163 and a disintegrin and metalloprotease thrombospondin like-9 (ADAMTS9) were established in-house using combinations of recombinantly expressed proteins, commercial and self-produced monoclonal and polyclonal antibodies. Sensitivity and specificity were optimized, with intra- and Inter assay variations for serum or plasma below 10% and 15%, respectively. We included 39 CVID patients of whom 27 showed clinically significant portal hypertension as defined by either the presence of esophageal varices, hypertensive gastropathy or ascites. Most patients presented with liver stiffness measurement (LSM) above 6.5 kPa suggesting significant fibrosis. **Results:** Patients with LSM above 6.5 kPa vs LSM below 6.5 kPa displayed significantly higher serum levels of TSP2 (118 vs 69 ng/ml) and IGFBP7 (187 vs 135 ng/ml). No significant difference was observed for TSP4, ADAMTS9 and CD163. Both TSP2 and IGFBP7 correlated well with LSM values. The underlying biochemistry as well as the results support a prominent role of TSP2 in liver fibrogenesis due to CVID, and of IGFBP7 in fibrogenic inflammation. Both parameters separated patients with LSM above 6.5 kPa and signs of portal hypertension from those with LSM below 6.5 kPa with an AUROC of 0.87 (TSP2) and 0.85 (IGFBP7). Furthermore, the combination of TSP2 & IGFBP7 showed the highest AUROC (0.91). **Conclusion:** The matricellular serum marker TSP2 and metabolism/fibrosis related marker IGFBP7 predicted advanced fibrosis and portal hypertension in CVID patients. The novel markers may support early antifibrotic interventions for CVID. Confirmation of these findings in larger, prospective cohort is on the way.



Disclosures: The following people have nothing to disclose: Rambabu Surabattula, Valentina Strohmeier, Anna-Maria Globig, Sudharani Myneni, Maximilian Heeg, Gerhard Kindle, Sigune Goldacker, Caroline Von Spee-Mayer, Michele Proietti, Birke Bausch, Dominik Bettinger, Michael Schultheiss, Robert Thimme, Klaus Warnatz, Detlef Schuppan

3164-A | SPLEEN STIFFNESS AS A NON-INVASIVE TEST TO EVALUATE ESOPHAGEAL VARICES NEEDING TREATMENT AND PORTAL PRESSURE GRADIENT IN LIVER CIRRHOSIS

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Background: One of the complications of liver cirrhosis is an increase in the stiffness of the spleen, which is thought to be related to changes in blood flow within the liver and the spleen. Spleen stiffness (SS) in liver cirrhosis has been studied as a potential diagnostic and prognostic tool, as well as a predictor of clinical outcomes. The purpose of this study is to find out whether SS value can predict the presence of esophageal varices or gastric varices and how it correlates with hepatic venous pressure gradient in patients with liver cirrhosis. **Methods:** Three hundred fifty-seven consecutive patients with liver cirrhosis were enrolled in this study between Sep 2021 and Jan 2023.

SS and liver stiffness (LS) were measured by Fibroscan® 630 Expert device. **Results:** The number of patients with any grade of esophageal varies, varices needing treatment (VNT), and gastric varices was 178 (52.3%), 107 (31.4%), and 32 (9.4%), respectively. SS had high predictive power for any grade of esophageal varix (Se 0.811, Sp 0.921, AUROC 0.863), VNT (Se 0.952, Sp 0.788, AUROC 0.841). SS was also effective in predicting gastric varices (Se 0.843, Sp 0.665, AUROC 0.683), Among a variety of predictive models, liver stiffness × spleen stiffness × spleen volume/platelet count predicted the presence of VNT most accurately (Se 0.907, Sp 0.771, AUROC 0.814). SS and HVPG showed a good relationship below HVPG 16mmHg ($p < 0.001$), but at a higher value, the correlation was poor. SS measurement failure occurred in a total of 28 patients (7.84%), and spleen volume smaller than 183 ml was closely related to measurement failure. **Conclusion**: SS is a very useful test for predicting esophageal varices, varices needing treatment and gastric varies in cirrhosis.

Disclosures: The following people have nothing to disclose: Jeong-Ju Yoo, Sang Gyune Kim, Young Seok Kim

3165-A | SPLEEN STIFFNESS DETERMINED BY SPLEEN-DEDICATED DEVICE ACCURATELY PREDICTED ESOPHAGEAL VARICES IN CIRRHOSIS PATIENTS

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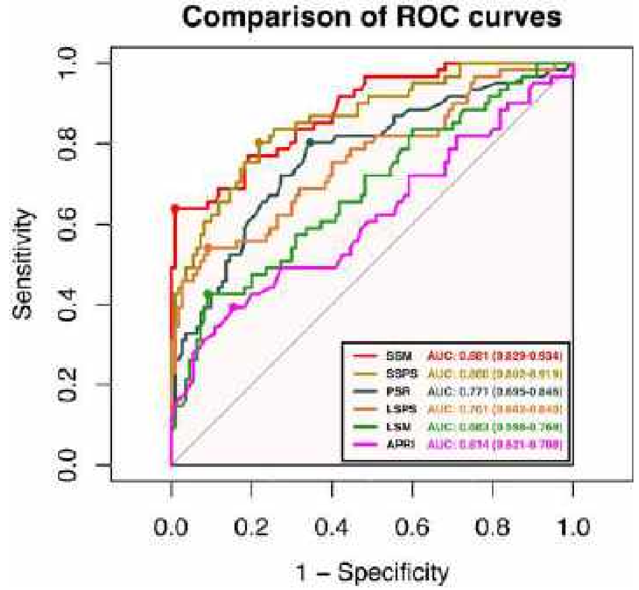
Background: The advantages of spleen stiffness in prediction of high-risk varices (HRV) in cirrhosis patients have been confirmed. Recently, a new device with 100Hz probe dedicated to spleen stiffness measure (SSM) was developed. The clinical applicability of SSM@100Hz in HRV prediction by comparing to other non-invasive tests (NITs) is still unknown. **Methods:** One hundred and seventy-one cirrhosis patients who performed esophagogastroduodenoscopy (EGD) examination were included. The SSM and liver stiffness measurement were evaluated by 100Hz probe and 50Hz probe, respectively. SSM of 22 healthy controls was also evaluated by 100Hz probe. **Results:** The failure rates of SSM examination of cirrhosis and controls were 2.9% and 4.5%, respectively. The means of SSM were 56.4 ± 21.6kpa and 13.8 ± 6.7 kPa in cirrhosis and controls. SSM increased paralleled with the severity of esophageal varices. The AUC of SSM for HRV prediction was 0.881(95%CI 0.829~0.934) with cut-off at 43.4kPa. The accuracy, false negative rate and EGD spare rate were 86.5%, 2.5% and 24.3%, respectively. For HRV prediction, SSM was comparable to expanded Baveno e and f and superior to other NITs. As to viral vs. non-viral cirrhosis and compensated vs. decompensated cirrhosis, the cut-off and performance of SSM were different. **Conclusion:** SSM@100Hz can predict HRV with high accuracy and low missed HRV rate. We suggested that SSM@100Hz could be used separately due to its simplicity and efficacy. Meanwhile, the cutoffs need further study according to cause of cirrhosis and liver function.



Disclosures: The following people have nothing to disclose: Jiqing Liu, Hangfei Xu, Weiyuan Liu, Hongmei Zu, Huiguo Ding, Fankun Meng, Jing Zhang

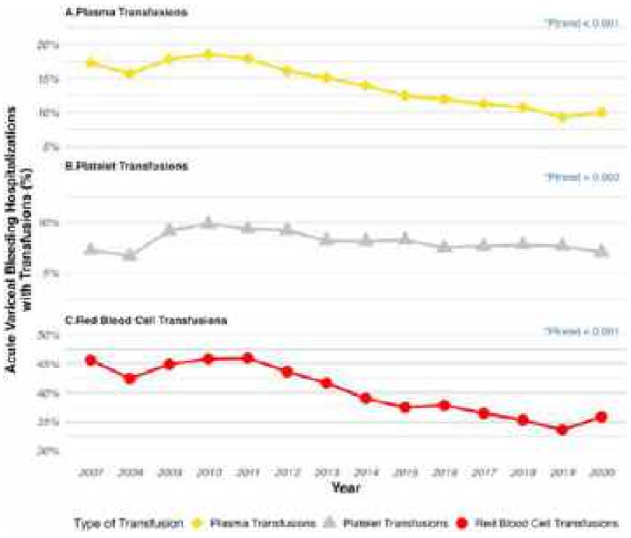
3166-A | TEMPORAL TRENDS IN RED BLOOD CELL, PLASMA, AND PLATELET TRANSFUSIONS AMONG US HOSPITALIZATIONS FOR ACUTE VARICEAL BLEEDING FROM 2007-2020

Pavan Vuddanda[1], Brett Fortune[2] and Arpan Mohanty[1], (1)Boston Medical Center, Boston, MA, (2)Montefiore Medical Center

Background: Acute variceal bleeding (AVB) in cirrhosis is associated with high morbidity and mortality. Blood transfusion is a crucial component in management of AVB and is essential for maintaining organ perfusion. However, aggressive volume expansion with blood transfusions is associated with higher portal pressures and increased risk of rebleeding. In the last decade, guidelines have recommended a restrictive packed red blood cell (PRBC) transfusion strategy and avoidance of using fresh frozen plasma (FFP) and platelets in AVB. National temporal trends in PRBC, FFP and platelet transfusion in AVB, in

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

response to these guidelines, have not been studied. **Methods:** We used the National Inpatient Sample, the largest all-payer inpatient database representing 94% to 97% of the US population, to evaluate national trends in PRBC, FFP and platelet transfusions in AVB from 2007 to 2020. Hospitalization for AVB for patients e 18 years were identified with appropriate ICD-9/10 codes. The three independent outcomes were percentage of hospitalizations with one or more PRBC, FFP and platelet transfusions, respectively. Trends analyses were conducted using join-point regression to estimate the average annual percent change (AAPC) with 95% CIs and the Cochrane-Armitage test was used to determine the significance of the trend. As there was an inflection point in 2010 determined by join-point regression, the analyses focused on trends in the pre-COVID era between 2010 to 2019. **Results:** Between 2010 and 2019 there were 329013 hospitalizations for AVB. The rate of PRBC transfusion decreased from 47% to 36% (AAPC -2.7%, 95% CI [-4.5, -0.9]). The rate of platelet transfusion decreased from 10% to 8.1% (AAPC = -2.8%, 95% CI [-4.1, -1.5]). The rate of FFP transfusion decreased from 19% to 10% (AAPC = -6.6%, 95% CI [-7.6, -5.5]). (Figure 1) Significant decrease in all transfusion types were seen in all strata of sex, admission type, and hospital region. When stratified by teaching hospital status, an increase in the trend of PRBC (AAPC 2.2%, 95% CI 1.5 to 2.8) and platelet transfusion (AAPC 2.0%, 95% CI, 0.3-3.8) was seen in urban teaching hospitals. **Conclusion:** The decline in PRBC, FFP and platelet transfusions suggest adoption of guidelines and evidence supporting restrictive transfusion strategies. Increase trend in PRBC and platelet transfusion in teaching hospitals may be reflective of sicker patients. Further studies are needed to define and optimizing FFP and platelet transfusion use in AVB. Figure 1. Temporal Trends in Red Blood Cell, Plasma, and Platelet Transfusions Among US Hospitalizations for Acute Variceal Bleeding from 2007-2020



Disclosures: Brett Fortune – W L Gore and Associates: Consultant, No, No;

Arpan Mohanty – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Consultant, No, Yes; Kinetix Group: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Pavan Vuddanda

3167-A | TRENDS AND ETIOLOGIES OF VARICEAL UPPER GASTROINTESTINAL BLEEDING HOSPITALIZATIONS IN THE UNITED STATES

Khaled Elfert[1,2], Vijay Gayam[3], Praneeth Bandaru[3], Tamta Chkhikvadze[4], Nithan Narendra[5] and Madhavi Reddy[3], (1)St. Barnabas Hospital, Bronx, NY, (2)Cuny School of Medicine, (3)The Brooklyn Hospital Center, (4)SUNY Downstate Health Sciences University, (5)St. Barnabas Hospital

Background: Variceal upper gastrointestinal bleeding (VUGIB) is a severe condition associated with portal hypertension and is a leading cause of mortality. Risk factors include hepatitis B and C, alcohol-related liver disease and non-alcoholic steatohepatitis (NASH) among others. **Methods:** In this study, we aimed to analyze the etiologies and trends of VUGIB hospitalizations in the United States between 2016 and 2020 using data from the National Inpatient Sample database. We included patients aged 18 years or older with a principal diagnosis of VUGIB, excluding elective admissions. Etiologies were determined based on ICD-10 diagnostic codes for secondary diagnoses. Trends over the years were examined using linear regression analysis. **Results:** Our study population comprised 36,190 hospitalizations. Over the study period, we observed a decline in the number of VUGIB hospitalizations, with 8,700 hospitalizations in 2016 decreasing to 6,125 hospitalizations in 2020. The analysis of etiologies revealed that 39.79% of patients had a secondary diagnosis of alcoholic liver disease, 19.73% had a secondary diagnosis of Hepatitis C viral infection, 10.32% had a secondary diagnosis of non-alcoholic steatohepatitis (NASH), and 5.89% had a secondary diagnosis of portal vein thrombosis. Less than 5% of all hospitalizations with VUGIB were attributed to chronic hepatitis B, primary biliary cholangitis, autoimmune hepatitis, primary sclerosing cholangitis, Budd-Chiari Syndrome, or hemochromatosis (Table 1). The proportion of patients with alcoholic liver disease decreased between 2016 and 2018 (from 43.7% to 36.1%), but increased between 2018 and 2020 (from 36.1% to 41.6%) (P-trend 0.0001). Conversely, the proportion of patients with Hepatitis C virus decreased from 22.3% in 2016 to 16.7% in 2020 (P-trend < 0.0001). **Conclusion:** Our study highlights a decrease in the number of hospitalizations for VUGIB from 2016 to 2020. Alcoholic liver disease was the most prevalent etiology, followed by Hepatitis C virus infection and NASH, with a decreasing trend in HCV-related VUGIB cases. The recent increase in the proportion of alcoholic liver disease-related VUGIB in 2020 may be associated with the heightened alcohol consumption during the COVID-19 pandemic.

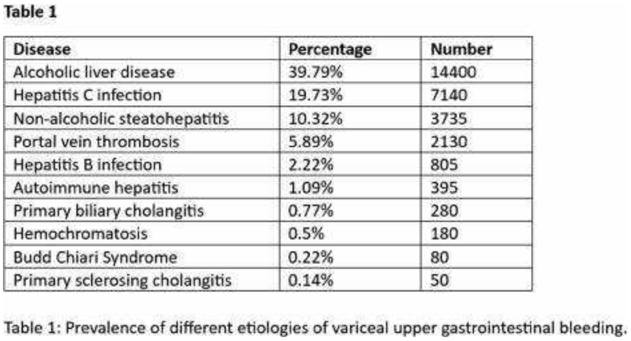


Table 1

Disease	Percentage	Number
Alcoholic liver disease	39.79%	14400
Hepatitis C infection	19.73%	7140
Non-alcoholic steatohepatitis	10.32%	3735
Portal vein thrombosis	5.89%	2130
Hepatitis B infection	2.22%	805
Autoimmune hepatitis	1.09%	395
Primary biliary cholangitis	0.77%	280
Hemochromatosis	0.5%	180
Budd Chiari Syndrome	0.22%	80
Primary sclerosing cholangitis	0.14%	50

Table 1: Prevalence of different etiologies of variceal upper gastrointestinal bleeding.

Disclosures: The following people have nothing to disclose: Khaled Elfert, Vijay Gayam, Praneeth Bandaru, Tamta Chkhikvadze, Nithan Narendra, Madhavi Reddy

3168-A | VITAMIN C DEFICIENCY IS PREVALENT IS PATIENTS PRESENTING WITH ACUTE VARICEAL BLEEDING AND CONFERS A POOR PROGNOSIS

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Background: Our group has previously demonstrated a surprisingly high prevalence of Vitamin C deficiency (VCD) in patients with upper gastrointestinal bleeding (UGIB). We aimed to prospectively analyse the prevalence of VCD in patients presenting with acute variceal bleeding (AVB) and its association with clinical outcomes. **Methods:** Adult patients e 18 years presenting with AVB were prospectively collected over a 34-month period (2020 – 2022) with fasting serum vitamin C levels measured on admission. Primary outcomes were: (i) the prevalence of VCD (defined as a Vitamin C level < 23 μmol/L, severe VCD < 12 μmol/L), as well as (ii) in-hospital mortality, (iii) rebleeding and (iv) a composite outcome of adverse events, encompassing in-hospital mortality, rebleeding and massive red cell transfusion stratified by VCD status. Secondary outcomes were prolonged hospital length of stay (LOS) (> 7 d) and the need for ICU admission. **Results:** In total, 74 patients with AVB were included in the study. Mean age was 54.9 ± 13.5 years and 52.7% were male. The median MELD score was 15 (IQR 12-18) and median Child-Pugh score was 8 (IQR 7-9). Oesophageal varices were found in 71 patients (95.9%) and gastric varices were found in 8 patients (10.8%). VCD was identified in 30 (40.5%) and severe VCD in 14 (18.9%) patients. The prevalence of VCD did not differ in Child-Pugh class B and C patients, compared to A (38.7% vs. 50%, p = 0.47). VCD was associated with significantly higher in-hospital mortality (30% vs. 6.8%, p < 0.01), increased rebleeding (33.3% vs. 4.5%, p < 0.01) and a non-significant trend towards a higher composite endpoint (53.3% vs. 31.8%, p = 0.07), compared to patients with normal vitamin C levels. VCD was also associated with prolonged hospital LOS (76.7% vs. 43.2%, p < 0.01) and increased ICU admissions (36.7% vs. 15.9%, p = 0.04). All multivariate logistic regression models indicated VCD was independently associated with higher in-patient mortality and rebleeding, even after adjusting for MELD (table 1). **Conclusion:** VCD is highly prevalent in patients presenting with AVB and deficiency is associated with higher in-hospital mortality and rebleeding independent of the severity of liver disease. Prospective interventional trials are required to investigate the impact of early vitamin C supplementation on clinical outcomes in AVB.

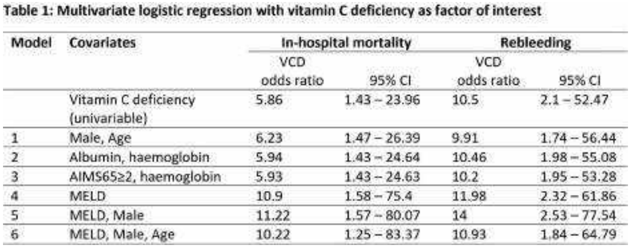

Table 1: Multivariate logistic regression with vitamin C deficiency as factor of interest

Model	Covariates	In-hospital mortality		Rebleeding	
		VCD odds ratio	95% CI	VCD odds ratio	95% CI
	Vitamin C deficiency (univariable)	5.86	1.43 – 23.96	10.5	2.1 – 52.47
1	Male, Age	6.23	1.47 – 26.39	9.91	1.74 – 56.44
2	Albumin, haemoglobin	5.94	1.43 – 24.64	10.46	1.98 – 55.08
3	AIMS65≥2, haemoglobin	5.93	1.43 – 24.63	10.2	1.95 – 53.28
4	MELD	10.9	1.58 – 75.4	11.98	2.32 – 61.86
5	MELD, Male	11.22	1.57 – 80.07	14	2.53 – 77.54
6	MELD, Male, Age	10.22	1.25 – 83.37	10.93	1.84 – 64.79

Disclosures: Samuel Hui – Roche: Speaking and Teaching, No, Yes;

Disclosure information not available at the time of publication: Joshua Abasszade, Phil Ha, Elaine Koh, Declan Connoley, Marcus Robertson

f 3200-A | A HUMAN THREE-DIMENSIONAL MULTICELLULAR LIVER MODEL FOR PREDICTING DRUG EFFICACY IN CHRONIC LIVER DISEASE★

Ainhoa Ferret Miñana, Francesco De Chiara and Javier Ramón Azcón, Institute for Bioengineering of Catalonia

Background: The pharmaceutical industry is currently facing increasing challenges in drug discovery due to long drug development times combined with low clinical trial success rates. Over 20% of approved drugs suffer from market withdrawal for severe liver injury at therapeutic doses, becoming a significant cause of death worldwide, with an estimated 2 million patients in the United States. Three-dimensional (3D) cellular models, obtained by mixing cells with a biomaterial in a pre-specified structure, are emerging as a physiologically relevant cellular microenvironment holding a great promise for drug safety and efficacy in the early phase of drug development. **Methods:** Here, we developed human 3D livers combining hepatocytes (HepaRG), hepatic stellate cells (HSCs) (LX-2), and immune cells (THP-1), the three main cell types of the liver, in a 2:1:1 ratio. We used a well-established mixture of gelatine methacryloyl (GelMA) and carboxymethyl cellulose methacrylate (CMCMA), a biodegradable and non-biodegradable material, respectively. Lithium Phenyl(2,4,6-trimethylbenzoyl)phosphonate was used as a photo-initiator. Cells were combined with the GelMA-CMCMA mixture (1:1) and exposed to UV light for 30 seconds. The 3D livers were kept in culture for up to 30 days in serum-free medium. They were challenged with acetaminophen and LPS, two well-described hepatotoxic compounds, to recreate the pathophysiological phenotype of liver damage in vitro. Dexamethasone was used as an anti-inflammatory drug to test the ability of 3D livers to predict drug efficacy. **Results:** The 3D livers did not show any signs of distress while resembling many characteristics of the native healthy liver. We evaluated the cell viability, morphology, and gene expression of hepatocytes, HSCs, and immune cells in the 3D livers during the 30 days. The LPS and acetaminophen challenge induced extensive liver damage characterized by HSC activation and proliferation. These cells acquired the typical myofibroblast phenotype of activated HSC in vivo. Moreover, we assessed gene expression markers of hepatocyte functionality, such as albumin, OTC, and CPS1, as well as the CYP3A4 enzyme activity, which were impaired upon treatments. The inflammation level of the system was measured by the transition from the THP-1 monocytes to macrophages releasing proinflammatory cytokines into the medium. Finally, the potent beneficial effect of dexamethasone was observed, both by reducing cell damage in hepatocytes and by decreasing HSC activation and collagen production. **Conclusion:** Human 3D livers are suitable for long-term cultures and can be used to test the toxicity and efficacy of drugs, as has been demonstrated with LPS and acetaminophen, and dexamethasone. These results also validated this multicellular system as a valuable tool for measuring liver damage and inflammation, as the 3D livers successfully displayed the characteristics of chronic liver damage in vitro.

Disclosures: The following people have nothing to disclose: Ainhoa Ferret Miñana, Francesco De Chiara, Javier Ramón Azcón

3201-A | A NOVEL PROGNOSTIC MODEL BASED ON PORTAL VEIN DIAMETER FOR PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

Qiao Zhang[1], Juan Li[1], Yushan Liu[1], Yamin Wang[1], Xiaoli Zhang[2], Taotao Yan[1,3], Yingren Zhao[1,4] and Yingli He[1,5], (1)The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China, (2)First Affiliated Hospital of Xi'an Jiaotong University, (3) Shaanxi Provincial Clinical Research Center for Infectious Diseases, Xi'an, Shaanxi, China, (4)Clinical Research Center for Infectious Disease, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China, (5)National Regional Infectious Diseases Center Co-Constructed By National Health Commission of PRC and People's Government of Shaanxi Province, Xi'an, Shaanxi, China

Background: The prompt and accurate prognostication of acute-on-chronic liver failure (ACLF) patients is crucial for clinical intervention and reducing mortality. Portal vein hypertension is a common and potentially fatal complication of ACLF. However, no current prediction models for ACLF have integrated portal vein parameters. Since portal vein diameter (PVD) can effectively reflect portal vein hypertension, this study aimed to investigate its value in predicting the short-term prognosis of ACLF patients and develop a novel nomogram prognostic model for ACLF patients. **Methods:** A prospective cohort of 127 ACLF patients was enrolled to develop the prognostic model for 90-day mortality, which was then validated in a prospective cohort of 105 ACLF patients. The PVD was assessed using computed tomography images within 7 days of ACLF diagnosis. Logistic regression analyses were performed to identify independent prognostic indicators and construct the nomogram prognostic model. Concordance index (C-index), receiver operating characteristics (ROC) and decision curve analysis were applied to compare the performance of nomogram, model for end-stage liver disease (MELD) score and Child-Turcotte-Pugh (CTP) score. **Results:**

1. A total of 232 ACLF patients were included, with a 90-day mortality rate of 42.24%.
2. The PVD was significantly higher in non-survivors than survivors (14.79 ± 73mm vs 13.18 ± 2.52mm, $P=0.027$).
3. PVD ($OR=310$, 95% CI: 1.065~1.612, $P=0.011$), age ($OR=1.055$, 95% CI: 1.001~1.111, $P=0.047$), neutrophil percentage ($OR=1.069$, 95% CI: 1.013~1.128, $P=0.015$), sex ($OR=0.097$, 95% CI: 0.020~0.479, $P=0.004$) and total bilirubin ($OR=1.009$, 95% CI: 1.003~1.015, $P=0.002$) were identified as independent predictors for the new PVD-based nomogram prognostic model, PANST (Figure1).
4. The C-index (0.878) of PANST score was higher than MELD score and CTP score (0.687, 0.639,

respectively; $P < 0.001$). The ROC and decision curves demonstrated that the PANST score was superior to MELD score and CTP score.

5. Subgroup analysis: the C-indices of PANST score for hepatitis B virus-related ACLF (HBV-ACLF) and non-HBV-ACLF patients (0.842/0.950) were significantly higher than those of MELD score (0.730/0.608; all $P < 0.05$) and CTP score (0.701/0.513, all $P < 0.05$).
6. Patients with a score exceeding 152.9 had a higher risk of death ($OR = 17.607$, 95% $CI = 5.694$~446, $P < 0.001$). Subgroup analysis yielded similar results (HBV-ACLF group: OR = 10.714, 95% *CI*: 2.879~39.800, $P < 0.001$; non-HBV-ACLF group: $OR = 63.000$, 95% *CI*: 4.957~800.677, $P = 0.001$).
7. These results were confirmed in the validation cohort (Figure2).

Conclusion: The inclusion of PVD in the novel prognostic model PANST exhibited high predictive accuracy for predicting 90-day mortality in ACLF patients, which was superior to MELD and CTP score.

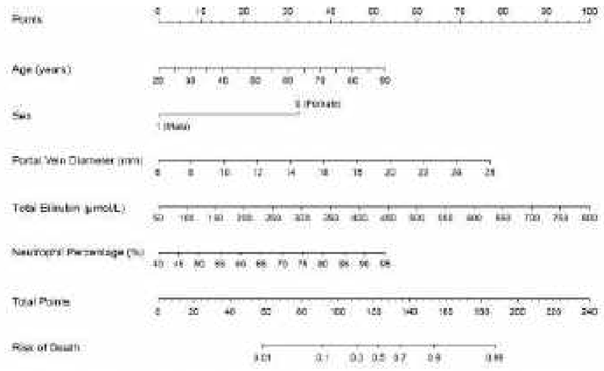

Figure 1 PANST, a novel nomogram prognostic model, including portal vein diameter, age, neutrophil percentage,sex and totalbilirubin for 90-day mortality in patients with ACLF. To apply the nomogram prognostic model, find the patient's value on each variable axis and add up the corresponding points to locate the total score on the "TotalPoints" axis. Then, draw a line down to the "Risk ofDeath" to determine the 90-day mortality probability for ACLFpatients. ACLF, acute-on-chronic liver failure.

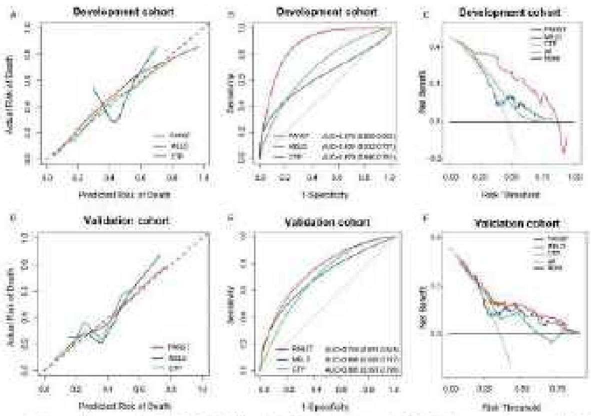

Figure 2 The calibration (A,D) , ROC (B,E) and DCA (C,F) curves of PANST prognostic model,MELD score, and CTP score for predicting90-day mortality in the development cohort and validation cohort of ACLF patients. ROC, Receiver operating characteristic; DCA, Decision Curve Analysis; PANST, the prognostic model based on PVD, age,neutrophil percentage, sex and total billirubin; MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh; ACLF,acute-on-chronic liver failure.

Disclosures: The following people have nothing to disclose: Qiao Zhang, Juan Li, Yushan Liu, Yamin Wang, Xiaoli Zhang, Taotao Yan, Yingren Zhao, Yingli He

3202-A | A NUTRITION-BASED RADIOMICS-CLINICAL MACHINE LEARNING MODEL TO PREDICT THE PROGNOSIS OF PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

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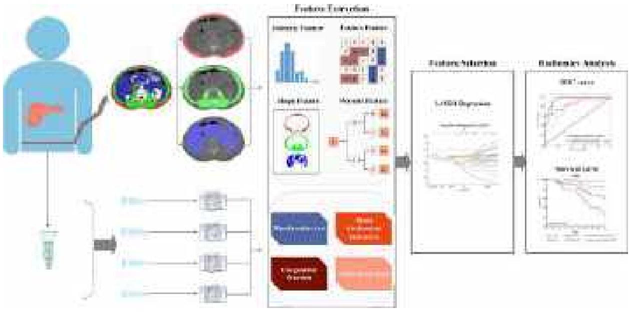
Background: Acute-on-chronic liver failure (ACLF) is a syndrome characterized by acute decompensation (AD) associated with chronic liver disease and organ failure, leading to high short-term mortality. Effective identification of patients with poor prognosis and early intervention are crucial for saving patients' lives. Meanwhile, the basic nutritional status of patients is vital in the prognosis of chronic liver diseases. Hence, the study aims to apply artificial intelligence to extract nutrition-based imaging features in ACLF patients and construct a radiomics-clinical prognostic model to predict the 90-day adverse prognosis. **Methods:** 163 ACLF patients who met the APSAL diagnostic criteria and had follow-up records were recruited from our hospital. The patients were randomly assigned to the training cohort ($n = 99$) and the test cohort ($n = 64$). The regions of interest of the third lumbar spine skeletal muscle, subcutaneous fat, and visceral fat were obtained during the enhanced CT arterial phase, and the imaging features were extracted. The blood routine and blood biochemistry were collected. The least absolute shrinkage and selection operator (LASSO) regression model was applied to select imaging features and form a new feature subset. Finally, the linear discriminant classifier was used for endpoint prediction. **Results:** In the training and test cohorts, 30.3% (30/99) and 29.7% (19/64) of patients experienced disease progression (death or liver transplantation), respectively. LASSO regression screened 15 features for constructing a radiomics-clinical model, most of which were texture features of skeletal muscles. The area under the curve (AUC) of this model in the test cohort was 0.873 (95% CI 0.773-0.972), with sensitivity and specificity of 0.895 and 0.711, respectively. The Delong test was used to compare the AUC of the radiomics-clinical model with sub-models (radiomics model and clinical model) and traditional classical models (MELD and MELD-Na). The results showed that the radiomics-clinical model was superior to any of the above models ($p < 0.05$).

Conclusion: The nutrition-based radiomics-clinical machine learning model can effectively predict the 90-day adverse prognosis of ACLF patients. This comprehensive model may provide a novel and valuable method for clinical practice to identify patients who require active intervention as early as possible, thereby improving the survival rate of ACLF patients.



Disclosures: The following people have nothing to disclose: Qian Zhang, Yunsong Peng, Xinhua Luo, Rongpin Wang, Hong Peng

f 3203-A | ALCOHOL BINGE EXACERBATES LIVER DAMAGE IN A NOVEL CHOLESTATIC MODEL OF ACUTE-ON-CHRONIC LIVER FAILURE BY PROMOTING NETs AND NECRO/PYRO-PTOTIC CELL DEATH

Marti Ortega-Ribera, Yuan Zhuang, Veronika Brezani, Radhika Joshi, Prashanth Thevkar Nagesh, Mrigya Babuta, Yanbo Wang and Gyongyi Szabo, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background: Acute-on-chronic liver failure (ACLF) is defined by systemic inflammation, multi-organ failure, and high short-term mortality in patients with advanced chronic liver disease (CLD). Alcohol abuse is one of the most frequent precipitating factors in ACLF; nevertheless, preclinical models fully mimicking this clinical setting are scarce. The aim of this study was to develop an alcohol-induced ACLF model & further dissect its underlying molecular mechanisms. **Methods:** Liver fibrosis was induced in 10-12 weeks old male C57BL/6 or gasdermin D knockout (GSDMD KO) mice by common bile duct ligation (BDL) for 28 days (n e 4 per group). Alcohol binge (5g/Kg) was given to a subgroup of animals to induce ACLF. Sham surgery groups receiving either alcohol or water binge were used as controls and tissue collection was performed 9 hours after binge. Human tissues from patients with cholestatic CLD or ACLF were provided by the Liver Tissue and Cell Distribution Center. **Results:** Hepatocellular damage after BDL was further aggravated by alcohol binge in the ACLF group as shown by higher transaminases and bilirubin, decreased albumin and coagulation factors expression compared to BDL. Endotoxin, tumor necrosis factor α and interleukin-6 levels were significantly increased in ACLF mice as compared to BDL. Moreover, alcohol binge in BDL mice resulted in hyperammonemia, sickness behavior (open-field test), increased blood urea nitrogen and creatinine suggesting hepatic encephalopathy-like features and kidney dysfunction in ACLF. Neutrophil count and extracellular trap (NET) release (citrullinated H3 and neutrophil elastase) were increased in serum and liver of ACLF mice compared to BDL. ACLF mice livers also exhibited increased necroptosis (RIP3 expression), inflammasome activation and pyroptosis (increased cleaved-GSDMD, IL-1β, and IL-18) without changes in apoptosis (caspase 3, caspase-cleaved-CK18) compared with BDL alone. *In vitro*, both ethanol and bile acids induced NET release from normal neutrophils. Furthermore, these cell-free NETs induced RIP upregulation in HepG2 cells. NETosis, pyroptosis and RIP3 activation were validated in human livers with ACLF. GSDMD KO mice were partially protected from ACLF compared to WT indicated by reduced neutrophil infiltration (Ly6G, CXCL1 & CXCL2) and reduced cell death (decreased RIP3 and IL-1β expression) in the liver. **Conclusion**: Our novel preclinical ACLF model involving alcohol binge in BDL mice mimics ACLF pathophysiology including acute liver damage, hepatocyte dysfunction, systemic inflammation, kidney injury and brain & coagulation impairment. Mechanistically, we show that ACLF occurs in the setting of neutrophil infiltration, NETosis and hepatocellular death involving inflammasome activation and necroptosis, which are attenuated upon GSDMD deletion.

Disclosures: Gyongyi Szabo – Cyta Therapeutics: Consultant, No, No; Durect: Consultant, No, No; Evive: Consultant, No, No; Glympse Bio: Consultant, No, No; Innovate Biopharmaceuticals: Consultant, No, No; Merck: Consultant, No, No; Novartis: Consultant, No, No; Pandion Therapeutics: Consultant, No, No; Pfizer: Consultant, No, No; Satellite Biosciences: Consultant, No, No; Surrozen: Consultant, No, No; Takeda: Consultant, No, No; Terra Firma: Consultant, No, No; Zomagen: Consultant, No, No; The following people have nothing to disclose: Marti Ortega-Ribera, Yuan Zhuang, Veronika Brezani, Radhika Joshi, Prashanth Thevkar Nagesh, Mrigya Babuta, Yanbo Wang

3204-A | APPLICATION OF DIFFERENT DIAGNOSTIC CRITERIA FOR ACUTE ON CHRONIC LIVER FAILURE IN PROGNOSIS ASSESSMENT ON PATIENTS WITH SEVERE ALCOHOLIC HEPATITIS

Fangyuan Meng, Yanhang Gao, Guangfei Yuan and Yue Sun, The First Hospital of Jilin University

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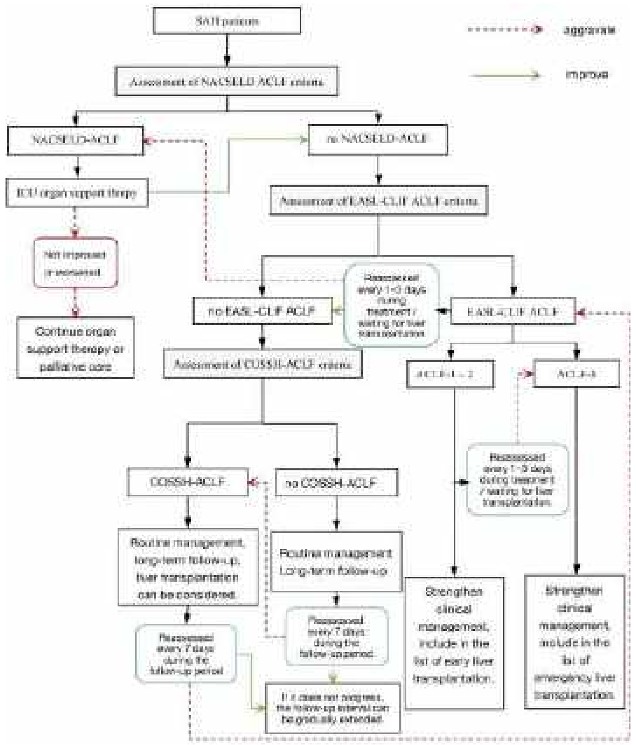
Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

Background: Severe alcoholic hepatitis (SAH) is the most serious form of alcohol-related liver diseases (ALD) with a high fatality rate. If ALD-acute on chronic liver failure (ACLF) is present, the disease progression will be accelerated. Currently, among many diagnostic criteria for ACLF, the definitions of EASL-CLIF ACLF, NACSELD ACLF and COSSH-ACLF are widely accepted. The purpose of this study was to explore the value of the above three diagnostic criteria in the prognosis assessment of patients with SAH. **Methods:** This study is a two-way cohort study. The data of 309 patients with SAH in the Department of Hepatology, the First Hospital of Jilin University from 2012 to 2022 were collected retrospectively and prospectively, including baseline data, incidence and type of organ failure, and survival data at 7, 28, 90 days after admission or diagnosis of ACLF. The effects of three diagnostic criteria for ACLF on the prognosis of patients with SAH were compared and analyzed. **Results:** Among the 309 SAH patients, 183 (59.2%), 106 (34.3%) and 16(5.2%) patients met the COSSH-ACLF, EASL-CLIF and NACSELD ACLF criteria, respectively. In predicting 7-day mortality, NACSELD criteria had higher overall accuracy (95.58% vs 67.69 % vs 42.86%, $P<0.001$), specificity (96.49% vs 67.25% vs 41.46%, $P<0.001$) and positive predictive value (37.50% vs 6.00% vs 4.00%, $P<0.001$) than EASL-CLIF criteria and COSSH-ACLF criteria. But the sensitivity is low. EASL-CLIF criteria also had higher overall accuracy (66.69% vs 42.86%, $P<0.001$) and specificity (67.25% vs 41.46%, $P<0.001$) than COSSH-ACLF criteria.In the prediction analysis of 28-day mortality, the performance was similar to that of 7-day mortality. In the 90-day mortality prediction, the sensitivity and negative predictive value of the NACSELD criteria decreased significantly, and the overall accuracy was equal to the EASL-CLIF criteria, which was still higher than the COSSH-ACLF criteria. EASL-CLIF criteria still had higher overall accuracy and specificity than COSSH-ACLF criteria. The 7, 28,and 90 days survival rates of patients who met the EASL-CLIF criteria but did not meet the NACSELD criteria were 97.8%, 80.2%, and 59.8%, respectively. **Conclusion:** The incidence of ALD-ACLF in SAH patients was higher, and the mortality increased significantly. NACSELD ACLF standard has higher overall accuracy in predicting short-term mortality, and can identify patients with very high mortality more accurately. EASL-CLIF and COSSH-ACLF have higher sensitivity, which can identify high-risk patients who benefit from supportive treatment and liver transplantation earlier. However, the standard specificity of COSSH-ACLF is low, and the overall accuracy does not show obvious advantages. Further evaluation of ALD-ACLF in patients with SAH is helpful to optimize the prognostic management strategy in order to improve the survival rate.


SAH patients
aggravate
improve
Assessment of NACSELD ACLF criteria
NACSELD-ACLF
no NACSELD-ACLF
ICU organ support therapy
Assessment of EASL-CLIF ACLF criteria
Not improved or worsened
Continue organ support therapy or palliative care
no EASL-CLIF ACLF
Reassessed every 1~3 days during treatment / waiting for liver transplantation
EASL-CLIF ACLF
Assessment of COSSH-ACLF criteria
ACLF-1~2
ACLF-3
COSSH-ACLF
no COSSH-ACLF
Reassessed every 1~3 days during treatment / waiting for liver transplantation
Routine management, long-term follow-up, liver transplantation can be considered.
Routine management Long-term follow-up
Strengthen clinical management, include in the list of early liver transplantation.
Strengthen clinical management, include in the list of emergency liver transplantation.
Reassessed every 7 days during the follow-up period
Reassessed every 7 days during the follow-up period
If it does not progress, the follow-up interval can be gradually extended.

Disclosures: The following people have nothing to disclose: Fangyuan Meng, Yanhang Gao, Guangfei Yuan, Yue Sun

3205-A | CHRONIC LIVER DISEASE AND RISK OF SHOCK IN ACUTE HEART FAILURE PATIENTS UNDERGOING ENDOSCOPIC PROCEDURES: AN ANALYSIS OF THE NATIONAL INPATIENT SAMPLE

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Background: Endoscopic procedures are commonly performed for diagnostic and therapeutic purposes in Acute Heart Failure (AHF) patients with gastrointestinal disorders. The risk of shock and associated risk in AHF patients undergoing endoscopic procedure is currently under-explored. This study aimed to utilize the National Inpatient Sample to investigate the incidence and risk factors for shock in AHF patients undergoing endoscopic procedures. **Methods**: This was a retrospective cohort study using the National Inpatient Sample Database from 2017 to 2020. Adult patients aged e 18 years with a primary diagnosis of Acute Heart Failure who underwent non-elective endoscopic procedures using the International Classification of Diseases, Tenth Revision (ICD-10). For this analysis, endoscopic

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

procedures refer to esophagoduodenoscopy (EGD) and colonoscopy. The primary outcome was the incidence of shock. Multivariate logistic regression analyses were performed to adjust for potential confounders and identify associated risk factors. A 2-sided $p < 0.05$ was considered significant throughout the analyses. STATA/SE 17.0 Stata Corp LLC was used for the data analyses. **Results**: A total of 3445 hospitalizations of patients with Acute Heart Failure who underwent endoscopic procedures were identified. Colonoscopy was performed more frequently than EGD in the study population. The mean age of AHF patients who underwent an endoscopic procedure was 68.5 years ($P < 0.01$). The incidence of shock was 17.6%. Patients with AHF who underwent endoscopic procedures had significantly higher risk of shock [Odds Ratio (OR) 3.1, 95% Confidence Interval (CI) 2.4 – 3.9, $p < 0.01$]. Chronic Liver Disease (CLD) was associated with the development of shock in AHF patients undergoing endoscopic procedures (OR 2.2, 95%CI 1.93 - 2.4, $p < 0.001$). Other associated risk factors include Chronic Kidney Disease (CKD) (OR 1.23, 95%CI 1.12 - 1.35, $p < 0.001$), presence of atrial fibrillation (OR 1.6, 95%CI 1.5 - 1.7, $p < 0.001$) and other arrhythmia (OR 2.0, 95%CI 1.8 - 2.3, $p < 0.001$). There was no statistically significant difference in the odds of shock between AHF patients undergoing EGD versus colonoscopy (OR 0.6, 95% CI 0.34 - 1.32, $p > 0.05$). **Conclusion**: This study suggests that the risk of shock in AHF patients undergoing endoscopic procedure was significant in patients with chronic liver disease. Other associated risk factors were CKD, the presence of atrial fibrillation and other arrhythmias. The overall risk of shock in AHF patient who underwent endoscopic procedure was also increased. Understanding the drivers of poor clinical outcomes in shock through further research in this patient population is imperative for better clinical decision making and patient care.

Disclosures: The following people have nothing to disclose: Ikechukwu Eze

Disclosure information not available at the time of publication: John Gharbin, Claudia Gyimah, Miriam Michael

3206-A | CLINICAL CHARACTERISTICS OF END-STAGE LIVER DISEASE COMPLICATED BY BACTERIAL OR FUNGAL INFECTIONS: A MULTI-CENTER RETROSPECTIVE STUDY FROM CENTRAL CHINA

Wei Liu[1,2], Qiuyu Cheng[1,2], Yunhui Liu[1,2], Zhongyuan Yang[1,2], Meng Zhang[1,2], Tingting Liu[1,2], Yuxin Niu[1,2], Xiaojing Wang[1,2], Tao Chen[1,2] and Qin Ning[1,2], (1) Institute and Department of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, (2)Tongji Medical College and State Key Laboratory for Diagnosis and Treatment of Severe Zoonostic Infectious Disease, Huazhong University of Science and Technology

Background: To analyze the clinical characteristics in patients with end-stage liver disease (ESLD) complicated by bacterial or fungal infections. **Methods:** A total of 1208 patients diagnosed with acute on chronic liver failure (ACLF), acute decompensation of liver cirrhosis (ADC), and chronic liver failure (CLF) were involved in this retrospective cohort study from 16 tertiary hospitals in January 2012 to December 2018 in central China. Clinical characteristics and mortality risk factors of these patients were analyzed. **Results:** Out of all 1208 ESLD patients, 565 (46.8%) were complicated by bacterial infections and 16 (1.3%) were complicated by fungal infections. Bacterial or fungal infections happened in 64.4%, 60.2% and 37.4% patients with ACLF, CLF and ADC respectively. Spontaneous peritonitis (51.1%) is the most common type of infection, followed by pneumonia (43.7%), urinary tract infection (7.9%), bacteremia (2.8%) and others (1.9%). 72 samples showed positive culture results, among which 28 (38.9%) were gram-positive organism, 28 (38.9%) were gram-negative organism and 16 (22.2%) were fungus. The most common strain was *coagulase-negative staphylococci* in gram-positive organisms and *Escherichia coli* in gram-negative organisms respectively. Patients with bacterial or fungal infections both showed significantly higher level of white blood cell (WBC) and procalcitonin (PCT), severer liver and coagulation dysfunction, and more likely to develop ascites, hepatorenal syndrome (HRS), hepatic encephalopathy (HE), upper gastrointestinal bleeding (UGB), and hepatopulmonary syndrome (HPS) than those without. Bacterial or fungal infections were mortality risk factors for patients with ESLD. CLF, ACLF and ADC with HRS were identified as independent predictors for poor outcomes in ESLD patients with bacterial or fungal infections. The mortality risk factors were HRS and increased total bilirubin (TBIL) and lactate dehydrogenase (LDH) level for ACLF, higher neutrophil (NEUT) count and HE for CLF and elevated PCT level for ADC. **Conclusion:** CLF, ACLF and ADC showed homogeneity in the occurrence and clinical characteristics of bacterial or fungal infection, which was an independent risk factor of mortality of ESLD. Key Words: end-stage liver disease, acute-on-chronic liver failure, chronic liver failure, acute decompensation of cirrhosis, infection

Disclosures: The following people have nothing to disclose: Wei Liu, Qiuyu Cheng, Yunhui Liu, Zhongyuan Yang, Meng Zhang, Tingting Liu, Yuxin Niu, Xiaojing Wang, Tao Chen, Qin Ning

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

Tian Tian[1], Chunbao Sun[2], Sreenivasulu Basha[2], Hua Wang[1] and Liya Pi[2], (1)Anhui Medical University, (2) Tulane University School of Medicine, New Orleans, LA

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

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

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

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

Background: Acute-on-chronic liver failure (ACLF) is an increasingly recognized syndrome in patients with cirrhosis, characterized by acute decompensation of cirrhosis that results in severe organ injury with high rates of short-term mortality. Liver transplantation is currently the only treatment to improve survival. A pilot study suggested that plasma exchange with human serum albumin 5% (PE-A5%) as a replacement fluid is feasible and safe in patients with ACLF and may improve organ function and survival. The aim of this study is to assess PE-A5% as a treatment for patients with ACLF in a pivotal study **Methods:** A phase 3, multicenter, randomized (1:1), controlled, parallel-group, open-label study (APACHE) compares standard medical treatment (SMT) + PE-A5% (treatment arm) to SMT alone (control arm). PE-A5% is performed using Albutein 5% (Grifols). Treatment schedule consists of two initial PE-A5% sessions on consecutive days followed by every other day PE-A5% (minimum 4, maximum 9 PE-A5%). Patients receive IVIG (200 mg/kg) after every 2 PE-A5% to prevent hypogammaglobulinemia-associated infections, and FFP after each PE-A5% to prevent coagulopathy. Eligible patients are adult (18-79 years old), with ACLF-1b, ACLF-2, or ACLF-3a at admission or during hospitalization. Main exclusion criteria are patients with ACLF-1a or ACLF-3b, ACLF > 10 days prior to randomization, septic shock requiring norepinephrine (> 0.3 μg/kg/min) or a second vasopressor, active infection, and severe respiratory failure. **Results:** Target enrollment is 380 patients with ACLF at high risk of hospital mortality. As of May 2023, enrollment is occurring at 26 sites across North America and Europe, with 244 patients screened and 208 patients randomized (54.7% of sample size). The primary efficacy endpoint is the 90-day overall survival. Secondary efficacy endpoints include 90-day transplant-free survival and 28-day overall survival. Main exploratory endpoints include overall and transplant-free survival at days 28 and 90, in-patient hospital and ICU stay, incidence of organ failures and ACLF course. Safety analyses include adverse events, vital signs, physical assessments, and laboratory tests. **Conclusion:** APACHE should provide pivotal results on the efficacy and safety of PE-A5% as a potential treatment to improve survival in ACLF (NCT03702920, EudraCT: 2016-001787-10).

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Jasmohan S. Bajaj – Bausch: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Grifols: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Sequana: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

Thierry Gustot – GoLiver Therapeutics: Advisor, No, No; Cellaïon: Advisor, No, No;

Thomas Reiberger – AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, Yes; Boehringer Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; MSD: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Myr Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, Yes; Philips Healthcare: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Siemens: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; AbbVie: Consultant, Yes, Yes; Boehringer Ingelheim: Consultant, Yes, No; Gilead: Consultant, Yes, Yes;

Mireia Torres – Grifols: Employee, Yes, No;

Peter Nelson – Grifols: Employee, Yes, No;

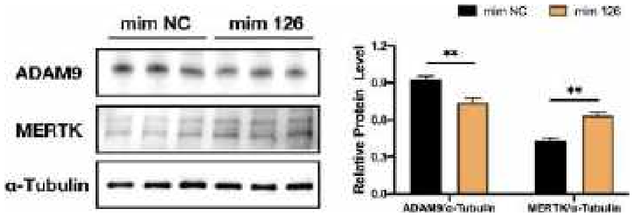
Javier Fernandez – Grifols: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;

The following people have nothing to disclose: Giovanni Perricone

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

Junyi Wang[1], Zhihui Li[2], Shibo Meng[3], Junfeng Chen[1], Bingliang Lin[3] and Jing Zhang[4], (1)The Third Affiliated Hospital of Sun Yat-Sen University, (2)Sun Yat-Sen University, (3)The Third Affiliated Hospital, Sun Yat-Sen University, (4)Department of Infectious Diseases, Third Affiliated Hospital of Sun Yat-Sen University

Background: Acute-on-Chronic liver failure is a disease with a high mortality rate, the only cure currently available is liver transplantation.Our previous study showed that intravenous injection of mesenchymal stem cells could improve survival rate of acute-on-chronic liver failure patients, and expressed higher levels of Mertk, which could promote macrophage phagocytosis of apoptotic cells and reduced the occurrence of secondary necrosis in the efferocytosis . Mertk can be cleaved by a cell membrane protein ADAM9 and subsequently loses its biological activity. MiR-126 is an upstream molecule of ADAM9 that can inhibit its generation.In this study,we aim to load miR-126 into exosomes of mesenchymal stem cells by electroporation as engineered exosomes,then apply it to the treatment of acute-on-chronic cell model and explore the mechanism. **Methods:** MiR-126 mimics and inhibitors were transfected into M1 polarization macrophages RAW264.7 induced by LPS in vitro,Mertk and ADAM9 were detected by western blotting,inflammatory and anti-inflammatory cytokines were tested by qPCR. Apoptotic AML12 cells were added and co-cultured with the transfected macrophages,apoptosis related proteins were detected by Western Blotting,efferocytosis/phagocytosis index were observed by fluorescence microscope.Finally,miR-126 loaded into the exosomes of mesenchymal stem cells co-cultured with M1 polarization macrophages,efferocytosis index and the expression of related signaling pathway proteins were detected. **Results:** Compared with the control group, transfection of miR-126 mimics resulted in a decrease in ADAM9 expression and an increase in Mertk expression in M1 macrophages. The qPCR results showed that the inflammatory cytokines in the transfection group decreased, while the anti-inflammatory factors increased compared to the control group. After co-culturing with apoptotic AML12 cells, the expression of cleaved caspase-3 decreased in the transfection group, while the expression of Bcl-2 increased; Efferocytosis index in the transfected group is enhanced compared to the control group under fluorescence microscope. **Conclusion:** After transfection with miR-126 mimics, the expression of Mertk increased, M2 polarization related proteins increased, the efferocytosis enhanced, and cellular inflammatory response weakened.



Disclosures: The following people have nothing to disclose: Junyi Wang, Zhihui Li, Shibo Meng, Junfeng Chen, Bingliang Lin, Jing Zhang

3210-A | EUTHYROID SICK SYNDROME INDICATES INCREASED RISK FOR ACUTE-ON-CHRONIC LIVER FAILURE AND MORTALITY IN PATIENTS WITH CIRRHOSIS

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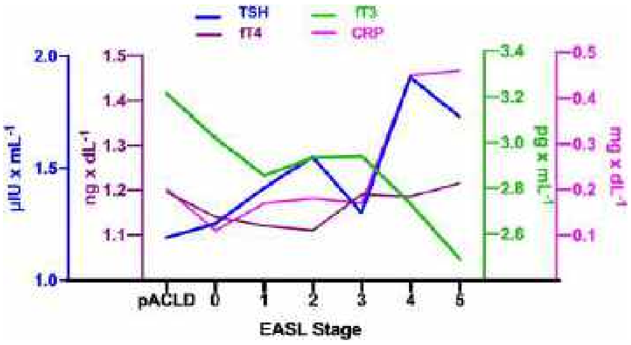
Background: Euthyroid sick syndrome as evident by low free triiodothyronine (fT3) levels has been described in patients with cirrhosis. While hepatic function impacts on transport, conversion and metabolism of thyroid hormones, hepatic metabolism is affected by thyroid hormones. We aimed to analyze the pituitary-thyroid axis in advanced chronic liver disease (ACLD) and the prognostic value of low fT3. **Methods:** Patients with ACLD (liver stiffness measurement e 10kPa or hepatic venous pressure gradient [HVPG] e 6mmHg) undergoing HVPG measurement between 04/2007-09/2022 with available thyroid stimulating hormone (TSH) levels were included. Exclusion criteria were hepatocellular carcinoma (HCC), liver transplantation, infections, portal vein thrombosis, vascular liver disease or intake of thyroid hormones. Clinical stages of ACLD were defined as: likely ACLD (L-ACLD): LSM e 10kPa+HVPG < 6mmHg, S0: subclinical portal hypertension (PH; HVPG 6-9mmHg), S1: clinically significant PH (CSPH), S2: CSPH with varices, S3: prior variceal bleeding, S4: prior non-bleeding hepatic decompensation and S5: prior further decompensation. **Results:** Overall, 647 patients with ACLD (median age: 54.8 y; 65.8% male) were included: 316 were compensated (i.e. cACLD; L-ACLD: n = 31; S0: n = 35; S1: n = 85; S2: n = 165), 331 were decompensated (i.e. dACLD; S3: n = 33; S4: n = 169; S5: n = 129). While median levels of TSH ($p < 0.001$; see Figure) and

C-reactive protein (CRP; $p < 0.001$) increased with progressive ACLD stage, fT3 levels (available in $n = 297$; $p < 0.001$) decreased and free thyroxin (fT4) levels did not change (available in $n = 328$; $p = 0.373$). 38 patients had low fT3 levels, with a higher prevalence in dACLD (dACLD: 17.3% vs cACLD: 7.0%; $p = 0.009$). Of note, the majority of patients (97.4%) with low fT3 exhibited normal TSH. In multivariate linear regression analysis, TSH (aB: 0.49; $p < 0.001$) and fT3 (aB: -0.17; $p = 0.048$) were associated with CRP per mg/dL adjusted for age, Child-Pugh score, creatinine, sodium and HVPG. Low fT3 was linked to higher risk of acute-on-chronic liver failure (ACLF; asHR: 5.3; 95% CI: 1.8-15.8; $p = 0.002$) and liver-related death (asHR: 7.5; 95%CI: 2.7-20.4; $p < 0.001$) considering HCC, etiological cure, LT and non-liver-related death as competing events. **Conclusion:** Increasing TSH and declining fT3 levels in more advanced ACLD stages are indicative of a low T3 (i.e. euthyroid sick) syndrome. Low fT3 was associated with systemic inflammation, a key disease driving mechanism. Importantly, low fT3 in patients with ACLD is an independent risk factor for ACLF and liver-related death and might identify patients who may benefit from therapeutic interventions (e.g. thyroid hormones, thyroid hormone receptor beta agonists).



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3211-A | GRANULOCYTE COLONY-STIMULATING FACTOR FOR PEOPLE IN ADVANCED CHRONIC LIVER DISEASE. A COCHRANE SYSTEMATIC REVIEW AND METANALYSIS

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Background: Advanced chronic liver disease (ACLD) is considered responsible for more than one million deaths annually worldwide. No treatment is available and liver transplantation remains the only curative option. Granulocyte colony-stimulating factor (G-CSF) is currently available for mobilization of haematopoietic stem cells from the bone marrow. Multiple courses of G-CSF infusion might be associated with improved hepatic regeneration, liver function, and survival. This systematic review assesses the benefits and harms of G-CSF. **Methods:** We followed standard Cochrane procedures. We included randomized clinical trials comparing G-CSF, independent of the schedule of administration, alone or combined with stem cell infusion, or with other co-interventions versus no intervention or placebo, in adults with chronic compensated or decompensated ACLD or acute-on chronic liver failure.

Primary outcomes were all-cause mortality, serious adverse events, and health-related quality of life Secondary outcomes were liver disease-related morbidity, nonserious adverse events, and liver function scores. We undertook meta-analyses and presented results using risk ratios (RR) for dichotomous outcomes, and I^2 values for heterogeneity. **Results:** 20 trials (1419 participants) were included. The experimental intervention was G-CSF alone, or G-CSF plus growth hormone, erythropoietin, N-acetyl cysteine, infusion of CD133- positive haemopoietic stem cells. Very low certainty evidence suggested: -a decrease in mortality with G-CSF (RR 0.53, 95% CI 0.38 to 0.72; $I^2=75\%$; 1419 participants; 20 trials) -no difference in serious adverse events (RR 1.03, 95% CI 0.66 to 1.61; $I^{2=}66\%$; 315 participants; 3 trials). Eight trials (518 participants) reported no serious adverse events. Two trials (165 participants) assessed the quality-of-life score and suggested an improvement of both the physical and mental component summary. **Conclusion:** G-CSF, alone or in combination, may decrease mortality in decompensated ACLD of whatever aetiology and with or without acute-on-chronic liver failure, but the certainty of evidence is very low because of high risk of bias, inconsistency, and imprecision. The results of trials conducted in Asia and Europe were discrepant; this could not be explained by differences in participants selection, intervention, and outcome measurement. Data on serious adverse events, health-related quality of life and secondary outcomes were few and inconsistently reported.

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3213-A | LIVER FAILURE VERSUS ORGAN FAILURE IN ACUTE ON CHRONIC LIVER FAILURE: SEQUENCE AND CONSEQUENCE

Young Chang, Soonchunhyang University

Background: Acute-on-chronic liver failure (ACLF) is a syndrome characterized by acute decompensation of chronic liver disease or cirrhosis associated with organ failures, resulting in high short-term mortality. This study aimed to determine the sequence and consequences of organ failures, particularly hepatic and renal failure, and to identify their impact on short-term survival rates in ACLF patients. **Methods:** We extracted 340 ACLF patients from the prospective Korean Acute-on-Chronic Liver Failure cohort. Timing of organ failure, especially hepatic failure and renal failure, was assessed and overall survival was compared according to organ failure sequence. Overall survival (OS) was estimated by Kaplan-Meyer survival analysis with log-rank test and multivariate survival analysis was conducted with Cox proportional hazards model. **Results:** Compared to the group without hepatic failure, the OS was worse in the group manifested by initial hepatic failure (adjusted hazard ratio [aHR] = 3.6; $p=0.008$), and in the group with hepatic failure during the disease period (aHR = 5.7; $p=0.002$). There was no difference in OS between the group without renal failure and the group manifested by initial renal failure (aHR = 0.8, $p=0.51$), but the group with renal failure during the disease period showed a poor prognosis (aHR = 1.9, $p=0.056$). Initial renal failure only group had significantly longer OS than initial hepatic failure group (aHR = 10.8, $p=0.02$). **Conclusion:** Organ failure that develops during hospitalization is more fatal than organ failure that manifested initially. ACLF manifested with initial renal failure has better prognosis than with initial hepatic failure. ACLF with initial renal failure show a great prognosis with 28-day survival rate of over 90%, but the prognosis is dismal if renal dysfunction develops during hospitalization.

Disclosures: The following people have nothing to disclose: Young Chang

3214-A | MARIJUANA USE IS ASSOCIATED WITH BETTER OUTCOMES IN PATIENTS WITH CIRRHOSIS

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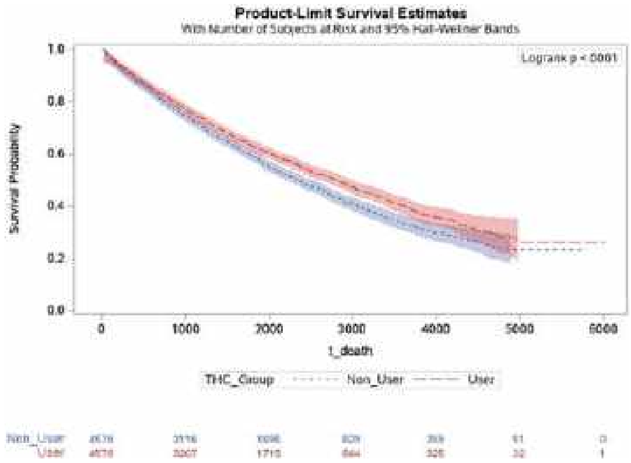
Background: Despite legalization and increasing use of marijuana in many states of the U.S., its effect on cirrhotic patients has not been well described. We performed a retrospective large database analysis using the Veterans Outcomes and Costs Associated with Liver Disease (VOCAL) cohort from VA Informatics and Computing Infrastructure. **Methods:** The VOCAL cohort includes all veterans with cirrhosis, receiving care between 2008 – 2016 at the Veterans Health Administration. All patients' urine and serum toxicology reports were utilized to define groups: If a patient had any positive result for marijuana, the patient was classified as a marijuana user (THC_User). All negative results classified the patient as a nonuser (THC_Nonuser) and someone who had never been tested, was classified as no test group (Not_Tested). Baseline characters were compared between the groups. Survival and decompensation were compared between groups using Kaplan-Meier Survival curve with Log Rank Test and Cumulative Incidence with Gray's Test after matching possible confounding variables with Mahalanobis Distance Matching. **Results:** Out of 129,981 cirrhotic veterans, 63,860 were in THC_Nonuser, 29,456 were in THC_User, and 36,665 were in Not_Tested groups. Regarding etiologies of cirrhosis, alcohol (either alcohol alone or alcohol with chronic hepatitis C, HCV) was the most common cause in THC_Nonuser group (55.6%) and THC_User group (65.7%). NASH was the most common cause in Not_Tested group (38.7%). NASH was more common in THC_Nonuser (21.9%) and Not_Tested (38.7%) groups than THC_User group (7.0%). Several comorbidities were more common in THC_Nonuser than THC_User group, including diabetes (59% vs 49%), chronic heart failure (CHF, 35% vs 25%), chronic kidney disease (CKD, 50% vs 25%). The median baseline MELD score was 6 (Interquartile Range 6-14) in all three groups. Most patients were Child-Turcotte Pugh class A (60%). After matching for age, BMI, baseline MELD score, impaired fasting glucose/diabetes, CKD and CHF, THC_User had significantly better survival than THC_Nonuser in alcoholic cirrhosis patients. ($p < 0.01$, Figure 1) There was no significant survival difference between THC_User and THC_Nonuser in HCV ($p = 0.58$) and NASH ($p = 0.51$) cirrhosis patients. THC_User had significantly less cumulative incidence of decompensation than THC_Nonuser in alcoholic ($p < 0.01$), NASH ($p < 0.01$), and HCV ($p < 0.01$) cirrhosis patients. **Conclusion:** In cirrhosis patients, marijuana use is correlated with better outcomes including decompensation and survival. Further studies are needed to identify the potential mechanism of marijuana use leading to better outcomes.



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3215-A | PERSISTENT ACLF: CHARACTERISTICS OF THE PATIENTS IN THE PHASE IIb HEP 102-DHELIVER STUDY

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Background: Acute-on-chronic liver failure (ACLF) is syndrome defined by acute decompensation of cirrhosis associated with single or multi-organ failures and high 28- and 90-day mortality between 20 and 80% or more according to the number of organ failures. The DHELIVER study is an ongoing multicenter Phase IIb RCT double-blinded POC trial that aims to demonstrate the efficacy of Human Allogeneic Liver-derived Progenitor Cells (HepaStem®) on overall survival in patients with persistent ACLF grades (G) 1 and 2. The purpose of the current analysis is to describe the characteristics of patients with ACLF who were randomized in the study. **Methods:** Patients with initial ACLF G1 or G2 (EASL-CLIF definition) were assessed at the beginning and at the end of screening, 3 to 7 days after the initial ACLF diagnosis. Only patients with confirmed persistent ACLF were randomized. **Results:** Up to 10-MAY-2023, 121 patients with ACLF (M/F 89/32), aged 52.0 ± 10 yrs (range: 25-73 yrs), were screened in 27 sites in 12 European countries. Among all screened patients, 77 had G1 (63.6%) and 44 G2 (36.4%). 46 patients were screen failures (SF), mostly because ACLF resolved (58.7%), they did not meet the enrollment criteria (21.7%) or because they died (10.9%) during screening. 75 patients (48 G1 and 27 G2) fulfilled all enrollment criteria and were randomized (M/F 59/16), with mean age 51.0 ± 10.9 yrs, slightly younger compared to SF (53.7 ± 9.4 yrs). In those randomized patients the etiology of cirrhosis was mainly alcohol alone (92.0% of G1, 100% of G2) or combined with other etiologies (6.3% of G1). Precipitating events of ACLF were mostly acute alcoholic hepatitis (AAH)/active alcoholism (up to 81.5% in G2) and bacterial infection (up to 25.5% in G1). Most G1 patients had liver failure (72.9%), primarily associated with mild or moderate hepatic encephalopathy (66.7%); while most patients with G2 had liver failure (96.3%), associated with coagulation failures (77.8%). Mean bilirubin, WBC and CRP did not differ in randomized patients with ACLF G1 and G2, MELD-Na and CLIF-ACLF scores were higher in G2 patients. Randomized patients with ACLF compared to SF had higher total bilirubin 22.0 vs 15.6 mg/dL; CRP 40.0 vs 33.4 mg/L and WBC 12.9 vs 10.0 10^9/L. MELD-Na was very similar between screen and randomized patients. **Conclusion:** Patients with persistent ACLF enrolled in DHELIVER study were characterized mainly by presence of liver failure (in G1) associated with coagulation failure (in G2). High level of bilirubin and significant systemic inflammation were recorded. Predominant etiology of cirrhosis was alcohol-related liver disease.

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3216-A | PERSISTENT SYSTEMIC INFLAMMATION IS IMPORTANT DRIVER OF ACUTE-ON-CHRONIC LIVER FAILURE AND ORGAN FAILURE DEVELOPMENT

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Background: We aimed to investigate the association between acute-on-chronic liver failure (ACLF) development and systemic inflammatory markers in acutely decompensated chronic liver disease patients. **Methods:** We enrolled 1,249 patients without ACLF at baseline in Korean ACLF cohort. Rrgan failure and ACLF were defined by European Association for the Study of the Liver-Chronic liver failure (EASL-CLIF) criteria. Primary outcome was ACLF development and new organ failure development within 1 year. **Results:** Most common etiology of chronic liver disease was alcohol (66.1%), followed by viral hepatitis (15.5%). Mean model for end-stage liver disease and CLIF-C AD score were 16.3 ± 5.4 and 49.7 ± 9.3, respectively. Patients with high C-reactive protein (CRP) (e 1.0 mg/dL), white blood cell count (WBC) (e $10.0x10^9/mm^3$), procalcitonin level (1.0 mg/dL) showed significantly higher 1-year ACLF development rate than patients with low CRP ($P < 0.001$), WBC ($P = 0.004$) and procalcitonin ($P = 0.014$), respectively. Those with systemic inflammatory response syndrome (SIRS) also had significantly higher ACLF development rate than those without SIRS ($P = 0.045$). Cox proportional hazard regression model showed that SIRS, bacterial infection, low albumin and Na levels, high bilirubin, international normalized ratio (INR), CRP, creatinine, and procalcitonin levels were significant factors in univariate analysis, and bilirubin (Hazard ratio (HR) 2.266, $P = 0.012$), INR (HR 6.047, $P < 0.001$). CRP (HR 2.242, $P = 0.011$), and procalcitonin ($HR = 2.437$, $P = 0.011$) level were independent factors for ACLF development. Those with high CRP level had significantly higher renal ($P < 0.001$), coagulation ($P < 0.001$), cerebral ($P = 0.013$), circulatory ($P = 0.009$) failure development ($P = 0.001$) than those with low CRP, and those with high procalcitonin had significantly higher renal failure development rate ($P = 0.032$). The ACLF development rate of the patients with low CRP at baseline but high CRP at 7th day was significantly higher than that of the patients with high CRP at baseline but low CRP at 7th day ($P = 0.01$) and similar to that of the patients with persistently high CRP ($P = 0.629$). The change of the SIRS also showed similar results to the CRP change. **Conclusion:** Persistent or worsening systemic inflammation is a main driver for development of organ failure and ACLF. The resolution of inflammation could reduce the ACLF development. Reducing systemic inflammation can be a treatment target to prevent disease progression.

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The following people have nothing to disclose: Do Seon Song, Hee Yeon Kim, Young Kul Jung, Sang Gyune Kim, Moon Young Kim, Jae Young Jang, Jung Gil Park, Jin Mo Yang
Disclosure information not available at the time of publication: Eileen Yoon, Soung Won Jeong, Sung Eun Kim, Won Kim

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Symbols: **f** , Poster of Distinction; ★, Foundation Award Recipient

3217-A | PREDICTIVE SCORES FOR MORTALITY IN MAFLD-RELATED ACUTE-ON-CHRONIC LIVER FAILURE (MAFLD-ACLF): DEVELOPMENT AND VALIDATION OF MAFLD-MELD-NA AND MAFLD-AARC SCORES

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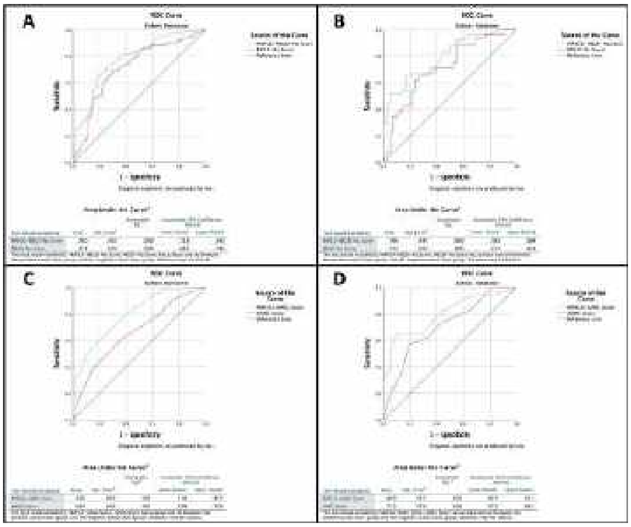
Background: With the increasing prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD), there is a corresponding increase in the prevalence of MAFLD-related acute-on-chronic liver failure (MAFLD-ACLF). Factors determining the outcome in these patients have not been well studied.

Methods: We identified MAFLD as the etiology of chronic liver disease among a prospective cohort of patients with ACLF from the Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium (AARC) database. MAFLD was considered the etiology after excluding other known etiologies (such as alcohol, HBV, HCV, etc.) from the cohort. We randomly divided the cohort into two well-matched groups: a derivative cohort (n = 258, comprising 70% of the patients) to identify factors determining the outcome and create a predictive model, and a validation cohort (n = 111, comprising 30% of the patients) to validate the model. The outcome was defined as death within 90 days from enrollment. Transplanted patients were excluded. Only the baseline clinical and laboratory features and severity scores were analyzed. **Results:** The derivative cohort consisted of 258 patients with a mean age of 53, of which 60% were males. Diabetes was present in 27% of the cohort, and hypertension in 29%. The dominant precipitating causes for ACLF included acute viral hepatitis in 32% and drug-induced liver injury in 29%. The MELD-Na and AARC scores at admission were 32 ± 6 and 10.4 ± 1.9, respectively. At the 90-day follow-up, only 132 (51%) patients survived. Non-viral etiology as a precipitant, diabetes, bilirubin, INR, and encephalopathy were found to be independent factors influencing mortality. By adding diabetes and etiology to the MELD-Na and AARC scores, we constructed the MAFLD-MELD-Na score (+12 points for diabetes and -12 points for viral etiology) and the MAFLD-AARC score (+5 for diabetes, -5 for viral etiology). Both of these scores performed significantly better than the general MELD-Na and AARC scores, both in the derivative cohort and the validation cohort (Figure). **Conclusion:** Nearly one in two patients with MAFLD-ACLF succumbs to death by day 90. The presence of diabetes and non-viral precipitant causes independently influence the outcome. The newly developed and validated MAFLD-MELD and MAFLD-AARC scores, calculated at baseline, reliably predict 90-day mortality in patients with MAFLD-ACLF.



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Disclosure information not available at the time of publication: Anand V. Kulkarni

3218-A | RESNET PREDICTION MODEL BASED ON SUBCAPSULAR OF LIVER 3D VASCULAR TREE SMI IMAGE OF PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE AND CONVOLUTIONAL NEURAL NETWORKS ESTABLISHED BY ARTIFICIAL INTELLIGENCE

Mingyue Xiao[1], Xuyang Li[2], Run Lin[2], Yuankai Wu[1], Jieyang Jin[1], Jie Ren[1], Yutian Chong[1], Ruixuan Wang[2] and Lili Wu[1], (1)The Third Affiliated Hospital of Sun Yat-Sen University, (2)Sun Yat-Sen University

Background: Acute on-chronic Liver Failure (ACLF) is the main type of liver failure in China. Early prognosis assessment is the key to treatment. Hepatic perfusion is the main determinant of liver repair and regeneration ability. Early non-invasive assessment of liver microperfusion can guide clinical treatment. Superb MicroVascular Imaging (SMI) can display low-speed blood flow with high vascular spatial resolution. However, there is no relevant standard and it is subjective. Advances in deep learning technology can supplement this deficiency. Based on the Deep Residual Network (ResNet), the 3D vascular tree SMI image under the liver capsule of ACLF patients was analyzed and the prediction model was established, aiming to reflect the prognosis of ACLF patients effectively and accurately in the early stage. **Methods:** Patients with ACLF admitted to the Department of Infectious Diseases of our center from June 2020 to October 2021 were examined by conventional ultrasound (US), contrast-enhanced ultrasound (CEUS) and SMI. Conventional US scan was used to find the best section, and the largest section of the right liver was shown in the intercostal space. Subsequently, CEUS was performed, and SMI was performed 2 minutes after CEUS to obtain 3D vascular tree images. The 3D images were manually segmented to obtain the most vascular information. We used a ResNet model with 50 layers to solve the problem of network optimization by adding a "residual module". The model adopted five-fold cross validation, and the data augmentation strategy was used to expand the data volume. The generalization performance of the model on tasks was evaluated using the receiver operating characteristic (ROC) curve and the precision-recall (PR) curve. Based on Layer-wise Relevance Propagation (LRP) method, the importance of features learned by the model from images was visualized. **Results:** A total of 54 patients with ACLF were enrolled, 10 patients died or underwent liver transplantation, and 44 patients were improved. A total of 72 data files were included in the model. After data enhancement, the proportion of data labeled 1 and 0 in each fold of the patient data was the same (25 groups), and one group contained 15 two-dimensional vascular maps. The false positive rate and true positive rate of the model were about 20% and 80%, respectively, and the area under the ROC curve was 0.831. The recall and precision of the model were close to 80%, and the average precision was 0.813. LRP can intuitively explain the positive and negative basis of the model's classification decision. **Conclusion:** The ResNet prediction model based on the SMI image of the subcapsular vascular tree can predict the prognosis of ACLF patients in the early stage non-invasively. The model has certain interpretability, which can provide effective new ideas for the diagnosis of ACLF.

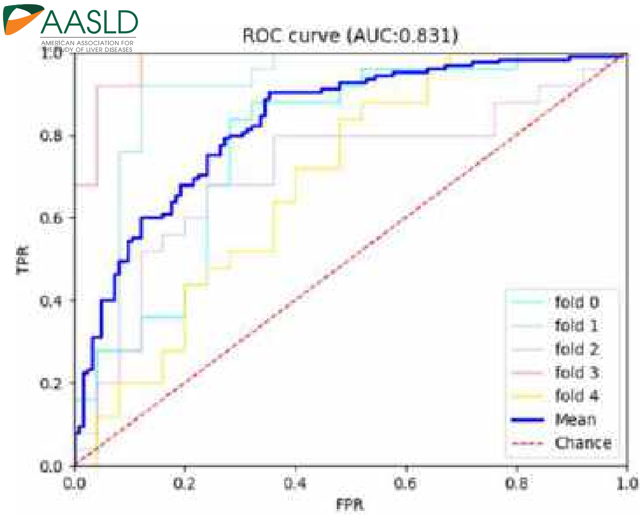


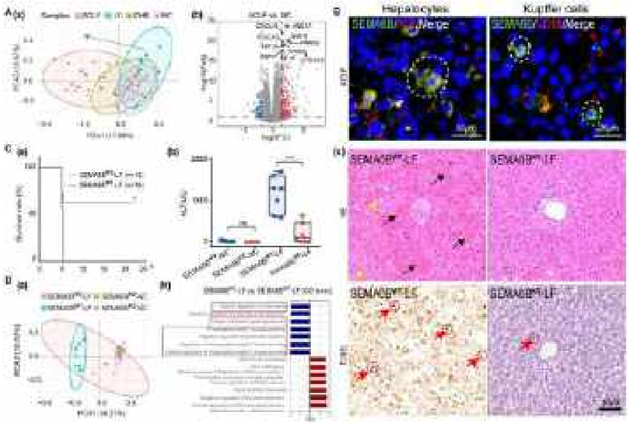
Figure 1. the receiver operating characteristic curve of the model

Disclosures: The following people have nothing to disclose: Mingyue Xiao, Xuyang Li, Run Lin, Yuankai Wu, Jieyang Jin, Jie Ren, Yutian Chong, Ruixuan Wang, Lili Wu

3219-A | SEMA6B INDUCES KUPFFER CELL INFLAMMATION AND HEPATOCYTE APOPTOSIS IN HEPATITIS B VIRUS-RELATED ACUTE-ON-CHRONIC LIVER FAILURE

Hui Yang[1], Qun Cai[2], Jiaxian Chen[1], Xi Liang[3], Jiaojiao Xin[1], Dongyan Shi[1] and Jun Li[1], (1)The First Affiliated Hospital, Zhejiang University School of Medicine, (2) Ningbo Medical Center Lihuili Hospital, Affiliated Lihuili Hospital of Ningbo University, (3)Taizhou Central Hospital (Taizhou University Hospital)

Background: Semaphorin-6B (SEMA6B) plays vital roles in pathogenesis of hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF), but its molecular basis is unclear. This study aims to elucidate the mechanisms of SEMA6B in HBV-ACLF. **Methods:** Prospective clinical data from 290 subjects with ACLF, liver cirrhosis (LC), chronic hepatitis B (CHB) and healthy control (NC) were studied, and 43 subjects (ACLF, n = 20; LC, n = 9; CHB, n = 10; NC, n = 14) among them underwent mRNA sequencing with peripheral blood mononuclear cells (PBMCs). The transcriptome was performed to clarify mechanisms of SEMA6B in ACLF, and validated in vitro with hepatocytes and macrophage, and in vivo with SEMA6B knockout mice. **Results:** PBMCs transcriptome showed that SEMA6B expression was significantly higher in ACLF patients than in LC, CHB and NC subjects (all, $P < 0.05$). SEMA6B high-expression in ACLF patients were significantly correlated to 28-/90-day mortality rates (all, $P < 0.05$), and inflammation-related genes including ICAM1, IL-10, TNF, IL-1α, IL-1β, CCL2 and apoptosis-related genes including Bim, Caspase-8 and Caspase-9 (all, $P < 0.05$). Immunofluorescence assessment in liver tissues of ACLF patients showed a high expression of SEMA6B in Kupffer cells and hepatocytes. SEMA6B over-expression in macrophages activated immune response and cytokine secretion (IL-6, IL-1β, IL-10, CCL2; all, $P < 0.05$). SEMA6B over-expression in hepatocytes inhibited the hepatocellular proliferation through G0/G1 cell-cycle phase arrestation and triggered the hepatocyte apoptosis. SEMA6B knockout mice with liver failure were rescued though improving liver functions and attenuating inflammatory response (TNF-α, IL-6, IL-1β, IL-10; all, $P < 0.05$), and decreasing hepatocyte apoptosis. A significant downregulation of six inflammation/apoptotic related biological processes were observed in SEMA6B knockout mice with liver failure. **Conclusion:** SEMA6B, as a potential biomarker for disease severity in the development and progression of ACLF, induces Kupffer cell inflammation and hepatocyte apoptosis in ACLF, and provides a novel clinical target for treating ACLF.



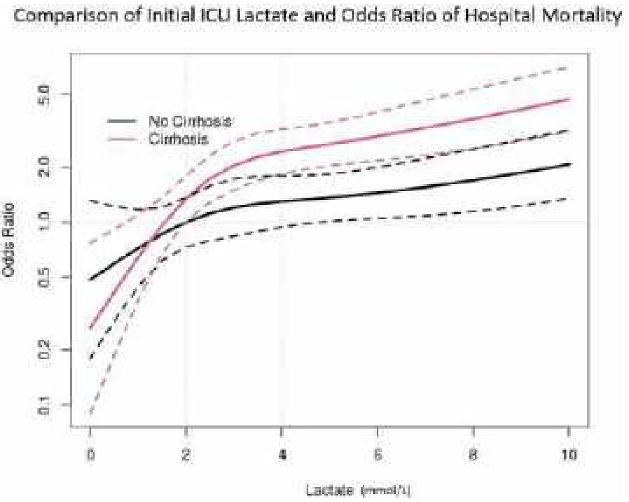
Disclosures: The following people have nothing to disclose: Hui Yang, Qun Cai, Jiaxian Chen, Xi Liang, Jiaojiao Xin, Dongyan Shi, Jun Li

f 3220-A | SERUM LACTATE AND MEAN ARTERIAL PRESSURE THRESHOLDS IN THE TREATMENT OF SEPTIC SHOCK IN PATIENTS WITH CIRRHOSIS: VALIDATION OF THE SEPSIS-3 GUIDELINES

Thomas Smith[1], Chansong Choi[2], Puru Rattan[3], Laura Piccolo Serafim[1], Alice GalloDeMoraes[3] and Douglas A. Simonetto[4], (1)Mayo Clinic School of Graduate Medical Education, (2)University of Nebraska Medical Center, (3)Mayo Clinic - Rochester, (4)Mayo Clinic Rochester, Rochester, MN

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

Background: Despite the 2016 Sepsis-3 guideline's lowering of serum lactate cutoff (2 mmol/L) to include patients with higher risk-adjusted hospital mortality, further investigation is needed in patients with known derangements in lactate metabolism and hemodynamics such as those with cirrhosis. Expert opinion also differs regarding optimal mean arterial pressure (MAP) targets during resuscitation in this population based on altered baseline hemodynamics. This study aims to investigate the association between initial serum lactate and resuscitation MAP on in-hospital mortality in patients with and without cirrhosis. **Methods**: Retrospective cohort study of patients admitted to a Mayo Health System ICU for treatment of septic shock between 2006 and 2021. Patients with identified infection source and vasopressors administered within 6 hours of ICU admission were included. Patients with cirrhosis documented on imaging and ICD codes were compared to patients without cirrhosis on ICD codes. Subgroups were created based on ICU-admission lactate levels (<2, 2-4, >4 mmol/L) and median 2-hour MAP (<60, 60-65, >60 mmHg), and in-hospital mortality and need for renal replacement therapy (RRT) was compared. The effect of median 24-hour MAP on in-hospital mortality was analyzed post-hoc. **Results**: We identified 595 patients with cirrhosis and 575 patients without cirrhosis admitted for treatment of septic shock. In those with cirrhosis, admission lactate 2-4 mmol/L was associated with increased in-hospital mortality compared with lactate <2 ($p = 0.035$, OR 1.69). Admission lactate >4 mmol/L was associated with increased in-hospital mortality in both cirrhosis ($p < 0.001$, OR 3.84) and non-cirrhosis groups ($p < 0.001$, OR 2.23). Admission lactate >4 mmol/L was associated with increased need for RRT during hospitalization in both the cirrhosis ($p < 0.001$, OR 3.46) and non-cirrhosis groups ($p < 0.001$, OR 2.53). Median 2-hour MAP 60-65 mmHg was not associated with increased in-hospital mortality in either the cirrhosis ($p = 0.55$) or non-cirrhosis subgroups ($p = 0.29$). However, in the cirrhosis group median 24-hour MAP 60-65 mmHg was associated with increased hospital mortality compared to MAP >65 ($p < 0.001$, OR 2.92). **Conclusion**: Patients with cirrhosis were found to have increased in-hospital mortality with initial ICU lactate >2 mmol/L, supporting the continued use of this as a cutoff for septic shock definition. Admission lactate >4 mmol/L was associated with increased RRT during hospitalization in both groups, and patients with cirrhosis and lactate >4 mmol/L may benefit from early renal evaluation and intervention. Although median 2-hour MAP 60-65 mmHg was not associated with increased hospital mortality in either group, median 24-hour MAP 60-65 mmHg was associated with increased hospital mortality for patients with cirrhosis and supports 65 mmHg as an optimal MAP target during resuscitation in this population.



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Disclosure information not available at the time of publication: Chansong Choi, Puru Rattan, Laura Piccolo Serafim, Alice GalloDeMoraes

3221-A | SURVIVAL AFTER ACUTE ON CHRONIC LIVER FAILURE: CHANGES WITH ERA AND IMPACT OF TRANSPLANTATION AND NON-TRANSPLANT INTERVENTIONS.

William Bernal, Mark John William McPhail, Francesca Maria Trovato, Eliza Montague-Johnstone, Georgina Kerry, Rajat Raja, Stacey Calvert, Pervez Khan, Sameer Patel, Tasneem Pirani, Robert Loveridge and Julia Wendon, King's College Hospital

Background: Acute on Chronic Liver Failure (ACLF) is a common complication of cirrhotic chronic liver disease (CLD) with high mortality but little is known of how survival has changed over time, and of the current relative impacts of medical interventions and liver transplantation (LT). We examined short- and longer-term survival of a large CLD patient cohort with unplanned admission to a LT centre specialist ICU over a 20-year period. **Methods:** Consecutive patients with CLD admitted 2000-2020 were studied, classified as Acute Decompensation (AD) or ACLF grades 1-3 according to EASL-CLIF criteria and by CLIF-SOFA Score. Era 1 of admission was 2000-06, Era 2 2007-12 and Era 3 2013-20. Data is reported as median (IQR) or n (%): analysis utilised Kaplan-Meier methods and logistic and Cox-regression. **Results:** 1828 patients (median age 52 (42-60) years, 61% male, 51% with alcohol-related CLD) were studied: 447 (24%) with AD, 319 (17%) with ACLF1, 407 (22%) ACLF2 and 655 (36%) ACLF3 on admission. Overall, 90-day and 1-year

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

survival rose from 29% and 23% in Era 1 to 49% and 39% in Era 3 ($p < 0.001$). Survival was lowest in ACLF3, but 1-year survival increased from 11% in Era 1 to 24% in Era 3 ($p < 0.007$). Overall, 232/1828 (12.7%) underwent LT at median 24 (8-130) days after ICU admission; the proportion increased from 41/422 (9.7%) in Era 1 to 134/719 (18.6%) in Era 3 ($p < 0.001$). In those transplanted 1-year survival was 90% compared to 26% in those who were not ($p < 0.001$): in ACLF3 93% vs. 11% ($p < 0.001$). Evaluating only patients managed without LT, on multivariate analysis adjusting for age, aetiology, indication for admission and illness severity, 1-year survival improved from from Era 1 to Era 2 (Odds Ratio 2.8 (95% CI 2.0-3.9)) and between Era 1 and Era 3 (3.2 (2.2-4.7), $P < 0.001$ for both), but not between Era 2 and 3 (1.15 (0.84-1.55) $p = 0.37$). **Conclusion:** Survival for critically ill patients with CLD has improved markedly over time, but that with medical care alone appears to have now plateaued. Survival with LT may be transformative but is utilised in only a minority of patients. However, without LT medium-term survival remains poor, particularly in those patients with ACLF3: patients surviving such an episode of ACLF should be assessed for LT. Novel medical therapies and/or improved access to LT are required to further improve survival.

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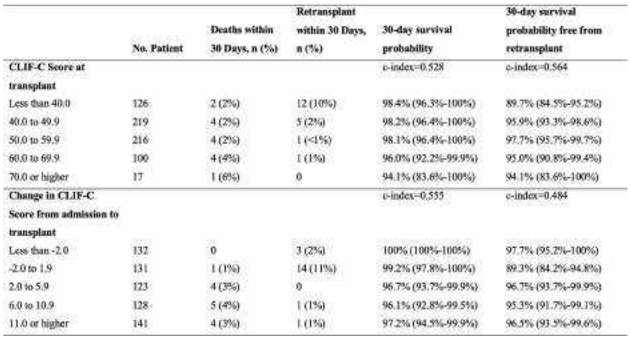
3222-A | THE CHRONIC LIVER FAILURE CONSORTIUM (CLIF-C) ACLF SCORE AS A PREDICTOR OF OVERALL SURVIVAL AFTER LIVER TRANSPLANTATION IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

Jorge Enrique Sinclair De Frías, Andrew Paul Keaveny, Trisha Singh, Ananya Vasudhar, Terri Menser, Colleen Ball, Philip Lowman, Devang K. Sanghavi, Kristopher P. Croome and Pablo Moreno-Franco, Mayo Clinic Florida, Ponte Vedra Beach, FL

Background: Acute-on-chronic liver failure (ACLF) in patients with decompensated chronic liver disease is associated with increased short-term mortality and liver transplantation (LT) is the only curative treatment. To facilitate more accurate prognostication in ACLF, the European Association for the Study of the Liver–Chronic Liver Failure (EASL-CLIF) consortium developed the CLIF-Consortium score for ACLF (CLIF-C score). This score is a validated prognostic tool for patients with ACLF. However, there are only limited data evaluating the CLIF-C in predicting survival after LT in patients with ACLF. **Methods:** We retrospectively studied all patients with cirrhosis and ACLF admitted to the intensive care unit (ICU) who underwent LT at our center between January 2010 and December 2021. Hazard ratios (HRs) and corresponding 95% confidence intervals were estimated from Cox proportional hazards regression, where patients were censored on the date of the last clinical follow-up. The concordance index (c-index) was estimated to evaluate the ability of CLIF-C to discriminate overall survival and survival free of retransplantation. Kaplan-Meier method was used to estimate cumulative survival probability post-LT according to CLIF-C categories. **Results:** Our cohort included 691 LT recipients; 61% were male (419/691), 84% white (577/691), the median age was 59 years (IQR 51-65, Range 18-75). The median time in ICU prior to LT was 2.7 days (1.2-10.5). The CLIF-C score was a median of 44.3 points (IQR 38.1-52.2) and 49.5 points (IQR 42.3-56.5) at time of admission to ICU and at LT, respectively. The median donor risk index was 1.4 (1.2-1.8). During a median clinical follow-up of 3.4 years (IQR 1.5-8.0 y), 189 patients died ($n = 155$). The probability of surviving 30 days and one-year post-LT was 97.4% (95% CI 96.2% to 98.6%) and 90.8% (95% CI 88.6% to 93.1%), respectively. Neither the CLIF-C score at time of LT or change in CLIF-C score from ICU admission to LT reliably predicted 30-day survival post-LT or 30-day survival free from transplant, with c-indices of 0.528 and 0.564, respectively (Table 1). **Conclusion:** The prognostic value of the CLIF-C score for predicting survival post-LT in our cohort of cirrhotic patients with ACLF in ICU was limited. Our data suggest an absolute CLIF-C score or change in CLIF-C should not be the sole determinant in deciding the futility of transplantation.

Table 1. 30-day transplant-free survival probabilities after liver transplant



	No. Patient	Deaths within 30 Days, n (%)	Retransplant within 30 Days, n (%)	30-day survival probability	30-day survival probability free from retransplant
CLIF-C Score at transplant				c-index=0.528	c-index=0.564
Less than 40.0	126	2 (2%)	12 (10%)	98.4% (96.3%-100%)	89.7% (84.5%-95.2%)
40.0 to 49.9	219	4 (2%)	5 (2%)	98.2% (96.4%-100%)	95.9% (93.3%-98.6%)
50.0 to 59.9	216	4 (2%)	1 (<1%)	98.1% (96.4%-100%)	97.7% (95.7%-99.7%)
60.0 to 69.9	100	4 (4%)	1 (1%)	96.0% (92.2%-99.9%)	95.0% (90.8%-99.4%)
70.0 or higher	17	1 (6%)	0	94.1% (83.6%-100%)	94.1% (83.6%-100%)
Change in CLIF-C Score from admission to transplant				c-index=0.555	c-index=0.484
Less than -2.0	132	0	3 (2%)	100% (100%-100%)	97.7% (95.2%-100%)
-2.0 to 1.9	131	1 (1%)	14 (11%)	99.2% (97.8%-100%)	89.3% (84.2%-94.8%)
2.0 to 5.9	123	4 (3%)	0	96.7% (93.7%-99.9%)	96.7% (93.7%-99.9%)
6.0 to 10.9	128	5 (4%)	1 (1%)	96.1% (92.8%-99.5%)	95.3% (91.7%-99.1%)
11.0 or higher	141	4 (3%)	1 (1%)	97.2% (94.5%-99.9%)	96.5% (93.5%-99.6%)

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3223-A | THE EFFECTIVENESS OF PLASMA EXCHANGE IN IMPROVING SHORT-TERM SURVIVAL IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

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Background: Acute-on-chronic liver failure (ACLF) is a clinical condition with a very high short-term mortality rate. Liver transplantation is the best available treatment for severe patients, increasing their chance of survival. Plasma exchange (PE) could be a viable and life-saving treatment option for ACLF patients in a country with limited liver donor resources. The purpose of this study is to determine the effect of PE on the short-term survival of ACLF patients. **Methods:** From January 2019 to July 2022, ACLF patients hospitalized to the University Medical Center in Ho Chi Minh City, Vietnam had a retrospective comparison of the treatment responses to PE and supportive medical care (SMC). Following enrollment in the Asian Pacific Association for the Study of the Liver (APASL), patients were diagnosed with ACLF. Analysis was done on the sequential liver biochemical tests, levels of consciousness, and survival rates. **Results:** 95 patients in total (72 patients in the SMC group and 23 patients in the PE group) met the inclusion criteria. The PE group had higher serum total bilirubin levels and lower white blood cell count at baseline than the SMC group; however, other variables were not significantly different. The cumulative survival rates at day 30 and day 90 in the PE group and SMC group were, respectively, 60.87% and 38.11% ($p = 0.036$), and 39.13% and 27.78% ($p = 0.303$). Overt hepatic encephalopathy, INR, lactate, ammonia, MELD, MELD-Na, AARC score, and PE were all related to the 30-day survival rate, but only PE was proven to be an independent factor for improving survival in multivariate analysis. Despite the fact that several factors were found to be associated with the survival rate at day 90, no single variable was identified as being significantly related. **Conclusion:** Regardless of the failure to improve the 90-day survival rate, the 30-day survival rate in the PE group was significantly higher than the SMC group, indicating that PE may be an effective treatment in prolonging patients' survival while waiting for a liver transplant.

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3224-A | TRANSPLANT SURVIVAL BENEFIT OF ACUTE-ON-CHRONIC LIVER FAILURE WITH CIRCULATORY FAILURE IN HBV POPULATION

Jinjin Luo[1], Yu Wu[2], Changze Hong[3], Peng Li[1], Meiqian Hu[1], Jiaojiao Xin[1], Jing Jiang[1], Dongyan Shi[1], Jinjun Chen[3], Yu Chen[2] and Jun Li[1], (1)The First Affiliated Hospital, Zhejiang University School of Medicine, (2) Beijing Youan Hospital Capital Medical University, Beijing, China, (3)Nanfang Hospital, Southern Medical University

Background: Circulatory failure (CF) is a severe type of extrahepatic organ failure in acute-on-chronic liver failure (ACLF). This study aimed to identify the prognosis of hepatitis B virus-related ACLF (HBV-ACLF) patients with CF and their survival benefit from liver transplantation (LT). **Methods:** Hospitalized patients with HBV-ACLF between January 2015 and December 2022 were enrolled from the Chinese Group on the Study of Severe Hepatitis B open cohort. **Results:** Among 2247 HBV-ACLF patients, 59 patients were diagnosed with CF at admission, 2188 patients were diagnosed with non-CF (163 developed CF during hospitalization, 2025 did not develop). HBV-ACLF patients who developed CF (median time: 10 (5-19) days) had more serious disease severity and worse prognosis (90-day LT-free mortality: 97.9% vs. 37.5%, $p < 0.001$) than those without CF. Age, white blood cell counts and international normalized ratio were the independent risk factors of CF development. Among 222 patients with CF, the main types of CF were distributive and hypovolemic shock. The unmatched analysis (LT/n = 35; non-LT/n = 187) and propensity score matching analysis (LT/n = 35; non-LT/n = 28) showed the 360-day survival rate of HBV-ACLF patients with CF undergone LT was higher than those without LT (54.3% vs. 4.8%; 54.3% vs. 7.1%, both $p < 0.001$). The stratification analysis further showed CF patients with INR < 3.5 had higher survival benefit from LT than those with INR ≥ 3.5 (360-day post-LT survival: 68.0% [52.0-89.0] vs. 20.0% [5.8-69.1], $p < 0.001$; net survival benefit rate: 60.0% vs. 20.6%, $p < 0.001$). **Conclusion:**

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

HBV-ACLF patients with CF exhibited a very poor prognosis and LT could significantly improve their survival. Patients with INR < 3.5 derived a higher net survival benefit from LT.

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3225-A | TRENDS IN ETIOLOGY OF ACUTE DECOMPENSATION AND ACUTE ON CHRONIC LIVER FAILURE: ANALYSIS FROM A TERTIARY CARE CENTER IN ASIA.

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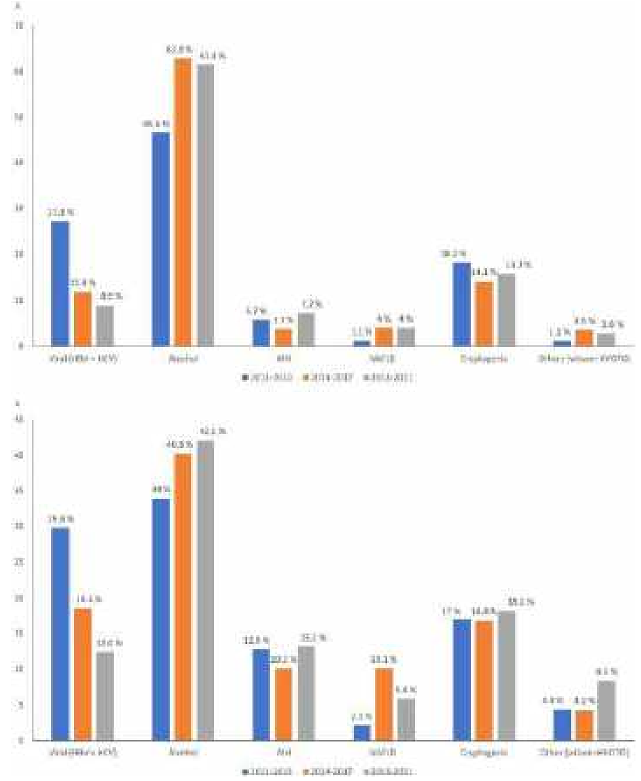
Background: Acute on chronic liver failure (ACLF) burden is increasing and is associated with high mortality. Alcohol, hepatitis viruses, autoimmune liver disease are important causes of cirrhosis; active alcoholism, sepsis and viral etiologies are common precipitants of ACLF. Etiologies of cirrhosis and acute precipitants vary across countries. Published data suggest that outcomes in ACLF vary with etiology. **Methods:** This was a retrospective analysis from a tertiary care center in Asia. All consecutive patients admitted with acute decompensation (AD) and ACLF were included. For analysing changing trends in etiology, we divided patients into 3 groups according to the time-period of admission: 2011-2013, 2014-2017 and 2018-2021. We analysed the differences in etiologies between the three groups. **Results:** We included 1150 patients, median (IQR) 42 (34-50) years, 914 (79.5%) males; AD: ACLF 287 (25.0%): 863 (75.0%). Etiologies of cirrhosis were alcohol 637 (55.4%), viral 154 (13.4%), autoimmune 83 (7.2%), cryptogenic 182 (15.8%), non-alcoholic fatty liver disease (NAFLD) 52 (4.5%) and others 42 (3.7%). Proportions of ACLF grades 1, 2, 3 were 287 (25.0%), 167 (14.5%), 325 (28.3%) and 371 (32.3%), respectively. The median CTP score, MELD-Na were 13 (11-14), 31.5 (25.5-37.4), respectively. The number of patients with AD/ACLF who were admitted/year in the hospital over time-intervals (2011-2013, 2014-2017 and 2018-2021) showed an increasing trend: 40, 115 and, 135, respectively. Out of total number of patients, the proportions of ACLF cases were 88/135 (65.2%), 347/466 (74.5%) and 428/549 (78.0%), respectively (P = 0.008). The median CLIF-C ACLF score increased over time, 48 (41-55), 51 (44-57) and 52 (44-59), respectively. Mortality rates were 61.4%, 88.2% and 87.1%, respectively. There was an increase in the proportion of patients with alcohol-related ACLF over time (46.6%, 62.8% and 61.4%), whereas viral-related ACLF reduced over time (27.3%, 11.8% and 8.9%), respectively (P < 0.001) (Figure 1a). Similar trends were seen in patients with AD (Figure 1b). **Conclusion:** Alcohol-related ACLF is increasing over time, with more severe disease. Alcohol is now the most common cause of hospital admission for ACLF. Viral etiology-related ACLF admissions are reducing over time. These findings are alarming, and public health interventions are needed to mitigate the future burden of alcohol-related liver disease. Figure 1. Trends in etiology of cirrhosis in a) ACLF, b) AD.



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3300-A | ACCURATE NON-CERULOPLASMIN COPPER AS A DIAGNOSTIC TEST FOR WILSON DISEASE IN ACUTE LIVER FAILURE

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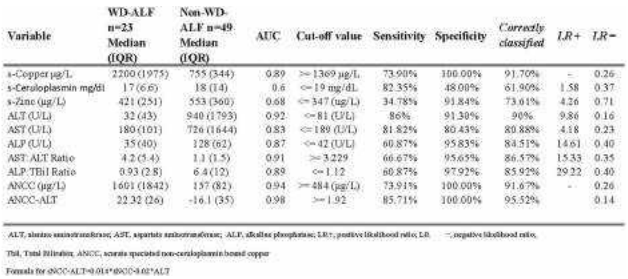
Background: Diagnosing Wilson disease (WD) presenting as acute liver failure (ALF-WD) is challenging but important as there are disease specific therapies to try to stabilize the patient while awaiting emergency liver transplantation. Methods for early diagnosis in adults, the alkaline phosphatase (ALP) to total bilirubin and AST to ALT ratios at presentation are readily available and provide acceptable diagnostic accuracy (Korman et al Hepatology 2008), while low serum zinc seems informative in children (Sintusek et al J Pediatr Gastroenterol Nutr 2016). Recently, a new method, the A*ccurate Non-Ceruloplasmin Copper* (ANCC) was developed (Solovvev et al Anal Chim Acta 2020). The **Aim** of this study was to determine the diagnostic utility of ANCC in the setting of acute ALF-WD, and explore other factors that may aid diagnostic accuracy in this setting. **Methods:** Serum samples and data were collected at admission from adult patients prospectively enrolled in the U.S. ALF Study. ANCC was measured by strong anion exchange chromatography coupled to triple quadrupole inductively coupled plasma mass spectrometry. Receiver operating characteristic analysis was performed for candidate variables. Using logistic regression analysis, a simple combined score of ANCC and ALT was developed (ANCC-ALT score). **Results:** ALF study patients with WD (23), acetaminophen (11), autoimmune (10), drug induced liver injury (13), and other etiologies (15)) were included in the study. Serum copper (s-Cu) and ANCC measurements were strongly correlated ($r = 0.76$, $P < 0.001$) in patients with ALF. ANCC (> 484 µg/L) was superior in identifying ALF-WD (AUROC of 0.94, Table). High s-Cu (> 1369 µg/L) and low ALP (≤ 42 (U/L)) and ALT (≤ 81 (U/L)) provided relevant diagnostic information with AUROC´s > 0.87. Combining ANCC and ALT into one score improved diagnostic accuracy, AUROC 0.98, sensitivity 85% and specificity 100% using a cutoff of 1.92. Serum ceruloplasmin was not statistically significantly lower in WD-ALF compared to other ALF etiologies. Adding ALP:total bilirubin ratio or AST:ALT ratio or serum zinc to ANCC did not improve the diagnostic yield for ALF-WD **Conclusion:** In ALF-WD, most s-Cu is not bound to ceruloplasmin. Both s-Cu and ANCC, with use of appropriate cutoff values, are100% specific for diagnosing WD-ALF. Sensitivity for diagnosis of ALF-WD was further increased using ANCC-ALT while maintaining 100% specificity. In adults with ALF, low serum zinc was not diagnostic for ALF-WD.



Variable	WD-ALF n=23 Median (IQR)	Non-WD-ALF n=49 Median (IQR)	AUC	Cut-off value	Sensitivity	Specificity	*Correctly classified*	*LR+*	*LR−*
s-Copper µg/L	2200 (1975)	755 (344)	0.89	>=1369 µg/L	73.90%	100.00%	91.70%	-	0.26
s-Ceruloplasmin mg/dl	17 (6.6)	18 (14)	0.6	<=19 mg/dL	82.35%	48.00%	61.90%	1.58	0.37
s-Zinc (µg/L)	421 (251)	553 (360)	0.68	<=347 (µg/L)	34.78%	91.84%	73.61%	4.26	0.71
ALT (U/L)	32 (43)	940 (1793)	0.92	<=81 (U/L)	86%	91.30%	90%	9.86	0.16
AST (U/L)	180 (101)	726 (1644)	0.83	<=189 (U/L)	81.82%	80.43%	80.88%	4.18	0.23
ALP (U/L)	35 (40)	128 (62)	0.87	<=42 (U/L)	60.87%	95.83%	84.51%	14.61	0.40
AST:ALT Ratio	4.2 (5.4)	1.1 (1.5)	0.91	>=3.229	66.67%	95.65%	86.57%	15.33	0.35
ALP:TBil Ratio	0.93 (2.8)	6.4 (12)	0.89	<=1.12	60.87%	97.92%	85.92%	29.22	0.40
ANCC (µg/L)	1601 (1842)	157 (82)	0.94	>=484 (µg/L)	73.91%	100.00%	91.67%	-	0.26
ANCC-ALT	22.32 (26)	-16.1 (35)	0.98	>=1.92	85.71%	100.00%	95.52%		0.14

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; LR+, positive likelihood ratio; LR −, negative likelihood ratio;

TBil, Total Bilirubin; ANCC, accurate speciated non-ceruloplasmin bound copper

Formula for aNCC-ALT=0.014*aNCC-0.02*ALT

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3301-A | ALCOHOL AND THE LIVER PHENOTYPE OF ADULTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY

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Background: Alpha-1 antitrypsin deficiency (AATD) arises from mutations in *SERPINA1* and predisposes to liver cirrhosis. However, the liver phenotype is variable and modifying factors are poorly understood. We studied the impact of alcohol consumption on liver-related parameters in individual's with the characteristic heterozygous/homozygous Pi*Z variant (Pi*MZ/Pi*ZZ genotype) found in the community-based United Kingdom Biobank (UKB) and the European Alpha1 liver consortium. **Methods:** Anamnestic data on alcohol consumption were evaluated in 17 145 Pi*MZ and 141 Pi*ZZ subjects as well as 425 002 non-carriers (Pi*MM) from the UKB. 561 Pi*ZZ individual's from the Alpha1 liver consortium were assessed including a measurement of carbohydrate deficient transferrin (CDT). Non-transgenic and Pi*Z mice were subjected to Lieber-DeCarli (LDC) diet. **Results:** $> 80\%$ of individual's reported no/low alcohol intake, while harmful consumption (women $\geq$ 40g/d, men $\geq$ 60g/d) was rare (~1% in most groups). In UKB participants with Pi*MM/Pi*MZ genotype, significant alcohol consumption (women 12-39 g/d, men 24-59 g/d) resulted only in a $< 30\%$ increase in transaminases above the upper limit of normal (ULN), while the effect on GGT was more pronounced (Pi*MM: 15.0% vs. 23.0%; Pi*MZ: 15.7% vs. 22.5%). In both genotypes, harmful alcohol intake led to an at least twofold increase in the proportion of Pi*MM/Pi*MZ subject with elevated transaminases, GGT serum levels, and elevated AST-to-platelet ratio (APRI). In Pi*ZZ individual's from both cohorts, moderate alcohol intake had no obvious impact on transaminase serum levels, although GGT levels were numerically more frequently elevated. In the European cohort, Pi*ZZ subjects with moderate alcohol consumption tended to have higher continuous attenuation parameters (CAP) suggestive of liver steatosis. 14% of Pi*ZZ individual's had elevated CDT serum levels ($\geq$ 1.7%). In univariable analysis, they displayed higher GGT levels (72.5 vs. 60.0 % ULN, $p = 0.011$) and APRI scores (0.36 vs. 0.30 units, $p = 0.006$). Among Pi*ZZ individual's from the European cohort who reported no/low alcohol consumption, those with increased CDT levels more often had signs of advanced liver disease. LDC diet did not increase AAT accumulation in Pi*Z mice, while its impact on collagen mRNA was similar in both genotypes. **Conclusion:** Moderate alcohol consumption seems to be tolerated in the majority of Pi*MZ and Pi*ZZ subjects. CDT values might be helpful in those with advanced fibrosis.

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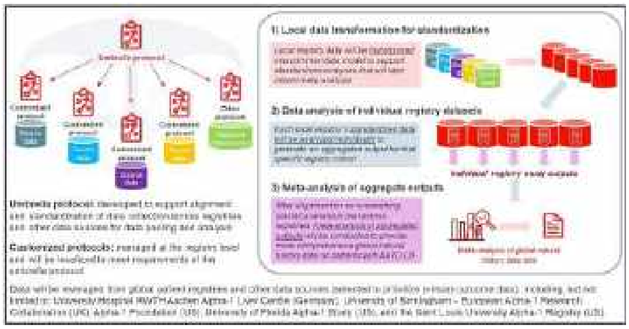
3302-A | ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE: A GLOBAL RETROSPECTIVE NATURAL HISTORY STUDY

Pavel Strnad[1], Jeffrey Teckman[2], Alice Turner[3], Jen-Chieh Chuang[4], May Hagiwara[4], Chitra Karki[4], Ed G. Marins[4], Kaili Ren[4], Anne E. Wyman[4], Angel Valladares[5], Monica P. Goldklang[6], Jeanine M. D'Armiento[6] and Virginia Clark[7], (1)University Hospital Rwth Aachen, Aachen, Germany, (2)Saint Louis University, St Louis, Missouri, US, (3)University of Birmingham, Birmingham, United Kingdom, (4)Takeda Development Center Americas, Inc., Cambridge, MA, USA, (5)Iqvia, New York, NY, USA, (6)Columbia University Irving Medical Center, New York, NY, (7) University of Florida, Gainesville, FL, USA

Background: Alpha-1 antitrypsin deficiency-associated liver disease (AATD-LD) is a rare genetic disease that is often initially asymptomatic and is underdiagnosed. The protease inhibitor (Pi) ZZ genotype confers the greatest risk of AATD-LD, and a liver transplant is the only way to resolve advanced disease. Owing to a lack of robust natural history data, our study aims to leverage real-world data using innovative methodology to examine the natural history of AATD-LD. **Methods:** This is a retrospective, longitudinal, multicenter, observational cohort study in adults with a confirmed diagnosis of AATD-LD and a documented Pi*MZ, Pi*SZ, or Pi*ZZ genotype. The study will leverage data from multiple registries and other data sources from the EU, UK, and US. An umbrella protocol approach will enable standardized definitions and methodology for data pooling and analyses, and customized protocols will enable the generation of standardized, aggregated outputs from each data source (Figure). Outcomes of interest include disease progression (advancement by ≥ 1 fibrosis stage, incidence of liver disease-related clinical events, or ≥ 3-point increase in Model for End-Stage Liver Disease score), all-cause mortality, and disease regression (decrease in ≥ 1 fibrosis stage). The study will also examine pulmonary function, diagnostic and monitoring patterns, health-related quality of life, and healthcare resource utilization. Analyses of outcomes by genotype and baseline fibrosis stage will also be conducted. All analyses will be summarized using descriptive statistics, except for time to disease progression which will be analyzed using Kaplan–Meier estimates. Meta-analysis of aggregated data will provide further insights into AATD-LD natural history. **Results:** The study began in Sept-2022, with finalization of the umbrella protocol and statistical analysis plan estimated by Sept-2023. Reporting of preliminary data from customized protocols is estimated in 2024 and the final meta-analysis in 2025. Additional registries and clinically rich data sources will be explored and added to the meta-analysis. **Conclusion:** Natural history studies of rare diseases using *de novo* registries are challenging. This study's umbrella protocol design and meta-analysis will leverage global patient registries and other data sources to generate comprehensive and robust insights into the natural history of AATD-LD and inform drug development, patient care, and disease monitoring. Writing assistance was provided by Matthew Reynolds of Oxford PharmaGenesis, Oxford, UK and funded by Takeda Development Center Americas, Inc.


1) Local data transformation for standardization
2) Data analysis of individual registry datasets
3) Meta-analysis of aggregate outputs

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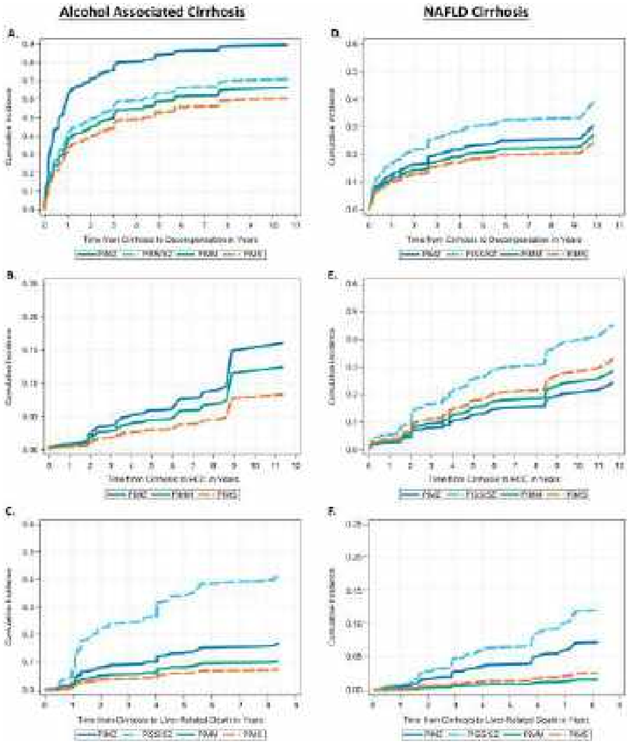
f 3303-A | ALPHA-1 ANTITRYPSIN PIMZ, PISS AND PISZ PHENOTYPES ARE ASSOCIATED WITH INCREASED LIVER RELATED DEATH IN ALCOHOL-ASSOCIATED AND NAFLD CIRRHOSIS

Sunny Sandhu[1], Dustin R Bastaich[2], David E. Kaplan[3], Tamar H. Taddei[4], Bassam Dahman[2], Binu V John[5] and VOCAL group of investigators, (1)University of Miami - Jackson Memorial Hospital, Miami, FL, (2)Virginia Commonwealth University, (3)Division of Gastroenterology and Hepatology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA, (4)Yale University, New Haven, CT, (5)University of Miami and Miami VA Health System, Miami, FL

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



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

Clavia R. Wooton-Kee[1], Ahmed Elsayed[1], Islam Mohamed[1], Fuad Zain Aloor[1], Prasun Jalal[1], Kenneth David Reginald Setchell[2], Ayse Coskun[3], Monica Narvaez-Rivas[4], Nagireddy Putluri[1], Michael L. Schilsky[3] and David D. Moore[5], (1)Baylor College of Medicine, (2)Cincinnati Children's Hospital Medical Center, Cincinnati, OH, (3)Yale School of Medicine, New Haven, CT, (4)Cincinnati Children's Hospital Medical Center, Cincinnati, OH, (5)University of California, Berkeley

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

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

(UPLC-MS/MS) in *Atp7b*$^{-/-}$, DKO$^{Atp7b:FXR}$, and wild-type mice, as well as healthy and WD males (WD-treatment positive) aged 26-65 (Baylor College of Medicine and Wilson's Disease Registry). **Results**: ECM-Receptor Interaction, Bile Secretion, and Tryptophan Metabolism were the most represented transcriptome pathways in *Atp7b*$^{-/-}$ vs. wild-type mice. Global hepatic FXR-binding events were reduced 22% in *Atp7b*$^{-/-}$ vs. wild-type mice ($p < 0.01$), supporting previous findings of reduced FXR activity in *Atp7b*$^{-/-}$ mice. FXR binding status revealed that positive FXR binding in upregulated genes mapped to the Focal Adhesion pathway and negative FXR binding in decreased genes mapped to the Metabolic pathway, which agrees with dysregulation of hepatic FXR activity and metabolic homeostasis. Tauro-cholic acid (T-CA), tauro-chenodeoxycholic acid (T-CDCA), and tauro-α/β-muricholic acid (T-MCA) bile acid concentrations were changed in *Atp7b*$^{-/-}$ mice: T-CA (13-fold increase, $P = 0.002$, serum; 1.6-fold, $P = 0.005$, liver); T-CDCA (10-fold, $p = 0.02$, serum); T-MCA (71-fold increase, $P = 0.006$, serum; 55% decrease, $P = 0.005$ liver). Expression of the bile acid-FXR regulated target genes Ostβ and Fgf15 was decreased in the small intestine of *Atp7b*$^{-/-}$ mice, which suggests impairment of bile flow. Changes in bile acid composition were exacerbated in *Atp7b:FXR* double knockout (DKO$^{Atp7b:FXR}$), indicating that *Atp7b*$^{-/-}$ mice retained partial FXR activity. Total bile acid measurement in serum of WD patients vs. healthy controls was not significantly changed (5-fold increase, $P = 0.2$). Comparison of bile acid profiles in WD patients with "liver", "neurological", or "mixed" disease vs. healthy controls revealed increased T-CDCA (39-fold increase, $P = 0.0002$) and glyco-CDCA (7.8-fold increase, $P < 0.0001$) in WD-liver vs. healthy controls. **Conclusion**: *Atp7b*$^{-/-}$ mice and WD patients exhibited changes in bile acid speciation, which is likely due to FXR dysfunction.These findings provide new insight into possible aberrant bile acid homeostasis in WD patients.

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Kenneth David Reginald Setchell – Asklepion Pharmaceuticals: Stock – privately held company (individual stocks and stock options), Yes, No; Travere Therapeutics: Consultant, Yes, No; Mirum Pharmaceuticals: Consultant, No, No; Aliveris s.r.l, Italy: Stock – privately held company (individual stocks and stock options), No, No;

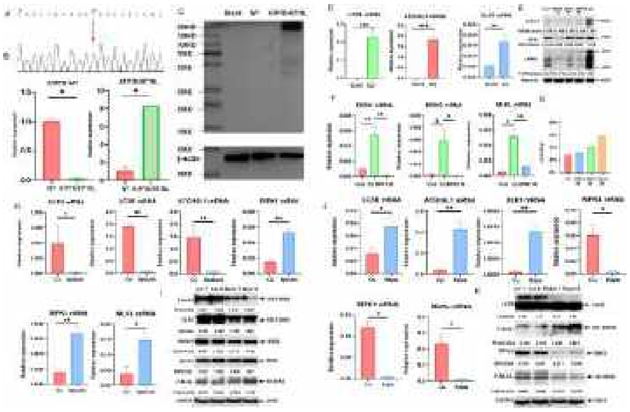
The following people have nothing to disclose: Ahmed Elsayed, Islam Mohamed, Fuad Zain Aloor, Ayse Coskun

Disclosure information not available at the time of publication: Monica Narvaez-Rivas, Nagireddy Putluri, Michael L. Schilsky, David D. Moore

3305-A | ATP7B R778L MUTANT HEPATOCYTES RESIST COPPER TOXICITY BY ACTIVATING AUTOPHAGY AND INHIBITING NECROPTOSIS

Shan Tang[1], *Chen Liang*[1], *Wei Hou*[1], *Zhongjie Hu*[1], *Xinyue Chen*[1], *Jing Zhao*[1], *Zhongping Duan*[2], *Li Bai*[1,3] *and Sujun Zheng*[1], *(1)Capital Mecical University Beijing Youan Hospital, (2)Beijing Youan Hospital Capital Medical University, Beijing, China, (3)Beijing Key Laboratory of Liver Failure and Artificial Liver Treatment Research, Beijing, China*

Background: Wilson's disease (WD) is an inherited disease characterized by copper metabolism disorder caused by the mutations in adenosine triphosphatase copper transporting β gene (ATP7B). Currently, WD cell and animal model targeting the most common R778L mutation in Asia is lacking. In addition, the mechanisms by which hepatocytes resist copper toxicity remain to be further elucidated. In this study, we aimed to construct a novel WD cell model with R778L mutation, and dissected the molecular basics of copper resistance. **Methods:** A novel HepG2 cell line stably expressing ATP7B R778L gene (R778L cell) was constructed. The expression of necroptosis- and autophagy-related molecules was detected by PCR and Western blot (WB) in wild-type (WT) HepG2 and R778L cells with or without $CuSO_4$ treatment. In addition, we detected and compared the levels of autophagy and necroptosis in $CuSO_4$-treated R778L cells with the activation and inhibition of autophagy. Moreover, the mRNA and protein levels of autophagy and necroptosis signaling molecules were compared in R778L cells with the overexpression and knockdown of Unc-51 Like Autophagy Activating Kinase 1 (ULK1) and Autophagy Related 16 Like 1 (ATG16L1). **Results:** We constructed successfully a R778L mutation HepG2 cell line. $CuSO_4$ triggered the enhanced expression of autophagy and necroptosis signaling molecules in WT HepG2 cells and R778L cells. Remarkably, higher levels of autophagy and necroptosis were observed in R778L cells compared with those in WT cells. Autophagy activation led to weaken necroptosis mediated by RIPK3 and MLKL, conversely, autophagy inhibition brought about enhanced necroptosis. At the molecular level, ULK1- and ATG16L1-overexpression resulted in reduced necroptosis level, and vice versa. **Conclusion:** ULK1- and ATG16L1-mediated autophagy activation protects hepatocytes against RIPK3- and MLKL-mediated necroptosis in our new WD cell model treated with $CuSO_4$. Targeted therapy by autophagy activation or necroptosis inhibition maybe a novel and effective strategy to treat WD.



Disclosures: The following people have nothing to disclose: Shan Tang, Chen Liang, Wei Hou, Zhongjie Hu, Xinyue Chen, Jing Zhao, Zhongping Duan, Li Bai, Sujun Zheng

3306-A | BELCESIRAN WAS WELL-TOLERATED AND REDUCED SERUM AAT LEVELS IN HEALTHY VOLUNTEERS IN A PHASE 1 STUDY: FINAL RESULTS

Michael Soliman[1,2], Dhruv Patel[1], Anne-Sophie Sejling[1,2], Mohamed Tawfik[2], Miao Yu[1] and Folke Sjoberg[3], (1)Novo Nordisk, (2)Novo Nordisk a/S, (3)TC Clinical Trial Consultants AB, Linköping University

Background: Alpha-1 antitrypsin deficiency (A1ATD) is a rare disease that leads to alpha-1 antitrypsin protein (AAT) misfolding, which may cause liver disease. Belcesiran is a novel Dicer-substrate small interfering RNA oligonucleotide that is designed to silence the mutant SERPINA1 gene in individual's with A1ATD. Here, we report long-term, final results from a first-in-human, Phase 1 study of belcesiren. **Methods:** This was a single ascending dose study in healthy volunteers (HVs; NCT04174118) randomized 2:1 to a single subcutaneous injection of belcesiran (0.1, 1.0, 3.0, 6.0 or 12.0 mg/kg) or placebo and followed until Day 57/end-of-treatment (EOT). At EOT, if serum AAT had not returned to ≥80% of baseline, HVs entered an additional, conditional follow-up period until serum AAT returned to ≥80% baseline. Overtly healthy, non-smoking males or females aged 18–55 years with serum AAT > 100 mg/dL, forced expiratory volume in one second (FEV1)/forced vital capacity ≥0.7 and FEV1 ≥85% predicted were eligible. The primary endpoints were safety and tolerability. Change in AAT concentration was a secondary endpoint. Spirometry and diffusing capacity of the lungs for carbon monoxide (DLCO) were performed to monitor pulmonary function. **Results:** Overall, 30 HVs were enrolled. Mean age was 36.7 years, most were male (n = 27). Robust, dose-dependent reductions in serum AAT were observed with belcesiran (Figure). Mean reduction from baseline ranged from 48–78% with belcesiran 1.0–12.0 mg. An average serum AAT reduction of > 70% was sustained for at least 12 weeks in the 6.0 mg/kg and 12 mg/kg cohorts. All HVs who completed the study and the conditional follow-up returned to AAT levels ≥80% baseline. No serious adverse events (AEs) were reported. 40 treatment-emergent AEs (TEAEs) occurred in 21 HVs (37 events [Grade 1], 3 events [Grade 2], 0 [Grade ≥3]). Grade 2 events were nasopharyngitis in 1 HV in the 0.1 mg/kg cohort and gastroenteritis and staph skin infection in 1 HV in the 6 mg/kg cohort. The most common TEAEs were injection site reactions (5/20 [belcesiran], 0/10 [placebo]) and headache (4/20 [belcesiran], 2/10 [placebo]). Twelve HVs experienced TEAEs that were considered treatment-related in the belcesiran group, all were mild severity (Grade 1). No clinically significant abnormalities in lung function were reported. **Conclusion:** In this first-in-human Phase I study, belcesiran was well-tolerated with dose-dependent and reversible effects on serum AAT levels in HVs.

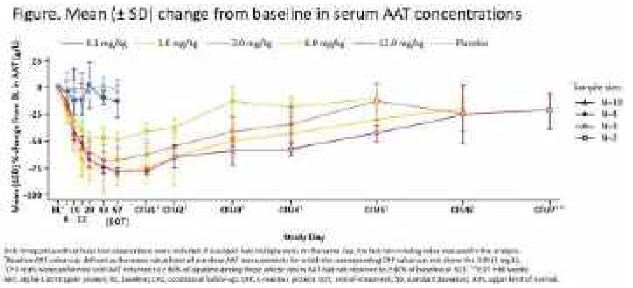


Figure. Mean (± SD) change from baseline in serum AAT concentrations

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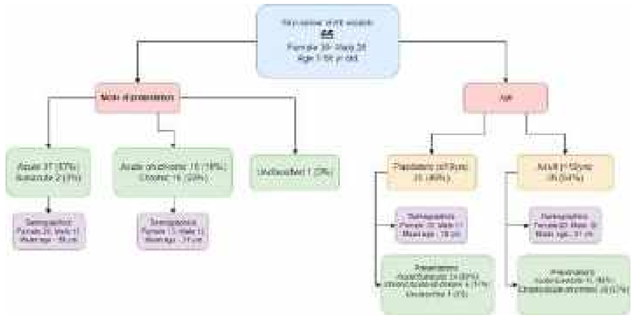
Mohamed Tawfik – Novo Nordisk: Employee, No, No; Novo Nordisk: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
Miao Yu – Novo Nordisk: Employee, No, No; Novo Nordisk: Stock – privately held company (individual stocks and stock options), No, No;
The following people have nothing to disclose: Folke Sjoberg

3307-A | BETTER UNDERSTANDING THE NATURAL HISTORY OF WILSON'S DISEASE THOUGH EXPLANT HISTOLOGY–PRELIMINARY ANALYSIS AND EXPERIENCE FROM A UK TERTIARY TRANSPLANT CENTRE

James Liu Yin, Deepak Joshi, Marianne Samyn, Varuna Aluvihare, Anil Dhawan, Rosa Miquel and Aftab Ala, King's College Hospital

Background: Wilson's disease (WD) is a life changing genetic metabolic condition that can present across many organ systems with devastating presentations e.g. acute liver failure, dysphasia and acute psychosis. Histological analysis of liver tissue is a key part of identifying WD and forms part of the diagnostic criteria of the internationally validated Leipzig scoring system. However, the significant variation and non-specific findings in histological appearance often proves a diagnostic challenge. King's College Hospital (KCH), London has the largest cohort of transplanted and non-transplanted adult and paediatric WD patients in the UK. Our aim is to perform a descriptive study of explant histology at KCH and correlate this with clinical presentation and disease progress. **Methods:** We reviewed explant histology of all patients transplanted for WD since 1990. Diagnosis of WD was made by a combination of genetics, clinical symptoms and biochemistry. We collected clinical data on these patients to confirm WD, exclude other liver conditions and to calculate the Leipzig score. All explants were independently assessed with an expert liver histopathologist to identify key histological features and correlate with clinical presentation. **Results:** We identified 65 explants from patients transplanted for WD (Figure 1). Preliminary findings showed a distinct histological pattern for acute, acute on chronic and chronic WD presentation and interestingly we found these findings did not fully correlate with their prior reported clinical presentation. Whilst commonly described features of WD such as female preponderance, steatosis, vacuolated nuclei and tissue copper staining were seen in most cases, there was significant variation on relative amount and distribution of lesions across the samples. Of particular note, was the unique combined micro-and-microvacuolar steatosis seen in discrete nodules, often in isolation. There was also a wide spectrum of distinct collapse/fibrosis seen across acute presentations, a key feature that requires further clarification. We identified marked variation in common histological findings between explants that we suspect is due to the multifactorial effects of age, treatment and other co-morbid factors potentially triggering decompensation. **Conclusion:** Histological examination of the explanted livers of patients with WD has confirmed the presence of previously described, non-specific, but characteristic microscopic lesions that we have compared with clinical presentation. Histological analysis correlated to clinical features could prove to be the key gateway to better understanding of the natural history, pathogenesis and characterisation of the unique presentations of WD requiring transplantation. Further international collaborative work is needed to achieve this goal which could expand to investigating response to treatment and disease progression at a cellular level.



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Disclosure information not available at the time of publication: Deepak Joshi, Marianne Samyn, Varuna Aluvihare, Anil Dhawan, Aftab Ala

f 3308-A | CHARACTERISTICS OF PATIENTS TREATED WITH GIVOSIRAN IN ELEVATE, A GLOBAL OBSERVATIONAL LONGITUDINAL REGISTRY OF PATIENTS WITH ACUTE HEPATIC PORPHYRIA

Bruce M. Wang[1], David Cassiman[2], Laurent Gouya[3], Eliane Sardh[4], Yanling Hu[5], Ana Camejo[5], Tom Brown[5] and Manisha Balwani[6], (1)University of California San Francisco Medical Center, (2)University Hospital Leuven, (3)Centre Français Des Porphyries, (4) Porphyria Centre Sweden, Centre for Inherited Metabolic Diseases, Karolinska Institutet, Karolinska University Hospital, (5)Alnylam Pharmaceuticals, (6) Icahn School of Medicine at Mount Sinai

Background: Acute hepatic porphyria (AHP) is a group of rare, chronic, multisystem disorders with acute attacks, progressive elements, and long-term complications. The ELEVATE registry (NCT04883905) is a global, prospective, observational real-world data collection study designed to investigate the natural history and management of patients with AHP and characterize the long-term safety and effectiveness of givosiran, an RNA interference therapeutic approved for the treatment of AHP in adults in the US and adults and adolescents age ≥12 years in the EU. This analysis

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

describes characteristics at enrollment of patients with AHP that have ever been treated with givosiran. **Methods:** Registry patients have a documented AHP diagnosis with biochemical and/or genetic testing, are managed as per standard of care, and no study-related procedures are recommended; medication is not provided. Data are collected at least once every 12 months via patient-reported outcome questionnaires, routine clinical encounters for AHP, or medical records. **Results:** A total of 84 patients that were ever treated with givosiran were enrolled (acute intermittent porphyria, N = 75; variegate porphyria, N = 6; hereditary coproporphyria, N = 2; type not reported, N = 1) as of March 2, 2023. Median (range) ages at AHP symptom onset, AHP diagnosis, and study consent were 29 (6–63), 30 (5–63), and 42 (14–71) years, respectively. The majority of patients are age ≥ 18 years (97.6% [82/84]), female (86.9% [73/84]), and white (77.4% [65/84]). Twenty-eight (33.3%) patients ever received medications other than givosiran for AHP; 25.0% had received hemin prophylaxis. Fourteen (16.7%) patients have history of chronic kidney disease and 10 (11.9%) had history of liver disease. The most common comorbid conditions at enrollment were anxiety (28.6% [24/84]), hypertension (27.4% [23/84]), and depression (20.2% [17/84]). The most frequently reported AHP symptoms upon ELEVATE enrollment were pain (47.6% [40/84]), nausea (31.0% [26/84]), fatigue (29.8% [25/84]), tingling, numbness, weakness or paralysis (26.2% [22/84]), and anxiety (23.8% [20/84]). **Conclusion:** These initial data from ELEVATE in patients with AHP ever treated with givosiran characterize comorbidities and symptoms in this population at enrollment. ELEVATE will enhance understanding of the natural history and management of patients with AHP, and the long-term safety and effectiveness of givosiran for AHP treatment.

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Yanling Hu – IQVIA: Consultant, Yes, No;

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Tom Brown – Alnylam Pharmaceuticals: Employee, Yes, No; Alnylam Pharmaceuticals: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

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3309-A | CLINICAL CHARACTERIZATION OF PATIENTS WITH WILSON'S DISEASE AT LEIPZIG UNIVERSITY MEDICAL CENTER

Magdalena Hahn[1], Johannes Wiegand[1], Madlen Matz-Soja[1], Maja Schirmer[1] and Thomas Berg[2], (1)Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany, (2) University Hospital of Leipzig

Background: Wilson's disease (WD) is rare and patients are referred to tertiary centers for treatment. We aimed to characterize the patient cohort at Leipzig University Medical Center regarding the use of the Leipzig Score for diagnosis, long-term outcome and especially the course of treatment in a real-world setting. **Methods:** All WD outpatients from Leipzig University Medical Centre, Division of Hepatology, from 2011-2020 were included. Data were anonymously and retrospectively collected from patients' records using the REDCap software. **Results:** A total of 34 patients were included, of which 20 were female. The majority (n = 13) presented with WD diagnosis, that was established earlier at different centers. In 50% data about establishment of diagnosis was lacking. In 4 cases WD was diagnosed at Leipzig

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

University Medical Center. Phenotype at establishment of Wilson's disease was mostly neurologic/psychiatric (n = 13), with (n = 5) and without concomitant liver disease (n = 2) and without investigation of liver disease (n = 6). 10 Patients presented with chronic liver disease and 5 patients with an acute liver failure. Diagnosed after family screening were 3 patients. One patient presented with Keyser-Fleischer corneal ring as single symptom. Liver biopsy was performed in 8 patients and molecular genetic analysis of ATPase7B gene mutations were evaluated in 8 patients. In none of the patients the Leipzig Score was performed as part of the initial diagnostic work-up. As initial treatment D-Penicillamin (DPA) was chosen in 25 patients, Trientine Dihydrochloride (TRI) in 5 patients, Zinc in two patients and combination of TRI and Zinc as well as DPA and Zinc in one patient respectively. No patient received Trientine Tretrahydrochloride as first medication. Half of the patients never changed medication in the course of disease (DPA n = 12, TRI n = 4, Zinc n = 1). Reasons for treatment modifications were side effects (28.2%), insufficient treatment response (25.6%), pregnancy (10.3%), insufficient adherence to treatment (5.1%) and others (36%). In the long-term follow-up, none of the patients suffered from acute or chronic liver failure, hepatocellular carcinoma, or required liver transplantation. At the end of follow-up liver cirrhosis was present in 19 patients and half of all patients had liver enzymes above upper limit of normal. A resolution of clinical symptoms was observed in less than half of all patients (n = 16). **Conclusion:** Albeit different available treatment options for WD, more than half of the patients developed liver cirrhosis and less than half of patients report resolution of clinical symptoms. Main reasons for changes in therapy are side-effects and insufficient therapy response, which highlight the importance of regular follow-up and screening for side-effects.

Disclosures: The following people have nothing to disclose: Magdalena Hahn, Johannes Wiegand, Madlen Matz-Soja, Maja Schirmer, Thomas Berg

3310-A | COMPARISON OF NON-CERULOPLASMIN COPPER ASSESSED BY PROTEIN SPECIATION (NCC-SP) AND EXCHANGEABLE COPPER (NCC-EX) IN ADULTS WITH WILSON DISEASE ENROLLED IN A RANDOMIZED TRIAL OF CHELATION THERAPY (CHELATE; NCT 03539952).

Peter Ott[1], Thomas Damgaard Sandahl[1], Omar F Kamlin[2], Michael L. Schilsky[3] and On Behalf of the CHELATE Trial Investigators, (1)Aarhus University, (2) Orphalan, (3)Yale University

Background: Non-ceruloplasmin bound copper (NCC) is the bioavailable or "exchangeable" (Cu) fraction in blood. Current guidelines(1) recommend a treatment target of 50-150 μg/L in patients with Wilson disease (WD). The Chelate trial enrolled 53 clinically stable WD patients on maintenance D-penicillamine (DPA) (2). After a 12-week run-in period, patients were randomized to either continue DPA (N = 27) or mg-to-mg change to trientine tetrahydrochloride (TETA4;N = 26) for 24 weeks study period + 24 weeks extension. The sponsor (Orphalan, France) planned to use NCC-Ex(3) to guide treatment and as primary endpoint. That was rejected by FDA so a new method, NCC-Sp(4), was developed and batch analyzed for the primary endpoint. Aim: We aimed to examine the relationship between NCC-Sp and NCC-Ex and its development over time during chelator treatment. **Methods:** Samples were collected at 4 weekly intervals from the initial screening test until primary endpoint (week 24 post-randomization) with a final sample at the end of the extension period (week 48). Cu was determined by ICP-MS. NCC-Sp is the measured ceruloplasmin-Cu following speciation of serum proteins by anion-exchange HPLC subtracted from total serum Cu(4). NCC-Ex utilized chelation of the NCC fraction by adding ETDA to serum to effect removal of loosely bound copper to proteins by ultracentrifugation. NCC-Ex was assessed in the filtrate (3). **Results:** Of 541 paired determinations of NCC-Sp and NCC-Ex (325 on DPA, 216 on TETA4), 28% of NCC-Sp and 48% of NCC-Ex were < 50 μg/L. NCC-Sp and NCC-Ex were strongly correlated without treatment effects (Figure). As judged by linear regression, the NCC-Ex/NCC-Sp ratio depended on NCC-Sp level: NCC-Sp 25μg/L, ratio 1.2; 50 μg/L, 0.97; 75μ/L, 0.84; 100μg/L, 0.77; 200μg/L, 0.67. In patients exclusively exposed to DPA (DPA arm;N = 27), NCC-Sp and NCC-Ex differed over time (Fig. Panel C). NCC-Ex was less variable than NCC-Sp which was more dynamic despite only minor dose changes (N = 4), partly explained by the relation of NCC-Sp level vs NCC-Ex/NCC-Sp ratio. The same relation was observed in the TETA4 arm (not shown). **Conclusion:** Values below 50μg/L in 28% to 48% suggest the need for revised and methodology specific target ranges for NCC-Sp and NCC-Ex. Though NCC-Sp and NCC-Ex strongly correlated, NCC-EX/NCC-Sp ratio was not constant. The deviation between these two methodologies to measure NCC challenges the interpretation of the dynamic change in NCC during the monitoring of treatment. Better understanding of these differences may help optimize treatment monitoring.

1. Schilsky ML et al Hepatology 2023;77:1428-1455.

2. Schilsky ML et al. Lancet Gastroenterol Hepatol 2022.
3. El Balkhi S et al Anal Bioanal Chem 2009;394:1477-1484.
4. Del Castillo Busto ME et al. Anal Bioanal Chem 2021

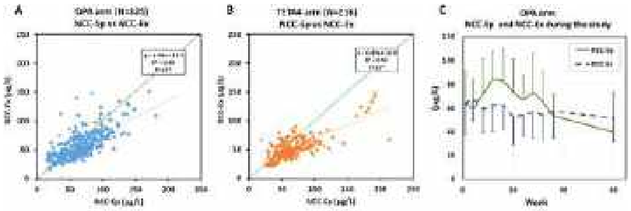


Figure. Comparison of Non-ceruloplasmin bound Copper by protein speciation (NCC-Sp) and Exchangeable Copper (NCC-Ex) during the CHELATE study. In Panels A and B the line of identity is dotted green and regression line in symbol colors. DPA: D-Penicillamine. TETA4: trientine 4HCl.

Disclosures: Peter Ott – Alexion: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Univar: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Vivet: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Orphalan: Speaking and Teaching, Yes, Yes;
Thomas Damgaard Sandahl – Vivet Therapeutics: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Orphalan: Speaking and Teaching, Yes, No; Univar: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Alexion: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Prime: Consultant, No, No; Arbomed: Consultant, No, No;
Omar F Kamlin – Orphalan: Employee, Yes, No;
Michael L. Schilsky – Alexion: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Orphalan: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Vivet Therapeutics: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Wilson Disease Association: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Arbomed: Consultant, No, No;

3311-A | CORRELATION BETWEEN AGE AND PROGRESSION OF LIVER DISEASE IN PATIENTS WITH LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D): DATA FROM THE INTERNATIONAL LAL-D REGISTRY

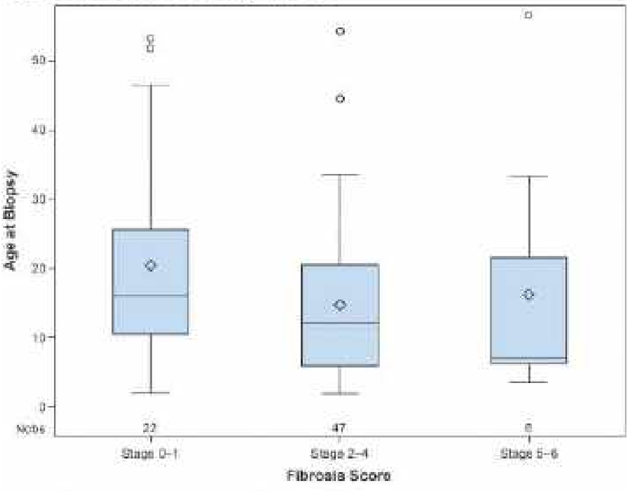
William F. Balistreri[1], Jennifer Evans[2], Florian Abel[2] and Lorenzo D'Antiga[3], (1)Cincinnati Children's Hospital Medical Center, Cincinnati, OH, (2)Alexion, Astrazeneca Rare Disease, (3)Azienda Ospedaliera Papa Giovanni XXIII

Background: Lysosomal acid lipase deficiency (LAL-D) is a rare, hereditary, lysosomal storage disease that may present at any age and can be associated with progressive chronic liver disease, liver fibrosis, and eventually cirrhosis. We analyzed data from the International LAL-D Registry to determine biopsy-assessed liver fibrosis severity and the use of the aspartate aminotransferase (AST) to platelet ratio index (APRI) as a noninvasive indicator of fibrosis severity. **Methods:** This was a retrospective observational study of treatment-naive children and adults with confirmed LAL-D identified from the LAL-D Registry (NCT01633489) through Apr 3, 2023. Patients with rapidly progressive (infantile) LAL-D were excluded. The age x fibrosis analysis utilized the first available Ishak-staged biopsy (or pathology score if Ishak stage was unavailable) for each patient and age at time of biopsy. The APRI x fibrosis analysis utilized the first available staged biopsy for patients with a corresponding APRI, which was based on AST and platelet levels obtained on the same day, and within 12 months prior to or one month post biopsy. Pre-treatment biopsies performed as part of the clinical program for sebelipase alfa were included. **Results:** Of 239 patients with available data, 77 had ≥ 1 staged liver biopsy (male, 60%; white, 90%); age: < 12 y, $n = 36$; $\geq 12 - < 18$ y, $n = 15$; ≥ 18 y, $n = 26$). Patients aged < 12 y tended to have a higher fibrosis stage than patients ≥ 12 y (ordinal regression using trichotomized fibrosis categories [stage 0−1, 2−4, and 5−6] odds ratio 2.71 [95% CI, 1.05−7.00]; $P = 0.039$). Median age tended to be lower with increasing fibrosis stage (Figure); however, analysis of variance showed no statistically significant

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

difference in average age among trichotomized fibrosis scores ($P = 0.2732$). Among 43 patients with biopsy fibrosis stage and corresponding APRI (male, 56%; white, 88%), median (Q1, Q3) APRI did not differ by fibrosis stage: stage 0 (0.40 [0.40, 0.40]; n = 1), stage 1 (0.88 [0.45, 1.06]; n = 9), stage 2 (0.55 [0.42, 0.82]; n = 9), stage 3 (0.47 [0.44, 0.71]; n = 13), stage 4 (0.42 [0.25, 1.06]; n = 4), stage 5 (0.42 [0.30, 0.55]; n = 2), stage 6 (0.73 [0.55, 1.50]; n = 5). Only two (40%) of five patients with stage 6 fibrosis had APRI ≥1.5, suggesting that APRI is a poor indicator of disease severity in patients with LAL-D. **Conclusion:** Results from the LAL-D Registry indicate that the degree of liver injury in LAL-D is variable, with advanced fibrosis observed across a broad age range. More severe liver injury was noted in patients presenting at younger age, possibly due to a more severe clinical phenotype as the indication for biopsy. APRI is a poor indicator of LAL-D severity. Future efforts to identify noninvasive parameters predictive of fibrosis in patients with LAL-D would be valuable for the management of this rare disease. Investigations for the diagnosis of LAL-D should be considered at any age, regardless of the degree of liver disease progression.

Figure. Liver Disease Severity and Age



Nobs: number of observations; lower whisker: Q1 − 1.5*IQR; bottom of box: first (lower) quartile; middle line of box: median; diamond: mean; top of box: third (upper) quartile; top whisker: Q3 + 1.5*IQR; circles: outliers.

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Jennifer Evans – Alexion, AstraZeneca Rare Disease: Employee, Yes, No;

Florian Abel – Alexion, AstraZeneca Rare Disease: Employee, Yes, No;

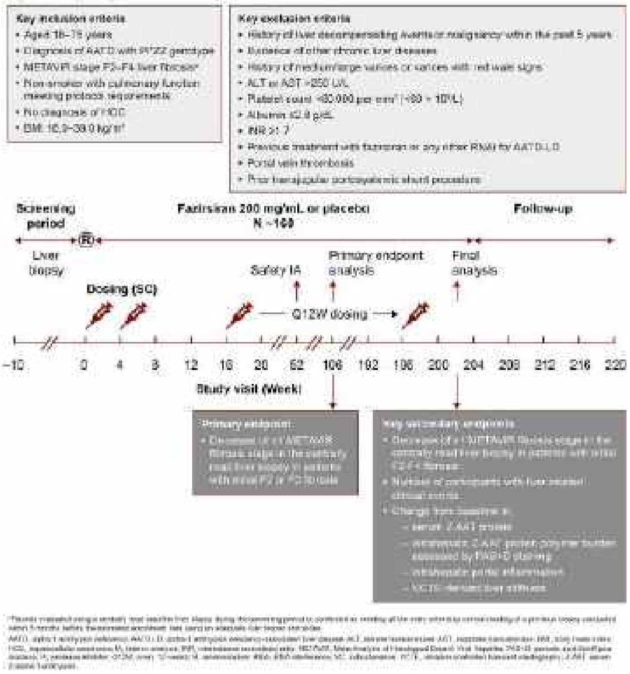
Lorenzo D'Antiga – Albireo, Alexion, Mirum, Selecta, Vivet, Spark, Tome, and Genespire: Consultant, No, No;

3312-A | DESIGN OF THE FIRST PHASE 3 STUDY (REDWOOD) EVALUATING FAZIRSIRAN IN ADULTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE

Susana Gonzalez[1], Anne E. Wyman[1], Pavel Strnad[2], Virginia Clark[3], Rohit Loomba[4], Charlie Strange[5], Jeffrey Teckman[6], Michael Hoy[1], Paresh Thakker[1], Lisi Wang[1], Ed G. Marins[1] and Nirav K. Desai[1], (1)Takeda Development Center Americas, Inc., Cambridge, MA, USA, (2)University Hospital Rwth Aachen, Aachen, Germany, (3)University of Florida, Gainesville, FL, USA, (4)University of California, San Diego, San Diego, CA, (5)Medical University of South Carolina, Charleston, SC, USA, (6)Saint Louis University, St. Louis, MO, USA

Background: Alpha-1 antitrypsin deficiency-associated liver disease (AATD-LD) is a rare genetic disease characterized by accumulation of misfolded AAT in hepatocytes resulting in low levels of circulating AAT. Patients with AATD and a homozygous "Z" mutation of the *SERPINA1* gene (Pi*ZZ) have an increased risk of liver disease (LD) progression, but have no approved pharmacologic treatment options. Fazirsiran is a small RNA interference (RNAi) therapeutic designed to reduce the production of AAT thereby preventing toxic accumulation of Z-AAT in the liver. In two phase 2 studies (NCT03946449, NCT03945292) in patients with AATD-LD and a Pi*ZZ genotype (AATD-LD-Pi*ZZ), fazirsiran reduced intrahepatic Z-AAT, improved biomarkers of liver injury and fibrosis, led to fibrosis regression and was well tolerated. The phase 3 Redwood trial was designed as a registrational study to further evaluate the efficacy and safety of fazirsiran in ~160 adults with AATD-LD-Pi*ZZ. **Methods:** Redwood is an ongoing multicenter, randomized, double-blind, placebo-controlled study (NCT05677971) that will enroll adults (18–75 y) with AATD-LD-Pi*ZZ. Patients will receive subcutaneous fazirsiran 200 mg or placebo on Day 1, Week 4 and then every 12 weeks until Week 196 (Figure). Eligible patients require a diagnosis of AATD with a Pi*ZZ genotype, METAVIR fibrosis stage F2, F3 or F4 at baseline, and must be non-smokers with lung function meeting protocol requirements. Exclusion criteria include a history of decompensated cirrhosis and evidence of other chronic liver diseases. The primary endpoint is a decrease from baseline of at least one METAVIR fibrosis stage in the centrally read liver biopsy at Week 106 in patients with initial F2 or F3 fibrosis. Key secondary endpoints (at Week 202) include a decrease of at least one METAVIR fibrosis stage in patients with initial F2, F3 or F4 fibrosis and disease progression as defined by a number of liver-related clinical events. Safety (including lung function) will be monitored over the duration of the study, with an interim safety assessment at Week 52 (Figure). **Results:** Patient recruitment began March 2023 and is ongoing. **Conclusion:** AATD-LD is a rare disease with no approved treatment options. Redwood is the largest, prospective, placebo-controlled, registrational study to evaluate the first RNAi therapeutic, fazirsiran, as a potential treatment for patients with AATD-LD-Pi*ZZ.

Figure. Study design


Key inclusion criteria
Aged 18–75 years
Diagnosis of AATD with Pi*ZZ genotype
METAVIR stage F2–F4 liver fibrosis
Non-smoker with pulmonary function meeting protocol requirements
No diagnosis of HCC
BMI 18.0–38.0 kg/m²
Key exclusion criteria
History of liver decompensating events or malignancy within the past 5 years
Evidence of other chronic liver diseases
History of medium/large varices or varices with red wale signs
ALT or AST >250 U/L
Platelet count <80,000 per mm³ (<80 × 10⁹/L)
Albumin ≤2.8 g/dL
INR ≥1.7
Previous treatment with fazirsiran or any other RNAi for AATD-LD
Portal vein thrombosis
Prior transjugular portosystemic shunt procedure
Screening period
Fazirsiran 200 mg/mL or placebo
N ~160
Follow-up
R
Liver biopsy
Dosing (SC)
Safety IA
Primary endpoint analysis
Final analysis
Q12W dosing
−10
0
4
8
12
16
20
52
106
192
196
200
204
208
212
216
220
Study visit (Week)
Primary endpoint
Key secondary endpoints

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Virginia Clark – NovoNordisk: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Takeda: Consultant, No, No; Vertex: Consultant, No, No;

Rohit Loomba – Eli Lilly: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol-Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boehringer-Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AstraZeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Arrowhead Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; 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Novartis: Consultant, No, No; NovoNordisk: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Sagimet Biosciences: Consultant, No, No; Theratechnologies: Consultant, No, No; 89 bio: Consultant, No, No; Terns Pharmaceuticals: Consultant, No, No; Viking Therapeutics: Consultant, No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Hanmi: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; 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3313-A | DIFFERENCES IN SYMPTOM SEVERITY AND RADIOLOGICAL PHENOTYPE BETWEEN PATIENTS WITH ISOLATED POLYCYSTIC LIVER DISEASE VERSUS COMBINED POLYCYSTIC KIDNEY AND LIVER DISEASE

Avisnata Das, Benjamin Giles, Aqeel Jamil, Joanna Dowman, Andrew Fowell and Richard James Aspinall, Portsmouth Hospitals University NHS Trust

Background: Polycystic Liver Disease (PLD) is a rare genetic condition, which can occur in isolation or as combined Polycystic Kidney and Liver Disease (PKLD). The Polycystic Liver Disease-specific Questionnaire (PLD-Q) and PLD-Q score are useful in assessing disease, with higher scores correlating with impaired quality of life. We wished to compare variations in PLD-Q scores, age of diagnosis of liver cysts, number and size of liver cysts between isolated PLD and combined PKLD patient groups. **Methods:** Patients were identified from a prospective departmental database in a large acute hospital. We evaluated PLD-Q scores in a fully phenotyped group of 10 patients with isolated PLD and 18 patients with combined PKLD where each of these patients had > 10 liver cysts. We also evaluated age of diagnosis of PLD, Qian's grade (based on number of liver cysts) and presence of one or more dominant liver cyst(s) (> 8 cm in size) in the two groups, with 11 patients in PLD arm and 29 patients in PLKD arm. **Results:** PLD-Q scores ranged from 17 to 83 with a mean of 44 and median of 45 in the isolated PLD group. In the PKLD group, the score varied from 3 to 61 with a higher mean of 53.3 and median of 57.6. Using independent sample *t*-test, the difference in the distributed means of scores between the two groups was at the margin of statistical significance ($p = 0.068$, 95% CI). The age of PLD diagnosis had a mean of 49.5 years, median of 52 years and varied from 23 to 70 in the PLD-only group while the mean, median and range were 53.3, 57.6 and 41 (32-73) respectively in the PKLD group. No statistically significant difference existed between the two means ($p = 0.234$, 95% CI). On abdominal imaging, in the isolated PLD group, 4 out of 11 (36%) had grade 2 liver cysts (11-20 cysts), 4 (36%) had grade 3 cysts (> 20) and 3 (28%) had Grade 4 cysts (> 20 cysts with symptomatic hepatomegaly). In the PKLD group of 29 patients, the number and percentages of Grade 2, Grade 3 and Grade 4 cysts were 3 (10.3%), 18 (62.1%) and 8 (27.6%) respectively. One or more dominant cysts were present in 3 (28%) patients with isolated PLD, and 9 (31%) patients with PKLD. **Conclusion:** The proportion of patients with > 20 liver cysts and the prevalence of dominant cysts were comparable between the PLD and PKLD groups. However, the PKLD group had higher mean and median PLD-Q scores compared to the isolated PLD group and the mean age of diagnosis of liver cysts was higher for the PKLD group. Patients with PKLD have a greater symptomatic burden than those with isolated PLD and delays in presentation or diagnosis may contribute to higher PLD-Q scores. We are exploring this relationship further using a national registry dataset.

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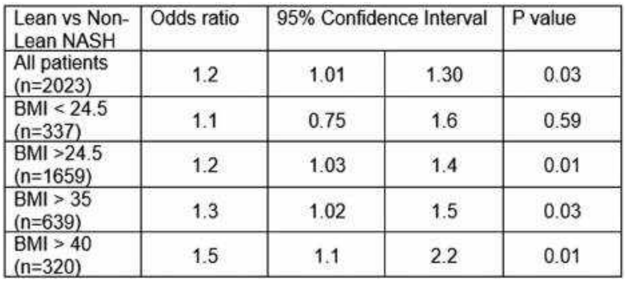
3314-A | DOES HETEROZYGOUS ALPHA-1-ANTITRYPSIN PI*MZ GENOTYPE INFLUENCE THE DEVELOPMENT OF HEPATIC EVENTS IN PATIENTS WITH LEAN NAFLD?

Sameer Prakash[1] and Arvind R. Murali[1,2], (1)University of Iowa Hospitals and Clinics, (2)Orlando Health

Background: Alpha-1antitrypsin (A1AT) Pi*MZ has been shown to increase the risk of liver related outcomes in patients with obesity and nonalcoholic fatty liver disease (NAFLD). More recently, patients with lean-NAFLD were shown to have worse liver related outcomes as compared to non-lean NAFLD. We aimed to study the interaction between A1AT Pi*MZ and lean-NAFLD in the development of liver related outcomes. **Methods:** Patients with NAFLD who also had A1AT genotyping performed from 2005-2020 were identified based on the ICD-10 codes. Clinical and demographic data were collected. We performed logistic regression analysis to determine the association between A1AT genotype and lean and non-lean NAFLD for the development of hepatic events. **Results:** A total of 2023 NAFLD patients, with 1796 Pi*MM and 226 Pi*MZ were included. Mean age was 56 (7.8) and 57% were males. Lean-NAFLD was seen in 337 (17%) patients, while 1685 (83%) patients had non-lean NAFLD. Among all NAFLD patients, A1AT MZ was associated with a significant increased risk of development of hepatic events, OR 1.2 (1.01-1.3, $p = 0.03$). Among patients with non-lean NAFLD, A1AT Pi*MZ significantly increased risk of hepatic events, OR 1.2 (1.03-1.40, $p = 0.01$), with the highest Odds noted among patients with $BMI > 40$, OR 1.5 (1.1-2.1, $p = 0.01$). However among patients with lean NAFLD, A1AT Pi*MZ was not significantly associated with an increased risk of hepatic events (OR 1.1, 0.75-1.6, $p = 0.59$). **Conclusion:** While A1AT PI*MZ variant significantly increases the risk of liver related events in patients with non-lean NAFLD, it interestingly, did not seem to significantly increase the risk of developing hepatic events in patients with lean-NAFLD. Further larger studies are needed to confirm our findings and understand the complex interaction between A1AT Pi*MZ variant and lean-NAFLD.



Lean vs Non-Lean NASH	Odds ratio	95% Confidence Interval		P value
All patients (n=2023)	1.2	1.01	1.30	0.03
BMI < 24.5 (n=337)	1.1	0.75	1.6	0.59
BMI >24.5 (n=1659)	1.2	1.03	1.4	0.01
BMI > 35 (n=639)	1.3	1.02	1.5	0.03
BMI > 40 (n=320)	1.5	1.1	2.2	0.01

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3315-A | EXPLORATION OF THE HEPATIC LIPIDOMIC PROFILE IN TWO MOUSE MODELS OF WILSON DISEASE.

Tagreed Mazi[1], Noreene M Shibata[2], Gaurav Vilas Sarode[2] and Valentina Medici[2], (1)King Saud University, (2)University of California Davis, Sacramento, CA

Background: Wilson disease (WD) is characterized by hepatic manifestations, including hepatocellular steatosis, inflammation, cirrhosis, and hepatic failure. WD is also associated with dysregulated lipid metabolism. Up to date, the underpinnings of hepatocellular inflammation and necrosis are not understood, especially in early stages of WD. It is thought that copper, by inducing the formation of reactive oxygen species (ROS), upregulates oxidative stress and the non-enzymatic oxidation of membrane-bound polyunsaturated fatty acids (PUFA), which consequently impair cellular structures and function. Products of PUFA oxidation are collectively known as oxylipins (OXL), which can also be produced via enzymatic pathways including lipoxygenases (LOXs), cyclooxygenases (COXs), cytochrome P450 monooxygenases (CYPs). These bioactive lipids modulate inflammation and are associated with hepatic inflammation. The goal of this study was to examine hepatic OXLs profile at early stages of WD in two established mouse models, the toxic milk mouse from The Jackson Laboratory (tx-j) and the *Atp7b* knockout mouse ($Atp7b^{-/-}$), compared to respective control mice with normal copper metabolism. **Methods:** Targeted lipidomic profiling of OXLs was performed by ultra-high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (UPLC-ESI-MS/MS) in livers from 19-20 weeks old male and female mice. **Results:** Compared to corresponding controls, both genotypes showed signs of hepatocellular inflammation on histological examination. There were altered hepatic OXL profiles, including higher levels of PUFA alcohols, diols, and ketones. The markers of oxidative stress, 9-HETE and 9-HEPE were higher in both genotypes, however, significant in tx-j mice. Some OXLs correlated positively with 9-HETE ($r > 0.4\text{-}0.7$, $p = < 0.05$, FDR-adjusted $p = < 0.2$). These findings indicate that early stages of WD are associated with upregulation of oxidative stress, non-enzymatic oxidative pathways, and LOX pathways. Prostaglandin and thromboxane levels were found higher in both mouse models, indicating upregulation of COX pathway. Both genotypes showed altered PUFA-epoxides, more marked in tx-j mice, suggesting altered CYP(s) activities. **Conclusion:** Our findings suggest that both non-enzymatic ROS-dependent and enzymatic PUFAs oxidation via COX and LOX pathways are associated with early stages of liver disease in WD. They also indicate altered CYPs activities in both animal models of WD. Our data highlight genotype-related variations, suggesting that in $Atp7b^{-/-}$ model there are likely compensatory protective mechanisms in response to copper toxicity and reacting to the inflammatory response.

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3316-A | HEPATIC BIOPRINTED TISSUE THERAPEUTICS (BTTS) AS A CELL THERAPY FOR MONOGENIC LIVER DISEASES INCLUDING PKU AND A1AT DEFICIENCY

Zainab A Bazzi, Stephanie A Campbell, Oksana Nemirovsky, Farin Vaez Livary, Fiona Li, Haley Tong, Rishima Agarwal, Matthew R Zeglinski, Lyndsey Hayes, Jaedyn D Foley, Paola Romero, Mahinur Efe, Reza Jalili, Simon Beyer, Tamer Mohamed, Samuel Wadsworth, Spiro Getsios, Rafal P Witek and Christopher Dickman, Aspect Biosystems

Background: Alpha-1 antitrypsin (A1AT) deficiency is caused by mutations in the *SERPINA1* gene, leading to significantly lower levels of blood A1AT. The absence of A1AT can result in destruction of the lung parenchyma resulting in emphysema. Phenylketonuria (PKU) is caused by mutations in the *PAH* gene, resulting in the inability of hepatocytes to convert phenylalanine to tyrosine. Therefore, individual's with PKU have elevated levels of plasma phenylalanine, and if left untreated, results in significant neurological disability. For both A1AT deficiency and PKU, the most efficacious treatment is liver transplantation; however, this option is problematic due to invasiveness, need for long-term immune suppression, and limited supply of donor livers. Herein, using proprietary microfluidic 3D bioprinting technology, we demonstrate the ability of our hepatic Bioprinted Tissue Therapeutics (BTTs) to replace the function of aberrant liver enzymes in PKU and A1AT deficiency. **Methods:** Primary human hepatocyte (PHH) spheroids were generated in the presence and absence of mesenchymal stem cells (MSCs). Aspect Biosystems' proprietary microfluidic 3D bioprinting technology was utilized to generate BTTs using hepatocyte-containing spheroids and alginate-based biomaterials. BTTs were challenged with disease-relevant levels of phenylalanine and implanted in immune-deficient mice to assess release of A1AT. Additionally, BTTs were assessed for cytochrome P450 activity, albumin secretion, viability, and gene expression. **Results:** Gene expression analysis demonstrated that BTTs express *PAH* and *SERPINA1*, indicating their potential ability to restore PAH and A1AT activity, respectively. Additionally, when challenged with disease-relevant levels of phenylalanine, BTTs with and without MSCs were able to metabolize >500 nmol phenylalanine/million PHHs/day. Furthermore, BTTs demonstrate secretory and additional metabolic functions, including albumin secretion (>10 μg/million cells/day) and CYP3A4 activity over a period of 7 days. When implanted into NSG mice, BTTs containing 1 million hepatocytes, produced human A1AT with levels peaking after 8 days at 2440 ng/mL. **Conclusion:** Hepatic BTTs have been shown to possess PAH activity *in vitro* and A1AT release *in vivo*. This demonstrates that BTTs have viable therapeutic potential for the treatment of PKU and A1AT deficiency. Further studies are warranted to assess the efficacy of BTTs on PKU and A1AT deficiency in small animal models.

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3317-A | HETEROZYGOSITY AND SERUM LEVELS FOR ALPHA-1 ANTITRYPSIN AS PREDICTORS OF WAITLIST MORTALITY IN LIVER TRANSPLANT CANDIDATES

Vinh Vincent Tran[1], Anjiya Shaikh[2], Christo Mathew[1], Ankur Patel[1], Kadon Caskey[1], Ronald Samuel[1], Abbas Rana[1], John A. Goss[1], N. Thao N. Galván[3], John M. Vierling[1], Avegail Flores[1], Rise Stribling[1], Gagan K. Sood[3], Fasiha Kanwal[4], Hashem B. El-Serag[1], Tzu-Hao (Howard) Lee[1] and George Cholankeril[1], (1)Baylor College of Medicine, (2)University of Connecticut, (3) Baylor College of Medicine, Houston, TX, (4)Michael E. Debakey VA Medical Center

Background: Heterozygosity for alpha-1-antitrypsin (A1AT) deficiency may increase risk for hepatic decompensation but the effect on outcomes in liver transplant (LT) candidates with advanced liver disease has yet to be examined. Our aim was to evaluate A1AT heterozygosity as a risk factor for waitlist mortality, and the potential predictive value of low serum A1AT levels in those with normal phenotype. **Methods:** We performed a retrospective cohort study in adult patients listed for LT from January 2017 to August 2018 with follow up to April 2023. As part of our transplant evaluation protocol, serum A1AT levels and phenotype testing were collected. MZ, MS, FM, and ZS phenotypes were considered heterozygotes. Sociodemographic and clinical characteristics were collected at time of waitlisting. A1AT heterozygote phenotypes and serum A1AT levels in patients with normal phenotypes were evaluated separately as predictors for waitlist dropout, defined as removal due to death or deterioration. Fine and Gray analyses were performed to assess risk of waitlist dropout, accounting for competing risks of undergoing LT, and delisting for clinical improvement. **Results:** 300 patients were waitlisted for LT, of which 15.3% ($n=46$) had heterozygous A1AT phenotypes for MZ, MS, MF, or ZS, and 6.0% ($n=18$) were heterozygotes for MZ phenotype. Serum A1AT cutoff <120 captured 94.4% of MZ heterozygotes and 60.9% of all A1AT heterozygotes. In the competing risk analyses, MZ (sHR, 3.46, 95% CI, 1.68 – 7.12) was associated with a higher risk for waitlist dropout than all other patients on the waitlist, with similar findings seen for all A1AT

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

heterozygotes (sHR, 2.45 95% CI, 1.38 – 4.37). In those with normal A1AT phenotypes, a decrease in serum A1AT levels (sHR, 0.99, 95% CI, 0.98 – 0.99) was associated with an increased risk for waitlist dropout. After adjusting for etiology, hepatocellular carcinoma, age, and MELD score, serum A1AT values < 120 (sHR, 2.79, 95% CI, 1.44-5.39) and < 100 (sHR, 6.38 95% CI, 2.24 – 18.10) were associated with a nearly three-fold and six-fold increased risk for waitlist dropout, respectively. **Conclusion:** Heterozygotes for A1AT with advanced liver disease are at higher risk for morality on the waitlist. A1AT heterozygosity and low serum A1AT levels in phenotypically normal patients may have prognostic value in assessing disease progression and warrant closer surveillance for waitlist management.

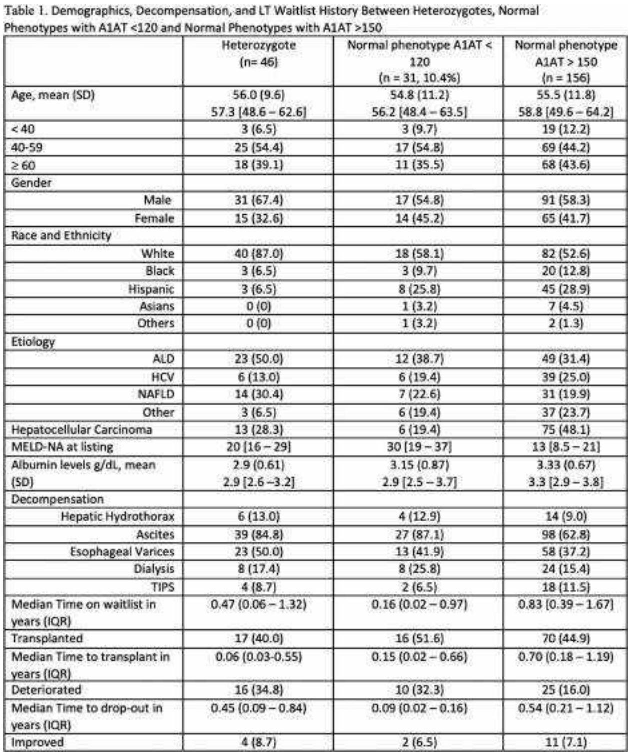

Table 1. Demographics, Decompensation, and LT Waitlist History Between Heterozygotes, Normal Phenotypes with A1AT <120 and Normal Phenotypes with A1AT >150

	Heterozygote (n= 46)	Normal phenotype A1AT < 120 (n = 31, 10.4%)	Normal phenotype A1AT > 150 (n = 156)
Age, mean (SD)	56.0 (9.6) 57.3 [48.6 – 62.6]	54.8 (11.2) 56.2 [48.4 – 63.5]	55.5 (11.8) 58.8 [49.6 – 64.2]
< 40	3 (6.5)	3 (9.7)	19 (12.2)
40-59	25 (54.4)	17 (54.8)	69 (44.2)
≥ 60	18 (39.1)	11 (35.5)	68 (43.6)
Gender			
Male	31 (67.4)	17 (54.8)	91 (58.3)
Female	15 (32.6)	14 (45.2)	65 (41.7)
Race and Ethnicity			
White	40 (87.0)	18 (58.1)	82 (52.6)
Black	3 (6.5)	3 (9.7)	20 (12.8)
Hispanic	3 (6.5)	8 (25.8)	45 (28.9)
Asians	0 (0)	1 (3.2)	7 (4.5)
Others	0 (0)	1 (3.2)	2 (1.3)
Etiology			
ALD	23 (50.0)	12 (38.7)	49 (31.4)
HCV	6 (13.0)	6 (19.4)	39 (25.0)
NAFLD	14 (30.4)	7 (22.6)	31 (19.9)
Other	3 (6.5)	6 (19.4)	37 (23.7)
Hepatocellular Carcinoma	13 (28.3)	6 (19.4)	75 (48.1)
MELD-NA at listing	20 [16 – 29]	30 [19 – 37]	13 [8.5 – 21]
Albumin levels g/dL, mean (SD)	2.9 (0.61) 2.9 [2.6 –3.2]	3.15 (0.87) 2.9 [2.5 – 3.7]	3.33 (0.67) 3.3 [2.9 – 3.8]
Decompensation			
Hepatic Hydrothorax	6 (13.0)	4 (12.9)	14 (9.0)
Ascites	39 (84.8)	27 (87.1)	98 (62.8)
Esophageal Varices	23 (50.0)	13 (41.9)	58 (37.2)
Dialysis	8 (17.4)	8 (25.8)	24 (15.4)
TIPS	4 (8.7)	2 (6.5)	18 (11.5)
Median Time on waitlist in years (IQR)	0.47 (0.06 – 1.32)	0.16 (0.02 – 0.97)	0.83 (0.39 – 1.67)
Transplanted	17 (40.0)	16 (51.6)	70 (44.9)
Median Time to transplant in years (IQR)	0.06 (0.03-0.55)	0.15 (0.02 – 0.66)	0.70 (0.18 – 1.19)
Deteriorated	16 (34.8)	10 (32.3)	25 (16.0)
Median Time to drop-out in years (IQR)	0.45 (0.09 – 0.84)	0.09 (0.02 – 0.16)	0.54 (0.21 – 1.12)
Improved	4 (8.7)	2 (6.5)	11 (7.1)

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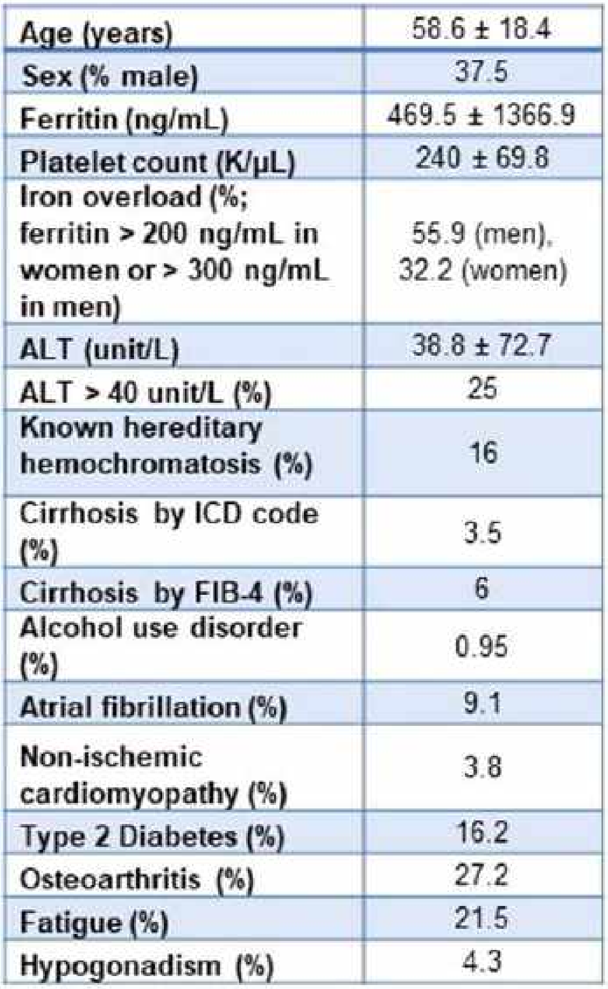
f 3318-A | HIGH PREVALENCE OF CIRRHOSIS AMONG HEREDITARY HEMOCHROMATOSIS INDIVIDUALS IN A LARGE POPULATION-BASED COHORT

Christopher Danford[1], Richard Gilroy[2], Nephi Walton[2], Michelle Lai[3] and Xuehong Zhang[4], (1)Intermountain Health, Millcreek, UT, (2)Intermountain Health, (3) Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (4)Brigham and Women's Hospital, Harvard Medical School

Background: Homozygosity for the C282Y mutation of the *HFE* gene is one of the most common genetic disorders in those of northern European descent affecting ~0.4% of the US population.[1] Lifetime cumulative incidence of cirrhosis in hereditary hemochromatosis (HH) is unknown, but has been previously reported to be low (0-2.5%) in unselected, population-based cohorts.[2] Cirrhosis due to HH is avoidable if identified and treated early, however, population-based screening is not currently recommended given our poor understanding of which patients are at highest risk and would benefit from treatment. Our aim was to evaluate the prevalence of cirrhosis in C282Y homozygous patients identified in HerediGene, an unselected population-based cohort through Intermountain Health. **Methods:** All adults (age > 18 y) who had blood drawn at an Intermountain lab were invited to participate in HerediGene starting in 2020. Subjects enrolled underwent genotyping and are linked to the Intermountain electronic medical record. Those who had genotyping data available between inception and December 2022 and were identified to be homozygous for the *HFE* C282Y mutation were included in the study. Cirrhosis was identified by either ICD-10 code or FIB-4 calculation with subsequent confirmation on manual chart review. Comorbidities were identified by ICD-10 code. **Results:** Among the first 106,828 patients enrolled in HerediGene, 486 (0.45%) were homozygous for the *HFE* C282Y variant with a mean ferritin of 469 ng/mL. Seventeen (3.5%) had cirrhosis by ICD code by a mean age of 58. When non-invasive screening for cirrhosis (FIB-4) was applied, an additional 14 patients with potential cirrhosis were identified, twelve of which were confirmed on manual chart review (n = 29, 6%). Only 78 (16%) of patients were previously aware of their diagnosis of HH (Table 1). There was no evidence that the 12 patients without an ICD code for cirrhosis identified by FIB-4 were aware of their diagnosis. **Conclusion:** Our data support that prevalence of cirrhosis among C282Y homozygotes is higher than previously reported and at a relatively young age. Prior reports are limited by small population size and inadequate phenotyping for the identification of cirrhosis. Cirrhosis from hemochromatosis is preventable. This data from an unselected, population-based cohort highlights the need for improved understanding of risk factors associated with the development of cirrhosis in HH to better inform population-wide screening.

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

Table 1. Demographic, laboratory findings, and associated diagnoses among C282Y homozygotes identified in HerediGene (n = 486). Mean and standard deviation reported.



Age (years)	58.6 ± 18.4
Sex (% male)	37.5
Ferritin (ng/mL)	469.5 ± 1366.9
Platelet count (K/µL)	240 ± 69.8
Iron overload (%; ferritin > 200 ng/mL in women or > 300 ng/mL in men)	55.9 (men), 32.2 (women)
ALT (unit/L)	38.8 ± 72.7
ALT > 40 unit/L (%)	25
Known hereditary hemochromatosis (%)	16
Cirrhosis by ICD code (%)	3.5
Cirrhosis by FIB-4 (%)	6
Alcohol use disorder (%)	0.95
Atrial fibrillation (%)	9.1
Non-ischemic cardiomyopathy (%)	3.8
Type 2 Diabetes (%)	16.2
Osteoarthritis (%)	27.2
Fatigue (%)	21.5
Hypogonadism (%)	4.3

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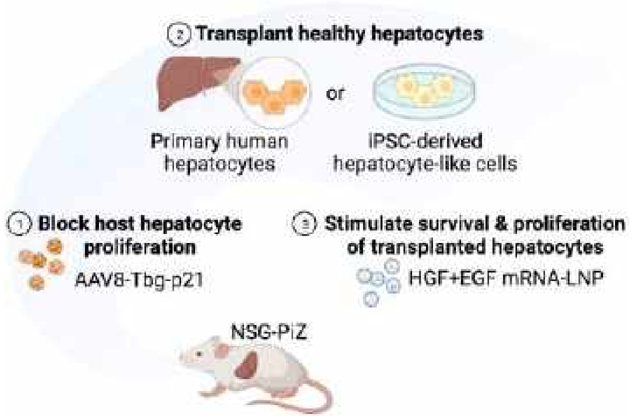
3319-A | HOST PRECONDITIONING AND TRANSIENT MITOGEN EXPRESSION VIA mRNA-LNP LEAD TO ROBUST PRIMARY HUMAN HEPATOCYTE ENGRAFTMENT AND TRANSIENT iPSC-DERIVED HEPATOCYTE SURVIVAL IN A MURINE MODEL OF AATD LIVER DISEASE

Anna R Smith[1], Fatima Rizvi[1], Elissa Everton[1], Anisah Adeagbo[1], Hua Liu[1], Ying Tam[2], Norbert Pardi[3], Drew Weissman[3] and Valerie Gouon-Evans[1], (1)Boston University School of Medicine, (2)Acuitas Therapeutics, (3) University of Pennsylvania Perelman School of Medicine

Background: Alpha-1 antitrypsin deficiency (AATD) is a genetic disease caused by a single base pair mutation of the *SERPINA1* gene and increases risk of liver and lung disease. The most common mutation causes AAT protein to misfold, leading to polymerization of AAT in hepatocytes, cell death, fibrosis, and cirrhosis. Liver transplantation is the only treatment for AATD patients that develop end stage liver disease, though donor organs are quite scarce. Alternatively, transplantation of healthy liver cells – either primary human hepatocytes (PHH) or induced pluripotent stem cell (iPSC) derived hepatocyte-like cells (HLC) – is a promising approach to restore liver function. PHH transplantation has been validated as safe in humans, yet major challenges that remain are low efficiency and lack of sustained benefit. HLC transplantation remains entirely preclinical, and factors that limit HLC engraftment in liver disease mouse models include poor survival, proliferation, and maturation of transplanted cells. We hypothesize that stimulating key regenerative pathways in transplanted hepatocytes using hepatocyte growth factor (HGF) and epidermal growth factor (EGF) and preconditioning the host liver with P21 expression to prevent host hepatocyte proliferation will improve survival, proliferation, and engraftment of PHHs and HLCs in an injured mouse liver. **Methods:** We established a safe way to transiently express HGF+EGF specifically in the liver using nonintegrative nucleoside-modified mRNA encapsulated in lipid nanoparticles (mRNA-LNP). We use AAV8-Tbg-P21 to precondition the host mouse liver with long lasting P21 expression in hepatocytes. NSG-PiZ mice serve as our injury model, recapitulating AATD liver disease. **Results:** We find that both preconditioning the host with AAV8-Tbg-P21 and the HGF+EGF mRNA-LNP treatments significantly augment transplanted PHH survival and proliferation in vivo, evidenced by histological quantification of transplanted cells and human serum albumin levels in comparison to control. Combined preconditioning with P21 and treatment with HGF+EGF leads to robust repopulation of the mouse liver with functional human cells (~30% for combined treatment vs. ~2% for control) and amelioration of AATD liver disease. Furthermore, HGF+EGF mRNA-LNP transiently improves transplanted iPSC-derived HLC survival in vivo. **Conclusion:** Thus, stimulating survival and proliferation in transplanted hepatocytes with HGF+EGF mRNA-LNP and blocking host hepatocyte proliferation with AAV8-Tbg-P21 augments PHH engraftment in the NSG-PiZ mouse, making these highly promising strategies to improve iPSC-derived HLC engraftment to treat human liver diseases.


② Transplant healthy hepatocytes
or
Primary human hepatocytes
iPSC-derived hepatocyte-like cells
① Block host hepatocyte proliferation
AAV8-Tbg-p21
③ Stimulate survival & proliferation of transplanted hepatocytes
HGF+EGF mRNA-LNP
NSG-PiZ

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3320-A | IDENTIFICATION OF PATIENTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE USING AN ARTIFICIAL INTELLIGENCE CLINICAL DECISION SUPPORT TOOL

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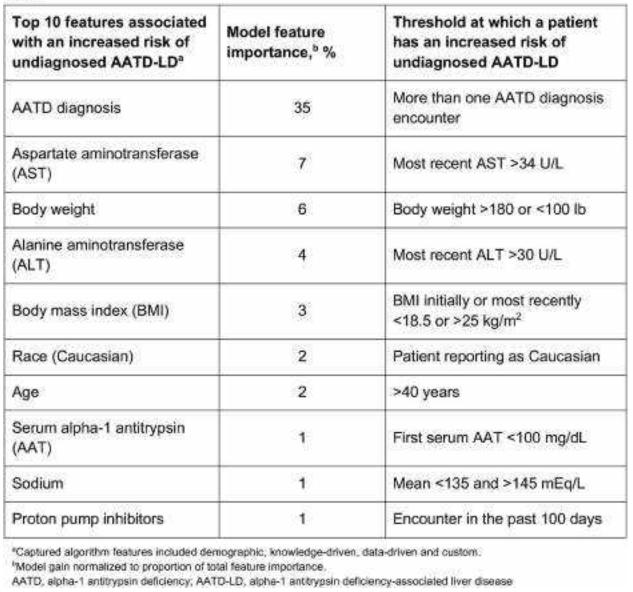
Background: Diagnosis (dx) of alpha-1 antitrypsin deficiency (AATD)-associated liver disease (LD) is challenging due to the variable risk and asymptomatic nature of the disease. An artificial intelligence/machine learning informed clinical decision support tool (AI/ML-CDST) may inform the identification of patients (pts) at risk of having undiagnosed AATD-LD. Here, we report the first-stage development of the AI/ML-CDST using data from the US IQVIA Ambulatory Electronic Medical Records (AEMR) database. **Methods:** The study population comprised pts aged ≥18 years with ≥1 encounter for any medical activity in the IQVIA AEMR database from Oct 2015 to Oct 2022. The positive cohort comprised pts with a recorded AATD dx (ICD-9/10 or SNOMED) and either a liver transplant or AATD-related liver conditions. The negative cohort comprised all other pts. For each pt, cross-sectional data with 12-month lookback and outcome periods with 1-month shift were generated. A cross-section that included the first date of AATD-LD (based on liver transplant or AATD-related liver conditions) in the outcome period was considered a positive cohort cross-section. All other cross-sections were considered negative. Algorithm features were captured within the database and metrics were engineered for each variable. Data were split into training, test and hold-out sets. An XGBoost algorithm was developed using temporal cross-validation on the training/test set. Recursive feature elimination was performed to evaluate the impact of algorithm simplification on model performance. Final model performance was evaluated on the hold-out set and assessed by fold-improvement over incidence of AATD-LD observed in the IQVIA AEMR data. **Results:** Of the 43 419 885 individual's in the IQVIA AEMR database, 1653 were pts with AATD-LD. Among the 400 features included to predict increased risk of underdiagnosed AATD-LD, prior AATD dx was the most predictive, followed by aspartate aminotransferase (AST) levels > 34 U/L and body weight > 180 or < 100 lb (Table). The AI/ML-CDST achieved an area under the curve of 0.8. **Conclusion:** The most predictive features of undiagnosed AATD-LD were prior AATD dx (35%) and AST levels (7%). However, as AATD is an underdiagnosed condition, the use of the AI/ML-CDST to identify pts with AATD-LD in the general population may be limited. Future model refinement and prospective validation can examine the utility of broad scale deployment of the tool, potentially in specialty practices, to support pt identification.

Table



Top 10 features associated with an increased risk of undiagnosed AATD-LD[a]	Model feature importance,[b] %	Threshold at which a patient has an increased risk of undiagnosed AATD-LD
AATD diagnosis	35	More than one AATD diagnosis encounter
Aspartate aminotransferase (AST)	7	Most recent AST >34 U/L
Body weight	6	Body weight >180 or <100 lb
Alanine aminotransferase (ALT)	4	Most recent ALT >30 U/L
Body mass index (BMI)	3	BMI initially or most recently <18.5 or >25 kg/m²
Race (Caucasian)	2	Patient reporting as Caucasian
Age	2	>40 years
Serum alpha-1 antitrypsin (AAT)	1	First serum AAT <100 mg/dL
Sodium	1	Mean <135 and >145 mEq/L
Proton pump inhibitors	1	Encounter in the past 100 days

[a] Captured algorithm features included demographic, knowledge-driven, data-driven and custom.
[b] Model gain normalized to proportion of total feature importance.
AATD, alpha-1 antitrypsin deficiency; AATD-LD, alpha-1 antitrypsin deficiency-associated liver disease

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Rohit Loomba – Aardvark Therapeutics: Consultant, No, No; Altimmune: Consultant, No, No; Anylam/Regeneron: Consultant, No, No; Amgen: Consultant, No, No; Arrowhead Pharmaceuticals: Consultant, No, No; AstraZeneca: Consultant, No, No; Bristol-Myer Squibb: Consultant, No, No; CohBar: Consultant, No, No; Eli Lilly: Consultant, No, No; Galmed Pharmaceuticals: Consultant, No, No; Gilead: Consultant, No, No; Glympse Bio: Consultant, No, No; Hightide: Consultant, No, No; Inipharma: Consultant, No, No; Intercept: Consultant, No, No; Inventiva: Consultant, No, No; Ionis: Consultant, No, No; Janssen Inc.: Consultant, No, No; Madrigal Pharmaceuticals: Consultant, No, No; Metacrine, Inc.: Consultant, No, No; NGM Biopharmaceuticals: Consultant, No, No; Novartis: Consultant, No, No; NovoNordisk: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Sagimet Biosciences: Consultant, No, No; Theratechnologies: Consultant, No, No; 89 bio: Consultant, No, No; Terns Pharmaceuticals: Consultant, No, No; Viking Therapeutics: Consultant, No, No; 89 bio: Stock – privately held company (individual stocks and stock options), No, No; Sagimet Biosciences: Stock – privately held company (individual stocks and stock options), No, No; Arrowhead Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AstraZeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boehringer-Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol-Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Eli Lilly: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Galectin Therapeutics: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Galmed Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Hanmi: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Inventiva: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Ionis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Janssen Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Madrigal Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant

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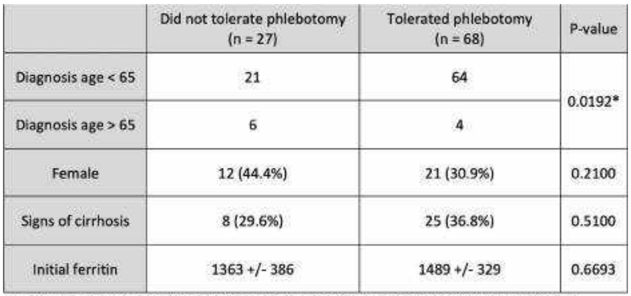
3321-A | INTOLERANCE TO PHLEBOTOMY IS COMMON IN OLDER HEMOCHROMATOSIS PATIENTS

Elias Kovoor[1], Yolanda Rodriguez Villalvazo[1] and Kyle E. Brown[2], (1)University of Iowa Carver College of Medicine, (2)University of Iowa Carver College of Medicine, Iowa City, IA

Background: Hereditary Hemochromatosis (HH) is a genetic disorder that can cause iron deposition and multiorgan damage. Since there is no physiologic mechanism to excrete iron, patients with HH undergo phlebotomy to mobilize excess iron stores. HH is most often diagnosed in middle-age, but occasionally is discovered later in life. We hypothesized that older adults might not tolerate the aggressive phlebotomy regimens commonly used to treat HH. **Methods:** Using hemochromatosis ICD codes to identify patients, we conducted a retrospective chart review of patients diagnosed with HH at our institution between 01/2000-9/2022. Only patients with C282Y/C282Y or C282Y/H63D genotypes and well-documented phlebotomy history were included. Baseline serologies, imaging, and biopsy findings were recorded, as were etiology of intolerance for phlebotomy such as episodes of hypotension, syncope, severe anxiety, or difficulty with venous access. **Results:** 95 patients met our inclusion criteria, 85 were diagnosed before age 65 and 10 were diagnosed at age > 65. Of the entire group, phlebotomy intolerance was reported in 27 (28.4%) patients. Among patients diagnosed at age < 65, 21/85 experienced phlebotomy intolerance; the proportion was significantly higher among those diagnosed at age > 65 years (6/10 [p = 0.0192]). Reported intolerance with phlebotomy occurred at similar rates among female and male patients and those with evidence of cirrhosis versus those without. Ferritin levels at diagnosis were also similar among patients who experienced intolerance to phlebotomy and those who did not. **Conclusion:** A surprisingly large proportion (28.4%) of patients undergoing phlebotomy for HH at our institution experience intolerance to phlebotomy. Patients diagnosed at age > 65 comprise a minority of HH patients, but this group had higher rates of intolerance to phlebotomy than those diagnosed before age 65. Clinicians should be aware of the possibility that HH patients diagnosed at older ages may have difficulties with phlebotomy and shared decision making may play a key role in management of these patients. The impact and optimal treatment of HH in this age group requires further study.



	Did not tolerate phlebotomy (n = 27)	Tolerated phlebotomy (n = 68)	P-value
Diagnosis age < 65	21	64	0.0192*
Diagnosis age > 65	6	4	
Female	12 (44.4%)	21 (30.9%)	0.2100
Signs of cirrhosis	8 (29.6%)	25 (36.8%)	0.5100
Initial ferritin	1363 +/- 386	1489 +/- 329	0.6693

Table 1: Characteristics of hemochromatosis patients based on tolerance to phlebotomy

Disclosures: The following people have nothing to disclose: Elias Kovoor, Kyle E. Brown

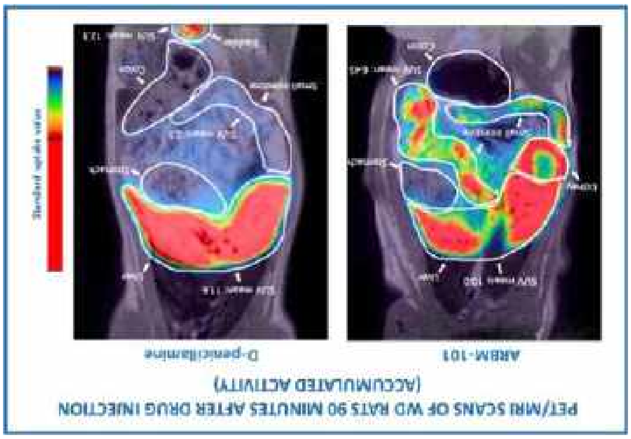
Disclosure information not available at the time of publication: Yolanda Rodriguez Villalvazo

3322-A | METHANOBACTIN RESTORES BILIARY COPPER EXCRETION IN WILSON DISEASE RATS VISUALIZED BY 64Cu PET/MRI

Emilie Munk[1], Mikkel Holm Vendelbo[1], Frederik Teicher Kirk[1], Mette Irene Theilgaard Simonsen[1], Aage Kristian Olsen Alstrup[1], Tamara Rieder[2], Tea Lund Laursen[1,3], Peter Ott[1], Hans Zischka[2,4] and Thomas Damgaard Sandahl[1], (1)Aarhus University, (2)Technical University Munich, (3)Randers Regional Hospital, (4)Helmholtz Center Munich, German Research Center for Environmental Health

Background: Methanobactins (MBs) are small peptides with a very high copper affinity currently under investigation in preclinical trials for the treatment of Wilson disease (WD). Chelation treatment with D-penicillamine

(DPA) and trientine facilitate urinary copper excretion. We aimed to investigate how MB affects *in-vivo* copper metabolism and excretion using 64-copper [^{64}Cu] PET/MRI in WD rats, compared to either DPA- or sham-treated, or to heterozygote control rats. **Methods:** Nineteen WD and four heterozygote control rats were injected intravenously with [^{64}Cu] and scanned one hour later. WD rats were then injected intraperitoneally with one dose of MB (ARBM-101 or MB-OB3b), DPA, or sodium chloride (sham) and scanned for 90 minutes and after 24 hours, while controls were not injected but scanned accordingly. [^{64}Cu] levels were estimated as the mean standard uptake value (g/ml) in volumes of interest in liver, kidney, bladder, and gut. **Results:** One hour after [^{64}Cu] injection, WD rats had elevated liver [^{64}Cu] activity compared to controls (9.0 ± 2.4 vs. 6.2 ± 1.9) and lower [^{64}Cu] activity in the gut (0.42 ± 0.24 vs. 2.87 ± 1.47) as expected. At 10-15 minutes after MB injection, [^{64}Cu] was visible in the small intestines of WD animals with levels equal to controls (2.2 ± 1.4) and that further increased to above control levels after 90 minutes (7.2 ± 4.9). [^{64}Cu] did not appear in the gut of DPA- or sham-treated rats, but DPA routed more [^{64}Cu] in the bladder (SUV = 7.9 ± 5.1 vs. 1.8 ± 2.2 in MB-treated rats). During the 90 minute-scan, liver [^{64}Cu] levels tended to decrease in MB-treated animals but were stationary in the other animals. From baseline to 24 hours after [^{64}Cu] injection, the liver [^{64}Cu] levels in control rats decreased by approximately 50%, whereas in MB-treated WD rats, liver [^{64}Cu] levels increased by 28%, DPA-treated by 76% and sham-treated by 40%. Fecal [^{64}Cu] increased by a factor 1000 upon injection with ARBM-101. **Conclusion:** In this study, a single dose of intraperitoneal MB rapidly facilitated biliary copper excretion in WD rats from comparable to double the level of controls. Liver [^{64}Cu] levels initially decreased within 90 minutes post-MB injection, followed by a subsequent rise at 24 hours, likely because of extra-hepatic [^{64}Cu] reaching the liver. DPA treatment did not show similar effects, but instead exhibited elevated bladder [^{64}Cu] activity. This suggests that a single dose of MB improves copper removal from the liver.



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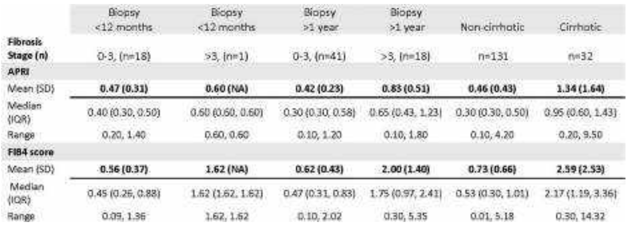
3323-A | NON-INVASIVE FIBROSIS SCORING IN PATIENTS WITH WILSON DISEASE: A CROSS SECTIONAL ANALYSIS OF THE WILSON DISEASE REGISTRY STUDY

Michael L. Schilsky[1,2], Uyen To[3], Regino P. Gonzalez-Peralta[4], Sanjiv Harpavat[5], Isabelle Mohr[6], Rima L. Fawaz[7], Adem Aydin[1], Pamela L. Valentino[8], Aftab Ala[9], Thomas Damgaard Sandahl[10], Kaitlin Maciejewski[1] and Ayse Coskun[3], (1)Yale University, (2) Yale School of Medicine, New Haven, CT, United States, (3)Yale School of Medicine, New Haven, CT, (4) Adventhealth for Children, (5)Texas Children's Liver Center - Baylor College of Medicine, Bellaire, TX, (6) University of Heidelberg, (7)Yale University, New Haven, CT, (8)Seattle Children's Hospital, (9)King's College Hospital, (10)Aarhus University

Background: Wilson disease (WD) typically results in liver injury and may affect extrahepatic organs, most notably the central nervous system. Endpoints for treatment include reversing liver injury and improving liver function. Hepatic fibrosis is an important consequence of liver injury in patients with WD, and there is increasing interest in estimating the degree of fibrosis non-invasively. The ability to follow hepatic fibrosis in WD in patients on treatment is important for clinical studies and standard practice. APRI and Fib4 estimates of fibrosis have proven useful for helping estimate the degree of fibrosis in other liver disorders, and some preliminary ranges for patients with WD were proposed (Paternostro et al Liver Int 2020). The Aim of this study was to determine the ranges for APRI and Fib4 in patients with Wilson disease and determine our ability to distinguish patients with cirrhosis from those with earlier stages of fibrosis. **Methods:** Data was analyzed for patients at enrollment in the WD Registry Study (n = 163, median (IQR) treatment 6.3 y (1.1, 20.0) with min 0, max 53.8 y). At the time of enrollment, site investigator determined the patient to be without or with cirrhosis based on liver biopsy, radiologic imaging and presence or absence of clinical signs of portal hypertension. Some patients (n = 19) had liver biopsy within 12 months of study entry, while others (n = 59) had liver biopsy > 1 year prior to enrollment. APRI and Fib4 was calculated from data at the time of study enrollment. **Results:** Data for the APRI and Fib4 calculations are shown in the Table below. Differences were statistically significant between mean values for APRI and Fib4 for patients with liver biopsy > 1 year of treatment before study entry with 0-3 fibrosis versus > 3 fibrosis, $p < 0.001$, and in investigator deemed non-cirrhotic versus cirrhotic, $p < 0.001$. As expected, values for these scores were higher in patients where the investigator deemed the patient to have cirrhosis. **Conclusion:** Both APRI and Fib4 scores may be useful to help identify patients with WD and cirrhosis which is important for clinical care and potentially for prognosis. Increasing our data collection will improve the accuracy and predictive value for these non-invasive fibrosis estimates in patients with WD. Additional analysis and correlation of longitudinal results for APRI and Fib4 with patient outcomes will help validate their use in treatment trials and in our standard of care practice.



	Biopsy <12 months	Biopsy <12 months	Biopsy >1 year	Biopsy >1 year	Non-cirrhotic	Cirrhotic
Fibrosis Stage (n)	0-3, (n=18)	>3, (n=1)	0-3, (n=41)	>3, (n=18)	n=131	n=32
APRI						
Mean (SD)	**0.47 (0.31)**	**0.60 (NA)**	**0.42 (0.23)**	**0.83 (0.51)**	**0.46 (0.43)**	**1.34 (1.64)**
Median (IQR)	0.40 (0.30, 0.50)	0.60 (0.60, 0.60)	0.30 (0.30, 0.58)	0.65 (0.43, 1.23)	0.30 (0.30, 0.50)	0.95 (0.60, 1.43)
Range	0.20, 1.40	0.60, 0.60	0.10, 1.20	0.10, 1.80	0.10, 4.20	0.20, 9.50
FIB4 score						
Mean (SD)	**0.56 (0.37)**	**1.62 (NA)**	**0.62 (0.43)**	**2.00 (1.40)**	**0.73 (0.66)**	**2.59 (2.53)**
Median (IQR)	0.45 (0.26, 0.88)	1.62 (1.62, 1.62)	0.47 (0.31, 0.83)	1.75 (0.97, 2.41)	0.53 (0.30, 1.01)	2.17 (1.19, 3.36)
Range	0.09, 1.36	1.62, 1.62	0.10, 2.02	0.30, 5.35	0.01, 5.18	0.30, 14.32

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Disclosure information not available at the time of publication: Sanjiv Harpavat, Isabelle Mohr, Rima L. Fawaz, Pamela L. Valentino, Aftab Ala, Kaitlin Maciejewski

f 3324-A | NON-INVASIVE FIBROSIS TESTS PREDICT LIVER-RELATED ENDPOINTS IN A LONGITUDINAL STUDY OF ADULTS WITH SEVERE ALPHA-1 ANTITRYPSIN DEFICIENCY (PI*ZZ GENOTYPE)

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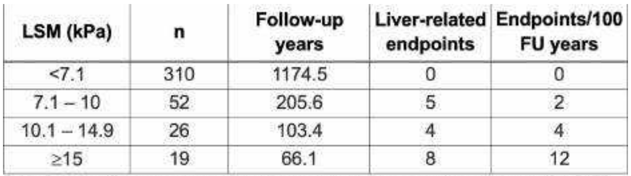
Background: Homozygous Pi*Z mutation (Pi*ZZ genotype) confers a strong predisposition to lung and liver disease. While phase 2 clinical trials suggested that treatment with small interfering RNA may improve Pi*ZZ-associated liver phenotype, very little is known about the natural disease course as well as factors predicting the development of liver-related endpoints. To change that, we evaluated risk factors and the predictive utility of non-invasive tests in the multi-center European Pi*ZZ liver cohort. **Methods:** 480 Pi*ZZ subjects without concomitant liver diseases or pathological alcohol consumption received a baseline clinical, laboratory, and elastographic assessment. 407 of them had a detailed follow-up interview at least 12 months after their baseline examination. **Results:** During a median follow-up of 3.8 years, 25 Pi*ZZ individual's deceased. The main causes of fatality were lung and liver disease, accounting for 9 and 8 deaths, respectively. 18/5 individual's received a lung/liver transplant. 17 Pi*ZZ subjects who developed a hepatic endpoint (liver transplant/death, or decompensated cirrhosis) presented with significantly higher BMI (28 vs. 24 kg/m^2, $p = 0.001$), liver stiffness measurement (14 vs. 5 kPa, $p = 6.0 \times 10^{-10}$), AST-to-platelet ratio index (APRI, 1.0 vs. 0.3 units, $p = 1.8 \times 10^{-7}$), fibrosis-4 index (3.6 vs. 1.3, $p = 3.0 \times 10^{-6}$), and liver enzymes in their baseline examination. Multivariate Cox regression analysis revealed LSM ≥ 15 kPa (aHR 40.3, 95% CI 11.0-147.8, $p = 2.4 \times 10^{-8}$) and APRI ≥ 1.0 units (aHR 37.3, 95% CI 10.3-135.5, $p = 3.9 \times 10^{-8}$) as strong predictors of liver-related endpoints. Notably, 310 individual's with LSM < 7.1 kPa at baseline did not develop any hepatic endpoint during their follow-up (Table 1). **Conclusion:** LSM and APRI accurately stratify Pi*ZZ individual's according to their risk of liver-related events. Thus, these non-invasive tests may allow risk stratification in clinical practice as well as selection for clinical trials.



LSM (kPa)	n	Follow-up years	Liver-related endpoints	Endpoints/100 FU years
<7.1	310	1174.5	0	0
7.1 – 10	52	205.6	5	2
10.1 – 14.9	26	103.4	4	4
≥15	19	66.1	8	12

Table 1: Liver stiffness measurement via vibration-controlled transient elastography stratifies Pi*ZZ individuals into risk categories. Abbreviations: LSM, liver stiffness measurement; FU, follow-up.

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Striedl, Monica Pons, Joan Genesca, Marc Miravitlles, Benedikt Schäfer, Heinz Zoller, Elmar Aigner, Pavel Strnad

3325-A | REMOVAL OF COPPER BY ATP7B EXPRESSION IN PRIMARY HEPATOCYTES FROM WILSON'S DISEASE PATIENTS

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Background: Wilson's disease (WD) is a rare disorder characterized by copper accumulation in vital organs as a result of the inability of the liver to remove excess copper from the body due to mutations in the ATP7B gene. Excess free copper can induce hepatotoxicity and ultimately liver failure, often requiring liver transplantation. We developed an *in vitro* human WD liver model using patient-derived hepatocytes and demonstrated efficacy of gene therapy to restore ATP7B function and lower intracellular copper. **Methods:** Liver explants were procured with consent from WD patients undergoing transplantation during acute liver failure. Hepatocytes were isolated and cryopreserved using conventional isolation protocols. WD hepatocytes were transduced with adenovirus containing full-length hATP7B gene, or GFP as a control, at various MOIs for 8 hrs and cultured for 10 days under static or hemodynamic and flow conditions using our REVEAL-Tx^{TM} technology. Several functional endpoints were assessed including ATP7B expression, intracellular copper, secreted ceruloplasmin, and copper-related genes. **Results:** All livers procured from WD patients were diseased and cirrhotic, yielding only limited quantities of functional hepatocytes suitable for *in vitro* studies. WD hepatocytes contained copper levels > 16-fold higher than normal hepatocytes, showed elevated gene expression of copper storage protein metallothionine and reduced gene expression of copper transporter CTR1. These biomarkers remained intact during culture. Bile canaliculi formation was similar between WD and normal hepatocytes. Expression of ATP7B at physiological levels in WD hepatocytes cultured under REVEAL-Tx^{TM} flow conditions resulted in a 30-40% reduction in intracellular copper after only 10 days in culture. Higher levels of ATP7B expression were effective on static culture. Under flow conditions, treatment with the copper chelator tetrathiomolybdate also resulted in a small reduction of intracellular copper. However, combination of gene and chelator therapy did not potentiate removal of copper, suggesting that a significant amount of the intracellular copper in WD hepatocytes may be stably bound to metallothionine. **Conclusion:** WD hepatocytes isolated from patients stably store high levels of copper. Expression of ATP7B in our WD liver model reduced intracellular copper, suggesting that gene therapy has the potential to restore ATP7B function and reduce excess copper stored in WD patient's livers.

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3326-A | TARGETING PKM2 IN NASH-HCC: CROSS TALK BETWEEN HEPATIC MACROPHAGE REGULATION AND TGF-BETA SIGNALING

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Background: Pyruvate kinase isozyme M2 (PKM2), a rate-limiting enzyme in glycolysis, mediates inflammation, ferroptosis and aerobic glycolysis (Warburg effect) in NASH-HCC. Increased macrophage PKM2 is associated with poor prognosis in HCC. We reported that liver-specific TGF-β/SMAD4 knockout mice develop hemochromatosis through hepcidin loss and increased iron absorption-a model for ferroptosis (*Cell Metab.* 2005;2:6). Recently, we found that liver-specific knockout of a TGF-β/SMAD adaptor βII-spectrin (SPTBN1^{LSKO}), blocks NASH and HCC, and βII-spectrin siRNA reverses NASH in human NASH 3D cultures (*Sci Transl Med.* 2021,13:624). Because TGF-β and PKM2 converge on ferroptosis, we examined whether βII-spectrin modulates PKM2 expression in NASH and HCC. **Methods:** HCC cells were treated with ASOs targeting PKM2. Western diet (WD) and DEN were given to SPTBN1^{Flox} (control) and SPTBN1 LSKO mice for NASH-associated HCC. Since antisense oligonucleotides (ASOs) promote a splicing switch from the cancer-associated PKM2 to the PKM1 isoform, we explored the potential of ASO-based PKM splice switching as a targeted therapy for liver cancer. PKM2 expression was determined by immunohistochemical labeling using liver sections of these mice. **Results:** ASO induced PKM splice switching and inhibited the growth of cultured HCC cells, and increased pyruvate-kinase activity and altered glucose metabolism. Increased PKM2 expression was observed in NASH and HCC Kupffer cells from control SPTBN1^{Flox} mice fed WD. In contrast, PKM2 expression in the liver was markedly reduced in SPTBN1^{LSKO} mice fed WD and DEN in which NASH and HCC are blocked. Additionally, we observed that microbiome profiles and TGF-β/SMAD3–regulated fibrosis were altered, and expression of inflammatory genes was significantly reduced in the LSKO mice compared to the NASH mice. **Conclusion:** Hepatocyte βII-spectrin knockdown decreased PKM2 expression in Kupffer cells, suppressing pro-inflammatory cytokine production, and blocking NASH-associated HCC. Our study suggests cross talk between stromal regulation of glycolysis and TGF-β signaling. The study provides new insight into molecular mechanisms for two disorders that preferentially affect males, hemochromatosis and HCC.

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3327-A | THE CLINICAL PRESENTATION AND CHARACTERIZATION OF WILSON DISEASE

Ashley O'Mara, Betsy Malkus, Serap Sankoh, Jack Allen and Jason Cataldo, Ultragenyx Pharmaceutical Inc.

Background: Wilson Disease (WD) is a rare disorder caused by mutations in the *ATP7B* gene (encodes transporter protein to regulate copper levels) that cause a toxic buildup of copper in the liver, brain, and other organs and can result in liver disease, neurological symptoms, and psychiatric behavioral disorders. An observational study was conducted to describe WD clinical presentation, capture the patient experience, and inform endpoint selection for future WD interventional studies. **Methods:** All participants had a confirmed diagnosis of WD and were prescribed standard of care (zinc and copper chelators). Medical history; patient-reported outcomes (PROs); clinician-reported outcomes (ClinROs); clinical performance tests of fine motor skills, strength, walking quality, speed, and endurance; and 24 hr urine and blood samples were completed at Day 0. PROs and 24 hr urine and blood samples were repeated on Days 15 and 30. Following Day 30, participants completed a qualitative interview. **Results:** This study included 16 participants (7 men, 9 women) with ages ranging from 14 to 70 years old. A copper-restricted diet was prescribed to 77% of participants; values of copper biomarkers were consistent with current therapeutic guidelines. Table 1 shows the clinical outcome assessment (COA) results. **Conclusion:** Study results demonstrate the broad spectrum of symptoms and impacts that patients with WD can experience. Given the heterogeneity of WD, selecting endpoints to adequately capture symptoms and impacts across all patients is challenging. Our findings suggest walking deficits and fatigue are experienced among patients with various clinical manifestations. Qualitative patient interviews are being conducted to further understand fatigue within the WD population and the context in which patients experience walking impairments.

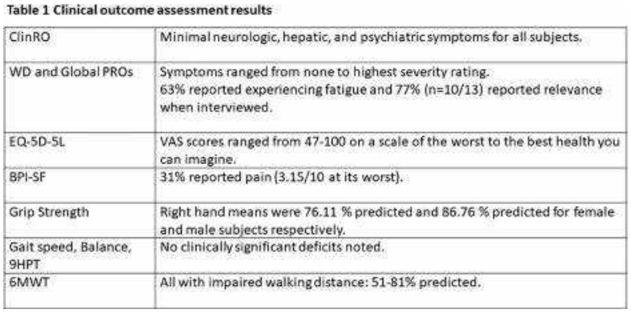

Table 1 Clinical outcome assessment results

ClinRO	Minimal neurologic, hepatic, and psychiatric symptoms for all subjects.
WD and Global PROs	Symptoms ranged from none to highest severity rating. 63% reported experiencing fatigue and 77% (n=10/13) reported relevance when interviewed.
EQ-5D-5L	VAS scores ranged from 47-100 on a scale of the worst to the best health you can imagine.
BPI-SF	31% reported pain (3.15/10 at its worst).
Grip Strength	Right hand means were 76.11 % predicted and 86.76 % predicted for female and male subjects respectively.
Gait speed, Balance, 9HPT	No clinically significant deficits noted.
6MWT	All with impaired walking distance: 51-81% predicted.

Disclosures: Ashley O'Mara – Ultragenyx Pharmaceutical, Inc.: Employee, Yes, No; Ultragenyx Pharmaceutical, Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;
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Jason Cataldo – Ultragenyx Pharmaceutical, Inc.: Employee, Yes, No; Ultragenyx Pharmaceutical, Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

3328-A | THE HIGHER RISK OF LIVER CIRRHOSIS IN PI*MZ SERPINA1 CARRIERS IS NOT CAUSED BY THE PRESENCE OF A DIFFERENT PRECIPITATING MUTATION

Sona Frankova[1], Zuzana Rabekova[2], Magdalena Nerolodova[2], Ondrej Fabian[2], Martin Kveton[2], Milan Jirsa[2] and Jan Sperl[1], (1)Department of Hepatogastroenterology, Institute for Clinical and

Experimental Medicine, Prague, Czech Republic, (2) Institute for Clinical and Experimental Medicine

Background: The homozygous carriage of the mutated Z allele at the rs28929474 locus in the *SERPINA1* alpha-1-antitrypsin (AAT) gene leads to pulmonary emphysema and liver cirrhosis. Recently, it has been shown that Pi*MZ heterozygotes have an increased risk of liver cirrhosis if they have liver disease of other aetiologies. The underlying mechanism of this risk has not yet been elucidated. The aim of our study was to test whether AAT also precipitates in hepatocytes in Pi*MZ heterozygotes and whether other variants in the *SERPINA1* gene localized in the trans position contribute to the higher risk of liver cirrhosis. **Methods:** The investigated cohort consisted of 1108 patients with advanced liver cirrhosis referred to liver transplantation between 1994 and 2020. The cohort consisted of 1021 Pi*MM homozygotes, 55 Pi*MZ heterozygotes, and 32 carriers of the Pi*MS genotype of the *SERPINA1* gene. Immunohistochemical examination with polyclonal anti-AAT antibody was performed in all available liver samples; in 46 of 55 Pi*MZ heterozygotes, in 10 of 18 Pi*MM homozygotes, and in 1 of 29 Pi*MS genotype carriers, i.e. in patients in whom the histological examination of the explanted liver revealed PAS-D (Periodic Acid-Schiff Diastase) positive granules in the cytoplasm of hepatocytes. Sanger sequencing of the coding regions and adjacent non-coding regions of the *SERPINA1* gene was performed in all 55 Pi*MZ heterozygotes, in 7 Pi*MM homozygotes, and in one Pi*MS genotype carrier with immunohistochemical evidence of AAT granules in hepatocytes. **Results:** Sequencing of the *SERPINA1* gene identified eight different single nucleotide substitutions in the study cohort. Of these eight variants, seven have already been described in the NCBI SNP database. One single nucleotide substitution c. 832 C > T was not reported in the database, and it can be assumed that it is a rare, previously undescribed variant. Six variants had the predicted missense effect on the amino acid sequence, i.e. the nucleotide change resulted in an amino acid substitution in the protein. In two cases, rs20546 and c. 832 C > T, the nucleotide substitution did not result in an amino acid substitution. The missense variant rs111850950 was described in the NCBI SNP database as having no clear clinical significance, while the remaining missense variants rs709932, rs20546, rs6647, and rs1303 - PiM3 are considered benign. **Conclusion:** The mechanism of liver damage in Pi*MZ heterozygotes is the same as in Pi*ZZ homozygotes and is caused by the proteinopathic effect of the precipitating variant AAT in the endoplasmic reticulum of the hepatocytes. The presence of other, previously unknown *SERPINA1* gene variants, is not the cause of AAT precipitation in hepatocytes and a higher risk of liver cirrhosis.

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3329-A | THE ROLE OF THE INTESTINE IN WILSON DISEASE: CHARACTERIZATION OF A NEW INTESTINE-SPECIFIC Atp7b KNOCK-OUT MOUSE MODEL.

Amanda Caceres[1], Noreene M Shibata[1], Gaurav Vilas Sarode[1], Tagreed Mazi[2], Margarida Bettencourt[1], Marie C. Heffern[1], Svetlana Lutsenko[3] and Valentina Medici[1], (1)University of California Davis, Sacramento, CA, (2) King Saud University, (3)Johns Hopkins University

Background: The clinical manifestations of Wilson disease (WD) are related to copper accumulation in the liver and brain, but little is known about the role of other organs expressing the ATP7B copper transporter on the metabolic changes characterizing WD. In organoids derived from intestinal epithelial cells from global knockout mice for the *Atp7b* gene ($Atp7b^{-/-}$) there is dysregulated lipid metabolism but the systemic effects of the intestinal *Atp7b* mutation and its significance in affecting the phenotype are unknown. To examine the metabolic consequences of intestine *Atp7b* inactivation in the absence of hepatic copper accumulation, we generated a new mouse strain, the $Atp7b^{\Delta IEC}$ mouse and characterized its phenotype over a time-course study. **Methods:** $Atp7b^{\Delta IEC}$ mice were generated using B6.Cg-Tg(Vil1-cre)997Gum/J mice from the Jackson Laboratory and $Atp7b^{Lox/Lox}$ mice. Cre-mediated removal of a 1.6-kb fragment in exon 2 results in enterocyte-specific *Atp7b* inactivation. $Atp7b^{\Delta IEC}$ mice were compared to wildtype mice with same genetic background (iWT). The *Atp7b* null global knockout ($Atp7b^{-/-}$) on a C57Bl/6 background was previously generated and compared to respective WT. Both male and female mice were studied at 9, 16, and 24 weeks of age. Liver histology, lipid metabolism parameters, including liver and plasma cholesterol and triglycerides levels, hepatic copper quantification were assessed. **Results:** At 9 and 16 weeks, $Atp7b^{-/-}$ mouse livers exhibit hepatocytes with irregular nuclei, mild inflammation, and no steatosis. However, at 24 weeks, $Atp7b^{-/-}$ mice display prominent irregularities in nuclei size, mild to moderate inflammation, and early fibrosis. Whereas at earlier ages, $Atp7b^{\Delta IEC}$ livers exhibit regular nuclei size, no steatosis, and no inflammation, at 24 weeks of age, they develop evidence of periportal inflammatory infiltrate and cytosolic glycogenosis. There was no difference in plasma cholesterol and triglyceride levels between the two mutant strains and their respective control mice. No changes in hepatic and enterocyte copper levels were seen in $Atp7b^{\Delta IEC}$ livers, whereas, as expected, hepatic copper was 20-40 times higher in *Atp7b* $^{-/-}$ mice compared to WT mice. At 16 weeks of age, compared with iWT, *Atp7b*$^{\Delta IEC}$ mice showed changes highlighting increased liver triglycerides, diglycerides, and unsaturated fatty acids. In plasma, *Atp7b*$^{\Delta IEC}$ mice showed higher levels of lysoPCs and lysoPEs and reduced sphingomyelins and ceramides. **Conclusion:** Intestine-specific *Atp7b* deficit affects systemic lipid metabolism as shown by lipidomic analysis independently from hepatic copper accumulation indicating evidence that WD phenotype is affected by organ-specific *ATP7B* variants.

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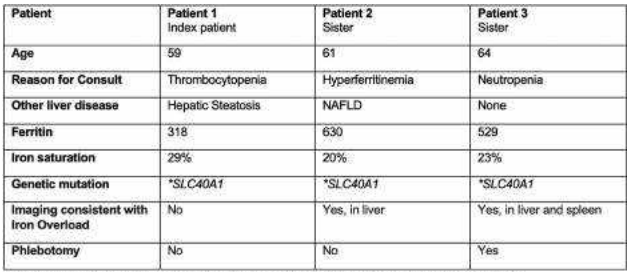
3330-A | WHAT TO CONSIDER WHEN RESULTS SHOW HYPERFERRITINEMIA AND NORMAL IRON SATURATION IN AN ASIAN POPULATION; IT COULD BE FERROPORTIN DISEASE: A FAMILY STUDY WITH SLC40A1 GENE MUTATION

Nairuti Shah[1], David Feldman[2] and Ira M. Jacobson[2], (1)NYU Langone Hospital - Long Island, (2)NYU Grossman School of Medicine

Background: Ferroportin, a transmembrane protein genetically encoded by *SLC40A1*, mediates iron export from intestinal cells to plasma. Ferroportin disease (FD), formerly known as hereditary hemochromatosis (HHC) type 4, is associated with dominant mutations in *SLC40A1* and is considered a rare disease. Classical FD (HHC type 4A) is due to loss of function mutations in *SLC40A1* that impair iron export. Affected patients usually have elevated ferritin but normal transferrin saturation (TSAT). We present a family of three sisters of Asian descent who share the same novel p.Met216Val mutation (c.646A > G) in *SLC40A1.* Despite sharing the same mutation, we found variable penetrance and disease severity within one family. **Methods:** Patient 1 the index patient is a 59 year-old woman initially evaluated for thrombocytopenia related to platelet clumping. She had hyperferritinemia from 318-424 and normal TSAT. Patient 2 is a 61 year-old woman with a history of nonalcoholic fatty liver disease (NAFLD) with ferritin 630 and normal TSAT. MRI of the abdomen showed diffuse hepatic steatosis with iron deposition. Patient 3 is a 64 year-old woman with a ferritin level of 529 and normal TSAT. MRI showed mild hepatic iron overload and splenic iron deposition. Her subsequent ferritin level was 652 and she had 4 phlebotomy sessions with ferritin 197. Repeat MRI showed resolution of hepatic iron overload and reduced splenic iron overload. All three patients are first degree relatives and genetic testing in all identified the p.Met216Val missense mutation in *SLC40A1* in the heterozygous state. **Results:** FD involves loss of function mutations in *SLC40A1* that impair the iron export efficiency of ferroportin leading to iron retention in reticuloendothelial cells and hyperferritinemia with normal TSAT. FD in later stages may have increased TSAT and iron accumulation in hepatocytes making it a progressive iron overload disorder. Therefore, it is important to test for the disease as it can often be confused with other common causes of hyperferritinemia with normal TSAT. **Conclusion:** FD should be considered in patients without typical features of type 1 (HFE) HHC. In Asian populations, such as this family of sisters, the HFE mutation is rarely detected, making awareness of FD in patients with features of genetic iron overload important. It is likely that disease presentation and penetrance of underlying mutations are affected by a patient's comorbidities, including age, metabolic syndrome and hepatic steatosis, making certain patients more susceptible to fibrosis in FD. Treatment if needed is with phlebotomy, which is often poorly tolerated and inefficient. Likely with more widespread testing the prevalence of the ferroportin mutation will become known. Further research is needed to better understand the mechanisms underlying this disorder and to develop effective treatments for affected individual's.



Patient	**Patient 1** Index patient	**Patient 2** Sister	**Patient 3** Sister
Age	59	61	64
Reason for Consult	Thrombocytopenia	Hyperferritinemia	Neutropenia
Other liver disease	Hepatic Steatosis	NAFLD	None
Ferritin	318	630	529
Iron saturation	29%	20%	23%
Genetic mutation	**SLC40A1*	**SLC40A1*	**SLC40A1*
Imaging consistent with Iron Overload	No	Yes, in liver	Yes, in liver and spleen
Phlebotomy	No	No	Yes

Table 1. Patient Characteristics. *Genetic testing was done by Invitae San Francisco CA

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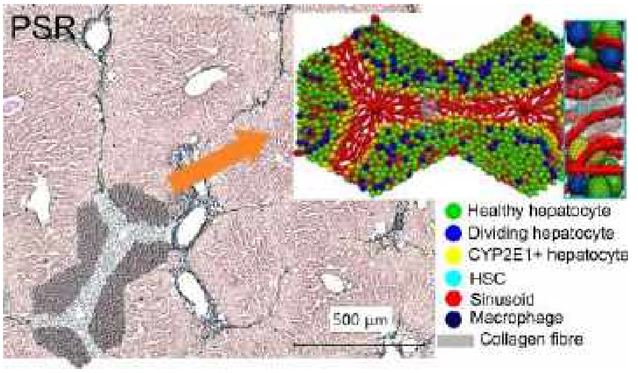
The following people have nothing to disclose: Nairuti Shah, David Feldman

3400-A | A DIGITAL LIVER TWIN DEMONSTRATING THE INTERPLAY BETWEEN BIOMECHANICS AND CELL KINETICS CAN EXPLAIN FIBROTIC SCAR FORMATION

Jieling Zhao[1], Seddik Hammad[2], Mathieu De Langlard[3], Pia Erdoesi[2], Yueni Li[4], Paul Van Liedekerke[5], Andreas Buttenschoen[6], Jan G. Hengstler[7], Matthias Ebert[8], Steven Dooley[9] and Dirk Drasdo[1,3], (1)Ifado, (2)Medical Faculty Mannheim Heidelberg University, Mannheim, (3)Inria, (4)Medical Faculty Mannheim Heidelberg University, Mannheim, Germany, (5)Ghent University, (6)University of Massachusetts Amherst, (7)Department of Toxicology, Leibniz Research Centre for Working Environment and Human Factors, Technical University Dortmund, Ardeystr 67, 44139, Dortmund, Germany, (8) Medical Faculty Mannheim, Heidelberg University, (9) University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

Background: Upon different types of liver injury, distinct patterns of fibrosis arise, such as extracellular matrix (ECM) septa connecting pericentral (CV) areas due to toxic injury. Formation of specific liver fibrosis patterns is a dynamic and multi-cellular process, which is difficult to uniquely explain by experiments both, in vivo and in vitro, and therefore not sufficiently understood. **Methods:** A well-designed digital liver twin is warranted to explore the possible mechanisms of fibrotic scar formation and progression as it permits a unique mapping from a set of hypothesized mechanisms to its consequences. The digital twin (DT) resolves liver microarchitecture including sinusoids, hepatocytes, hepatic stellate cells (HSCs), macrophages (Mph) and the ECM network, and integrates biomechanics and cell kinetics to study the mechanistic interplay of chronic injury-mediated formation of septal fibrotic walls based on iterative sets of experiments informing the model. Quantitative measures of fibrosis pattern-characterizing parameters were obtained through analysis of 2D and 3D images from mouse experiments to inform the DT. **Results:** The DT investigates the orchestration of cell types during septal fibrosis development and the mechanical interaction of cell populations with the ECM network. Using this DT, a potential scenario distinguishing regeneration of a characteristic cell death pattern after acute hepatotoxic insult and repeated hepatotoxic exposure leading to formation of septal fibrotic walls is proposed based on the spatial pattern of CYP2E1 (key metabolic enzyme) expressing cells. The attraction of activated HSC and Mph is controlled by damage-associated molecular patterns (DAMPs), which are governed by the spatial-temporal localization of CYP2E1 expressing hepatocytes. In addition, the remaining (healthy) cells proliferate to replace the dead hepatocytes, thereby mechanically compressing the fibrotic collagen network into "wall"-like shapes. DT predictions are quantitatively comparable with experimental findings using CYP2E1-disturbed mice upon CCl4 injections. To predict further players in septal fibrosis formation, DT-simulations upon perturbations (e.g. inhibition of hepatocyte proliferation, migration of HSC and phagocytic activity of Mph) are performed and permit DT validation. **Conclusion:** With the above, the DT predicts that septal fibrosis is driven by the spatial-temporal distribution of CYP2E1 expressing cells (source of DAMPs) and shaped by hepatocyte proliferation. The DT can be extended to investigate the switch from advanced fibrosis or cirrhosis to cancer setting.



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The following people have nothing to disclose: Jieling Zhao, Seddik Hammad, Mathieu De Langlard, Pia Erdoesi, Yueni Li, Paul Van Liedekerke, Andreas Buttenschoen, Matthias Ebert, Steven Dooley, Dirk Drasdo

3401-A | ABHD17B REGULATES HEPATIC STELLATE CELL ACTIVITY TO PROMOTE LIVER FIBROSIS

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Background: Chronic liver injury leads to hepatic stellate cell (HSC) activation and transdifferentiation into HSC myofibroblasts, which produce the extracellular matrix (ECM) responsible for fibrosis. While inhibiting the fibrotic activity of HSC myofibroblast has the potential to reduce progression and promote resolution of fibrosis, there are currently no therapies directed at interfering with the activity of these cells. **Methods:** We performed a high-throughput screen using small interfering RNAs (siRNAs) in primary human HSC myofibroblasts to identify gene products necessary to maintain the fibrotic phenotype. The primary screen analyzed siRNAs targeting > 7,500 mRNAs and > 2,000 long noncoding RNAs (lncRNAs), quantifying lipid accumulation as a phenotypic readout for HSC inactivation. The primary screen was performed with four siRNA duplexes for each target RNA. A deconvolution screen was then applied to assess the activity of each individual siRNA duplex for hits in the primary screen, and final candidates were evaluated to determine how siRNAs impacted expression of *COL1A1* and *ACTA2*. This analysis identified ABHD17B (Abhydrolase domain containing 17B, depalmitoylase) as a potential regular of HSC activity. ABDH17B was depleted in multiple primary human HSC lines, and the fibrotic activity of HSCs was evaluated by mRNA and protein expression. *Abhd17b-/-* mice were then challenged with carbon tetrachloride (CCl_4) as a model of chronic liver injury. Structural analysis of ABHD17B with molecular dynamics simulations following *de novo* folding with AlphaFold was performed to identify key amino acids in the hydrolase pocket of ABHD17B, and mass spectrometry was carried out to identify protein partners. **Results:** Depletion of ABHD17B in multiple primary human HSC lines resulted in reduced expression of *COL1A1* and *ACTA2*, and RNA-seq demonstrated a broader impact on ECM genes. Through mutation analysis, the active serine residue for hydrolase activity was defined, and mutation of this residue appeared to affect expression of *COL1A1*. Mice deficient in *Abhd17b* developed less liver fibrosis when exposed to CCl_4, and mass spectrometry analysis suggested that ABHD17B may promote fibrosis by allowing HSCs to respond to profibrotic cues from their environment. **Conclusion:** ABDH17B promotes expression of collagen and ECM proteins in HSC myofibroblasts to promote liver fibrosis. Targeting ABHD17B may have potential as an antifibrotic therapy.

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3402-A | ASK1/p38 AXIS INHIBITION BLOCKS THE RELEASE OF MITOCHONDRIAL “DANGER SIGNALS” FROM HEPATOCYTES AND SUPPRESSES PROGRESSION TO CIRRHOSIS AND LIVER CANCER

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Background: Apoptosis Signal-regulating Kinase 1 (ASK1) is activated by various pathological stimuli and induce cell apoptosis via downstream p38 activation. We studied the effect of pharmacological ASK1 inhibition on cirrhosis and its sequalae using comprehensive preclinical in vivo and in vitro systems. **Methods:** Short- (4-6 weeks) and long-term (24-44 weeks) ASK1 inhibition using small molecule GS-444217 was tested in thioacetamide-induced and BALB/c.*Mdr2-/-* murine models of cirrhosis and hepatocellular carcinoma (HCC), and in vitro using primary hepatocyte cell death assays. **Results:** Short-term GS-444217 therapy in both models strongly reduced phosphorylated p38, hepatocyte death, and fibrosis by up to 50%. In vitro and in vivo, profibrogenic release of mitochondrial DAMP mtDNA from dying hepatocytes was blocked by ASK1 or p38 inhibition. Long-term (24 weeks) therapy in BALbc.Mdr2-/- model resulted in moderate 25% reduction in bridging fibrosis, but not in net collagen deposition. Despite this, development of cirrhosis was effectively prevented, with strongly reduced $p21^{+}$ hepatocyte staining (by 72%), serum ammonia levels (by 46%) and portal pressure (average 6.07 vs 8.53 mmHg in controls). Extended ASK1 inhibition for 44 weeks in aged BALB/c.*Mdr2-/-* mice resulted in markedly reduced tumor number and size by ~50% compared to control group. **Conclusion:** ASK1 inhibition suppresses profibrogenic release of mtDNA from dying hepatocytes in p38-dependent manner and protects from liver fibrosis. Long-term ASK1 targeting resulted in diminished net antifibrotic effect, but the progression to liver cirrhosis and cancer in BALBc/$Mdr2^{-/-}$ mice was effectively inhibited. These data support the clinical evaluation of ASK1 inhibitors in fibrotic liver diseases.

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The following people have nothing to disclose: Zhenwei Peng, Guangyan Wei, Pinzhu Huang, Ping An, Shuangshuang Zhao, Yi Lin, Li Tan, Kahini Vaid, Disha Skelton-Badlani, Imad A. Nasser, Ming Kuang, Yury V. Popov

3403-A | C-C MOTIF CHEMOKINE RECEPTOR 2 INHIBITION REDUCES LIVER FIBROSIS BY RESTORING THE IMMUNE CELL LANDSCAPE

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Background: The accumulation of extracellular matrix (ECM) proteins in the liver leads to liver fibrosis and end-stage liver cirrhosis. C-C motif chemokine receptor 2 (CCR2) is an attractive target for treating liver fibrosis. However, limited investigations have been conducted to explore the mechanism by which CCR2 inhibition reduces ECM accumulation and liver fibrosis, which is the focus of this study. **Methods:** Liver injury and liver fibrosis were induced by carbon tetrachloride(CCl_4) in wild-type mice and *Ccr2* knockout ($Ccr2^{-/-}$) mice. Mice in the control group (olive oil group) were i.p. injected with olive oil for 6 weeks. For the murine preventive model, wild-type mice were i.p. administered 4 dosages of CVC (15 mg/kg body weight, Selleck #S8512) and 2 dosages of CCl_4 per week for 6 consecutive weeks. For the murine treatment model, mice were i.p. injected with CCl_4 for 3 weeks to induce liver fibrosis, and then 4 dosages of CVC and 2 dosages of CCl_4 per week were administered for another 3 weeks. For the acute liver injury experiment in $Ccr2^{-/-}$ mice, 2 doses of CCl_4 were i.p. injected. All mice were sacrificed 48 hours by an overdose of pentobarbital sodium after the final injection, and livers were taken for subsequent experiments. **Results:** CCR2 was upregulated in murine and human fibrotic livers. Pharmacological CCR2 inhibition with cenicriviroc (CVC) reduced ECM accumulation and liver fibrosis in prevention and treatment administration. In single-cell RNA sequencing (scRNA-seq), CVC was demonstrated to alleviate liver fibrosis by restoring the macrophage and neutrophil landscape. CVC administration and CCR2 deletion can also inhibit the hepatic accumulation of inflammatory FSCN1$^+$ macrophages and HERC6$^+$ neutrophils. Pathway analysis indicated that the STAT1, NFκB, and ERK signaling pathways might be involved in the antifibrotic effects of CVC. Consistently, *Ccr2* knockout decreased phosphorylated STAT1, NFkB, and ERK in the liver. *In vitro*, CVC could transcriptionally suppress crucial profibrotic genes (*Xaf1*, *Slfn4*, *Slfn8, Ifi213*, and *Il1b*) in macrophages by inactivating the STAT1/NFkB/ERK signaling pathways. **Conclusion:** In conclusion, this study depicts a novel mechanism by which CVC alleviates ECM accumulation in liver fibrosis by restoring the immune cell landscape. CVC can inhibit profibrotic gene transcription *via* inactivating the CCR2-STAT1/NFkB/ERK signaling pathways.

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3404-A | CONNECTIVE TISSUE GROWTH FACTOR IN LIVER SINUSOIDAL ENDOTHELIAL CELLS DRIVES LIVER FIBROGENESIS AND PORTAL HYPERTENSION IN CONGESTIVE HEPATOPATHY

Seiya Kato[1], Hayato Hikita[1], Akira Doi[2], Kazuhiro Murai[1], Yuki Tahata[2], Akira Nishio[3], Kunimaro Furuta[1], Takahiro Kodama[2], Tomohide Tatsumi[2] and Tetsuo Takehara[2], (1)Osaka University, Graduate School of Medicine, (2)Osaka University Graduate School of Medicine, (3)Osaka University Graduate School of Medicine, Bethesda, MD

Background: The detail mechanism of pathogenesis in congestive hepatopathy, such as right-sided heart failure, post-Fontan surgery and Budd-Chiari syndrome, remains unclear. We aimed to elucidate it focusing on the mechano-stress response in liver sinusoidal endothelial cells (LSECs). **Methods:** Partial IVC ligation (pIVCL) was performed to induce hepatic congestion in mice. Single-cell RNA sequencing (scRNA-seq) was performed using livers from the mice with pIVCL and sham operation. As in vitro experiments, primary murine LSECs or TMNK-1 cells, human liver endothelial cell line was subjected to mechano-stress including periodic mechanical stretch and hydrostatic pressure stimulation. **Results:** In the pIVCL group, portal venous pressure was significantly elevated 2 weeks after surgery compared with the sham group, and liver fibrosis was observed mainly in Zone3, which developed over time. Liver tumors were observed in half of the mice at 48 weeks after pIVCL. The scRNA-seq results showed that the expression of YAP/TAZ target genes, which play a central role in mechano-stress responses, was upregulated in LSECs in the pIVCL group, and that connective tissue growth factor (CTGF) was the most greatly upregulated gene in the whole LSEC population and more upregulated in zone 3 LSECs than in zone 1 LSECs. LSECs isolated from pIVCL-treated mice showed increased expression of YAP/TAZ target genes including CTGF, and the YAP/p-YAP ratio was increased at the protein level. In vitro experiments showed that the expression of YAP/TAZ target genes was upregulated in murine LSECs and TMNK-1 cells by mechanical stretch or hydrostatic pressure stimulation. The mechano-stress-induced CTGF upregulation in TMNK-1 cells was suppressed by siRNA-induced silencing of YAP/TAZ or YAP inhibitors. We generated tamoxifen-inducible endothelial cell-specific CTGF knockout mice (Cdh5-CreERT2+ CTGF$^{fl/fl}$), followed by pIVCL. CTGF KO in endothelial cells decreased the amount of intrahepatic hydroxyproline, Sirius red staining positive area in liver tissue sections and portal venous pressure in pIVCL-treated mice. **Conclusion:** In congestive hepatopathy, mechano-stress in the liver sinusoids activates YAP/TAZ and enhances CTGF expression in LSECs, which may contribute to the development of liver fibrosis and portal hypertension.

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3405-A | DELETION OF IGFBP7 INHIBITS THE PRO-FIBROGENIC EFFECTS OF M1 MACROPHAGES THROUGH YAP TARGET GENES

James C. Reed, Dana Lau-Corona, Min Xu, Charlotte Warner, Volney Spalding, Shadi Salloum and Raymond T. Chung, Massachusetts General Hospital and Harvard Medical School

Background: Insulin-like growth factor binding protein 7 (IGFBP7) has been implicated in the development of steatosis and fibrosis in NAFLD and NASH through partially known mechanisms. IGFBP7 is highly expressed in hepatic stellate cells (HSCs), macrophages, and other immune cells. It has been demonstrated that silencing IGFBP7 in liver macrophages reduces hepatic steatosis. Under pathological conditions, liver macrophages can polarize into distinct phenotypes (M1 and M2), which play crucial roles in promoting inflammation and liver fibrosis. In this study, we sought to investigate the contribution of macrophage-derived IGFBP7 to the activation of pro-fibrogenic programs and pathways that mediate this activation. **Methods:** U937-derived macrophages were transfected with small interfering RNA (siRNA) targeting IGFBP7. Furthermore, macrophages were polarized into M1 (IFN-γ and LPS) or M2 (IL-4/IL-13) phenotypes, with and without IGFBP7 silencing. Hepatic stellate cells (HSCs) were then exposed to conditioned media obtained from M0, M1, or M2 macrophages, both with and without TGF-β. Changes in gene expression associated with fibrosis and YAP-target genes were evaluated using quantitative real-time polymerase chain reaction (qRT-PCR). **Results:** Silencing of IGFBP7 in U937-derived M0 macrophages resulted in increased expression of genes associated with regenerative macrophages (e.g., MMP12, MMP13, IGF-1), while decreasing the expression of genes associated with inflammatory macrophages (e.g., TNF-α). Culturing HSCs in conditioned medium from M1 macrophages upregulated the expression of fibrosis-related genes (CTGF, TIMP1) and YAP-regulated genes (ANKRD1, CYR61). However, silencing IGFBP7 in M1 macrophages inhibited the ability of the corresponding conditioned medium to induce the upregulation of these genes in HSCs. Importantly, this inhibitory effect was not reversed by the addition of TGF-β to the culture medium. **Conclusion:** Our study provides evidence that IGFBP7 plays a central role in mediating the pro-fibrogenic properties of M1 macrophages on HSCs through the activation of YAP target genes. Further study is required to elucidate the precise molecular mechanisms by which IGFBP7 exerts its fibrogenic effects, but these findings highlight IGFBP7 as a possible therapeutic target for blockade of liver fibrosis.

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The following people have nothing to disclose: James C. Reed, Min Xu, Charlotte Warner, Volney Spalding, Shadi Salloum

3406-A | DEVELOPMENT OF ORALLY ADMINISTRABLE NUCLEIC ACID WITH LIVER FIBROSIS-IMPROVING EFFECT

Yoshiki Murakami[1,2], Masakatsu Takanashi[3], Tomohiro Umezu[1] and Masahiko Kuroda[1], (1)Tokyo Medical University, (2)Asahi University, (3)Azabu University

Background: There are currently no drugs primarily targeted for liver fibrosis. The current treatment of liver fibrosis is to prevent the progressing fibrosis by controlling the underlying disease, or to wait for the extracellular matrix accumulated as a result of inflammation to be absorbed naturally. Liver transplantation is the only treatment for severe liver cirrhosis. Previously, we have shown that treatment of miR-29a has an effect of promoting improvement of liver fibrosis in mouse chronic liver disease model. To investigate effective nucleic acid therapy with smaller doses, a modified nucleic acid was prepared based on the seed sequence of miR-29a. **Methods:** Modified nucleic acid constructed DNA-RNA hybrid with Fluoro and LNA substituents in 2' position. Liver fibrosis murine models (carbon tetrachloride) was used as chronic liver injury. Nucleic acid was dissolved in saline and orally administered, and a group administered with only saline was used as a comparison control. All cases were followed up for 7 weeks. (1) Carbon tetrachloride (CCL4) was administered for 5 weeks, followed by modified nucleic acid administration for 2 weeks (W). (2) CCL4 was administered for 7W, and nucleic acid was used in combination for the last 2W. Hepatic fibrosis and inflammation were evaluated by histological analysis. **Results:** We at first examined the localization of modified nucleic acids when administered orally. Mice labeled with Alexa647 on modified nucleic acid and fasted for 18 hours were orally administered with saline and sacrificed 2, 4, 24 hours later. When the labeled nucleic acid was observed on IVIS imaging system, the nucleic acid reached the small intestine after 2 hours and was not detected in the intestinal tract after 24 hours. The distribution of nucleic acids was observed in the liver and urinary system. After CCL4 stimulation, modified nucleic acid by oral administration for 2W, liver fibrosis-improving effect was observed as compared with the saline administered group. In addition, when stimulation with CCL4 was continued for 7W, and oral administration of modified nucleic acids for the last 2W, showed inhibitory effect on the progression of fibrosis compared to the saline administered group. **Conclusion:** we newly developed nuclease resistant nucleic acid. It was showed that this nucleic acid exhibits an anti-fibrotic effect orally without the use of liposome preparations, and is expected to be useful as a new method for treating fibrosis.

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3407-A | DIFFERENT ROLE OF GLUTAMINOLYSIS IN LUNG AND LIVER FIBROSIS

Ayse Okesli Armlovich, Olga Gulyaeva, Saritha Kusam, Yeonju Lee, Wallace Liu, Wesley Minto, Kelly Staiger, Devan Naduthambi, Tina Mistry, Minji Seung, Kelli Boyd, Bhanu Singh, Bruno Marchand, Lauri Diehl, Grant Budas, Anna Zagorska and Jamie Bates, Gilead Sciences, Inc.

Background: Activated fibroblasts are responsible for the deposition of extracellular matrix driving liver and lung fibrosis[1]. Glutaminolysis driven by GLS1 is required for metabolic reprogramming of hepatic stellate cells (HSCs) and lung fibroblasts (LFs) in vitro[2,3]. GLS1 protein expression increases in the scar region in human F4 NASH, whereas hepatocyte-restricted GLS2 decreases3. GLS1i reduced fibrosis markers in an acute liver fibrosis model (single injection of CCl4)[4] and a bleomycin model (BleoM) of idiopathic pulmonary fibrosis (IPF)[5]. **Methods:** GLS1/GLS2 expression was validated using immunohistochemistry, immunofluorescence. HSC/LFs were treated with TGFβ +/- GLS1i (48h), analyzed for procollagen and αSMA with ELISA and imaging. GLS1i IPN-60090 was tested at 100, 30, 10, and 3 mg/kg BID in a rat choline deficient high fat diet (CDHFD) model (6 wks diet plus 6 wks dosing) and mouse BleoM (dosing day 7-21). **Results:** In F4 NASH, GLS1 is in fibroblasts, immune cells, and vascular endothelial cells. In IPF, GLS1 is in fibroblasts, epithelial cells, and immune cells. GLS1$^+$PDGFRα$^+$ area increased ~4x in both IPF and NASH in comparison to healthy samples. GLS2 expression was undetected in IPF. Similar expression patterns were observed in the animal models. In LFs, GLS1i blocked TGFβ-induced cellular pro-collagen and α-SMA with a EC$_{50}$ of 70 ± 7 and 53 ± 8 nM, respectively. Glutamate (Glu) was reduced (EC50 of 76 ± 35 nM), with concurrent increase in glutamine (Gln). Similar effects were observed in HSCs. In CDHFD model, GLS1i exacerbated fibrosis by increasing PSR$^+$ area 1.3x and α-SMA+ area 1.6x in 30 mg/kg group. Liver toxicity was observed in 100 mg/kg group after 2 wks. In BleoM, GLS1i reduced Ashcroft score significantly from 4 to 2.5, and PSR$^+$ area from 2.2% to 0.5%. Liver Gln and Glu levels both increased 3.5x and 1.4x in the CDHFD model, whereas lung Gln levels increased 1.7x without significant change in Glu levels in BleoM. **Conclusion:** In liver and lung fibrosis GLS1 expression is elevated, however, GLS1$^+$ cell types and GLS2 expression differ in these organs. GLS1i resulted in opposite outcomes in liver vs lung fibrosis models. This could be due to differences in (1) mode of action in different cell types (2) adaptation mechanisms or (3) off-target effects of GLS1i. Additional studies are required to further understand the divergent roles of glutaminolysis in lung and liver fibrosis.

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3408-A | DISRUPTING DNA OF NEUTROPHIL EXTRACELLULAR TRAPS ATTENUATES ACTIVATION OF HEPATIC STELLATE CELLS AND AMELIORATES LIVER FIBROSIS IN A MODEL OF ALCOHOL PLUS NASH DIET INDUCED STEATOHEPATITIS.

Mrigya Babuta, Caroline Morel, Marcelle Ribeiro, Christopher Copeland, Prashanth Thevkar Nagesh, Yanbo Wang, Yuan Zhuang, Marti Ortega-Ribera, Jeeval Metha, Imad A. Nasser and Gyongyi Szabo, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background: Heavy alcohol use in obesity and non-alcoholic steatohepatitis (NASH) is associated with increased liver damage, fibrosis, and liver-related death. Mechanisms by which alcohol increases progression of NASH are unclear. Here, we aim to identify cellular and molecular mechanisms through which repeated alcohol binges exacerbate liver injury in a high fat-cholesterol-sugar diet (NASH diet) induced model of NASH. **Methods:** 8-10 weeks old male

C57BL/6 mice received either chow or NASH diet for 3 months with or without weekly alcohol binges. Liver tissue was analyzed for fibrosis and inflammation markers by immunohistochemistry, qPCR and western blotting. Neutrophil infiltration and neutrophil extracellular traps (NETs) were examined via Flow Cytometry, ELISA and immunofluorescence. **Results:** Alcohol binges in a diet-induced model of NASH lead to increased liver injury (transaminases level), profound fibrosis [protein level alpha-smooth muscle actin (α-SMA) and vimentin], neutrophil infiltration ($Ly6G^+$) and NETs formation (neutrophil elastase and citrullinated histone) compared to lean and NASH alone mice. We discovered that alcohol binge induced NETs *in vitro* an *in vivo* in the liver that was higher in NASH diet fed mice. The alcohol-induced cell-free NETs induced a robust pro-fibrotic phenotype in HSCs *in vitro* indicated by increased α-SMA and collagen 1 expression. Additionally, cell-free NETs promoted a pro-inflammatory phenotype in monocytes as evidenced by increased production of interleukin 1β, monocyte chemoattractant protein 1 and tumor necrosis factor-α. Abrogation of the fibrillar structure of NETs by DNase treatment prevented activated phenotype in both HSCs and monocytes. Furthermore, *in vitro*, reconstitution of NETs by culturing HSCs with recombinant citrullinated histone and DNA lead to activation of HSCs. Interestingly, alcohol-induced production of NETs and sensing of NETs by HSCs and monocytes was NLRP3 inflammasome dependent. *In vivo* inhibition of NLRP3 either by administration of MCC950 (NLRP3-inhibitor), or genetic deletion of NLRP3, significantly attenuated liver damage, neutrophil infiltration, NETs formation and fibrosis in steatohepatitis model. A similar protective phenotype was observed when NETs were disrupted by DNase treatment *in vivo*. **Conclusion:** We show that alcohol binges plus NASH induce steatohepatitis, neutrophil infiltration, NETs and fibrosis. Cell-free NETs directly induce pro-fibrotic stellate cells and pro-inflammatory monocyte phenotypes. Inhibition of NLRP3 or NET disruption by DNase treatment can prevent stellate cell and monocyte activation both *in vitro* and *in vivo* and attenuating liver injury. Thus, inhibition of NETs and/or NLRP3 may represent a therapeutic target to combat the pro-fibrotic effects of alcohol in NASH.

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3409-A | DKK3-EXPRESSING FIBROBLASTS PROMOTE HCC/ICC TUMOR PROGRESSION

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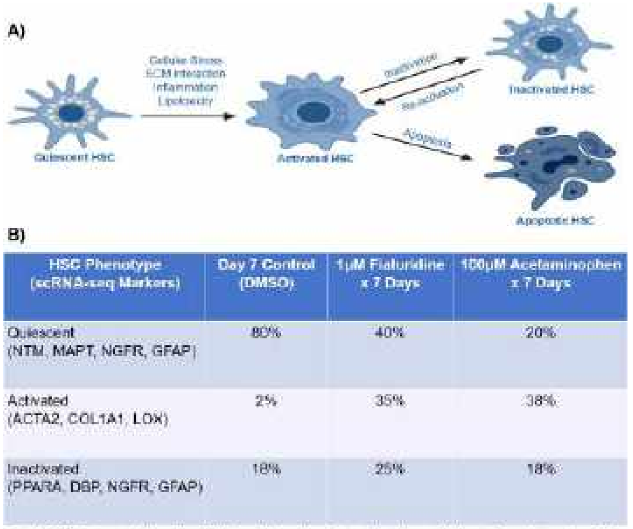
Background: Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCC) are the two most common primary liver cancers occurring in the chronic inflamed liver. The liver tumor microenvironment (TME) consists of different cell populations including cancer cells, infiltrating immune cells, endothelial cells and cancer associated fibroblasts (CAFs). CAFs are a very heterogenous cell-population within the TME, and they have a substantial influence on the development and progression of cancer through a wide variety of mechanisms including, secretion of cytokines and growth factors. We have identified a glycoprotein DKK3 specifically expressed in the liver tumor area by CAFs and we aim to investigate the potential of genetic or therapeutic suppression of DKK3 in controlling the liver cancer progression. **Methods:** Non-alcoholic steatohepatitis (NASH)-HCC model: C57BL/6 and DKK3 knockout ($DKK3^{-/-}$) mice were fed with choline-deficient high fat diet for 12 months to induce NASH and NASH-HCC. iCC model: To develop an iCC model, six-eight-week old mice were injected through hydrodynamic tail vein injection with different combinations of tumor oncogene plasmids and were characterized 6-8 weeks post injection. CAF isolation: CAFs were isolated by in situ liver perfusion/in vitro digestion and gradient centrifugation. Cells were further purified and sorted by negative selection strategy (EpCAM-CD45-CD31-) and submitted to the 10x genomics for library preparation and scRNA sequencing. Sphere formation: DKK3 knockout LX2 cells or control LX2 cells co-cultured with either hepatoma cell line, Hep3b, or cholangiocarcinoma cell line, Hucct-1, in ultra-low attachment plate to form spheres. **Results:** Co-localization of DKK3 and αSMA in fibrotic TME shows that activated fibroblasts are responsible for DKK3 expression in HCC and iCC. scRNA seq analysis not only confirmed our histological observations but also revealed that the two most common fibroblast subsets including inflammatory CAFs and myofibroblastic CAFs are high expressors of DKK3. Notably, these findings are corroborated in human primary liver cancers. The comparison between tumor growth in wild type and knockout mice in NASH-HCC model shows the significant reduction in tumor size in DKK3$^{-/-}$ livers compare to wild type counterparts. This is corroborated with reduced proliferation of cancer cells in the absence of DKK3+ fibroblasts. Notably, CD44v6 + cancer cells are barely seen in knockout tumors while the corresponding control wild type HCC are enriched with CD44v6+ cancer cells. In iCC model the number of large lesions was significantly higher in wild type mice when compared to DKK3$^{-/-}$ mice. In addition, deletion of DKK3 results in higher infiltration of immune cells into the tumor. **Conclusion:** DKK3 is expressed by activated fibroblasts within tumors and DKK3+ fibroblasts have a tumor promoting activity in both primary liver cancer types, HCC and iCC.

Disclosures: The following people have nothing to disclose: Neda Yahoo, Florian Müller, Paula Cantallops Vilà, Mirian Fernández Vaquero, Silvia Affo, Mathias Heikenwälder

3410-A | DRUG-INDUCED PERTURBATIONS OF NON-PARENCHYMAL STELLATE CELLS IN HUMAN LIVER ORGANOIDS USING CELL PAINTING AND SINGLE-CELL RNA SEQUENCING

Sophia Meyer[1], Charles Zhang[1], Robert J. Fontana[2] and Jonathan Sexton[3], (1)University of Michigan, (2) University of Michigan Medical Center, Ann Arbor, MI, (3)University of Michigan Medical Center

Background: In efforts to develop more physiologic in vitro models of human drug-induced liver injury (DILI), directed differentiation of stem cells towards human liver cells and multicellular human liver organoids (HLOs) have been developed. Here, we employ a multicellular HLO microfluidic chip platform as a model of DILI that is composed of ~60% hepatocytes, ~20-30% hepatic stellate cells (HSCs), and < 1% tissue-resident macrophages. There are limited in vitro HSC models that are capable of exhibiting physiologically relevant quiescent and activated states. We hypothesize that the HSC population of our HLO model is capable of drug-specific fibrotic intercellular signaling. **Methods:** Induced pluripotent stem cell line 72.3 was differentiated into definitive endoderm and then to HLOs over 28 days. HLOs were dispersed into single cells and cultured either on 384-well plates or microfluidic chips (HLO-chips). After 7 days of culture, cells were harvested for CYP450 expression quantification by qRT-PCR or CYP450 activity with 1- and 2-hour drug incubation by LC-MS. Mature HLO-chips at day 7 were cultured with either acetaminophen or fialuridine for an additional 7 days and stained for high-content imaging or harvested for single-cell RNA sequencing using NovaSeq 600. **Results:** Our HLO model is primarily composed of functional hepatocytes as evidenced by biomarkers, CYP450 expression, and CYP450 activity. The hepatic stellate cell population accounts for ~20-30% of the HLO population identified by reelin and desmin expression and 3-5% of HSCs express α-SMA. Under acetaminophen and fialuridine treatment, the hepatocyte population demonstrated evidence of intrinsic hepatotoxicity with elevated ALT and AST and decreased albumin expression. scRNA-seq analysis of the HSC population showed three distinct transcriptional profiles including an activated HSC state that was characterized by higher expression of inflammatory and cell proliferation markers. In addition, we observed a greater than 30% increase in the activated HSC population upon treatment with acetaminophen and fialuridine. Morphological profiling of distinct HSC phenotypes with high-content imaging will be presented. **Conclusion:** Along with parenchymal function displayed by hepatocytes, HSCs from our HLO model display mechanotransduction competency that can be specifically perturbed by hepatotoxic drug treatment. The HSC population is activated under drug treatment and cell signaling is specifically perturbed. Further development of the HLO-derived HSC may provide a superior bioassay system for modeling hepatic stellate cell dynamics.



HSC Phenotype (scRNA-seq Markers)	Day 7 Control (DMSO)	1µM Fialuridine x 7 Days	100µM Acetaminophen x 7 Days
Quiescent (NTM, MAPT, NGFR, GFAP)	80%	40%	20%
Activated (ACTA2, COL1A1, LOX)	2%	35%	38%
Inactivated (PPARA, DBP, NGFR, GFAP)	18%	25%	18%

Fig 1. A) Scheme of hepatic stellate cell mechanotransduction and phenotype dynamics. **B)** Population statistics of HSC phenotypes between drug treatments and control groups where markers of quiescent, activated, and inactivated HSCs were analyzed between clusters in scRNA-seq data and thus characterized based on relative expression.

Disclosures: The following people have nothing to disclose: Sophia Meyer, Charles Zhang, Robert J. Fontana

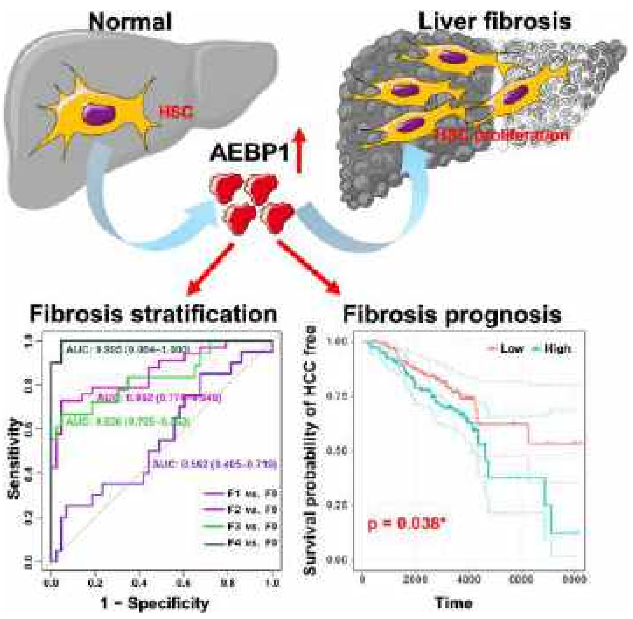
Disclosure information not available at the time of publication: Jonathan Sexton

3411-A | FIBROBLAST-SPECIFIC ADIPOCYTE ENHANCER BINDING PROTEIN 1 IS A POTENTIAL PATHOLOGICAL TRIGGER AND PROGNOSTIC MARKER FOR LIVER FIBROSIS INDEPENDENT OF ETIOLOGY

Wen Zhang[1,2], Yujia Li[3], Wei Chen[4,5], Ning Zhang[1,2], Yameng Sun[1,2], Shuyan Chen[1,2], Tao Huang[4,5] and Hong You[1,2], (1)Liver Research Center, Beijing Friendship Hospital, Capital Medical University, (2) Beijing Key Laboratory of Translational Medicine in Liver Cirrhosis, National Clinical Research Center of Digestive Diseases, Beijing, China, (3)Emory National Primate Research Center, Emory University, (4)Beijing Clinical Research Institute, Beijing, China, (5) Experimental and Translational Research Center, Beijing Friendship Hospital, Capital Medical University

Background: The glycosylated adipocyte enhancer binding protein 1 (AEBP1) is an extracellular protein involved in adipogenesis, epithelial-mesenchymal transition, epithelial cell hyperplasia and collagen fibrillogenesis. The main study objective was to analyze the potential of AEBP1 as a pathological target or prognostic marker for liver fibrosis regardless of etiology. **Methods:** Dysregulation pattern, clinical relevance and biological significance of *AEBP1* gene in liver fibrosis were analyzed using publicly available transcriptomic profiles, different liver fibrosis mouse models, biological databases, and *AEBP1* gene silence followed by RNA sequencing in human hepatic stellate cells (HSCs). **Results:** *AEBP1* was upregulated and positively correlated with liver fibrogenesis independent of any etiology, which was further verified in liver fibrosis mouse models induced by different pathogenic factors. Higher expression of liver *AEBP1* gene had potential to predict poor prognosis in liver fibrosis. Systematical bioinformatics analyses revealed *AEBP1* expression was HSCs-specific and associated with ECM remodeling and its downstream mechanical-chemical signaling transition. *AEBP1* knockdown by specific siRNAs in HSCs inhibited ECM-receptor interaction and immune-related pathways as well as HSCs proliferation.

Conclusion: Our current study confirmed high expression of *AEBP1* was specifically associated with liver fibrosis and predicted its poor prognosis and the role of AEBP1 in HSCs, providing a new insight for understanding AEBP1 in liver fibrosis.



Disclosures: The following people have nothing to disclose: Wen Zhang, Yujia Li, Wei Chen, Ning Zhang, Yameng Sun, Shuyan Chen, Tao Huang, Hong You

3412-A | FIBULIN-1 DEFICIENCY ALLEVIATES LIVER FIBROSIS THROUGH INHIBITING HEPATIC STELLATE CELLS ACTIVATION VIA p38 MAPK PATHWAY

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Fibulin-1 deficiency alleviates liver fibrosis through inhibiting hepatic stellate cells activation via p38 MAPK pathway Jingyu Zhang[1#], Wenshan Zhao[1#],Wen Xie[1*] [1]Center of Liver Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, China; **Background:** The stablization of elastin has been linked with reversibility of fibrosis. Fibulin-1 could participate in elastin assembly which promoted its stability. However, the role of Fibulin-1 in liver fibrosis has not been characterized. **Methods:** We examined the expression and localization of Fibulin-1 in CCl_4-induced liver fibrosis mouse models and cirrhosis patients. We constructed Fibulin-1-siRNA and overexpression plasmid to investigate the influence of Fibulin-1 on HSCs. Furthermore, we inhibited the expression of Fibulin-1 *in vivo* to observe the effect on elastin deposition and liver fibrosis reversal. Moreover, the regulation of elastin in different conditions on HSCs were detected. Finally, we used transcriptomic analysis to screen out the possible mechanism of Fibulin-1 in fibrosis and further confirmation was preformed *in vitro*. **Results:** Firstly, we found that Fibulin-1 level was increased in liver fibrosis models and plasma of cirrhosis patients, in parallel with significant accumulation of Fibulin-1 in cirrhosis stage. Fuctional analyses showed that Fibulin-1 silencing in HSCs could inhibit the HSCs activation, while the opposite effects were detected in Fibulin-1 overexpression. Moreover, Fibulin-1 depletion in CCl_4-induced liver fibrosis models could markedly ameliorated fibrosis progression, accompanied with decreased expression of profibrogenic genes and insoluble elastin contents. Furthermore, Fibulin-1D increased during liver fibrogenesis, rather than Fibulin1C, which might play a major role in elastin assembly. The stiffness of elastin combined with Fibulin-1D recombinant protein was dramatically increased than that of elastin alone. Based on these coated-plate models, LX-2 cells co-cultured with elastin and Fibulin-1D showed a higher expression levels of α-SMA, elastin and collagen I than those in elastin. Mechanistically, integrated RNA-sequencing and bioinformatic analysis indicated that Fibulin-1 mediated p38 MAPK pathway activation and inhibitor of p38 was used for further confirmation *in vitro*. **Conclusion:** Fibulin-1 deficiency alleviated liver fibrosis through reducing insoluble elastin, HSCs activation and p38 MAPK pathway might participate in the function of Fibulin-1.

Disclosures: The following people have nothing to disclose: Jingyu Zhang, Wen Xie

Disclosure information not available at the time of publication: Wenshan Zhao

3413-A | GADD45 α- REGULATES HEPATIC STELLATE CELL ACTIVATION

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Background: Chronic liver disease is a global health concern resulting from sustained liver injury. Liver damage activates hepatic stellate cells (HSCs) which deposit extracellular matrix proteins to drive fibrosis. Activated HSCs exhibit endoplasmic reticulum (ER) stress which induces the Unfolded Protein Response (UPR). UPR signaling in activated HSCs promotes fibrogenesis, but the profibrotic mechanisms downstream of the UPR are unclear. Our prior work showed that HSC activation and survival is dependent on UPR signaling downstream of Activating Transcription Factor 6α (ATF6α). Published scRNAseq analysis of HSCs isolated from CCl_4-treated mice revealed increased expression of Growth arrest and DNA-damage-inducible protein (GADD45A) compared to HSCs from controls. GADD45A is a UPR responsive protein which binds and modifies kinases and is implicated in cell survival. These data led us to study whether ATF6α facilitates HSC activation and fibrogenesis through GADD45A. **Methods:** RNAseq data from cirrhotic or non-cirrhotic livers was analyzed for *GADD45a* expression (GSE14323). Primary human HSCs (hHSCs) were treated with TGFβ ± ATF6α inhibitor Ceapin-A7 for 24h and analyzed by Western blot and qPCR. HSCs were isolated from non-fibrotic patients, immortalized, treated with TGFβ for 24h, and analyzed by mass spectrometry. LX-2 cells (immortalized HSCs) were transfected with siRNA targeting GADD45A or a scrambled oligo, and treated with vehicle or TGFβ. HSC activation was analyzed by qPCR, Western blot, or microscopy. *Gadd45a* $^{fl/fl}$ and *Gadd45a*$^{HSC\ \Delta/\Delta}$ mice received biweekly injections of CCl_4 or vehicle for 6 weeks before livers were harvested. Fibrosis markers were analyzed by hydroxyproline assay, Sirius Red staining, Western blot, and qPCR. **Results:** GADD45a expression increased in patients with cirrhosis and in hHSCs treated with TGFβ. TGFβ induction of GADD45a was blocked by ATF6α inhibition ($p < 0.05$). Proteomics analysis of HSCs isolated from patients revealed significant changes in several GADD45A binding partners (MAPK14, AURKA, CLEC3B, DNM2) following TGFβ treatment, and altered signaling downstream of GADD45A binding partners IRGM and p53. siRNA-mediated knockdown of GADD45A mitigated HSC activation and fibrogenesis, limiting both procollagen I induction by TGFβ and collagen I deposition ($p < 0.001$). In contrast to our *in vitro* findings, conditional deletion of *Gadd45α* from HSCs did not limit CCl_4-induced liver injury and increased *Col1a1* expression. **Conclusion:** We show that GADD45A is important for HSC activation and fibrogenesis downstream of ATF6α *in vitro*, but this role did not translate *in vivo*. This could be due to the diverse roles of GADD45A binding partners in HSCs or discrepancies between mouse and human HSCs. Future work will focus on understanding how GADD45A regulates HSC activation through its downstream targets, and how these mechanisms are differentially regulated between humans and mice.

Disclosures: The following people have nothing to disclose: Jessica Maiers, Wenjun Zhang, Burcin Ekser

Disclosure information not available at the time of publication: Reese A Baxter, Ethan D Goins, Alexander Jackson, Zachary Hanquier

3414-A | GALECTIN-9+ MACROPHAGES ATTENUATE LIVER FIBROSIS BY SUPPRESSING ACTIVATED HEPATIC STELLATE CELLS THROUGH TIM-3

Chaerin Woo, Tom Ryu, Min Jeong Kim, Song Hwa Hong and Won-Il Jeong, Kaist

Background: Liver fibrosis is characterized by the excessive accumulation of extracellular matrix, and currently, there is no standard treatment available. Recent studies have reported a correlation between serum galectin-9 levels and the extent of liver fibrosis in patients. However, the involvement of galectin-9 and its receptor, T-cell immunoglobulin mucin domain-containing-3 (Tim-3), in liver fibrosis remains unclear. Therefore, we investigated the specific cell types for the expression of galectin-9 and Tim-3, and their roles in the liver fibrogenesis. **Methods:** Liver fibrosis was induced in C57BL/6 wild-type (WT), Tim-3 knockout (Tim-3KO), and hepatic stellate cell (HSC)-specific Tim-3 conditional knockout (Tim-3$^{\Delta HSCs}$) mice. Serum and liver samples were collected for the biochemical and histopathological assessments including Sirius red staining and immunofluorescent staining, and the analyses of qRT-PCR and bulk-RNA sequencing. The liver mononuclear cells (MNCs) were subjected to flow cytometry analysis. Primary HSCs were isolated and cultured for subsequent *in vitro* experiments. **Results:** At sacrifice, serum levels of galectin-9 significantly increased in fibrotic WT mice compared to the control WT mice. In addition, qRT-PCR and FACS analyses revealed the increased expression of galectin-9 in CD11b$^+$Ly6G$^+$ neutrophils and CD11b$^+$F4/80$^+$ macrophages. Immunofluorescent staining showed that most galectin-9-expressing cells were macrophages and localized in fibrotic septa. However, Tim-3KO mice showed more increased liver fibrosis with Sirius red staining and elevated mRNA expression of *Acta2* and *Col1a1* than those of WT mice. Interestingly, bulk-RNA sequencing analysis demonstrated an upregulation of Tim-3 mRNA in activated WT HSCs compared to quiescent WT HSCs, which was also confirmed by qRT-PCR analysis. Moreover, treatments of recombinant galectin-9 decreased *Acta2* and *Col1a1* mRNA levels in activated WT HSCs but not in Tim-3-deficient HSCs. Furthermore, liver fibrosis was more severe in Tim-3$^{\Delta HSCs}$ mice than WT mice, with increased collagen accumulation and higher mRNA levels of *Acta2* and *Col1a1* in liver tissues. **Conclusion:** Our findings suggest that the galectin-9/Tim-3 axis contributes to the attenuation of liver fibrosis by suppressing HSC activation. Therefore, the interplay between galectin-9$^+$ macrophages and Tim-3$^+$ HSCs could be a potential therapeutic intervention for liver fibrosis.

Disclosures: The following people have nothing to disclose: Chaerin Woo, Tom Ryu, Min Jeong Kim, Song Hwa Hong, Won-Il Jeong

f 3415-A | GLYCOLYSIS-DEPENDENT EXTRACELLULAR VESICLES FROM HEPATIC STELLATE CELLS PROMOTE IN VIVO LIVER FIBROSIS.

Shalil Khanal[1], Ivan Vuckovic[1], Song Zhang[1], Vijay Shah[2] and Enis Kostallari[3], (1)Mayo Clinic, (2)Mayo Clinic Rochester, Rochester, MN, (3)Mayo Clinic, Rochester, Rochester, MN

Background: Platelet-derived growth factor (PDGF)-activated hepatic stellate cells (HSCs) release fibrogenic extracellular vesicles (EVs), important in cell-to-cell communication. Moreover, activated HSCs display increased glycolysis. While we have previously demonstrated that glycolysis is involved in EV release and liver fibrosis, the aim of this study is to decipher the mechanism of how HSC-specific glycolysis promotes biogenesis of fibrogenic EVs and how transplanting these EVs *in vivo* amplifies liver fibrosis. **Methods:** Primary human HSCs were examined by Glucose-Glo^{TM} assay, nuclear magnetic resonance (NMR) immunofluorescence (IF), electron microscopy (EM), qPCR and western blot (WB). *In vivo,* EVs were transplanted intraperitoneally, and liver fibrosis was induced by carbon tetrachloride (CCl$_4$) administration. **Results:** *In vitro*, PDGF increased glucose consumption (Glucose-Glo^{TM}, $n = 3$, $p < 0.05$) and lactate production (NMR, $n = 3$, $p < 0.05$) as compared to vehicle, suggesting that PDGF increases glycolysis in HSCs. Since PDGF also enhances HSC-derived EV biogenesis and subsequent release, we examined the effect of glycolysis on EV biogenesis. HSCs were treated with glucose or 2-deoxyglucose (2DG), where 2DG is a modified glucose that cannot be metabolized. Compared to glucose, 2DG significantly decreased multivesicular body (MVB)-associated CD63 staining by 2-fold (IF, $n = 5$, $p < 0.05$) and intraluminal vesicle number per MVB by 1.5-fold (EM, $n = 3$, $p < 0.05$), suggesting that glycolysis promotes EV biogenesis. Functionally, EVs from glucose-treated donor HSCs enhanced mRNA and protein levels of collagen 1 alpha 1 (Col1a1) and alpha smooth muscle actin (αSMA) in recipient HSCs by 1.5-2-fold compared to no-glucose condition. This was abrogated by EVs from 2DG-treated donor HSCs ($n = 4$, $p < 0.05$). To investigate the fibrogenic role of glycolysis-dependent EVs *in vivo*, we performed a mouse-to-mouse EV transplant. We utilized glycolysis-deficient donor mice where hexokinase 2 (HK2) is deleted specifically in PDGFRβ$^+$ HSCs, namely HK2$^{\Delta HSC}$ mice, and their HK2$^{fl/fl}$ controls. Compared to control, EVs from CCl$_4$-treated HK2$^{fl/fl}$ donor mice significantly increased Sirius red staining, Col1a1 and aSMA mRNA levels by 2.5, 3 and 2-fold, respectively. However, fibrosis was reduced when recipient mice were administered with EVs isolated from CCl$_4$-treated HK2$^{\Delta HSC}$ mice (9-10 mice/group, $p < 0.05$). **Conclusion:** Our results suggest that HSC-specific glycolysis promotes EV biogenesis to amplify fibrosis *in vitro* and *in vivo*.

Disclosures: The following people have nothing to disclose: Shalil Khanal, Vijay Shah, Enis Kostallari

Disclosure information not available at the time of publication: Ivan Vuckovic, Song Zhang

3416-A | HEPATIC STELLATE CELL-DERIVED THROMBOSPONDIN-2 AS A NOVEL THERAPEUTIC TARGET FOR LIVER FIBROSIS

Ning Zhang[1], Xiaoning Wu[2], Wen Zhang[1], Xuzhen Yan[3], Anjian Xu[1], Qi Han[4], Aiting Yang[3], Hong You[1] and Wei Chen[1], (1)Liver Research Center, Beijing Friendship Hospital, Capital Medical University, (2)Liver Research Center, Beijing Friendship Hospital, Capital Medical University, National Clinical Research Center of Digestive Diseases, Beijing, China, (3)Beijing Clinical Research Institute, Beijing, China, (4)Beijing Key Laboratory of Translational Medicine in Liver Cirrhosis, National Clinical Research Center of Digestive Diseases, Beijing, China

Background: Thrombospondin-2 (THBS2) dysregulation is closely associated with liver fibrosis regardless of etiology, and emerging to be a potential circulating biomarker. However, whether and how THBS2 acts a prominent role in the pathogenesis of liver fibrosis has not been elucidated yet. **Methods:** The *in vivo* effects of silencing *Thbs2* in hepatic stellate cells (HSCs) were examined using an adeno-associated virus vector (serotype 6, AAV6) containing short hairpin RNAs (shRNAs) targeting *Thbs2*, under the regulatory control of cytomegalovirus (CMV), U6 or smooth muscle α-actin (αSMA) promoter, in carbon tetrachloride (CCl_4) induced liver fibrosis mouse models. Crosstalk between THBS2 and toll-like receptor 4 (TLR4) as well as the cascaded signaling was systematically investigated in mouse models, primary HSCs, and human HSC cell lines. **Results:** THBS2 was predominantly expressed in activated HSCs and dynamically increased with liver fibrosis progression and decreased in regression. Selective interference of HSC *Thbs2* evidently retarded fibrosis progression and intrahepatic inflammatory infiltration (~55% inhibition) in mouse models challenged by CCl_4 intoxication. Mechanically, extracellular THBS2, as a dimer, specifically recognized and directly bound to TLR4 receptor, activating HSCs via stimulating downstream profibrotic focal adhesion kinase (FAK)/transforming growth factor beta (TGF-β) pathways. Disruption of THBS2-TLR4-FAK/TGF-β signaling axis notably alleviated HSC activation and liver fibrosis aggravation. **Conclusion:** THBS2 plays a crucial role in HSC activation and liver fibrosis progression through TLR4-FAK/TGF-β signaling in an autocrine manner. Therapies targeting HSC *Thbs2* via AAV6 vector-capsulated shRNA may represent a novel promising strategy to prevent or treat liver fibrosis.

Disclosures: The following people have nothing to disclose: Ning Zhang, Xiaoning Wu, Xuzhen Yan, Qi Han, Aiting Yang, Hong You, Wei Chen

Disclosure information not available at the time of publication: Wen Zhang, Anjian Xu

3417-A | HYDRONIDONE AMELIORATES LIVER FIBROSIS BY INHIBITING ACTIVATION OF HEPATIC STELLATE CELLS VIA Smad7-MEDIATED DEGRADATION OF TGFΒRI

Xianjun Xu[1], Yuecheng Guo[1], Xin Luo[1], Zhenyang Shen[1], Zhongshang Sun[2], Bo Shen[1], Cui Zhou[1], Junjun Wang[1], Jingyi Lu[1], Qingqing Zhang[1], Yanping Ye[3], Ying Luo[3], Ying Qu[1], Xiaobo Cai[1], Hui Dong[1] and Lungen Lu[1], (1)Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, (2)Huaian First People's Hospital, Nanjing Medical University, (3)Continent Pharmaceuticals Co., Ltd.

Background: Liver fibrosis is a wound-healing reaction that eventually leads to cirrhosis. Hydronidone (HDD) is a new pyridine derivative with the potential to treat liver fibrosis. In this study, we explored the antifibrotic effects of HDD and its potential mode of action. **Methods:** Histology, western blot, immunofluorescence staining, and RT-qPCR were used to detect the antifibrotic effect of HDD on 3, 5-diethoxycarbonyl-1, 4-dihydropyridine (DDC) and carbon tetrachloride (CCl_4) mouse hepatic fibrosis models. The effects of HDD on the activation of hepatic stellate cells were detected by western blot, immunofluorescence staining and RT-qPCR. Transcriptome sequencing analysis of HDD in hepatic stellate cells. Intervention of Smad7 in hepatic stellate cells with lentivirus and plasmid. The effect of HDD on transforming growth factor β receptor I (TGFβRI) was detected by western blot and immunoprecipitation. Construction of adeno-associated virus targeting Smad7 in hepatic stellate cells. **Results:** In DDC and CCl_4 mouse hepatic fibrosis models, HDD alleviated liver damage, collagen accumulation, decreased the expression of fibrosis-related genes, and inhibited the activation of hepatic stellate cells. HDD decreased the expression of fibrosis gene in hepatic stellate cells. HDD significantly up-regulated Smad7 expression and inhibited TGFβ-Smad signaling pathway in hepatic stellate cells. HDD promoted Caveolin-1 (Cav-1) mediated TGFβRI degradation via Smad7. Specific knockdown of Smad7 in vivo blocked the antifibrosis effect of HDD. **Conclusion:** HDD ameliorates liver fibrosis by inhibiting hepatic stellate cells activation via Smad7-mediated TGFβRI degradation. HDD is a potential drug candidate for the treatment of liver fibrosis.

Figure 1. HDD significantly improved liver fibrosis in CCl_4 and DDC mouse hepatic fibrosis models

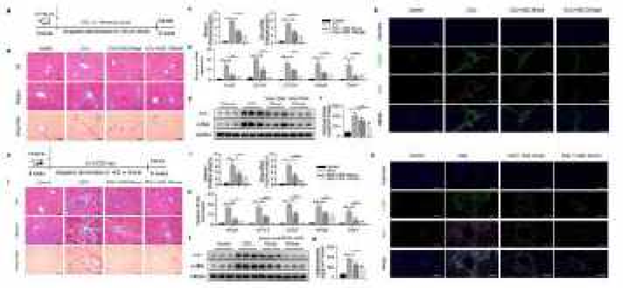


Figure 2. HDD inhibited the activation of hepatic stellate cells via Smad7

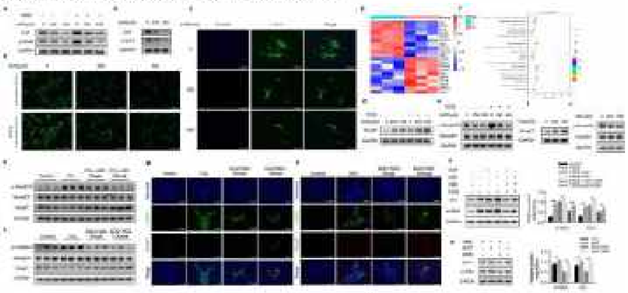


Figure 3. HDD promoted Cav-1-mediated degradation of TGFβR1 via Smad7 in a ubiquitin-proteasome dependent pathway

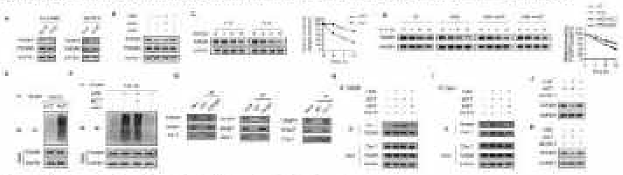
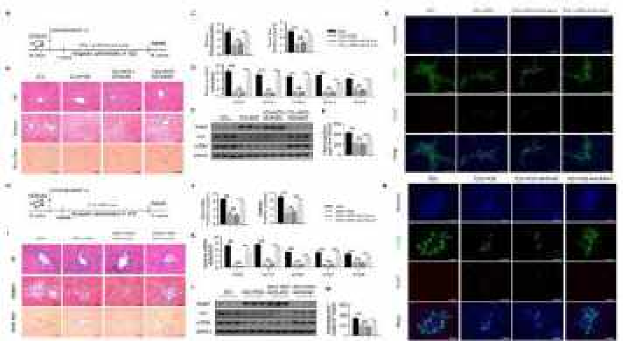


Figure 4. Knockdown of Smad7 diminished antifibrotic effect of HDD in mice



Disclosures: The following people have nothing to disclose: Xianjun Xu, Yuecheng Guo, Xin Luo, Zhenyang Shen, Zhongshang Sun, Bo Shen, Cui Zhou, Junjun Wang, Jingyi Lu, Qingqing Zhang, Yanping Ye, Ying Luo, Ying Qu, Xiaobo Cai, Hui Dong, Lungen Lu

3418-A | INHIBITION OF ENDOGENOUS HYDROGEN SULFIDE PRODUCTION REDUCES ACTIVATION OF HEPATIC STELLATE CELLS VIA THE INDUCTION OF CELLULAR SENESCENCE

Sandra A. Serna Salas[1], Turtushikh Damba[2], Mengfan Zhang[3], Zongmei Wu[1], Harry Van Goor[4], Javier Ventura-Juarez[5], Martin Humberto Munoz-Ortega[5], Manon Buist-Homan[6] and Han Moshage[1], (1)University Medical Center Groningen, (2)Mongolian National University of Medical Sciences, (3)Hospital of Zhengzhou University, (4)Umcg, (5)Universidad Autonoma De Aguascalientes, (6)University Medical Center of Groningen

Background: In fibrogenesis, quiescent hepatic stellate cells (HSCs) transdifferentiate into activated myofibroblast-like cells and produce large amounts of extracellular matrix. Cellular senescence is characterized by irreversible cell-cycle arrest, arrested cell proliferation and the acquisition of the senescence associated secretory phenotype (SASP) and reversal of HSCs activation. We hypothesized that inhibition of endogenous H_2S production induces cellular senescence and reduces activation of HSCs. **Methods:** Rat HSCs were isolated and cultured-activated and treated with H_2S slow releasing donor GYY4137 and/or DL-propargylglycine (DL-PAG), an inhibitor of the H_2S producing enzyme CTH, as well as the PI3K inhibitor LY294002. Senescence was determined by measuring the cell-cycle arrest markers Cdkn1a, p53, the SASP marker Il-6 and the activity of the senescence marker β-galactosidase. **Results:** CTH expression was significantly increased in fully activated HSCs compared to quiescent HSCs. Inhibition of CTH reduced proliferation and expression of fibrotic markers Col1a1 and Acta2 in HSCs and increased the cell-cycle arrest markers Cdkn1a, p53 and the SASP marker Il-6 as well as the number of β-galactosidase positive senescent HSCs was increased. H_2S donor GYY4137 partially restored the proliferation of senescent HSCs and attenuated the DL-PAG-induced senescent phenotype. Inhibition of PI3K partially reversed the senescence phenotype of HSCs induced by DL- PAG. **Conclusion:** Inhibition of endogenous H_2S production reduces HSCs activation via induction of cellular senescence in a PI3K-Akt dependent manner. Our results suggest that cell specific inhibition of endogenous H_2S production could be novel target for anti-fibrotic therapy via induction of cell senescence.

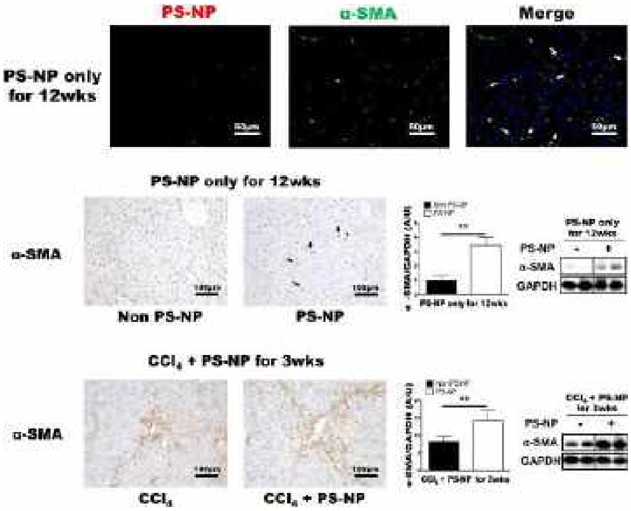
Disclosures: The following people have nothing to disclose: Sandra A. Serna Salas, Turtushikh Damba, Mengfan Zhang, Zongmei Wu, Harry Van Goor, Javier Ventura-Juarez, Martin Humberto Munoz-Ortega, Manon Buist-Homan, Han Moshage

3419-A | LONG-TERM ACCUMULATIONS OF POLYSTYRENE NANOPLASTICS SPECIFICALLY ACTIVATE HEPATIC STELLATE CELLS

Jae-Hyuk Yim, Su-Min Baek, Tae-Un Kim, Woo Jun Kim and Jin-Kyu Park, Kyungpook National University

Background: As plastics use increased, nanoplastics ingestion frequently increased by food or water due to environmental pollution. There have been several studies

showing that the ingestion of nanoplastics can cause damages to the marine lives by accumulation of nanoplastics in livers, kidneys, and brains. However, there is a lack of studies on how the accumulation of nanoplastics can cause organ damages in mammals over a long period of time. Therefore, we assessed the effects of long-term accumulation of nanoplastics on mammal liver and evaluated the risk of liver fibrogenesis. **Methods:** Liver fibrosis was induced by CCl_4 and polystyrene nanoplastics (PS-NPs) were injected 5 times a week for 12 weeks. Gross examination and histopathological analysis, serum biochemistry, immunofluorescence (IF) and immunohistochemistry (IHC) were performed to assess liver injury and fibrosis. Western blot and qRT-PCR were performed to reveal the related genes. **Results:** For 12 weeks, a scattered accumulation of PS-NP was observed in mice livers. Interestingly, some of PS-NPs were accumulated in α-SMA positive cells. When examining the α-SMA positive expression level in liver administered with PS-NP compared to liver without PS-NP, a higher number of extravascular α-SMA positive spindle cells were observed in PS-NP administered group. Furthermore, in western blot, it was found that the expression of α-SMA protein in the liver tissue was significantly increased in the PS-NP administrated group compared with the non PS-NP group. To analyze the effect of PS-NP on activation of hepatic stellate cells (HSCs), mice were treated with CCl_4 and PS-NP to induce liver fibrosis for 3 weeks. As a result of CCl_4 and PS-NP administration, it was confirmed that the number of α-SMA positive cells significantly increased, and α-SMA protein expression levels also increased by PS-NP administrations. **Conclusion:** This study has shown that long-term administration of PS-NPs were generally accumulated in the HSCs, thereby causing activation of these cells. HSCs, a key cell for inducing liver fibrogenesis, showed a higher α-SMA expression levels in the PS-NP treated groups compared with those non PS-NP treated groups in the CCl_4 group, which suggests continuous consumption of PS-NP promotes liver fibrosis by PS-NP induced HSC activations.



Disclosures: The following people have nothing to disclose: Jae-Hyuk Yim, Su-Min Baek, Tae-Un Kim, Woo Jun Kim, Jin-Kyu Park

3420-A | MAGP1 DEFICIENCY AUGMENTS EXTRACELLULAR MATRIX STABILITY AND RETARDS LIVER FIBROSIS REGRESSION VIA UPREGULATING MATRIX LOXL1

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Background: Microfibril-associated glycoprotein 1 (MAGP1) is a glycoprotein in the extracellular matrix (ECM) involved in the formation of microfibrillar skeletal structures. Up to present, the relationship between MAGP1 and liver fibrosis has not been reported yet. Herein, we aim to investigate the expression pattern, potential role, and possible mechanisms of MAGP1 involved in liver fibrosis. **Methods:** The expression pattern of MAGP1 in liver fibrosis was examined using publicly available transcriptomic gene expression profiles, tissue array of cirrhotic patients and carbon tetrachloride (CCl_4)-induced liver fibrosis mouse models. The roles of MAGP1 in liver fibrosis progression and regression were investigated using *Mfap2*(MAGP1 gene) knockout mice (*Mfap2*$^{-/-}$) undergoing CCl_4 injection or cessation. Mechanisms of MAGP1 deficiency involved in ECM stability and liver fibrosis regression were further explored using tissue decellularization, mass spectrometry proteomics, bulk RNA sequencing, and *in vitro* studies with human hepatic stellate cells (HSCs). **Results:** MAGP1 was predominantly expressed in activated HSCs and dynamically increased with liver fibrosis progression and decreased in regression. *Mfap2* knockout had no significant effect on liver fibrosis progression but increased ECM inflammatory infiltration and activated hepatic focal adhesion signal. However, interestingly, *Mfap2* ablation delayed the reversal of liver fibrosis after CCl_4 cessation. Liver decellularization followed by mass spectrometry proteomics revealed a significant increase in ECM insoluble collagen I and lysyl oxidase-like 1 protein (LOXL1) in *Mfap2*$^{-/-}$ mice compared to their littermates, which represented a possible cause resulting in the inhibition of liver fibrosis regression after

Mfap2 ablation. Further *in vitro* experiments in human HSCs confirmed overexpression of MAGP1 could inhibit LOXL1 expression, highlighting a compensatory crosstalk with each other. **Conclusion:** MAGP1 deficiency significantly promoted ECM stability and delayed liver fibrosis regression, compensatively by increasing matrix LOXL1 level. Our study might gain novel knowledge underlying liver fibrosis regression.

Disclosures: The following people have nothing to disclose: Wen Zhang, Wei Chen, Ning Zhang, Yameng Sun, Shuyan Chen, Xuzhen Yan, Qi Han, Aiting Yang, Hong You

3421-A | MECHANISM OF LIVER FIBROSIS CAUSED BY AUTOPHAGY-DEFICIENCY

Arissa Mercer, Bilon Khambu and Xiao-Ming Yin, Tulane University School of Medicine, New Orleans, LA

Background: Autophagy-deficiency in hepatocytes presents liver pathologies such as liver injury, inflammation, and fibrosis similar to common liver diseases affected by autophagy impairment. It is unknown how fibrosis develops in livers that are autophagy deficient. This study aims to examine the kinetics and mechanism of liver fibrosis development in autophagy-deficient livers. **Methods:** A conditional and inducible model of liver specific Atg7 knockout was characterized for liver fibrosis. Atg7 deletion was induced by tamoxifen injection on days 1 and 2. Trichrome C staining and Desmin or aSMA immunofluorescence staining or immunohistochemistry were used to assess the presence of fibrosis and the upregulation of fibrosis-related cells. Quantitative polymerase reaction and immunoblotting were used to examine fibrotic genes and proteins. **Results:** We found that Trichrome C staining for collagen was increased on the 20th day following Atg7 knockout. We also saw that markers for hepatic stellate cells and portal fibroblasts were increased in a pattern aligning with their involvement in the initiation and continuation of hepatic fibrosis. **Conclusion:** Autophagy-deficient livers activate portal fibroblasts (PF) and hepatic stellate cells (HSC) following an injury to the liver. The activation of PFs and HSCs can lead to the development of liver fibrosis in autophagy-deficient livers. The underlying signaling mechanism of PF and HSC activation and fibrosis development in the autophagy-deficient liver is currently being investigated. This study will be clinically relevant in understanding molecular events that are important in the early stages of liver diseases.

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Disclosure information not available at the time of publication: Xiao-Ming Yin

3422-A | MEDIUM-CHAIN FATTY ACIDS SUPPRESS COLLAGEN PRODUCTION AND ALTER THE PHENOTYPE OF HEPATIC STELLATE CELLS

Masashi Sakaki, Joo-Ri Kim-Kaneyama, Masahito Noguchi, Aya Miyauchi, Takahiro Fuji, Yumi Otoyama, Yoko Nakajima, Ikuya Sugiura, Jun Arai, Yuki Ichikawa, Shojiro Uozumi, Yuu Shimozuma, Manabu Uchikoshi and Hitoshi Yoshida, Showa University

Background: Medium-chain fatty acids (MCFAs) contain C6–C10 fatty acids that are absorbed from the upper gastrointestinal tract, transported to the liver via the portal vein, and rapidly become an energy source for hepatocytes. MCFA supplementation improves the metabolic pathology of adult-onset type II citrullinemia which pathogenesis is impairment of glycolysis, lipogenesis, and energy metabolism in hepatocytes by providing hepatocyte energy supply. Hence, the metabolic functions of the liver may be directly influenced by dietary intake of MCFAs. However, the detailed mechanism remains unclear. MCFAs may affect the pathogenesis of NASH, and in vitro, MCFAs may suppress collagen production in hepatic stellate cells (HSC) and alter the phenotype of HSC. **Methods:** NASH-HCC model mice (STZ-HFD) were divided into 4 groups at 10 weeks on (1) control fat diet, (2) medium-chain fatty triglyceride (MCT) diet (C8:C10 = 60%:40%), (3) long-chain triglyceride (LCT) diet, and (4) high carbo diet, and liver tissue steatosis, inflammation and fibrosis were evaluated at 15 weeks. The effects to the hepatic stellate cells of MCFA (C6, C8, C10) on hepatic stellate cells were evaluated in vitro using LX-2 and human hepatocytes (hHSC). **Results:** In the mouse model, MCT diet significantly inhibited steatosis, ballooning, and fibrosis compared to the control group ($p < 0.05$), and C10 stimulation significantly inhibited LX-2 and hHSC collagen production in vitro ($p = 0.039$, $p = 0.\ 0062$). Furthermore, C10 stimulation significantly decreased PDGFRβ($p < 0.0001$) and PAI-1($p < 0.0001$) expression and induced FOXO1 phosphorylation in hHSC. Inactivation of FOXO1 with FOXO1 inhibitor significantly suppressed collagen production in a concentration-dependent manner and attenuated the expression of PAI-1. **Conclusion:** MCFAs have beneficial effects on NASH pathology. C10 may suppress collagen production and alter the phenotype of HSC through FOXO1.

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

f 3423-A | MMP2+MMP14+TIMP2+ HEPATIC STELLATE CELLS IN LIVER TUMOR VS. LIVER FIBROSIS

Gurmehr Brar[1], Hye Yeon Choi[1], Issei Tsuchiya[1], Natalie Osterlund[1], Janice Seol[1], Linda S. Sher[2] and Hidekatzu Tsukamoto[1], (1)University of Southern California, (2)University of Southern California, Los Angeles, CA

Background: Hepatic stellate cells (HSC) co-expressing MMP2, MMP14, and TIMP2 (triple$^+$), activate MMP2 to mediate both matrix remodeling in liver fibrogenesis and tumor promotion via generation of a COL1 fragment and its binding to DDR1. However, how triple$^+$ HSC differ in liver fibrosis vs. tumor is largely unknown. **Aim:** We aimed to compare transcriptomic profiles of triple$^+$ HSC in liver tumor vs. fibrosis and identify potential tumor promoter genes uniquely expressed by HCC-associated triple$^+$ HSC in mice and patients. **Methods:** Liver IB analysis was performed for pro- vs. activated-MMP2 and intact vs. cleaved COL1 on *Col1a1-GFP* mice with F1-F2 liver fibrosis by alcohol-associated hepatitis (AH), bile-duct ligation (BDL), or CCl4 injections (CCl4) and with HCC by DEN injection and Western alcohol diet (DEN). Col1a1-GFP$^+$ HSC with vitamin A$^+$ (VitA$^+$) or VitA$^-$ were isolated by FACS and subjected to scRNA-seq. Aggregated sequencing data were filtered by *Mmp2*, *Mmp14*, and *Timp2* expression to compare transcriptomes of *Lrat*$^+$ triple$^+$ vs. *Lrat*$^+$ triple$^-$ cells. Patient HCC scRNA-seq data at scAtlasLC of NCI were re-analyzed and 10x Visium spatial transcriptomic analysis performed on patient HCC. **Results:** Active MMP2 and cleaved COL1 were similarly increased in the liver of all 4 models. The percentages of VitA$^+$ *Lrat*$^+$ triple$^+$ and VitA$^-$ *Lrat*$^+$ triple$^+$ cells in total *Lrat*$^+$ HSC were: 33% and 25% in AH, 36% and 52% in BDL, 74% and 64% in CCl4, 17% and 32% in DEN. Despite the lower %, the DEN triple$^+$ cells exhibited distinct transcriptomic profiles vs. the fibrosis models. Twenty-eight and 27 upregulated DEGs were identified in VitA$^+$ triple$^+$ and VitA$^-$ triple$^+$ cells in DEN vs. the fibrosis models. Upregulated DEGs shared by DEN VitA$^+$ and VitA$^-$ *Lrat*$^+$triple$^+$ cells included those implicated in angiogenesis (*Angptl6*), cell growth (*Efemp1*), chemotherapy resistance (*Inmt*), M2 macrophage polarization and EMT (*Bmp4*), and lipid transfer (*Pltp*). VitA$^+$triple$^+$ unique DEGs included *Ecm1* implicated in angiogenesis and *Plvap,* a VEGF-regulated gene in tumor-associated vascular fenestration. VitA$^-$ triple$^+$ unique DEGs included *Ccl19* involved in caner growth, *Sertad1*, a CDK4 stimulator and immunosuppressive *Gsn*. Human HCC spatial transcriptomic analysis revealed the close proximity of *ACTA2*$^+$triple$^+$ spots with *AFP*$^+$ or *HNF4A*$^+$*YAP1*$^+$ spots in HCC nodules and upregulation of the murine DEN triple$^+$ DEGs in *ACTA2*$^+$ triple$^+$ vs. *ACTA2*$^+$ triple$^-$ spots. Re-analysis of patient HCC scRNA-seq data confirmed *MMP2*$^+$ CAF are largely *MMP14*$^+$*TIMP2*$^+$ and their higher expression of the murine triple$^+$ DEGs such as *EFEMP1*, *INMT*, *BMP4*, and *PLTP*. **Conclusion:** HCC-associated triple$^+$ HSC express a unique set of genes with potential tumor promoting activities vs. triple$^+$ cells in liver fibrosis. The triple$^+$ aHSC in patient HCC with these genes upregulated and localized close to HCC cells, suggest their tumor promoting roles in addition to and independent of the COL1-DDR1 mechanism.

Disclosures: Hidekatzu Tsukamoto – HepaTX: Consultant, No, No;

The following people have nothing to disclose: Gurmehr Brar, Hye Yeon Choi, Issei Tsuchiya, Natalie Osterlund, Janice Seol, Linda S. Sher

3424-A | NEUTROPHIL GRANULOCYTES ARE INVOLVED IN THE DEVITALIZATION OF SCHISTOSOMA MANSONI EGGS

Ricarda Nadja Sölter, Verena Von Bülow, Dorothee Dreizler, Grit Stampa, Thomas Quack, Christoph Gero Grevelding, Max Möscheid, Annette Tschuschner, Heike Müller, Martin Roderfeld and Elke Roeb, Justus-Liebig-University, Giessen

Background: *Schistosoma mansoni* is a widespread parasitic disease with over 250 million people affected worldwide and is characterized by a complex lifecycle starting with the egg excretion with the feces. The larval stage of the cercariae can penetrate human skin. The schistosome couples migrate into the mesenterial veins, where they start the egg production. However, 50% of the eggs are flooded with the blood stream into different organs, like the liver, where they induce a chronic inflammation, leading to liver fibrosis and in combination with for example hepatitis B or C to hepatocellular carcinoma. The immune response is a crucial part of the granuloma formation and the resulting liver fibrosis. It is important to understand this process, to find treatments for *S. mansoni* infections and to stop the development of fibrosis and the carcinogenesis. **Methods:** In an animal experiment 4 groups of C57BL/6 mice were investigated. At the age of 8 weeks, they were infected with 100 cercariae of *Schistosoma mansoni*. 2 groups were also treated with Diethylnitrosamin at the age of 2 weeks to induce hepatocellular carcinoma. In total, 1 group was treated with DEN and infected with *S. mansoni.* Serving as controls, 1 group was treated with DEN and one group was infected with *S. mansoni.* The last group served as a super control. We did a histological grading of the liver tissue focusing on the inflammation and immunohistochemistry stainings of myeloperoxidase and CD-11b. Furthermore, a cocultivation of *S. mansoni* eggs and myeloperoxidase was performed. **Results:** *S. mansoni* infection leads to hepatic inflammation. During the histological grading, about 20% of the eggs seemed to be devitalized. Around and partly in these eggs are myeloperoxidase and CD-11b positive cells. Furthermore, the nuclear shapes are histologically identical to neutrophile granulocytes. The cocultivation of myeloperoxidase and *S. mansoni* eggs resulted in a higher percentage of calcein positive, vital eggs in the heat-inactivated myeloperoxidase group compared with the active myeloperoxidase, meaning the myeloperoxidase devitalize *S. mansoni* eggs *in vitro.* **Conclusion:** In total, neutrophil granulocytes seem to be involved in the destruction of *S. mansoni* eggs in the liver of infected mice. Myeloperoxidase can devitalize the *S. mansoni* eggs *in vivo* and *in vitro.* It might be one of the key substances in the inflammatory responses of the immune system to fight the chronic liver fibrosis, induced by misguided and stuck *S. mansoni* eggs in the liver.

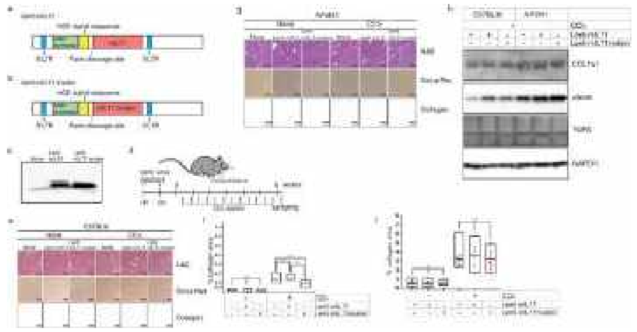
Disclosures: Elke Roeb – Gilead, Abbvie, Pfizer, Falk foundation, Merz, BMS, Intercept, Madrigal, Norgine,: Speaking and Teaching, No, Yes;

The following people have nothing to disclose: Ricarda Nadja Sölter, Verena Von Bülow, Dorothee Dreizler, Grit Stampa, Thomas Quack, Christoph Gero Grevelding, Max Möscheid, Annette Tschuschner, Heike Müller, Martin Roderfeld

3425-A | OVEREXPRESSION OF AP5M1 IN LIVER ENHANCES CCI4-INDUCED LIVER FIBROSIS BY ACTIVATING TGF-Β AND IL11

Ju-Yeon Cho, Tae-Hyoung Kim, Seung-Hyun Myung, Ji-Hye Han and Junghee Park, Chosun University

Background: In the initiation of liver fibrosis, transforming growth factor (TGF)-β plays an important role in the activation of hepatic stellate cells. Dysregulation of TGFβ1 and downstream IL-11 is associated with fibrotic diseases and a recent study reported that IL11 played a crucial role in the development of non-alcoholic steatohepatitis in mouse models. AP5M1, also called MUDENG, is known to participate in cell death and has been reported to be involved in Golgi trafficking. In a previous study by the authors, MUDENG transgenic mice demonstrated rapid development of fibrosis compared to C57BL/6N mice. In this study, we further identified the physiological effects of AP5M1 in mouse liver with overexpression and suppression of IL11. **Methods:** Eight 8-weeks-old male human AP5M1 transgenic (hAP5M1-Tg) mice and eight C57BL/6N male mice were injected with carbon tetrachloride (CCl_4) at a concentration of 2 μl per 1 g of mouse body weight intraperitoneally twice weekly (1:7 dilution with Olive oil). Lenti-mIL11 and Lenti-mIL11 mutein viruses were injected intraperitoneally into 6-week-old mice and intranasally into the mice after a week. (Fig1a-d) Livers were harvested at baseline for control and biweekly after intraperitoneal injection of CCl_4. The difference in the percent collagen area of the MUDENG transgenic mice and C57BL/6N mice was evaluated. Opensource software ImageJ (distributed by NIH) was used to calculate the collagen proportionate area of the liver after undergoing picoSirius red staining. **Results:** The collagen proportionate area (CPA) in C57BL/6N mice infected with Lenti:mIL11 or Lenti:mIL 11 mutein showed no difference in the absence of liver injury caused by CCl_4. However, CCl_4 injected Lenti:mIL11 mutein infected C57BL/6N mice demonstrated significantly reduced collagen accumulation in the liver tissue compared to Lenti:mIL11 infected C57BL/6N mice. (Fig 1e-f) In hAP5M1 transgenic mice, the infection of Lenti: mIL11 or Lenti:mIL 11 mutein showed no significant difference in the CPA. (Fig1g, 1i) The expression levels of collagen, α-SMA, and TGF-β were higher in the liver of hAP5M1-Tg mice challenged with CCl_4 than in the liver of C57BL/6 mice. (Fig1h) **Conclusion:** Overexpression of hAP5M1 enhances liver fibrosis caused by intraperitoneal injection of CCl_4. Compared to previous reported studies demonstrating that IL11 is a key factor of TGF-β-mediated liver fibrosis, C57BL/6N mice injected with Lenti:mIL11 mutein showed significantly reduced collagen accumulation in the liver. The application of IL11 mutein may be considered as a potential treatment method for alleviating liver fibrosis.



Disclosures: The following people have nothing to disclose: Ju-Yeon Cho

Disclosure information not available at the time of publication: Tae-Hyoung Kim, Seung-Hyun Myung, Ji-Hye Han, Junghee Park

3426-A | ROLE OF CEACAM1 IN NASH-ASSOCIATED HEPATIC FIBROSIS

Raziyeh Abdolahipour[1], Harrison T Muturi[1] and Sonia Najjar[2], (1)Ohio University, (2)University of Toledo

Background: Non-alcoholic Fatty Liver disease (NAFLD/NASH) has reached an epidemic rise amounting to a global prevalence of about 25% - 60% in obese individual's and in patients with type 2 diabetes. NASH, a chronic state of liver inflammation and injury, implicates activation of hepatic stellate cells and their transformation into myofibroblasts. This leads to excessive production of extracellular matrix (ECM) and collagen deposition, which destroys the architecture of the liver and causes liver fibrosis and dysfunction. Insulin-resistant obese subjects with NAFLD show low hepatic levels of CEACAM1, a plasma membrane glycoprotein that mediates insulin clearance and repression of fatty acid synthase activity in hepatocytes upon its phosphorylation by the insulin receptor tyrosine kinase. Consistently, CEACAM1 null mice (*Cc1−/−*) display spontaneous hyperinsulinemia and steatohepatitis with hepatic fibrosis when fed a regular diet. Feeding wild-type mice with a high-fat diet reduces CEACAM1 transcription via a mechanism depending on the activation of PPARα by free fatty acids (FFA). We herein tested whether GAN diet similarly reduces hepatic CEACAM1 expression by a PPARα-dependent mechanism and whether this leads to hepatic fibrosis. **Methods:** Knockin mice (Δ*Ppre*) bearing a mutation on the well-conserved PPRE on Ceacam1 promoter were generated and fed a GAN diet (2% cholesterol, 22% fructose, and 20% fatty acids) for 24 weeks to examine whether they are protected against GAN-induced hepatic fibrosis. Metabolic characterization, Western blot analysis and Sirius red staining were conducted to evaluate their NASH phenotype. **Results:** Mutating PPRE/RXRa on Ceacam1 promoter protected CEACAM1 against high-fat diet (45%). Interestingly, GAN diet caused insulin resistance, inflammation, and chicken-wire bridging fibrosis in wild-type but not in Δ*Ppre* knockin mice. In parallel, GAN diet caused a reduction in hepatic CEACAM1 protein levels in wild type but not in Δ*ppre* mice. **Conclusion:** Together, the data assign a key role for CEACAM1 repression in the pathogenesis of hepatic fibrosis.

Disclosures: The following people have nothing to disclose: Raziyeh Abdolahipour, Harrison T Muturi, Sonia Najjar

3427-A | SECRETOME OF SENESCENT HEPATIC STELLATE CELLS FAVORS MALIGNANT TRANSFORMATION FROM NONALCOHOLIC STEATOHEPATITIS-FIBROTIC PROGRESSION TO HEPATOCELLULAR CARCINOMA

Yuan Zhou[1], Li Zhang[1], Yue Ma[1], Li Xie[1], Yongyu Yang[1], Cheng Jin[1], Hui Chen[1], Jia Ding[2] and Jian Wu[1,3,4], (1)Dept. of Medical Microbiology, Fudan University School of Basic Medical Sciences, Shanghai 200032, China, (2)Shanghai Jing'an District Central Hospital, (3)Fudan University, Department of Gastroenterology and Hepatology, Zhongshan Hospital, Shanghai, China, (4)Shanghai Institute of Liver Diseases, Fudan University Shanghai Medical College, Shanghai 200032, China

Background: Hepatic fibrosis is a premalignant lesion, and how injured hepatocytes transform into malignancy in a fibrotic microenvironment is poorly understood. Senescence is one of major fates of activated hepatic stellate cells (HSCs). Paucity of literature is available regarding the influence of senescent HSCs on behaviors of steatotic hepatocytes. **Methods:** A mouse model of nonalcoholic steatohepatitis (NASH)-fibrosis-hepatocellular carcinoma (HCC) was established to recapitulate the progression from NASH to HCC by feeding high fat/calorie diet plus high fructose and glucose in drinking water (HFCD-HF/G) for 14 months. Senescent HSCs were identified in the mouse model and human NASH-HCC specimens. *In vitro* models of senescent HSCs were established from two perspectives including drug-induced DNA damage and cellular senescence due to natural replicative failure. Secretome of senescent HSCs was analyzed by label-free mass-spectrum (NanoRPLC-MS/MS) and verified quantitatively. **Results:** Senescent HSCs were increased along with the progression from nonalcoholic fatty liver (NAFL) (3.82%), NASH to NASH-fibrosis (12.57%), and reached a peak at the stage of advanced fibrosis (40.41%) and then decreased when hepatocellular dysplasia (22.86%) or HCC (14.58%) was developed. Critical components, such as platelet-derived growth factor, tumor necrosis factor, Y-box-binding protein 1 and vimentin affecting proliferation, epithelial-mesenchymal transition (EMT) or migration were identified from secretome of senescent HSCs. Two major secretary ligands for Hedgehog and Wnt signaling pathways, sonic Hedgehog (SHh) and Wnt-10b, were further verified by ELISA. Immunofluorescent staining and quantitative RT-PCR assays demonstrated that secretome of senescent HSCs might activate morphogenic Hedgehog or oncogenic Wnt signaling pathways to accelerate malignant transformation from steatotic or dysplastic hepatocytes. Primary hepatocytes stimulated with conditioned medium from or co-cultured with senescent HSCs exhibited an enhanced proliferating or EMT profile including increased expression levels of pluripotent genes, such as c-Myc, Oct-4, KLF-4, Nanog and Sox-2, and EMT-related genes, such as N-cadherin and vimentin. **Conclusion:** Senescent HSCs secreted a characterized profile of proteins favoring malignant transformation of steatotic or dysplastic hepatocytes through activating morphogenic Hedgehog or oncogenic Wnt signaling pathways in the progression of from NASH to malignancy. This initial discovery facilitates to develop preventive

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

strategies for NASH-HCC development by blocking fibrotic progression in NASH.

Disclosures: The following people have nothing to disclose: Yuan Zhou, Li Zhang, Yue Ma, Li Xie, Yongyu Yang, Hui Chen, Jia Ding, Jian Wu

Disclosure information not available at the time of publication: Cheng Jin

3428-A | SIRT7 PROTECTS LIVER FIBROSIS BY SUPPRESSING STELLATE CELL ACTIVATION VIA THE TGF-Β/SMAD2/3 PATHWAY

Cong Ding, Bohao Liu, Tingzi Yu, Wang Zhiqiang, Wenbin Tang and Zhuan Li, Hunan Normal University

Background: SIRT7 belongs to class III HDACs deacetylases, which regulates histone and non-histone protein acetylation and play critical role in various biological processes. Aberrant expression of SIRT7 is associated with tumorigenesis and tumor progression of liver cancer. However, the involvement of SIRT7 in hepatic fibrosis has not been fully elucidated. **Methods:** SIRT7 expression levels in human liver were examined by WB and IHC. Myeloid cell-specific knockout mice (LysM-Cre $SIRT7^{-/-}$) were generated by crossing $SIRT7^{flox/flox}$ mice with LysM-Cre mice. LysM-Cre SIRT7 and control mice ($Srit7^{flox/flox}$) were intraperitoneally injected CCl4 to induce liver fibrosis. The liver fibrosis was assessed by measuring fibrosis markers and associated genes. Primary hepatic stellate cells isolated to examine the effect of SIRT7 on HSC activation. The interaction of SIRT7 and SMAD2/3 were analyzed in vitro using overexpression, inhibitor, and immunoprecipitation assays. **Results:** SIRT7 expression were gradual decreased as it from hepatitis, fibrosis to cirrhosis patients, with minimal SIRT7 expression observed in cirrhosis but a significant increase in liver cancer samples. IHC indicated that SIRT7 primary expressed in nonparenchymal cell in hepatitis and fibrotic liver but predominantly expressed in hepatocyte in liver cancer. LysM-Cre $SIRT7^{-/-}$ resulted in significantly elevated alanine aminotransferase (ALT) levels, liver fibrosis and inflammation compared with wild-type mice after CCl4 administration. In response to TGF-β, $SIRT7^{-/-}$ primary hepatic stellate cells showed significant elevated α-SMA expression, mRNA related to HSC activation, and protein expression of α-SMA, smad2/3, and p-smad2. Inhibition of smad2/3 phosphorylation using a selective TGFβR (ALK5) inhibitor reversed SIRT7-mediated stellate cell hyperactivity. Mechanistically, we revealed that SIRT7 interacts with and deacetylates smad2/3 in LX2 cells. Overexpression of SIRT7 inhibited the TGF-β/smad2/3 signaling pathway. Most importantly, we observed that ALK5 abolished stellate cell activation and liver fibrosis in LysM-Cre SIRT7 mice after CCl4. **Conclusion:** Our findings demonstrate that SIRT7 directly modulates hepatic stellate cell activation by regulating the acetylation of SMAD2/3, thereby influencing the progression of liver fibrosis.

Disclosures: The following people have nothing to disclose: Cong Ding, Tingzi Yu

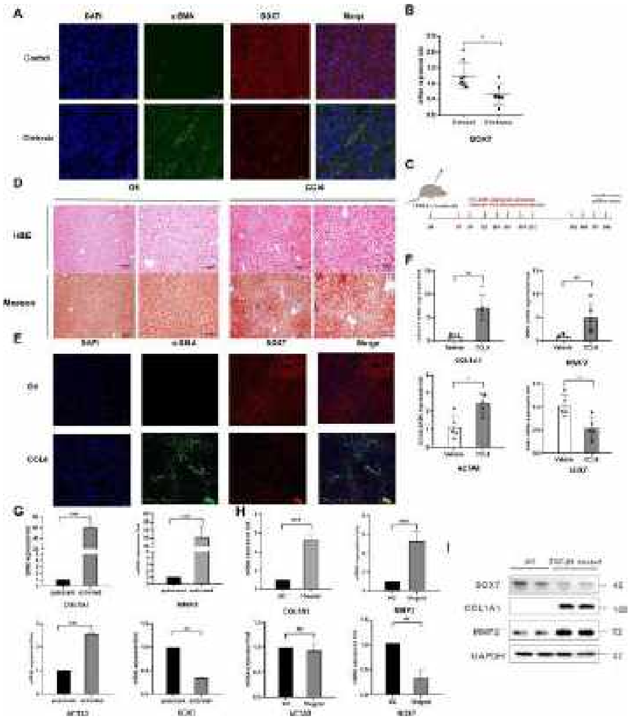
Disclosure information not available at the time of publication: Bohao Liu, Wang Zhiqiang, Wenbin Tang, Zhuan Li

f 3429-A | SOX7 ATTENUATES HEPATIC STELLATE CELL ACTIVATION AND LIVER FIBROSIS VIA REPRESSING Β-CATENIN AND TGFβ/SMAD SIGNALING PATHWAYS

Yuwei Liu and Junqi Niu, The First Hospital of Jilin University

Background: Liver fibrosis (LF) occurs after chronic liver injuries. Hepatic stellate cells (HSCs) activation is the essential pathological process of LF. The transcription factor SRY-related high mobility group box 7(SOX7) has been studied in angiogenesis and tumorigenesis, such as hepatocarcinogenesis. However, the role of SOX7 in hepatic stellate cell activation and liver fibrogenesis has not yet been investigated. In the current study, we explored the effect of SOX7 on liver fibrogenesis and the underlying molecular mechanism. **Methods:** We first screened the potential core transcription factors through differential expression analysis of HSCs microarray data and weighted gene co-expression network analysis (WGCNA) of liver tissue microarray data among GEO datasets and chose SOX7 for further investigation. Histological and transcriptome analyses on human cirrhotic livers were performed. Carbon tetrachloride (CCL4) treatment and bile duct ligation surgery were employed to induce liver fibrosis in mice. To establish in vitro activated cell model, LX-2 cells were stimulated with recombinant human transforming growth factor β1 (TGFβ1). The mRNA and protein levels of SOX7 and fibrogenic genes were compared in liver tissue with and without fibrosis and in quiescent and activated HSCs. Then, HSCs activation, proliferation, apoptosis, and modulated pathways were detected in SOX7 knockdown and overexpressed LX-2 cells. **Results:** SOX7 was decreased markedly in human and mouse fibrotic livers, particularly at the fibrotic foci. SOX7 was also downregulated in primary activated HSCs and TGFβ1 stimulated LX-2 cells. SOX7 knockdown promoted activation and proliferation of LX-2 cells while inhibiting their apoptosis. On the other hand, overexpression of SOX7 suppressed the activation and proliferation of HSCs. Mechanistically, SOX7 attenuates HSCs activation and LF by decreasing the expression of β-catenin and phosphorylation of SMAD2 and SMAD3 induced by TGFβ1. **Conclusion**:

SOX7 attenuates HSCs activation and LF via repressing β-catenin and TGFβ/Smad signaling pathways. Targeting SOX7, therefore, could be a potential novel therapeutic strategy to ameliorate LF.



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3430-A | STELLATE CELL WNTS REGULATE ENDOTHELIAL CELL-HEPATOCYTE ZONATION TO BALANCE HEPATIC METABOLISM-PROLIFERATION HOMEOSTASIS

Anya Singh-Varma[1]*, Shikai Hu*[1]*, Leon Min*[1]*, Brandon M. Lehrich*[2]*, Minakshi Poddar*[2]*, Ian Sipula*[1]*, Fiona M Bello*[1]*, Amber M Vandevender*[1]*, Sucha Singh*[2]*, Aaron W. Bell*[3]*, Michael Jurczak*[1]*, Silvia Liu*[2] *and Satdarshan (Paul) Monga*[2]*, (1)University of Pittsburgh School of Medicine, (2)University of Pittsburgh, (3)University of Pittsburgh, Sewickley, PA*

Background: The liver, a main regulator of homeostasis, is histologically organized into metabolic zones defined by distinct gene expression along the portal-central axis for functional division of labor. Current understanding of the maintenance of zonation defines endothelial cells (ECs) in pericentral zones as the source of Wnt2 and Wnt9b, which regulate hepatocyte ß-catenin activity and gene expression in this zone. Here, we investigate if there is any role of Wnts from hepatic stellate cells (HSCs) by characterizing mice incapable of secreting Wnts from these cells. **Methods:** Male and female HSC-specific Wntless (Wls) knockout (KO) mice were generated by interbreeding Wls-floxed mice and lecithin retinol acyl-transferase-driven Cre transgenic mice. Single nuclei RNA sequencing (snRNA), single cell spatial transcriptomics (scST), and immunohistochemistry (IHC) were performed to identify changes in gene expression and zonation between KO and littermate controls. Metabolism was assessed by bile acid composition and Oroboros and proliferation assessed after partial hepatectomy (PH) and acetaminophen (APAP) challenge. **Results:** No difference in baseline liver functions were evident in HSC-Wls KO versus controls. KO mice were overall smaller and had a greater lean-to-fat mass body composition than controls ($p < 0.05$). scST, validated with IHC, revealed expanded expression of normally pericentral genes like *Cyp2e1*, *Cyp7a1*, and *Cyp1a2* to mid- and periportal zones. Additionally, midzonal and periportal markers showed retracted expression to the periportal zone. Ingenuity Pathway Analysis on snRNA sequencing identified significant upregulation of xenobiotic, cholesterol, and bile acid metabolic pathways in hepatocytes. Bile acid analysis confirmed increased bile acid synthesis in KOs. Oroboros O2k Respirometry on mitochondria from KO livers demonstrated increased fatty acid metabolism and efficiency. Intriguingly, the observed zonation changes were not due to altered HSC zonation but rather pericentralization of sinusoidal ECs throughout the hepatic lobule as seen by altered Fabp4, c-Kit, and Wnt2 expression. Analysis of liver regeneration following insult by APAP toxicity or PH revealed impaired hepatocyte regeneration measured by Ccnd1 and Ki67 positive hepatocytes. **Conclusion:** HSC-Wnts regulate zonation of ECs and hepatocytes, to serve as the master regulator of metabolism and proliferation balance in the liver.

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Disclosure information not available at the time of publication: Ian Sipula, Fiona M Bello, Amber M Vandevender, Aaron W. Bell, Michael Jurczak, Silvia Liu

3431-A | STUDY ON SPLEEN REGULATING LIVER IMMUNITY THROUGH B CELL-DERIVED GABA AND AFFECTING THE PROGRESSION OF LIVER FIBROSIS

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Engineering Research Center of Biodiagnositics and Biotherapy, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China., (2)Shaanxi Provincial Clinical Research Center for Liver and Spleen Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China., (3)Shaanxi International Cooperation Base for Inflammation and Immunity, Xi'an, China

Background: Chronic liver disease is a serious threat to human health. Hepatic fibrosis is a key stage in the progression of chronic liver disease. Immune cells of liver participate in the process of liver fibrosis to varying degrees. The spleen can influence the progression of liver fibrosis by regulating liver immune cells, but the mechanism is still unknown. GABA is a major inhibitory neurotransmitter regulating interneuronal communication, which has also been fully proved to determine the fate of immune cells recently. GABA is synthesized and secreted by B cells outside the brain. B cells are important immune cells in the spleen and liver. Whether B cell-derived GABA plays a role in spleen regulating liver immunity and affecting the progression of liver fibrosis is worth study. **Methods:** In this study, flow analysis has demonstrated that B lymphocytes, especially $CD86^+$ B cells in liver of CCl_4-induced liver fibrosis mice was significantly increased compared with control group. And splenectomy reduced the proportion of B lymphocytes and $CD86^+$ B cells in liver of CCl_4-induced liver fibrosis mice. LC-MS analysis revealed that the content of GABA in liver and serum was significantly increased in the CCl_4-induced liver fibrosis mice compared with control group. However, the content of GABA in liver and serum was reduced in the liver fibrosis mice with splenectomy. Histopathological staining revealed that the degree of liver fibrosis in mice with splenectomy was alleviated. While, this situation was reversed by B cell reinfusion. It is also revealed that feeding GABA aggravated the degree of liver fibrosis in the CCl_4-induced liver fibrosis mice. Cell experiments showed that GABA could regulate the secretion of CCL2 and TGF-β by macrophage Raw264.7, which made JS1 highly express α-SMA and promote fibrosis. **Results:** Therefore, GABA content was increased with increased B lymphocytes in fibrosis mice. Increased GABA resulted in more secretion of CCL2 and TGF-β by macrophage, which made hepatic stellate cells expressed higher α-SMA and promoted fibrosis. However, splenectomy can reduce B lymphocytes and GABA content. **Conclusion:** Thus, the spleen may affect the progress of liver fibrosis by influencing the production of GABA by B cells to regulate liver immunity. Key words: liver fibrosis, spleen, B cells, GABA, immune regulation

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3432-A | TGFβ2 UPREGULATION ON REACTIVE CHOLANGIOCYTES LIMITS THE THERAPEUTIC EFFICACY OF TGFβ TRAP RAP-1332 IN MOUSE MODELS OF CHRONIC BILIARY INJURY AND FIBROSIS

Pinzhu Huang[1], Monica Shipman[1], Disha Skelton-Badlani[1], Richard Chen[2,3], Shekar Suragani[3], Patrick Andre[3], Wen Gao[1], Heansika Matta[1] and Yury V. Popov[4], (1)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (2)Merck & Co., Inc, (3)Acceleron Pharma Inc, (4)Harvard Medical School, Boston, MA

Background: RAP-1332 (murine ortholog of ACE-1334), is a new recombinant Fc fusion protein that functions as a ligand trap for TGFβ1 and TGFβ3 isoforms, but spares TGFβ2. Herein we report therapeutic effect of RAP-1332 in direct comparison with non-isoform selective TGFβ signaling inhibitor of ALK5, in mouse models of primary sclerosing cholangitis (PSC)-like biliary injury and fibrosis. **Methods:** RAP-1332 (1, 3 and 10 mg/kg twice a week) or ALK5 inhibitor (SB-525334, 30 mg/kg/day) was tested in clinically relevant mouse model of PSC-like mouse models of pre-established biliary fibrosis (BALBc.Mdr2-/-, n = 6-12/group) starting at 4 weeks (early therapy) or 6 weeks (delayed therapy) of age for the following 4-6 weeks, respectively. Portal venous pressure (PVP), serum liver function tests and histologic analyses were assessed at study endpoint. 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) feeding model of sclerosing cholangitis was used as a second, mechanistically different validation model. **Results:** Non-selective TGFβ suppression using Alk5 inhibitor led to readily detectable improvement of all liver injury and fibrosis parameters in both Mdr2-/- and DDC models. In contrast, both early and delayed administration of RAP-1332 into Mdr2-/- mice did not ameliorate PVP, splenomegaly, liver function, and liver fibrosis at low and medium doses, and led to paradoxical worsening of disease at high dose. In delayed therapy arm, ALT and AST were increased by 53.50% and 44.14%, respectively at high 10 mg/kg dose RAP-1332. Exacerbated ductular reaction and worsened periductular fibrosis was observed in mice receiving high dose of TGFβ1/3 trap, with 2-fold increase of collagen (histologically via morphometry) and 69.59% increase of hepatic hydroxyproline content compared to placebo. Likewise, TGFβ1/3 trapping by 10 mg/kg RAP-1332 in DDC model led to similar exacerbation of biliary injury and fibrosis, (40.23% increased hepatic hydroxyproline content).

Realtime PCR and *in situ* hybridization showed remarkable upregulation of TGFβ2 expression on actively proliferating reactive cholangiocytes. This was accompanied by adjacent expansion of α-SMA+ hepatic stellate cell and exacerbated inflammation (CD45+ and CD68+ cells). **Conclusion:** Our results suggest that selective blocking TGFβ1 and TGFβ3 in chronic biliary fibrosing disease is inefficient due to compensatory upregulation of TGFβ2 on reactive cholangiocytes. This non-dispensable pathological role of TGFβ2 should be accounted for in future design of TGFβ traps and therapeutic TGFβ targeting.

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Disclosure information not available at the time of publication: Monica Shipman, Richard Chen, Shekar Suragani, Patrick Andre

3433-A | THERAPEUTIC INHIBITION OF MIR-155 ATTENUATES LIVER FIBROSIS VIA THE TGFβ/SMADS/ STAT3 AXIS

Shashi Bala[1], Yuan Zhuang[1], Prashanth Thevkar Nagesh[1], Adam Zivny[1], Yanbo Wang[1], Jun Xie[2], Guangping Gao[2] and Gyongyi Szabo[1], (1)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (2)UMass Chan Medical School

Background: Most chronic liver diseases progress to liver fibrosis, which if left untreated, can lead to cirrhosis and end-stage liver disease. miRNA-targeted therapeutics has become attractive approaches to treat diseases. miR-155 is a multifactorial miRNA that is uniquely expressed in both non-parenchymal and parenchymal cells in the liver. In this study, we investigated the therapeutic potential of miR-155 inhibition in a well-established mouse model of liver fibrosis, bile-duct ligation (BDL) and evaluated the role of miR-155 in chronic liver fibrosis using miR-155 deficient mice. **Methods:** WT and miR-155 knockout (KO) mice were subjected to carbon tetrachloride (CCl_4) for 9 weeks or BDL for 2 weeks. For therapeutic inhibition of miR-155, rAAV8-scrambled or rAAV8-anti-miR-155 tough decoy was administered in BDL-induced liver fibrosis mouse model. *In vitro*, miR-155 gain- and loss-of-function studies were performed in human LX2 cells and isolated mouse primary hepatic stellate cells (HSCs) were used for gene expression and biochemical studies. **Results:** Liver miR-155 expression was elevated in patients with cirrhosis and in the mouse models of liver fibrosis (BDL or CCl_4) compared to normal controls. Liver fibrosis was significantly reduced in miR-155 KO mice after CCl4 administration or BDL. The administration of a rAAV8-anti-miR-155 tough decoy inhibitor *in vivo* significantly reduced liver damage and fibrosis in BDL. We found that BDL-induced protein levels of αSMA, vimentin, TGFβ, total SMAD 2/3, p-SMAD 2/3 and p-STAT3 were attenuated in anti-miR-155 treated mice compared to control mice revealing mechanistic insights into regulation of fibrotic pathways by miR-155. Consistent with the fibrosis promoting role of miR-155, hepatic stellate cells from miR-155 KO mice showed attenuation in the expression of activation, fibrosis and mesenchymal markers. *In vitro*, miR-155 gain- and loss-of-function as well as rescue studies using STAT3 inhibitor revealed that miR-155 regulates activation of stellate cells in part via STAT3 signaling. **Conclusion**: Our findings highlight miR-155 as an important regulator of liver fibrosis via its ability to modulate hepatic steallate cell activation via multiple molecular targets of the fibrogenesis pathway. Therapeutic inhibition of miR-155 might be an effective approach to ameliorate liver fibrosis.

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The following people have nothing to disclose: Prashanth Thevkar Nagesh, Yanbo Wang

Disclosure information not available at the time of publication: Shashi Bala, Yuan Zhuang, Adam Zivny, Jun Xie, Guangping Gao

f 3434-A | TREATMENT STRATEGY FOR LIVER FIBROSIS BASED ON Tcf21-INDUCED DEACTIVATION OF FIBROGENIC HEPATIC STELLATE CELLS

Takayo Yanagawa[1,2], Noriaki Hirayama[1], Jumpei Yasuda[1], Harumi Ogawa[1], Sachie Nakao[1], Mayumi Watanabe[1], Kota Tsuruya[3], Yoshitaka Arase[3], Tatehiro Kagawa[3] and Yutaka Inagaki[1], (1)Center for Matrix Biology and Medicine, Graduate School of Medicine, Tokai University, (2)Department of Physiology, Tokai University School of Medicine, (3)Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokai University School of Medicine

Background: Despite many attempts to suppress activation of hepatic stellate cells (HSCs) or inhibit excessive collagen production in activated HSCs, their application to anti-fibrotic treatment has not been established yet. We recently identified Tcf21 as a deactivation factor of fibrogenic HSCs. Adeno-associated virus-mediated *Tcf21* transfer into cultured HSCs and mice with experimental liver fibrosis not only suppressed fibrogenic gene expression but also restored the quiescent HSC marker expression both *in vitro* and *in vivo*. This change in gene expression profile of HSCs was accompanied by regression of steatohepatitis and fibrosis as well as improved hepatic architecture and function. In the present study, we explored the mode of action of Tcf21 and identified several small molecules that mimic the anti-fibrotic effect of Tcf21. **Methods:** *In silico* homology modeling and docking simulations were used to predict the minimal functional region of Tcf21 and for screening of small molecules that act as Tcf21 agonists. Anti-fibrotic effects of the candidate molecules were examined using primary human HSCs *in vitro* and experimental murine liver fibrosis models *in vivo*. **Results:** *In silico* homology modeling uncovered the ternary structure of the complex composed of Tcf21, its counterpart Tcf3, and target DNA. It also predicted a contiguous 28 amino acid sequence of Tcf21 that is essential for its binding to both Tcf3 and DNA. Transfection experiments revealed that the suppressive effect of this Tcf21 peptide on type I collagen gene transcription was comparable to that of full length Tcf21 in the presence of Tcf3. *In silico* screening of *ca* 7.7 million compounds identified 63 candidates that mimic the ternary structure of the functional Tcf21 peptide. Some of them suppressed expression of *ACTA2*, a representative target gene of Tcf21/Tcf3, in primary human HSCs in dose- and time-dependent manners. Administration of these small molecules to mice with experimental liver fibrosis inhibited *Acta2* and type I collagen gene expression, resulting in suppression of liver fibrosis without any overt adverse effects. **Conclusion:** A combination of *in silico* drug discovery methodology and *in vitro*/*in vivo* verification determined the minimal functional region of Tcf21 that mediates its anti-fibrotic effect and identified several hit compounds that mimic the anti-fibrotic action of Tcf21. These findings eventually lead to development of novel therapy for intractable liver fibrosis.

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The following people have nothing to disclose: Takayo Yanagawa, Noriaki Hirayama, Jumpei Yasuda, Harumi Ogawa, Sachie Nakao, Mayumi Watanabe

3435-A | USE OF DEEP LEARNING AND ARTIFICIAL INTELLIGENCE ALGORITHMS TO ANALYZE MACROPHAGES IN THE HEPATIC MICROENVIRONMENT

Omar A Saldarriaga[1], Esteban Arroyave[1], Daniel Millian[2], Timothy Wanninger[3], Daniel Bao[1], Sundus Bhatti[1], Michael Kueht[1], Moghe Akshata[1], Santhoshi Krishnan[4], Arvind Rao[5], Michael Zeitlin, Denis Papp and Heather Lynne Stevenson-Lerner[1], (1)University of Texas Medical Branch, (2)University of Texas Southwestern Medical Center, (3)University of Texas - Houston, (4)Rice, (5)University of Michigan

Background: We use several cutting-edge platforms that preserve the tissue architecture to study macrophages *in situ* within the hepatic microenvironment. **Methods:** Using imaging analysis software platforms with artificial intelligence capabilities, we custom design algorithms that allow us to not only quantify the numbers of macrophages within the liver and their spatial location but also their interaction with other phenotypes. We then compare the transcriptomic signatures of liver biopsies from patients using GeoMx digital spatial profiling and nCounter technology, enabling the identification of key biological pathways and biomarkers that portend poor outcomes. Using these platforms and algorithms, we study a variety of liver diseases including autoimmune hepatitis, non-alcoholic steatohepatitis, and infectious diseases such as viral hepatitis C and ebolavirus. We hypothesized that the heterogeneity of macrophages and associated gene expression profiles in different types of liver disease could explain the variability in the progression of injury and may provide potential targets for therapy. **Results:** Digital spatial profiling and multiplexed stained liver biopsies were scanned with imaging platforms. The heterogeneity of these various macrophage populations in the different types of liver disease was evaluated using deep learning/artificial intelligence applications to generate phenotype profiles, heat map matrices, t-distributed stochastic neighbor embedding plots (t-SNE) (Visiopharm®, MATLAB 2020a), and uniform manifold approximation and projection for dimension reduction (UMAP) comparisons. Variations in individual patients in each disease type were assessed using AVM software (Aqumin®) and showed that several patients within each disease group had variable expressions of specific genes that correlated with clinical outcome and severity of the liver injury. **Conclusion:** In summary, the use of custom-designed algorithms in several different types of liver disease revealed similar proinflammatory mediators within the hepatic microenvironment that included the enrichment of specific phenotypes, like those that were Mac387 positive. These findings suggest that intrahepatic macrophages, including proinflammatory phenotypes, are common critical contributors to immunopathogenesis in a variety of liver diseases.

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Disclosure information not available at the time of publication: Omar A Saldarriaga, Esteban Arroyave, Daniel Millian, Timothy Wanninger, Daniel Bao, Sundus Bhatti, Michael Kueht, Santhoshi Krishnan, Arvind Rao, Michael Zeitlin, Denis Papp

3436-A | ZNF469 AS A NOVEL PRO-FIBROTIC FACTOR IN LIVER FIBROSIS

Chaiyaboot Ariyachet, Faculty of Medicine, Chulalongkorn University

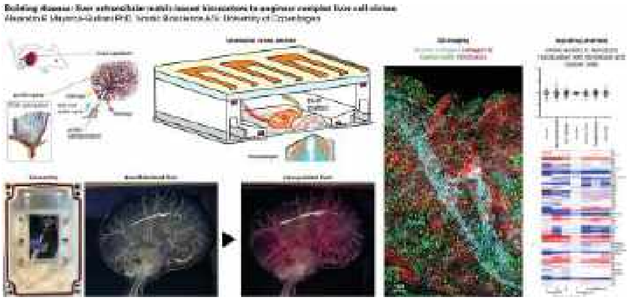
Background: Activation of quiescent hepatic stellate cells (HSCs) into proliferative myofibroblasts drives liver fibrosis; nevertheless, transcriptional network that promotes such the process remains elusive. From RNA sequencing data of human HSCs and liver tissues, we identified a putative zinc-finger transcription factor, ZNF469, upregulated upon HSC activation and in human cirrhotic livers. Thus, we hypothesized ZNF469 as a potential pro-fibrotic factor and aimed to elucidate its function in HSC activation. **Methods:** We modulated expression levels of ZNF469 in primary human HSCs and examined activation phenotypes including proliferation, migration, and collagen production. We then examined if TGF-b pathway regulated ZNF469 expression. We further cloned a full-length open reading frame (ORF) of ZNF469 with an epitope tag to study protein localization and perform chromatin immunoprecipitation (ChIP). Finally, we performed the RNA sequencing experiment of ZNF469-knockdown cells to assess its impact on gene expression in HSCs. **Results:** Knockdown expression of ZNF469 in primary human HSCs impaired proliferation, migration, and collagen production. In addition, ZNF469 suppression reduced deposition of collagen in HSC spheroids. Conversely, overexpression of ZNF469 in HSCs yielded the opposite results. TGF-beta can promote expression of ZNF469 in a Smad3-dependent manner. A cluster of Smad3 binding sites was found at the ZNF469 promoter, and the binding of Smad3 was enhanced upon TGF-beta stimulation. We successfully cloned a full-length ORF of ZNF469 (~12 kb) with an epitope tag and identified a nuclear localization of the protein. ChIP assays revealed the presence of ZNF469 at the promoter of fibrotic genes, supporting its function as a transcription factor. RNA sequencing data of ZNF469-knockdown HSCs revealed downregulation of several genes involved in biosynthesis of extracellular cellular matrix. **Conclusion:** ZNF469 is a profibrotic transcription factor that promotes activation phenotypes in myofibroblasts. We are testing its antifibrotic potential *in vivo* by development of adeno-associated virus (AAV) to suppress expression of ZNF469 in fibrotic livers. Together, this study will advance our understanding in transcriptional regulation of activated HSCs and suggest ZNF469 as a novel target for antifibrotic therapy.

Disclosures: The following people have nothing to disclose: Chaiyaboot Ariyachet

f 3437-A | BUILDING DISEASE: LIVER EXTRACELLULAR MATRIX-BASED BIOREACTORS TO ENGINEER COMPLEX LIVER CELL NICHES

Alejandro Mayorca Guiliani, Nordic Bioscience a/S

Background: The extracellular matrix (ECM) spanning the liver determines the architecture of its interconnected vascularity and the regularity of its parenchyma. ECM is an interwoven network that includes more than 300 proteins and glycans, organized to provide biomechanical support and biochemical orientation to all liver cells. Native liver ECM topography is enormously complex and cannot be replicated with current manufacturing technology, however, the centrality of the ECM in disease progression and collective cell behavior calls for disease models that factor this complexity in. Here, we present a liver bioreactor where cells are challenged to organize a 3D cell niche while being regulated by a microenvironment that retains the biological cues provided by the ECM. **Methods:** The hepatic bioreactor was designed to fit in a microscope stage and provide sterility, humidity, temperature, perfusion and waste removal. An optical window allows monitoring while set in a 2-photon microscope. To source native ECM, we performed post-mortem microsurgery in mice to catheterize the portal vein, resect a hepatic lobe and connect it to the bioreactor. Surgery was followed by decellularization, perfusion and cell repopulation. As proof-of-concept, we repopulated the liver matrix with cancer cells, fibroblasts, and macrophages to rebuild the liver metastatic niche. We then repopulated with human cells from colorectal liver metastasis aiming to recreate a human metastatic niche. To validate the bioreactor, we immunostained the liver matrix and evaluated ECM remodeling and global kinase signaling compared to *in vivo* and *in vitro* signaling. **Results:** The hepatic bioreactor successfully hosts ECM repopulation, under microscopic monitoring, longer than 21 days. It captured cell colonization in 3D and high-resolution, detecting cell division, migration, apoptosis, and cancer cell extravasation. We also imaged ECM remodeling driven by cancer cells and fibroblasts, thus simulating fibrosis and cell niche formation. Kinome phosphorylating activity in the bioreactor approximates to that found *in vivo*, thus suggesting that ECM imposes *in vivo*-like patterns of cell signaling. **Conclusion:** The ECM hepatic bioreactor is a novel, flexible disease model that opens the possibility to build engineered liver cell niches and experimental setups that would be impossible *in vitro* or *in vivo*. Cells in this system recapitulate *in vivo* signaling and remodel native ECM, suggesting its potential as drug development model.



Disclosures: Alejandro Mayorca Guiliani – Nordic Bioscience: Employee, Yes, No;

3438-A | DUAL $\alpha V\beta 6/\alpha V\beta 1$ INTEGRIN INHIBITOR BEXOTEGRAST ATTENUATES PROFIBROGENIC GENE EXPRESSION ACROSS MULTIPLE PATHOLOGIC CELL TYPES IN HUMAN LIVER EXPLANT TISSUE WITH BILIARY FIBROSIS

Johanna Schaub, Steve Ho, Chris S Her, Richard Ahn, Vikram Rao, Mahru An, Scott Turner and Martin Decaris, Pliant Therapeutics

Background: Bexotegrast (PLN-74809), a dual inhibitor of TGF-β-activating integrins $\alpha_V\beta_6$ and $\alpha_V\beta_1$, is currently in clinical development for the treatment of primary sclerosing cholangitis (PSC). To examine the effects of bexotegrast on the pathogenesis of PSC, we combined 10x single nuclei RNA sequencing (snRNA-Seq) with the precision-cut liver slice (PCLivS) platform to characterize the response of unique cell populations in fibrotic PSC and primary biliary cholangitis (PBC) PCLivS to bexotegrast treatment. **Methods:** Liver explants were collected from patients with PSC ($n = 3$) and PBC ($n = 1$) at the time of transplant. PCLivS were generated and cultured for 2 days in the presence of bexotegrast or vehicle (DMSO). A TGF-β receptor I kinase inhibitor (ALK5i; R-268712) was evaluated as a positive control for TGF-β signalling inhibition. Nuclei were isolated from two pooled slices per treatment and processed for single nuclear barcoding using 10x Chromium Next GEM 3' HT kits. Resulting libraries were sequenced, processed using CellRanger, and analyzed using Seurat. Custom annotation of cell types was performed using gene markers from published data sets. Differential gene expression was determined using a non-parametric Wilcoxon rank sum test. Analysis focused on genes with log2 fold-change > 0.5 and an FDR < 0.05. **Results:** snRNA-Seq analysis of PCLivS showed clear effects from bexotegrast treatment on distinct subpopulations of mesenchymal cells, endothelial cells, and cholangiocytes previously shown to be relevant in the pathogenesis of fibrotic liver disease. Bexotegrast significantly reduced type I collagen (*COL1A1)* expression in *PDGFRA*-high myofibroblasts composed of activated portal fibroblasts (*GREM1*$^{+}$) and activated hepatic stellate cells (*NGFR*$^{+}$) when compared to vehicle. Top gene ontologies (GO) for the genes downregulated by bexotegrast in myofibroblasts include "collagen fibril organization" (GO:0030199) and "extracellular matrix organization" (GO:0030198). In addition, bexotegrast significantly reduced the expression of profibrogenic ligands such as *PDGFB* in scar-associated endothelial cells (*CD34*$^{+}$*PLVAP*$^{+}$) and significantly reduced the expression of *ITGB6* and *EPHB2* in cholangiocytes. Reduction of profibrogenic gene expression from bexotegrast treatment across these cell types was similar in degree to that from ALK5i. **Conclusion:** Bexotegrast treatment resulted in clear reductions in profibrogenic gene expression across multiple pathologic cell populations in PCLivS prepared from human liver explants with biliary fibrosis. The similar degree of antifibrotic effect from bexotegrast compared to ALK5i in these experiments demonstrates the importance of the $\alpha_V\beta_6/\alpha_V\beta_1$ integrin-TGF-β activation pathway in fibrotic biliary disease. These data support ongoing clinical studies evaluating the anti-fibrotic effects of bexotegrast in PSC.

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3439-A | GENDER DIFFERENCES IN REPAIR MECHANISMS OF CHRONIC CHOLANGIOPATHIES WITH PROGRESSIVE FIBROSIS

Massimiliano Cadamuro[1], Labjona Haxhiaj[2], Chiara Montanaro[2], Erica Villa[3], Annarosa Floreani[2], Nora Cazzagon[2], Giovannella Baggio[2], Mario Strazzabosco[4], Paolo Simioni[2,5] and Luca Fabris[2,4,5], (1)Univeristy of Padua, (2)University of Padova, (3)Clinica Universitaria Policlinico Modena, (4)Yale University, New Haven, CT, (5)Padua University-Hospital

Background: In chronic liver disease pathophysiology, gender dimorphism is much less characterized compared with degenerative disorders affecting other organs. Repair mechanisms are instrumental to direct fibrogenesis and progression of chronic inflammatory conditions. Therefore, we investigated the gender-specific differences in tissue repair culminating in liver fibrogenesis and sustained by activation of hepatic progenitor cells (HPC) and ductular ductular reaction (DR) in two models of diseases of the biliary epithelium (cholangiopathies) featuring progressive fibrosis. We considered the Pkhd1$^{del4/del4}$ and the Mdr2$^{-/-}$ mouse models, orthologous of the human congenital hepatic fibrosis/Caroli's disease (CHF/CD) and primary sclerosing cholangitis (PSC), respectively, and in sections of human PSC and CHF/CD. **Methods:** Serial sections of liver tissue specimens of PSC ($n = 9$ M/$n = 5$ F) and CHF/CD ($n = 3$ M/$n = 1$ F), along with Pkhd1$^{del4/del4}$ ($n = 11$ M/$n = 23$ F), and Mdr2$^{-/-}$ mice ($n = 5$ M/$n = 3$ F), were stained with Sirius Red (histological staining) and with immunohistochemistry for myofibroblasts (α-SMA), macrophages (CD68, human samples only), and RDC/DR (K19). Extent of DR, fibrosis, inflammation and number of HPC were evaluated with computer-assisted morphometry. **Results:** In both mouse models and human diseases, fibrosis resulted higher in M compared with F, without significant differences in myofibroblast accumulation and HPC activation. In both Mdr2$^{-/-}$ mice and PSC patients, extension of DR was more prominent in M than F, whereas in Pkhd1$^{del4/del4}$ mice, dysgenetic biliary lesions were greater in F than in M. In addition, in PSC samples, the number of CD68+ macrophages was higher in M as respect to F. Similar trends were also found in human CHF/CD samples. **Conclusion:** This study shows gender-specific differences in tissue repair mechanisms of the biliary epithelium in both mouse models and human samples of PSC and CHF/CD. In particular, we found more severe fibrogenesis associated with more intense inflammatory infiltrate dominated by macrophages in males compared to females, thereby providing mechanistic evidence of the more severe clinical course of chronic liver diseases affecting men as reported in viral and metabolic etiologies.

Disclosures: The following people have nothing to disclose: Massimiliano Cadamuro, Labjona Haxhiaj, Chiara Montanaro, Erica Villa, Annarosa Floreani, Nora Cazzagon, Giovannella Baggio, Mario Strazzabosco, Paolo Simioni, Luca Fabris

3440-A | GULLIVER-2: A SUBGROUP ANALYSIS COMPARING TRANSAMINASE AND MODEL FOR END-STAGE LIVER DISEASE RESPONSES IN GB1211- VS PLACEBO-TREATED PATIENTS WITHOUT PHENOTYPIC NON-ALCOHOLIC STEATOHEPATITIS

Bertil Erik Lindmark[1], *Dimitar Tonev*[1], *De Phung*[1], *Vassilios Aslanis*[1], *Becky Smith*[1], *Robert Slack*[2], *Fredrik Zetterberg*[1], *Brian Jacoby*[1], *Mike Gray*[1], *Zahari Krastev*[3] *and Jordan Genov*[4], *(1)Galecto Biotech, (2)Galecto Biotech AB, (3)Comac Medical Ltd, (4)University Multiprofile Hospital for Active Treatment (UMHAT) "Tsaritsa Yoanna - Isul"*

Background: Galectin-3 (Gal-3) is a beta-galactoside binding lectin which regulates liver inflammation and fibrosis; high levels of Gal-3 correlate with severe liver disease. GB1211, a novel oral Gal-3 inhibitor, has shown potential in preclinical studies for reducing fibrosis and offering hepatocellular protection, as indicated by a reduction in transaminase leakage. Part 2 of the GULLIVER-2 trial (NCT05009680) is a Phase 2, double-blind, placebo-controlled study of patients (pts) with Child-Pugh B liver cirrhosis. Prior analyses demonstrated that GB1211 reduced transaminases and gamma-glutamyl transferase in the overall population. Among pts who completed 12 weeks of therapy, those treated with GB1211 had a decrease in model for end-stage liver disease (MELD) score of −1.4 vs an increase of +0.5 in pts who received placebo (Lindmark et al. AASLD 2022). Here, we compare the effect of GB1211 vs placebo in a subset of the GULLIVER-2 Part 2 study population, where pts with phenotypic non-alcoholic steatohepatitis (NASH) were excluded, to assess whether etiology affects pt response. **Methods:** Pts were randomized 1:1 to GB1211 100 mg twice daily or matched placebo for 12 weeks. Pts with phenotypic NASH were identified based on medical history, body mass index, and controlled attenuation parameter (CAP) values. The following parameters were assessed using percentage change from baseline: clinical biochemistry, MELD score, steatosis (assessed by CAP), and biomarkers (Gal-3 and cytokeratin-18 [M65]). **Results:** Thirty pts were randomized to GB1211 (n = 15) or placebo (n = 15). Five pts met the selection criteria for phenotypic NASH and were excluded from this analysis: 4 in the GB1211 group and 1 in the placebo group. Improvements were observed with GB1211 vs placebo for all parameters (Table); this was comparable with the total population. Of note, the MELD score decreased in pts treated with GB1211 but increased in pts treated with placebo (mean percentage change from baseline: −8.07 and +8.77, respectively; difference [95% confidence interval]: −16.83 [−37.79, 4.12]). **Conclusion:** The effects of GB1211 in pts without phenotypic NASH were consistent with those seen in the overall population of pts with Child-Pugh B liver cirrhosis (Lindmark et al. AASLD 2022). The safety and efficacy of GB1211 will be further explored in future studies in a defined population with NASH, as well as in pts with alcohol-related liver disease.

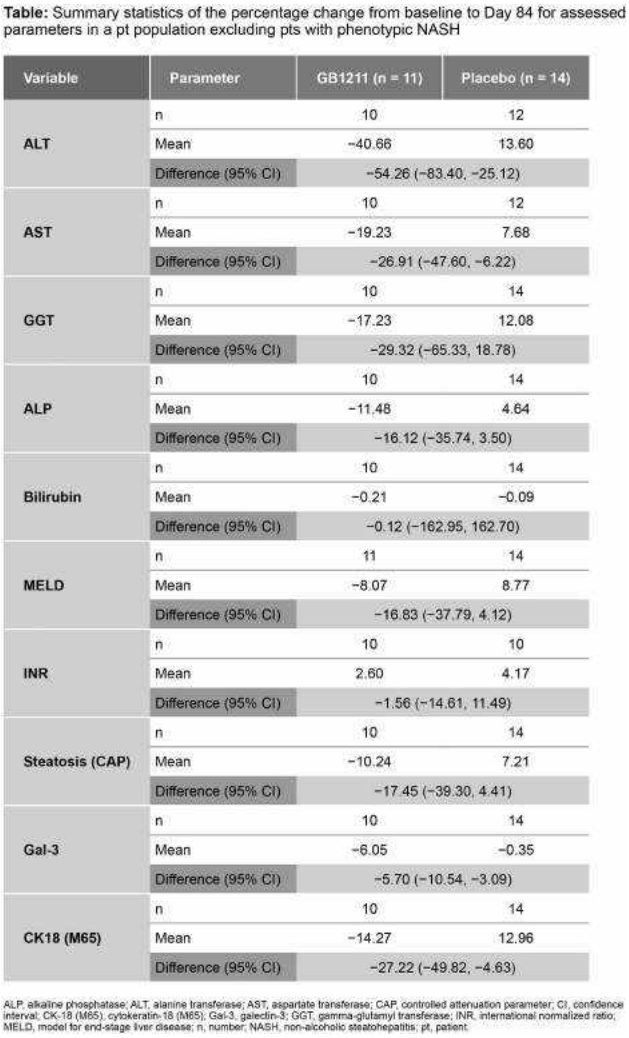

Table: Summary statistics of the percentage change from baseline to Day 84 for assessed parameters in a pt population excluding pts with phenotypic NASH

Variable	Parameter	GB1211 (n = 11)	Placebo (n = 14)
ALT	n	10	12
	Mean	−40.66	13.60
	Difference (95% CI)	−54.26 (−83.40, −25.12)	
AST	n	10	12
	Mean	−19.23	7.68
	Difference (95% CI)	−26.91 (−47.60, −6.22)	
GGT	n	10	14
	Mean	−17.23	12.08
	Difference (95% CI)	−29.32 (−65.33, 18.78)	
ALP	n	10	14
	Mean	−11.48	4.64
	Difference (95% CI)	−16.12 (−35.74, 3.50)	
Bilirubin	n	10	14
	Mean	−0.21	−0.09
	Difference (95% CI)	−0.12 (−162.95, 162.70)	
MELD	n	11	14
	Mean	−8.07	8.77
	Difference (95% CI)	−16.83 (−37.79, 4.12)	
INR	n	10	10
	Mean	2.60	4.17
	Difference (95% CI)	−1.56 (−14.61, 11.49)	
Steatosis (CAP)	n	10	14
	Mean	−10.24	7.21
	Difference (95% CI)	−17.45 (−39.30, 4.41)	
Gal-3	n	10	14
	Mean	−6.05	−0.35
	Difference (95% CI)	−5.70 (−10.54, −3.09)	
CK18 (M65)	n	10	14
	Mean	−14.27	12.96
	Difference (95% CI)	−27.22 (−49.82, −4.63)	

ALP, alkaline phosphatase; ALT, alanine transferase; AST, aspartate transferase; CAP, controlled attenuation parameter; CI, confidence interval; CK-18 (M65), cytokeratin-18 (M65); Gal-3, galectin-3; GGT, gamma-glutamyl transferase; INR, international normalized ratio; MELD, model for end-stage liver disease; n, number; NASH, non-alcoholic steatohepatitis; pt, patient

Disclosures: Bertil Erik Lindmark – Galecto Biotech: Employee, Yes, No; Galecto Biotech: Stock – privately held company (individual stocks and stock options), Yes, No; ALK-abello: Employee, No, No; ALK-abello: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No; Aqilion AB: Employee, No, No; Aqilion AB: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;

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The following people have nothing to disclose: Zahari Krastev, Jordan Genov

3441-A | HUMAN AMNION EPITHELIAL CELL TRANSPLANTATION IS SAFE AND WELL TOLERATED IN PATIENTS WITH COMPENSATED CIRRHOSIS – A FIRST IN HUMAN TRIAL

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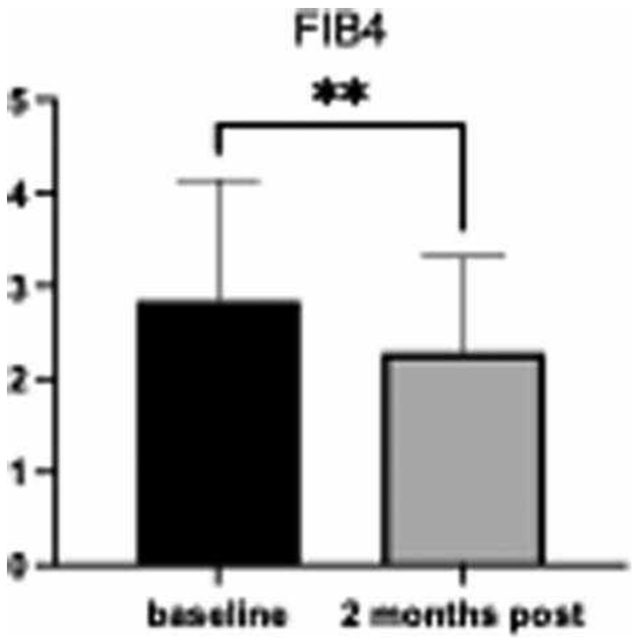
Background: We conducted a Phase 1 clinical trial to assess the safety and tolerability of human amnion epithelial cells (hAEC) in patients with compensated cirrhosis. hAEC are placental stem cells with anti-inflammatory and anti-fibrotic properties. **Methods:** We examined administering increasing hAEC doses and two doses over time in 9 patients in 3 cohorts (median age 57 years; 8 with NAFLD and 1 with prior HCV infection). Patients in cohort 1 (n = 3) received 0.5 x 10^6/kg hAEC in one IV infusion. Patients in cohort 2 (n = 3) received 1 x 10^6/kg hAEC in one IV infusion. Patients in cohort 3 received 1x10^6/kg hAEC at day 0 and at day 28. Follow-up to post-infusion day 56 is reported here. **Results:** No serious adverse events occurred. Six patients experienced no study related adverse events while 3 patients reported headaches that were possibly infusion related; all were mild (Grade 1). We observed a transient decrease in serum platelet levels in all patients which returned to near or above baseline screening values by day 5 post infusion. We observed significantly lower FIB-4 values at day 58 (Figure, $p = 0.007$). While not statistically significant, median serum AST values and liver stiffness measurements at day 56 were lower than at baseline. Hepatic venous pressure gradient (HVPG) was elevated at baseline in all patients except one patient whose baseline HVPG was 5 mm Hg. This patient was clinically cirrhotic with portal hypertension based on ultrasound findings, LSM 75 kPa and low serum platelets. At 2 months post infusion, this patient showed an increase in HVPG from 5 to 13 mm Hg likely reflecting the true portal pressure gradient. In 4 patients, there was a decline in HVPG at 2 months. Four patients showed either no change or a small increase in HVPG. **Conclusion:** Intravenous infusion of allogeneic hAEC in patients with compensated cirrhosis at the doses used in this study was safe and well tolerated. There was no difference between patients who received a single dose compared with those who received two doses. Promising signals of decreased hepatic inflammation, liver stiffness and portal hypertension support larger studies to understand which patients may benefit from this therapy.



Disclosures: The following people have nothing to disclose: William Sievert
Disclosure information not available at the time of publication: Rebecca Lim, Sherryne Leanne Warner, Alexander D. Hodge, Gregory Moore, Jeanne Correia, Siow Chan, Mihiri Goonetilleke, Stuart Lyon

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

Moying Li[1], Timo Itzel[1], Nathally Espinosa-Montagut[2], Thomas Falconer[3], Jimmy Daza[1], Jimyung Park[4], Jae Youn Cheong[4], Rae Woong Park[4], Isabella Wiest[1], Matthias Ebert[1], George Hripcsak[3] and Andreas Teufel[1], (1)Medical Faculty Mannheim, Heidelberg University, (2)School of Medicine, Universidad De Los Andes, (3)Columbia University Irving Medical Center, New York, NY, (4)Ajou University Graduate School of Medicine

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

Disclosures: The following people have nothing to disclose: Moying Li, Timo Itzel, Nathally Espinosa-Montagut, Thomas Falconer, Jimmy Daza, Jimyung Park, Jae Youn Cheong, Rae Woong Park, Isabella Wiest, Matthias Ebert, George Hripcsak, Andreas Teufel

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

Kutbuddin Akbary[1], Elaine Lay Khim Chng[2], Ya-Yun Ren[1], Dean Tai[2], Jonathan Andrew Fallowfield[3], Timothy James Kendall[4], Nikolai V. Naoumov[5], David E Kleiner[6] and Arun Sanyal[7], (1)Histoindex Pte Ltd, (2) Histoindex Pte Ltd, Singapore, (3)University of Edinburgh, (4)The University of Edinburgh, (5)Novarits Pharma AG, London, United Kingdom, (6)Laboratory of Pathology, National Cancer Institute, Bethesda, MD, (7) Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

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

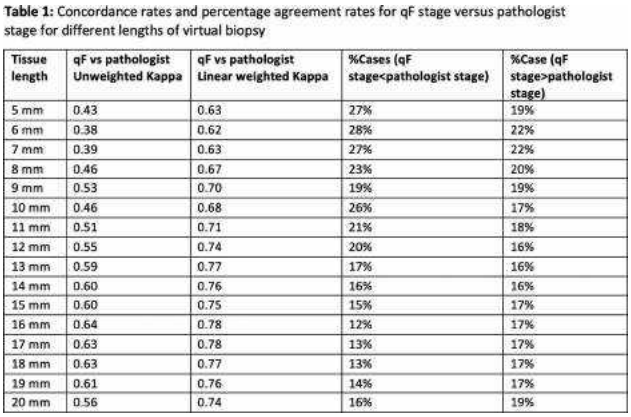


Table 1: Concordance rates and percentage agreement rates for qF stage versus pathologist stage for different lengths of virtual biopsy

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

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Disclosure information not available at the time of publication: Jonathan Andrew Fallowfield, Timothy James Kendall, Nikolai V. Naoumov

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

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

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

Background: Hepatocyte nuclear factor 4 alpha (HNF4α) is a nuclear receptor and master regulator of liver development and function. HNF4α expression is dysregulated in fibrotic liver disease and upregulation of this key transcription factor has been shown to improve hepatocyte function. The HNF4α gene is driven by two promoters, with isoforms derived from the P1 promoter demonstrating enhanced transcriptional activity associated with therapeutic benefit. The OMEGA platform develops programmable mRNA medicines called Omega Epigenomic Controllers (OECs) that precisely tune gene expression by site-specifically modulating epigenetic state and can be delivered using tissue-specific lipid nanoparticles (LNPs). Using OECs to induce selective upregulation of the P1 isoform of HNF4α in a liver-specific manner represents a novel therapeutic strategy for the treatment of fibrotic liver disease. **Methods:** The multigenic Insulated Genomic Domain and component sequences driving epigenetic control of the human *HNF4A* gene were interrogated and OECs were designed to modulate its expression. AML (K562) and hepatic stellate (LX-2) cell lines and primary human hepatocytes were transfected with LNP-encapsulated OECs (LNP-OEC) and qPCR or IHC was performed to assess HNF4α expression. For the *in vitro* fibrosis assay, LX-2 cells were treated with TGFβ1 and transfected with LNP-encapsulated OECs, and changes in expression of pro-fibrotic markers were measured by qPCR. To measure *in vivo* induction of HNF4α, a single dose of LNP-encapsulated OEC was administered intravenously to humanized $Fah^{-/-}$/$Rag2^{-/-}$/$Il2rg^{-/-}$ (FRG) mice and qPCR was performed to measure HNF4α expression. **Results:** Treatment with single OECs or combinations of OECs in K562 and LX-2 cells resulted in robust upregulation of total HNF4α mRNA levels and corresponding increases in HNF4α protein levels were observed. Treatment of primary human hepatocytes with OECs resulted in a strong induction of HNF4α P1 promoter isoforms compared with minimal effect on P2 promoter isoforms. Col1a1 and αSMA expression was significantly reduced (~50%) in LX-2 cells following treatment with a combination of OECs. A single, optimized OEC was developed that led to durable induction of HNF4α mRNA levels (up to 10 d, as intended/programmed) in both K562 cells and primary human hepatocytes. Administration of a single dose of the optimized OEC to the FRG mouse resulted in a significant induction of HNF4α mRNA compared with untreated mice. **Conclusion:** We demonstrate the ability to increase the expression of HNF4α with OEC treatment both *in vitro* and *in vivo*. In addition, this modulation preferentially induces the upregulation HNF4α P1 promoter isoforms resulting in inhibition of fibrotic responses *in vitro*. Future studies will test the efficacy of this upregulation in liver disease models and further explore the therapeutic potential of epigenomic targeting of HNF4α in fibrotic liver disease.

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3445-A | INHIBITION OF HISTONE DEACETYLASE (HDAC) DECREASES LIVER FIBROSIS IN MICE

Devadoss J. Samuvel[1], John J. Lemasters[1], C. James Chou[1,2] and Zhi Zhong[1], (1)Medical University of South Carolina, (2)Neuroene Therapeutics

Background: Liver fibrosis/cirrhosis is one of the most common causes of death in adults world-wide for which effective therapy is unavailable. Some HDAC isoforms stimulate fibrosis. In this study, we explored the therapeutic effects of novel, potent HDAC1,2,3 inhibitors (HDACi) on liver fibrosis. **Methods**: To determine the effects of HDACi in vitro, human immortalized hepatic stellate cells (hTERT cells) were cultured for 24h and then incubated with LP342 (0.1 and 0.3 μM), a lead of the new HDACi, or vehicle for 48h. To determine the effects of HDACi *in vivo*, mice were treated with CCl_4 twice weekly for 6wk to induce liver fibrosis. LP340 (0.05mg/kg, ig), another lead HDACi, was given during the last 2 weeks of CCl_4 treatment. **Results**: Cultured hTERT cells underwent activation as indicated by expression of α-smooth muscle actin (αSMA) and collagen-1α1. LP342 inhibited hTERT cell activation dose-dependently. SnoN binds to Smad4, thus acting as a negative regulator of profibrotic TGFβ/Smad signaling. miR23a promotes TGFβ signaling by decreasing SnoN. LP342 markedly decreased miR23a and TGFβ downstream signaling molecule phospho-Smad2/3 in cultured hTERT cells. After 6wk of CCl_4 treatment in vivo, ALT increased, and cell swelling, steatosis, cell death, and leukocyte infiltration occurred in livers. Moreover, TNFα and myeloperoxidase markedly increased, indicating inflammation. LP340 decreased liver injury and inflammation. After CCl_4 treatment, αSMA increased ~80% and collagen-1α1 expression increased ~6-fold, indicating HSC activation and fibrogenesis. Moreover, fibrosis, indicated by increased trichrome staining in liver sections, occurred primarily in the pericentral regions with bridging fibrosis also occurring. LP340 blunted the increases of αSMA, collagen-1α1 and trichrome staining. After CCl_4 treatment, formation of potent profibrotic cytokine TGFβ and phospho-Smad2/3 markedly increased, which LP340 blunted. Moreover, miR23a increased ~7-fold and SnoN decreased ~50% after CCl_4, both blunted by LP340. By contrast, LP340 had no effect on MMP9 expression. LP340 markedly increased acetylated histone-3 but did not increase acetylated tubulin, indicating inhibition of

Class-I but not Class-II HDAC *in vivo*. **Conclusion**: These novel HDACi markedly decrease miR23a and inhibit TGFβ/Smad signaling and are a promising new therapy for liver fibrosis

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The following people have nothing to disclose: John J. Lemasters

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3446-A | INHIBITION OF INTEGRIN αVβ1 ATTENUATES PROFIBROGENIC GENE EXPRESSION BY MYOFIBROBLASTS IN FIBROTIC HUMAN LIVER EXPLANTS

Steve Ho, Mahru An, Richard Ahn, Vikram Rao, Scott Turner, Martin Decaris and Johanna Schaub, Pliant Therapeutics

Background: Integrin $\alpha_V\beta_1$ is a (myo)fibroblast-specific integrin that activates transforming growth factor (TGF)-β, promoting fibrogenesis. Inhibition of $\alpha_V\beta_1$ is antifibrotic in mouse models of liver fibrosis; however, data in human tissue are limited. Precision-cut liver slices (PCLivS) bridge the gap between cell-based models and *in vivo* models of liver fibrosis, providing a translational assay platform for investigating fibrogenesis in small sections of intact fibrotic human tissue cultured *ex vivo*. Here we use human PCLivS and single nuclei RNA-Seq (snRNA-Seq) to evaluate the effects of an $\alpha_V\beta_1$-selective inhibitor on individual cell populations present in fibrotic human liver tissue. **Methods:** Human liver tissue with or without evidence of fibrosis (fibrotic and normal, respectively) was obtained from rejected organ donors. PCLivS were generated from fibrotic liver tissue and cultured for 2 days in the presence of an $\alpha_V\beta_1$-selective inhibitor, a TGF-β receptor I kinase inhibitor (ALK5i; R-268712) or vehicle (DMSO). Intact nuclei were isolated from slices using a combination of detergent-based lysis, mechanical disruption, and filtration. Transcriptomic analysis of PCLivS single nuclei was performed using 10x Chromium Next GEM 3' technology. Custom annotation of cell types was performed using gene markers established from recently published data sets. Integrin $\alpha_V\beta_1$ protein levels in donor tissues were quantified by custom Meso Scale Discovery electrochemiluminescence assay. **Results:** Fibrotic livers had elevated $\alpha_V\beta_1$ protein concentrations relative to normal livers. Sequencing of single nuclei isolated from cultured PCLivS identified multiple unique cell populations, with hepatocytes, cholangiocytes, myofibroblasts, and endothelial cells comprising the most abundant annotated clusters. Differential gene expression analysis on the myofibroblast cluster showed $\alpha_V\beta_1$ inhibition significantly reduced *COL1A1* expression ($FDR < 0.05$) as well as several other genes related to collagen-containing extracellular matrix (GO:0062023), such as *BGN*, *GREM1*, and *CTHRC1*. Overlap in the specific genes downregulated by $\alpha_V\beta_1$ inhibition and ALK5i was observed, with a similar degree of effect from $\alpha_V\beta_1$ inhibition and TGF-β receptor signalling inhibition with ALK5i. **Conclusion:** Treatment of fibrotic human PCLivS with an $\alpha_V\beta_1$ inhibitor resulted in clear reductions in profibrogenic gene expression by myofibroblasts. The overlap with the effect of ALK5i demonstrates the importance of the $\alpha_V\beta_1$ integrin-TGF-β activation pathway in fibrotic liver disease. These data support $\alpha_V\beta_1$ integrin inhibition as a promising approach for targeted inhibition of TGF-β signalling in fibrotic liver disease.

Disclosures: Johanna Schaub – Pliant Therapeutics: Employee, Yes, No; Pliant Therapeutics: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Disclosure information not available at the time of publication: Steve Ho, Mahru An, Richard Ahn, Vikram Rao, Scott Turner, Martin Decaris

3447-A | MACROPHAGES EXPRESSING CX3CR1 ORCHESTRATE THE REGRESSION OF MURINE LIVER FIBROSIS

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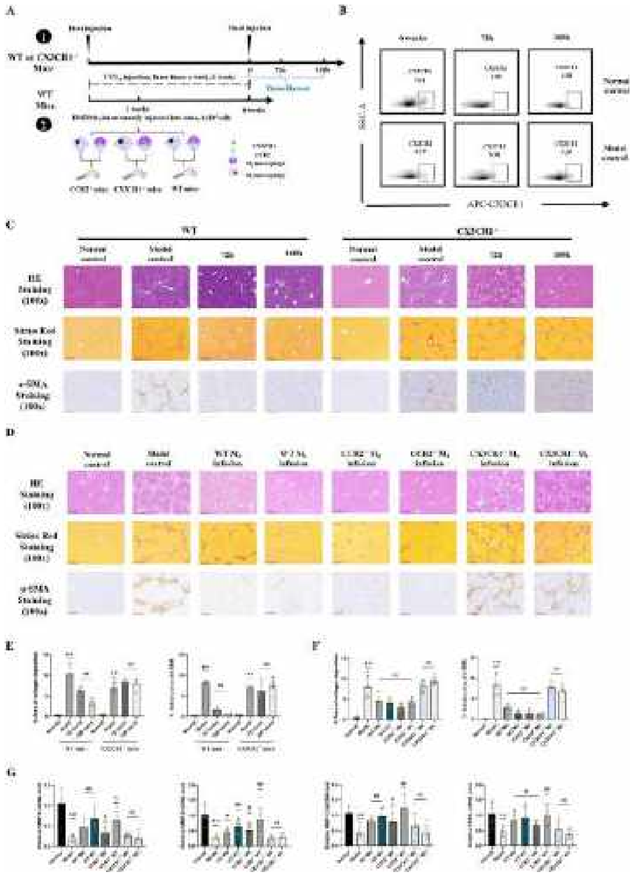
Background: The critical role played by macrophages in chronic liver damage has been established, with the identification of distinct subpopulations that either promote fibrosis or counteract it. This research aims to uncover the specific phenotype of macrophages that exhibit anti-fibrotic effects and to shed light on the mechanisms underlying this phenomenon. **Methods:** Wild type (WT) and $CX3CR1^{-/-}$ mice were administered carbon tetrachloride (CCL_4) via injection for a duration of 6 weeks to induce liver fibrosis. After the final injection of CCl_4, the mice were allowed to recover for 3 days or a week. In the macrophages infusion experiment, Bone marrow-derived macrophages (BMDMs) from WT, $CX3CR1^{-/-}$ or $CCR2^{-/-}$ mice were polarized into M_0 or M_1 macrophages, respectively.

These BMDMs were administered to mice at start of the third weeks through the tail vein. The progression of fibrosis and associated molecular changes were subsequently assessed. **Results:** During the process of liver fibrosis regression in mouse models induced by CCL4, there was an increase in the number of macrophages expressing CX3CR1. However, the recovery from liver fibrosis and the inhibition of activated hepatic stellate cells (HSCs) were prevented in CX3CR1-deficient conditions. Results from cytotherapy experiments showed that BMDMs obtained from both WT and CCR2$^{-/-}$ mice, whether M_0 or M_1, were effective in reducing liver fibrosis. However, BMDMs from CX3CR1$^{-/-}$ mice did not show significant effectiveness in combating liver fibrosis. The mechanism is likely due to the production of matrix metalloproteinases (MMPs) and TNF-related apoptosis-inducing ligand (TRAIL), which promote collagen degradation and induce HSCs apoptosis, respectively. **Conclusion:** An increased number of CX3CR1-expressing macrophages contributed to the accelerated resolution of fibrosis, providing a potential therapeutic strategy for addressing this pathological condition. Key Words: Liver fibrosis; CX3CR1; Macrophage; Degradation; Hepatic stellate cells Figure 1. Macrophages that expressed CX3CR1 played a role in hastening the resolution of fibrosis.

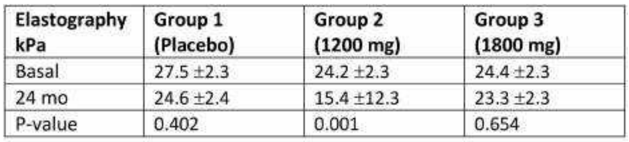


Disclosures: The following people have nothing to disclose: Dabing Ping, Lu Xing, Kai Huang, Xin Sun, Xudong Hu, Chenghai Liu

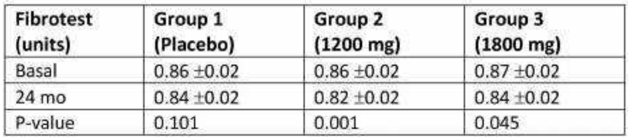
3448-A | PROLONGED-RELEASE PIRFENIDONE IN PATIENTS WITH COMPENSATED CIRRHOSIS. FINAL RESULTS OF THE MULTICENTER STUDY ODISEA, CONTROLLED AGAINST PLACEBO, PLUS STANDARDIZED CARE

Linda Elsa Munoz-Espinosa[1], Aldo Torre[2], Laura Cisneros[3], Iaarah Montalvo-Gordon[4], Rene Male[5], Scherezada Mejía[6], Juan Ramón Aguilar-Ramírez[4], Javier Lizardi-Cervera[4], María Eugenia Icaza-Chávez[7], Frida Gasca[4], Larissa Hernandez-Hernandez[4], Paula Cordero-Perez[1], Luis Alberto Chi Cervera[7], Lilian Torres Made[8], Fatima Rodríguez-Alvarez[9], Graciela Tapia[10] and Jorge Luis Poo[4], (1)University Hospital "José Eleuterio Gonzalez", Uanl, (2)Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, (3)Investigaciones Medicas Cisneros, Monterrey, NL, Mexico, (4)Grupo Mexicano Para El Estudio De Las Enfermedades Hepáticas, (5)Instituto De Salud Digestiva, (6)Hospital Juarez De Mexico, (7) Hospital Star Médica, (8)Instituto De La Salud Digestiva, (9)Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán, (10)Facultad De Medicina Veterinaria y Zootecnia. U.N.a.M.

Background: Advanced liver fibrosis (ALF) is a predictor of adverse prognosis in chronic liver disease. In addition to etiological treatment, a new approach to stop or reverse residual fibrosis is desirable. Our aim was to assess efficacy and safety of a prolonged-release pirfenidone formulation (PR-PFD) compared to placebo, plus standardized care, in patients with compensated liver cirrhosis. **Methods:** 180 patients with ALF (F4 by elastography) of various causes, were randomly assigned to 3 groups: placebo (G1), PR-PFD: 1200 mg/d (G2) or 1800 mg/d (G3), plus standardized care, during 24 months. All participants underwent standard lab tests, quality of life assessment, elastography, fibrotest, liver US and endoscopy at baseline, and 12 and 24 months. **Results:** 165 patients were eligible for the efficacy and 180 for the safety analysis. At baseline, demographics, etiology, stage of cirrhosis, Child-Pugh or MELD scores , quality of life or fatigue scales , and liver stiffness (kPa) and Fibrotest (units) scores (mean ± 1SE) were similar between groups (multivariate mixed model). The estimated fibrosis scores presented a significant reduction, mainly in G2 (Table). Decompensations were detected in 19 patients: variceal bleeding (5), encephalopathy (4), hepatocarcinoma (4) with similar distribution between groups. Ascites (12) was more frequent in the placebo group (p = 0.003). G2 patients presented significant improvements between baseline and 24 months in: ALT (43.5 ± 3.8 vs 31.3 ± 4.8 UI/L, $p = 0.003$), albumin (4.2 ± 0.06 vs 4.5 ± 0.07 g/dL, $p < 0.001$); total bilirubin (0.90 ± 0.08 vs 0.65 ± 0.10 mg/dL, $p < 0.001$); platelets (121.7 ± 7.8 vs 144.3 ± 9.7 $x10^3/\mu L$, $p < 0.001$), MELD (9.73 ± 0.32 vs 9.03 ± 0.40, $p = 0.022$) and quality of life (83.7 ± 1.5 vs 90.9 ± 1.9 %, $p = 0.002$). Adverse events were mainly mild from the GI tract (n = 48, 46, and 35) and skin (n = 15, 22, and 12), in G1, G2, and G3, respectively. **Conclusion:** Prolonged-release pirfenidone at a dose of 1200 mg significantly decreased indirect fibrosis markers at 24 months and induced improvement in LFTs, MELD, and quality of life in compensated cirrhosis, and without safety concerns. Ethics Committee number HI14-004



Elastography kPa	Group 1 (Placebo)	Group 2 (1200 mg)	Group 3 (1800 mg)
Basal	27.5 ±2.3	24.2 ±2.3	24.4 ±2.3
24 mo	24.6 ±2.4	15.4 ±12.3	23.3 ±2.3
P-value	0.402	0.001	0.654



Fibrotest (units)	Group 1 (Placebo)	Group 2 (1200 mg)	Group 3 (1800 mg)
Basal	0.86 ±0.02	0.86 ±0.02	0.87 ±0.02
24 mo	0.84 ±0.02	0.82 ±0.02	0.84 ±0.02
P-value	0.101	0.001	0.045

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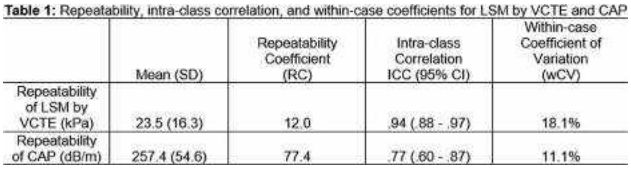
3449-A | REPEATABILITY OF LIVER STIFFNESS MEASUREMENT BY VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY AND CONTROLLED ATTENUATION PARAMETER IN PATIENTS WITH CIRRHOSIS

Daniel Q Huang[1], Nabil Noureddin[2], Jaclyn Bergstrom[3], Maral Amangurbanova[3], Egbert Madamba[3], Christie Hernandez[3], Claude B. Sirlin[3] and Rohit Loomba[4], (1) National University Health System (NUHS), (2)University of California San Diego, (3)University of California, San Diego, (4)University of California, San Diego, San Diego, CA

Background: The regulatory qualification of non-invasive tests (NITs) for liver fibrosis severity assessment is a major unmet need for drug development and clinical care in cirrhosis. Ultrasound-based methods such as vibration-controlled transient elastography (VCTE) evaluate liver stiffness measurement (LSM) and controlled attenuation parameter as a marker for fibrosis severity and steatosis, respectively. Repeated use of VCTE has the potential to assess disease response and progression. However, this potential application has been limited by a paucity of repeatability data in the patient population at risk. The aim of this prospective study from the San Diego Cirrhosis Registry was to address this knowledge gap and contribute to the evidentiary basis needed for the qualification of ultrasound-based methods in various contexts of use in clinical trials and practice. **Methods:** A prospective cohort of adults with suspected or established cirrhosis underwent two FibroScan examinations (Fibroscan Expert 630, Echosens, France) on the same day performed by the same experienced operator. LSM by VCTE and CAP measurements were reported and analyzed in units of kPa and dB/m, respectively. The primary endpoint was the same-day/same-operator repeatability coefficient (RC), which represents the value under which the difference between repeated measurements should fall with a 95% probability. Secondary outcomes include the intra-class correlation coefficient (ICC) which represents the proportion of total variation explained by between-patient differences rather than measurement variation, and the within-case coefficient of variation (wCV), which represents the ratio of within-patient variation to overall measurement values. **Results:** Same day repeat scans were available in 36 participants. The mean age was 60 years, 56% were women, mean BMI was 30.5 kg/m^2). The percentage of cases due to nonalcoholic steatohepatitis, alcohol, and hepatitis C virus, were 42%, 25%, and 14%, , respectively. RC was 12.0 kPa for LSM by VCTE and 77.4 B/m for CAP, meaning that any change greater than those values has a 95% probability to reflect true change rather than measurement error. ICC was excellent for LSM (.94) and fair for CAP (.77), while wCV indicate that the within-patient variation is close to the overall measurement values for LSM and CAP (Table 1). **Conclusion:** LSM and CAP measurement by FibroScan 630 model, demonstrated good repeatability within patients with cirrhosis. These repeatability estimates are likely to inform ultrasound-based NIT qualification by defining the values that are expected to reflect a true change in the context of clinical trials or clinical care.

Table 1: Repeatability, intra-class correlation, and within-case coefficients for LSM by VCTE and CAP



	Mean (SD)	Repeatability Coefficient (RC)	Intra-class Correlation ICC (95% CI)	Within-case Coefficient of Variation (wCV)
Repeatability of LSM by VCTE (kPa)	23.5 (16.3)	12.0	.94 (.88 - .97)	18.1%
Repeatability of CAP (dB/m)	257.4 (54.6)	77.4	.77 (.60 - .87)	11.1%

Disclosures: Rohit Loomba – Aardvark Therapeutics: Consultant, No, No; Altimmune: Consultant, No, No;

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The following people have nothing to disclose: Daniel Q Huang, Nabil Noureddin, Maral Amangurbanova
Disclosure information not available at the time of publication: Jaclyn Bergstrom, Egbert Madamba, Christie Hernandez, Claude B. Sirlin

3450-A | SIGNIFICANTLY HIGHER INCIDENCE OF CIRRHOSIS AND THE RELATED CLINICAL PRESENTATION IN ELDERLY PATIENT

Ke-Qin Hu and Hien Lau, UC Irvine

Background: The prevalence of chronic liver diseases (CLDs) in elderly patients (≥ 60 y old by WHO) is increasing. This study was aimed to assess the clinical presentation, incidence of cirrhosis and associated factors in elderly patients (pts). **Methods:** A single-center retrospective study of 454 consecutive pts with CLDs, regular follow-ups and liver biopsy at the UCIMC Liver Clinic. Clinical, histological, imaging and laboratory data were collected for statistical analysis. **Results:** The mean age $\pm$ SD was 56 ± 14 years old; 230 pts were male (49.9%). Chronic hepatitis C (CHC) and B (CHB) and non-alcoholic fatty liver disease (NAFLD) were the main causes of CLDs, i.e. 89 (20.0%), 83 (18.6%) and 122 (27.4%), respectively. Compared to 205 pts < 60 years old, 249 elderly pts (54.8%) carried significant higher incidences of cirrhosis (58.0% vs 42.0%, $p < 0.01$), decompensation (58.4% vs 41.6%, $p = 0.01$), diabetes mellitus (DM) (41.4% vs 31.0%, $p = 0.02$), hyperlipidemia (HLD) (57.1% vs 46.4%, $p = 0.02$), diuretics use (60.2% vs 39.8%, $p < 0.01$), biopsy-proven fibrosis stage 3-4 (55.8% vs 44.2%, $p < 0.01$), stage 3-4 fibrosis on sheer-wave elastography (SWE) (56.8% vs 43.2%, $p < 0.01$), FIB-4 score > 1.45 (64.0% vs 40.0%, $p < 0.01$). In multivariate analysis, female gender (95% CI: .39-.90; $p = 0.01$) and cirrhosis (95% CI: .22-.57; $p < 0.01$) were significantly associated with pts ≥ 60 years old, independently to decompensation, DM or HLD. Compared to 91 elderly pts with biopsy-proven stage 0-2 fibrosis, 86 elderly pts with stage 3-4 fibrosis were significantly associated with CHC as the primary CLD (61.7% vs 38.3%, $p = 0.04$), 3 different CLDs (56.8% vs 43.2%, $p < 0.01$), DM (62.5% vs 37.5%, $p < 0.01$), splenomegaly on ultrasound (62.5% vs 37.5%, $p < 0.01$), albumin < 3.5 g/dL (66.7% vs 33.3%, $p < 0.01$), and INR ≥ 1.2 (78.6% vs 21.4%, $p < 0.01$). Multivariate analysis showed that having ≥ 3 different CLDs (95% CI: 1.0-6.8; $p = 0.04$), DM (95% CI: 1.3-7.2; $p < 0.01$), INR ≥ 1.2 (95% CI: 1.7-21.1; $p < 0.01$), and platelet $\leq 120\text{x}10^9$/L (95% CI: 1.3-8.3; $p = 0.01$) were independently associated with biopsy-proven stage 3-4 fibrosis in elderly patients. SWE showing stage 3-4 fibrosis (69.6% vs 30.4%, $p < 0.01$), APRI score > 1 (63.0% vs 37.0%, $p < 0.01$), and FIB-4 score > 2.67 (57.0% vs 43.0%, $p < 0.01$) were significantly associated with biopsy-proven stage 3-4 fibrosis in these patients. **Conclusion:** Elderly pts with CLDs have higher incidences of cirrhosis and decompensation. Female gender and cirrhosis were independently associated with being elderly with CLDs. Elderly pts with biopsy-proven stage 3-4 fibrosis were more likely to have ≥ 3 different CLDs, DM, thrombocytopenia, and elevated INR. SWE, APRI and FIB-4 scores were all well-associated with histological hepatic fibrosis in elderly pts.

Disclosures: Ke-Qin Hu – Gilead: Speaking and Teaching, No, No; Intercept: Speaking and Teaching, No, No;
The following people have nothing to disclose: Hien Lau

f 3451-A | TARGETING THE HEDGEHOG PATHWAY TRANSCRIPTION EFFECTOR Gli2 IS A NOVEL THERAPEUTIC STRATEGY FOR SEVERE SCHISTOSOMIASIS MANSONI FIBROSIS AND PORTAL HYPERTENSION

Thiago De Almeida Pereira, Stanford University School of Medicine, San Francisco, CA, Paula Vidigal, School of Medicine, Federal University of Minas Gerais, Anna Mae Diehl, Duke University, Thomas Wynn, Pfizer and Philip Beachy, Stanford University School of Medicine

Background: Schistosomiasis is a major cause of liver fibrosis and portal hypertension in the Global South. IL13 and Hedgehog (Hh) signaling pathways have both been implicated in the pathogenesis of fibrosis and could be potential therapeutic targets. Our aims were to determine if there is cross-talk between IL13 and Hh pathways and if Hh pathway inhibitors could be used as anti-fibrotic therapy in schistosomiasis mansoni. **Methods:** Hh/IL13 signaling were investigated by qRT-PCR, immunohistochemistry and ELISA in uninfected healthy transplant donors ($n = 22$), infected hepatointestinal schistosomiasis patients (liver granulomas, low fibrosis, $n = 17$), infected hepatosplenic patients (advanced fibrosis and portal hypertension $n = 72$); in *Schistosoma mansoni* infected mice (wild-type, IL13Rα1-/- and TKO (IL-10-/- IL12p40-/-IL13Rα2-/-) treated with anti-IL13 antibody, Hh pathway inhibitors (Smoothened antagonists Vismodegib or XL139 vs Gli2 antagonists Arsenic Trioxide (ATO) or HPI vs Vehicle), in mice overexpressing IL13 (plasmid) and in human liver cells stimulated with recombinant IL13 (rIL13) and treated with STAT6 siRNA, Vismodegib or HPI). This study was approved by the human and animal ethics committees of Federal University of Minas Gerais, Duke University, NIH, and Stanford University. **Results:** Hh signaling is upregulated in human schistosomiasis and correlates with IL13, fibrosis stage, and severity of portal hypertension. Overexpression of IL13 (plasmid, infected TKO mice, rIL13) induced Hh ligand production/pathway activation; lack of IL13 signaling (IL13Rα1-/- infected mice, anti-IL13 antibody, STAT6 siRNA) implicated in reduced Hh pathway, indicating that Hh signaling is dependent on IL13. STAT6 Chromatin Immunoprecipitation assay further demonstrated that STAT6 directly binds to the promoter region and regulates the transcription of Hh ligands (Ihh, Dhh) and transcription factors (Gli1, Gli2, Gli3). Smoothened antagonists Vismodegib or XL139 effectively blocked inflammation and fibrosis during acute schistosomiasis but failed to inhibit Hh signaling, inflammation, and fibrogenesis when treatment was initiated in the chronic phase due to Smoothened-independent IL13-mediated Gli2 activation. Gli2 inhibition with ATO or HPI in the chronic phase impaired Hh signaling, inflammation, and fibrogenesis. **Conclusion:** Activation of the Hh pathway in schistosomiasis is highly dependent on IL13-mediated signaling. Targeting Hh pathway with Gli2 antagonists may be a novel therapeutic strategy to treat schistosomiasis fibrosis and portal hypertension.

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The following people have nothing to disclose: Thiago De Almeida Pereira

Disclosure information not available at the time of publication: Paula Vidigal, Thomas Wynn, Philip Beachy

3452-A | THE RELATIONSHIP BETWEEN LIVER FIBROSIS AND HEMOSIDEROSIS IN PATIENTS WITH UNTREATED HEPATITIS C

Shahana Prakash[1], Amelia Fierro-Fine[2], Anthony Snow[1], Sarag Boukhar[3] and Kyle E. Brown[4], (1) University of Iowa Hospitals and Clinics, (2)St. Cloud Hospital, (3)Robert Wood Johnson Medical School, (4) University of Iowa Carver College of Medicine, Iowa City, IA

Background: Evidence of dysregulated iron metabolism is seen in several common forms of chronic liver disease, including hepatitis C infection (HCV). Variable proportions of HCV patients have abnormal serum iron tests, with secondary hepatic iron deposition occurring primarily in subjects with significant fibrosis. To evaluate the relationship between iron deposition and fibrosis, it is essential to establish the temporal sequence of hemosiderosis vis-a-vis fibrosis progression. To address this question, we examined changes in iron deposition (grade and localization) and fibrosis over time in HCV patients who underwent serial liver biopsies in the pre-direct acting antiviral (DAA) era. **Methods:** HCV patients who underwent > 1 liver biopsy at our institution between 1996 and 2015 and who had HCV viremia at the time of all biopsies were selected for study. The first and last liver biopsies for each subject were selected for review. Two pathologists independently scored hepatocyte iron deposition using the method of Scheuer; Kupffer cell (KC) iron was graded as none, mild, moderate, or severe. Liver fibrosis was staged according to the Batts-Ludwig scoring system. Spearman correlation coefficients between fibrosis and iron scores were computed using SPSS 28. **Results:** We identified 107 HCV with > 1 liver biopsies performed between 1996 and 2015. Of the entire cohort, 39/107 (36%) of patients demonstrated progression of liver fibrosis (Group A), while fibrosis remained stable or appeared to improve in 68/107 patients (64%) (Group B). The time interval between liver biopsies did not differ between the groups (Group A: 5.5 years; Group B: 5.8 years; $p = 0.7$). Fibrosis stage on the first biopsy showed a weak but significant correlation with the KC iron score on the same biopsy ($\rho = 0.20$; $p = 0.04$). The fibrosis stage on the second biopsy correlated with the initial KC iron score ($\rho = 0.27$; $p = 0.005$) as well as the second KC iron score ($\rho = 0.29$; $p = 0.003$). There was also a significant positive correlation between change in fibrosis stage

and both the second KC iron score ($\rho = 0.23$; $p = 0.02$) and the change in Scheuer score ($\rho = 0.22$; $p = 0.02$). **Conclusion:** Serial biopsies done in the pre-DAA era provide a unique resource to address basic questions about changes that accompany increases in fibrosis over time. Our data show that KC iron is more closely associated with fibrosis progression than hepatocyte iron, but the relationship between iron deposition in either cell type and fibrosis progression is weak.

Disclosures: The following people have nothing to disclose: Shahana Prakash, Kyle E. Brown

Disclosure information not available at the time of publication: Amelia Fierro-Fine, Anthony Snow, Sarag Boukhar

f 3453-A | A CCR2-TARGETED PET PROBE FOR LIVER FIBROSIS DETECTION AND STAGING IN PRECLINICAL MODELS

Tuo Shao, Wenyu Lin and Raymond T. Chung, Massachusetts General Hospital and Harvard Medical School

Background: Hepatic stellate cell (HSC) and Kupffer cell activation are accompanied by increased expression of chemokines and chemokine receptors, including CC-chemokine receptor 2 (CCR2). Molecular imaging targeting the CCR2 could provide a non-invasive means of evaluating the expression and function of the CCR2 on activated HSCs (aHSCs) and macrophages in the injured liver, and thus provide important prognostic information in chronic liver disease. ^{68}Ga-DOTA-ECL1i is a radiotracer specific for CCR2. In this study, we sought to compare differences in uptake of the ^{68}Ga-DOTA-ECL1i between normal and injured liver to evaluate its utility for assessment of fibrogenesis. **Methods:** We used PET/CT to assess changes in CCR2 binding of intravenously-administered ^{68}Ga-DOTA-ECL1i in the livers of mice with bile duct ligation (BDL)- and carbon-tetrachloride (CCl_4)-induced liver fibrosis compared with controls. We performed Sirius red staining to assess liver fibrosis, immunofluorescence to identify the location of CCR2 expressed in fibrotic liver, and measured protein and messenger RNA expression of CCR2, F4/80 and alpha smooth muscle actin (α-SMA) in control and fibrotic livers. Autoradiography was performed to evaluate tracer uptake in liver sections both in animal models. **Results:** Fibrotic mouse livers displayed enhanced ^{68}Ga-DOTA-ECL1i uptake and retention. The radiotracer was demonstrated to bind specifically to CCR2 mainly expressed on aHSCs and Kupffer cells. The hepatic radiotracer uptake at 30 min post-injection was higher in fibrotic livers compared to control livers. Autoradiography and histopathology confirmed the PET imaging results. Further, the mRNA and protein level of CCR2 and its signaling complex were higher in CCl_4 and BDL models compared to controls. Autoradiography confirmed the PET imaging finding of high radioactivity binding in fibrotic liver in both animal models. **Conclusion:** Imaging hepatic CCR2 with PET and ^{68}Ga-DOTA-ECL1i offers a potential noninvasive method for monitoring the progression of liver fibrosis.

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The following people have nothing to disclose: Tuo Shao, Wenyu Lin

3454-A | BIOMARKERS OF FIBROSIS AND PORTAL HYPERTENSION OF FONTAN-ASSOCIATED LIVER DISEASE IN CHILDREN AND ADULTS

Chaowapong Jarasvaraparn, Jessica Thoe, Andrew Rodenbarger, Howard C. Masuoka, Mark Payne, Larry Wayne Markham and Jean P Molleston, Indiana University

Background: Fontan-associated liver disease (FALD) refers to structural and functional changes of the liver caused by hemodynamic changes from Fontan circulation. Currently, liver biopsy is the standard to assess liver fibrosis. We investigated correlation of biomarkers with severity of fibrosis on liver biopsy and portal hypertension in children and adults with FALD. **Methods**: A retrospective study of Fontan patients > 10 years old who underwent liver biopsy was reviewed. Liver biopsy reports were used by the congestive hepatic fibrosis staging including 0 (no), 1 (central zone fibrosis), 2 (central and portal fibrosis), 3 (bridging fibrosis), and 4 (cirrhosis). Advanced liver disease (ALD) was defined as bridging fibrosis and/or cirrhosis. AST-to platelet ratio index (APRI) and Fibrosis-4 (FIB-4) were used as non-invasive fibrosis scores. Liver stiffness (LS) from FibroScan

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

and features of portal hypertension which were calculated using the VAST (one point each for Varices, Ascites, Splenomegaly, Thrombocytopenia) were obtained; VAST score ≥ 2 signifies portal hypertension. Fontan pressure, wedge and free hepatic venous pressure (HVP) were obtained at the same time with liver biopsy. Hepatic venous pressure gradient (HVPG) was calculated as wedge HVP minus free HVP. **Results**: Among 66 patients (47 adults and 19 children), ALD was observed in 26/47 (55.3%) of adults and 13/19 (68.4%) of children. ALD was significantly associated with lower platelet count, higher APRI, and higher FIB-4. Liver fibrosis score correlated with APRI (0.34, $p = 0.02$) and FIB-4 (0.47, $p = 0.001$) in adults, not children. FIB-4 was the only diagnostic marker for prediction of ALD in FALD (FIB-4 > 0.57, sensitivity 71.8%, specificity 48.2%, AUC 0.67 ± 0.07, $p = 0.02$). Liver fibrosis score from biopsy in adults and children with ALD were similar. LS correlated with Fontan pressure (0.62, $p = 0.003$), wedge HVP (0.61, $p = 0.003$), and free HVP (0.63, $p = 0.002$), not liver fibrosis score from biopsy. Patients with significant portal hypertension had lower albumin (3.77 vs. 4.47, $p = 0.01$), higher Fontan pressure (17.11 vs 12.9, $p = 0.001$), higher HVPG (1.28 vs. 0.94, $p = 0.03$) and higher fibrosis score from biopsy (3.19 vs. 2.48, $p = 0.002$) than without significant portal hypertension. **Conclusion**: APRI and FIB-4 had modest discrimination to identify adults with ALD, not children, indicating that these values may be followed as a marker of FALD progression. LS reflects Fontan pressure but not biopsy fibrosis score. Portal hypertension in FALD is possibly caused by elevated venous pressure and liver fibrosis. Further prospective studies are essential to develop non-invasive biomarkers for screening FALD.

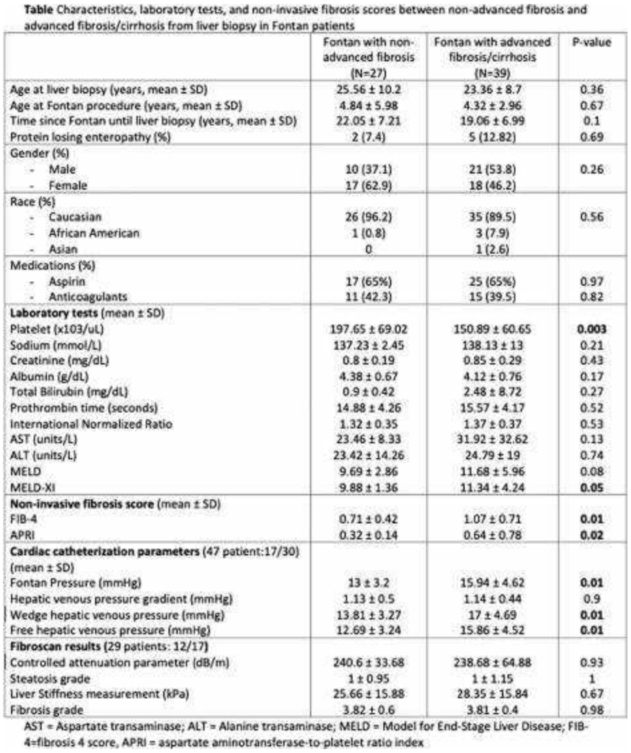


Table Characteristics, laboratory tests, and non-invasive fibrosis scores between non-advanced fibrosis and advanced fibrosis/cirrhosis from liver biopsy in Fontan patients

	Fontan with non-advanced fibrosis (N=27)	Fontan with advanced fibrosis/cirrhosis (N=39)	P-value
Age at liver biopsy (years, mean ± SD)	25.56 ± 10.2	23.36 ± 8.7	0.36
Age at Fontan procedure (years, mean ± SD)	4.84 ± 5.98	4.32 ± 2.96	0.67
Time since Fontan until liver biopsy (years, mean ± SD)	22.05 ± 7.21	19.06 ± 6.99	0.1
Protein losing enteropathy (%)	2 (7.4)	5 (12.82)	0.69
Gender (%)			
- Male	10 (37.1)	21 (53.8)	0.26
- Female	17 (62.9)	18 (46.2)	
Race (%)			
- Caucasian	26 (96.2)	35 (89.5)	0.56
- African American	1 (0.8)	3 (7.9)	
- Asian	0	1 (2.6)	
Medications (%)			
- Aspirin	17 (65%)	25 (65%)	0.97
- Anticoagulants	11 (42.3)	15 (39.5)	0.82
Laboratory tests (mean ± SD)			
Platelet (x103/uL)	197.65 ± 69.02	150.89 ± 60.65	**0.003**
Sodium (mmol/L)	137.23 ± 2.45	138.13 ± 13	0.21
Creatinine (mg/dL)	0.8 ± 0.19	0.85 ± 0.29	0.43
Albumin (g/dL)	4.38 ± 0.67	4.12 ± 0.76	0.17
Total Bilirubin (mg/dL)	0.9 ± 0.42	2.48 ± 8.72	0.27
Prothrombin time (seconds)	14.88 ± 4.26	15.57 ± 4.17	0.52
International Normalized Ratio	1.32 ± 0.35	1.37 ± 0.37	0.53
AST (units/L)	23.46 ± 8.33	31.92 ± 32.62	0.13
ALT (units/L)	23.42 ± 14.26	24.79 ± 19	0.74
MELD	9.69 ± 2.86	11.68 ± 5.96	0.08
MELD-XI	9.88 ± 1.36	11.34 ± 4.24	**0.05**
Non-invasive fibrosis score (mean ± SD)			
FIB-4	0.71 ± 0.42	1.07 ± 0.71	**0.01**
APRI	0.32 ± 0.14	0.64 ± 0.78	**0.02**
Cardiac catheterization parameters (47 patient:17/30) (mean ± SD)			
Fontan Pressure (mmHg)	13 ± 3.2	15.94 ± 4.62	**0.01**
Hepatic venous pressure gradient (mmHg)	1.13 ± 0.5	1.14 ± 0.44	0.9
Wedge hepatic venous pressure (mmHg)	13.81 ± 3.27	17 ± 4.69	**0.01**
Free hepatic venous pressure (mmHg)	12.69 ± 3.24	15.86 ± 4.52	**0.01**
Fibroscan results (29 patients: 12/17)			
Controlled attenuation parameter (dB/m)	240.6 ± 33.68	238.68 ± 64.88	0.93
Steatosis grade	1 ± 0.95	1 ± 1.15	1
Liver Stiffness measurement (kPa)	25.66 ± 15.88	28.35 ± 15.84	0.67
Fibrosis grade	3.82 ± 0.6	3.81 ± 0.4	0.98

AST = Aspartate transaminase; ALT = Alanine transaminase; MELD = Model for End-Stage Liver Disease; FIB-4=fibrosis 4 score, APRI = aspartate aminotransferase-to-platelet ratio index

Disclosures: The following people have nothing to disclose: Chaowapong Jarasvaraparn, Jessica Thoe, Andrew Rodenbarger, Howard C. Masuoka, Mark Payne, Larry Wayne Markham, Jean P Molleston

3455-A | DETERMINING THE OPTIMAL TRANSIENT ELASTOGRAPHY CUTOFFS IN CHRONIC HEPATITIS B PATIENTS WITH CONCURRENT HEPATIC STEATOSIS

Fajuan Rui[1], Xiaoming Xu[1], Wenjing Ni[1], Liang Xu[2], Jeff Liang[3], Yee Hui Yeo[3] and Jie Li[4], (1)Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China, (2)Clinical School of the Second People's Hospital, Tianjin Medical University, Tianjin, China, (3)Cedars-Sinai Medical Center, Los Angeles, CA, (4)Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China

Background: Transient elastography (TE) is a non-invasive method for diagnosing liver fibrosis through liver stiffness measurement. The current cutoff values of TE are designed to assess liver fibrosis in patients with a singular liver disease, such as chronic hepatitis B (CHB) or non-alcoholic fatty liver disease (NAFLD). However, the cutoff value of TE in CHB patients with concurrent hepatic steatosis (HS) remains unverified. Using biopsy as the gold standard, this study aims to establish the optimal cutoff for TE for this cohort. **Methods:** This study consecutively enrolled CHB patients with concurrent HS who underwent liver biopsy and Fibroscan at the Tianjin Second People's Hospital between January 2016 and September 2021. The area under the receiver operating characteristic curve (AUROC), sensitivity (SE), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV) of contemporary TE cutoff for patients with CHB or NAFLD (9.7kPa) was calculated. The optimal TE cutoff for patients with concurrent CHB and NAFLD was estimated using the Youden index. The Delong test was used to compare the differences between AUROCs of the contemporary and optimal cutoffs. Subgroup analysis by body mass index (BMI) was conducted. **Results:** We included 613 CHB patients with concurrent HS, with a median age of 36 years (IQR: 30-46). Seventy-four patients had advanced fibrosis. The recommended TE cutoff for patients with CHB or NAFLD was 9.7 kPa, and the corresponding AUROC was 0.681, with SE at 55.41%, SP at 80.71%, PPV at 28.30%, and NPV at 92.90% (Table). At the optimal cutoff value (8.8 kPa), the corresponding AUROC was 0.733, significantly higher than 0.681 ($P = 0.015$). The SE, SP, PPV, and NPV of the optimal cutoff values (8.8

kPa) were 70.27%, 76.25%, 28.9%, and 94.9%, respectively. The SE, PPV, and NPV of the optimal cutoff value (8.8 kPa) were higher than those of the existing cutoff value (9.7 kPa). Subgroup analysis showed that for patients with a BMI < 25 kg/m^2, the optimal cutoff (8.8 kPa) AUROC was 0.708, significantly surpassing the corresponding value of the contemporary cutoff (AUROC = 0.566) ($P = 0.003$). In patients with BMI ≥ 25 kg/m^2, the optimal cutoff AUROC was 0.742, exceeding that of the contemporary cutoff (AUROC = 0.737), although without significant difference ($P = 0.747$). **Conclusion:** The optimal TE cutoff for assessing advanced fibrosis in CHB patients with concurrent HS was 8.8 kPa, lower than 9.7 kPa in CHB patients. In CHB patients with concurrent HS, a more stringent TE value is needed to enable more precise advanced fibrosis evaluation. The findings warrant further validation.

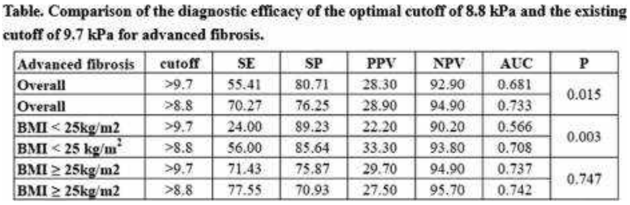


Table. Comparison of the diagnostic efficacy of the optimal cutoff of 8.8 kPa and the existing cutoff of 9.7 kPa for advanced fibrosis.

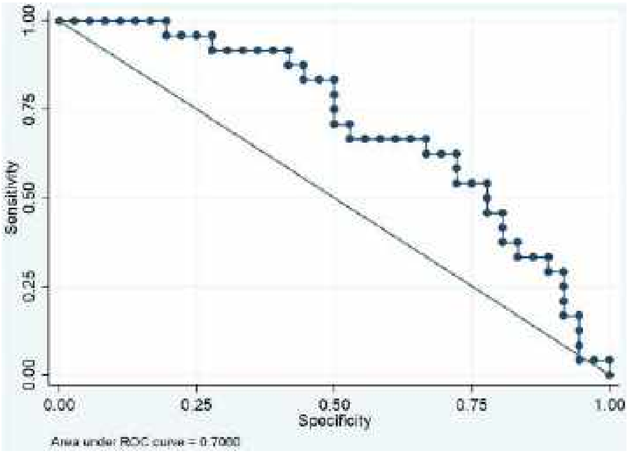
Advanced fibrosis	cutoff	SE	SP	PPV	NPV	AUC	P
Overall	>9.7	55.41	80.71	28.30	92.90	0.681	0.015
Overall	>8.8	70.27	76.25	28.90	94.90	0.733	
BMI < 25kg/m2	>9.7	24.00	89.23	22.20	90.20	0.566	0.003
BMI < 25 kg/m^2	>8.8	56.00	85.64	33.30	93.80	0.708	
BMI ≥ 25kg/m2	>9.7	71.43	75.87	29.70	94.90	0.737	0.747
BMI ≥ 25kg/m2	>8.8	77.55	70.93	27.50	95.70	0.742	

Disclosures: The following people have nothing to disclose: Fajuan Rui, Xiaoming Xu, Wenjing Ni, Liang Xu, Jeff Liang, Yee Hui Yeo, Jie Li

3456-A | DOES SENESCENT CHANGE IN SPLEEN AFFECT SPLENOMEGALY IN ELDERLY PATIENTS WITH LIVER CIRRHOSIS?

Yunjeong Lee and Jin-Wook Kim, Seoul National University Bundang Hospital

Background: Splenomegaly has been considered a classic hallmark of portal hypertension and frequently used as a diagnostic criterion for liver cirrhosis. Meanwhile, it is also known that the size of spleen shrinks gradually over the later decades of life because of ageing-related changes to spleen architecture. However, the change in spleen volume has not been thoroughly evaluated in elderly patients with advanced hepatic fibrosis. This study aimed to elucidate the pattern and diagnostic significance of splenomegaly in elderly patients with hepatic fibrosis by measuring spleen volume and liver-to-spleen volume ratio (LSVR) from computed tomography (CT) images. **Methods:** In this observational cohort study, all patients were identified who received both liver biopsy and liver CT studies in our institute between July 2004 and December 2022 and classified into two groups: control and geriatric group (≥ 75 y). Propensity score matching was used to balance the two groups. Whole spleen and liver volumes were measured on abdominal CT scan images using Inobitec DICOM Viewer. Comparison between the two groups was done using a two-sample t-test with equal variances in Stata/SE 14.0. ROC analysis was used to assess the diagnostic performance of each parameter. **Results:** Both groups included all histologic grades of fibrosis (F0 8.1%, F1 23.7%, F2 23.7%, F3 12.6%, F4 31.9% in geriatric group and F0 9.3%, F1 22.0%, F2 20.1%, F3 6.9%, F4 41.7% in control group). In control group, patients with advanced fibrosis (METAVIR F3 and F4) had significantly larger spleen volume (277 cm^3) compared to F0-F2(163 cm^3) ($p < 0.001$). However, in geriatric group, patients with F3-F4 showed no statistically significant difference in spleen volumes compared to those with stage F0-F2 (174 vs 129 cm^3, respectively; $p = 0.051$). Whereas, the area under the ROC curve of spleen showed that the same cut-off volume for F3-F4 was similar between control and geriatric group (0.691 vs 0.692; cut-off, 158 vs 128 cm^3 for sensitivity of 70%, respectively; $p = 0.991$). Also, the ROC curve analysis generated a similar result when comparing spleen volumes in patients with liver cirrhosis (F4) and the others (F0-F3) between control and geriatric group (0.677 vs 0.706 (Fig.); cut-off, 159 vs 128 cm^3, respectively; $p = 0.696$). For LSVR, the area under the ROC curve showed no significant differences when comparing the volumes not only for F0-F2 vs. F3-F4(0.282 vs 0.301; cut-off, 4.165 vs. 5.317 for sensitivity of 70%, respectively; $p = 0.802$) but also for F0-F3 vs. F4 (0.308 vs 0.284; cut-off, 4.303 vs. 5.317; $p = 0.74$) as well. **Conclusion:** In elderly patients, splenomegaly may not seem as evident with advanced hepatic fibrosis as younger patients, however, the cutoff values from ROC curve analysis was not different from those in younger population. Spleen volume may still be used for the prediction of advanced fibrosis since our ROC analysis showed similar AUC values between control and geriatric groups.



Disclosures: The following people have nothing to disclose: Yunjeong Lee, Jin-Wook Kim

3457-A | HEPATITIS B, HEPATITIS C AND ALCOHOL-RELATED DECOMPENSATED CIRRHOSIS: FACTORS AFFECTING RECOMPENSATION

Umang Arora[1], Vishwa Vadodaria[1], Sanil Garg[1], Ritik Mahaveer Goyal[2], Ishan Gupta[1], Gurasis Boparai[1], Shubham Mehta[1], Rosemary Jha[1], Isha Singh[1], Hari Narayan A[1], Sabreena Sheikh[1], Manas Vaishnav[1], Raju Sharma[1] and Dr Shalimar[1], (1)All India Institute of Medical Sciences, New Delhi, (2)Rutgers New Jersey Medical School

Background: Recompensation of cirrhosis describes a subset of patients with decompensated cirrhosis who achieve sustained clinical improvement following etiology-specific treatments, as defined by the Baveno VII consensus. Effective etiology-specific treatments include antivirals for hepatitis B virus (HBV) and hepatitis C virus (HCV), and abstinence from alcohol. The present study assessed factors associated with cirrhosis and adverse prognosis, such as sarcopenia and osteopenia, among patients who developed recompensation from decompensated cirrhosis. **Methods:** A case-control study was performed- cases included patients who achieved recompensation, and controls were patients who remained decompensated. Patients with cirrhosis due to HBV, HCV or alcohol who received etiology-specific treatment after decompensation were included. Patients with hepatocellular carcinoma diagnosed within 6 months of presentation, and those with two etiological factors such as coinfections or significant alcohol use in a patient with chronic viral hepatitis, were excluded. Anthropometric, biochemical, liver stiffness measurements (LSM) were recorded. Computed tomography (CT) parameters included sarcopenia {L3 vertebral skeletal muscle index below 38 cm^2/m^3 (women) or 42 cm^2/m^2(men)}, and osteoporosis (L1 vertebra attenuation $\leq$ 149 Hounsefield Units). Comparison between the two groups was performed using chi2 for categorical variables and Mann Whitney U test for continuous variables that were expressed as median (interquartile range). **Results:** A total of 109 patients with decompensated cirrhosis were analysed (n = 40: recompensated, n = 69: remained decompensated). The etiology of cirrhosis was HBV (n = 35), HCV (n = 35) and alcohol (n = 39). Median duration of follow-up was 2.8 (1.1 - 6.1) years. A larger proportion of patients with recompensated cirrhosis had viral etiology compared to alcohol-related cirrhosis (77% vs 23%, p = 0.03). There were no differences in body mass index (BMI), prevalence of diabetes and baseline liver function parameters between the 2 groups. (Table 1) However, those with recompensation had a significantly lower median age at index presentation and baseline MELD score. The MELD-sarcopenia score was borderline significant (p = 0.051). LSM showed a significantly greater decline in patients with recompensation (-21.7 vs 3.4 kPa, p = 0.013). Baseline Child-Pugh score, LSM, or prevalence of sarcopenia or osteopenia were not associated with the occurrence of recompensation (P > 0.05). There was no difference between the two groups in the time of initiation of treatment after decompensation (92 d vs 112 d, p = 0.93). **Conclusion:** Sarcopenia, osteoporosis, or time to treatment initiation were not associated with the occurrence of recompensation in this case-control study. Lower MELD score at baseline and greater decline in liver stiffness measurements on follow-up correlated with recompensation.

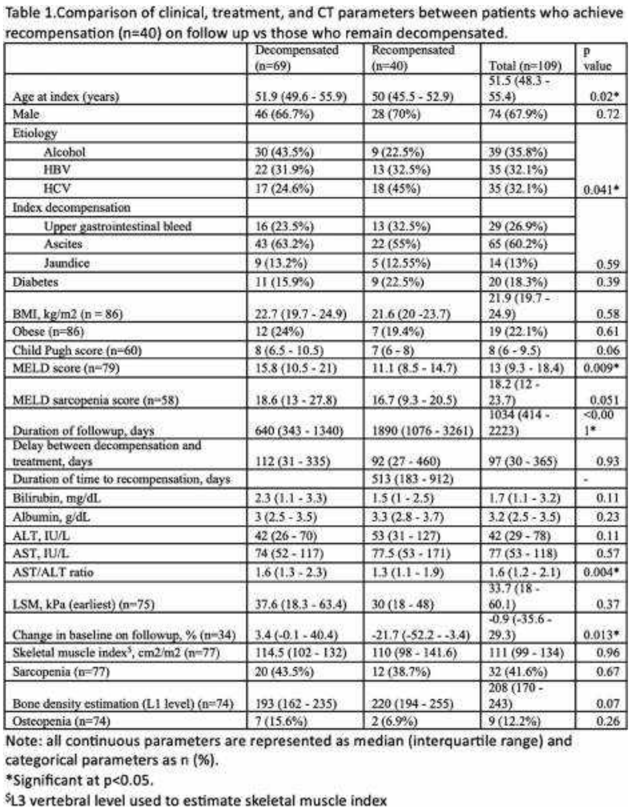


Table 1.Comparison of clinical, treatment, and CT parameters between patients who achieve recompensation (n=40) on follow up vs those who remain decompensated.

	Decompensated (n=69)	Recompensated (n=40)	Total (n=109)	p value
Age at index (years)	51.9 (49.6 - 55.9)	50 (45.5 - 52.9)	51.5 (48.3 - 55.4)	0.02*
Male	46 (66.7%)	28 (70%)	74 (67.9%)	0.72
Etiology				
Alcohol	30 (43.5%)	9 (22.5%)	39 (35.8%)	
HBV	22 (31.9%)	13 (32.5%)	35 (32.1%)	
HCV	17 (24.6%)	18 (45%)	35 (32.1%)	0.041*
Index decompensation				
Upper gastrointestinal bleed	16 (23.5%)	13 (32.5%)	29 (26.9%)	
Ascites	43 (63.2%)	22 (55%)	65 (60.2%)	
Jaundice	9 (13.2%)	5 (12.55%)	14 (13%)	0.59
Diabetes	11 (15.9%)	9 (22.5%)	20 (18.3%)	0.39
BMI, kg/m2 (n = 86)	22.7 (19.7 - 24.9)	21.6 (20 -23.7)	21.9 (19.7 - 24.9)	0.58
Obese (n=86)	12 (24%)	7 (19.4%)	19 (22.1%)	0.61
Child Pugh score (n=60)	8 (6.5 - 10.5)	7 (6 - 8)	8 (6 - 9.5)	0.06
MELD score (n=79)	15.8 (10.5 - 21)	11.1 (8.5 - 14.7)	13 (9.3 - 18.4)	0.009*
MELD sarcopenia score (n=58)	18.6 (13 - 27.8)	16.7 (9.3 - 20.5)	18.2 (12 - 23.7)	0.051
Duration of followup, days	640 (343 - 1340)	1890 (1076 - 3261)	1034 (414 - 2223)	<0.001*
Delay between decompensation and treatment, days	112 (31 - 335)	92 (27 - 460)	97 (30 - 365)	0.93
Duration of time to recompensation, days		513 (183 - 912)		-
Bilirubin, mg/dL	2.3 (1.1 - 3.3)	1.5 (1 - 2.5)	1.7 (1.1 - 3.2)	0.11
Albumin, g/dL	3 (2.5 - 3.5)	3.3 (2.8 - 3.7)	3.2 (2.5 - 3.5)	0.23
ALT, IU/L	42 (26 - 70)	53 (31 - 127)	42 (29 - 78)	0.11
AST, IU/L	74 (52 - 117)	77.5 (53 - 171)	77 (53 - 118)	0.57
AST/ALT ratio	1.6 (1.3 - 2.3)	1.3 (1.1 - 1.9)	1.6 (1.2 - 2.1)	0.004*
LSM, kPa (earliest) (n=75)	37.6 (18.3 - 63.4)	30 (18 - 48)	33.7 (18 - 60.1)	0.37
Change in baseline on followup, % (n=34)	3.4 (-0.1 - 40.4)	-21.7 (-52.2 - -3.4)	-0.9 (-35.6 - 29.3)	0.013*
Skeletal muscle index$^{\$}$, cm2/m2 (n=77)	114.5 (102 - 132)	110 (98 - 141.6)	111 (99 - 134)	0.96
Sarcopenia (n=77)	20 (43.5%)	12 (38.7%)	32 (41.6%)	0.67
Bone density estimation (L1 level) (n=74)	193 (162 - 235)	220 (194 - 255)	208 (170 - 243)	0.07
Osteopenia (n=74)	7 (15.6%)	2 (6.9%)	9 (12.2%)	0.26

Note: all continuous parameters are represented as median (interquartile range) and categorical parameters as n (%).

*Significant at p<0.05.

$^{\$}$L3 vertebral level used to estimate skeletal muscle index

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3458-A | METABOLIC BIOMARKER CONSTELLATIONS ALLOW SIMULTANEOUS AND INTEGRATED LIVER AND KIDNEY FUNCTION MONITORING IN CHRONIC LIVER DISEASE

Frank Stämmler[1], Laurence Derain-Dubourg[2], Sandrine Lemoine[2], Jeffrey Meeusen[3], Surendra Dasari[3], John Lieske[3], Andrew Robertson[1] and Eric Schiffer[1], (1) Numares AG, (2)Hospices Civils De Lyon, (3)Mayo Clinic

Background: Renal impairment often occurs in liver disease. Altered hemodynamics and creatinine metabolism in liver disease causes overestimation of glomerular filtration rate (GFR) using creatinine-based GFR estimating equations (eGFR). Accurate liver function testing often requires ascites and hepatic encephalopathy grading, which are subjective and difficult to obtain. Using nuclear magnetic resonance (NMR), our group has clinically and analytically validated an eGFR based on valine, myoinositol, and creatinine - in combination with cystatin-C, age, and sex (*AXINON*® GFR$_{\text{NMR}}$). A test determining different aspects of liver function such as Child-Pugh class has also been developed on the same NMR platform. We present the performance of these renal and liver function tests in chronic liver disease. **Methods:** For eGFR estimation, we compared equations in a multicenter retrospective study of 203 chronic liver disease patients with a measured GFR (mGFR) (iothalamate or inulin clearance). Serum was analyzed to estimate GFR based on GFR$_{\text{NMR}}$, CKD-EPI$_{2021}$Cr (eGFR based on creatinine alone) and CKD-EPI$_{2021}$Cr-Cys (creatinine and cystatin C). For liver function estimation, a logistic regression model was built on 709 and evaluated on 300 cirrhotic patients undergoing hepatocellular carcinoma surveillance. **Results:** Compared to mGFR, GFR$_{\text{NMR}}$ had a mean bias of -1.64 mL/min/1.73m^2 [-3.43 - 0.16], statistically smaller than both CKD-EPI$_{2021}$Cr of 7.5 [4.9 - 9.8], and CDK-EPI$_{2021}$Cr-Cys of -2.9 [-4.8 - -1.3]. P$_{30}$ was similar in GFR$_{\text{NMR}}$ and CKD-EPI$_{2021}$Cr-Cys (83% [79 - 89] and 86% [81 - 90]) but lower for CKD-EPI$_{2021}$Cr (74% [68 – 80]). P$_{15}$ was highest for GFR$_{\text{NMR}}$ at 59% [53 - 65] compared to 47% [40 - 53] for CKD-EPI$_{2021}$Cr and 54% [47 - 61] for CKD-EPI$_{2021}$Cr-Cys. Concordant classification by mGFR CKD stage was highest for GFR$_{\text{NMR}}$ at 59%, 54% for CKD-EPI$_{2021}$Cr-Cys, and 51% for CKD-EPI$_{2021}$Cr-Cys respectively. Liver function score evaluation yielded an AUC of 0.89 (CI: 0.86-0.93) for differentiation of Child-Pugh A from B/C. Furthermore, a strong correlation of 0.76 (CI: 0.71 - 0.81; Pearson) between the overall model score with the Child-Pugh score was observed. **Conclusion:** These findings confirm that the addition of NMR-analyzed myoinositol and valine improved the correlation of GFR$_{\text{NMR}}$ with mGFR concerning bias and precision in liver disease, and accurately differentiates liver function scoring. NMR offers a novel method to simultaneously determine both renal and hepatic function in chronic liver disease patients.

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Disclosure information not available at the time of publication: Frank Stämmler, Laurence Derain-Dubourg, Sandrine Lemoine, Jeffrey Meeusen, Surendra Dasari, John Lieske, Eric Schiffer

3459-A | NOVEL SERUM FIBROSIS MARKERS TO PREDICT RAPID LIVER FIBROSIS PROGRESSION POST LIVER TRANSPLANT

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Background: Liver transplantation (LTX) is the only curative treatment option for end stage liver disease. However, up to 30% of patients develop recurrent cirrhosis (RC) post LTX within 5 years. In view of emerging antifibrotic therapies, there is an urgent need of non-invasive serum biomarkers to predict RC after LTX. We established and validated novel liver fibrosis serum markers in LTX patients with no, moderate and severe fibrosis progression followed-up for up to > 5 years post-transplant. **Methods:** ELISA assays measuring the matricellular fibrosis marker thrombospondin-2 (TSP2) and the metabolism/fibrosis-related marker insulin-like growth factor binding protein-7 (IGFBP7) were established using combinations of recombinantly expressed protein, commercial and proprietary monoclonal/polyclonal antibodies. CD163 and GDF15 were measured via commercially available sandwich ELISAs. Sensitivity and specificity for serum or plasma showed intra- and inter assay variations below 10% and 15%, resp. 45 LTX patients were divided into super-rapid (< 1 y), rapid progressors (3-5 y) after LTX and non-progressors. Serum markers were determined at 3,6 and 12 months post-LTX in a subset of 19 rapid-progressors to cirrhosis within 1 year. **Results:** Levels of TSP2 & CD163 were significantly increased in RC < 1 year (mean 253 & 1409 ng/ml, resp.) at 3,6 & 12 months after LTX compared to non-progressors (mean 86.9 & 705 ng/ml, resp) at 1, 2 & 3 years. IGFBP7 and GDF15, were not significantly different. RC < 1 vs non-progressors at 1 year after LTX were clearly differentiated with: TSP2: 261 vs 94, CD163: 1136 vs 716 ng/ml, and IGFBP7: 376 vs 549. 3 years after LTX, all markers were significantly elevated in rapid progressors vs non-progressors (TSP2: 224 vs 90; IGFBP7: 537 vs 362; CD163: 1176 vs 639 ng/ml; GDF15: 2433 vs 1146 pg/ml). The AUROC values to distinguish progressors from non-progressors were 0.90, 0.846 and 0.85 for the combination of TSP2 & IGFBP7, TSP2 & CD163 and TSP2, IGFBP7 & CD163, resp. The combination of all 4 markers also differentiated rapid progressors vs RC < 1 with an AUROC of 0.76. All serum markers were significantly elevated in patients who finally died vs surviving patients. **Conclusion:** The matricellular fibrosis marker TSP2 reflects fibrogenesis and predict rapid fibrosis progression in patients post LTX. Other markers contributed to prediction at later stages post LTX. The novel markers may support early antifibrotic interventions post LTX.

Disclosures: The following people have nothing to disclose: Rambabu Surabattula, Sudharani Myneni, Tim Zimmermann, Detlef Schuppan

3460-A | OPTIMAL DUAL CUT-OFFS OF LIVER STIFFNESS FOR COMPENSATED ADVANCED CHRONIC LIVER DISEASE IN ON-TREATMENT PATIENTS WITH CHRONIC HEPATITIS B

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Background: The risk of disease progression is significantly reduced but not eliminated in patients with chronic hepatitis B (CHB) who has initiated antiviral treatment. Identifying the compensated advanced chronic liver disease (cACLD) is important for on-treatment monitoring. However, dual cut-offs for cACLD in on-treatment patients with CHB are unclear. **Methods:** Adult CHB patients from three clinical studies (NCT01938781, NCT01938820, NCT01943617) who had liver biopsy and LSM simultaneously at least 6 months after initiation of antiviral treatment were enrolled. Compensated advanced chronic liver disease was defined as ≥F3 according to the METAVIR scoring system. LSM were performed with FibroScan (Echosens, Paris, France) or Fibrotouch (Wuxi Hisky Medical Technology Co., Ltd., Wuxi, China). The performance of LSM to identify cACLD in on-treatment CHB patients was analyzed by using area under receiver operating characteristic curve (AUROC). **Results:** A total of 816 patients were enrolled and randomly divided into training set and validation set at a ratio of 2:1. In the training set, about 74.3% (404/544) of them were male with a median age was 42.0 (34.3, 49.7) and the mean duration from initiation of antiviral treatment to liver biopsy was 1.5 (1.0, 3.1) years. Most patients were treated with Entecavir (85.3%) and achieved HBVDNA undetectable as well as ALT normalization at the liver biopsy. There were 205 (37.7%) patients staged ≥F3 with METAVIR scoring system. The Baveno **e** cut-offs of < 10 and > 15 kPa showed 56% sensitivity and 98% specificity to exclude and diagnose cACLD, respectively. Examining the ROC curve, a more optimal dual cut-off at < 7 and > 11 kPa, with 90% sensitivity and 90% specificity for excluding and diagnosing cACLD (AUC = 0.83, 95%CI:0.79-0.86, P < 0.001) were derived. The new threshold is much lower than the previous Baveno **e** LSM cut-off which was adopted for different etiologies of chronic liver diseases. With this new threshold, misclassified patients decreased 5.3% (10.5% to 5.2%) for excluding cACLD. Results in the validation set were similar with the training set. **Conclusion:** The optimal dual cut-off of liver stiffness measurement to exclude and diagnose compensated advanced liver disease were < 7 kPa and > 11 kPa in on-treatment patients with chronic hepatitis B.

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f 3461-A | PNPLA3-rs738409 CG/GG GENOTYPE IS STRONGLY ASSOCIATED WITH ADVANCED HISTOLOGIC FIBROSIS AND HIGH RISK ENHANCED LIVER FIBROSIS (ELF) SCORE

Zobair M. Younossi[1,2,3], James M. Estep[1,2,3], Sean Felix[1], Brian P. Lam[1,2,3], Elena Younossi[1], Nagashree Gundu-Rao[4], Leyla De Avila[1], Huong Pham[1], Rebecca Cable[1], Jillian K. Price[1], Andrei Racila[1] and Maria

Stepanova[5], (1)Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, (2)Center for Liver Disease, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, VA, (3)Inova Medicine, Inova Health System, Falls Church, VA, (4)Division of Endocrinology, Inova Health System, Falls Church, VA, (5)Center for Outcomes Research in Liver Diseases, Washington, DC

Background: Genetic risk factors have been linked to histologic stage of fibrosis in NAFLD. These associations with non-invasive biomarkers such as ELF have not been established. **Methods:** Clinical data, serum and whole blood were collected from consented patients with NAFLD. In addition to standard laboratory test (liver enzymes, platelet count, to calculate FIB-4), ELF score was measured (ADVIA Centaur, Siemens Healthineers). Genomic DNA was extracted from the whole blood [QIAamp DNA Blood Mini Kit (Qiagen)] and used for determination of minor allele frequency for genomic loci rs641738 (MBOAT7), rs58542926 (TM6SF2), rs738409 (PNPLA3), rs62305723 (HSD1713B) using CFX96 (Bio-Rad). Individual alleles were evaluated for the association with elevated (≥ 9.8) and high (≥ 11.3) ELF, elevated ($\underline{>}2.67$) and high (≥ 3.25) FIB-4 as well as advanced histologic fibrosis (Metavir stage 3 or 4) in NAFLD. **Results:** There were 1072 NAFLD patients: 57 ± 14 years, 57% male, BMI 34.4 ± 9.2, 33% type 2 diabetes. Of these patients, 83% had low ELF score (< 9.8) and 2.2% had high ELF (≥ 11.3). Furthermore, 8.5% had elevated and 4.9% had high FIB-4 scores. Of the 4 studied SNPs, only *PNPLA3*-rs738409 (51% CC, 42% CG, 7% GG) was significantly ($p < 0.05$) associated with higher ELF scores: elevated ELF 12% in CC vs. 19% in CG/GG, high ELF 0.6% in CC vs. 3.6% in CG/GG (both $p < 0.01$). The same allele was also associated with elevated (6.0% in CC vs. 9.9% in CG/GG) and high (3.1% vs. 6.3%, respectively) FIB-4 scores (both $p < 0.05$), as well with having advanced histologic fibrosis among patients who had a liver biopsy (13% in CC vs. 30% in CG/GG, $p = 0.0011$). However, among patients who had liver stiffness measurement (LSM) by transient elastography, there was no association of LSM with the allele ($p > 0.05$). In multivariate analysis adjusted for age, sex, BMI and type 2 diabetes, having *PNPLA3*-rs738409 CG/GG genotype was independently associated with higher risks of elevated and high ELF and FIB-4 scores as well as advanced histologic fibrosis: odds ratio (OR) = 1.78 (1.22-2.59) for elevated ELF, OR = 5.78 (1.66-20.10) for high ELF (both $p < 0.01$); OR = 2.04 (1.19-3.50) for elevated FIB-4, OR = 2.23 (1.12-4.46) for high FIB-4 (both $p < 0.025$); OR = 2.48 (1.21-5.09) ($p = 0.013$) for advanced histologic fibrosis. **Conclusion:** In patients with NAFLD, the polymorphism rs738409 in the *PNPLA3* gene was associated with having advanced histologic fibrosis and its surrogates such as ELF score.

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3462-A | POINT OF CARE REAL WORLD HOLOGIC MACH40 AND FIBROSCAN COMPARED TO FIB4 FIBROSIS RISK GUIDELINE BASED

Allan Weston, SSM Health St Anthony and Jennifer Rickman, Digestive Health Center of the Four States, LLC

Background: NAFLD is widespread and frequently asymptomatic and diagnosed only after complications related to cirrhosis become manifest. Multiple risk factors have been identified including BMI > 30, DM, and HTN. Detection of fatty liver and fibrosis severity using simple blood studies to determine FIB4 score has been advanced in AASLD and AACE guidelines. If the FIB4 score is indeterminate or high risk, then liver stiffness measurement (LSM) by Elastography is recommended. The LSM measurement then re-stratifies the risk as low, indeterminate or high. Guidelines state that Transient Vibration Elastography (TVE) is preferred over 2D Shearwave Elastography (SWE). Several different SWE US platforms are available for clinical use which has generated conflicting data on SWE accuracy; however, Hologic (previously SuperSonic) utilizes propriety software that generates ultrafast, reliable, reproducible LSM. The newest generation MACH40 Hologic system has additional features that provide not only LSM but also liver viscosity and liver speed. **Methods:** Consecutive patients seen over a 5 month period who were either being seen for f/u of NASH or known Cirrhosis (of any cause) or as new referrals for either abnormal liver function tests, concern for NASH or abnormal imaging of the liver underwent point of care sequential FIBROSCAN imaging to obtain a fibrosis score and CAP value followed by transabdominal US imaging using MACH 40 platform to obtain 2D SWE score, liver viscosity value, liver speed followed by Hepatic Renal Ratio (HRR) value. Data was collected regarding demographics, BMI, alcohol consumption, smoking history, medical illnesses, and laboratory data used to determine FIB4 score and NAFLD Fibrosis score. STATA was used to examine what features are predictive of success of obtaining a LSM score by MACH40 vs TVE. LSM scores obtained by TVE and 2D SWE were also compared to FIB4 fibrosis risk stratification and liver viscosity. **Results:** 85 pts underwent MACH40 scanning and 82 concurrent TVE: LSM were obtained in 97.6% for SWE and only 81.7% for TVE. Both cases of unreliable/unattainable SWE. TVE was also unsuccessful: both pts morbidly obese, wheelchair bound and had ascites. Features predictive of inability to obtain TVE included skin to liver distance > 3.5 cm ($p < 0.00001$) and presence of ascites ($p < 0.00001$) but not BMI. FIB4 using lab data +/- 60 days was available for 55 pts. High risk FIB4 score was confirmed as high risk LSM score by TVE 54.5% compared to 68.1% for SWE. Low risk FIB4 score was confirmed as low risk LSM score by TVE 53.8% compared to 76.9% for SWE. Liver Viscosity scores were significantly higher for high risk LSM group compared with low risk LSM group. **Conclusion:** MACH40 US is able to generate LSM in significantly more patients and has higher congruence with FiB4 risk stratifcation than TVE. Liver viscosity scores above 3.2 Pa.s obtained with MACH40 are significantly more likey to reflect high risk LSM group.

Disclosures: The following people have nothing to disclose: Allan Weston, Jennifer Rickman

3463-A | PSEUDOCIRRHOSIS: UNVEILING AN UNCONVENTIONAL HEPATIC MASQUERADE

Kikelomo Olaosebikan[1], Ahmed Shehadah[2], Elizabeth Soladoye[1] and Raissa Nana Sede Mbakop Forlemu[1], (1)Piedmont Athens Regional, Athens, GA, (2) Rochester General Hospital

Background: Pseudocirrhosis is a rare hepatic complication typically associated with chemotherapy use. It manifests as morphological changes in the liver that closely resemble cirrhosis, despite lacking the typical histopathological changes. While primarily seen in metastatic breast cancer, it has also been reported in other malignancies. We present a unique case of pseudocirrhosis leading to the diagnosis of primary lung malignancy. **Methods:** A 76 y.o. Female with a significant smoking history presented to the hospital with worsening abdominal pain, fatigue, and unintentional weight loss over three months. Initial evaluations at multiple hospitals suggested cirrhosis based on hepatomegaly and a cirrhotic picture on an abdominal CT scan, despite no risk factors or clinical evidence. She was cachectic, non-jaundiced, normal bowel sounds, no distention, moderate epigastric tenderness, and no fluid thrill. Laboratory investigations revealed elevated lipase, liver enzymes, and normal total bilirubin, and platelets. MRI abdomen showed numerous liver nodules suggestive of metastatic disease, likely indicative of pseudocirrhosis. Subsequent CT chest revealed a right middle lung mass with mediastinal adenopathy, consistent with primary lung malignancy. However, the patient declined further testing. **Results:** This case highlights the importance of avoiding premature closure in the evaluation of suspected cirrhosis or abnormal liver enzymes. The initial misdiagnosis delayed the recognition of primary lung malignancy. Pseudocirrhosis was not initially considered due to its rare occurrence in non-chemotherapy patients. However, the imaging findings were attributed to the lung malignancy, which was overlooked in earlier studies. Thus, considering pseudocirrhosis as a potential cause of cirrhosis-like imaging findings is crucial, even in the absence of chemotherapy. Pseudocirrhosis associated with primary lung malignancy is uncommon. Existing literature reports only a few cases, mostly involving liver metastasis and imaging findings resembling cirrhosis. The pathophysiology of pseudocirrhosis varies and can overlap. In chemotherapy-naive patients, pseudocirrhosis has been associated with factors such as tumor size, progression, and desmoplastic reactions. Diagnosing pseudocirrhosis can be challenging, as it is rarely observed on pre-chemotherapy imaging. Capsular retraction, delayed contrast uptake, and morphological liver changes are characteristic features of pseudocirrhosis, mimicking untreated liver metastases or cirrhosis. **Conclusion:** Pseudocirrhosis should be considered in patients with cirrhosis-like imaging findings, even in the absence of chemotherapy history. This case report underscores the importance of including pseudocirrhosis in the differential diagnosis of liver diseases, emphasizing the significance of early detection and treatment for optimal patient outcomes.

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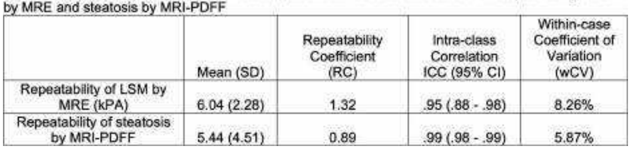
3464-A | REPEATABILITY OF LIVER STIFFNESS MEASUREMENT BY MAGNETIC RESONANCE ELASTOGRAPHY AND REPEATABILITY OF STEATOSIS MEASUREMENT BY MRI PROTON DENSITY FAT FRACTION IN PATIENTS WITH CIRRHOSIS

Daniel Q Huang[1], Nabil Noureddin[1], Jaclyn Bergstrom[1], Maral Amangurbanova[1], Egbert Madamba[1], Christie Hernandez[1], Claude B. Sirlin[1] and Rohit Loomba[2], (1) University of California, San Diego, (2)University of California, San Diego, San Diego, CA

Background: The regulatory qualification of non-invasive tests (NITs) for liver fibrosis severity assessment is a major unmet need for drug development and clinical care in cirrhosis. Non-invasive imaging tests such as magnetic resonance elastography evaluate liver stiffness measurement (LSM) for fibrosis severity, and magnetic resonance imaging proton density fat fraction-(MRI-PDFF) evaluates steatosis. Repeated use of non-invasive imaging tests has the potential to assess disease response and progression. However, this potential application has been limited by a paucity of repeatability data in the patient population at risk. The aim of this prospective study from the San Diego Cirrhosis Registry was to address this knowledge gap and contribute to the evidentiary basis needed for the qualification of MRI-based methods in various contexts of use in clinical trials and practice. **Methods:** A prospective cohort of adults with suspected or established cirrhosis underwent two MRI exams (including MRI-PDFF and MRE) on the same day. The primary endpoint was the same-day/same-operator repeatability coefficient (RC), which represents the value under which the difference between repeated measurements should fall with a 95% probability. The intra-class correlation coefficient (ICC) which represents the proportion of total variation explained by between-patient differences rather than measurement variation, and the within-case coefficient of variation (wCV), which represents the ratio of within-patient variation to overall measurement value, were also evaluated. **Results:** Same day repeat MRIs were available in 25 participants. The mean age was 61 years, 70% were women, mean body mass index (BMI) was 29.8 kg/m^2. RC was 1.32 kPa, and 0.89 for LSM by MRE, and steatosis by MRI-PDFF, respectively, meaning that any change greater than those values has a 95% probability to reflect true change rather than measurement error. ICC was excellent for LSM by MRE (.95) and steatosis by MRI-PDFF (.99), while wCV indicated that the within-patient variation was close to the overall measurement values for MRE and MRI-PDFF (Table 1). **Conclusion:** LSM and steatosis measurements by MRE, and MRI-PDFF, demonstrated good repeatability within patients with cirrhosis. These repeatability estimates are likely to inform MRI-based NIT qualification by defining the values that are expected to reflect a true change in the context of clinical trials or clinical care.

Table 1: Repeatability, intra-class correlation, and within-case coefficients for the repeatability of LSM by MRE and steatosis by MRI-PDFF



	Mean (SD)	Repeatability Coefficient (RC)	Intra-class Correlation ICC (95% CI)	Within-case Coefficient of Variation (wCV)
Repeatability of LSM by MRE (kPA)	6.04 (2.28)	1.32	.95 (.88 - .98)	8.26%
Repeatability of steatosis by MRI-PDFF	5.44 (4.51)	0.89	.99 (.98 - .99)	5.87%

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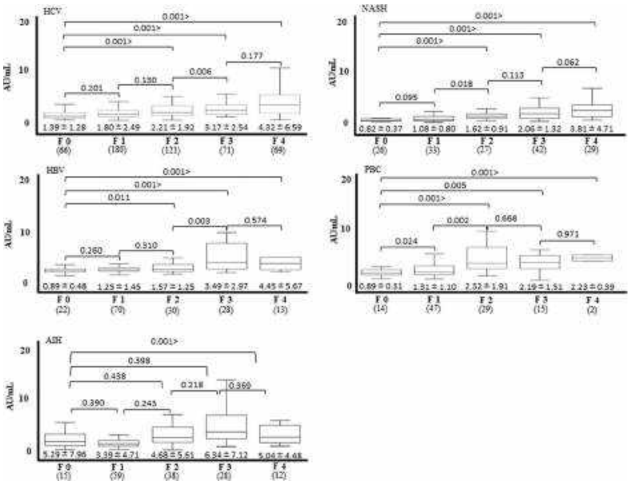
3465-A | SERUM MAC-2 BINDING PROTEIN GLYCOSYLATION ISOMER (M2BPGi) SHOWS DIFFERENT VALUES IN DIFFERENT LIVER DISEASES BY THE NEWLY DEVELOPED QUANTITATIVE M2BPGi METHOD, STRONGLY SUGGESTING THE EXISTENCE OF SUBTYPES OF M2BPGi

Haruki Uojima[1], Masashi Mizokam[1], Kazumi Yamasaki[2], Masaya Sugiyama[1], Ken Shirabe[3], Kiyoaki Ito[4], Yasuhiro Asahina[5], Takumi Kawaguchi[6], Hidenori Toyoda[7], Masayuki Kurosaki[8], Akinobu Taketomi[9], Takeji Umemura[10], Kentaro Matsuura[11], Hiroko Iijima[12], Sohji Nishina[13], Hiroshi Yatsuhashi[2], Masayoshi Kage[14] and Hisashi HIdaka[15], (1)National Center for Global Health and Medicine, (2)Nagasaki Medical Center, (3) Gunma University, (4)Aichi Medical University, (5)Tokyo Medical and Dental University, (6)Kurume University School of Medicine, (7)Ogaki Municipal Hospital, (8) Musashino Red Cross Hospital, Tokyo, Japan, (9) Hokkaido University Graduate School of Medicine, (10) Shinshu University of Medicine, (11)Nagoya City University Graduate School of Medical Sciences Nagoya, (12)Hyogo Medical University, Nishinomiya, Japan, (13)Kawasaki Medical School, (14)Kurume University, (15)Kitasato University School of Medicine

Background: Currently, research on glycoproteins as a "third life chain" is progressing rapidly. We developed a semiquantitative method to measure WFA-positive Mac-2-binding protein glycan isomer (M2BPGi) as a serum marker for liver fibrosis. M2BPGi is currently used clinically as an alternative to liver biopsy. In this study, we developed a more accurate quantification method for M2BPGi and investigated the quantification method for M2BPGi in various liver diseases. **Methods:** This multicenter study was conducted at thirteen locations in Japan. The inclusion criteria were chronic liver disease (CLD) diagnosed by the combination of the specific laboratory tests and liver biopsy. The clinical data, serum samples, and pathological slides of the enrolled patients were collected to the research center. We evaluated the confidence ratio of the M2BPGi-Qt levels by the new methods of quantitative system and the M2BPGi levels by the current methods of semi-quantitative system to validate the clinical utility of the new method. We also evaluate the influence of fibrosis to the M2BPG-Qt levels in the different etiologies of CLD by the quantitative measurement. If a correlation between fibrosis and M2BPGi in a particular etiology was absence, we analyze other clinical factors which influence of M2BPGI besides liver fibrosis. **Results:** A total of 1108 patients were recruited to the measurement of M2BPGi. The numbers of patients with hepatitis C virus (HCV), hepatitis B virus (HBV), non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis (AIH), primary biliary cholangitis(PBC) and Alcoholic liver disease (ALD) were 507, 163, 158, 152, 111,17, respectively. The correlation coefficient between M2BPGi-Qt and M2BPGi was very strong in all range. $(R = 0.987, \ p < 0.001)$. M2BPGi-Qt levels increased with the progression of liver fibrosis in patients with HCV, HBV, NAFLD, and PBC. ALD was not evaluated due to insufficient cases. No significant difference was observed between fibrosis stage and M2BPGi-Qt levels in patients with AIH. (Figure 1). Of the analyzed clinical factors, the degree of liver inflammation was positively correlated with M2BPGi levels in patients with AIH. **Conclusion:** The quantitative M2BPGi measurement system revealed that the diffidence of M2BPGi levels according to the etiology of liver disease depends on both the progression of liver fibrosis and the degree of liver inflammation. The result strongly suggesting the existence of subtypes of M2BPGi.



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3466-A | THE CROSS-LINKED TYPE III COLLAGEN BIOMARKER, CTX-III, REFLECTS FIBROSIS RESOLUTION AND IS RELATED TO INTERVENTION AND SURVIVAL IN CHRONIC LIVER DISEASE

Alejandro Mayorca Guiliani[1], Ida Lønsmann Sorribes[2], Peder Frederiksen[1], Emilie Skovgaard[1,3], Martin Pehrsson[1], Judith Ertle[4], Corinna Schoelch[5], Robert Schierwagen[6], Michael Praktiknjo[7], Morten Karsdal[8], Diana J. Leeming[2], Flemming Bendtsen[9], Julie Steen Pedersen[10] and Jonel Trebicka[6], (1)Nordic Bioscience a/S, (2)Nordic Bioscience A/S, (3)University of Copenhagen, (4)Boehringer Ingelheim International Gmbh, (5)Boehringer Ingelheim Pharma Gmbh, (6) University Hospital Münster, (7)University of Bonn, (8) Nordic Bioscience a/S, Denmark, (9)Hvidovre Hospital, (10)Copenhagen University Hospital of Koege

Background: The liver extracellular matrix (ECM) is a scaffold of proteins and glycans supporting all liver cells. Progressing fibrosis results in increased ECM deposition. Thus, fibrosis regression, upon insult removal or therapy, should tilt the balance towards ECM degradation. As therapies against fibrosis advance, biomarkers to prognosticate and monitor fibrosis regression become a necessity. Here, we aimed to investigate whether a MMP degraded and cross-linked fragment of type III collagen, called CTX-III, could: 1) mark decreasing disease activity and regression after intervention and 2) predict survival in chronic liver disease. **Methods:** We homogenized human liver segments (healthy $n = 1$; diagnosed with steatohepatitis $n = 2$; steatohepatitis and bridging fibrosis $n = 2$; steatohepatitis, ballooning and bridging fibrosis $n = 1$) and measured CTX-III using ELISA. Blood samples were collected from patients undergoing bariatric surgery ($n = 65$ with blood samples taken at 3-, 6-, and 12-months follow-up) and transjugular intrahepatic porto-systemic shunt (TIPS) ($n = 86$). Biomarkers CTX-III and PRO-C3 were measured in an

automated high precision platform. **Results:** We confirmed *in vitro* that CTX-III is present in the human liver tissue, with higher levels in diseased tissue. Then, we assessed the monitoring properties of CTX-III in a non-alcoholic fatty liver disease cohort (NAS Score 0 points = 0 patients; 1 = 6; 2 = 19; 3 = 16; 4 = 10; 5 = 13; 6 = 1; 7 = 0, 8 = 0) and liver fibrosis (F0 = 1; F1 = 55; F2 = 8; F3 and F4 = 0) undergoing bariatric surgery. We found a 23% (IQR 4-63%) median CTX-III increase after surgery ($p \leq 0.001$), while PRO-C3 showed a non-significant increase ($p = 0.161$). CTX-III increase coincided with decreases in body mass index and liver enzymes (ALT $p = 0.006$; GGT $p = < 0.001$). We then measured CTX-III and PRO-C3 in a cohort with decompensated cirrhosis receiving TIPS. A CTX-III:PRO-C3 ratio below the median was associated with shorter transplant-free survival (Hazard ratio 1.69, 95% CI 1.02-2.86; $p = 0.04$). **Conclusion***: In vitro*, increased CTX-III suggests diseased ECMs are richer in crosslinked collagen. When measured in patients undergoing bariatric surgery, CTX-III levels suggest increased ECM degradation, and thus CTX-III potential as a monitoring biomarker associated with liver structure remodeling. Additionally, assessing both ECM formation (PRO-C3) and degradation (CTX-III) might aid in prognosis stratification of patients with decompensated cirrhosis.

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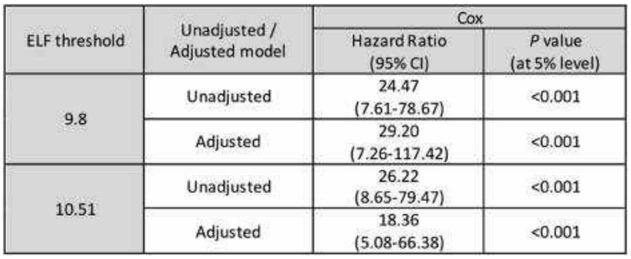
3467-A | THE ENHANCED LIVER FIBROSIS TEST IS ASSOCIATED WITH DEVELOPMENT OF CIRRHOSIS AND HEPATOCELLULAR CARCINOMA IN INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS

Paul M Trembling[1], Sheila M Grecian[2], Mark W J Strachan[2], William M. Rosenberg[1] and Jonathan A Fallowfield[3], (1)University College London, (2)Western General Hospital, Edinburgh, (3)University of Edinburgh

Background: The Enhanced Liver Fibrosis (ELF) test accurately stratifies liver fibrosis severity, monitors changes in fibrosis and predicts liver-related events in patients with a range of chronic liver diseases. Type 2 diabetes mellitus (T2DM) is a major metabolic risk factor for liver fibrosis and progression to cirrhosis and hepatocellular carcinoma (HCC), yet non-invasive tools for predicting such outcomes are not well established in this population. The Edinburgh Type 2 Diabetes Study is a prospective population-based cohort study investigating the role of potential risk factors in the development of complications of T2DM. A total of 1066 men and women with T2DM, aged 60-75 years at baseline, were recruited between 2006 and 2007. We aimed to estimate association between ELF and development of cirrhosis and / or HCC (events) in this population. **Methods:** In a nested sub-study of 254 participants, ELF scores were measured one and four years after recruitment. Participants were followed up for incident events. Cox proportional hazards analysis was performed estimating association of year-1 ELF at thresholds of 9.8 and 10.51 (established thresholds for advanced fibrosis) with events, adjusted for age and baseline biochemical parameters (high serum ALT & AST, low platelet count). Immortal time bias was evaluated using time-dependent Cox analysis, using time of sample where ELF first reached threshold. **Results:** Over a median follow-up period of 10 years, 14 (4%) participants experienced pre-specified events. Mean ELF scores in 'no event' and 'event' groups were 8.86 (SD 0.85) and 10.13 (SD 1.45) respectively. Significant associations between ELF score and events were seen at both thresholds (table). Hazard ratios (not shown) were similar using ELF as a time-dependent variable, indicating immortal time is not a confounder. The AUROC for ELF for predicting events was 0.8 (95% CI 0.6-1.0). Higher initial ELF score was associated with an increased risk of events, such that a one-unit higher ELF score was associated with 27% greater risk of cirrhosis and / or HCC. Mean change in ELF score per year was higher in the events group (0.13 v 0.09 / year, $P = 0.94$). **Conclusion:** There is significant association between ELF score and progression to cirrhosis / HCC in this cohort of older individual's with T2DM. These data indicate that the ELF test may be a useful clinical prognostic tool in this setting, enabling risk stratification and better targeting of care.



ELF threshold	Unadjusted / Adjusted model	Cox	
		Hazard Ratio (95% CI)	*P* value (at 5% level)
9.8	Unadjusted	24.47 (7.61-78.67)	<0.001
	Adjusted	29.20 (7.26-117.42)	<0.001
10.51	Unadjusted	26.22 (8.65-79.47)	<0.001
	Adjusted	18.36 (5.08-66.38)	<0.001

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3468-A | THE VALIDATION STUDY OF LIVER STIFFNESS MEASUREMENT BY ULTRASOUND-BASED ELASTOGRAPHY IN THE PRESENCE OF CO-EXISTING INFLAMMATION

Ryosuke Kasuga, Nobuhito Taniki, Po-sung Chu, Rei Morikawa, Takaya Tabuchi, Fumie Noguchi, Yukie Nakadai, Mayuko Kondo, Takanori Kanai and Nobuhiro Nakamoto, Keio University School of Medicine

Background: Elastography is used for noninvasive measurement of liver stiffness. It is previously reported that measured value of elastography varies under the influence of inflammation. However, the details regarding the impact of inflammation on liver stiffness has not been well established. In the current study, we aimed to develop strategy for the best use of elastography to evaluate patients at risk for liver fibrosis in the presence of co-existing inflammation. **Methods:** We retrospectively recruited 274 patients who underwent liver tissue biopsies performed since January 2018 in our institution. This study is approved by local institutional IRB (no. 20170202). Histological fibrosis and inflammation were evaluated according to the METAVIR fibrosis and activity score and we defined active inflammation as METAVIR A2 and 3 grade. We assessed the diagnostic performance of elastography including Vibration-Controlled Transient Elastography: VCTE (Fibroscan; Echosens) and Shear Wave Elastography: SWE (Logiq-E9; GE) using ROC analysis focusing on accuracy to discriminate each fibrosis stage at the presence of inflammation. And we also compared elastography with other non-invasive predictors that define fibrosis; serum biomakers (4COL7S, M2BPGi, ATX), scoring systems (FIB-4 index, APRI). **Results:** The underlying liver diseases were viral hepatitis in 80 cases (29%) and non-viral hepatitis in 194 cases(71%). METAVIR fibrosis stage was F0 in 81 cases(30%), F1 in 47 cases(17%), F2 in 42 cases(15%), F3 in 33 cases(12%), F4 in 71 cases(26%). The AUROC of FIB-4 index for each fibrosis stage F = 0 vs F ≥ 1, F ≤ 1 vs F ≥ 2, F ≤ 2 vs F ≥ 3, F ≤ 3 vs F4 were 0.72, 0.76, 0.76, 0.76, and FIB-4 index provided the highest diagnostic accuracy among serum bio-markers and scoring systems. The AUROCs of VCTE and SWE were 0.88, 0.90, 0.91, 0.93 and 0.85, 0.88, 0.87, 0.86. In cases with active inflammation, AUROC of FIB4 index significantly decreased by 0.63, 0.68, 0.69, 0.68 while VCTE (0.88, 0.87, 0.87, 0.91) and SWE (0.82, 0.82, 0.82, 0.91) were still effective. On the other hand, the measurement values of VCTE and SWE tended to increase at the presence of inflammation especially in mild fibrosis stage. VCTE values of A0,1 vs A2,3 were 6.3 vs 8.0 kPa (P = 0.0005) and SWE values were 1.41 vs 1.54 m/s (P = 0.012) in F0 stage, 7.6 vs 11.5 (P = 0.064), 1.51 vs 1.68 (P = 0.177) in F1, 12 .2 vs 15.9 (P = 0.062), 1.72 vs 1.86 (P = 0.098) in F2, 16.0 vs 15.8 (P = 0.810), 1.88 vs 1.93 (P = 0.678) in F3, 33.4 vs 27.7 (P = 0.728), 2.02 vs 2.19 (P = 0.149) in F4. **Conclusion:** Our findings revealed that ultrasound-based elastography can distinguish fibrosis stage with accuracy even in the presence of active inflammation. Since overestimation of liver stiffness induced by inflammation occurs only in mild fibrosis stage, the risk of overestimation can be avoided by raising cut-off value in such specific cases.

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3469-A | VISUALIZED TRANSIENT ELASTOGRAPHY TO ASSESS FIBROSIS AND STEATOSIS IN PATIENTS WITH CHRONIC LIVER DISEASE

Andres M. Corona[1], Uche C. Ezeh[1], Maria Lourdes Olson[1], Katheryn Dae[1], Edisson J. Aguilera Herrera[1], Jiovanna N. Fernandez[1], Francheska Escobar[1], Jasmina Kovacevic[2], Leopoldo R. Arosemena[1], Emmanuel Thomas[1], Diane Sabogal[1] and Eugene R. Schiff[1], (1)University of Miami Miller School of Medicine, Schiff Center for Liver Diseases, (2)University of Florida College of Medicine

Background: Assessment of liver fibrosis and steatosis in patients with chronic liver disease (CLD) is important for risk-stratification and management decisions. Various non-invasive techniques including transient elastography and laboratory-based scoring systems are used in practice for fibrosis staging in CLD. The purpose of this study was to compare fibrosis and steatosis measurements between the FibroScan® 630 (vibration-controlled transient elastography, VCTE) and the recently developed Hepatus Series Diagnostic ultrasound system® (visualized transient elastography, ViTE). **Methods:** We performed a prospective study of 48 patients with CLD at the Schiff Center for Liver Diseases between August 2022 to March 2023. We reported descriptive continuous variables as mean ± standard deviation (SD). The shapiro-wilk test was conducted to determine the normality of the data. We used a paired t-test to compare the means of the VCTE kPa vs. ViTE kPa and a wilcoxon signed-rank test to compare the means of the VCTE CAP vs. ViTE LiSA. We used Pearson correlation (r) to assess whether there was an association between BMI, height and weight and the aforementioned clinical values. IBM SPSS v28 was used to conduct statistical analysis and

$p < 0.05$ was considered statistically significant. **Results:** Among the 48 patients, the mean age (years) was 52.7 (13.88), the mean BMI was 30.675 (0.97), weight (lbs.) was 198.77 (7.00), and height (cm) was 170.70 (1.56) (Table 1). The mean VCTE kPa was 8.33 (4.92) and ViTE kPa 8.38 (4.13). There was no statistically significant difference between their mean values ($p = 0.868$). The mean VCTE CAP was 284.44 (7.55) and ViTE LiSA was 276.58 (7.71). There was no statistically significant difference in the VCTE CAP compared to ViTE LiSA ($p = 0.133$). There was a statistically significant, moderate positive correlation between VCTE kPA ($r = 0.326$, $p = 0.024$), ViTE kPA ($r = 0.326$, $p = 0.024$) and VCTE CAP ($r = 0.370$, $p = 0.010$) and weight. There was no statistically significant correlation between height and VCTE kPa, VCTE CAP, ViTE kPa, and ViTE LiSA ($p > .05$). Additionally, there was a statistically significant, moderate positive correlation between VCTE kPA ($r = 0.402$, $p = 0.005$), ViTE kPA ($r = 0.527$, $p = < 0.001$), ViTE LiSA ($r = 0.315$, $p = 0.029$), VCTE CAP ($r = 0.429$, $p = 0.002$) and BMI. **Conclusion:** Our data indicates similar liver fibrosis and steatosis measurements between VCTE and ViTE. ViTE's real-time visual guidance may offer a quicker and more reliable method for non-invasive liver fibrosis staging. Further studies evaluating the accuracy of ViTE compared to VCTE across BMI classes with a larger cohort are warranted.

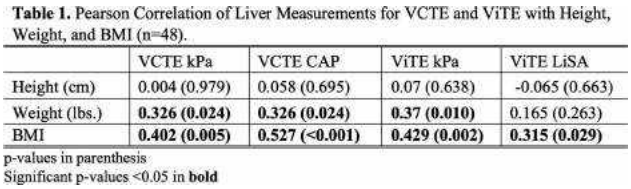

Table 1. Pearson Correlation of Liver Measurements for VCTE and ViTE with Height, Weight, and BMI (n=48).

	VCTE kPa	VCTE CAP	ViTE kPa	ViTE LiSA
Height (cm)	0.004 (0.979)	0.058 (0.695)	0.07 (0.638)	-0.065 (0.663)
Weight (lbs.)	**0.326 (0.024)**	**0.326 (0.024)**	**0.37 (0.010)**	0.165 (0.263)
BMI	**0.402 (0.005)**	**0.527 (<0.001)**	**0.429 (0.002)**	**0.315 (0.029)**

p-values in parenthesis
Significant p-values <0.05 in **bold**

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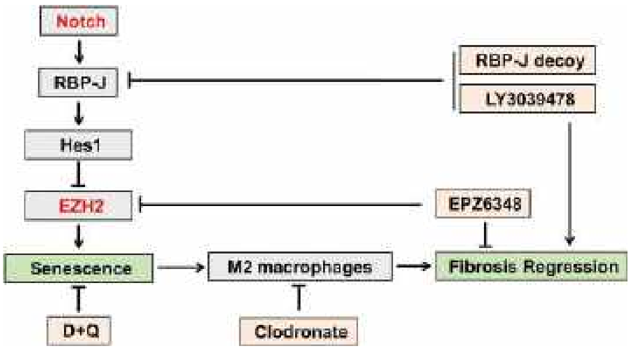
3470-A | CELLULAR SENESCENCE PRIMES LIVER FIBROSIS REGRESSION THROUGH NOTCH-EZH2

Ping Song and Lin Wang, Fourth Military Medical University

Background: Liver fibrosis is reversible once the injury is removed. Cellular senescence which plays a pivotal role in wound healing potentially drives liver fibrosis regression. However, the involved mechanism has not been fully elucidated. **Methods:** Senescent cells were detected by SA-β-gal staining and removed by dasatinib and quercetin. Macrophages were depleted by Clodronate. EZH2 signaling was blocked by EPZ6438. Disruption of Notch in macrophages was achieved by Lyz2- Cre RBP-J$^{f/f}$ transgenic mice. Notch signaling was blocked by Ly3039478 or exosome-mediated RBP-J decoy oligodeoxynucleotides. **Results:** At the initiation of liver fibrosis regression, accumulated senescent cells were detected by SA-β-gal staining. Marker genes of senescence were upregulated meanwhile. Flowcytometry combined with single-cell RNA sequencing analyses revealed that most of senescent cells were liver non-parenchymal cells, especially Kupffer cells and liver endothelial cells. Removing senescent cells by dasatinib and quercetin, alleviated hepatic cellular senescence, impeded fibrosis regression and disrupted liver sinusoids. Besides, clearance of senescent cells not only decreased senescent macrophages but also shrank the proportion of anti-inflammatory M2 macrophages through apoptotic pathway. Subsequently, macrophages were depleted by Clodronate, which diminished hepatic senescent cells and impaired fibrosis regression. Mechanistically, the change of the epigenetic regulator EZH2 accompanied with the emergence of hepatic senescent cells while liver fibrosis regressed. Blocking EZH2 signaling by EPZ6438 reduced hepatic senescent cells and macrophages, decelerating liver fibrosis regression. Moreover, the promoter region of EZH2 was transcriptionally suppressed by Notch-Hes1 signaling. Disruption of Notch in macrophages using Lyz2-Cre RBP-J$^{f/f}$ transgenic mice, enhanced hepatic cellular senescence and facilitated fibrosis regression by upregulating EZH2 and blocking EZH2 abrogated the above effects caused by Notch deficiency. Ultimately, adopting Notch inhibitor Ly3039478 or exosome-mediated RBP-J decoy oligodeoxynucleotides accelerated liver fibrosis regression by augmenting hepatic cellular senescence. **Conclusion:** Blockage of Notch promoted the accumulation of EZH2-regulated senescent cells to initiate liver fibrosis regression, providing a promising treatment of liver fibrosis.



Disclosures: The following people have nothing to disclose: Ping Song, Lin Wang

3471-A | MARCO-POSITIVE MACROPHAGES DEMONSTRATE ANTI-INFLAMMATORY PHENOTYPE COMPARED TO MARCO-NEGATIVE MACROPHAGES DURING LIVER INJURY.

Sofia Jerez[1], Shawna Cooper[1], Usman Yaqoob[2], Abid Anwar[3], Enis Kostallari[3], Nidhi Jalan-Sakrikar[2], Man Xie[1], Bushra Arif[1], Sheng Cao[2] and Vijay Shah[2], (1) Mayo Clinic, (2)Mayo Clinic Rochester, Rochester, MN, (3)Mayo Clinic, Rochester, MN

Background: The **Ma**crophage **R**eceptor with **Co**llagen Structure protein (MARCO) is a scavenger receptor predominantly expressed on healthy tissue-resident macrophages (Macs), including Kupffer cells in the liver. It is known that Macs can exhibit anti- or pro-inflammatory properties, thereby regulating inflammation. At the same time, chronic inflammation is a key factor in hepatic fibrosis. However, the role of MARCO and its expression in liver Macs during liver diseases remains unknown. This study aims to identify MARCO-dependent differences between subsets of liver Macs and analyze the role of MARCO-expressing Macs during liver fibrosis. **Methods:** Single-cell RNA-sequencing (scRNAseq) and spatial transcriptomics (ST) (10x genomics), as well as Immunohistochemistry (IHC) and immunofluorescence (IF) staining was performed on livers from olive oil and carbon tetrachloride (CCl_4)-treated mice. Liver non-parenchymal cells (NPCs) were isolated from vehicle- or lipopolysaccharide (LPS)-injected mice and analyzed by flow cytometry. For *in vitro* studies, RAW264.7 Macs cell line, which is deficient in MARCO, was used for overexpression studies using transient plasmid-expression of MARCO and inflammatory stimulus with LPS. nCounter inflammation assay (NanoString), was used to analyze changes in gene expression. Validation was done by qPCR. **Results:** scRNAseq data shows two Macs subsets, distinguishable by their MARCO expression. MARCO$^+$ population was found to be increased in CCL_4-treated mice (Log2FC 3.6, *p = 3.55e-17*, 56% in CCl_4 vs. 16% in Olive oil). IHC and ST data show that MARCO$^+$ Macs were located in non-fibrotic areas, and MARCO$^-$ Macs were populated in zones with fibrosis. Also, flow cytometry of primary isolated NPCs shows an increase in the MARCO$^+$ population in response to LPS-induced liver injury (57.6% in LPS vs. 21.8% in vehicle). *In vitro* studies with MARCO-expressing Raw264.7 cells show downregulation of Tnf gene expression on MARCO$^+$ Macs compared to MARCO$^-$ population (log2FC -0.5, *p = 0.02*). nCounter assay, also show reduced expression of inflammatory cytokines, including Il12b, Il6, Ccl5, Cxcl2, and lower expression of Nfkb1 gene, which encodes a main regulator of inflammatory cytokines expression (n = 2). Finally, MARCO$^+$ cells demonstrated cytoskeletal remodeling and reduced migration capacity. These results suggest they may have an immune regulatory role in the immune niche of the liver, playing a possible anti-fibrotic role by reducing inflammation. **Conclusion:** MARCO$^+$ cells exhibit anti-inflammatory genes expression suggesting immunomodulatory effects in response to injury. This Macs subset, through their modulation of immune responses, migration, and involvement in actin filament remodeling, may play a role in mitigating liver inflammation, and consequently, in the development of fibrosis. Ongoing studies will help elucidate the underlying mechanisms and therapeutic potential of MARCO$^+$ macrophages.

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3500-C | A HUMAN LIVER-ON-A-CHIP MODEL FOR STUDYING THE ROLE OF LSECS IN ALCOHOL-RELATED LIVER DISEASE

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Background: Alcohol-related liver disease (ALD) is associated with excessive alcohol intake and abuse. Hepatic steatosis followed by steatohepatitis characterized by liver injury and inflammation occurs during the initial stage of ALD. Subsequently, the ALD spectrum progresses from reversible fatty liver to acute alcoholic hepatitis, chronic fibrosis and cirrhosis which are irreversible.

A 3D in vitro hepatic micro-physiological system, Liver-on-a-Chip, is designed to recapitulate in vivo functional conditions of the liver microenvironment using human-originated cells. In this project, we aim to investigate the role of liver sinusoidal endothelial cells (LSEC), the first defense hepatic barrier against insults from blood, in ALD and whether a human ALD Liver-on-a-Chip can be used to model alcohol-induced fatty liver and injury. **Methods:** To recreate the hepatocyte-sinusoidal interface, hepatocytes were cultured in the upper channel on top of the ECM-coated membrane whereas LSECs were cultured on the lower channel to allow cell-cell interaction. To model human ALD, the biomimetic Liver-on-a-Chip was subjected to EtOH exposure. **Results:** We have established an ALD Liver-on-a-Chip model that can better mimic alcohol-induced injury compared to conventional 2D plate system. Our Liver-on-a-Chip demonstrated high cellular activity, active expression of biochemical indicators (albumin, urea) and improved expression of alcohol metabolizing enzymes (ADH1, CYP2E1, ALDH2). Treatment of the Liver-on-a-Chip with EtOH augmented EtOH-induced hepatocyte damage compared with 2D system. Moreover, we discovered that LSECs are protective in alcohol-related liver injury by contributing to the clearance of acetaldehyde via Aldehyde Dehydrogenase 2 (ALDH2) expression on a Liver-on-a-Chip. We also showed that ALDH2 silencing in LSEC causes acetaldehyde overload and enhanced hepatocyte damage under EtOH exposure. **Conclusion:** Our study demonstrates that ALDH2-mediated aldehyde metabolism in LSECs is a novel underlying mechanism for ALD. This has prompted us to propose the future therapy for ALD by targeting LSECs.

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3501-C | A MULTI-DISCIPLINARY ALCOHOL-ASSOCIATED LIVER DISEASE CLINIC: THE ONE YEAR EXPERIENCE AT A TERTIARY CARE CENTER

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Background: Alcohol-associated liver disease (ALD) is increasing in prevalence and currently the leading indication for liver transplantation in the US. Multidisciplinary treatment for ALD and alcohol use disorder (AUD) is the recommended standard of care but infrequently implemented. Herein we describe the early experience of a multi-disciplinary ALD/AUD clinic after one year of operation at a single tertiary care center. **Methods:** The mult-disciplinary ALD/AUD clinic opened in November 2021. At the initial visit, each patient was evaluated by a hepatologist, addiction medicine specialist or counselor and social worker. Eligible patients had varying severities of ALD with less than 6 months of alcohol abstinence and a willingness to speak with an addiction medicine provider. Psychosocial questionnaires, hepatic function labs and non-invasive measures of hepatic fibrosis were collected. **Results:** 80 new patients were seen during the clinic's first year of operation. Average age was 48 years-old (range 24-75), and 40 (50%) were males. 59 patients (74%) had severe AUD, 14 (18%) moderate and 7 (9%) mild. 68% had co-morbid psychological conditions (95% reported an anxiety disorder) and 53% co-morbid substance use disorders. 44% of patients reported having some degree of consequence related to their alcohol or drug use, as reported on their Drug Abuse Screening Test. At the initial visit, only 21% reported prior pharmaceutical treatment for AUD and 66% reported non-pharmaceutical treatment. After their first visit, 54 patients (68%) initiated relapse prevention medication (a majority utilizing gabapentin) and 64 (80%) committed to addiction counseling. Following their first visit, 64 patients (80%) had at least one follow up appointment. At first follow-up visit, 64 patients (56%) had initiated addiction counseling and 53 (66%) started relapse prevention medication. 46 (72%) patients had stopped alcohol use completely while 42 (47%) reported episodic cravings. Between their initial visit and first follow-up, 23 patients (36%) had at least one hospitalization or ED visit; 48% for relapse to alcohol use, 30% for complications of ALD, and 22% for problems unrelated to ALD or AUD. Of the initial cohort of patients, 70% remain active in the ALD/AUD clinic, 7% expired, and 18% were lost to follow up. **Conclusion:** A mult-disciplinary approach to treatment of ALD is the recommended standard of care. We demonstrate the feasibility of establishing a mult-disciplinary clinic to provide the most comprehensive care for patients with ALD while incorporating use of pharmacotherapy for AUD.

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3502-C | A NOVEL VALIDATED MODEL FOR CLINICAL DIAGNOSIS OF ALCOHOL-ASSOCIATED HEPATITIS

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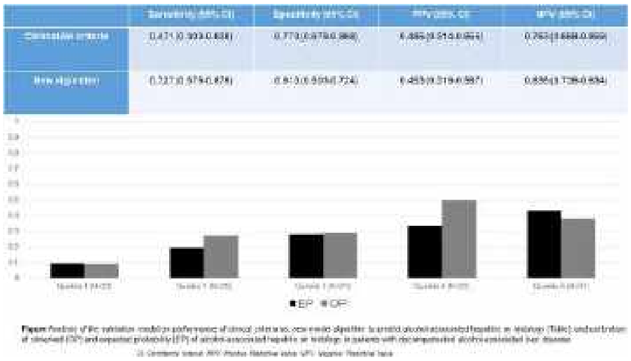
Kamath[10], Shiv Kumar Sarin[11] and Yong-Fang Kuo[12], (1)University of South Dakota, (2)Icahn School of Medicine at Mount Sinai, (3)University of Pennsylvania, (4)Stanford University School of Medicine, (5)UPMC, (6)Ilbs, (7)U Penn, (8)Post Graduate Institute of Medical Education and Research, Chandigarh, India, (9)Barcelona Clinic, Barcelona, Spain, (10)Mayo Clinic, Rochester, MN, (11)Institute of Liver and Biliary Sciences, (12) University of Texas Medical Branch

Background: Alcohol-associated hepatitis (AH) is a unique clinical syndrome, with new onset or worsening of jaundice, with 90-day mortality of up to 90% in most severe forms. NIAAA has proposed clinical criteria for AH diagnosis (AST > 50 and < 400 IU/L, serum bilirubin [SB] > 3 mg/dL, presentation within 60 d from last alcohol use) for management and for enrollment in clinical trials. However, these criteria are not evidence-based. We performed this multicenter study with the aim of validating NIAAA clinical criteria for diagnosis in patients with alcohol-associated liver disease (ALD). **Methods:** Two cohorts of ALD patients, first one from two centers on patients receiving liver biopsy for clinical management and the second from four centers on liver transplant recipients. Gold standard for AH diagnosis was defined on liver histology, with presence of hepatocyte ballooning, neutrophilic lobular inflammation, and Mallory hyaline (definite AH). Patients with AST > 400, non-ALD etiology, bile duct obstruction, and liver cancer were excluded. **Results:** Among 416 patients (250 biopsied [2014-18] and 166 explants [2002-22]), 267 met clinical AH criteria. Of 219 with histology (biopsy or explant) obtained within 30 d from presentation (median age 42 yrs., 79% males, 45% whites, 3% ACLF, 29% steroids, median days to last drink 52 d, median MELD score 36), 63 (29%) had definite AH. The cohort was randomly split (1:1) to training (n = 110) and validation (n = 109) datasets. The accuracy and c-statistics to predict definite AH was 0.573 using NIAAA criteria and 0.724 based on: *-0.424 + 0.0040*AST + (- 0.0674)*AST/ALT + (-0.0114)*days from last drink + (-0.0064)*SB*. The new algorithm in the validation model a) had a c-statistics of 0.651 with accurate classification of definite AH in 80% (Brier score 0.204), b) performed better than NIAAA criteria at a cut-off score of 0.291, and c) showed good calibration between expected and observed probability, correlation coefficient 0.839 (Figure). **Conclusion:** A novel validated model based on AST, AST/ALT ratio, serum bilirubin is more accurate compared to the current clinical criteria, for clinical diagnosis of AH and for recruitment of patients into clinical trials. Larger prospective studies are needed to validate these findings.



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3503-C | A PHASE 2a, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY, TOLERABILITY, EFFICACY, AND PHARMACOKINETICS OF INT-787 IN SUBJECTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS: STUDY DESIGN, OBJECTIVES, AND NOVEL ASSESSMENTS

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Background: Severe alcohol-associated hepatitis (sAH) is the most acute and serious form of alcohol-associated liver disease. It is identified clinically by the presence of jaundice, hepatitis, and systemic inflammatory response, which results in significant morbidity and mortality. Currently, therapeutic options for sAH are limited, with corticosteroids improving only short-term survival. INT-787 is a potent farnesoid X receptor (FXR) agonist and a potential treatment option for sAH. Preclinical studies of FXR agonists have demonstrated improvements in hepatic steatosis, inflammation, fibrosis, and intestinal mucosal integrity, as well as reductions in plasma endotoxin and bile acids, in various liver-related disorders. The goal of our study is to evaluate the safety, tolerability, early efficacy, and pharmacokinetics (PK) of INT-787 in patients with sAH. **Methods:** In this phase 2a, randomized, double-blind, placebo-controlled, multicenter, dose-escalation proof-of-concept study, oral INT-787 will be administered to patients with a diagnosis of sAH, with a Model for End-Stage Liver Disease-Sodium (MELD-Na) score of 18-25. Five dose cohorts are planned, starting at 5 mg (Figure 1). Each cohort includes 10 randomized subjects (4:1) receiving INT-787 or placebo for 28 days. If there are no significant safety or tolerability concerns, dose escalation for the next cohort will not exceed a 3-fold increase. The maximum cohort dose will not exceed 120 mg. Corticosteroids will not be used during the study. Subjects will undergo a 7-day screening period, followed by a 28-day treatment period, with a 56-day follow-up. The primary endpoint is the assessment of sAH disease progression by Lille score. Secondary endpoints include changes in MELD-Na score, occurrence of infectious complications, clinical outcomes (short- and intermediate-term mortality or liver transplant), and PK. Safety and tolerability will be determined by adverse events, laboratory assessments, electrocardiograms, vital signs, and physical examinations; hepatic and renal safety of INT-787 in sAH will be assessed by expert adjudication committees blinded to treatment. Other novel assessments include serum markers of bacterial translocation (LBP, 16S rDNA), stool microbiome analysis, and alpha-1-antitrypsin. **Results:** 50 patients are being targeted at 25 investigation sites globally. Study completion is targeted for May 2024. **Conclusion:** INT-787 is a promising FXR agonist with preclinical data supporting its exploration in the treatment of sAH.

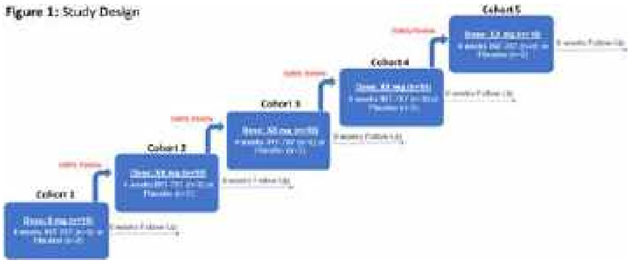
Figure 1: Study Design

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3504-C | ACUTE ETHANOL INDUCTION AND SUBCELLULAR LOCALIZATION OF HEPATIC CYP2E1

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Background: Alcohol is known to increase hepatic levels of the cytochrome P450 2E1 (CYP2E1), particularly in the endoplasmic reticulum (or microsomal fraction) and to some extent in the mitochondria of hepatocytes. CYP2E1 is well known to metabolize ethanol to acetaldehyde in a parallel pathway to alcohol dehydrogenase. Interestingly, the half-life of CYP2E1 is much longer in the mitochondria ($>$24h) compared to the endoplasmic reticulum (~8h). Therefore, we hypothesized that after acute ethanol induction of CYP2E1, the endoplasmic reticulum form would rapidly clear while the mitochondrial form would persist. **Methods:** To test the temporal expression of CYP2E1 following acute alcohol ingestion, young female C57BL/6J mice were given voluntary access to ethanol (or water) for two hours and allowed to drink. Mice we sacrificed immediately following drinking (0h) and 24 and 48 hours later. Protein levels and subcellular localization were determined using multiplexed immunofluorescent staining with antibodies against CYP2E1 and markers of the mitochondria (COX4) and endoplasmic reticulum (Calreticulin). **Results:** The relative expression of CYP2E1 in the liver of mice treated with acute levels of ethanol was $>$2-fold higher ($p < 0.001$) than the control group in the 0h group, and correlated with the amount of alcohol consumed ($p < 0.05$). The increase was partly driven by a subtle increase in the radius of expression from the central vein. In contrast, there was no statistical significance in CYP2E1 levels at 24 or 48h post-drinking mice when compared to the control, indicating that the overall induction of CYP2E1 was transient, which agrees with previous studies. For subcellular localization, super-resolution Airyscan confocal microscopy was performed to maximize resolution of the mitochondria and ER. Deconvolution with Huygen's software and calculation of co-localization between CYP2E1 and organellar markers are ongoing. **Conclusion:** We find that acute voluntary drinking in mice triggers increased pericentral CYP2E1 that correlates with amount of ethanol consumed and clears within 24h. Ultimately the results of this study will provide insight into the subcellular distribution of CYP2E1 at baseline, immediately following drinking, and in the following days.

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3505-C | AGE DEPENDENT RISK FACTORS FOR THE DEVELOPMENT OF ALCOHOL-RELATED LIVER DISEASE: A POPULATION-BASED COHORT STUDY

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Background: Mortality associated with alcohol-related liver disease (ALD) is rising, particularly in younger patients. However, the factors influencing this concerning epidemiological trend remain unclear. In this study, we aimed to assess age dependent risk factors for the development of ALD in patients with alcohol use disorder (AUD). **Methods:** 9,207 patients with AUD and without a history of ALD were identified within the Mass General Brigham health system via ICD-9,10 coding. These patients were stratified into five age groups ($<$40, 40-50, 50-60, 60-70, $>$70 y) and were followed for incident ALD, the primary outcome of the study. Multivariate regression models were used to examine the association of risk factors with ALD diagnosis, stratified by age. **Results:** Over a median follow up of 11.8 years, 69/2278 (3%), 109/1263 (9%), 189/1976 (9%), 224/1969 (11%), and 117/1721 (7%) of AUD patients aged $<$40, 40-50, 50-60, 60-70, and $>$70 years, respectively, developed ALD. The distribution of female patients was highest in younger age groups (49% in $<$40 vs 33% in $>$70 y). A diagnosis of severe AUD conferred an age-dependent increased risk for ALD, with highest impact in those $<$ 40 ($<$40: HR 15.4, 95%CI 7.18-33.07, $p < 0.005$; 40-50: HR 8.13, 95%CI 4.62-14.32, $p < 0.005$; 50-60: HR 5.88, 95%CI 3.85-8.98, $p < 0.005$; 60-70: HR 4.22, 95%CI 3.03-5.87, $p < 0.005$; $>$70: HR 4.01, 95%CI 2.71-5.93, $p < 0.005$). Hepatitis B also increased the risk of ALD incident in patients $<$40 years (HR 3.65, CI 1.11-12.05, $p = 0.034$) but was not significantly associated in other age groups. Moderate to high intensity exercise had a protective effect in older patients (60-70 years: HR 0.41, CI 0.19-0.91, $p = 0.028$; $>$70 years: HR 0.12, CI 0.02-0.97, $p = 0.046$), but not in patients $<$40 years. Psychotherapy prior to ALD diagnosis was associated with a greater degree of protection against ALD in patients $<$40 years (HR 0.36, 95%CI 0.21-0.61, $p < 0.005$) compared to older patients. AUD pharmacotherapy prior to ALD diagnosis was statistically more protective in all age categories except for patients $<$40 (HR 0.69, 95%CI 0.41-1.17, $p = 0.166$). **Conclusion:** Despite the overall lower incidence of ALD among younger patients, diagnoses of severe AUD and comorbid hepatitis B were strongly associated with incident ALD. Further, AUD psychotherapy has a superior protective effect on ALD incidence in the youngest age group (<40 y), whereas exercise and pharmacotherapy associated with less protection.

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Disclosure information not available at the time of publication: Prasanna K Challa, Augustin Vannier, Russell P. Goodman, Esperance Schaefer, Jay Luther

3506-C | ALARMING TRENDS IN ALCOHOLIC LIVER DISEASE MORTALITY RATES AMONG ALL RACES IN THE US OVER TWO DECADES

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Background: The prevalence of alcoholic liver disease (ALD) has been increasing in the United States, with alcohol-related liver cirrhosis emerging as the second leading cause of liver-related deaths. This abstract aims to provide an inclusive overview of ALD across all races in the United States. **Methods:** In this study, we utilized the Wide-ranging Online Data for Epidemiologic Research (WONDER) database provided by the U.S. Centers for Disease Control and Prevention to identify patients who had died due to alcoholic liver disease, as determined by an ICD-code version (C70.x) registered as the underlying cause of death. We then examined and compared trends in alcoholic liver disease-related mortality rates across all races (including White, Black, Asian or Pacific Islander, and American Indian or Alaska Native) in the United States between 1999 and 2020. Age-adjusted mortality rates were calculated per 1000,000 persons (PMP), standardized to the US census data from 1999, and stratified by race. **Results:** During the period from1999 to 2020, the study identified a total of 371,751 deaths related to alcoholic liver disease across all races, resulting in an overall age-adjusted mortality rate of 50.7 (PMP). Out of these deaths, 322,879 were in White individual's, 30,942 in Black individual's, 13,301 in Asian or Pacific Islander individual's, and 4,629 in American Indian or Alaska Native individual's. The overall age-adjusted mortality were 172.9 PMP, 53.5 PMP, 36.1 PMP, and 12.8 in the American Indian or Alaska Native, White, Black, Asian or Pacific Islander populations respectively. Furthermore, over the 21-year period, the study observed an 8% decrease in age-adjusted mortality rates among Black individual's, from 50.5 PMP in 1999 to 46.5 PMP in 2020. However, the rates increased significantly among other racial groups, with a 99% increase in White individual's (from 42.8 PMP in 1999 to 85.2 PMP in 2020), a 98% increase in Asian or Pacific Islander individual's (from 10.3 PMP in 1999 to 20.4 PMP in 2020), and a 66% increase in American Indian or Alaska Native individual's (from 162.9 PMP in 1999 to 270.3 PMP in 2020). **Conclusion:** In conclusion, the findings of this study suggest that alcoholic liver disease-related mortality rates varied significantly among different racial groups in the United States between 1999 and 2020. Specifically, the highest mortality rates were observed in American Indian or Alaska Native individual's, while the lowest rates were observed in Asian or Pacific Islander individual's. Additionally, the mortality rate was found to be twice as high in White individual's compared to Black individual's. Notably, the study also observed a decrease in alcoholic liver disease-related mortality rates among Black individual's over the 21-year period, whereas rates increased among all other racial groups.

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3507-C | ALBUMIN PROTECTS AGAINST ETHANOL-INDUCED LIVER INJURY

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Background: Rising alcohol consumption during the pandemic has led to concurrent increases in alcohol-associated liver disease (ALD). There is an urgent need to identify novel mechanisms of early ALD progression that are potential therapeutic targets, as late-stage ALD has poor prognosis and limited treatment options. Albumin, a liver-derived circulating protein, plays key roles in oncotic pressure, molecular transport, and immune response. Circulating albumin is decreased, and albumin supplementation is used therapeutically in late-stage ALD, but whether circulating albumin levels change earlier in ALD or albumin plays a role in ALD progression is unknown. **Methods:** To determine how albumin levels change and correlate with other clinical parameters after heavy ethanol consumption, we analyzed clinical data from Li et al. (2017) comparing healthy controls, heavy drinkers, and heavy drinkers that have been abstinent >10d. Albumin knockout mice (ALB KO) were used as a model to investigate how albumin affects ethanol-induced liver injury and changes in vascular function. ALB heterozygous (ALB

Het) were found to have similar liver and serum protein levels of albumin to WT mice and were used as a control group. Blood pressure (BP) was measured 3h after vehicle or 5g/kg ethanol gavage using PV catheterization. **Results:** Plasma albumin levels were lowest in heavy drinkers and increased in abstinent heavy drinkers but remained lower than healthy controls. Albumin levels were also negatively correlated with AUDIT scores in both heavy drinking groups. To determine whether these decreases in albumin may contribute to progression of ALD, we subjected ALB KO and ALB Het mice to the 10d + binge model of ethanol consumption (NIAAA model) and found that ALB KO mice exhibited worse liver injury than ALB Het mice. Pathway analysis of liver tissue RNA-seq identified perturbations in bile acid metabolism, inflammation, and vascular function. We further analyzed our clinical dataset and found that plasma albumin is correlated with lymphocyte and platelet counts in heavy drinkers, and positively correlated with BP heavy drinkers, indicating that systemic functions of albumin in the circulatory and immune systems may also affect liver injury. The BP of ALB KO mice was lower at baseline and further decreased after ethanol gavage compared to controls, confirming the BP-albumin correlation. **Conclusion:** Heavy drinking alone is sufficient to decrease plasma albumin, indicating that albumin decreases are an early event in ALD progression. Studies in our mouse model show that albumin protects against ethanol-induced liver injury through tissue-specific and systemic mechanisms, likely including cardiovascular and immune system alterations that are under investigation. Our findings point to a previously unrecognized role for albumin in ALD progression, and further studies are needed to determine the potential of albumin as a treatment in early ALD.

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Disclosure information not available at the time of publication: Taylor Lehner, Janos Paloczi, Yuhong Lin, Pal Pacher, Bin Gao

3508-C | ALCOHOL CONSUMPTION DECREASES PLASMA PERFLUOROOCTANOIC SULFONATE (PFOS) LEVELS

Tyler C. Gripshover[1], *Frederick Ekuban*[1], *Kushal Biswas*[2], *Banrida Wahlang*[1], *Kimberly Head*[1], *Dhimiter Bello*[2] *and Matthew Cave*[1], *(1)University of Louisville, Louisville, KY, (2)University of Massachusetts Lowell*

Background: Perfluoroalkyl Substances (PFAS) are a large family of surfactant-like toxicants that are considered persistent organic pollutants. PFAS exposures have been associated with several adverse health effects including dyslipidemia. While mechanistic PFAS studies are still emerging, one consistent observation is activation of the peroxisome proliferator activating receptor alpha (PPARα). Furthermore, research suggests that PFAS require active transport during distribution, one class of transporters being organic anion transporting polypeptides (OATPs). We recently characterized a model for how polychlorinated biphenyl 126 enhanced alcohol-associated liver disease (ALD). However, there are no known reports on how PFAS may enhance ALD or perhaps how alcohol consumption influences PFAS kinetics. We hypothesize that perfluorooctane sulfonic acid (PFOS) will promote hepatic steatosis and dyslipidemia and ethanol will disrupt PFOS tissue partitioning. **Methods:** Male C57BL/6J mice were fed *ad libitum* Lieber-DeCarli diet with 5% EtOH or control diet for 15 days. Beginning on day 6, mice were exposed to 1 mg/kg/day PFOS or vehicle (2% Tween-80) *via* oral gavage. At euthanasia, blood and tissue samples were collected for downstream analyses. **Results:** Steatosis and hepatomegaly were observed in mice fed the EtOH diet and exposed to PFOS; however, a significant interaction effect was not evident. PFOS was capable of activating PPARα, as shown by target gene induction (*Cyp4a10*). Interestingly, both PFOS and EtOH activated CAR *via* its target gene induction (*Cyp2b10*). We did observe significantly enhanced expression of *Cd36* and *Fabp1*, which are involved in lipid scavenging and transport, due to PFOS in EtOH-fed mice. Furthermore, hepatic gene expression of PFOS transporters, *Slco1a1* and *Slco1b2*, were decreased 90% and 40%, respectively, by EtOH. Mean plasma PFOS levels were significantly decreased by ~40%, by EtOH feeding, implying that alcohol consumption may impact PFOS partitioning or excretion. **Conclusion:** Overall, this study demonstrated that PFOS was unable to promote ALD, unlike our previous model. However, the importance in this study lies that plasma PFOS was significantly decreased with chronic EtOH feeding. This may be a special consideration for future PFOS research as EtOH consumption may impact tissue partitioning. Future studies will measure PFOS partitioning in other organs of interest, such as the liver and kidney, to further understand lifestyle factor influences on PFOS distribution.

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The following people have nothing to disclose: Tyler C. Gripshover, Frederick Ekuban, Kushal Biswas, Banrida Wahlang, Kimberly Head, Dhimiter Bello

f 3509-C | ALCOHOL INDUCED EPIGENETIC CHANGES PREVENT FIBROSIS RESOLUTION AFTER ALCOHOL CESSATION IN MICE.

Michael Schonfeld, Steven A. Weinman and Irina Tikhanovich, University of Kansas Medical Center

Background: Alcohol-associated liver disease (ALD) is a major cause of alcohol related mortality. Recently we identified hepatic H3K4 demethylases KDM5B and KDM5C as important epigenetic regulators of alcohol response in the liver. In this study we aimed to study the role of KDM5-demethylases in ALD resolution. **Methods:** Mice were fed a combination of Western diet with alcohol in the drinking water for 20 weeks (WDA model), for resolution experiments mice were biopsied at the end of the feeding and placed on chow diet for 2-8 weeks. To assess the role of demethylases, male and female *Kdm5b* floxed and *Kdm5c* floxed mice were treated with AAV-Control, AAV-CMV. Cre or AAV-TBG.Cre vectors at the time of alcohol withdrawal. Gene expression and epigenetic changes were assessed using RNA-seq and scATAC-seq. Cell-cell communication was studied using *in vitro* hepatocyte – non-parenchymal cell co-culture experiments. **Results:** We found that alcohol induced pathological changes in cell-cell communication in the liver that are in part mediated by KDM5B and KDM5C-dependent epigenetic changes in hepatocytes. These changes correlated with defects in fibrosis resolution after alcohol cessation in ALD mice. scATAC-seq analysis showed that during ALD resolution epigenetic cell states largely reverted to control conditions. In addition, we found unique epigenetic cell states distinct from both control and alcohol states and identified associated transcriptional regulators, epigenetic regulators including H3K4 demethylases, and nuclear receptors including LXRα. Using cell type specific knockout mice, we found that loss of KDM5B/KDM5C demethylases promoted fibrosis resolution after alcohol cessation. This mechanism involved changes in hepatocyte-macrophage crosstalk and LXRα activation, which we identified to be critical for pro-resolving macrophage phenotype and the fibrosis resolution process. LXR inhibition prevented fibrosis resolution in KDM5B/KDM5C deficient mice. **Conclusion:** In summary, KDM5B and KDM5C demethylases are regulators of cell-cell crosstalk involved in fibrosis resolution.

Disclosures: The following people have nothing to disclose: Michael Schonfeld, Steven A. Weinman, Irina Tikhanovich

3510-C | ALCOHOL MODULATES HEPATIC AMYLOID BETA AND LIPID METABOLISM IN APP/PS1 MOUSE MODEL OF ALZHEIMER'S DISEASE

Veronika Brezani, Radhika Joshi, Marti Ortega-Ribera, Mrigya Babuta, Yanbo Wang and Gyongyi Szabo, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background: Chronic alcohol abuse impairs liver function and increases the risk of dementia. In Alzheimer's disease (AD), the leading cause of dementia, the liver is thought to play an important role in maintaining lipid metabolism and clearance of the neurotoxic amyloid-β (Aβ) peptide from the circulation. However, the contribution of alcohol-induced hepatic changes on peripheral AD features remains unexplored. Thus, we aim to evaluate hepatic lipid metabolism and Aβ clearance in the preclinical dual insult model of AD and alcohol abuse. **Methods**: Twelve to fifteen-month-old wild type (WT) or APP/PS1 mice received either water or ethanol binges (3.5 g/kg, i.g.) every other day for 28 days. Lipid and alcohol metabolism, amyloid precursor protein (APP) processing and Aβ clearance were assessed in the liver by qPCR. **Results**: We found that alcohol binges significantly increased serum alanine transaminase (ALT) levels only in the APP/PS1 mice compared to water treatment, suggesting increased alcohol-induced liver damage in AD mice. Moreover, enzymes (alcohol dehydrogenase 1, aldehyde dehydrogenase 2, and cytochrome P450 2E1) and regulators (farnesoid X receptor) involved in alcohol metabolism were markedly increased in APP/PS1 mice treated with alcohol compared to WT controls, indicating dysregulated alcohol metabolism. Next, we investigated the regulation of lipid metabolism, and we observed increased expression of molecules involved in fatty acid uptake (fatty acid transport protein 1, cluster of differentiation 36), oxidation (peroxisome proliferator-activated receptor alpha), de novo lipogenesis (fatty acid synthase), and hepatic lipid export (apolipoprotein B, phosphatidylethanolamine N-methyltransferase) in alcohol-treated APP/PS1 mice compared to APP/PS1 alone or alcohol-treated WT mice. Apolipoprotein E, a major risk factor for AD and a key regulator of lipoprotein metabolism was also upregulated in alcohol-treated APP/PS1 mice further supporting evidence of lipid dysregulation. Lastly, we observed that alcohol binges increased APP expression as well as the components of the molecular machinery involved in APP processing (beta-secretase 1, a disintegrin and metalloprotease 10) and Aβ clearance (low-density lipoprotein receptor-related protein 1, insulin-degrading enzyme) compared to that of water-treated APP/PS1 mice indicating increased turnover of Aβ. **Conclusion**: We show for the first time that AD mice are more susceptible to alcohol-induced liver damage compared to WT. Our results suggest that chronic alcohol exposure modulates the production and metabolism of hepatic lipids and Aβ which could be linked to altered alcohol metabolism in a mouse model of AD.

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Disclosure information not available at the time of publication: Marti Ortega-Ribera

3511-C | ALCOHOL RELAPSE AFTER LIVER TRANSPLANT FOR ALCOHOL ASSOCIATED LIVER DISEASES

Georgios Voidonikolas, Jill Frese, Ju Dong Yang, Todd Brennan, Kambiz Kosari, Justin Steggerda, Tsuyoshi Todo, Steven Wisel, Alexander Kuo, Walid S. Ayoub, Hirsh Trivedi, Allen Chen, Benjamin Ferrel, Amy Christianson, Nicholas Nissen and Irene Kim, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Alcohol-associated liver disease is the leading indication for liver transplant surgery in the United States. There is a lack of consensus on selecting an appropriate candidate for liver transplantation among patients with alcohol-associated liver diseases. We aim to report the frequency of alcohol relapse after liver transplantation and risk factors for post-transplant alcohol use. **Methods:** All patients who received liver transplantation for alcohol-associated liver diseases (with/without alcoholic hepatitis) between 03/2015-09/2021 were identified from the institutional liver transplant database. Demographical, clinical, and psychosocial features of recipients were extracted from the database. Baseline characteristics were summarized as mean or median for continuous variables and as n (%) for categorical data. We obtained p-values using Kruskal-Wallis rank sum test for continuous variables and Pearson's Chi-squared test for categorical variables. **Results:** A total of 214 patients were included. The majority of patients (80%) were male and half of the recipients were Hispanic. Twenty-three patients (10.8%) were transplanted for severe alcoholic hepatitis. A total of 49 patients (24.6%) had an alcohol relapse after liver transplantation. Patients with relapse were younger than those without relapse (48 vs. 52-year-old, $P=0.01$). There was a trend toward higher risk of relapse in Non-Hispanic White than Hispanic, and other ethnicity (31.4% vs. 19.8% vs. 20%, $P=0.18$). The proportion of relapse was similar between patients with/without alcoholic hepatitis (28.6% vs.24.4, $P=0.68$) and median length of sobriety prior to liver transplant was similar in recipients with vs. without relapse (6 vs. 6 mo, $P=0.62$). Additionally, proportion of relapse was similar regardless of previous rehab attempt, DUI or EOTH-related legal consequences, history of substance abuse, and comorbid psychiatric illness. There was a trend toward a lower risk of relapse among those with good social support than those with fair or limited social support (23.4% vs., 34.6%, $P=0.23$). Proportion of relapse was higher among those with noncompliance to post-transplant clinic visit vs. compliant patients (52.5% vs. 22.3%, $P<0.01$). Mean SALT scores were 2.6, 2.3, for patients with, and without relapse, respectively ($P=0.54$). Mean SIPAT scores were 19.2, 16.1, for patients with, and without relapse, respectively ($P=0.09$). **Conclusion:** A quarter of patients who underwent liver transplantation have alcohol relapse. Relapse occurs more frequently in younger patients and those who were not compliant with clinic follow up. Alcoholic hepatitis and median length sobriety prior to liver transplant were not associated with post-transplant alcohol relapse.

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3512-C | ALCOHOL RELAPSE AFTER LIVER TRANSPLANTATION: RISK FACTORS, OUTCOMES, AND A COMPARISON OF RISK STRATIFICATION MODELS

Karen Young[1], Yuval Patel[2], Benson Hoffman[1], Sarah Peskoe[1], Shein-Chung Chow[1], Karli Erhart[1], Jennifer Jackson[1] and Stephanie Garbarino[1], (1)Duke University, (2)Baylor College of Medicine

Background: Alcohol-related liver disease (ALD) is a leading cause of liver transplantation (LT) in the United States (1-3). Considering transplantation for ALD requires weighing the risk of alcohol relapse, which can lead to allograft failure (4). Multiple studies have examined factors and created scoring systems to predict relapse after LT, such as the SALT and HALT scores (5, 6). We aimed to assess risk factors and compare the effectiveness of SALT and HALT scores at predicting relapse after LT at our large transplant center. **Methods:** This was a retrospective chart review of 69 adults who underwent LT for ALD at Duke University Hospital from 1/1/2018 to 1/1/2021. Primary outcome variables included relapse detected post-LT, severity of relapse, and evidence of graft dysfunction. Data analysis included generalized linear models to assess associations between relapse risk factors and outcome measures, as well as concordance statistics when applying the SALT and HALT scores. **Results:** 67 patients with a median follow up time of 43 months after LT were included. Eighteen (27%) experienced any relapse of alcohol after LT. Out of those who relapsed, 15 (83%) had heavy alcohol use (i.e., > 2 drinks/day for men and > 1 drink/day for women) and three of those patients (17%) experienced graft dysfunction (i.e., biopsy grade 3 or greater of fibrosis, signs of portal hypertension, or jaundice). Factors associated with a significant risk of relapse included younger age, prior relapse, significant psychiatric co-morbidities, alcohol use after cirrhosis diagnosis, shorter duration of abstinence prior to LT listing, and prior participation in an alcohol treatment program (Table 1). When applying the SALT and HALT scores to this data using area under the curve (AUC) modeling, these scores indicated good discrimination (AUC = 0.69 and 0.66, respectively). **Conclusion:** Several clinical risk factors for alcohol relapse after LT were identified in our cohort, as with previously published data. In our cohort, heavy alcohol use prior to transplant and legal issues did not predict relapse, which is a common component of prediction scores. Less than 5% of patients transplanted for ALD at our center had graft dysfunction due to relapse after LT, suggesting overall good graft outcomes even in those that unfortunately relapsed. The HALT and SALT scores interestingly had underwhelming predictive value in our cohort, suggesting the need for further optimization of prediction scores. References: please see link

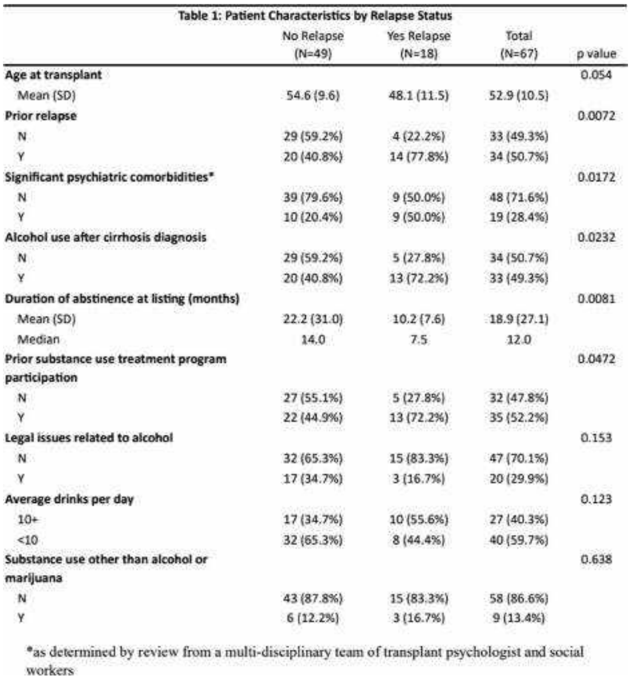

Table 1: Patient Characteristics by Relapse Status

	No Relapse (N=49)	Yes Relapse (N=18)	Total (N=67)	p value
Age at transplant				0.054
Mean (SD)	54.6 (9.6)	48.1 (11.5)	52.9 (10.5)	
Prior relapse				0.0072
N	29 (59.2%)	4 (22.2%)	33 (49.3%)	
Y	20 (40.8%)	14 (77.8%)	34 (50.7%)	
Significant psychiatric comorbidities*				0.0172
N	39 (79.6%)	9 (50.0%)	48 (71.6%)	
Y	10 (20.4%)	9 (50.0%)	19 (28.4%)	
Alcohol use after cirrhosis diagnosis				0.0232
N	29 (59.2%)	5 (27.8%)	34 (50.7%)	
Y	20 (40.8%)	13 (72.2%)	33 (49.3%)	
Duration of abstinence at listing (months)				0.0081
Mean (SD)	22.2 (31.0)	10.2 (7.6)	18.9 (27.1)	
Median	14.0	7.5	12.0	
Prior substance use treatment program participation				0.0472
N	27 (55.1%)	5 (27.8%)	32 (47.8%)	
Y	22 (44.9%)	13 (72.2%)	35 (52.2%)	
Legal issues related to alcohol				0.153
N	32 (65.3%)	15 (83.3%)	47 (70.1%)	
Y	17 (34.7%)	3 (16.7%)	20 (29.9%)	
Average drinks per day				0.123
10+	17 (34.7%)	10 (55.6%)	27 (40.3%)	
<10	32 (65.3%)	8 (44.4%)	40 (59.7%)	
Substance use other than alcohol or marijuana				0.638
N	43 (87.8%)	15 (83.3%)	58 (86.6%)	
Y	6 (12.2%)	3 (16.7%)	9 (13.4%)	

*as determined by review from a multi-disciplinary team of transplant psychologist and social workers

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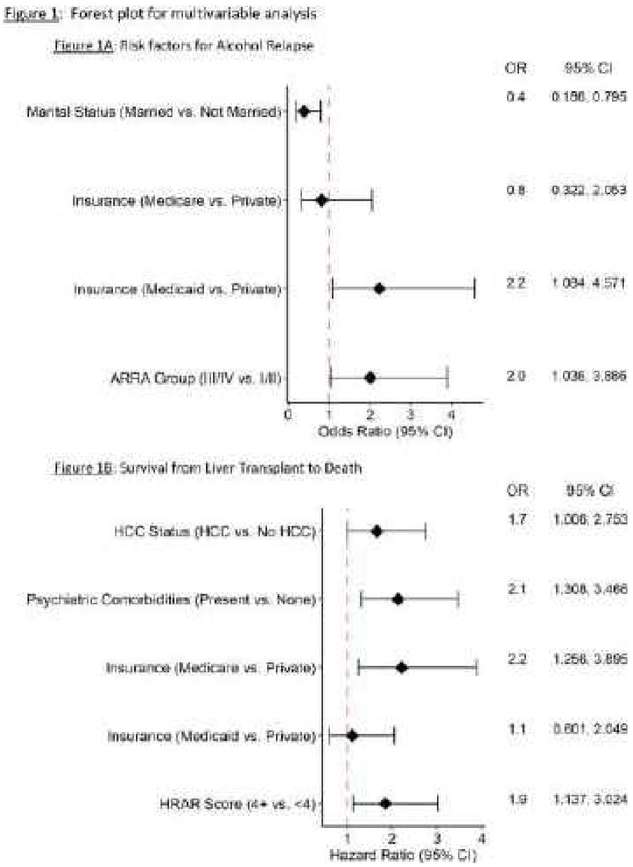
3513-C | ALCOHOL RELAPSE SCORES AND INDIVIDUAL SOCIAL DETERMINANTS OF HEALTH PREDICT ALCOHOL RELAPSE AFTER LIVER TRANSPLANT

Yara Sarkis[1], Elizabeth Williams[1], Maria Guarnizo Ortiz[1], Saad Saadat[1], Allie Carter[2], Lauren D. Nephew[2] and John Holden[1], (1)Indiana University School of Medicine, (2)Indiana University

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



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Disclosure information not available at the time of publication: Allie Carter

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

Brittany Bromfield[1], Sebastian Niezen[1], Vera Yakovchenko[2], Patrick Spoutz[3], Timothy R. Morgan[4], Jasmohan S. Bajaj[5], Rachel Bachrach[2,6], Ponni Perumalswami[7,8] and Shari S. Rogal[2,6], (1)University of Pittsburgh Medical Center, (2)VA Pittsburgh Healthcare System, (3)Veterans Integrated Service Network 20, (4) VA Long Beach Healthcare System, (5)Virginia Commonwealth University and Central Virginia Veterans Healthcare System, (6)University of Pittsburgh, (7)VA Ann Arbor Healthcare System, (8) University of Michigan

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

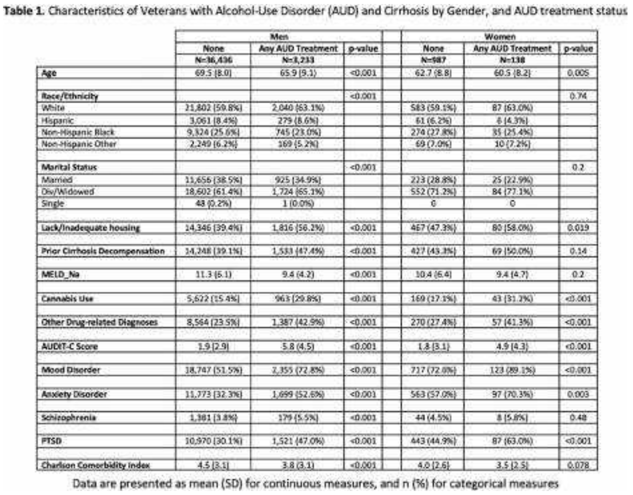

Table 1. Characteristics of Veterans with Alcohol-Use Disorder (AUD) and Cirrhosis by Gender, and AUD treatment status

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

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

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3515-C | ALCOHOLIC LIVER DISEASE AND CARDIAC ARRHYTHMIA

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Background: About half of the people with cirrhosis go on to develop cirrhotic cardiomyopathy and cardiovascular death is the leading cause of mortality in patients with alcohol use disorder. A strong association has been shown between serum bilirubin levels and arrhythmia. Bile acids have been thought to cause QT prolongation. Cardiac arrhythmia, importantly QT prolongation is responsible for the sudden cardiac death rather than ischemic heart disease. Paroxysmal tachycardia can occur in patients with alcoholic liver disease even in the absence of left ventricular dysfunction. **Methods:** This is a retrospective analysis of the National Inpatient Survey (NIS) database of the year 2020. We identified adults aged 18 and above with the discharge diagnosis of Alcoholic Liver Disease with and without cardiac arrhythmias using the International Classification of Disease-10 (ICD-10). Then, we analyzed them separately in terms of prevalence by age, sex and race along with inpatient mortality, inpatient morbidity and mean length of stay (LOS). **Results:** A total of 82620 patients were diagnosed with alcoholic liver disease (ALD) out of which 7365 were found to have different types of arrhythmias. Atrial fibrillation (64.02%) was the most common followed by ventricular tachycardia/ fibrillation (28.38%) with long QT being present in 7.6%. The mean age of people with ALD was 52.94 ± 0.11 whereas that of people with ALD and cardiac arrhythmia was 60.93 ± 2.81 years ($p < 0.001$). Hypertension was present in 32.64% of patient with ALD without arrhythmia and 28.78% of patients with arrhythmia (p-value 0.004) whereas coronary artery disease was present only in 5.46 % of patients with ALD without arrhythmia and 19.08% of patients with arrhythmia (p-value 0.000). Similarly, 3.49% of ALD patients without arrhythmia had heart failure while 16.9 % of patients with arrhythmia had heart failure (p-value 0.0000). Hyperlipidemia was present in 13.42% of patient with ALD without arrhythmia and 25.87% of patients with arrhythmia (p-value 0.000) The mortality rate of patients with ALD and arrhythmia was 9.64% whereas 4.67% mortality was recorded in patients without arrhythmia. ($P = 0.0000$). Patients with ALD and arrhythmia had mean length 5.81 ± 0.7 days of stay in the hospital whereas those without arrhythmia had 8 ± 0.27 days. **Conclusion:** Patients with ALD tend to develop various types of arrhythmia like atrial fibrillation, ventricular tachycardia/ fibrillation and long QT syndrome. The cardiovascular morbidity in patients with ALD along with arrhythmia was higher compared to those without arrhythmia. Additionally, the mean length of hospital stay and mortality were also higher in the group with ALD and arrhythmia.

Disclosures: The following people have nothing to disclose: Ayusha Poudel, Manoj Ghimire, Anurag Adhikari, Sajana Poudel

3516-C | ALCOHOLIC LIVER DISEASE IN PEOPLE WITH HIV IN LOW- AND MIDDLE-INCOME COUNTRIES: PREVALENCE AND FACTORS ASSOCIATED WITH SEVERITY OF HEPATIC FIBROSIS

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Background: In people with HIV (PWHIV) in the US, active alcohol use is associated with alcohol-associated liver disease (ALD). Worldwide 5% of global disease burden is attributable to alcohol consumption. Among PWHIV 30% have alcohol use disorder. ALD has not been explored in PWHIV in low- and middle-income countries. We aimed to determine the prevalence of ALD and associated fibrosis severity in PWHIV. **Methods:** PWHIV $\geq$ 40 years and $\geq$ 6 months on antiretroviral therapy were prospectively enrolled in the Sentinel Research Network (SRN) of the IeDEA (International epidemiology Databases to Evaluate AIDS) consortium (Asia-Pacific, Central Africa, East Africa, Southern Africa, West Africa, Caribbean, Central and South America networks) were analyzed. All participants who completed AUDIT questionnaire to determine alcohol use and had reliable Vibration Controlled Transient Elastography using FibroScan® ($\geq$ 10 valid reads & $\leq$ 30% IQR) to determine hepatic steatosis and fibrosis were included. ALD was defined as a Controlled Attenuation Parameter $\geq$ 285dB/m and an AUDIT-score $\geq$ 7 in females and $\geq$ 8 in males. Clinically significant fibrosis (CSF) was defined as Liver Stiffness Measurement (LSM) $\geq$ 8.6kPa. Metabolic syndrome was defined based on ATP-III definition. Analysis was performed using SAS. **Results:** There were 2333 PWHIV in the IeDEA-SRN cohort, 57% females, with median age of 51 (46, 56) years, median BMI of 25 (22, 28) kg/m^2; 8% had diabetes, 23% had hypertension, 55% had dyslipidemia and 28% had metabolic syndrome. Hazardous alcohol use was seen in

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

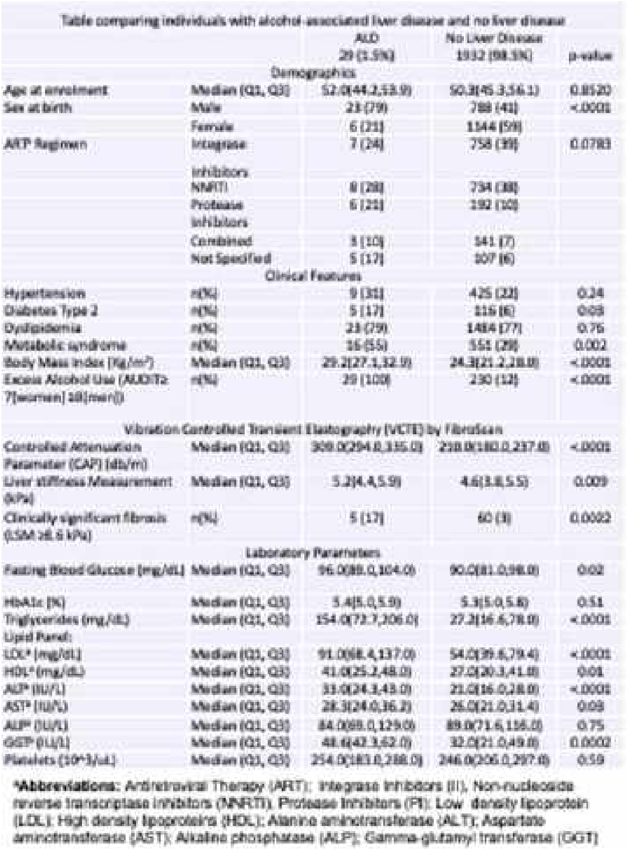

Table comparing individuals with alcohol-associated liver disease and no liver disease

		ALD 29 (1.5%)	No Liver Disease 1932 (98.5%)	p-value
Demographics				
Age at enrolment	Median (Q1, Q3)	52.0(44.2,53.9)	50.3(45.3,56.1)	0.8520
Sex at birth	Male	23 (79)	788 (41)	<.0001
	Female	6 (21)	1144 (59)	
ART Regimen	Integrase inhibitors	7 (24)	758 (39)	0.0783
	NNRTI	8 (28)	734 (38)	
	Protease inhibitors	6 (21)	192 (10)	
	Combined	3 (10)	141 (7)	
	Not Specified	5 (17)	107 (6)	
Clinical Features				
Hypertension	n(%)	9 (31)	425 (22)	0.24
Diabetes Type 2	n(%)	5 (17)	116 (6)	0.03
Dyslipidemia	n(%)	23 (79)	1484 (77)	0.76
Metabolic syndrome	n(%)	16 (55)	551 (29)	0.002
Body Mass Index (Kg/m²)	Median (Q1, Q3)	29.2(27.1,32.9)	24.3(21.2,28.0)	<.0001
Excess Alcohol Use (AUDIT≥ 7[women] 10[men])	n(%)	29 (100)	230 (12)	<.0001
Vibration Controlled Transient Elastography (VCTE) by FibroScan				
Controlled Attenuation Parameter (CAP) (db/m)	Median (Q1, Q3)	309.0(294.0,335.0)	210.0(180.0,237.0)	<.0001
Liver stiffness Measurement (kPa)	Median (Q1, Q3)	5.2(4.4,5.9)	4.6(3.8,5.5)	0.009
Clinically significant fibrosis (LSM ≥8.6 kPa)	n(%)	5 (17)	60 (3)	0.0022
Laboratory Parameters				
Fasting Blood Glucose (mg/dL)	Median (Q1, Q3)	96.0(88.0,104.0)	90.0(81.0,98.0)	0.02
HbA1c (%)	Median (Q1, Q3)	5.4(5.0,5.9)	5.3(5.0,5.8)	0.51
Triglycerides (mg/dL)	Median (Q1, Q3)	154.0(72.7,206.0)	27.2(16.6,78.0)	<.0001
Lipid Panel:				
LDL* (mg/dL)	Median (Q1, Q3)	91.0(68.4,137.0)	54.0(39.6,79.4)	<.0001
HDL* (mg/dL)	Median (Q1, Q3)	41.0(25.2,48.0)	27.0(20.3,41.0)	0.01
ALT* (IU/L)	Median (Q1, Q3)	33.0(24.3,43.0)	21.0(16.0,28.0)	<.0001
AST* (IU/L)	Median (Q1, Q3)	28.3(24.0,36.2)	26.0(21.0,31.4)	0.09
ALP* (IU/L)	Median (Q1, Q3)	84.0(69.0,129.0)	89.0(71.6,116.0)	0.75
GGT* (IU/L)	Median (Q1, Q3)	48.6(42.3,62.0)	32.0(21.0,49.0)	0.0002
Platelets (10^3/uL)	Median (Q1, Q3)	254.0(183.0,288.0)	246.0(206.0,297.0)	0.59

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

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

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

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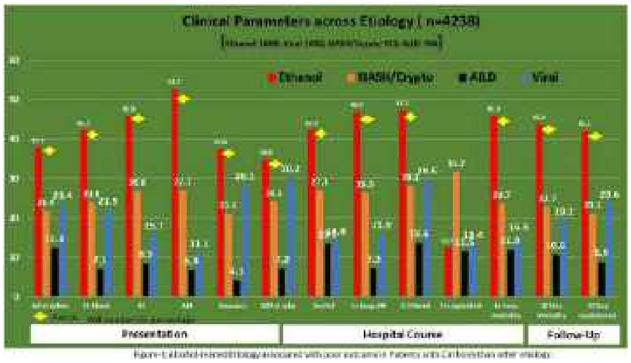
Background: The burden of cirrhosis, especially due to alcohol and metabolic factors is increasing, more so during the pandemic period. However, the impact of these various etiologies of cirrhosis across different regions of the world remains unclear. **Methods:** The multi-national CLEARED consortium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

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



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

Jose Luis Perez Hernandez[1]*, Fatima Higuera De La Tijera*[2]*, Oscar Morales Gutierrez*[3]*, Ernaldo Jacinto Morales Mairena*[1] *and Maria Argentina Diaz Castro III*[1]*, (1)Hospital General De Mexico "DR Eduardo Liceaga",* *(2)Hospital General De México "Eduardo Liceaga", Saint Luke School of Medicine, Mexico City, Mexico, (3) Hospital General De Mexico "Eduardo Liceaga"*

Background: Alcohol-related liver disease is becoming more common worldwide. Recently, women's alcohol consumption has increased significantly, raising the risk of developing alcohol-associated hepatitis, cirrhosis, and hepatocellular carcinoma. Greater susceptibility to alcohol-related liver damage seems to confer higher mortality and decompensation risk in women. Our study aimed to assess mortality rate and alcohol consumption patterns in female patients with alcohol-related cirrhosis. **Methods:** We conducted a single-center retrospective cohort study of patients hospitalized for chronic alcohol consumption at the General Hospital of Mexico "Dr. Eduardo Liceaga" between 2018 and 2021. The electronic patients' medical records were used to estimate the survival rate after the first hospitalization with the Kaplan-Meier curve for women and men. **Results:** One hundred ninety-two electronic patients' medical records were included (50% women). The mortality rate during the first hospital hospitalization was 32.8% (61.9% for women and 38.9% for men). The mean age for survival after chronic alcohol consumption was significantly lower for women [33.8 ± 1.6 (95%CI, 30.5-37.1)] compared with men [37.0 ± 1.2 (95%CI, 35.4-38.6)] ($p = 0.002$). The median for the onset of chronic alcohol consumption was statistically significantly older in women than in men (18 vs. 16.5 years old, respectively; $p < 0.001$). The median for alcohol consumption was statistically significantly lower in women than in men (160 vs. 290 g, respectively; $p < 0.0001$), and also the time of chronic alcohol consumption (24.5 vs. 30 y; respectively; $p < 0.001$) **Conclusion:** Mortality due to alcohol-related liver damage is higher in women than in men; it is associated with a lower amount of g/day alcohol consumption, a shorter period of continued chronic consumption, and a lower age at the onset of drinking. Mortality in women in the coming years could increase since there is evidence of a prevalence increase in alcohol consumption within this group.

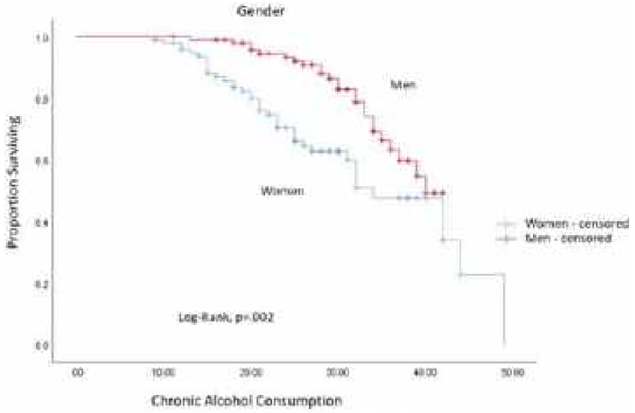

FIGURE 1. THE SURVIVAL CURVE

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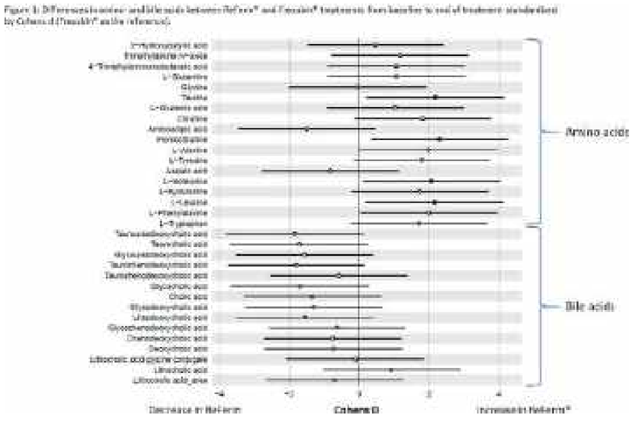
f 3519-C | AN OAT DRINK FERMENTED BY LACTOBACILLUS PLANTARUM REDUCES FORMATION OF LIVER FIBROSIS VIA BENEFICIAL EFFECTS ON THE GUT MICROBIOME AND CIRCULATING BILE ACIDS IN PATIENTS WITH ADVANCED ALCOHOL-RELATED LIVER DISEASE: A 24-WEEK RANDOMIZED CONTROLLED TRIAL

Johanne Kragh Hansen[1,2], Camilla D Hansen[1,2], Mads Israelsen[1,2], Suguru Nishijima[3], Peter Andersen[2], Karolina Sulek[4], Ida Falk Villesen[2], Katrine Holtz Thorhauge[1,2], Katrine Prier Lindvig[1,2], Nikolaj Torp[1,2], Stine Johansen[1,2], Maria Kjaergaard[1,2], Jane Jensen[2], Simon Sørensen[2], Gitte Hedegaard Jensen[5], Sönke Detlefsen[1,5], Diana Lemming[6], Sara Stinson[7], Angelos Margiolakiotis[7], Evelina Stankevic[7], Andressa de Zawadzki[6], Morten Karsdal[6], Marisa Keller[3], Michael Kuhn[3], Tommi Raimo Leo Suvitaival[4], Hans Israelsen[8], Cristina Legido-Quigley[4], Peer Bork[3], Maja Thiele[1,2], Torben Hansen[7] and Aleksander Krag[1,2], (1) Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, (2)Centre for Liver Research, Department of Gastroenterology and Hepatology, Odense University Hospital, (3)European Molecular Biology Laboratory, Embl, Heidelberg, (4) Steno Diabetes Center Copenhagen, (5)Department of Pathology, Odense University Hospital, (6)Nordic Bioscience a/S, Denmark, (7)Novo Nordisk Foundation Center for Basic Metabolic Research, Cbmr, University of Copenhagen, (8)Nordic Rebalance a/S, Denmark

Background: Gut dysbiosis and permeability are suggested treatment targets for alcohol-related liver disease (ArLD). ReFerm®, a post-biotic drink made from an oat composition fermented with *Lactobacillus plantarum 299v*, improves the gut barrier in patients with irritable bowel syndrome. We investigated the effect of ReFerm® on formation of liver fibrosis by hepatic stellate cell activity, composition of gut microbiome, and circulatory bile and amino acids in patients with compensated advanced chronic liver disease (cACLD) related to alcohol. **Methods:** We randomized 56 patients with cACLD 1:1 to receive ReFerm® or Fresubin®, a medical protein-rich supplement, for 24 weeks, with liver biopsies, plasma, and stool collected at baseline and end-of-treatment. We assessed hepatic stellate cell activity by immunohistochemistry of liver biopsies for quantification of α-smooth muscle actin (α-SMA) using automated digital imaging analysis. Primary outcome was ≥10% reduction in α-SMA. Compliance was assessed every two

weeks. Microbiome composition was analyzed by shotgun metagenomics, and concentrations of plasma amino- and bile acids were obtained by liquid chromatography-mass spectrometry (LC-QQQ, Agilent). To facilitate comparison across outcome measures, the treatment effect was standardized as Cohens d. **Results:** Median age was 63 years (57-67), most patients were male (83%) mainly with cirrhosis (F2/F3/F4 = 4/15/33). Baseline alcohol intake was 36 grams/day, comparable between groups during the study. Thirteen in the ReFerm® group and 18 in the Fresubin® group achieved high compliance (> 85%). In the Referm® group, 8/20 (40%) of patients improved ≥ 10% in α-SMA compared to 4/20 (20%) in the Fresubin® group (OR = 2.3; 95%CI 0.6-9.5; p = 0.246). In patients with high compliance, ReFerm® significantly improved α-SMA compared to Fresubin® (OR = 5.6; 95%CI 1.2-27.1; p = 0.032). Increasing compliance of ReFerm® correlated with improvements in α-SMA (Rho = -0.6623, P = 0.0011). Referm® decreased the abundance of *Flavonifractor platii* and *Veillonella dispar* (p = 0.0118, p = 0.0129), two species that have been associated with liver fibrosis formation. We found a clear tendency of plasma bile acids decreasing in the ReFerm® group compared to the Fresubin® group, a possible sign of better liver performance. The reversed tendency was found within plasma amino acids, as ReFerm® increased amino acids overall compared to the Fresubin® group, hereof four significantly (Taurine (p = 0.037), Homocitrulline (p = 0.028), L-Isoleucine (p = 0.046), and L-Leucine(p = 0.039)). There is increasing evidence that these amino acids benefit the liver, especially in the advanced stage of fibrosis. **Conclusion:** Treatment of advanced ArLD with the post-biotic drink ReFerm® reduces liver fibrosis formation by decreasing α-SMA. ReFerm® may act via a reduction in gut microbes driving fibrogenesis and improvements in circulating bile and amino acids.



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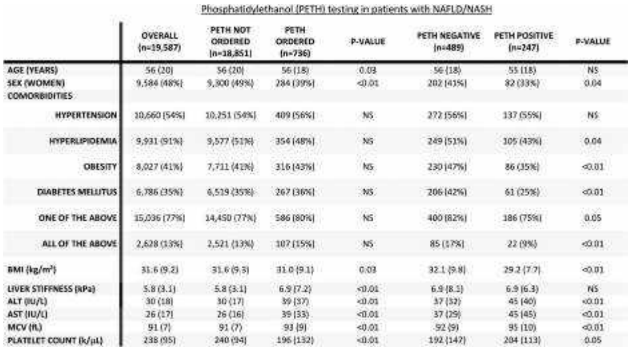
3520-C | ANSWERS RISING FROM THE (N)ASHES - THE USE OF PHOSPHATIDYLETHANOL TESTING AMONG PATIENTS WITH NAFLD/NASH

Zachary Fricker[1,2] and Annabel McLaughlin[1], (1)Beth Isreal Deaconess Medical Center, West Newton, MA, (2)Harvard Medical School

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

Background: Non-Alcoholic fatty liver disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH) may overlap with or be exacerbated by alcohol-use. This creates diagnostic uncertainty and may result in inappropriate counseling for patients. Clinical history alone may be inadequate to identify patients with inappropriate alcohol use. The role for, current use, and yield of biochemical testing for durable alcohol metabolites, e.g., phosphatidylethanol (PETH) remains uncertain. **Methods:** We retrospectively reviewed all outpatients seen at our center since January 1, 2020 with a diagnosis of NAFLD/NASH and without prior diagnosis of any alcohol-related condition (via ICD-10 codes). We identified comorbidities informing likelihood of NAFLD (DM, HTN, HL, and obesity, as well as BMI). We collected laboratory data (AST, ALT, PLT, and MCV) as well as liver stiffness (by VCTE) when available. We identified all PETH measurements and categorized as positive or negative at a threshold of $> =20$ ng/mL, chosen to reflect a minimum level of alcohol use likely associated with greater risk of hepatic fibrosis. Logistic regression was used to identify parameters associated with a positive PETH result. **Results:** We identified 19,587 eligible patients. Of these, 736 (3.8%) had PETH results. Of those tested, 247/736 (34%) had positive PETH results. We found that PETH testing was performed and yielded positive results more often in men. Positive PETH results were also associated with metabolic comorbidities and more abnormal laboratory values (see table). Multivariable logistic regression revealed independent associations between positive PETH result and male sex (OR 1.8, 95%CI 1.04-3.2), AST (OR 1.03 per IU/L, 95% CI 1.01-1.04), and MCV (OR 1.04 per fL, 95%CI 1.01-1.09). As a predictor of positive PETH results, a simple model with these parameters yielded an AUROC = 0.73. **Conclusion:** This study reflects current practice at our academic medical center and demonstrates the relatively high rate of inappropriate alcohol use among patients with NAFLD suggesting a potential for misdiagnosis and an area for risk reduction even in the absence of otherwise harmful alcohol use. We identified several factors associated with the presence of a positive test result which are readily apparent and could help inform real-time clinical decisions. Further study may improve predictive capacity and could determine a cost-effective threshold for testing. These retrospective results should be interpreted with caution until confirmed prospectively.



Phosphatidylethanol (PETH) testing in patients with NAFLD/NASH

	OVERALL (n=19,587)	PETH NOT ORDERED (n=18,851)	PETH ORDERED (n=736)	P-VALUE	PETH NEGATIVE (n=489)	PETH POSITIVE (n=247)	P-VALUE
AGE (YEARS)	56 (20)	56 (20)	56 (18)	0.03	56 (18)	55 (18)	NS
SEX (WOMEN)	9,584 (48%)	9,300 (49%)	284 (39%)	<0.01	202 (41%)	82 (33%)	0.04
COMORBIDITIES							
HYPERTENSION	10,660 (54%)	10,251 (54%)	409 (56%)	NS	272 (56%)	137 (55%)	NS
HYPERLIPIDEMIA	9,931 (91%)	9,577 (51%)	354 (48%)	NS	249 (51%)	105 (43%)	0.04
OBESITY	8,027 (41%)	7,711 (41%)	316 (43%)	NS	230 (47%)	86 (35%)	<0.01
DIABETES MELLITUS	6,786 (35%)	6,519 (35%)	267 (36%)	NS	206 (42%)	61 (25%)	<0.01
ONE OF THE ABOVE	15,036 (77%)	14,450 (77%)	586 (80%)	NS	400 (82%)	186 (75%)	0.05
ALL OF THE ABOVE	2,628 (13%)	2,521 (13%)	107 (15%)	NS	85 (17%)	22 (9%)	<0.01
BMI (kg/m²)	31.6 (9.2)	31.6 (9.3)	31.0 (9.1)	0.03	32.1 (9.8)	29.2 (7.7)	<0.01
LIVER STIFFNESS (kPa)	5.8 (3.1)	5.8 (3.1)	6.9 (7.2)	<0.01	6.9 (8.1)	6.9 (6.3)	NS
ALT (IU/L)	30 (18)	30 (17)	39 (37)	<0.01	37 (32)	45 (40)	<0.01
AST (IU/L)	26 (17)	26 (16)	39 (33)	<0.01	37 (29)	45 (45)	<0.01
MCV (fL)	91 (7)	91 (7)	93 (9)	<0.01	92 (9)	95 (10)	<0.01
PLATELET COUNT (k/µL)	238 (95)	240 (94)	196 (132)	<0.01	192 (147)	204 (113)	0.05

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3521-C | ASPIRIN AND NSAIDS ARE ASSOCIATED WITH REDUCED MORTALITY AND CANCER RISK IN PATIENTS WITH CHRONIC LIVER DISEASES

Knut Stokkeland[1,2], *Karin Söderberg Löfdal*[2], *Pär Villner*[2] *and Johan Frank*[1,2], *(1)Region Stockholm, (2) Karolinska Institutet*

Background: Anti-inflammatory drugs such as aspirin and NSAIDs may be beneficial in chronic liver diseases. We aimed to explore the possible effect of exposure of anti-inflammatory drugs in patients with chronic liver disease. **Methods:** A population-based cohort of patients with chronic liver disease between 2005 and 2020 (n = 21 439) was studied. All patients had been hospitalized in Region Stockholm. Data from the Patient Register, the Prescribed Drug Register, the Death Certificate Register, the Cancer Register, two laboratories and the Stockholm Center for Health Data primary care database were used. We analyzed death, adverse liver events (bleeding esophageal varices, hospitalization for liver disease, liver cancer and liver transplantation), liver cancers and all cancers in relation to drug exposure. **Results:** Mean age at diagnosis ranged from 48.9 years for viral hepatitis and 65.9 years for primary biliary cholangitis. Total follow-up time was 147 045 patient-years during which 10 279 patients (47.9%) died. There were 4 206 patients exposed to ASA and 6 756 exposed to NSAIDs. The was a reduced risk of mortality for all patients exposed to NSAIDs aHR 0.68, 95% CI 0.64-0.72, and a reduction in risk for ASA HR 0.86, 95%CI 0.82-0.91 after adjusting for comorbidities (Charlson comorbidity index) and severity of the liver disease (MELD-score). Similar mortality risks reductions were seen for immunomodulators and antivirals. There was a reduced risk for all cancers when patients were exposed to ASA HR 0.68 95%CI 0.63-0.73 and NSAIDs aHR 0.80, 95%CI 0.75-0.86. There was a reduced risk for liver cancer in patients exposed to ASA aHR 0.48, 95%CI 0.41-0.57 and to NSAIDs aHR 0.71, 95%CI 0.62-0.82. Patients with alcohol-associated liver disease exposed to ASA had a reduced mortality risk, aHR 0.82, 95%CI 0.76-0.89 and exposed to NSAIDs the mortality risk was also reduced aHR 0.74, 95%CI 0.69-0.80. For the risk of liver cancer there was a reduced risk when exposed to ASA aHR 0.40, 95%CI 0.31-0.51 and NSAIDs aHR 0.79, 95%CI 0.65-0.97. **Conclusion:** Exposure to aspirin or NSAIDs in patients with chronic liver diseases was associated with decreased mortality risk and reduced cancer risks including risk for liver cancer.

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Disclosure information not available at the time of publication: Karin Söderberg Löfdal, Pär Villner, Johan Frank

3522-C | ASSOCIATION OF HEPATOLOGY CONSULT AND RECURRENCE OF ALCOHOL USE IN ALCOHOL USE DISORDER IN INPATIENT TREATMENT POPULATION

Hanna Blaney[1], Mian Khalid[1], Bilal Asif[1], Alex Yang[1], Anusha Vittal[1], David Goldman[1], David George[1], Yvonne Horneffer[1], Nancy Diazgranadanos[1] and Theo Heller[2], (1)National Institute of Health, (2)Translational Hepatology Section, Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

Background: Alcohol-associated liver-disease (ALD) is a common and severe complication of excessive alcohol use. Alcohol cessation is the only intervention that both prevents and halts progressions of ALD. Studies have suggested the patients with more advanced liver disease on biopsy have lower rates of rapid recurrence of alcohol use. However, little is known on whether extensive evaluation of the liver with a hepatologist affects outcomes of AUD in treatment seeking patients without known advanced liver disease. The aim of this study was to assess the relationship between recurrence of alcohol use and consultation with a hepatologist in treatment seeking patients with AUD. **Methods:** Patients with AUD were enrolled in a 4-week multidisciplinary inpatient treatment program at the NIH. Laboratory values were collected at admission, weeks 1 and 3. Beginning 2018, most of these patients were seen by Hepatology with Fibroscan performed at weeks 1, 2, and 4. Patients enrolled in this program prior to 2018 and patients who did not see Hepatology (due to unavailability of hepatology consultation) served as controls. After discharge, all patients were invited to submit AUDIT questionnaires at week 26. AUDIT-C was used as a surrogate for recurrence of alcohol use. Analyses comparing AUDIT responses between groups were performed. **Results:** 242 patients were admitted during the study period, with 143 patients seen by hepatology. Of the hepatology group, 87 (60.8%) patients completed AUDIT at week 26 v 46 (46%) of the controls (p = 0.74). There were no significant differences in baseline characteristics between groups including laboratory results, admission AUDIT (p = 0.79), and baseline drinking patterns. There was no difference in rates of prescribing AUD therapy, with 51 patients (59%) in the hepatology group and 21 patients (48%) in the control group receiving medication on discharge (p = 0.24). At week 26, 39 (45%) patients the hepatology group v 31 (70%) in controls (p = 0.006) answered affirmatively to Question 1 having any alcohol (> 0 to “how often do you have a drink containing alcohol?”), with mean scores of 1.46 and 2.09, respectively (p = 0.053). Patients seen by hepatology had decreased rates of hazardous alcohol use as defined by AUDIT-C (> 3 for females or greater than 4 for males) compared to controls, with 36 (41%) v 29 (66%) (p = 0.008) patients, respectively, reporting hazardous use. **Conclusion:** Patients who saw hepatology during inpatient treatment of AUD had significantly lower rates of recurrence of alcohol use at 26 weeks than patients who did not have hepatology evaluation. Patients seen by hepatology also had lower rates of hazardous drinking as defined by AUDIT-C. These finding suggest that hepatology evaluation during inpatient treatment of AUD may influence behavior and ultimately lead to decreased rates of early recurrence of alcohol use.

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3523-C | ASSOCIATION OF PROGNOSIS AND RESPONSIVENESS TO STEROID WITH GUT MICROBIOME IN SEVERE ALCOHOLIC HEPATITIS

Jae Hyun Yoon[1], Sung Bum Cho[2], Ga Ram You[2] and Sung Kyu Choi[1], (1)Chonnam National University Hospital, (2)Hwasun Chonnam National University Hospital

Background: Severe alcoholic hepatitis has been well known to have grave prognosis. Despite many attempts, therapeutic agents or interventions has failed to improve survival outcome and only systemic steroid showed modest survival benefit in limited studies. However, with the pandemic of COVID-19, the amount of alcohol consumption demonstrated increasing tendency and alcohol related health problem has been raised as social problem for long time. The association between gut microbiome and alcoholic liver disease such as hepatitis, or cirrhosis has been previously proposed. However, the role of gut microbiome in prediction of prognosis and response to systemic steroid has not been studied. Hence, we investigated the relationship between gut microbiome and patients course in severe alcoholic hepatitis. **Methods:** From March of 2021 to January of 2023, total 36 patients were enrolled and finally 20 patients were eligible for microbiome analysis. Severe alcoholic patients were defined as patients who took alcohol more than 100g/d in previous one month and Maddrey's Discriminant Function Score $\geq$ 32. Patients with combined etiology of acute hepatitis such as viral hepatitis, and drug induced liver injury were all excluded. 16S rRNA amplicon sequencing was used to analyze the gut microbiota in enrolled patients from stool. The primary endpoint was 6-month survival and the definition of response to systemic steroid was Lille model score $>$ 0.45 after 1 week of systemic steroid. **Results:** Among 20 patients, 75.0% patients were male and the mean age was 47.43. The mean MELD score was 22 and Maddrey's discriminant factor was 53.48. We analyzed the averaged taxonomic compositions of the microbiome taxonomic profiling (MTP) set and *Fusobacteriaceae and Bacteroidales* was more prominent in patients who survived and also *Fusobacterium nercogenes* was abundant in patients who survived while *Rothia mucilaginosa* was more abundant in patients who did not survive. Furthermore, we analysized the taxonomic composition of the MTP sets between who underwent systemic steroid treatment. Patients who responded to systemic steroid had more abundant family of *Fusobacteriaceae* and *Bacteroidales*, especially *Fusobacterium necrogenes* and *Bacteroides caccae* while patients who did not respond do systemic steroid had abundant family of *Micrococcales*, especially *Rothia mucilaginosa.* **Conclusion:** The composition of gut microbiome may aid in prediction of prognosis and responsiveness to systemic steroid treatment.

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3524-C | BACTERIODES THETAIOTAOMICRON PROTECT AGAINST ALCOHOL-ASSOCIATED LIVER DISEASE THROUGH INTESTINAL ILC3 IN MICE

Mukesh Kumar Sriwastva, Chao Lei, Zhishan Xu, Zhongbin Deng, Irina A. Kirpich and Craig J. McClain, University of Louisville, Louisville, KY

Background: The gut microbiota is a major player in alcoholic liver disease (ALD) progression via the gut-liver axis. *Bacteroides* thetaiotaomicron (*Bt*) is a major component of the intestinal microbiota and contribute to the interactions between the microbiota and the gastrointestinal tract. *Bt* produce multiple capsular polysaccharides (CPS), cell surface components that play roles in modulating host immunity. Group 3 innate lymphoid cells (ILC3s) are innate immune effectors that contribute to intestinal epithelial cells (IEC) homeostasis and produce IL-22, a cytokine can ameliorate alcohol-induced liver injury. Our goal is to test the hypothesis that boat and its-related CPS prevent the ALD development by regulating the crosstalk between IEC and gut immune cells, particularly via IL-22-producing ILC3. **Methods:** WT C57B/6J male mice were subjected to chronic EtOH feeding model. The mice were given *Bt* with and without CPS by oral gavage daily. Liver injury was assessed by plasma ALT and AST. Hepatic fat accumulation was examined by Oil Red O staining and liver triglyceride measurement. Liver inflammation was evaluated by the expression of pro-inflammatory cytokines, and neutrophil infiltration. Expression of genes involved in mucosal barrier and mucin production was evaluated in the IEC. Immune response to Bt treatment was evaluated in the lamina propria immune cells. **Results:** *Bt*-treatment attenuated hepatic steatosis, reduced the levels of ALT and AST and the infiltration of neutrophils. *Bt*-treated mice displayed reduced systemic inflammation, enhanced mucin production and increased IL-22-producing ILC3. Mechanistically, Bt treatment resulted in increased AhR transcription and activity in IEC, which was mediated by CPS. We further demonstrated that *Bt* treatment promote IEC AhR-dependent IL-23 secretion. IEC-derived IL-23 promotes the secretion of IL-22 by ILC3s, which attenuate the ALD via gut-liver axis. **Conclusion:** *Bt* supplementation can maintain intestinal immune homeostasis and ameliorate experimental ALD. *Bt*-related CPS induce IEC AhR activation. AhR/IL-23 axis prevent the alcohol-induced liver injury through regulation of intestinal IL-22$^+$ ILC3. *Bt* could serve as a novel probiotic to treat ALD in the future.

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3525-C | BINGE ALCOHOL INTAKE IN OBESITY INCREASES SERUM AND HEPATIC ETHYL ARACHIDONATE AND EXACERBATES LIVER INJURY

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Background: Obesity and alcohol consumption work synergistically to exacerbate liver injury. However, the underlying mechanisms are still unclear. We investigated alcohol-induced changes in lipid metabolism and their influence on liver pathogenesis during alcohol consumption in obesity. **Methods:** 6-week-old C57BL/6J male mice were fed a high-fat diet (HFD) or normal diet (ND) for 8 weeks. On the last day of HFD/ND feeding, mice were given a single dose of ethanol (5 g/kg body weight) or isocaloric maltodextrin by oral gavage. We analyzed a total of four groups: HFD-ethanol, HFD-maltodextrin, ND-ethanol, and ND- maltodextrin. AML12 cells, a cell line of murine hepatocytes, were treated with ethyl arachidonate. **Results:** Nine hours after oral gavage, the HFD-ethanol group showed increased serum ALT level, increased number of TUNEL-positive cells in liver tissue, and increased serum caspase 3/7 activity compared to the other three groups, indicating increased hepatocyte apoptosis. The protein expression levels of PERK in the liver of HDF-ethanol group were increased compared to the other three groups. Metabolomic analysis of liver tissue at three hours after oral gavage showed that the HFD-ethanol group showed a different lipid distribution than both the HFD-maltodextrin and ND-ethanol groups. Ethyl arachidonate was significantly elevated in liver tissue in the HFD-ethanol group compared to the HFD-maltodextrin and ND-ethanol groups, respectively. Serum metabolomic analysis revealed that ethyl arachidonate was significantly elevated in the HFD-ethanol group compared to the HFD-maltodextrin and ND-ethanol groups, respectively. The expression of FAEE carboxylesterase in liver tissue was not significantly different between the HFD-ethanol group and HFD-maltodextrin or ND-ethanol group, suggesting that ethanol intake in obesity increases the synthesis of ethyl arachidonate in serum and its influx into the liver. Ethyl arachidonate treatment decreased viable cell number in AML12 cells in a concentration-dependent manner. Ethyl arachidonate-treated AML12 showed increased expression levels of ER stress-related and oxidative stress-related proteins. **Conclusion:** Ethanol intake in obesity increases ethyl arachidonate in serum and liver tissue, contributing to exacerbation of liver injury.

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3526-C | BURDEN OF INVASIVE FUNGAL DISEASE IN PATIENTS WITH SEVERE ALCOHOLIC HEPATITIS IN FRANCE: A 2012-2021 NATIONAL RETROSPECTIVE STUDY

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Background: There is a lack of knowledge on the burden of invasive fungal disease in patients with severe alcoholic hepatitis. **Methods:** Among the 1,438,049 patients diagnosed with alcohol use disorders in French hospitals between 2012 and 2021, we selected individual's with hepatic failure, portal hypertension bleeding, transjugular liver biopsy, or extrahepatic organ failure within 4 weeks following the diagnosis of alcoholic hepatitis. Our primary objective was to investigate the incidence of invasive fungal disease abd to assess the associated risk factors. We examined the 6-month mortality rate as an outcome measure. The main exposure was invasive fungal disease, while bacterial pneumonia served as the control exposure. To assess the strength of the associations, we employed multivariate logistic regression models and Cox proportional hazards models stratified by age categories, severe comorbidities, and deprivation. **Results:** The sample comprised 30,361 patients. Median (interquartile range) age was 55.0 (47.0-62.0) years and 73% were men. Invasive fungal disease [invasive candidosis (n = 269, 0.9%); aspergillosis (n = 105, 0.3%); pneumocystosis (n = 47, 0.2%); cryptococcosis (n = 3, 0.01%)] and bacterial pneumonia were diagnosed in 411 (1.4%) and 8,787 (10.8%) of patients, respectively. Approximately one-fifth (19.7%) of patients were documented with sepsis, and one-fourth progressed to extrahepatic organ failure. The 6-month mortality rate was ~1/4 (26.5%). Multivariate associations comprised younger ages [aOR 0.73 per decade, 95% CI (0.66-0.81) $P < 0.001$]; sepsis [aOR 3.32, (2.63-4.21) $P < 0.001$]; bacterial pneumonia [aOR 3.09 (2.48-3.85) $P < 0.001$]; extrahepatic organ failure [aOR 2.19 (1.72-2.80) $P < 0.001$]; severe comorbidities [aOR 1.14 (1.00-1.30) $P < 0.001$]; and 6-month mortality [aOR 2.98 (2.40-3.71) $P < 0.001$]. The probabilities of 6-month survival (95% CI) were 72.2 (71.7-72.7) and 40.5 (35.9-45.9) percent without and with invasive fungal disease, respectively ($P < 0.001$), and 73.3 (72.8-73.9) and 63.2 (61.7-64.6) percent without and with bacterial pneumonia, respectively ($P < 0.001$). Invasive fungal disease was associated with an independent, increased, instant, risk of 6-month death of ~80% [aHR 1.81 95% CI (1.58-2.08), $P < 0.001$]. Bacterial pneumonia was not associated with mortality. **Conclusion:** Invasive fungal disease, and not bacterial pneumonia, increased the risk of 6-month mortality in patients with severe alcoholic hepatitis in France 2012-2021.

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3527-C | CCR4+CXCR5+ PERIPHERAL MYELOID CELLS MAY SERVE AS A CELLULAR BIOMARKER OF ELEVATED INFECTION RISK IN PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS

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Background: Individual's with alcohol-associated hepatitis (AH) are at increased risk of developing bacterial infections, which is frequently a cause of mortality. This risk is independent of corticosteroid therapy suggesting that there is inherent immune dysfunction in AH which predisposes to infection. Furthermore, the immune mechanisms driving this risk are not well understood. In this study, we hypothesized that AH causes immune dysfunction within peripheral blood mononuclear cells (PBMC) and that there are cellular biomarkers of infection risk that may aid in risk stratification of AH patients being considered for corticosteroid therapy. **Methods:** We analyzed PBMC from patients enrolled in the AlcHepNet observational study using CyTOF and CITE-seq—a single-cell RNA-seq platform that provides cell-surface protein data. Retrospectively, patients with AH were compared to those that subsequently developed a clinically significant infection within 30 days of collection (AH-inf). These were also compared to healthy controls (HC) and heavy drinkers without AH (HD). The CyTOF analysis included 40 patients, and the CITE-seq analysis included 12 patients (3 per group). Clustering and marker analysis was performed with Cytobank (CITRUS; CyTOF) and Seurat (CITE-seq). **Results:** HC PBMC were predominantly lymphocytes (78 ± 2%; mean ± SEM), but there was a progressive loss of total lymphocytes among HD (49 ± 9%), AH (52 ± 9%), and AH-inf (32 ± 5%) patients respectively ($p < 0.01$). This trend was due to a loss of NK cells, cytotoxic T cells, and naïve T cells. Analysis of the myeloid compartment revealed an inverse trend. That is, the average number of myeloid cells per patient in the AH-inf group ($8.0 \times 10^4 \pm 0.9$) was significantly higher than HC ($4.6 \times 10^4 \pm 0.8$, $p = 0.02$) and AH ($5 \times 10^4 \pm 1$, $p = 0.06$) groups. This was due to expansion of a myeloid cluster that was lower in HLA-DR expression ($p < 0.01$) and enriched for CCR4 and CXCR5 (AH-inf 46 ± 6%, AH 24 ± 6%, HC 1.9 ± 0.9, $p < 0.01$). CITE-seq analysis of the AH-inf myeloid cells suggested that it they had an immune-regulatory phenotype compared to controls. **Conclusion:** AH patients at-risk for infection have a PBMC compartment that is dominated by HLA-$DR^{low}CCR4^{+}CXCR5^{+}$ monocytes. Prior published studies in mice and humans suggest that these molecules are markers of an immune-regulatory phenotype. This population may serve as a novel biomarker of infection risk in patients with AH. Further prospective and functional studies are necessary to confirm this possibility.

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3528-C | CHARACTERIZATION, PROGNOSTIC FACTORS, AND SURVIVAL IN MODERATE ALCOHOL-ASSOCIATED HEPATITIS: A MULTICENTER STUDY

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Background: Alcohol-associated hepatitis (AH) corresponds to a severe entity with high short-term mortality; however, few studies have been published in patients with moderate or "no-severe" AH. Aim: To characterize patients with moderate AH in a global study, identify characteristics, define prognostic factors and survival at 30, 90, and 180 days.

Methods: We conducted a retrospective cohort study, which included patients with moderate AH between 2009-2019. Moderate AH was defined as MELD $\leq$ 20 at presentation. We analyze the baseline and clinical characteristics. We performed a multiple logistic regression to assess potential factors associated with mortality in moderate AH.

Results: Five hundred sixty-four patients with moderate AH were included (24 centers, 12 countries). Median age 48 ± 11.6 years, were 29.2% female, and 46.2.5% Caucasian. 51.7% of the cohort had cirrhosis, and 18.9% underwent liver transplantation. The MELD score on admission was 17 [6-20]. In the entire cohort, 37.7% used corticosteroids during the hospitalization and only 0.61% developed an acute kidney injury. Survival rates at 30, 90, and 180 days were 90.8%, 85.4%, and 81.1%, respectively. The most frequent causes of death were multiple organ failure (30.4%) and infections (11.5%). In the multivariate-adjusted model, we observed that variables independently associated with mortality were infections (OR 6.5, 95%CI: 2.1–24.4; $p < 0.001$) and age (OR 0.9, 95%CI: 0.88–0.99; $p < 0.001$). The mortality at 30, 90 and 180 days was not associated with sex, MELD-Na at admission, history of cirrhosis, or the use of corticosteroids.

Conclusion: Patients with moderate AH have a clinical course with lower mortality compared to severe cases, however, it is up to 20% at 6 months. Infections are associated with higher mortality and are the most important cause of death in these patients.

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3529-C | CHARACTERIZING GHRELIN'S ROLE IN DYSREGULATING GLP-1 MEDIATED ORGAN CROSSTALK AND PROMOTING THE DEVELOPMENT OF ALCOHOL-ASSOCIATED FATTY LIVER DISEASE

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Background: Increasing evidence implicates dysregulated organ-organ crosstalk (gut-pancreas-adipose-liver) in the pathogenesis of alcohol-associated fatty liver disease (AFLD). Considering that the organ crosstalk is majorly regulated by peptide hormones, we previously reported that the chronic alcohol-induced increase in circulating ghrelin levels and the consequent reduction in insulin and adiponectin secretion from the pancreas and adipose tissue, respectively, ultimately leads to fat accumulation in the liver. In further elucidating the detrimental role of ghrelin signaling in AFLD pathogenesis, we recently reported that chronic ethanol administration increases the levels of serum glucagon-like peptide-1 (GLP-1, an incretin that increase insulin secretion/insulin sensitivity and hepatic lipid oxidation) in wildtype (WT) rats but not in ghrelin receptor knockout (GHSR KO) rats. However, while the increased serum GLP-1 in WT ethanol-fed rats did not improve insulin sensitivity or hepatic oxidation, GHSR KO ethanol-fed rats showed higher insulin sensitivity and hepatic fatty acid oxidation despite normal GLP-1 levels. This indicated that ghrelin/GHSR likely interferes with GLP-1 receptor (GLP-1R) mediated signaling. This study was conducted to understand the effect of ghrelin/GHSR signaling on GLP-1 function. **Methods:** To achieve our objective, hepatocytes freshly isolated from chow-fed rats were cultured overnight in the presence of 500 µM oleic acid to induce fat accumulation and then incubated for another 4h in serum-free media with or without ghrelin (10 nM) and/or GLP-1 analog, exendin-4 (20 nM). To identify the receptor interactions, hepatocytes transfected with fluorescently labeled GHSR (RFP) and GLP-1R (GFP) plasmids, were treated with ghrelin for 4h followed by examination by Confocal microscopy. In addition, receptor-receptor interactions were examined by immunoprecipitating GLP-1R (by GFP) in the cellular lysates of these cells and subjecting them to further analyses. **Results:** Treatment of oleic-acid-loaded hepatocytes with the GLP-1 analog, extendin-4, reduced triglyceride content; this effect was blocked by ghrelin treatment. Confocal microscopic examination revealed increased co-localization of GHSR and GLP-1R in ghrelin treated transfected hepatocytes. This increased receptor interactions were also confirmed with Western Blot analysis of the GLP-1R immunoprecipitated sample which showed significantly increased intensity of GHSR protein. Proteomic analysis revealed that ghrelin induced loss of signal transduction molecules downstream of GLP-1R. **Conclusion:** These results indicate a fundamental role of the alcohol increased ghrelin in impairing GLP-1-mediated signal transduction in hepatocytes (and likely other organs such as pancreas and adipose) to promote the development of AFLD.

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3530-C | CHRONIC ETHANOL FEEDING PREDISPOSES MICE TO CHOLESTATIC LIVER INJURY IN ASSOCIATION WITH INFILTRATED NEUTROPHILS

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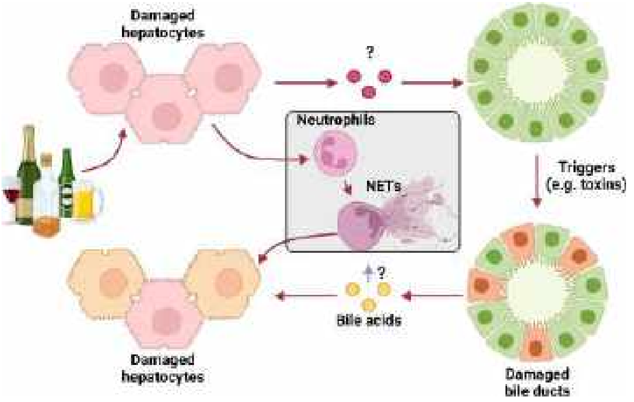
Background: Alcohol-associated hepatitis (AH) is a severe, potentially life-threatening form of alcohol-associated liver disease (ALD) with limited therapeutic options. Existing evidence shows that the presence of biliary dysfunction and cholestasis are common in AH patients and can worsen AH prognosis, but the impact of cholestasis on ALD progression is largely unknown. **Methods:** To examine whether ethanol (EtOH) feeding can promote the susceptibility of mice to cholestasis, we included a subtoxic dose of α-naphthylisothiocyanate (ANIT), a well-studied intrahepatic cholestasis inducer, in an alcohol feeding model, as a second hit. C57BL6 mice were fed with an EtOH diet for 10 days or 4 weeks, followed by ANIT administration 48 hours before sample collection. Bulk RNAseq was performed to determine hepatic transcriptomic changes. Differentially expressed genes (DEGs) were identified by EBSeq analysis. Anti-LY6G antibody was given to deplete neutrophils in mice. DNase I was given to promote the degradation of neutrophil extracellular traps (NETs) in mice. **Results:** We found that ANIT caused limited liver injury in mice fed EtOH for 10 days. In the 4-week group, serum levels of ALT, AST, total bile acids (TBA), and hepatic levels of TBA were significantly increased in mice following EtOH feeding with ANIT, indicating that ANIT synergistically enhanced EtOH-induced liver injury. RNAseq data indicated that either EtOH or ANIT caused transcriptomic changes in the liver compared with pair-fed mice. Intriguingly, in addition to DEGs found in EtOH-fed mice and pair-fed mice with ANIT, we identified 299 genes uniquely altered in EtOH-fed mice with ANIT. Functional analysis of DEGs suggested an enrichment of genes related to inflammatory response. Histologically, the livers of 4-week EtOH-fed mice with ANIT displayed cholangitis, necrosis, and neutrophil infiltration around the periportal area as shown by H&E and LY6G staining. Hepatic Cit-H3 levels, a marker of NETs, were increased in EtOH-fed mice with ANIT as shown by immunostaining and immunoblotting. Either anti-LY6G antibody or DNase I treatment can improve the liver damage in EtOH-fed mice with ANIT. **Conclusion:** Taken together, our results indicate that chronic EtOH feeding predisposes mice to cholestasis and that a subtoxic dose of ANIT pushes EtOH-induced liver damage towards a more severe phenotype with strong inflammation. The evidence suggests a treatment scheme in mice that may be useful for studying connections between cholestasis and AH.



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3531-C | COLLABORATIVE CARE FOR ALCOHOL-ASSOCIATED LIVER DISEASE: INTEGRATION OF A BEHAVIORAL HEALTH PROVIDER INTO A HEPATOLOGY CLINIC

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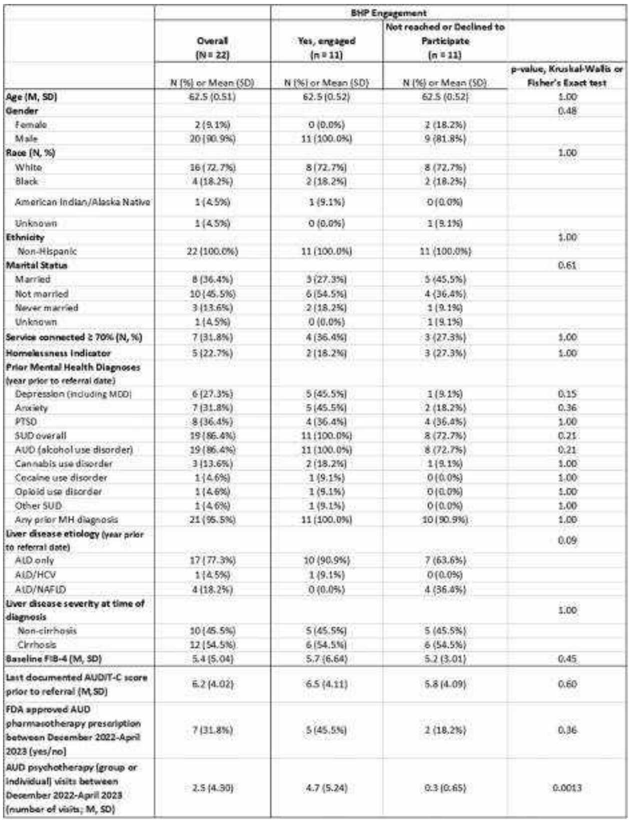
Background: The hepatology visit is an important engagement opportunity for alcohol-related care in patients with alcohol-associated liver disease (ALD). The Veterans Health Administration (VHA) has initiated a pilot program to integrate a behavioral health provider (BHP) into liver clinics at designated facilities. Quality improvement analyses will assess its impact on alcohol use disorder (AUD) treatment. **Methods:** Hepatologists at 3 VHA facilities developed a clinical workflow to refer all patients with ALD and hazardous alcohol use to a BHP co-located in a hepatology clinic. Patient data were obtained from chart review and the VHA Corporate Data Warehouse. Completing more than a single encounter with the BHP was considered engaged with the BHP. We used Kruskal-Wallis and Fisher's Exact tests to assess 1) baseline differences between referred patients by engagement with the BHP and 2) associations between engagement with the BHP and receipt of evidence-based AUD treatments (pharmacotherapy, psychotherapy) after referral. Analyses examined all ALD patients referred to a BHP at one hepatology clinic from 12//1/2022 through 4/1/2023. **Results:** 22 patients were referred to the BHP; 11 successfully engaged, 3 could not be reached and 8 declined to participate. Common patient-reported reasons for declining BHP visits were believing they could quit on their own (36.4%) and having quit alcohol use by the time the BHP attempted to engage with them (27.3%). Among all referred patients, the mean age was 62.5 ± 0.5 years, 90.9% were male, 72.7% White, 18.2% Black, and 45.5% not married. Additionally, in all referred patients 22.7% had unstable housing and 95.5% had a prior mental health diagnosis (Table 1). Out of all patients referred, 18.2% had concomitant non-alcohol fatty liver disease, 4.5% had hepatitis C virus infection, and 54.5% had a diagnosis of cirrhosis. There were no significant differences by engagement with the BHP. During the pilot period, patients who were engaged with the BHP had more AUD psychotherapy visits (4.7 vs. 0.3, $p < 0.01$) and trended toward higher AUD pharmacotherapy prescriptions (45.5% vs. 18.2%, $p = 0.36$) after referral. **Conclusion:** Early findings from the pilot program suggest that having a BHP co-located in a hepatology clinic resulted in a higher number of AUD psychotherapy visits for engaged ALD patients. Integrating BHPs in hepatology clinic may improve AUD treatment uptake.



		BHP Engagement		
	Overall (N = 22)	**Yes, engaged (n = 11)**	**Not reached or Declined to Participate (n = 11)**	
	N (%) or Mean (SD)	N (%) or Mean (SD)	N (%) or Mean (SD)	**p-value, Kruskal-Wallis or Fisher's Exact test**
Age (M, SD)	62.5 (0.51)	62.5 (0.52)	62.5 (0.52)	1.00
Gender				0.48
Female	2 (9.1%)	0 (0.0%)	2 (18.2%)	
Male	20 (90.9%)	11 (100.0%)	9 (81.8%)	
Race (N, %)				1.00
White	16 (72.7%)	8 (72.7%)	8 (72.7%)	
Black	4 (18.2%)	2 (18.2%)	2 (18.2%)	
American Indian/Alaska Native	1 (4.5%)	1 (9.1%)	0 (0.0%)	
Unknown	1 (4.5%)	0 (0.0%)	1 (9.1%)	
Ethnicity				1.00
Non-Hispanic	22 (100.0%)	11 (100.0%)	11 (100.0%)	
Marital Status				0.61
Married	8 (36.4%)	3 (27.3%)	5 (45.5%)	
Not married	10 (45.5%)	6 (54.5%)	4 (36.4%)	
Never married	3 (13.6%)	2 (18.2%)	1 (9.1%)	
Unknown	1 (4.5%)	0 (0.0%)	1 (9.1%)	
Service connected ≥ 70% (N, %)	7 (31.8%)	4 (36.4%)	3 (27.3%)	1.00
Homelessness Indicator	5 (22.7%)	2 (18.2%)	3 (27.3%)	1.00
Prior Mental Health Diagnoses (year prior to referral date)				
Depression (including MDD)	6 (27.3%)	5 (45.5%)	1 (9.1%)	0.15
Anxiety	7 (31.8%)	5 (45.5%)	2 (18.2%)	0.36
PTSD	8 (36.4%)	4 (36.4%)	4 (36.4%)	1.00
SUD overall	19 (86.4%)	11 (100.0%)	8 (72.7%)	0.21
AUD (alcohol use disorder)	19 (86.4%)	11 (100.0%)	8 (72.7%)	0.21
Cannabis use disorder	3 (13.6%)	2 (18.2%)	1 (9.1%)	1.00
Cocaine use disorder	1 (4.6%)	1 (9.1%)	0 (0.0%)	1.00
Opioid use disorder	1 (4.6%)	1 (9.1%)	0 (0.0%)	1.00
Other SUD	1 (4.6%)	1 (9.1%)	0 (0.0%)	1.00
Any prior MH diagnosis	21 (95.5%)	11 (100.0%)	10 (90.9%)	1.00
Liver disease etiology (year prior to referral date)				0.09
ALD only	17 (77.3%)	10 (90.9%)	7 (63.6%)	
ALD/HCV	1 (4.5%)	1 (9.1%)	0 (0.0%)	
ALD/NAFLD	4 (18.2%)	0 (0.0%)	4 (36.4%)	
Liver disease severity at time of diagnosis				1.00
Non-cirrhosis	10 (45.5%)	5 (45.5%)	5 (45.5%)	
Cirrhosis	12 (54.5%)	6 (54.5%)	6 (54.5%)	
Baseline FIB-4 (M, SD)	5.4 (5.04)	5.7 (6.64)	5.2 (3.01)	0.45
Last documented AUDIT-C score prior to referral (M,SD)	6.2 (4.02)	6.5 (4.11)	5.8 (4.09)	0.60
FDA approved AUD pharmacotherapy prescription between December 2022-April 2023 (yes/no)	7 (31.8%)	5 (45.5%)	2 (18.2%)	0.36
AUD psychotherapy (group or individual) visits between December 2022-April 2023 (number of visits; M, SD)	2.5 (4.30)	4.7 (5.24)	0.3 (0.65)	0.0013

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Disclosure information not available at the time of publication: Mayank Jayaram, Brittany L Cornwell, Benjamin R. Szymanski, Bridget Mahoney, Amanda Marshall, David Oslin, John F McCarthy, Ira R. Katz

3532-C | DEMOGRAPHICS AND UNDERLYING LIVER DISEASE AS PREDICTORS IN ALCOHOLIC HEPATITIS

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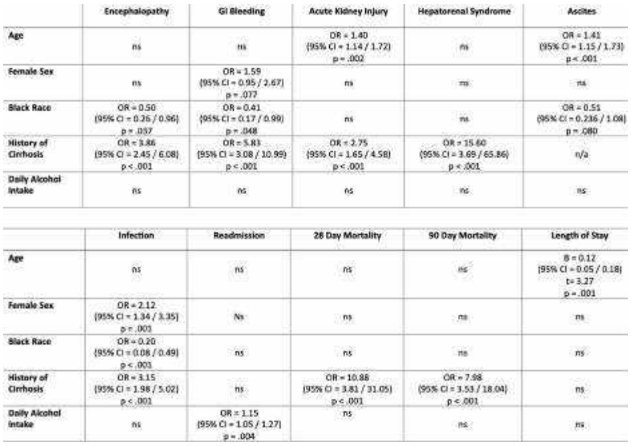
Background: Alcoholic hepatitis confers high short-term mortality and affects diverse groups of patients regardless of age, sex, race, and co-morbidities. We aimed to examine underlying demographics and liver disease including cirrhosis, hepatitis C and B (HCV, HBV), and quantity of alcohol consumed as predictors of outcomes in this population. **Methods:** This retrospective study included all patients admitted for alcoholic hepatitis at a large urban hospital from 2020 to 2022. A subgroup for severe alcoholic hepatitis (SAH) defined as Maddrey's discriminant function > 32 was also analyzed. Outcomes recorded during hospitalization included hepatic encephalopathy (HE), gastrointestinal bleeding (GIB), ascites, acute kidney injury (AKI), hepatorenal syndrome (HRS), bacterial infections, readmissions, length of stay (LOS), and mortality at 28 and 90 days. We conducted a series of logistic regression analyses using a backward step procedure to identify significant predictors of various outcomes. **Results:** 425 patients were included in the main analysis. Average age was 47.97 (SD 11.95), 68% male and 32% female, 70.8% white, 14.8% black, and 14.4% others such as Hispanics and Asians. On admission, 56.7% had a documented history of cirrhosis, 13.6% had a history of HCV, and 2.4% had a history of HBV. Patients in this study consumed 210.25 grams (SD 165.97) of alcohol or approximately 15 standard drinks per day on average. The subgroup receiving corticosteroid therapy for SAH included 126 patients. In the analyses examining mortality as the outcome, history of cirrhosis was the only significant predictor (28-day: OR = 10.88, 95% CI = 3.81/.05, 90-day: OR = 7.98, 95% CI = 3.53/18.04). History of cirrhosis was also a significant predictor of HE, GIB, AKI, HRS, and infection. Increased age was a predictor for AKI, ascites, and longer LOS. Female sex was significantly associated with higher rates of bacterial infection. Black race was significantly associated with lower rates of HE, GIB, and infection. Quantity of alcohol consumed per day was associated with higher rates of readmission. History of HCV and HBV did not achieve statistical significance with regards to any outcomes, including in the corticosteroid therapy group. **Conclusion:** In this retrospective study, history of cirrhosis was clearly the most influential predictor of mortality and outcomes in alcoholic hepatitis. History of HCV was irrelevant, although there was no differentiation between active and treated HCV. Furthermore, older age, female sex, and non-black race were all associated with higher rates of certain complications.



	Encephalopathy	GI Bleeding	Acute Kidney Injury	Hepatorenal Syndrome	Ascites
Age	ns	ns	OR = 1.40 (95% CI = 1.14 / 1.72) p = .002	ns	OR = 1.41 (95% CI = 1.15 / 1.73) p < .001
Female Sex	ns	OR = 1.59 (95% CI = 0.95 / 2.67) p = .077	ns	ns	ns
Black Race	OR = 0.50 (95% CI = 0.26 / 0.96) p = .037	OR = 0.41 (95% CI = 0.17 / 0.99) p = .048	ns	ns	OR = 0.51 (95% CI = 0.236 / 1.08) p = .080
History of Cirrhosis	OR = 3.86 (95% CI = 2.45 / 6.08) p < .001	OR = 5.83 (95% CI = 3.08 / 10.99) p < .001	OR = 2.75 (95% CI = 1.65 / 4.58) p < .001	OR = 15.60 (95% CI = 3.69 / 65.86) p < .001	n/a
Daily Alcohol Intake	ns	ns	ns	ns	ns

	Infection	Readmission	28 Day Mortality	90 Day Mortality	Length of Stay
Age	ns	ns	ns	ns	B = 0.12 (95% CI = 0.05 / 0.18) t= 3.27 p = .001
Female Sex	OR = 2.12 (95% CI = 1.34 / 3.35) p = .001	Ns	ns	ns	ns
Black Race	OR = 0.20 (95% CI = 0.08 / 0.49) p < .001	ns	ns	ns	ns
History of Cirrhosis	OR = 3.15 (95% CI = 1.98 / 5.02) p < .001	ns	OR = 10.88 (95% CI = 3.81 / 31.05) p < .001	OR = 7.98 (95% CI = 3.53 / 18.04) p < .001	ns
Daily Alcohol Intake	ns	OR = 1.15 (95% CI = 1.05 / 1.27) p = .004	ns	ns	ns

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f 3533-C | DETERMINANTS OF RISKS ASSOCIATED WITH ALCOHOL-ASSOCIATED HEPATITIS: A COMPREHENSIVE ANALYSIS OF THE ALL OF US COHORT

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Background: Alcohol-associated hepatitis (AH) is a severe adverse health outcome associated with alcohol use disorder (AUD). Social determinants of health (SDoH), such as healthcare resources and incomes, affect health outcomes and risks. However, their roles in the association with the risk for AH are elusive. The NIH-sponsored All of Us (AoU) program was initiated to collect a wide range of data to drive discoveries that may identify risks and improve overall health. The data provide comprehensive real-world information of US population, including under-represented minorities. We aimed to determine the SDoH and the risk for AH by performing comprehensive analyses of the AoU data. **Methods**: The study cohort was selected from the AoU population using the latest data (as of 04/18/2023 with 413,376 participants). We included participants who have baseline survey data and longitudinal electronic medical record (EMR) information. Baseline demographics, co-morbidities, health insurance status, AUDIT-C score (positive score, defined as > = 5 for men and > = 4 for women, was considered as AUD), and the use of AUD-related medications (disulfiram, naltrexone, or acamprosate) were queried. Subjects with history of AH (using ICD9: 571.1; ICD10: K70.1, K70.10, and K70.11) prior to the enrollment into AoU were excluded in the study cohort. The primary outcome was the diagnosis of AH during the follow up. Participants were followed until the diagnosis of AH or the study closure date of July 1, 2022. A Cox proportional hazard model is used to evaluate SDoH and other factors associated with the development of AH. **Results**: A total of 208,496 with EMR and survey data comprised the study cohort (median age 58 y, 62% women, 43% from minority groups with 18% Hispanics). At enrollment, 22.5% had positive AUDIT-C score, 28% on AUD-related medications, and 93% with health insurance (36% employer-based, 21% Medicare, 17% Medicaid, and 19% from other providers). During the median follow-up of 1,095 days, 213 participants were diagnosed with AH. Using the Cox proportional hazard model, the following factors were associated with the development of AH during follow up: On Medicaid (aHR:3.6, 95%CI: 2.4-5.5, compared to employer-based) or no health insurance (aHR:2.4, 95%CI:1.5 – 3.7, compared to employer-based), positive AUDIT-C score at baseline (aHR:11.63, 95%CI:8.5-16), and age (aHR:1.69, 95%CI:0.97-2.94 for 45-65 years old compared to the 18-35 age group). **Conclusion**: Our results from the real-world AoU data suggested the health insurance status, (notably those with Medicaid or without insurance) and positive AUDIT-C score were independent risk factors associated with the development of AH. AUDIT-C administration and early intervention for those with positive score should be implemented to prevent AH development.

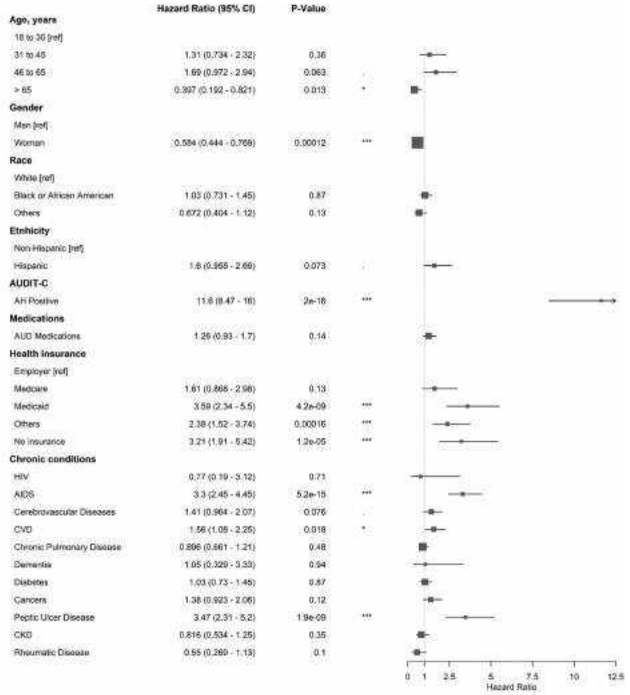

Fig 1: Adjusted hazard ratios with 95% CI and P-values for factors associated with the development of AH

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The following people have nothing to disclose: Chenxi Xiong, Xiang Liu, Wanzhu Tu, Jing Su

3534-C ǀ DEVELOPING AND VALIDATING NOVEL CODING ALGORITHMS TO IMPROVE CASE IDENTIFICATION ACCURACY FOR ALCOHOL- AND NON-ALCOHOL-RELATED CIRRHOSIS IN ADMINISTRATIVE DATABASES.

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Background: Alcohol- (AC) and non-alcohol-related cirrhosis (NAC) epidemiology studies are limited by the accuracy of available administrative case definitions. In this study, we examined and compared the performance of previously used and newly developed case definitions in identifying AC and NAC hospitalizations in Calgary, Canada. **Methods:** We randomly selected 700 hospitalizations from the Discharge Abstract Database using International Classification of Diseases 10th revision (ICD-10) codes for AC, NAC, alcohol use disorder (AUD), and decompensated cirrhosis-related conditions (DC) from 2008-22. For AC case identification, we evaluated the standard approach using the AC code alone, as well as 2 novel AC case definitions that selected admissions with, (i) an AUD and DC code together, or (ii) using either the AC code alone, or both an AUD and DC code together. For NAC case identification, we evaluated the standard approach using a NAC code alone, and 2 novel case definitions that selected admissions with, (i) a NAC code alone, excluding AC, alcohol-related hepatitis (AH), and AUD codes (NAC1), or (ii) both a NAC and DC code together, excluding AC, AH, and AUD codes (NAC2). Using electronic medical record (EMR) review as the reference standard, we calculated case definition positive predictive value (PPV), sensitivity, and area under the receiver operating characteristic curve (AUROC). We used AUROC tests of equality to identify statistical differences between case definitions. **Results:** Of the 700 hospitalizations, 671 had available EMRs (median age 60; 62% male), and 252 had AC, 195 NAC, 54 AH, and 263 AUD. Table 1 shows case definition accuracy estimates and ICD-10 codes used. The novel AC case definition selecting admissions with either the AC code alone or DC and AUD codes together had a PPV of 93% and was more sensitive (76% vs 44-63%) and accurate (AUROC 0.86 vs 0.71-0.81, $p < 0.001$) than the other novel and standard AC case definitions. The novel NAC1 case definition had similar PPV (84% vs 84%) but better sensitivity (57% vs 52%) and AUROC (0.76 vs 0.74, $p = 0.006$) compared to novel NAC2 case definition. The novel NAC1 case definition had better PPV (84% vs 79%) but similar sensitivity (57% vs 57%) and AUROC (0.76 vs 0.76, $p = 0.14$) compared to the standard approach using a NAC code alone (not excluding AC/AH/AUD codes). **Conclusion:** Newly developed administrative case definitions show enhanced accuracy for identifying AC and NAC hospitalizations. Future studies evaluating our proposed algorithms in different databases are warranted.

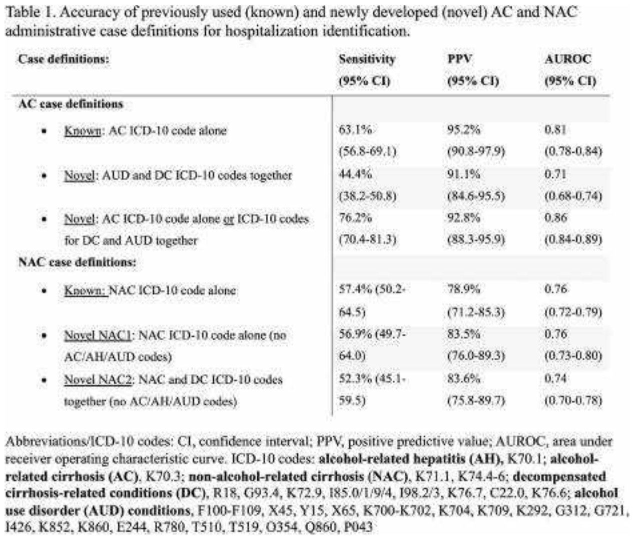

Table 1. Accuracy of previously used (known) and newly developed (novel) AC and NAC administrative case definitions for hospitalization identification.

Case definitions:	Sensitivity (95% CI)	PPV (95% CI)	AUROC (95% CI)
AC case definitions			
• Known: AC ICD-10 code alone	63.1% (56.8-69.1)	95.2% (90.8-97.9)	0.81 (0.78-0.84)
• Novel: AUD and DC ICD-10 codes together	44.4% (38.2-50.8)	91.1% (84.6-95.5)	0.71 (0.68-0.74)
• Novel: AC ICD-10 code alone or ICD-10 codes for DC and AUD together	76.2% (70.4-81.3)	92.8% (88.3-95.9)	0.86 (0.84-0.89)
NAC case definitions:			
• Known: NAC ICD-10 code alone	57.4% (50.2-64.5)	78.9% (71.2-85.3)	0.76 (0.72-0.79)
• Novel NAC1: NAC ICD-10 code alone (no AC/AH/AUD codes)	56.9% (49.7-64.0)	83.5% (76.0-89.3)	0.76 (0.73-0.80)
• Novel NAC2: NAC and DC ICD-10 codes together (no AC/AH/AUD codes)	52.3% (45.1-59.5)	83.6% (75.8-89.7)	0.74 (0.70-0.78)

Abbreviations/ICD-10 codes: CI, confidence interval; PPV, positive predictive value; AUROC, area under receiver operating characteristic curve. ICD-10 codes: **alcohol-related hepatitis (AH)**, K70.1; **alcohol-related cirrhosis (AC)**, K70.3; **non-alcohol-related cirrhosis (NAC)**, K71.1, K74.4-6; **decompensated cirrhosis-related conditions (DC)**, R18, G93.4, K72.9, I85.0/1/9/4, I98.2/3, K76.7, C22.0, K76.6; **alcohol use disorder (AUD) conditions**, F100-F109, X45, Y15, X65, K700-K702, K704, K709, K292, G312, G721, I426, K852, K860, E244, R780, T510, T519, O354, Q860, P043

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3535-C | DEVELOPMENT OF ADVANCED LIVER DISEASE IN PATIENTS WITH RADIOLOGICALLY PROVEN ALCOHOL ASSOCIATED FATTY LIVER DISEASE

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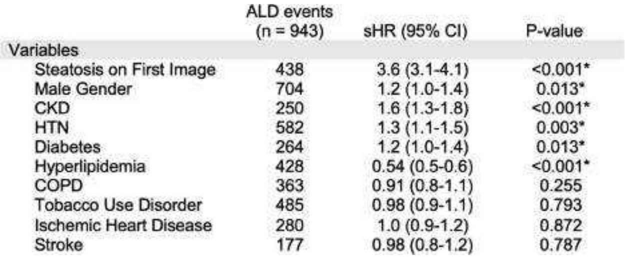
Background: Alcohol associated liver disease (ALD) is linked with significant mortality and is the number one indication for liver transplantation. Detecting ALD at an early stage is challenging, and most cases are diagnosed late. We aim to study whether radiological liver imaging can aid in early detection and improve patient outcomes in ALD. **Methods:** In this single-center retrospective study, we used ICD, 9th and 10th revision, to establish a cohort of 12,527 patients with alcohol use disorder (AUD) from the Massachusetts General Brigham (MGB) system between January 1979 and December 2022. We utilized ICD coding, liver imaging studies, and a keyword-based text mining algorithm to extract critical clinical features and classify liver images into three subgroups: normal, steatosis, or cirrhosis. We then applied cox regression models to estimate hazard ratios (HR) with time to ALD as the dependent variable and examined the influence of various comorbidity measures on this outcome. **Results:** In our cohort,

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



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

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Disclosure information not available at the time of publication: Adedayo Okanlawon, Russell P. Goodman, Esperance Schaefer, Jay Luther

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

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Background: Alcoholic liver disease (ALD) is a serious worldwide health problem. Diammonium glycyrrhizinate (DG) is a medicinal form of glycyrrhizic acid (GA) extracted from licorice roots with anti-inflammatory properties. Some of its beneficial effects in vivo are reported to involve viral hepatitis. Here, we evaluated the potential and the possible mechanism of DG protecting against ethanol-induced liver injury in vitro and in vivo. **Methods:** We investigated the effects of DG on liver lipid metabolism, oxidative stress, and inflammation, induced by chronic plus binge alcohol feeding in mice in vivo by using biochemical assays, qPCR, and histology analyses. Analyses of RNAseq expression were conducted to explore potential targets exploited by DG to protect against ALD. In vitro, mouse cell line, AML12 cells were treated with DG (50μM) prior to ethanol (400 mM) for 24 h. Cell viability was analyzed by CCK8, and protein expressions were assessed by Western blot. **Results:** Chronic treatment with DG alleviated the chronic and binge alcohol-induced liver injury and inflammation, as well as the lipid deposition in hepatocytes. It also beneficially influenced hepatic metabolic and oxidative stress dysregulation. Mice liver tissue RNAseq expression indicated that DEAD-box protein 5 (DDX5) may be a potential target exploited by DG to protect against ALD. The expression of DDX5 was significantly reduced in the ethanol-treated group, following the downregulation of signal transducer and activator of transcription 1 (STAT1), and DG increased the expression of DDX5 and STAT1. These protective effects of DG against alcohol-induced liver injury were attenuated in DDX5 deficient cell line, indicating the beneficial effects of DG in ethanol-induced liver injury by up-regulating the DDX5/STAT1 pathway. **Conclusion:** DG prevented ethanol-induced hepatic injury associated with oxidative stress, inflammation, and steatosis via up-regulating the DDX5/STAT1 pathway.

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Disclosure information not available at the time of publication: Hongqin Xu, Xiuzhu Gao

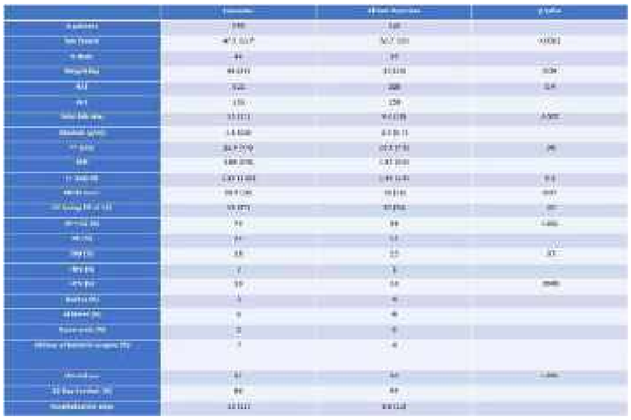
3537-C | DIFFERENCES IN THE CLINICAL PRESENTATION OF ACUTE ALCOHOLIC HEPATITIS BETWEEN CAUCASIANS AND AFRICAN AMERICANS

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

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

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

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



Disclosures: Amon Asgharpour – Galectin: Consultant, No, No;

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

should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Astra Zeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
The following people have nothing to disclose: Yiwei Hang, Marcus Allen Healey, Geetha Ramalingam, Ekaterina Smirnova, Vaishali Patel, Hannah Lee, Scott C. Matherly, Mohammad S. Siddiqui, Joel P. Wedd, Richard K. Sterling
Disclosure information not available at the time of publication: Velimir A. Luketic

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

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

Background: The liver macrophage pool consists of both embryonic-derived Kupffer Cells (eKCs) and infiltrating monocyte/macrophages (IMs). During disease states, these populations are dynamic with some eKCs replaced by monocyte-derived mKCs. We previously showed that replacement of CD163+ eKCs with newly formed CD163- mKCs leads to liver failure suggesting that eKCs are required for maintenance of liver function. The **Aim** of this study was to identify the origin, stability and function of KC subsets in ALD. **Methods:** C57BL/6J mice were fed a high fat (WD) diet with ad-libitum 10%-20% alcohol in the drinking water for 16 to 52 weeks (WDA model). Cx3Cr1-ER-Cre x Rosa26-mT/mG lineage tracer mice were used to evaluate the origin of KC subsets. scRNAseq was performed on total liver CD45+ cells isolated from the WDA mice model. Co-culture experiments were performed to evaluate the hepatoprotective properties of KCs. **Results:** Abundance of CD163+ KCs declined from 90% to 75% to 5% of total KCs at 0, 16 and 52 weeks of WDA diet, respectively. Tamoxifen injection of Cx3Cr1-ER-mT/mG tracer mice resulted in labeling of IMs and CD163- KCs at 1 week, but CD163+ cells remained unlabeled. At 4 weeks after injection, there was still no appearance of label in the CD163+ KCs demonstrating that they did not arise from CD163- KCs. scRNAseq with RNA velocity analysis showed that KC and IM cell identity was stable in chow-fed mice. In both WD and WDA mice, cell identity was in flux and IMs were direct precursors of CD163- KCs. In the absence of alcohol (WD only), CD163- KCs further transitioned to form CD163+ KCs, but in the presence of alcohol this transition was slowed suggesting a block of new KC maturation. Co-culture of isolated hepatocytes with CD163+ KCs preserved hepatocyte albumin production while CD163- KCs lacked this hepatoprotective effect. Gene set enrichment analysis showed that CD163+ KCs most resembled macrophages associated with hepatoprotection and fibrosis resolution while CD163- KCs most resembled lipid-associated macrophages (LAMs). **Conclusion:** CD163 expression identifies a KC subset that is largely embryonic in origin, is antifibrotic, and is critical for support of liver function during alcohol exposure. With increasing time of alcohol exposure, these KCs are progressively replaced by monocyte-derived CD163- KCs that are less hepatoprotective. We propose that loss of protective KCs may contribute to alcohol induced ACLF, as occurs in alcoholic hepatitis.
Disclosures: The following people have nothing to disclose: Sheetalnath Rooge, Kyo Sasaki, Irina Tikhanovich, Steven A. Weinman
Disclosure information not available at the time of publication: Isabel Aranzazu Pulido Ruiz, Kyle Yuquimpo, Heer Mehta, Ann Wozniak, Sumedha Gunewardena

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

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

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

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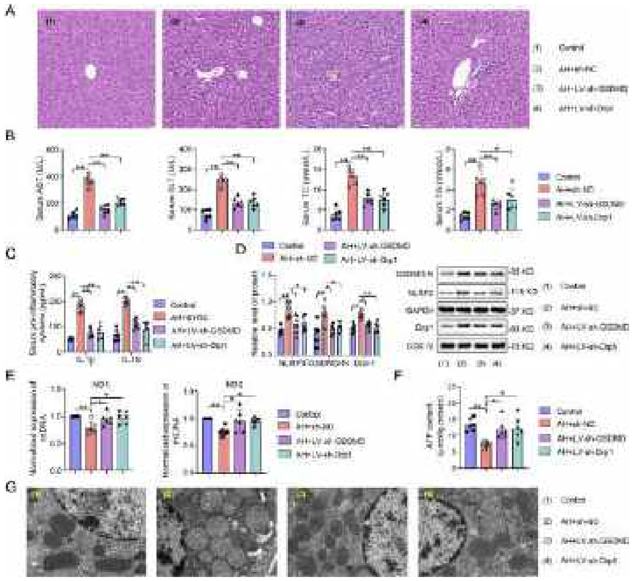
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

AST, ALT, TC and TG. The levels of IL-1b, IL-18, inflammasome associated proteins and hepatocyte death were allowed for determination of pyroptosis. Mitochondrial dysfunction was tested via mitochondrial DNA (mtDNA) level, ROS generation, mitochondrial membrane potential, ATP content, mitochondrial function related protein levels and morphological changes of mitochondria. **Results:** AH induced GSDMD activation with increased protein expression of GSDMD-N, NLRP3 and Caspase-11 in liver tissues. Downregulation of GSDMD alleviated alcohol induced hepatocyte pyroptosis. Alcohol also causes mitochondrial dysfunction of hepatocytes in AH, which was ameliorated by GSDMD inhibition. Moreover, improvement of mitochondrial function suppressed alcohol induced hepatocytes pyroptosis. Further, GSDMD or Drp1 knockdown improved AH induced liver injury accompanied with decreased hepatocyte pyroptosis. **Conclusion:** Drp1 regulates GSDMD mediated mitochondrial dysfunction and hepatocyte pyroptosis during AH induced inflammation and liver injury. These findings may pave the way to develop new therapeutic treatment for AH.



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3540-C | DYSREGULATED CYCLIC NUCLEOTIDE METABOLISM IN ALCOHOL ASSOCIATED STEATOHEPATITIS: IMPLICATIONS FOR NOVEL TARGETED THERAPIES

Diego Montoya-Durango[1], Mary Nancy Walter[1], Walter Rodriguez-Alvarez[1], Yali Wang[1], Claudio Maldonado[1], Shirish Barve[1], Craig J. McClain[1,2] and Leila Gobejishvili[1], (1)University of Louisville, Louisville, KY, (2)Robley Rex VAMC

Background: Cyclic nucleotides are second messengers, which play significant roles in numerous biological processes including cell proliferation, differentiation, and inflammatory response. Previous work has shown that cAMP and cGMP signaling regulates various pathways in liver cells, including Kupffer cells, hepatocytes and hepatic sinusoids. Importantly, it has been shown that cAMP levels and enzymes involved in cAMP signaling are affected by alcohol. Although the role of cyclic nucleotide signaling is strongly implicated in several pathological pathways in liver diseases, the studies detailing the changes in cyclic nucleotide metabolism in ALD are lacking. **Methods:** Male C57B/6 mice were used in an intragastric model of alcohol-associated steatohepatitis (ASH) for 8 weeks. Liver transcriptome analysis was performed to examine the effect of alcohol on regulators of cyclic AMP and GMP levels and signaling. cAMP and cGMP levels were measured in mouse as well as in human healthy donor and alcohol associated hepatitis (AH) patient livers. Plasma ALT, AST, histologic grading as well as protein and real time qPCR analyses were performed to evaluate steatosis, liver inflammation and injury. **Results:** Our results show significant changes in several phosphodiesterases (PDE), with specificity to degrade cAMP (Pde4a, Pde4d, Pde8a) or cGMP (Pde5a and Pde9a), as well as dual specificity PDEs (Pde1a, Pde3b, Pde10a) in ASH mouse livers. Adenylyl cyclases (AC) 7 and 9, which are responsible for cAMP generation, were also affected by alcohol. Importantly, adenosine receptor 1, which has been implicated in the pathogenesis of liver diseases, was significantly increased by alcohol. Adrenoceptors 1 and 3 (Adrb), which couple with stimulatory G protein to regulate cAMP and cGMP signaling, were significantly decreased. Additionally, beta arrestin 2, which interacts with cAMP specific PDE4D to desensitize G protein coupled receptor to generate cAMP, was significantly increased by alcohol. Notably, we observed that cAMP levels are much higher than cGMP in the livers of humans and mice; however, alcohol affected them differently. Specifically, cGMP levels were higher in AH patients and ASH mice livers compared to controls. As expected, these changes in liver cyclic nucleotide signaling were associated with increased inflammation, steatosis, apoptosis and fibrogenesis. **Conclusion:** These data strongly implicate dysregulated cAMP and cGMP signaling in pathogenesis of ASH. Ongoing studies to identify changes of these regulators in a cell-specific manner could lead to the development of novel targeted therapies for ASH.

Disclosures: The following people have nothing to disclose: Diego Montoya-Durango, Craig J. McClain, Leila Gobejishvili

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

Disclosure information not available at the time of publication: Mary Nancy Walter, Walter Rodriguez-Alvarez, Yali Wang, Claudio Maldonado, Shirish Barve

3541-C | EARLY LIVER TRANSPLANT FOR SEVERE ALCOHOL-ASSOCIATED HEPATITIS: HOW DOES REFERRING PROVIDER UNDERSTANDING OF MANDATED SOBRIETY IMPACT REFERRAL FOR EVALUATION?

Elizabeth Stonesifer and Eugene Lengerich, Penn State

Background: Severe alcohol-associated hepatitis (SAH) has high morbidity and mortality. Historically, six months of sobriety was required prior to liver transplantation (LT), however most SAH patients do not meet this criterion. Clinical practice guidelines now suggest LT may be offered to highly select individual's with SAH with shorter time-periods of sobriety. The impact of this change in practice on real-life referral patterns for LT remains unknown. For these reasons, we aimed to assess referring providers' knowledge, attitudes, and practices regarding LT evaluation referral of patients with SAH and less than six months of sobriety. **Methods:** We conducted a survey of community gastroenterology and primary care providers who routinely refer patients to our tertiary care academic LT center. Surveys were sent to 10,604 providers with 31 complete responses. Respondents were diverse (see Figure 1). Transplant Hepatologists at academic LT centers served as the control group. **Results:** Relative to referring providers, Transplant Hepatologists agreed 68.5% more with statements indicating knowledge of current guidelines regarding appropriate referral for LT evaluation for SAH ($p < 0.001$). They agreed 32.3% less with statements stating SAH patients should not be evaluated for LT and that SAH patients are less worthy of LT evaluation than patients with other forms of liver disease ($p < 0.001$). They agreed 70.4% with referring a patient with SAH for liver transplant evaluation ($p < 0.001$). Mean survey responses are presented in Figure 1. **Conclusion:** Community gastroenterologist and primary care providers have low understanding of current clinical practice guidelines for appropriate referral of patients with SAH for LT evaluation. There is a clear, unmet need to provide outreach and education about clinical practice guidelines for SAH, including when it is appropriate for a patient to be referred for early LT evaluation. While future study is needed to validate these findings with a larger, more geographically diverse sample, this work nonetheless remains an important as we look to improve access to life-saving LT for those most in need.

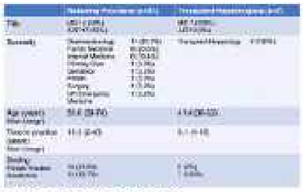

Table 1. Characteristics of sample population

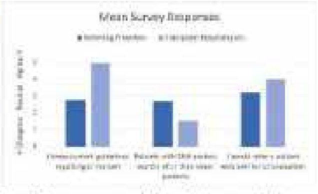

Figure 1. Mean survey responses of Referring Providers compared with Transplant Hepatologists

Disclosures: The following people have nothing to disclose: Elizabeth Stonesifer

Disclosure information not available at the time of publication: Eugene Lengerich

3542-C | EFFECT OF OMEGA 5 FATTY ACID AS AN ADYUVANT TREATMENT TO PREDNISONE IN PATIENTS WITH SEVERE ALCOHOLIC HEPATITIS

Jacqueline Cordova Gallardo[1], Abigail Hernández-Barragan[2], Diana Munguía-Ramos[1], Froylan David Martinez-Sanchez[1], Marisela Hernández-Santillan[2], Moises Martínez-Castillo[2], Erika Karina Tenorio-Aguirre[1], Paola Vazquez-Cardenas[1], Daniel Santana-Vargas[2], Antonio Lopez-Gomez[1] and Gabriela Gutierrez-Reyes[2], (1)Hospital General Manuel Gea González, (2)Universidad Nacional Autónoma De México (UNAM)

Background: In Mexico, alcoholic liver disease is the fourth cause of mortality. Patients with severe alcoholic hepatitis have a high mortality at 28 days and 6 months, patients receiving standard therapy with predniso(lo)ne that are non responders (Lille > 0.45) have a survival of 53.3 ± 5.1 % to 28 days. At present, there is not a completely effective treatment for non responders patients, with a high mortality, so it is necessary to look for other therapeutic strategies. The omega-5 fatty acid (punicic acid) has been considered a powerful antioxidant, it is an agonist of PPAR gamma, has been shown to reduce lipid peroxidation, and restore levels of antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase. It has also been shown to inhibit the expression of proinflammatory cytokines (such as IL6, IL8, IL23, IL12 and TNFalpha) through PPAR and modulation delta. The aim of this study is to evaluate the effect of Omega 5 fatty acid on survival at 28 days at 6 months. **Methods:** A Randomized Double-blind clinical trial, which included 20 patients for standard treatment (Group A: Prednisone 40 mg a day + Placebo (manufactured by the same laboratory with the same presentation and physical appearance) and 20 patients for combined treatment (Group B: Prednisone 40 mg per day + nanoemulsifiyied pomegranate seed oil rich in Omega 5 fatty acid (2 capsules of 0.64g each / day). Both groups receive 28 days of treatment. **Results:** Both

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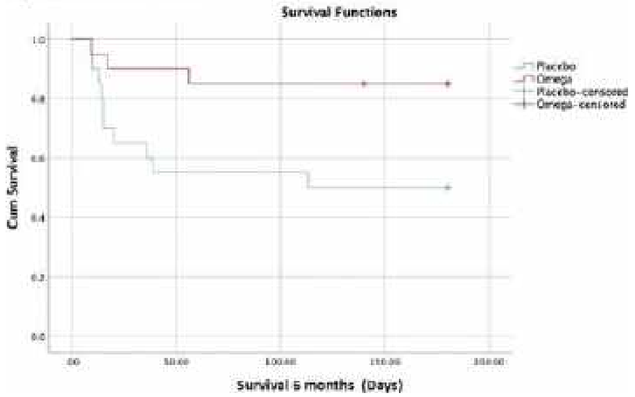
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

groups had similar characteristics with no difference among severity of the disease, neither alcohol consumption. Mean age was 44.2 ± 10.15 years old, the patients included were mainly men 85% (group A) and 90% (group B). The mean Mdf score was 69.51 ± 22.04 (group A) and 62.62 ± 25.14 (group B). Body mass index 27.3 ± 4.68 (group A) and 27.24 ± 4.91 (group B), alcohol consumption in grams per day were 447.58 ± 304.33 (group A) and 423.2 ± 232.78 (group B). Years of alcohol consumption were 16.49 ± 12.41(group A) and 15.08 ± 13.33 (group B). Both groups exert similar steroids response with no difference in Lille score, mean Lille score group A 0.46 ± 0.33 and group B 0.36 ± 0.28; with 10 responders in group A and 12 responders in group B. (p 0.385) For the survival rate, group B had a reduced mortality at 28-days and 6 months in Kapplan-Meier plot ($p = 0.046$). After adjusting by confounding factors, there was no difference in survival at day 28 between both groups (HR = 0.147, IC 95% (0.018-1.221). However, at 6-months group B had a better survival than group A ($p = 0.025$) with an HR = 0.243 (0.67-0.887). (Figure 1) **Conclusion:** The addition of omega 5 to prednisone treatment in patients with severe alcoholic hepatitis had a beneficial effect, increasing survival at 6 months despite the lack of reponse to prednisone.

Figure 1. Survival at 6 months



Disclosures: The following people have nothing to disclose: Jacqueline Cordova Gallardo, Abigail Hernández-Barragan, Diana Munguía-Ramos, Froylan David Martinez-Sanchez, Marisela Hernández-Santillan, Moises Martínez-Castillo, Erika Karina Tenorio-Aguirre, Paola Vazquez-Cardenas, Daniel Santana-Vargas, Antonio Lopez-Gomez, Gabriela Gutierrez-Reyes

3543-C | EMERGENCY SERVICES UTILIZATION BY PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS: AN ANALYSIS OF NATIONAL TRENDS

Shreya Sengupta[1], *Akhil Anand*[1], *Rocio Lopez*[2], *Jeremy Weleff*[3], *Philip Wang*[1], *Annette Bellar*[1], *Amy Attaway*[1], *Nicole M. Welch*[1] *and Srinivasan Dasarathy*[4], *(1)Cleveland Clinic, (2)University of Colorado, (3)Yale University, (4)Cleveland Clinic, Cleveland, OH, United States*

Background: Alcohol-associated hepatitis (AH) is the most severe form of alcohol-associated liver disease (ALD) and accounts for 0.83% of all hospital admissions in the United States. Published data on national trends in AH have focused on inpatient characteristics and outcomes, even though 80% of patients are admitted through the ED. Utilization trends and characteristics of patients presenting to the ED with AH are not known. To better understand the burden of ALD in the US, we evaluated the rates, characteristics, and outcomes of ED visits for AH in adults using data from the Nationwide Emergency Department Sample (NEDS). **Methods:** ED visits for adults aged 18 years or older were analyzed using discharge data from NEDS between January 1, 2016, and December 31, 2019. If the principal diagnosis during the ED visit was AH, this visit was classified as primary AH. Secondary AH was defined if AH was co-listed with a principal diagnosis. Numbers of patients evaluated, severity of disease, complications of liver disease, and discharge disposition were analyzed. Crude and adjusted rates were analyzed, and temporal trends were evaluated using logistic regression with orthogonal polynomial contrasts for each year. **Results:** From 2016-2019, there were 466,014,370 ED visits, of which 448,984 (0.096%) were for AH. The majority of ED visits for AH (80.6%) were for secondary AH; 85.9% (311,008/362,100) had a primary diagnosis closely linked to AH, indicating that AH was the main reason for ED utilization. The mean age was 47 years, and 66% of patients were male. ED visits for AH were most common in people aged 45-64 years (50.9%) followed by those aged 25-44 years (40.8%). Younger patients were more likely to have primary AH, while older patients were more likely to have secondary AH. The most common complications of liver disease were cirrhosis (62.5%), ascites (24.5%), and acute kidney injury or AKI (17.4%), all of which increased during the study period. Although the total number of ED visits did not change over the study period, the overall crude rate of AH increased from 85 to 106 per 100,000 ED visits. **Conclusion:** We show that the incidence of ED visits for AH increased annually prior to the COVID-19 pandemic. Patients with AH who presented to the ED were younger and had more severe illness with the majority presenting with co-existing cirrhosis or complications of portal hypertension. Given the progressive increase in ED visits for AH, optimizing health care utilization will require screening for alcohol use disorder in primary care settings to allow for early diagnosis before severe illness necessitates emergent care.

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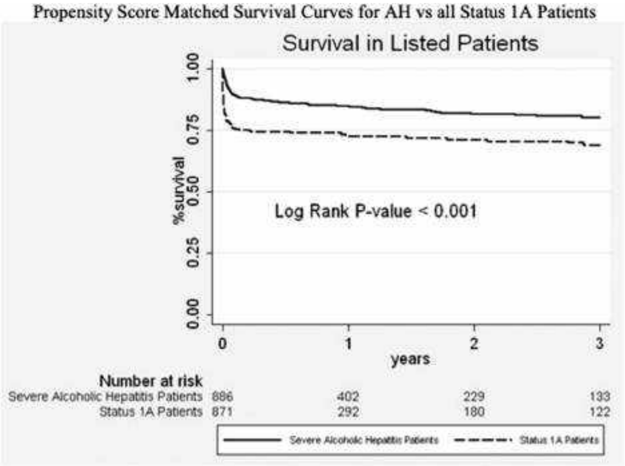
Disclosure information not available at the time of publication: Rocio Lopez, Jeremy Weleff, Philip Wang, Amy Attaway

3544-C | EVALUATING INTENTION-TO-TREAT SURVIVAL FOR LIVER TRANSPLANTATION IN ALCOHOL-ASSOCIATED HEPATITIS COMPARED TO STATUS 1A FROM ACUTE LIVER FAILURE

Ankur Patel[1], Christo Mathew[1], Tzu-Hao (Howard) Lee[1], Ruben Hernaez[2], Peter Lymberopoulos[3], Anshul Bhatnagar[1], Anjiya Shaikh[4], Vinh Vincent Tran[1], Donghee Kim[5], Aijaz Ahmed[6], John A. Goss[1], Abbas Rana[1], Fasiha Kanwal[1], Gene Y. Im[7] and George Cholankeril[1], (1)Baylor College of Medicine, (2)Baylor College of Medicine, Houston, TX, (3)SUNY Downstate Medical Center, (4)University of Connecticut, (5) Stanford University Medical Center, (6)Stanford University School of Medicine, (7)Icahn School of Medicine at Mount Sinai

Background: Although post-transplant survival remains superior for patients with severe acute alcohol-associated hepatitis (AAH), other metrics to measure success with liver transplant (LT) including intention-to-treat (ITT) survival from listing and post-LT length of stay (LOS) utilization are lacking. For AAH patients, there are no data comparing these metrics with other causes of acute liver failure (ALF). Therefore, our aim was to evaluate ITT survival and LOS in patients with AAH patients compared to ALF patients with Status 1A listing. **Methods:** Using the UNOS registry, we retrospectively analyzed clinical outcomes among adult patients who were listed for LT with AAH and Status 1A in the United States between January 1, 2011 and June 29, 2021. AAH patients were propensity matched to Status 1A patients with respect to age, sex, race/ethnicity, MELD score at listing, and date of listing. We used Kaplan Meir survival methods to perform ITT analysis from listing in AAH patients and Status 1A patients. Subgroup analyses were performed comparing patients with AAH to patients with ALF from acetaminophen overdose (APAP) and acute hepatitis B virus (HBV). Cox Hazard regression analyses was used to determine risk factors associated with increased post-LT LOS. **Results:** A total of 3,844 patients were listed for LT with either AAH (n = 886, 23%) or as Status 1A (n = 2958, 77%). Overall, ITT survival at 3 years from LT was similar in AAH patients and status 1A patients (3-year survival: 94.4% vs 91.4%, P = 0.29). With propensity-matched analysis, AAH patients had higher survival benefit with listing for LT compared to Status 1A patients, (3-year survival: 80.3% vs 68.8%, P < 0.001). Upon stratification, patients with AAH that received LT had higher 3-year survival rates from listing than Status 1A patients with HBV or APAP that received LT (3-year survival: AAH, 80.2% vs HBV, 63.7% vs APAP, 67.9%, P < 0.001). On multivariable analysis, AAH LT recipients (n = 670) had significantly higher post-LT LOS (HR 2.48, 95% CI: 1.90-3.25) than patients transplanted with Status 1A. Black race, higher MELD at listing, and hemodialysis were also associated with increased LOS. **Conclusion:** AAH patients have higher survival benefit with waitlisting for LT compared to other Status 1A patients, but require higher utilization of resources in the post-LT recovery period. These data can help guide future metrics for post-LT success in this population.



Disclosures: Gene Y. Im – Korro Bio: Consultant, No, No; Surrozen: Consultant, No, No; Echosens: Grant/ Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

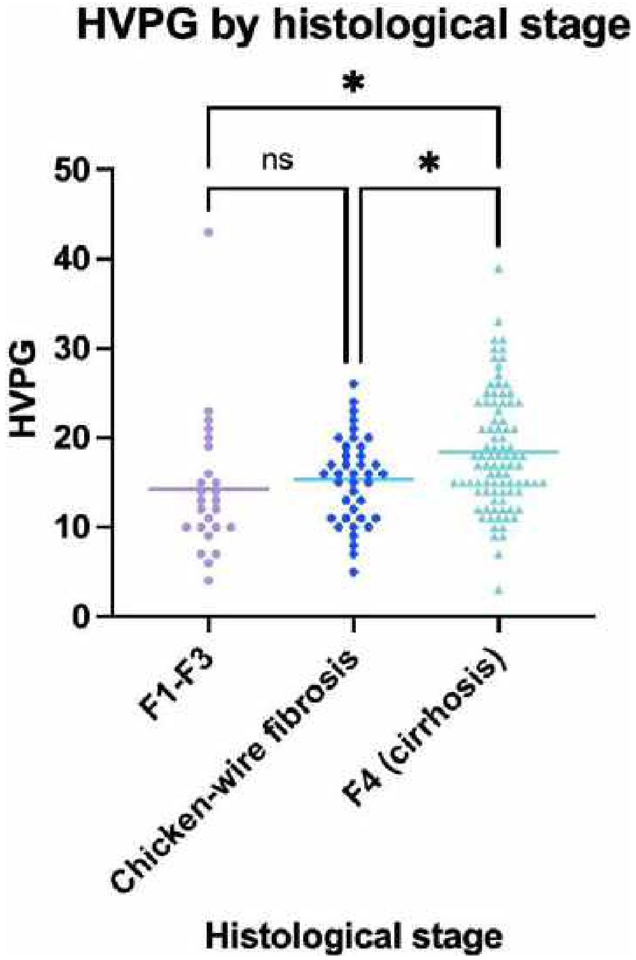
The following people have nothing to disclose: Ankur Patel, Christo Mathew, Tzu-Hao (Howard) Lee, Anshul Bhatnagar, Anjiya Shaikh, Vinh Vincent Tran, Donghee Kim, Aijaz Ahmed, Abbas Rana, Fasiha Kanwal, George Cholankeril

Disclosure information not available at the time of publication: Ruben Hernaez, Peter Lymberopoulos, John A. Goss

3545-C | EVALUATION OF PORTAL HYPERTENSION IN PATIENTS WITH ACUTE ALCOHOL-ASSOCIATED HEPATITIS

Sara Hatoum and Don C. Rockey, Medical University of South Carolina

Background: Alcohol-associated hepatitis (AAH) is an acute form of liver injury resulting from excessive alcohol use. Most patients with AAH have significant fibrosis, or underlying cirrhosis of the liver and many may have associated portal hypertension - even when cirrhosis is not present. The gold standard technique for measuring portal hypertension is the hepatic venous pressure gradient (HVPG). Here, we aimed to assess the prevalence of portal hypertension in patients with AAH and examine the correlation between HVPG level and histological stage. **Methods:** In this cohort analysis, we examined consecutive patients with definite AAH who were admitted to an academic medical center between 2012 and 2022 and underwent HVPG measurement. Patients were considered to have definite AAH if they met clinical and histological criteria including neutrophilic lobular inflammation, degenerative changes in hepatocytes, steatosis, and pericellular fibrosis (based on NIAAA Alcoholic Hepatitis Consortia criteria). They were classified into 3 groups based on trichrome staging of their biopsies: noncirrhotic (F1-F3), cirrhotic (F4), and unable to stage (i.e., described as "chicken-wire fibrosis"). One-way ANOVA was used to compare mean HVPG among the three groups. **Results:** The cohort included 154 patients with histologically proven acute AAH (age 44, range 22-73; 47% female). Ascites and documented esophageal varices were present in 147 and 54 patients, respectively. The average HVPG overall was 17.0 ± 5.1 mmHg. 141 (92%) patients had clinically significant portal hypertension (HVPG $\geq$ 10 mmHg) and 90 (58%) patients had histological evidence of cirrhosis (Figure). Cirrhotic patients had significantly higher HVPG levels than noncirrhotic patients (18.4 ± 6.5 vs.14.2 ± 7.8 mmHg, $p = 0.02$) (Figure). The HVPG in patients with chicken-wire fibrosis was less than those with cirrhosis (15.3 ± 4.9 vs.18.4 ± 6.5 mmHg), this difference was statistically significant ($p = 0.03$). There was no significant difference in HVPG among patients with F1 to F3 fibrosis and those with chicken-wire fibrosis ($p = 0.8$) (Figure). **Conclusion:** Clinically significant portal hypertension is pervasive in patients with AAH, regardless of the degree of fibrosis and patients with cirrhosis had the highest level of portal hypertension. We speculate that the cause of portal hypertension in patients with only F1-F3 fibrosis was related to steatosis and hepatocyte swelling. Finally, we conclude that there is a positive correlation between histological stage and HVPG level in patients with AAH.



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The following people have nothing to disclose: Sara Hatoum

3546-C | EXOCYTOSIS OF HEPATIC GLUTAMATE VESICLES DRIVES ALCOHOL-ASSOCIATED LIVER INJURY BY STIMULATING KUPFFER CELLS

Keungmo Yang, Tom Ryu, Song Hwa Hong, Min Jeong Kim, Chaerin Woo, Katherine Po Sin Chung, Sung Eun Choi, Tolulope Esther Falana, Kyurae Kim, Kippeum Lee and Won-Il Jeong, Kaist

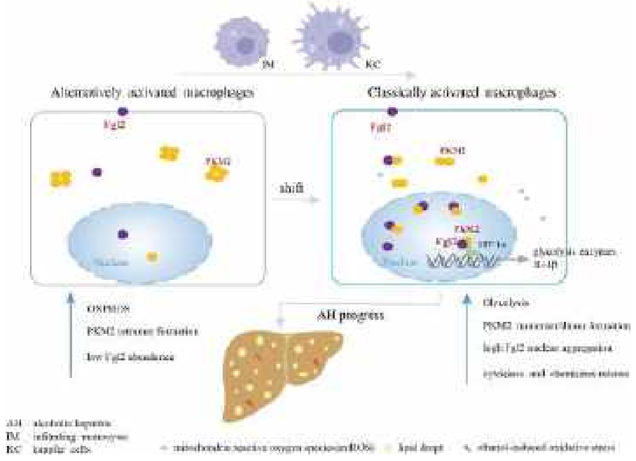
Background: Although alcohol-associated fatty liver (AFL) can progress to the more severe alcohol-associated steatohepatitis (ASH), the underlying mechanism of this transition remains unclear. We previously reported elevated hepatic glutamate levels and its metabotropic glutamate receptor 5 (mGluR5) in both animal models and patients with alcohol-associated liver disease (ALD). Consequently, we hypothesized that glutamate/mGluR5-related signaling pathways might play a significant role in ethanol-induced liver inflammation. **Methods:** C57BL/6J and Kupffer cell-specific *Grm5* knockout (GRM5$^{\Delta KC}$) mice were administered the binge-on-chronic (NIAAA) model to mimic ASH in humans. To identify the glutamate vesicles and spatial proximity between hepatocytes (HEPs) and Kupffer cells (KCs), electron microscopy (EM) and hydrogel-mediated tissue expansion were used. Also, *in vivo* calcium (Ca^{2+}) imaging, bulk RNA-sequencing and flow cytometry analysis were also performed. **Results:** Chronic alcohol consumption increased glutamate production (*Aldh4a1*), uptake (*Slc17a8*), and storage (*Slc1a2*)-related genes, resulting in elevated glutamate content in the liver. Furthermore, tissue expansion techniques revealed the accumulation of glutamate vesicles specifically in the perivenous HEPs. RNA-sequencing analysis showed a significant increase in SNARE complex-related genes involved in the exocytosis of glutamate vesicles. Electron microscopy also indicated close contact between ballooned HEPs and KCs. Under these conditions, *in vivo* Ca^{2+} imaging showed that binge drinking triggered glutamate release through Ca^{2+}-mediated exocytosis. The released glutamate then stimulated mGluR5 in neighboring KCs, leading to increased reactive oxygen species (ROS) production and subsequent HEP injury along with recruitment of neutrophils. We further demonstrated that genetic and pharmacological inhibition of mGluR5 in KCs suppressed glutamate-mediated ROS generation and mitigated liver injury in the NIAAA model. Lastly, similar findings were observed in liver biopsies from ASH patients, and mGluR5-mediated ROS production was observed in human primary KCs. **Conclusion:** Taken together, these findings indicate that chronic alcohol consumption induces the formation of glutamate vesicles in perivenous HEPs. Subsequent exocytosis of these vesicles stimulates mGluR5 in KCs and promotes alcohol-associated liver injury by ROS generation.

Disclosures: The following people have nothing to disclose: Keungmo Yang, Tom Ryu, Song Hwa Hong, Min Jeong Kim, Chaerin Woo, Katherine Po Sin Chung, Sung Eun Choi, Tolulope Esther Falana, Kyurae Kim, Kippeum Lee, Won-Il Jeong

3547-C | FIBRINOGEN-LIKE PROTEIN 2 REGULATES MACROPHAGE GLYCOLYTIC REPROGRAMMING VIA DIRECTLY TARGETING PKM2 AND EXACERBATES ALCOHOLIC LIVER INJURY

Xue Hu[1], Xiaoyang Wan[1], Yuting Diao[1], Zhe Shen[2], Zhongwei Zhang[3], Peng Wang[1], Danqing Hu[1], Xiaojing Wang[4], Weiming Yan[1], Chaohui Yu[2], Xiaoping Luo[3], *Hongwu Wang[1] and Qin Ning[5], (1)State Key Laboratory for Diagnosis and Treatment of Severe Zoonotic Infectious Diseases, Department and Institute of Infectious Disease, Tongji Hospital�Tongji Medical College, Huazhong University of Science and Technology, (2)The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, (3)Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, (4)Tongji Medical College and State Key Laboratory for Diagnosis and Treatment of Severe Zoonostic Infectious Disease, Huazhong University of Science and Technology, (5)Institute and Department of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology*

Background: Switching of macrophage activation phenotype affects pathogenesis of alcoholic liver diseases, metabolic reprogramming can provide the corresponding energy basis for macrophage phenotypes, but the molecular mechanism of immune metabolism regulating the activation of proinflammatory macrophages remains unclear. Herein we show that Fibrinogen-like protein 2 (Fgl2) promotes macrophage activation by regulating aerobic glycolysis in alcoholic hepatitis. **Methods:** Fgl2 expression was examined in alcoholic hepatitis patients and healthy controls. Liver from wild-type (WT) and Fgl2-knockout (KO) mice fed ethanol liquid diet or control diet were analyzed for liver injury and macrophage activation. Fgl2 overexpression THP-1 cell line was used to find interacting partner through immunoprecipitation plus mass spectrometry. Naive bone marrow derived macrophages stimulated with LPS and ethanol were performed for cell experiment. **Results:** Fgl2 expression was significantly elevated in macrophages from alcoholic liver tissues of both humans and mice. Fgl2 depletion ameliorated ethanol diet-induced hepatic steatosis and oxidative injury, as demonstrated by attenuated infiltration of monocytes/macrophages and decreased expression of proinflammatory factors. Fgl2 exhibited enhanced proinflammatory M1 polarization and glycolysis pathway activation in vivo and in vitro. Fgl2 interacted with the M2 isoform of pyruvate kinase in macrophages and facilitated its nuclear translocation, thus promoting glycolysis in M1 macrophage and secretion of proinflammatory cytokines. Furthermore, Fgl2 overexpression in THP-1 cells enhances PKM2-dependent glycolysis and inflammation, which could be reversed by activation of enzymatic PKM2 using DASA58. **Conclusion:** Taken together, Fgl2 promotes the progression of ALD by inducing macrophage polarization and inflammation based on the intracellular PKM2-mediated metabolic reprogramming of macrophages. More importantly, this study revealed the regulation of Fgl2 on glycolysis dependent immune response, providing important insights into the Warburg like metabolic changes of macrophages. Our research provides a new mechanism to link the metabolism and inflammation of macrophages with the progression of alcoholic liver injury.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Alternatively activated macrophages
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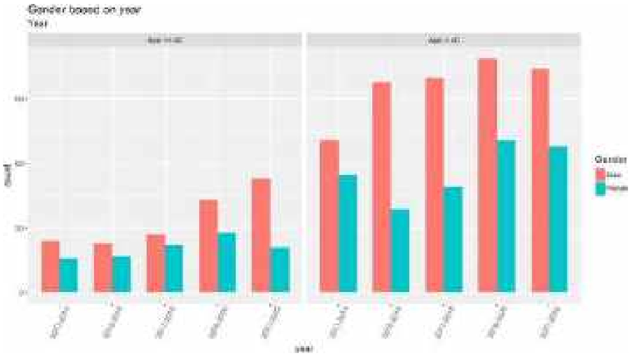
high Fgl2 nuclear aggregation
cytokines and chemokines release
AH alcoholic hepatitis
IM infiltrating monocytes
KC kupffer cells
mitochondria reactive oxygen species(ROS)
lipid drop
ethanol-induced oxidative stress

Disclosures: The following people have nothing to disclose: Xue Hu, Xiaoyang Wan, Yuting Diao, Zhe Shen, Zhongwei Zhang, Peng Wang, Danqing Hu, Xiaojing Wang, Weiming Yan, Chaohui Yu, Xiaoping Luo, Hongwu Wang, Qin Ning

3548-C | GENDER DIFFERENCES IN CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS

Anahita Rabiee, Praveena Narayanan, Bashar A Kadhim, Pramod K. Mistry and Tamar H. Taddei, Yale University, New Haven, CT

Background: The role of gender in susceptibility, presentation, and severity of alcohol associated liver disease has been previously investigated, however the data are not as clear in alcohol associated hepatitis (AH). Our goal was to assess the characteristics, severity, and outcomes among patients admitted with AH to our health system between 2013 to 2022. **Methods:** All patients with AH admitted to a single tertiary health system between 2013 and 2022 were retrospectively reviewed. Patients had to have an AH ICD code *and* meet clinical criteria (total bilirubin $> =3$, AST/ALT > 1.5, AST and ALT < 400). Data from the first admission meeting these criteria were collected for each patient. Biopsy reports were reviewed when available within 14 days of the index admission by a senior gastroenterology/hepatology fellow. Continuous variables with non-normal distributions were compared using Mann-Whitney U test, and categorical variables were compared using Chi square test. **Results:** A total of 2,572 patients had an ICD code for AH, however only 1,042 (40.5%) met clinical AH criteria, among whom 387 (37%) were female. AH events increased in both genders over the time studied (Figure 1). No significant difference between genders was observed in age at presentation (median: 50) or MELD-Na (median: 24). Severe AH, defined as MELD-Na above 20 on admission, was present in 65% of women and 63% of men (p = 0.64). History of bariatric surgery was present in 5% of women vs 0.5% of men (p = < 0.001). The 30-day and 90-day mortality did not differ between groups (30-day M: 12% vs F: 15%; 90-day mortality: M: 19% vs F:21%). The above results did not change when performing a sensitivity analysis restricting the comparison to patients with severe AH. A total of 200 patients received a liver biopsy within 14 days of index admission; women were more likely to receive a liver biopsy (24% vs 16%, p = 0.003). Characteristics of AH were present on 89% of biopsy reports. The prevalence of advanced fibrosis was 98% in women and 90% in men (p = 0.09); the prevalence of cirrhosis was 69% vs 67% in women and men, respectively (p = 0.9). Other characteristics such as degree of steatosis, steatohepatitis, Mallory-Denk bodies, and ballooning degeneration were similar between groups. **Conclusion:** In our retrospective single health system study, we observed an increase in AH among both men and women over time. There was no statistically significant difference in age, MELD-Na, and short-term mortality among groups. Women were more likely to receive a liver biopsy. Among patients who had a liver biopsy confirming the diagnosis of AH, advanced fibrosis and cirrhosis were present in 94% and 68% of patients, respectively.



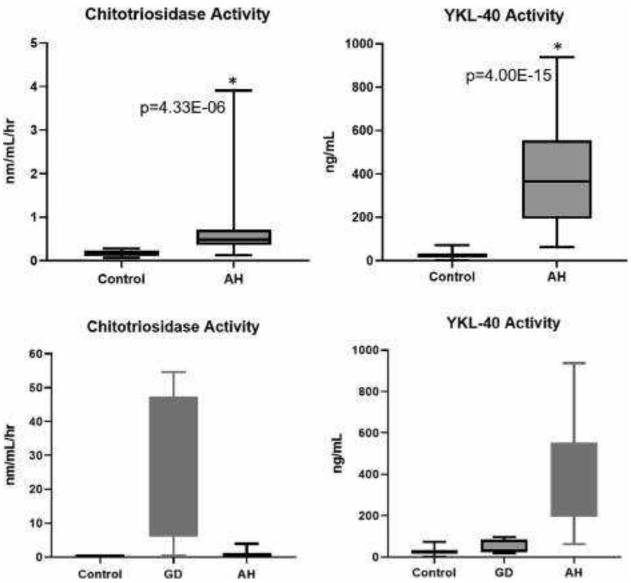
Disclosures: The following people have nothing to disclose: Anahita Rabiee, Praveena Narayanan

Disclosure information not available at the time of publication: Bashar A Kadhim, Pramod K. Mistry, Tamar H. Taddei

3549-C | GENETIC POLYMORPHISMS IN CHIT1 GENE AND LEVELS OF PLASMA CHITOTRIOSIDASE AND YKL-40 IN ALCOHOL-ASSOCIATED HEPATITIS

Praveena Narayanan[1], Jiapeng Ruan[1], Shiny Nair[1], Johannes Aerts[2] and Pramod K. Mistry[1], (1)Yale University, New Haven, CT, (2)Leiden University

Background: There is a higher risk of fungal infections in alcohol-associated hepatitis (AH) and emerging evidence implicate mycobiome changes in its pathogenesis. The human Chitinase 1 (*CHIT1*) gene encodes chitotriosidase, a chitin-hydrolyzing enzyme that exhibits potent antifungal activity. *CHIT1* and its non-enzymatic relative, Chitinase 3-like 1 (YKL-40), participate in the innate immune response in the setting of lipid metabolism dysregulation and have been studied in chronic inflammatory liver disease. However, their role in acute liver disease, particularly in AH, has not been explored. *CHIT1* is a highly polymorphic gene with up to 6% prevalence of homozygous null allele (*dup24*) in some populations; however, there is significant ethnic variability. We sought to study the prevalence and the effect of the most frequent *CHIT1* gene variants, *dup24* and *p.G102S,* in AH. Concurrently, we evaluated plasma chitotriosidase activities and YKL-40 levels as potential biomarkers for AH. **Methods:** Fifty patients admitted with AH and 11 healthy controls were studied. Genomic DNA was extracted from peripheral blood of AH patients, and *CHIT1* genotyping was performed as part of a more extensive whole exome sequencing (WES) analysis. Plasma chitotriosidase enzymatic activity and YKL-40 levels were evaluated. Additionally, we measured plasma chitotriosidase in patients with Gaucher disease (GD), as a disease control for another lipid storage disorder. Correlation analyses were run using two tailed student t-test. **Results:** Of 50 AH patients, 70% were male and 82% were Non-Hispanic White (remainder 9/50 included 7 Hispanic, one Black, and one Asian-Indian). Mean age was 46 years and mean MELD-Na 29 (range 17 to 40); there was a 30% (15/50) 90-day mortality. *CHIT1* genotyping showed that 36/50 (72%) patients harbored either *dup24* or the *p.G102S* variant (PolyPhen score 0.998). Of the 7 Hispanic patients with AH, 100% carried either variant (5/7 71% *dup24, 2/7 p.G102S*). Chitotriosidase and YKL-40 levels were significantly elevated in AH compared to healthy controls. There was a positive correlation between chitotriosidase and YKL-40 levels (r = 0.404, p = 0.0036) in AH. When the AH cohort was compared to GD cohort, chitotriosidase was less elevated, but YKL-40 was elevated by 13-fold. Within the AH cohort, there was no significant correlation between chitotriosidase and YKL-40 and MELD-Na, WBC, presence of infection, 30-day, or 90-day mortality. **Conclusion:** The majority of AH patients (72%) harbored at least one severe *CHIT1* variant. AH patients had significantly elevated plasma chitotriosidase and YKL-40 compared to healthy controls. In contrast to GD, in AH, chitotriosidase was markedly lower and YKL-40 significantly elevated. Larger sample size of AH patients alongside comparator cohorts (e.g. with NASH) will allow for validation of our findings upon which these biomarkers may leverage to promising therapeutic targets.



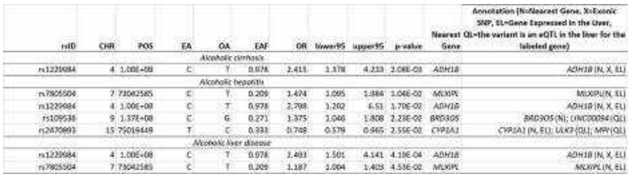
Disclosures: The following people have nothing to disclose: Praveena Narayanan

Disclosure information not available at the time of publication: Jiapeng Ruan, Shiny Nair, Johannes Aerts, Pramod K. Mistry

3550-C | GENETIC VARIATION NEAR MLXIPL, BRD3OS, AND CYP1A1 CONTRIBUTE TO RISK OF ALCOHOLIC HEPATITIS

Antonino Oliveri[1], Kelly Cushing[2], Yanhua Chen[1] and Elizabeth K. Speliotes[3], (1)University of Michigan, (2) University of Michigan Medical Center, (3)University of Michigan Medical School

Background: Alcoholic-related liver diseases (ALD) are associated with substantial morbidity and mortality. Identifying genetic predictors of disease can improve risk stratification efforts and provide insight into novel therapeutic targets. The aims of this study were to 1) determine if alcohol consumption risk loci associate with effects on ALD, and 2) identify subset-specific effects in alcoholic hepatitis (AH) and alcoholic cirrhosis (AC). **Methods:** A genome wide association study of alcohol consumption in the UK Biobank cohort was performed. Variants associating with alcohol consumption at $p < 5e\text{-}08$ were tested for association with ALD, AH, and AC in the UK Biobank using established ICD-10 codes (ALD: K70.1 and/or K70.3, AH: K70.1, AC: K70.3). Significant variants were defined as those reaching a p-value $\leq$ 0.05. Implicated variants and genes were evaluated for eQTL and gene expression effects in liver in the GTEx Portal. **Results:** A total of 23 variants significantly associated with alcohol consumption with the strongest effects observed for rs1229984-C (*ADH1B*, $p = 3.7e\text{-}154$), rs28712821-A (*KLB*, $p = 2.4E\text{-}34$), and rs1260326-C (GCKR, $p = 6.5E\text{-}30$). Of the 23 alcohol intake variants, 2 associated with ALD (*ADH1B*-rs1229984-C [$p = 0.000419$], *MLXIPL*-rs7805504-C [$p = 0.0453$]), 4 associated with AH (*MLXIPL*-rs7805504-C [$p = 0.0104$]; *ADH1B*-rs1229984-C [$p = 0.017$]; *BRD3OS*-rs109536-C [$p = 0.0223$]; *CYP1A1*-rs2470893-T [$p = 0.0255$]), and 1 associated with AC (*ADH1B*-rs1229984-C [$p = 0.00208$]). Several implicated genes were found to be expressed in the liver (*ADH1B, MLXIPL, CYP1A1*) and several genes were found to serve as variant-specific eQTLs in the liver (*LINC00094, ULK3, MPI*). **Conclusion:** Genetic contribution to risk of ALD, AH, and AC is overlapping (*ADH1B*). However, AH has several unique contributors to disease risk including genetic variation near *MLXIPL, BRD3OS,* and *CYP1A1.* This suggests there are common and unique ways to curb alcoholic liver disease. Further studies will help us to understand the functional effects of these genes on the risk of AH.



rsID	CHR	POS	EA	OA	EAF	OR	lower95	upper95	p-value	Nearest Gene	Annotation (N=Nearest Gene, X=Exonic SNP, EL=Gene Expressed in the Liver, QL=the variant is an eQTL in the liver for the labeled gene)
					Alcoholic cirrhosis						
rs1229984	4	1.00E+08	C	T	0.978	2.415	1.378	4.233	2.08E-03	ADH1B	ADH1B (N, X, EL)
					Alcoholic hepatitis						
rs7805504	7	73042585	C	T	0.209	1.474	1.095	1.984	1.04E-02	MLXIPL	MLXIPL (N, EL)
rs1229984	4	1.00E+08	C	T	0.978	2.798	1.202	6.51	1.70E-02	ADH1B	ADH1B (N, X, EL)
rs109536	9	1.37E+08	C	G	0.271	1.375	1.046	1.808	2.23E-02	BRD3OS	BRD3OS (N); LINC00094 (QL)
rs2470893	15	75019449	T	C	0.333	0.749	0.579	0.965	2.55E-02	CYP1A1	CYP1A1 (N, EL); ULK3 (QL); MPI (QL)
					Alcoholic liver disease						
rs1229984	4	1.00E+08	C	T	0.978	2.493	1.501	4.141	4.19E-04	ADH1B	ADH1B (N, X, EL)
rs7805504	7	73042585	C	T	0.209	1.187	1.004	1.403	4.53E-02	MLXIPL	MLXIPL (N, EL)

Disclosures: The following people have nothing to disclose: Antonino Oliveri, Kelly Cushing

Elizabeth K. Speliotes:

Disclosure information not available at the time of publication: Yanhua Chen

3551-C | Glp1-AGONIST REDUCES ALCOHOL INTAKE AND LIVER INFLAMMATION IN A MOUSE MODEL OF ALCOHOL-INDUCED ACUTE HEPATITIS

Frhaan Zahrawi, Suyavaran Arumugam, Bubu A Banini and Wajahat Z. Mehal, Yale University, New Haven, CT

Background: Background and Aims: Therapeutic strategies for alcohol use disorder (AUD) and alcohol associated hepatitis (AH) are limited. Glucagon like peptide 1 agonists (GLP-1A) are a recently developed class of incretin mimetics that increase satiety and decrease appetite, and are approved for treating obesity and diabetes mellitus. To date, data suggest that GLP-1As reduce AUD and protect against various acute and chronic liver injury. In this study, we tested the effectiveness of the GLP-1A semaglutide on alcohol consumption and alcohol-induced hepatic effects in an AH mouse model. **Methods:** Adult C57-BL6J/N male mice 12-14 weeks old were maintained under ambient room temperature on a 12 h/12 h light/dark cycle. After

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

acclimatized to Lieber-Decarli ’82 liquid control diet for 5 days ad libitum, mice were separated into 4 groups: Group 1 (n = 4) - control liquid diet; Group 2 (n = 8) - Lieber Decarli diet; Group 3 (n = 8) - Lieber Decarli diet with daily subcutaneous injection of semaglutide; and Group 4 (n = 4) - control diet with semaglutide treatment. Group 3 and 4 mice were injected with escalating doses of semaglutide as follows: 1 nmol/kg on days 1-2; 3 nmol/kg on days 3-4; 10 nmol/kg on days 5-6; 30 nmol/kg target dose on day 7 after which they were continued on target dose until day 15. On day 16, mice were gavaged (5g/kg of body weight alcohol for groups 2 and 3 and 9g/kg of body weight maltose dextrin for groups 1 and 4) and were euthanized after 9 hr. Body weight and food consumption were tracked daily. Upon sacrifice, liver tissue samples were harvested for further analyses. **Results:** The mice from Group 2 (on Lieber Decarli diet) lost weight initially compared to Group 1 mice on control diet, but regained weight starting on day 10. In contrast, mice in Group 3 treated with semaglutide while on Lieber Decarli diet lost body weight throughout drug treatment. Body weight of Group 3 mice at day 14 was significantly reduced compared to Group 2 ($P < 0.0001$). Group 3 mice also showed significantly reduced alcohol diet intake compared to Group 2 ($P < 0.0001$). The overall food intake was significantly lower in Group 3 mice compared to Group 2, as evident from area under curve (AOC) analysis (AOC 5.358 for Group 3 vs 7.094 for Group 2). These findings also correlated with changes in liver weight among the different groups. Group 2 liver showed sinusoidal hepatocytes with microvesicular steatosis with pyknotic nuclei, while group 3 liver histology showed significant suppression of these changes. Group 3 also showed a reduction in sinusoidal congestion and inflammatory cell infiltration. **Conclusion:** The GLP-1A semaglutide significantly inhibits alcohol diet consumption and reduces body and liver weight in a murine model of AH. Further molecular studies are needed to ascertain the beneficial effects of semaglutide on alcohol consumption and hepatic effects.

Disclosures: The following people have nothing to disclose: Frhaan Zahrawi, Wajahat Z. Mehal

Disclosure information not available at the time of publication: Suyavaran Arumugam, Bubu A Banini

3552-C | HEPATIC RECOVERY IN PATIENTS WITH ALCOHOL ASSOCIATED LIVER DISEASE EVALUATED FOR EARLY LIVER TRANSPLANTATION

Allison J. Kwong[1], Weiyu Wu[2], Erick Sandoval[3], Kaleb Tesfai[3], Gurpreet Judge[4] and Veeral Ajmera[3], (1) Stanford University, (2)Stanford University, Redwood City, CA, United States, (3)University of California, San Diego, (4)Stanford University, Tracy, CA

Background: Alcohol-associated liver disease (ALD) has become the leading cause of liver transplant (LT) in the United States, with increased prevalence of ALD and wider acceptance of early LT for the most acute cases including severe alcohol-associated hepatitis (AH). We evaluated outcomes and predictors of hepatic recovery among patients with ALD and less than 6 months of abstinence from alcohol who were considered for early LT. **Methods:** This retrospective cohort included adult patients with ALD and less than 6 months from last alcohol use who were evaluated for early LT between 2017 to 2021 at two transplant centers with a high median MELD at transplant. Outcomes included death, transplant, Model for End-Stage Liver Disease (MELD) score, Child-Pugh class, and alcohol use. Multivariable Cox regression analysis was used to evaluate predictors of death and transplant-free survival. Hepatic recovery was defined as Child-Pugh class A after 6, 12, and 24 months in patients who did not receive transplant. **Results:** During the study period, 198 patients were evaluated for early LT, 94 (47%) of whom were listed and 69 (35%) transplanted. The median age was 48 years (IQR 40- 55), 36% were men, and 62% were white. The median MELD was 31 (IQR 24-38); the median time from last drink was 62 days (IQR 28-114); and 67% met NIAAA criteria for AH. The overall transplant-free survival was 35.7% at 1 year and 31.4% at 2 years. Male sex and higher BMI, bilirubin, INR, creatinine, AST, ALT, and WBC were associated with increased mortality risk. In the multivariable Cox regression analysis, significant predictors of death without transplant included INR (HR 2.22, 95% CI 1.72-2.88) and creatinine (HR 1.24, 95% CI 1.09-1.40), whereas bilirubin was not predictive (HR 1.01, 95% CI 0.97-1.04) (Table). Among the 69 patients who survived without transplant, 17% achieved Child-Pugh class A at 6 months, 43% at 12 months, and 46% at 24 months. A marked decrease in MELD was observed over 2 years of follow-up, with the greatest reduction in the first 6 months (Figure). During the follow-up period, 19 (28%) patients had a detected relapse, i.e. return to alcohol use. **Conclusion:** In patients with decompensated ALD evaluated for but not receiving early LT, higher than expected rates of hepatic recovery were observed in long-term follow-up. INR and creatinine may be more relevant predictors of transplant-free survival than bilirubin in this population. Improved prognostication is needed to better represent the risk of mortality without LT in patients with ALD and limited sobriety and to identify those who may and may not require LT.

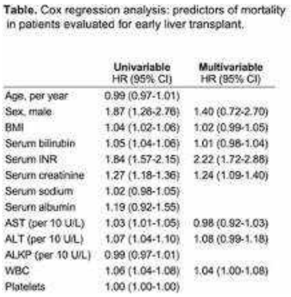


Table. Cox regression analysis: predictors of mortality in patients evaluated for early liver transplant.

	Univariable HR (95% CI)	Multivariable HR (95% CI)
Age, per year	0.99 (0.97-1.01)	
Sex, male	1.87 (1.26-2.76)	1.40 (0.72-2.70)
BMI	1.04 (1.02-1.06)	1.02 (0.99-1.05)
Serum bilirubin	1.05 (1.04-1.06)	1.01 (0.98-1.04)
Serum INR	1.84 (1.57-2.15)	2.22 (1.72-2.88)
Serum creatinine	1.27 (1.18-1.36)	1.24 (1.09-1.40)
Serum sodium	1.02 (0.98-1.05)	
Serum albumin	1.19 (0.92-1.55)	
AST (per 10 U/L)	1.03 (1.01-1.05)	0.98 (0.92-1.03)
ALT (per 10 U/L)	1.07 (1.04-1.10)	1.08 (0.99-1.18)
ALKP (per 10 U/L)	0.99 (0.97-1.01)	
WBC	1.06 (1.04-1.08)	1.04 (1.00-1.08)
Platelets	1.00 (1.00-1.00)	

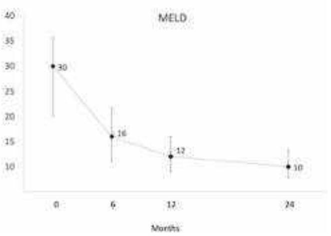


Figure. MELD trend among patients who survived without transplant over 24 months of follow-up. Points = median; bars = interquartile range.

Disclosures: The following people have nothing to disclose: Allison J. Kwong, Kaleb Tesfai, Veeral Ajmera
Disclosure information not available at the time of publication: Weiyu Wu, Erick Sandoval, Gurpreet Judge

3553-C | HEPATIC REDUCTIVE STRESS INFLUENCES ALCOHOL CONSUMPTION

Nirajan Shrestha[1], Byungchang Jin[1] and Russell P. Goodman[2], (1)Massachusetts General Hospital and Harvard Medical School, Boston, MA, (2) Massachusetts General Hospital

Background: Alcohol use disorder (AUD) is a medical condition characterized by an impaired ability to stop or control alcohol use. Heavy alcohol can lead to alcohol-associated liver disease (ALD) and cirrhosis. Genome-wide association studies (GWASs) have shown that alcohol use is highly polygenic, with about half of the risk of AUD being genetic. One genetic locus associated with alcohol use is the glucokinase regulator (*GCKR)*, where a common genetic variant is associated with decreased alcohol consumption. Recent work in our lab has shown that this variant increases hepatic NADH/NAD$^+$ levels (reductive stress), activating the carbohydrate-responsive element-binding protein (ChREBP), which in turn increases fibroblast growth factor 21 (FGF21) levels. As it is well established that FGF21 regulates alcohol consumption, we hypothesized that reductive stress might influence alcohol consumption. **Methods:** We utilized a novel transgenic mouse model, mitochondrial-targeted *Lactobacillus brevis* NADH oxidase (MitoLbNOX; Alb$^{Cre/+}$), which lowers reductive stress in the liver. We performed a two-bottle choice experiment to study alcohol consumption in the mice model. Briefly, mice are singly housed in a standard cage, and the regular water bottle is replaced with two ball-bearing sipper tubes. Mice are exposed to water in both tubes for two days and to increasing concentrations of ethanol (3%, 6%, and 10%; 4 d for each concentration) in one tube and water in another. The water and ethanol consumption are recorded daily. On the final day of the procedure, mice are euthanized under 4% of isoflurane. All animal experiments are approved by MGH Institutional Animal Care and Use Committee. **Results:** In this study, we observed that MitoLbNOX; Alb$^{Cre/+}$ transgenic mice, which have lower hepatic reductive stress, have a higher intake of ethanol in both male and female mice compared to control mice. In addition to alcohol intake, alcohol preference is also higher in MitoLbNOX; Alb$^{Cre/+}$ transgenic mice. Interestingly, female mice have higher alcohol preferences than male mice. **Conclusion:** In conclusion, the mice with lower hepatic reductive stress have higher alcohol preference, supporting that the effect of *GCKR* on alcohol consumption is via reductive stress. The effect of hepatic NADH/NAD$^+$ may be associated with ChREBP, as ChREBP senses reductive stress and regulates FGF21. Hence, further research is required to explore whether changes in alcohol intake due to hepatic reductive stress are mediated through ChREBP.

Disclosures: The following people have nothing to disclose: Nirajan Shrestha, Byungchang Jin
Disclosure information not available at the time of publication: Russell P. Goodman

3554-C | HEPATIC TET1 ALLEVIATES ALCOHOLIC FIBROSIS AND HEPATITIS VIA DOWNREGULATING IL-6

Muhammad Azhar Nisar[1], Hongze Chen[1], Nicholas Jabara[1], Eve Elkins[1], Sonali Notani[1], Bilon Khambu[1], Peng-Sheng Ting[2], Tung-Sung Tseng[3], Hui-Yi Lin[3], Shaolei Lu[4], Xuewei Bai[5] and Chiung-kuei Huang[1], (1) Tulane University School of Medicine, New Orleans, LA, (2)Johns Hopkins University, (3)Louisiana State University Health Sciences Center, (4)Alpert Medical School of Brown University, (5)The First Affiliated Hospital of Harbin Medical University

Background: Alcohol associated liver disease (ALD) is significantly correlated with cirrhosis and hepatic-associated death, with untreated fibrotic liver, regardless of the underlying cause, potentially advancing to cirrhosis in human patients. DNA methylation has been explored in the context of ALD progression. DNA demethylation is involved in 5-hydroxymethylcytosine (5hmC) formation catalyzed by the Ten-eleven translocation methylcytosine dioxygenase (TET) family proteins. Hepatic cell death has been linked to downregulated TET1 and 5hmC in ALD. The current study aimed to investigate the involvement of TET1 in the progression of ALD. **Methods:** Whole body and liver specific TET1 knockout (KO) mice were fed with a 5% alcohol liquid diet to induce ALD. Biochemical and

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

histological assays were adopted to characterize ALD progression. Molecular approaches were utilized for determining underlying mechanisms in the TET1-mediated ALD. **Results:** We found that TET1 deficiency facilitated the development of alcoholic liver fibrosis and inflammation. These were accompanied by an upregulation in the expression of α smooth muscle actin and collagen, markers indicative of increased fibrosis, and by an increase of macrophages and Interleukin (IL) 1β, markers of inflammation. Mechanistically, there was an elevation of IL-6 levels in the liver-specific TET1 KO mouse model. The IL-6 mediated mitogen-activated protein kinase signaling cascade is also decreased in these mice. IL-6 is epigenetically activated by TET1 KO, indicating that alcohol-mediated TET1 downregulation affects the inflammatory responses and fibrosis possibly through IL-6, thereby exacerbating ALD progression. **Conclusion:** In conclusion, our findings demonstrate the protective role of TET1 in ALD and the involvement of TET1-mediated DNA demethylation in controlling inflammatory responses and fibrosis. Activation of TET1 may serve as a potential therapeutic strategy in alleviating ALD.

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3555-C | HEPATIC YES-ASSOCIATED PROTEIN (YAP) DELETION AMELIORATES ALCOHOLIC LIVER DISEASE BY REGULATING HEPATIC LIPID ACCUMULATION AND INFLAMMATION

Tuo Shao, Andre Jeyarajan, Min Xu, Shadi Salloum, Wenyu Lin and Raymond T. Chung, Massachusetts General Hospital and Harvard Medical School

Background: Alcohol-associated liver disease (ALD) is a major public health threat worldwide. There are few agents with clinical activity against alcohol associated liver injury, in large part because the pathogenesis of ALD is not well understood. Several studies have demonstrated that cell injury, inflammation and regeneration are key factors in alcohol-induced liver injury. Hippo/Yes-associated protein (YAP) is a promising therapeutic target central to liver regeneration and inflammation. Since hepatocyte injury is a major driver in the pathogenesis of ALD, whether alcohol induces liver inflammation and attenuates liver regeneration by dysregulating the YAP signaling pathway in hepatocytes is unknown. **Methods:** We generated mice with hepatocyte-specific deletion of YAP ($YAP^{flox/flox}$ mice were injected with adeno-associated virus, AAV8-TBG-Cre), and animals were gradually habituated to a Lieber-DeCarli liquid diet with 5% ethanol over a period of 1 week, then maintained on the 5% diet or isocaloric maltose dextrin for 8 weeks or treated with the YAP inhibitor verteporfin every other day for 4 weeks. Serum ALT and AST, endotoxin level, and lipid panel were assessed; Liver: YAP/p-YAP protein/gene, H&E staining, Oil-Red-O staining, F4/80, neutrophil, proinflammatory cytokines and liver triglyceride (TG) content were measured. HepG2 cells were treated with alcohol for three days or Dimethyloxallyl Glycine (DMOG, HIF-PH inhibitor) for 24 hours or verteporfin for 6-12 hours. YAP and HIF1a expression were analyzed. **Results:** Alcohol feeding significantly increased serum levels of ALT, AST and LPS in WT mice. These elevations were ameliorated in $YAP^{-/-}$ mice. Hepatic triglyceride accumulation increased in the presence of alcohol was improved in $YAP^{-/-}$ mice. Similarly, verteporfin treatment reversed liver steatosis in WT mice. Hepatocyte YAP deletion also resulted in a marked decrease in hepatic macrophage, neutrophil and inflammatory cytokine and chemokine expression (TNF-a ~3 fold, IL-6 ~2 fold and MCP-1 ~1.5 fold). In HepG2 cells, alcohol exposure and DMOG treatment increased nuclear YAP and HIF1a co-expression. However, verteporfin treatment significantly reduced both YAP nuclear translocation and HIF1a expression after alcohol exposure in HepG2 cells. **Conclusion:** Our results demonstrate that hepatocyte YAP activation is a critical driver of alcohol induced liver disease and that inhibition of YAP may represent a novel approach for the treatment of ALD.

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The following people have nothing to disclose: Tuo Shao, Andre Jeyarajan, Min Xu, Shadi Salloum, Wenyu Lin

3556-C | HEPATOCYTES AND NEUTROPHILS INCREASE OXIDATIVE STRESS AND CONTRIBUTE TO ALCOHOL-MEDIATED LIVER INJURY AND INFLAMMATION IN MYELOID TLR4 DEFICIENT MICE

Abhishek Mandal, Anuradha Ratna, Jeevitha Thanikasalam, Evelyn Kurt-Jones and Pranoti Mandrekar, University of Massachusetts Chan Medical School

Background: Alcohol associated liver disease (AALD) is characterized by a spectrum of liver pathophysiology including steatosis, inflammation, and fibrosis. Studies report whole body TLR4 deficiency is protective in AALD. However, the precise role of liver cell specific TLR4 in AALD is not clearly understood. Here, we investigate the role of myeloid-specific and hepatocyte-specific TLR4 deletion in alcohol mediated liver injury and inflammation. **Methods:** Hepatocyte-specific (HEP-TLR4KO) and myeloid-specific TLR4 deficient (M-TLR4KO) mice were generated and subjected to chronic-plus multiple binge alcohol diet. Markers of liver injury, oxidative stress, inflammatory cytokines, immune cell markers were measured. In vivo neutrophil neutralization using anti-Ly6G antibody was assessed. To assess cellular mechanisms, cytokine profiles in macrophages and hepatocytes of M-TLR4KO mice were investigated. **Results:** Our results show high serum ALT and liver triglycerides in alcohol-fed M-TLR4KO mice, indicating sustained liver injury and steatosis. Markers of oxidative stress Cyp2e1, NADPH oxidase 4 (NOX4) and ER stress marker, GRP78 are increased in alcohol fed M-TLR4KO mice. Alcohol-induced expression of TNF-α, IL-6, IL-1β was significantly reduced in M-TLR4KO livers whereas CCL2/MCP-1 ($P < 0.05$) and MIP-1α ($p < 0.0001$) was significantly induced in M-TLR4KO mice. Neutrophil marker Ly6G ($p < 0.0001$), CXCR2 ($p < 0.005$), Elane ($p < 0.05$) and MPO+ cells were induced in M-TLR4KO alcohol livers, indicating neutrophil infiltration. However, expression of immune cell markers F4/80, CD11c were reduced in M-TLR4KO alcohol livers. Finally, in vivo neutrophil neutralization reduced serum ALT, liver triglyceride, pro-inflammatory cytokines, TNFα, IL-6, IL-1β, CCL2 and oxidative stress markers, NOX4 and GRP78. To unravel cellular source of chemokines in M-TLR4KO mice, we isolated macrophages and primary hepatocytes. BMDMs from M-TLR4KO mice show decrease in LPS induced, but not PAM3CSK4 or Poly I:C mediated cytokines TNFα, IL-6, CCL-2 and IL-1β. Instead, LPS stimulation increased TNFα and rTNFα up-regulated CCL2 and IL-6 in chronic alcohol exposed primary hepatocytes from M-TLR4KO mice. Our results suggest that chronic alcohol induced CCL2 in hepatocytes contributes to neutrophil infiltration and injury in M-TLR4KO mice. **Conclusion:** Chronic alcohol associated liver injury and inflammation is independent of myeloid TLR4 and is driven by hepatocyte induced chemokines and neutrophil infiltration.

Disclosures: Pranoti Mandrekar: PS Mandrekar
Disclosure information not available at the time of publication: Anuradha Ratna, Jeevitha Thanikasalam, Evelyn Kurt-Jones

3557-C | HEPATOCYTE-SPECIFIC DEFICIENCY OF DDIT4 ATTENUATES ALCOHOL-MEDIATED HEPATIC DAMAGE

Taek Kyong Kim[1], Yoonsu Ha[1,2] and Seung-Jin Kim[2], (1)Kangwon National University, (2)Global/Gangwon Innovative Biologics-Regional Leading Research Center (GIB-RLRC)

Background: Alcohol-related liver disease is a widespread disease with a variety of pathophysiological spectrums including steatosis, alcoholic steatohepatitis (ASH), alcoholic liver fibrosis, and hepatocellular carcinoma (HCC). DDIT4 (DNA-damage-inducible transcript 4, also known as REDD1) is a highly conserved cellular stress-responsive protein induced by stress signals such as hypoxia, DNA damage, reactive oxygen species (ROS), and ER stress. DDIT4 has been reported to exhibit various regulatory functions against different mammalian cells through inhibition of the mammalian target of Rapamycin (mTOR) pathway. However, the role of DDIT4 during alcohol-induced hepatic injury remains largely undefined. In this study, we aimed to investigate the function of hepatocyte DDIT4 in the development of ASH. In this study, we aimed to investigate the function of hepatocyte DDIT4 in the development of ASH. **Methods:** To explore the function of hepatocyte DDIT4 in the progression of alcoholic steatohepatitis (ASH), mice with hepatocyte-specific deletion of DDIT4 (DDIT4-LKO) were generated. Then, mice were fed 3-months High-fat diet plus multiple binge ethanol to mimic ASH. **Results:** Genetic deletion of DDIT4 in hepatocytes decreased ASH-induced hepatic damages. In particular, loss of DDIT4 in hepatocytes significantly ameliorates ASH-induced liver injury, as evidence by low levels of serum ALT and AST compared with the control group. Furthermore, RNA sequencing analyses reveal that the RAC-PAK-MAPK signaling pathways were significantly decreased in the liver of ASH-induced DDIT4-LKO mice to compare with ASH-induced WT mice. In consistent with RNA sequencing results, immunoblotting showed that the MAPK, fibrotic and apoptotic signaling pathways were significantly decreased in the liver of ASH-induced DDIT4-LKO mice compared with ASH-induced WT mice. **Conclusion:** Taken together, our results demonstrate that downregulation of DDIT4 is crucial for reducing ASH-induced hepatic damage via the attenuation of RAC-PAK-MAPK signaling axis and support the hypothesis that DDIT4 could be a therapeutic target for the control of alcohol-mediated hepatic damage.

Disclosures: The following people have nothing to disclose: Taek Kyong Kim, Yoonsu Ha, Seung-Jin Kim

3558-C | HEPATOLOGY REFERRAL DECREASES THE INCIDENCE OF READMISSION IN PATIENTS WITH ALCOHOLIC HEPATITIS

Nariman Hossein-Javaheri[1], Alexander Mark Carlson[2], Kevin Yang[1], Naren Srinath Nallapeta[1] and Thomas Mahl[1], (1)University at Buffalo, (2)University at Buffalo, Orchard Park, NY

Background: Alcohol abuse and liver disease are associated with high rates of hospital readmission, but factors linking alcoholic hepatitis (AH) to readmission are not well understood. Specifically, we aimed to determine the incidence of 90-day readmission in patients with AH who were referred to clinical hepatology upon discharge. **Methods:** 250 patients with a diagnosis cirrhosis or hepatic steatosis admitted for AH were identified and divided into two groups based on referral and readmission. Furthermore, length of stay (LOS), admission MELD scores, symptoms of decompensation including ascites, encephalopathy and gastrointestinal bleeding (GIB), and 90-day mortality rates, were compared between the two groups. Significance was assessed based on two-tailed t-test and $p < 0.05$ was deemed significant. **Results:** Readmission rate in persons who were referred to hepatology was 41% vs 52.6% in those who were not referred ($p = 0.03$). Those who were referred had a complicated hospitalization with a greater LOS (11 vs 7.6 d; $p = 0.02$), higher MELD scores (15 vs 9; $p < 0.001$), greater incidence of GIB (21% vs 10%; $p < 0.05$) and ascites (36.2% vs 10.8%; $p < 0.001$) but not encephalopathy (23.2% vs 23.9%; $p = 0.9$). Although patients who were referred to hepatology had decreased 90- day mortality (5.8% vs 10.2%), the difference between the two groups was not significant ($p = 0.1$). **Conclusion:** Referral to hepatology significantly reduces the rate of 90-day readmission in patients with AH. Patients with a complicated hospitalization including greater LOS, higher MELD scores on admission, and adverse complications of liver disease (specifically GIB and ascites) were more likely to be referred to a liver clinic. Considering the severity of liver disease, a greater incidence of re-hospitalization is expected in those with advanced and complicated AH. However, it appears that referral to a hepatologist upon discharge can significantly reduce rates of readmission but does not significantly reduce 90-day mortality rates. Given the high probability of hospitalization in AH, it is important to understand factors that contribute to readmission. These factors are potentially helpful for the development of consensus based guidelines, treatment strategies, and patient safety to reduced frequent hospitalization in persons with alcoholic hepatitis.

Disclosures: The following people have nothing to disclose: Nariman Hossein-Javaheri, Alexander Mark Carlson, Kevin Yang, Naren Srinath Nallapeta, Thomas Mahl

3559-C | HEPATOTOXIC EFFECTS OF ALCOHOL AND HIV: SPREADING OF LIVER INFLAMMATION BY APOPTOTIC BODIES

Siva S Koganti[1,2], Moses New-Aaron[1,2], Haritha Chava[1,2], Kusum K. Kharbanda[1,2] and Natalia Osna[1,2], (1)University of Nebraska Medical Center, (2)Veterans Affairs Nebraska-Western Iowa Health Care System

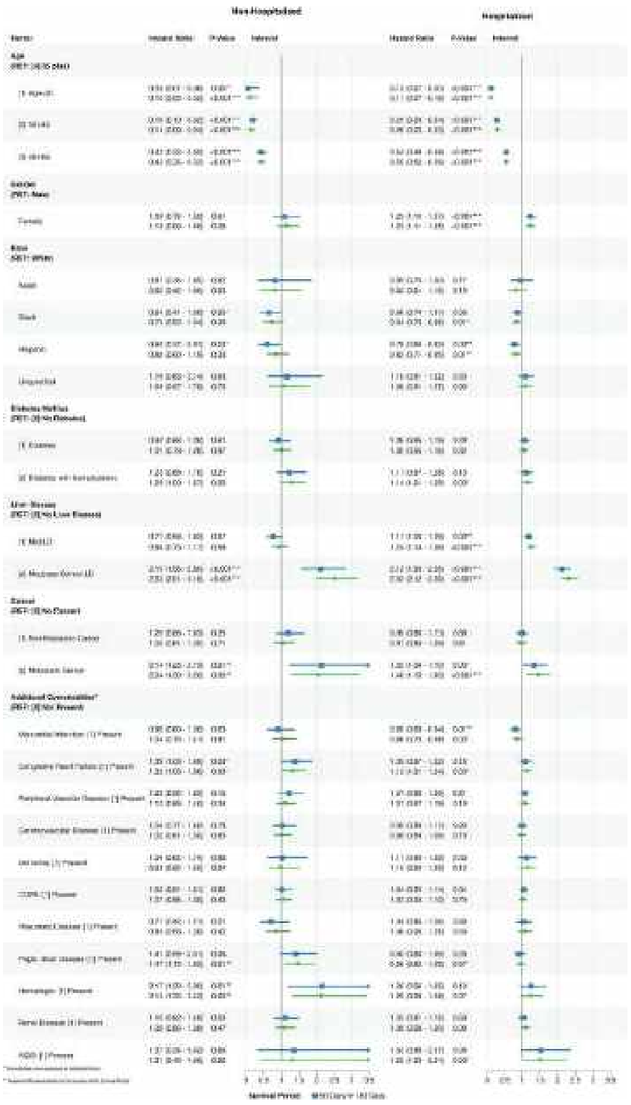
Background: About 48% of HIV-infected individual's are alcohol abusers, which tremendously potentiates HIV-induced hepatotoxicity leading to progressive liver damage and cirrhosis. The mechanisms behind these events are unclear. We recently reported that exposure to HIV and acetaldehyde induces apoptosis in hepatocytes leading to apoptotic bodies (ABs) formation. As revealed from AB's proteomic studies, the enriched datasets target various pro-inflammatory cytokines and inflammasomes, leading to extensive hepatocyte death. Since only a limited number of hepatocytes sense HIV initially, the overall goal of this study was to investigate the key mechanisms underlying progressive hepatotoxicity spread in the liver. We hypothesize that this may happen via engulfment of ABs derived from HIV- and acetaldehyde-generating system (AGS)-exposed hepatocytes ($AB_{AGS+HIV}$) by neighboring hepatocytes via Asialoglycoprotein receptor (ASGP-R). **Methods:** Huh7.5-CYP2E1 (RLW) cells were pretreated for 24 h with AGS, then exposed overnight to $HIV\text{-}1_{ADA}$ and put back on AGS for 96h. Thereafter, ABs were isolated from cell suspension and quantified by Nano-Tracking Analysis (NTA). The ABs were processed for proteomics studies. The obtained datasets carried out functional annotation as well as pathway analysis using Qiagen's Ingenuity pathway analysis (IPA). In addition, $AB_{AGS+HIV}$ were incubated with untreated RLW cells (4:1 to 3:1 ratio) to test proinflammatory genes by RT-PCR and proteins by Western blot. **Results:** Proteomic analysis of $AB_{AGS+HIV}$ along with IPA showed the enrichment of proteins associated with HIV particles, apoptosis, fibrosis, and oxidative stress. Overall, functional annotation explains the potential mechanisms of progressive damage signals pointing toward sustained liver fibrosis and HCC. When exposed to $AB_{AGS+HIV}$, RLW cells have shown a significant dose-dependent increase in cellular expression of TNFα and no change in IL-6 and IL1β. Fluorescently measured proteasome activity was suppressed in RLW $_{HIV+AGS}$ by oxidative stress. As known, TNFα supports cell survival in case downstream signaling is not blocked, and TNFα-induced activation of the NFκβ pathway requires IKβ dissociation. IKβ is a proteasome substrate, which degradation is impaired in hepatocytes exposed to HIV and AGS, thereby limiting activation of this pathway by $AB_{AGS+HIV}$ internalization. **Conclusion:** $AB_{AGS+HIV}$-triggered induction of TNFα combined with the suppression of IKβ proteasomal degradation is responsible for the hepatotoxicity spread and the progression of HIV-ethanol metabolism-induced liver injury.

Disclosures: The following people have nothing to disclose: Siva S Koganti, Moses New-Aaron, Haritha Chava, Kusum K. Kharbanda, Natalia Osna

3560-C | HOSPITALIZATION AND MORTALITY IN COMMERCIALLY INSURED PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS

Suthat Liangpunsakul[1,2], Wanzhu Tu[3], Chi Mai Nguyen[3], Ryan Healey[3], Yang Li[3], Svetlana Radaeva[4], Samer Gawrieh[5], Ramon Bataller[6] and Jing Su[3], (1)Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, (2) Roudebush Veterans Administration Medical Center, Indianapolis, in, (3)Department of Biostatistics and Health Data, Indiana University School of Medicine, Indianapolis, in, (4)National Institutes of Health, Bethesda, MD, (5)Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, in, (6) Barcelona Clinic, Barcelona, Spain

Background: Estimates of mortality in patients with alcohol-associated hepatitis (AH) vary significantly by disease severity, patient population, and study methods. Individual's covered by commercial insurance plans account for much of the clinical population in the United States. Yet, AH-related hospitalization and mortality of commercially insured patients have not been well described. Objectives: To describe the clinical characteristics, hospitalization, and mortality in commercially insured patients with AH diagnoses and clinical factors associated with mortality. **Methods:** We analyzed the administrative health claims data from Optum's Clinformatics® Data Mart (CDM) database, which contained the diagnosis, clinical care records, and mortality in members of large commercial and Medicare Advantage health plans. We identified individual's with AH diagnoses between 2007 and 2021 and examined the 90- and 180-day mortality rates in hospitalized and non-hospitalized patients. **Results:** We identified 49,995 unique patients from 71,260,839 insured individual's. We analyzed data from 32,001 patients that had at least one year of continuous insurance coverage prior to AH diagnoses. Of these, 20,912 were hospitalized within seven days of diagnosis. Mortality rates were markedly higher in hospitalized patients. Ninety and 180-day mortality rates were 12.0% (95% CI [11.6%, 12.5%]) and 16.0% (95% CI [15.4%, 16.5%]) respectively for the hospitalized patients and 3.1% (95% CI [2.8%, 3.4%]) and 5.1% (95% CI [4.6%, 5.5%]) for the non-hospitalized patients. Among the clinical factors associated with mortality, prior diagnosis of liver disease was strongly associated with an increased risk of death. In hospitalized patients, a history of moderate-to-severe liver disease was associated with a more than doubled risk of 180-day mortality (Adjusted HR = 2.31, 95% CI: [2.10, 2.54], Figure 1). **Conclusion:** AH carries significant short and intermediate-term mortality. In commercially insured patients, the risk of death is more than doubled in patients with pre-existing liver disease. The findings of the current study highlight the chronic disease context of this acute condition and the need for combination therapies to more effectively alleviate the damages caused by acute inflammation and long-term alcohol use disorder.



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Disclosure information not available at the time of publication: Chi Mai Nguyen, Ryan Healey, Yang Li, Svetlana Radaeva

3561-C | HOSPITALIZATIONS IN PATIENTS WITH ALCOHOL USE DISORDER AND ASSOCIATIONS WITH OUTCOMES BEFORE AND AFTER COVID-19

Sophie Hansen[1,2], *Christopher Danford*[2], *Jorge Sanchez-Garcia*[2] *and Richard Gilroy*[2], *(1)University of Utah, (2)Intermountain Health*

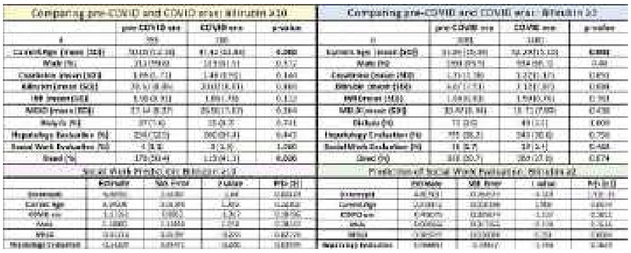
Background: Existing evidence supports an increase in alcohol consumption during the COVID-19 pandemic and suggests greater hospitalizations for, and a younger age in those presenting with decompensated disease. These publications appear more commonly associated with transplant programs and diverse demographic sources. This study examines the impact of COVID-19 upon the frequency, acuity of hospitalizations, and outcomes across an entire health system of 23 hospitals. **Methods:** We conducted an electronic medical record search for all patients admitted to any of 23 hospitals in an integrated medical system from January 1, 2018 to May 1, 2022. We included all patients with a primary admitting diagnosis for alcohol-associated diagnoses (F10.10, F10.20, Z78.9, K70.30, F10.939, K70.10, F10.90, K70.9, K70.0, F10.931) and then separated to examine those with a bilirubin < 2 mg/dL, > 2 mg/dL, and > 10 mg/dL and separated for elevated AST and ALT ratios consistent with the characteristics for alcoholic hepatitis. We then divided the patients into equal pre- (1/1/2018-2/28/2020) and post-COVID (3/1/2020-5/1/2022) eras and with sufficient time to allow at least 1 year follow-up. We compared the total volume of patients admitted with alcohol-related diagnoses, and clinical characteristics between the two eras, readmission and mortality data using unpaired t-test and chi-square test as appropriate for means and proportions respectively. We also evaluated variables for predictive of risk of death using logistic regression. **Results:** In summary:

- There was no difference in the total number of admission with an alcohol-associated liver disorder or alcoholic hepatitis between the two eras.
- There was no increase in mortality in patients with high MELD scores admitted during the COVID-19 era as compared to the pre-COVID-19 era.

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

- Patient age predicted mortality in patients with high MELD scores.
- The presence of a hepatology evaluation had no impact upon mortality.
- Less than 2% of patients with or without a high MELD scores had a social work evaluation.
- There was no change in the percentage of social work encounters between the pre-COVID-19 and the COVID-19 era.

Conclusion: In contrast to previous studies, an increase in the total admissions for alcohol associated diagnosis did not occur and mortality for those with overt decompensation did not change. Although the number of cases did not change, the proportion admitted for alcohol did increase creating a perception of more alcohol use associated admissions to the system. Unfortunately, patients admitted with alcohol use were rarely connected to social work care.



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Disclosure information not available at the time of publication: Jorge Sanchez-Garcia

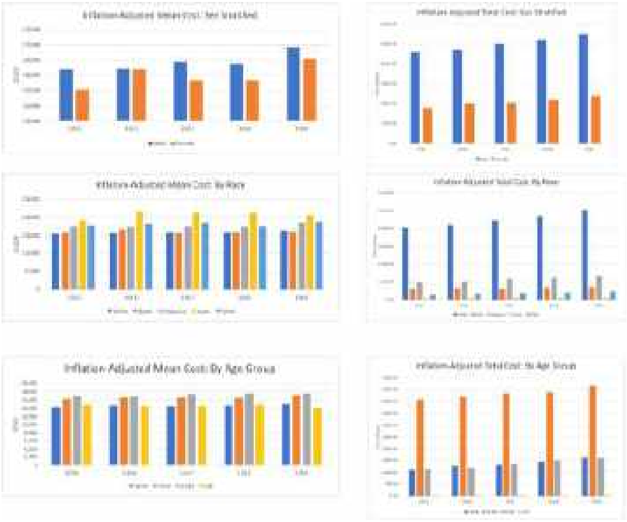
3562-C | IDENTIFYING GENDER AND RACIAL DISPARITIES IN ALCOHOL USE DISORDER: A COST ANALYSIS

Chun-Wei Pan, John H. Stroger Jr. Hospital of Cook County, Neethi Dasu, Jefferson Health NJ, Chun-Han Lo, University of Nevada and Yaser Khalid, Wright Center for Gme/Geisinger Health System

Background: Alcohol-related liver disease (ALD) is a global health and economic burden, especially in the US. Between 2015-2019, there was a rising prevalence of conditions like steatosis, hepatitis, and liver cirrhosis. ALD accounted for 50% of liver disease deaths in people aged 15 and above in 2016. High-cost hospital admissions for ALD complications add to the financial burden. Effective prevention and treatment strategies are needed to address this escalating issue. Our study aims to elucidate the healthcare burden of ALD through an examination of specific demographic factors. **Methods:** This retrospective analysis utilizes the National Inpatient Sample to select cases of ALD, encompassing alcoholic hepatitis, alcoholic cirrhosis, alcoholic fatty liver disease, and other alcohol-related liver diseases. These cases were identified using their respective International Classification of Diseases (ICD-10) codes. To assess the economic burden, all total and mean costs were calculated using the inflation-adjusted cost-to-charge ratio. **Results:**

- From our analysis, costs from 2015-2019 were presented in millions of dollars (6,376.50m, 6,678.00m, 7,020.00m, 7,333.80m, 7,890.00m). When stratified into age groups, 18-44 (1,122.70m, 1,250.80m, 1,300.00m, 1,438.20m, 1,620.00m), 45-64 (4,076.60m, 4,208.20m, 4,336.80m, 4,386.00m, 4,640.00m), 65-84 (1,155.40m, 1,187.20m, 1,341.60m, 1,489.20m, 1,600.00m), > 85 (29.98m, 32.65m, 38.06m, 37.13m, 35.30m). By sex: male (4,588.90m, 4,695.80m, 4,992.00m, 5,191.80m, 5,500.00m), female (1,787.60m, 1,982.20m, 2,028.00m, 2,172.60m, 2,390.00m). By race: White (4,000.30m, 4,208.20m, 4,461.60m, 4,702.20m, 5,070.00m), black (636.56m, 668.86m, 660.40m, 701.76m, 730.00m), Hispanics (989.72m, 1,046.22m, 1,164.80m, 1,234.20m, 1,340.00m), Asian (85.02m, 93.92m, 109.20m, 109.14m, 118.00m), Others (323.73m, 362.52m, 395.20m, 404.94m, 457.00m).
- On a mean total cost basis: Amongst Males, cost increased from $16,194 (95% CI:15,742-16,646) in 2015 to $16,911 (95% CI: 16,471-17,351) in 2019. In females- cost increased from $15,530 (95% CI: 14,980-16,079) to $16,537 (95%CI: 16,020-17,055)
- Regarding race- Asians had the highest mean cost in 2016- $19,117 (95% CI: 17,011-21,222), which increased to 20,679 (95 % CI: 18,678-22,681) in 2019. On an inflation-adjusted basis, the 65-84 age group had the highest mean cost. In 2016 noted to be $17,111 (95% CI: 16,593-17,628) and increased to $17,576 (95% CI: 17,134-18,019) in 2019

Conclusion: Our analysis of the 2015-2019 National Cohort revealed rising costs of ALD; total costs increased from $6,376.50m to $7,890.00m after adjusting for inflation. Costs varied by age, sex, and race. The 45-64 age group and males accounted for higher costs, while the mean cost was highest among Asians and the 65-84 age group. This rising economic burden points toward the urgent need for effective interventions.

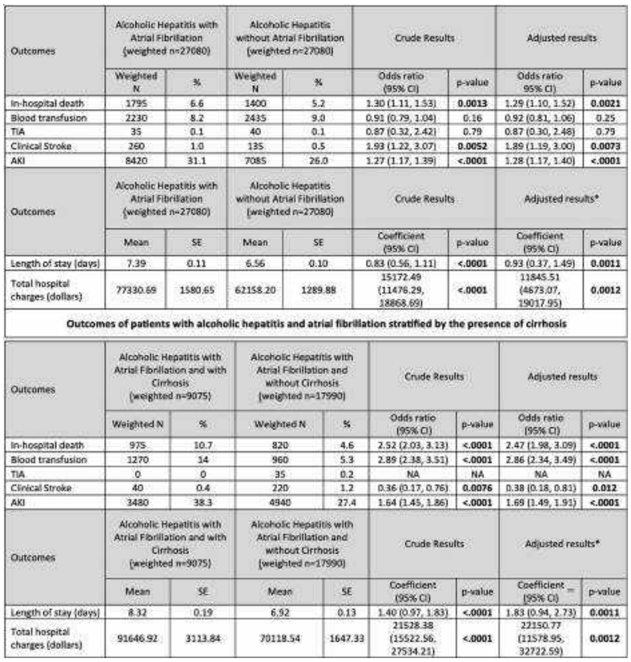


Disclosures: The following people have nothing to disclose: Chun-Wei Pan, Neethi Dasu, Chun-Han Lo, Yaser Khalid

3563-C | IMPACT OF ATRIAL FIBRILLATION ON IN-HOSPITAL OUTCOMES IN ALCOHOL-ASSOCIATED HEPATITIS PATIENTS: A NATIONWIDE ANALYSIS

Harshavardhan Sanekommu[1], Sobaan Taj[1], Jayasree Ravilla[2], Brett Miller[1], Alejandro CruzPonce[1], Qaiser Shahzad[1], Aidan Farrell[3], Muhammad Umair Akmal[4], RIda Mah Noor[5], Reza Akhtar[1], Mohammad Hossain[1] and Arif Asif[1], (1)Hackensack Meridian Jersey Shore University Medical Center, (2)Monmouth Medical Center, (3)Hackensack Meridian University School of Medicine, (4)Kazakh National Medical University, (5) International University of Kyrgyzstan-International School of Medicine

Background: Alcohol consumption is a significant risk factor for atrial fibrillation (AF). AF in cirrhotic patients is linked to adverse outcomes. However, the outcomes of AF in the context of acute alcohol-associated hepatitis (AH) have yet to be investigated. **Methods:** This retrospective cohort study utilized data from the National Inpatient Sample database, covering the period from 2016 to 2019. The study population consisted of hospitalized adults diagnosed with AH, identified using International Classification of Diseases, 10th revision, and Clinical Modification codes. Patients were divided into two groups, according to their history of AF. Subgroup analysis with and without cirrhosis was conducted amongst the group with AF. Statistical analysis involved propensity score matching, weighted means and percentages, t-tests, chi-square tests, multivariate logistic and linear regression using SAS 9.4 software. **Results:** The AH group with AF had a weighted sample size of 479,845, while the AH group without AF had a weighted sample size of 27,665. After matching for baseline characteristics, each group retained a weighted sample size of 27,080. Patients with AH and AF had a higher in-hospital mortality rate (6.6%) compared to those without AF (5.2%) (adjusted odds ratio:1.29, 95% CI: 1.10-1.52, p = 0.021). Patients with AF had higher odds of experiencing a clinical stroke (OR = 1.89, 95% CI: 1.19-3.00, p = 0.073) and developing acute kidney injury (AKI) (OR = 1.28, 95% CI: 1.17-1.40, p < 0.0001). Longer hospital stays (mean difference = 0.93 d, 95% CI: 0.37-1.49, p = 0.0011) and higher total hospital charges (mean difference = $11,845, 95% CI: $4,673-$19,017, p < 0.0001) were observed for patients with AF. No significant differences were found in the odds of blood transfusion and transient ischemic attack. Among patients with AH and AF, 33.5% had cirrhosis (n = 9,075). Cirrhosis was associated with higher risk of death (OR: 2.52, p < 0.0001) and blood transfusion (OR: 2.89, p < 0.0001), lower odds of stroke (OR: 0.36, p = 0.0076), higher odds of kidney injury (OR: 1.64, p < 0.0001), longer stay (mean difference: 1.40 d, p < 0.0001), and higher charges (mean difference: $21,528, p < 0.0001). **Conclusion:** Patients with AH and AF have elevated risks of in-hospital mortality, stroke, AKI, prolonged hospitalization and increased healthcare costs. The presence of underlying cirrhosis exacerbates these adverse outcomes. Appropriate management of AH and AF, especially in cirrhotic population, is essential for optimizing outcomes.



Outcomes	Alcoholic Hepatitis with Atrial Fibrillation (weighted n=27080)		Alcoholic Hepatitis without Atrial Fibrillation (weighted n=27080)		Crude Results		Adjusted results	
	Weighted N	%	Weighted N	%	Odds ratio (95% CI)	p-value	Odds ratio 95% CI)	p-value
In-hospital death	1795	6.6	1400	5.2	1.30 (1.11, 1.53)	**0.0013**	1.29 (1.10, 1.52)	**0.0021**
Blood transfusion	2230	8.2	2435	9.0	0.91 (0.79, 1.04)	0.16	0.92 (0.81, 1.06)	0.25
TIA	35	0.1	40	0.1	0.87 (0.32, 2.42)	0.79	0.87 (0.30, 2.48)	0.79
Clinical Stroke	260	1.0	135	0.5	1.93 (1.22, 3.07)	**0.0052**	1.89 (1.19, 3.00)	**0.0073**
AKI	8420	31.1	7085	26.0	1.27 (1.17, 1.39)	**<.0001**	1.28 (1.17, 1.40)	**<.0001**

Outcomes	Alcoholic Hepatitis with Atrial Fibrillation (weighted n=27080)		Alcoholic Hepatitis without Atrial Fibrillation (weighted n=27080)		Crude Results		Adjusted results*	
	Mean	SE	Mean	SE	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Length of stay (days)	7.39	0.11	6.56	0.10	0.83 (0.56, 1.11)	**<.0001**	0.93 (0.37, 1.49)	**0.0011**
Total hospital charges (dollars)	77330.69	1580.65	62158.20	1289.88	15172.49 (11476.29, 18868.69)	**<.0001**	11845.51 (4673.07, 19017.95)	**0.0012**

Outcomes of patients with alcoholic hepatitis and atrial fibrillation stratified by the presence of cirrhosis

Outcomes	Alcoholic Hepatitis with Atrial Fibrillation and with Cirrhosis (weighted n=9075)		Alcoholic Hepatitis with Atrial Fibrillation and without Cirrhosis (weighted n=17990)		Crude Results		Adjusted results	
	Weighted N	%	Weighted N	%	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
In-hospital death	975	10.7	820	4.6	2.52 (2.03, 3.13)	**<.0001**	2.47 (1.98, 3.09)	**<.0001**
Blood transfusion	1270	14	960	5.3	2.89 (2.38, 3.51)	**<.0001**	2.86 (2.34, 3.49)	**<.0001**
TIA	0	0	35	0.2	NA	NA	NA	NA
Clinical Stroke	40	0.4	220	1.2	0.36 (0.17, 0.76)	**0.0076**	0.38 (0.18, 0.81)	**0.012**
AKI	3480	38.3	4940	27.4	1.64 (1.45, 1.86)	**<.0001**	1.69 (1.49, 1.91)	**<.0001**

Outcomes	Alcoholic Hepatitis with Atrial Fibrillation and with Cirrhosis (weighted n=9075)		Alcoholic Hepatitis with Atrial Fibrillation and without Cirrhosis (weighted n=17990)		Crude Results		Adjusted results*	
	Mean	SE	Mean	SE	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Length of stay (days)	8.32	0.19	6.92	0.13	1.40 (0.97, 1.83)	**<.0001**	1.83 (0.94, 2.73)	**0.0011**
Total hospital charges (dollars)	91646.92	3113.84	70118.54	1647.33	21528.38 (15522.56, 27534.21)	**<.0001**	22150.77 (11578.95, 32722.59)	**0.0012**

Disclosures: The following people have nothing to disclose: Harshavardhan Sanekommu, Sobaan Taj, Jayasree Ravilla, Brett Miller, Alejandro CruzPonce,

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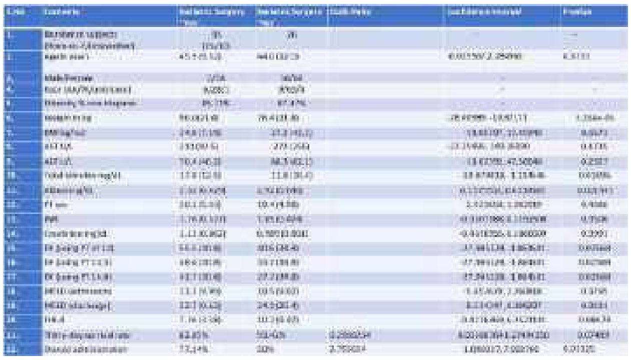
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

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

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

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

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



Disclosures: Amon Asgharpour – Galectin: Consultant, No, No;

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

The following people have nothing to disclose: Marcus Allen Healey, Geetha Ramalingam, Yiwei Hang, Ekaterina Smirnova, Vaishali Patel, Hannah Lee, Scott C. Matherly, Mohammad S. Siddiqui, Joel P. Wedd, Richard K. Sterling

Disclosure information not available at the time of publication: Velimir A. Luketic

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

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

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

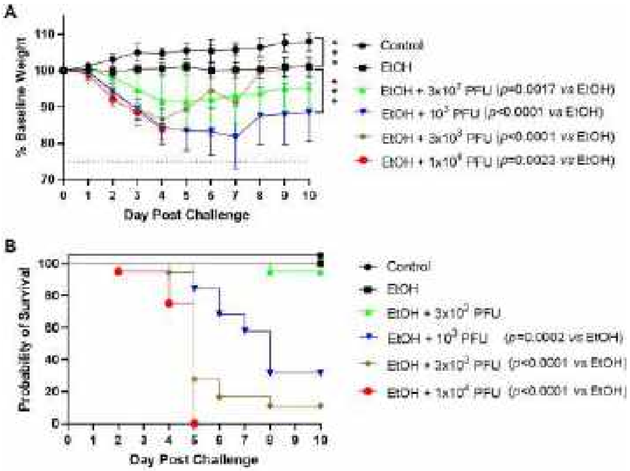


Fig 1. Clinical characteristics of mice receiving variable doses of SARS-CoV-2. **A**. Percentage of initial weight loss. **B**) Survival. The number of mice per group at the time of infection was the following: EtOH (n=14), EtOH+$3x10^2$ PFU (n=20); EtOH+10^3 PFU (n=19); EtOH+$3x10^3$ PFU (n=18); EtOH+$1x10^4$ PFU (n=20). *P* values determined by unpaired Student's *t*-test (weight change) and Mantel-Cox tests (survival).

Disclosures: The following people have nothing to disclose: Smita Ghare, Dennis Warner, Josiah Hardesty, Jeffrey Warner, Paula Chilton, Jiyeon Lee, Jingwen Zhang, Lihua Zhang, Min Wan, Jon Gabbard, Charles Anderson, Lalit Batra, Chithra Sreenivasan, Jennifer Kraenzle, Matthew McCulley, Stephanie McCoy, Dibson Dibe Gondim, Shirish Barve, Wenke Feng, Jian Zheng, Kenneth Palmer, Craig J. McClain, Irina A. Kirpich

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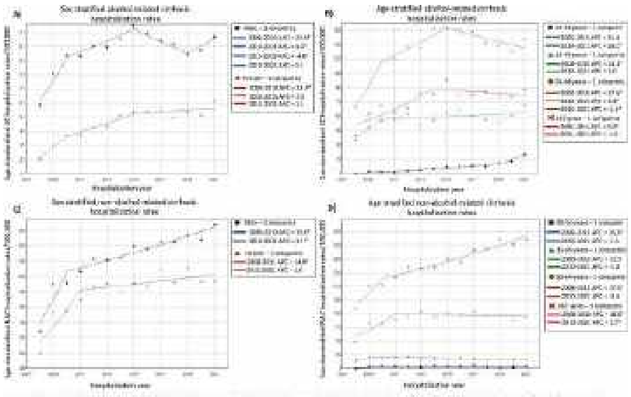
f 3566-C | IMPACT OF THE COVID-19 PANDEMIC ON TEMPORAL TRENDS IN ALCOHOL-RELATED AND NON-ALCOHOL-RELATED CIRRHOSIS HOSPITALIZATIONS: A CANADIAN POPULATION-BASED STUDY.

Liam Andrew Swain[1], *Jenny Godley*[1], *Juan G. Abraldes*[2], *Mayur Brahmania*[3] *and Abdel-Aziz Shaheen*[3], *(1)University of Calgary, (2)University of Alberta, AB, Canada, (3)Cumming School of Medicine, University of Calgary, Calgary, AB, Canada*

Background: Few studies have examined the impact of the COVID-19 pandemic on hospitalization rates for alcohol - (AC) and non-alcohol-related cirrhosis (NAC) separately in relation to age and sex. We aimed to examine sex and age stratified temporal changes in AC and NAC hospitalizations before the pandemic (2008-19) and during the pandemic (2020-21) in Alberta, Canada. **Methods:** We used validated international classification of diseases 10th revision (ICD-10) administrative case definitions to select all adult (≥20 y) AC and NAC hospitalizations from the Discharge Abstract Database (DAD) from April 2008 to March 2021. AC was defined as admissions coded with either the AC ICD-10 code alone, or both an alcohol use disorder (AUD) and decompensated cirrhosis-related condition code together. NAC was defined as admissions with either a NAC or a decompensated cirrhosis-related condition ICD-10 code, excluding all AC, alcohol-related hepatitis (AH), and AUD codes. Age and sex standardized hospitalization rates/100,000 population were calculated using the 2016 Canada Census population estimates for Canada and Alberta. Temporal trends in yearly AC and NAC hospitalization rates were assessed using Joinpoint analysis and annual percent change (APC) stratified according to sex (male/female) and age groups (20-34, 35-49, 50-64, 65+ years). **Results:** We identified 28,884 AC (66% male; median age 55 y) and 40,026 NAC hospitalizations (54% male; median age 64 y) during our study period. Annual AC sex-stratified hospitalizations rates (Fig. 1A) decreased for men from 2015-19 (APC -4%; 95% confidence interval [CI], -7 to -2), and plateaued during the pandemic (2019-21), whereas rates in women were not affected by the pandemic, remaining stable from 2010-21. Age-stratification (Fig. 1B) showed a significant decrease in AC hospitalization rates for the 50-64 age group from 2015-21 (APC -2%; CI, -7 to -0.5]) that was not altered by the pandemic. However, in the 20-34 age group, AC hospitalization rates increased during the pandemic (2019-21; APC 28%; CI, 12-42). AC hospitalization rates remained stable for the 35-49 and ≥65 age groups after 2010 and 2014 respectively, and were not affected by the pandemic. Sex-stratified NAC hospitalization rates (Fig. 1C) were not affected by the pandemic and remained stable in women from 2011-21 but increased in men from 2010-21 (APC 2%; CI 1-3). Age-stratification showed NAC hospitalization rates (Fig. 1D) were not impacted by the pandemic but increased in those ≥65 years from 2010-21 (APC 3%; CI, 1-4), and remained stable for all other age groups from 2011-21. **Conclusion:** AC hospitalization rates among younger patients and men increased during the pandemic. NAC hospitalization rates have steadily increased particularly in men and older patients with no impact of the pandemic on their trajectories.



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

Disclosures: Juan G. Abraldes – Cook: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boehringer Ingelheim: Consultant, No, No; AstraZeneca: Consultant, No, No; 89bio: Consultant, No, No; Inventiva: Consultant, No, No;

Abdel-Aziz Shaheen – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Liam Andrew Swain, Jenny Godley, Mayur Brahmania

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

Paul Thomes[1], Rujani Mahmud[1], Terrence M. Donohue[1], Mark A. McNiven[2] and Carol A. Casey[1], (1) University of Nebraska Medical Center, (2)Mayo Clinic

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

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3568-C | INCIDENCE OF ACUTE KIDNEY INJURY IN PATIENTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS – DATA FROM A MULTICENTER CLINICAL TRIAL OF ANAKINRA PLUS ZINC VS. PREDNISONE

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

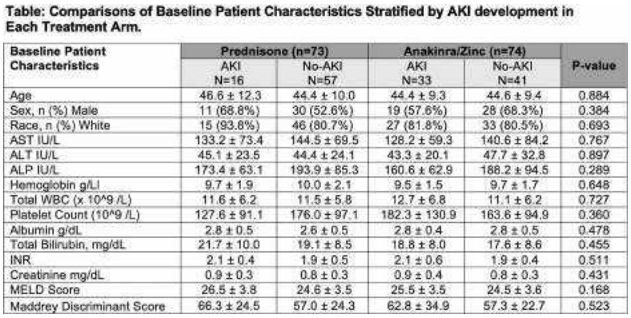

Table: Comparisons of Baseline Patient Characteristics Stratified by AKI development in Each Treatment Arm.

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

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Disclosure information not available at the time of publication: Muhammad Yahya Jan, Qing Tang, Yunpeng Yu, Moyinoluwa Taiwo, Patrick S. Kamath, Mack C. Mitchell, Svetlana Radaeva

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

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

Low-risk SAH patients exhibited the highest clinically significant indicator of liver injury progression (AST: ALT) and lowest LTDH. In SAH, AST:ALT was significantly associated at high effect ($R^2 = 0.539$, $p = 0.031$) with LTDH, AUDIT and CONUT in a multivariable regression model. In SAH with intermediate risk of mortality, AST:ALT was influenced by CONUT and LTDH at a high significant effect ($R^2 = 0.657$, $p = 0.017$). **Conclusion:** SAH exhibits rapid liver injury progression when mortality risk is still low. The interplay of chronic and recent heavy drinking, and nutrition has a pivotal role in liver injury severity in SAH. Engaging checkpoint assessments for chronic and heavy drinking and nutritional status can help strategize preemptive medical management in SAH patients at high mortality risk.

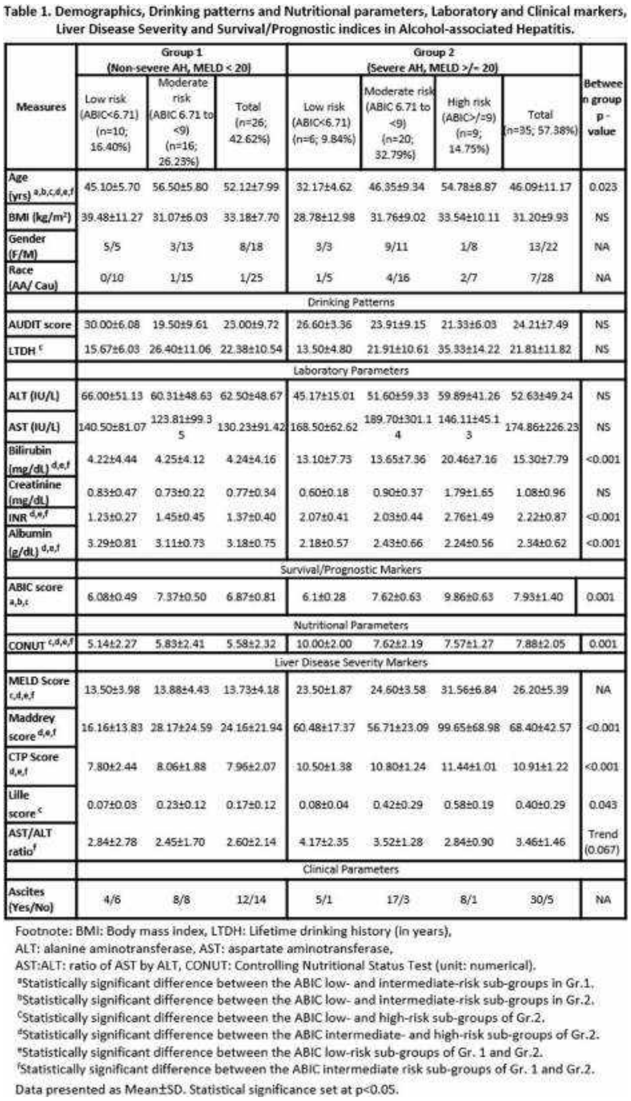

Table 1. Demographics, Drinking patterns and Nutritional parameters, Laboratory and Clinical markers, Liver Disease Severity and Survival/Prognostic indices in Alcohol-associated Hepatitis.

Measures	Group 1 (Non-severe AH, MELD < 20)			Group 2 (Severe AH, MELD >/= 20)				Between group p-value
	Low risk (ABIC<6.71) (n=10; 16.40%)	Moderate risk (ABIC 6.71 to <9) (n=16; 26.23%)	Total (n=26; 42.62%)	Low risk (ABIC<6.71) (n=6; 9.84%)	Moderate risk (ABIC 6.71 to <9) (n=20; 32.79%)	High risk (ABIC>/=9) (n=9; 14.75%)	Total (n=35; 57.38%)	
Age (yrs) ^{a,b,c,d,e,f}	45.10±5.70	56.50±5.80	52.12±7.99	32.17±4.62	46.35±9.34	54.78±8.87	46.09±11.17	0.023
BMI (kg/m²)	39.48±11.27	31.07±6.03	33.18±7.70	28.78±12.98	31.76±9.02	33.54±10.11	31.20±9.93	NS
Gender (F/M)	5/5	3/13	8/18	3/3	9/11	1/8	13/22	NA
Race (AA/ Cau)	0/10	1/15	1/25	1/5	4/16	2/7	7/28	NA
	Drinking Patterns							
AUDIT score	30.00±6.08	19.50±9.61	25.00±9.72	26.60±3.36	23.91±9.15	21.33±6.03	24.21±7.49	NS
LTDH ^{c}	15.67±6.03	26.40±11.06	22.38±10.54	13.50±4.80	21.91±10.61	35.33±14.22	21.81±11.82	NS
	Laboratory Parameters							
ALT (IU/L)	66.00±51.13	60.31±48.63	62.50±48.67	45.17±15.01	51.60±59.33	59.89±41.26	52.63±49.24	NS
AST (IU/L)	140.50±81.07	123.81±99.35	130.23±91.42	168.50±62.62	189.70±301.14	146.11±45.13	174.86±226.23	NS
Bilirubin (mg/dL) ^{d,e,f}	4.22±4.44	4.25±4.12	4.24±4.16	13.10±7.73	13.65±7.36	20.46±7.16	15.30±7.79	<0.001
Creatinine (mg/dL)	0.83±0.47	0.73±0.22	0.77±0.34	0.60±0.18	0.90±0.37	1.79±1.65	1.08±0.96	NS
INR ^{d,e,f}	1.23±0.27	1.45±0.45	1.37±0.40	2.07±0.41	2.03±0.44	2.76±1.49	2.22±0.87	<0.001
Albumin (g/dL) ^{d,e,f}	3.29±0.81	3.11±0.73	3.18±0.75	2.18±0.57	2.43±0.66	2.24±0.56	2.34±0.62	<0.001
	Survival/Prognostic Markers							
ABIC score ^{a,b,c}	6.08±0.49	7.37±0.50	6.87±0.81	6.1±0.28	7.62±0.63	9.86±0.63	7.93±1.40	0.001
	Nutritional Parameters							
CONUT ^{c,d,e,f}	5.14±2.27	5.83±2.41	5.58±2.32	10.00±2.00	7.62±2.19	7.57±1.27	7.88±2.05	0.001
	Liver Disease Severity Markers							
MELD Score ^{c,d,e,f}	13.50±3.98	13.88±4.43	13.73±4.18	23.50±1.87	24.60±3.58	31.56±6.84	26.20±5.39	NA
Maddrey score ^{d,e,f}	16.16±13.83	28.17±24.59	24.16±21.94	60.48±17.37	56.71±23.09	99.65±68.98	68.40±42.57	<0.001
CTP Score ^{d,e,f}	7.80±2.44	8.06±1.88	7.96±2.07	10.50±1.38	10.80±1.24	11.44±1.01	10.91±1.22	<0.001
Lille score ^{c}	0.07±0.03	0.23±0.12	0.17±0.12	0.08±0.04	0.42±0.29	0.58±0.19	0.40±0.29	0.043
AST/ALT ratio ^{f}	2.84±2.78	2.45±1.70	2.60±2.14	4.17±2.35	3.52±1.28	2.84±0.90	3.46±1.46	Trend (0.067)
	Clinical Parameters							
Ascites (Yes/No)	4/6	8/8	12/14	5/1	17/3	8/1	30/5	NA

Footnote: BMI: Body mass index, LTDH: Lifetime drinking history (in years),
ALT: alanine aminotransferase, AST: aspartate aminotransferase,
AST:ALT: ratio of AST by ALT, CONUT: Controlling Nutritional Status Test (unit: numerical).
[a] Statistically significant difference between the ABIC low- and intermediate-risk sub-groups in Gr.1.
[b] Statistically significant difference between the ABIC low- and intermediate-risk sub-groups in Gr.2.
[c] Statistically significant difference between the ABIC low- and high-risk sub-groups of Gr.2.
[d] Statistically significant difference between the ABIC intermediate- and high-risk sub-groups of Gr.2.
[e] Statistically significant difference between the ABIC low-risk sub-groups of Gr. 1 and Gr.2.
[f] Statistically significant difference between the ABIC intermediate risk sub-groups of Gr. 1 and Gr.2.
Data presented as Mean±SD. Statistical significance set at $p<0.05$.

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3570-C | LIVER SPECIFIC GLOMERULAR FILTRATION RATE EQUATIONS PROVIDE MODEST IMPROVEMENT IN 28-DAY OUTCOME PREDICTION IN ALCOHOL-ASSOCIATED HEPATITIS

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Background: MELD is commonly used to determine disease severity and mortality risk in alcohol-associated hepatitis (AH). AH patients often demonstrate elevated serum bilirubin, and hyperbilirubinemia can interfere with serum creatinine (sCr) assays. In addition, sCr is related to muscle mass and may misclassify glomerular filtration rate (GFR) due to gender differences in body composition. Aims: 1) to compare the performance of generalized and liver-specific GFR models in patients with AH, and 2) assess GFR-based liver disease models for outcome prediction in AH. **Methods:** this was a retrospective study of patients hospitalized with probable or definite AH from January 2016 to March 2020 at the University of Pittsburgh Medical Center (N = 205) and University of California Davis (N = 181). Clinical, demographic and laboratory data were obtained at admission. GFR was assessed using general models including Chronic Kidney Disease Epidemiology (CKD-EPI), modification of diet in renal disease-4 (MDRD-4), and European Kidney Function Consortium (EKFC) equations as well as liver-specific models including Royal Free Hospital (RFH) and GFR assessment in liver disease (GRAIL) equations. AUROC analysis was used to compare performance of GFR-based liver function models (GRAIL-MELD, GEMA) and MELD for predicting 28-day survival. **Results:** 174 (55.6%) women and 212 (44.4%) men were included. In patients with bilirubin < 20 mg/dl, GFR estimated by GRAIL was consistently greater than GFR estimated by other models, while estimated GFR were similar between models for bilirubin ≥ 20 mg/dl. In patients with sCr < 1.5 mg/dl, sCr [0.86 (IQR 0.70 – 1.01 mg/dl vs 0.70 (0.54-0.90) mg/dl, p = 0.001] and GFR by GRAIL [112.3 (IQR 98.5 – 129.5 ml/min/1.73m^2) vs 106.6 (91.6-123.5 ml/min/1.73m^2,p = 0.0359] were higher in men, while all other models demonstrated no significant gender differences in GFR. In patients with sCr ≥ 1.5 mg/dl, there were no significant gender differences in GFR or sCr. MELD was increased in men compared to women [24 (19-31) vs. 22 (19-27), p = 0.011], but there were no significant gender differences in MELD-GRAIL [22 (17-28) vs 20 (17-26), p = 0.1166] or GEMA [22 (17-28) – 19 (16-26), p = 0.0673]. In the whole patient population, MELD-GRAIL demonstrated slightly higher accuracy compared to MELD and GEMA for 28-day survival [0.813 (95% CI 0.759 – 0.867) vs 0.781 (0.721 – 0.842) vs 0.786 (0.724-0.847),

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

p = 0.042] with sensitivity of 0.81 and specificity 0.72 at an optimal cutoff of 24. In women, there were no significant differences in model accuracy. In men, MELD-GRAIL demonstrated a trend toward greater accuracy compared to MELD and GEMA [0.826 (95% CI 0.758 – 0.895) vs 0.792 (0.717 – 0.867) vs.0.792 (0.713 – 0.871), p = 0.071]. **Conclusion:** GFR models vary widely with serum bilirubin levels. MELD-GRAIL and GEMA models exhibit reduced gender variation, and MELD-GRAIL exhibits slightly increased accuracy for 28-day mortality in AH.

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3571-C | LIVER TRANSPLANT ACTIVITY FOR ALCOHOL-ASSOCIATED HEPATITIS AFTER OPTN DIAGNOSIS UPDATES

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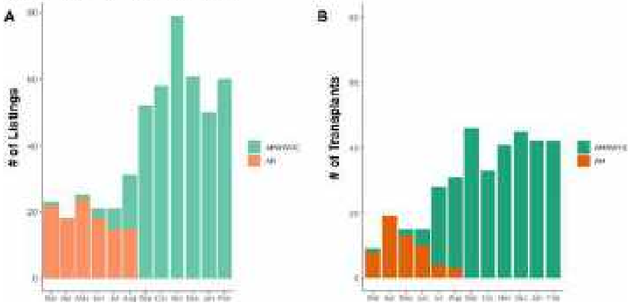
Background: Diagnosis codes for alcohol-associated liver disease (ALD) and specifically alcohol-associated hepatitis (AH) in the OPTN registry have been inconsistent, with only an estimated 35% of patients being correctly designated as AH. In response, the OPTN proposed to update the alcohol-related diagnoses to allow for more accurate and complete data collection regarding ALD transplant activity in the United States. This policy was implemented on August 30, 2022. We analyze temporal trends in diagnosis reporting for ALD, including AH, comparing the 6 months before and after this policy change. **Methods:** We reviewed new adult registrations and transplants in the OPTN registry from 3/1/2022 to 2/28/2023. On 8/30/2022, the diagnosis code for “Acute alcoholic hepatitis” [AH] (4217) was replaced by “Acute alcohol-associated hepatitis with or without cirrhosis” [AHWWOC] (4218) . In parallel, the diagnosis code for “Alcoholic cirrhosis” [AC] (4215) was replaced by “Alcohol associated cirrhosis without acute alcohol associated hepatitis” (4219). We evaluated national trends in listings and transplants with a primary diagnosis of ALD based on these diagnosis codes. **Results:** There were 12,825 new registrations, of which 460 (3.6%) were for AH and 4430 (34.5%) were for AC. Before the diagnosis update, 5.1% of listings for ALD were classified as AH (4217), compared to 13.5% as AHWWOC (4218) after the update (Figure A). Patients listed under the new diagnosis code for AH had a lower MELD score at listing (37 v 32, p < 0.01), were older (46 v 41 y, p < 0.01), and were less likely to be white (71.0% v. 77.7%, p = 0.047) compared to the previous diagnosis code for AH. Using the new diagnosis codes, patients with AH had higher MELD (32 v 24, p < 0.01), were younger (46 v 54, p < 0.01), and were more likely to be privately insured (60.8% v 54.4%, p = 0.004) compared to those with AC. There were 9,176 transplants, 366 (4.0%) for AH and 2948 (32.1%) for AC — 4.6% of transplants for ALD were classified as AH (4217), compared to 14.9% as AHWWOC (4218) (Figure B). Using the new diagnosis codes, AH transplants used younger donors (36 v 40 y, p = 0.02) and were less likely to use DCD donors (4.2% v 10.5%, p = 0.001) compared to AC transplants. **Conclusion:** We observed a 3-fold increase in reported AH cases after update to the OPTN diagnosis codes for ALD, with greater representation of older and non-white populations. AH patients appear distinct from the general ALD population in terms of candidate selection as well as the donors they receive. Wider education regarding the appropriate use of diagnosis codes and standardized disease definitions will contribute to a more complete and accurate national registry database and enhance future analyses.

Figure. Monthly (A) listings and (B) transplants for alcohol-associated hepatitis (AH) in the United States from 03/01/2022 to 02/28/2023 as designated in the OPTN registry. Updated diagnosis codes for AH were implemented on 8/30/2022. AH = Acute alcoholic hepatitis (4217); AHWWOC = Alcohol-associated hepatitis with or without cirrhosis (4218)



Disclosures: Scott W. Biggins: Scott Biggins, Allison J. Kwong

3572-C | LIVER VOLUME PREDICTS MORTALITY IN ALCOHOL ASSOCIATED LIVER DISEASE

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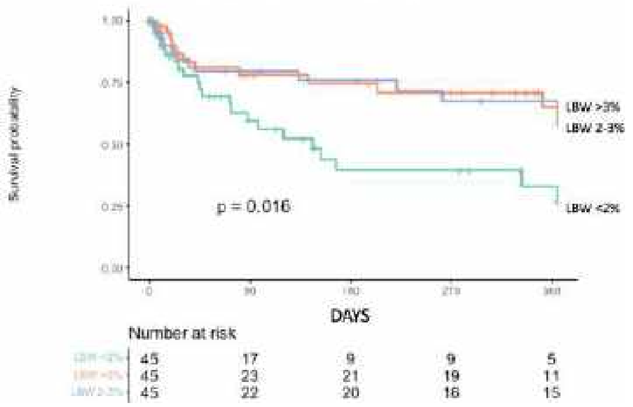
Background: Alcohol-associated liver disease (ALD) presents as a spectrum, ranging from fatty liver to decompensation with jaundice and advanced cirrhosis. Steatosis, hepatocellular injury, and inflammation may be reflected on cross-sectional imaging as diffuse enlargement of the liver, and progression of ALD, and over time may result in parenchymal atrophy with fibrosis and cirrhosis. The evidence linking radiological parameters such as liver volume with outcomes in ALD is limited. We hypothesized that increased liver volume in patients presenting with decompensated ALD could reflect hepatic reserve and predict survival. **Methods:** We identified patients hospitalized at our center between 2018 and 2022 who had decompensated ALD and alcohol use within the past 6 months and included those who had CT imaging performed during the index admission. Liver volumes were obtained using manual segmentation. A linear regression was used to assess the relationship between liver volume and anthropometric variables, as well as time since last alcohol use. We used multivariable Cox regression analysis to evaluate the association between liver volume and 1-year transplant-free survival, adjusted for the MELD-Na score. **Results:** There were 136 patients with a median age of 44 years (IQR 38-52), median BMI of 29.2 (IQR 24.9-33.6), and median MELD-Na of 32 (IQR 25-38). Forty-nine patients (36%) were transplanted, 46 patients (34%) died, and 41 patients (30%) were alive at the end of follow-up. The median liver volume was 2216 cm^3 (IQR 1481-3124). Increased weight was associated with increased liver volume, whereas sex, height, and time since last alcohol use were not. A standardized metric of liver-body weight ratio was used to predict outcome, with increased liver-body weight ratio being predictive of transplant-free survival in a bivariate model adjusted for MELD-Na (HR 0.96, 95% CI 0.94-0.98). A liver-body weight ratio < 2% was associated with an increased risk of death, with a 1-year transplant-free survival of 26.3% at 1 year p = 0.016 (Figure). **Conclusion:** Opportunistic CT measurements of imaging done for other clinical purposes may provide valuable prognostic information. In this high-MELD population with ALD, greater liver volume was predictive of transplant-free survival independent of MELD-Na. Volumetric measurements of the liver may be used to risk stratify patients with decompensated ALD and identify those with the potential for hepatic recovery without liver transplantation. Automated segmentation of liver imaging may enable more widespread use of liver volume as a clinical predictor in ALD.

Figure. Kaplan-Meier survival curve for 1-year mortality, stratified by liver-body weight (LBW) ratio, with censoring for liver transplantation.



Disclosures: The following people have nothing to disclose: Richie Manikat, Allison J. Kwong

Disclosure information not available at the time of publication: Weiyu Wu, Paul Yien Kwo, Nishita Kothary, Akshay Chaudhari

f 3573-C | LONG NONCODING RNA H19 MEDIATES ALCOHOL-ASSOCIATED LIVER DISEASE THROUGH ITS BINDING TO PTBP1 RESULTING IN AN ALTERNATIVE SPLICING OF BHMT AND DYSREGULATION OF METHIONINE METABOLISM

Zhihong Yang[1], Jing Ma[1], Nazmul Huda[1], Yanchao Jiang[1], Hui Gao[1] and Suthat Liangpunsakul[2,3], (1) Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, in, (2)Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, (3)Roudebush Veterans Administration Medical Center, Indianapolis, in

Background: Alcohol-associated liver disease (ALD) is a prevalent liver disorder with no effective treatment. LncRNA H19 (H19), a paternal imprinted lncRNA with its expression only in maternal allele, has been implicated in various diseases. However, its role in ALD pathogenesis remains elusive. We conducted a translational study to explore the mechanism of H19 in ALD pathogenesis. **Methods**: H19 levels were examined in liver tissues from healthy controls (HC, n = 21), alcoholic hepatitis (AH,n = 5), and alcoholic cirrhosis (AC,n = 32) patients. For mechanistic studies, H19 maternal specific knock out ($H19^{Mat+/-}$) and overly expressed hepatic H19 ($H19^{Hep\text{-}OE}$, using AAV8, with a liver specific TBG promoter) mice were used for the gain or loss of function studies. Mice were subjected to chronic plus binge ethanol feeding model. **Results**: Hepatic H19 level was significantly increased in patients with AH and AC compared to HC. In chronic plus binge alcohol feeding model, hepatic H19 level was highly increased in ethanol-fed mice. Overexpression of hepatic *H19* worsened alcohol-induced steatosis and promoted liver injury with significant increase in serum transaminase. Alcohol-induced steatosis and liver injury were ameliorated in ethanol-fed $H19^{Mat+/-}$ mice. To dissect the mechanism, we performed the metabolomic analysis and found a significant reduction of hepatic methionine in $H19^{Hep\text{-}OE}$ mice. We examined each enzyme involving in methionine metabolism and found a marked reduction in betaine-homocysteine methyltransferase (BHMT) expression, a key enzyme in converting betaine and homocysteine to methionine. LncRNAs regulate coding genes by its interaction with specific protein. Using an RNA pull-down with biotin-

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labeled H19, we found an interaction between H19 and PTBP1, an RNA-binding protein regulating alternative splicing. Intriguingly, the interaction of H19-PTBP1 led to an increase in the splice variant, Bhmt202, which lacks protein coding ability and a decrease in BHMT protein coding isoform, Bhmt201, causing a reduction in BHMT protein and methionine level (See Fig. 1). The restoration of hepatic BHMT using AAV-BHMT ameliorated alcohol-induced liver injury in *H19*$^{Hep\text{-}OE}$ mice. **Conclusion**: H19-PTBP1 mediates alternative splicing of BHMT, leading to an increase in the splice variant with limited protein coding ability, a reduction in hepatic methionine, and alcohol-induced liver injury. H19-PTBP1-BHMT axis is a potential therapeutic target for ALD.

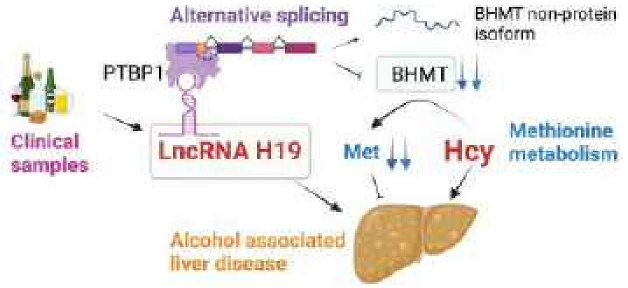

Figure 1: A schematic diagram represents the molecular mechanism of the long non-coding RNA (lncRNA) H19 in regulating alcohol-associated liver disease (ALD). Alcohol intake triggers an upregulation of H19 expression. H19 interacts with PTBP1, resulting in the disruption of alternative splicing of BHMT, a key enzyme in methionine metabolism. This disruption leads to an increase in the non-protein isoform of BHMT and an inhibition of the BHMT protein isoform, leading to a decline in methionine (Met) levels and alcohol-induced liver injury. H19-PTBP1-BHMT axis is a potential therapeutic target for ALD.

Disclosures: Suthat Liangpunsakul – Surrozen: Consultant, No, No; Durect: Consultant, No, No;
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3574-C | METABOLIC PERTURBATION IN ALCOHOLIC FATTY LIVER PRIMES HEPATOCYTE INJURY THROUGH DISCORDANT TRANSMISSION OF TRANSCRIPTOME ALTERATIONS TO PROTEOME

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Background: Alcohol fatty liver (AFL) and nonalcoholic fatty liver (NAFL), the initial stages of alcoholic and nonalcoholic fatty liver disease, respectively, serve as the prerequisites for disease progression to their advanced stages. ALF and NAFL are histologically identical, share genetic risk factors, and are distinguished solely by clinical context. Thus, it remains undefined whether they represent distinctive or shared pathophysiology, the elucidation of which entails a physiological, human-relevant study model. **Methods:** Human hepatocytes (HH), either primary or humanized liver chimeric mice (HLCM)- derived, were cultured for 7 days in medium containing DMSO and other hepatocyte-specific supplements to facilitate recovery from cellular stress triggered by the procurement process and to maintain the cell fate of matured hepatocyte. The HH were then treated for 7 days with either ethanol or free fatty acid-sugar cocktail to establish in vitro models of AFL and NAFL, during which time DMSO was replaced with DMSO2 due to its potent inhibitory effect on multitude of hepatic functions. HH of AFL and NAFL were applied for mRNA-seq, ribosome profiling, and quantitative proteomics to decipher the dynamics between the transcriptome, translatome, and proteome. The results obtained with in vitro studies were validated through in vivo experiments with HLCM. **Results:** In vitro cultured HH metabolized alcohol at a rate equivalent to those in the human liver. Moreover, HH treated with alcohol, or a free fatty acid-sugar cocktail developed a comparable level of macrovesicular steatosis. Despite the identical cellular morphology, the mRNA-seq analysis revealed substantial differences in the number and type of differentially expressed genes, with a small proportion of genes exhibiting overlap. Furthermore, polysome profiling studies demonstrated a significant dissociation of ribosomes from mRNAs in AFL-HH but not with NAFL, indicating that the metabolic stress in AFL induces global translatome suppression. Subsequent studies showed that the translatome inhibition is largely due to a defect in translation elongation rather than translation initiation. We also found that translatome inefficiency contributes to the development of cell toxicity. **Conclusion:** Our work revealed a marked inhibition of translatome and consequential discordance between transcriptome and proteome in HH of AFL, revealing a previously unrecognized mechanism of cell toxicity in alcoholic liver disease.

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individual's institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
The following people have nothing to disclose: Go Sugahara, Meng Li, Yuji Ishida, Jae-Jin Lee, Hyungjin Eoh, Chise Tateno, Takeshi Saito
Disclosure information not available at the time of publication: Hayato Muranaka

f 3575-C | N3 PUFA SUPPLEMENTATION ATTENUATES ENDOTOXEMIA AND LIVER INJURY IN EARLY STAGE OF ALCOHOL-ASSOCIATED LIVER DISEASE

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Background: Early-stage alcohol-associated liver disease (ES-ALD) is often defined as an elevated ALT level in the setting of heavy drinking. We and others have reported that ~35-60% of heavy drinking patients with alcohol use disorder (AUD) in alcohol treatment programs have elevated liver enzymes and ES-ALD. ALD pathogenesis is influenced by multiple factors including dietary fatty acids. Preclinical studies in mice showed that n3 PUFA supplementation or endogenous increase in n3 PUFAs attenuated experimental ALD. The goal of the current study was to examine the effects of n3 PUFA supplementation on liver injury and intestinal permeability in a human population of heavy drinking individual's. **Methods:** Individual's with AUD were admitted to an NIH inpatient treatment program for 21 days. At discharge, subjects were randomized to either 2 g/day of n3 PUFAs (EPA+DHA, n = 46) or placebo (n = 48) for 12 weeks. The cerebrospinal fluid (CSF) fatty acid profile, plasma markers of liver injury (ALT, AST, and GGT) and endotoxemia were evaluated at randomization (baseline = hospital discharge) and at the conclusion of the study. Significant differences were determined by paired Student's *t* test ($p < 0.05$). **Results:** The targeted lipidomic analysis revealed that 12-week n3 PUFA supplementation resulted in significant increase in CSF n3 PUFAs EPA and DHA, which was not a case in a placebo group (Fig. 1A-B), suggesting the adherence of the study participants to the treatment protocol. Compared to placebo, n3 PUFA supplementation was associated with a substantial reduction in ALT, GGT but not AST levels among the whole patient cohort (Fig.1-C-D). In those patients (37%) who had ES-ALD at the time of randomization (based on ALT > 40 U/L), n3 PUFA supplementation was associated with a significant reduction in all three enzymes, ALT, AST and GGT. As an indirect marker of intestinal permeability, endotoxin levels were unchanged in the n3 PUFA supplemented group over the course of the study, but there was a significant increase in the placebo arm. There was a greater return to drinking in the placebo arm, which could have influenced both liver injury and endotoxemia. **Conclusion:** Our data suggested that n3 PUFA supplementation in heavy drinking individual's had beneficial effects on liver injury and endotoxemia. Further investigations are needed on the mechanistic role of n3 PUFAs in the pathogenesis of ALD, and possibly AUD.

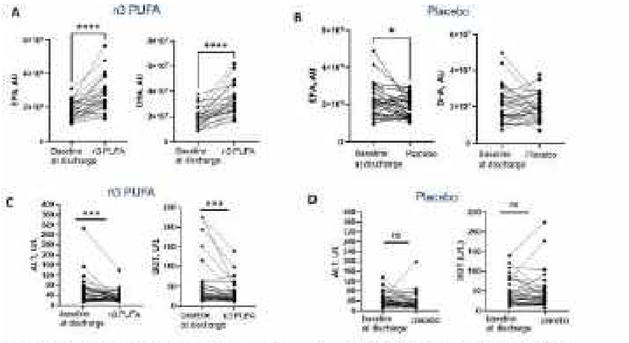

Fig. 1.: Targeted lipidomic analysis and evaluation of liver injury in heavy drinking individuals randomized to n3 PUFA supplementation or placebo arm. Cerebrospinal fluid n3 PUFAs, EPA and DHA (A-B), and plasma ALT and GGT levels (C-D) in patients at baseline (at discharge from alcohol treatment program) and after 12-week n3 PUFA supplementation. n=46 (n3 PUFA group [2 g/day EPA+DHA], and n=48 (placebo group. Paired Student's t test *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Disclosures: The following people have nothing to disclose: Alison Floyd, Jeffrey Warner, Josiah Hardesty, Dennis Warner, Joe Hibbeln, Craig J. McClain, Irina A. Kirpich

3576-C | NEUTROPHILS-TO-LYMPHOCYTES RATIO ASSOCIATES WITH OUTCOME AND ETIOLOGY OF ACUTE DECOMPENSATION OF ADVANCED CHRONIC LIVER DISEASE

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Background: The neutrophil-to-lymphocyte ratio (NLR) has been introduced in critical care medicine as an indicator of systemic inflammation (1). In the same vein, in patients with acute decompensation (AD) of advanced chronic liver disease (ACLD) and in

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acute-on-chronic liver failure (ACLF), NLR has emerged as promising predictor of survival (2,3). Albeit NLR maintains its predictive value across the spectrum of ACLD etiologies, more granular data on NLR values by etiology is scarce. Aim: In this registry study, we aimed to investigate predictive value of NLR in AD/ACLF and to see if NLR values differ according to etiology of ACLF. **Methods:** Since 2014, the cirrhosis registry RH7 (NCT04767945) has been enrolling consecutive consenting adults admitted to tertiary liver unit with ACLD. For the purpose of this study, we have identified (per protocol) patients with AD/ACLF based on EF-CLIF criteria. The cohort was then divided into three etiological groups: viral, alcoholic, and "other." We compared NLR on admission (NLR-0) and on day 7 of hospital stay (NLR-7) within each etiological group and, evaluated association of NLRs with mortality at days 28, 90, and at one year. We adopted NLR > 3 and NLR > 6 as the upper limit of normal range and upper limit of grey zone, respectively. **Results:** From 1109 patients in RH7 as of May, 2020, 283 have been identified with AD: 73.1% with alcohol-associated liver disease (ALD), 7.8% with viral hepatitis, and 19.1% with other etiologies. The average age was 51.3 years, 41% were females. NLR-0 and NLR-7 values were determined for 283 and 186 patients, respectively. Elevated NLR-0 and NLR-7 values were observed in 77.4% and 74.2% of patients, respectively. NLR-0 values were significantly higher in patients with alcoholic etiology (80.2%) compared to viral (50%) and "other" etiologies (77.8%) ($p < 0.01$). Both NLR-0 and NLR-7 values were significantly lower in survivors compared to non-survivors in all three etiological groups ($p < 0.01$); in multivariate regression analysis adjusted for usual predictors of survival in AD/ACLF, NLR was independent predictor of mortality ($p < 0.001$). There were no significant differences between NLR-0 and NLR-7 values. **Conclusion:** Three of four patients admitted with AD/ACLF have elevated baseline NLR which lends support to the immuno-pathogenesis of this syndrome. Elevated NLR-0 and NLR-7 values were associated with increased mortality, regardless of the etiology of AD/ACLF; in closer view however, NLR differed according to etiology and was highest in ALD. Dynamics of NLR over the first week of AD/ACLF has been negligible and delta NRL contributed no additional prognostic value. NLR can be considered an independent prognostic marker of AD/ACLF, providing insight in the immuno-pathophysiology of AD/ACLF and teasing us to be levered as a therapeutic target.

Disclosures: Lubomir Skladaný – ABBVIE: Speaking and Teaching, No, No; Gilead: Speaking and Teaching, No, No; ProMed: Speaking and Teaching, No, No; Worwag: Speaking and Teaching, No, No;

The following people have nothing to disclose: Daniel Ján Havaj, Svetlana Adamcova Selcanova, Juan Pablo Arab

Disclosure information not available at the time of publication: Daniela Žilinčanová, Natalia Bystrianska, Peter Jarčuαka

3577-C | NEW ROLE OF CALPAIN ACTIVITY IN EXPERIMENTAL ALCOHOL-RELATED LIVER DISEASE

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Background: Although the progression of alcohol-related liver disease (ALD) is well documented, there is still need for new approaches to prevent and treat this disease in at-risk individual's. We showed previously that the pattern of degraded proteins in plasma samples from experimental and human ALD differs dramatically from healthy livers; informatic analysis suggested robust elevated activation of the cysteine proteases Calpains 1 and/or 2 (Capn1/2) in both human and experimental ALD. Although Calpain 1/2 have been identified as key players of inflammation and remodeling in other organs, they have not been investigated in ALD. The purpose of the current study was to investigate the impact of targeted disruption of hepatic Calpain 1/2 activity in a preclinical mouse model of ALD. **Methods:** Mice were injected with recombinant adeno-associated virus type 8 vectors (rAAV8; 1×10^{11} PFU/mouse, i.p.) encoding shRNA against Capn4 (*Capns1*; a shared regulatory subunit of Capn1/2), or control scrambled rAAV8 vectors. Mice were subsequently given ethanol diet or control (PF) for 10 days with additional gavage 'binge' of alcohol on day 11, according to the NIAAA model. Tissue and RNA were extracted for further analysis. Major endpoints were assessed by histology, biochemical analyses and/or gene expression. **Results:** rAAV8-mediated knockdown of Capn4 mediated a robust and stable suppression of hepatic *Capns1* expression, coupled with a nearly complete abrogation of detectable Capn1/2 enzyme activity. As expected, ethanol feeding caused robust inflammatory liver injury, characterized by steatosis, inflammation and cell death. Capn4 knockdown significantly attenuated lipid accumulation caused by alcohol as evidenced by histologic and biochemical assessment of lipids (e.g., FFA and TG). Despite these protective effects against alcohol-induced steatosis, Capn4 knockdown did not attenuate the increases in plasma transaminases caused by alcohol. Interestingly, Capn4 knockdown led to a more robust accumulation of neutrophils (PMN) after alcohol exposure, as well as hepatic expression of *Ly6g* mRNA. **Conclusion:** Taken together, these results identify previously unidentified roles of Calpain activity in alcohol-related liver disease. Specifically, these results indicate that Calpain activity plays a key role in lipid accumulation caused by alcohol. However, rAAV8 knockdown of Capn4 enhanced neutrophil accumulation after alcohol and thereby did not protect against overall indices of liver injury. Since calpain activity has previously been shown to contribute to neutrophil apoptosis, a more targeted delivery of Capn1/2 inhibitors may therefore confer protective effects in ALD.

Disclosures: The following people have nothing to disclose: Jiang Li, Juliane I. Beier, Panagiotis V. Benos, Michael Merchant, Gavin E. Arteel

Disclosure information not available at the time of publication: Olivia B. Bannister, Charis-Marie Vanderpuye, Gina Wang

3578-C | NOGO-B (RETICULON 4B) DELETION PROMOTES ANTI-INFLAMMATORY MACROPHAGE POLARIZATION AND PROTECTS AGAINST ALCOHOL-INDUCED LIVER INJURY

Yilin Yang[1], Nao Kawaguchi[2], Jain Jeong[2], Yu Jun[3], Matthew McConnell[1], Teruo Utsumi[4] and Yasuko Iwakiri[2], (1)Yale University, New Haven, CT, (2)Yale School of Medicine, New Haven, CT, (3)Temple University, (4)VA Connecticut Health Care

Background: Nogo-B (a.k.a., Reticulon 4B) is an endoplasmic reticulum (ER) resident protein and maintains ER tubular structure. Macrophage Nogo-B correlates with the severity of liver injury in patients with alcohol-associated liver disease (ALD). We hypothesized that macrophage Nogo-B deletion would ameliorate ALD by reducing macrophage-mediated inflammation. **Methods:** Macrophage-specific Nogo-B knockout (NGB Mϕ KO) mice and littermate wild-type (WT) control ($\text{Nogo-B}^{f/f}$) mice were fed chow or high-fat diet (HFD, 60% kcal% fat) for 3 months, followed by single maltose or ethanol gavage (5 g/kg body weight). Primary bone marrow-derived macrophages (BMDM) and Kupffer cells were isolated from Nogo-B KO and their age-matched littermate WT mice. **Results:** NGB Mϕ KO mice ($n = 10$) showed a 40% lower ALT level ($p < 0.01$), 30% decreased neutrophil infiltration ($p < 0.01$), and decreased expression of pro-inflammatory cytokines, including TNF-α (75% decrease, $p < 0.05$), IL-1β (85% decrease, $p < 0.01$) and IL-6 (80% decrease, $p < 0.01$), compared to WT mice ($n = 9$) in response to HFD with alcohol. Mechanistically, we hypothesized that altered ER structure due to Nogo-B KO promotes macrophages to be pro-inflammatory type. Structural analysis of macrophage ER using fluorescent microscopy and transmission electron microscopy (TEM) indicated that Nogo-B KO increased sheet ER structure with decreased tubular ER (1.12-fold, $p < 0.05$). When we knockdown REEP5 (another ER tubular protein), similar to NGB KO, sheet ER was increased with diminished tubular ER (1.2-fold, $p < 0.01$) in BMDM. Further, REEP5 suppression inhibited pro-inflammatory polarization by decreasing IL-6 (44%, $p < 0.001$), IL-1β (15%, $p < 0.05$) and TNF-α (45%, $p < 0.001$) in BMDM, similar to NGB KO, suggesting structural alteration of ER (increased sheet to tubular ER ratio) leads to anti-inflammatory macrophage polarization. TEM analysis also showed NGB KO reduced tubular ER-mitochondria contacts (45% decrease, $p < 0.001$) and restored mitochondrial size (1.7-fold, $p < 0.001$) in LPS-treated BMDM. Further, Seahorse analysis indicated that decreased ER-mitochondria contact protected mitochondrial function (respiration rate) (1.9-fold increase, $p < 0.01$) compared to WT macrophages, suggesting a mechanistic link between ER-mitochondrial contact, metabolic alteration, and macrophage polarization. **Conclusion:** Our data supports a mechanistic role for Nogo-B as a molecular switch that functions via modulation of ER structure and metabolic function to promote an anti-inflammatory macrophage phenotype and protect against ALD. Nogo-B may therefore serve as a novel therapeutic target for the treatment of ALD.

Disclosures: The following people have nothing to disclose: Yilin Yang, Jain Jeong, Matthew McConnell, Yasuko Iwakiri

Disclosure information not available at the time of publication: Nao Kawaguchi, Yu Jun, Teruo Utsumi

3579-C | NON-CODING RNA DYSREGULATION IS ASSOCIATED WITH DISEASE SEVERITY IN ALCOHOLIC HEPATITIS

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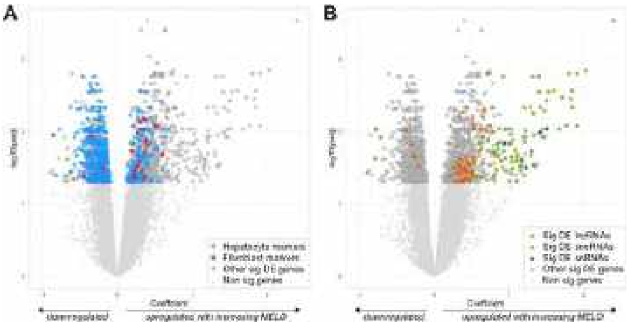
Background: Alcoholic hepatitis (AH) has a high mortality rate; however, disease mechanisms are still poorly understood. We profiled hepatic gene expression of patients with varying AH severity, to define molecular mechanisms of AH. **Methods:** Baseline liver tissue biopsies were obtained from participants with severe AH enrolled in the ISAIAH clinical trial ($n = 30$; 47% female). RNA was extracted and sequenced; differential expression (DE) analysis for Model for End-

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



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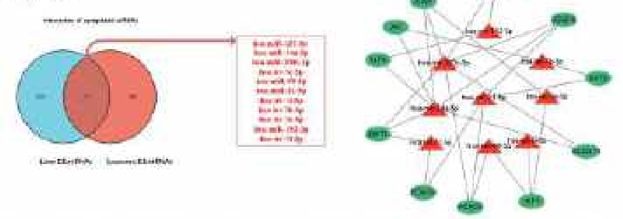
3580-C | NOVEL CIRCULATING EXOSOMAL MIRNAS AND mRNA NETWORK OFFERS PATHOPHYSIOLOGIC INSIGHTS AND POTENTIAL FOR NEW BIOMARKER DISCOVERY AND THERAPEUTIC TARGETS IN PATIENTS WITH SEVERE ALCOHOL ASSOCIATED HEPATITIS (SAH)

Jing Zeng[1,2], Srinivas Koduru[3], Derrick Zhao[1], Yun-Ling Tai[1], Xuan Wang[1], Emily Gurley[1], Faridoddin Mirshahi[4], Arun Sanyal[4], Huiping Zhou[1] and Puneet Puri[4,5], (1) Department of Microbiology and Immunology, Medical College of Virginia and Mcguire Veterans Affairs Medical Center, Virginia Commonwealth University, Richmond, VA, (2)Department of Gastroenterology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China, (3)Gene Arrays, Omelette Inc, Seaford, NY, USA, (4)Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA, (5)Division of Gastroenterology, Hepatology, and Nutrition, Richmond VA Medical Center, Richmond, VA

Background: Severe alcohol associated hepatitis (SAH) is associated with liver and multi-organ failure, resulting in a high demand for liver transplants and increased mortality. The pathogenesis of SAH involves various molecular mechanisms, including the dysregulation of microRNAs (miRs). Our hypothesis is that patients with SAH exhibit dysregulated circulating exosomal miRNAs (CE-miRs). To test this hypothesis, we examined the expression profiles and functions of hepatic miRNAs (H-miRs) and CE-miRs in SAH patients compared to healthy controls (HC). **Methods:** We extracted serum exosomes and isolated total RNA from exosomes and liver tissue. CE-miRs was analyzed using PartekFlow, while NanoString nCounter was employed for hepatic miRNAs (H-miRs). Potential target genes were identified using TargetScan and mirnet v2.0. Protein-protein interaction (PPI) networks were constructed using STRING database, and Cytoscape software was used to visualize hub genes. GSE28619 dataset data analysis were performed using ROSALIND® platform along with CE-miRs and H-miRs. **Results:** Our study included 25 patients, comprising 16 SAH patients (CE-miR n = 13, H-miR n = 3) and 9 HC (CE-miR n = 6, H-miR n = 3). In depth miR-seq data analysis revealed 78 differentially expressed CE-miRs (DE-CE-miRs). Among them, 50 were upregulated, while 28 were downregulated in SAH patients compared to HC. SAH liver tissue data exhibited 173 differentially expressed H-miRs (DE-H-miRs) compared to HC. Interestingly, among the upregulated DE-H-miRs, 11 CE-miRs were also upregulated in SAH patients. GO and KEGG analyses were performed to predict target genes for these 11 overlapping DE-miRs, and a PPI network analysis identified the top 50 hub genes. Using the GSE28619 dataset, we found that 12 out of the 50 identified hub genes were significantly downregulated in SAH patients compared to HC. These downregulated genes represent potential targets of the 9 upregulated CE-miRs (Figure 1). Moreover, these DE-miRs are associated with multiple signaling pathways related to cancer, including apoptosis, stress response and angiogenesis. **Conclusion:** The overlapping DE-miRs found in the liver and circulating exosomes are associated with severe alcohol-associated hepatitis (SAH). These findings indicate their potential as diagnostic and prognostic markers, as well as therapeutic targets for SAH. The upregulation of hsa-miR-152-3p may have cancer-protective effects and warrants further evaluation. **Keywords:** alcoholic hepatitis, miRNA, gene, exosome, expression profile, microarray analysis

Figure 1



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

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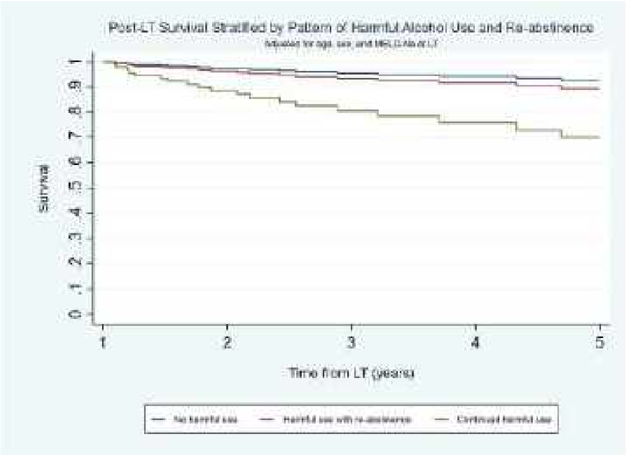
Huiping Zhou:

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

Matthew Dukewich[1], *Jennifer L. Dodge*[1], *Michael R. Lucey*[2], *John P. Rice*[3], *Kirti Shetty*[4], *Neha R. Jakhete*[5], *Gene Y. Im*[6], *Ethan M. Weinberg*[7], *Christine C Hsu*[8], *Coleman I. Smith[9], R. Mark Ghobrial[10], George Therapondos[11], Mohamed Galal Shoreibah[12], Mahmoud Aryan[13], Sheila L. Eswaran[14], Oren Fix[15], Haripriya Maddur[16], Norah Terrault[1] and Brian P. Lee[1], (1)University of Southern California, (2)University of Wisconsin School of Medicine and Public Health, Madison, WI, (3)University of Wisconsin, (4)Department of Hepatology and Liver Transplantation, the University of Maryland, School of Medicine, Baltimore, MD, USA., (5)University of Maryland, (6)Icahn School of Medicine at Mount Sinai, (7)University of Pennsylvania, (8) National Institute of Health, (9)Georgetown University Hospital, (10)Houston Methodist Hospital, Houston, TX, (11)Ochsner Medical Center, (12)University of Alabama at Birmingham, Birmingham, AL, (13)University of Alabama at Birmingham, (14)Rush University Medical Center, (15)University of North Carolina at Chapel Hill, (16)Largo Medical Center, Lutz, FL*

Background: While early (i.e. without mandated period of abstinence) liver transplant) for alcohol-associated hepatitis (AH) is the fastest growing indication for LT in the US and Europe, return to drinking occurs in up to 40% of LT recipients. Although harmful alcohol use post-LT is associated with poor outcomes, the effect of establishing sustained abstinence after relapse (i.e. re-abstinence) is understudied. **Methods:** In this multi-center (12 US LT centers) cohort, we included consecutive LT recipients for clinically-diagnosed severe AH between 2006-2021. Harmful alcohol use was defined by NIAAA criteria of "binge" ($\geq$5 [men] or $>$4 [women] drinks in $<$24 hours) or "frequent" ($\geq$4 d in one week) by clinical interview or phosphatidylethanol (Peth) $>$20ng/mL. Re-abstinence was $>$12 consecutive months without harmful alcohol use following any post-LT harmful alcohol use. Multivariable Cox regression estimated survival, adjusted for age, sex, and MELD-Na score at LT with post-LT all-cause mortality as the outcome, with analysis beginning at 1-year post-LT to minimize survivorship bias. Logistic regression was used in an exploratory multivariable analysis to identify factors associated with continued harmful alcohol use. **Results:** Among 357 LT recipients (57% male, mean age 42, mean MELD-Na at LT 38) with median post-LT follow-up of 2.2 years (IQR 1.1 – 3.6), 67 (19%) had any post-LT harmful alcohol use, of which 30 (45%) had re-abstinence. In multivariable analysis, any post-LT harmful alcohol use was associated with death (aHR 2.2, p = 0.04). However, 3- and 5-year post-LT survival (adjusted for age, sex, MELD-Na) was similar among LT recipients without harmful alcohol use vs. re-abstinence (95% and 92% vs. 93% and 89%, p = 0.84), while significantly lower among LT recipients with continued harmful alcohol use without re-abstinence (81% and 70%, p = 0.003) (Figure). Among LT recipients with continued harmful alcohol use (N = 37) vs. re-abstinence (N = 30), median time to first post-LT alcohol use was similar (340 vs. 252 d, p = 0.68), but median estimated exposure to post-LT harmful alcohol use was higher (12 mo vs 7 mo, p = 0.02). In multivariable analysis, male sex was the only risk factor for continued harmful alcohol use (vs. re-abstinence) (aOR 3.1, p = 0.046). **Conclusion:** In a cohort of LT for AH recipients, re-abstinence (vs. continued harmful alcohol use) restored 3- and 5-year survival to rates similar to LT recipients without any episode of post-LT harmful alcohol use. We identified novel differences and risk factors for continued post-LT harmful alcohol use vs. re-abstinence. These findings should inform strategies that provide early recognition of return to harmful use and enable treatments to restore abstinence that ultimately improve survival among LT recipients for AH.



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3582-C | Nrf2 ACTIVATOR OMAVELOXOLONE PROTECTS MICE FROM ALCOHOL INDUCED LIVER INJURY

Claire Montgomery, Gino Cortopassi and Joy Jiang, UC Davis

Background: Alcohol-induced oxidative stress is a hallmark and major pathogenic factor of alcohol-associated liver disease (ALD). The nuclear factor erythroid 2–related factor 2 (Nrf2), a master antioxidant gene, has been shown to mediate protective signaling in response to oxidative stress in multiple types of liver injuries including ALD. Omaveloxolone is a potent Nrf2 activator and approved by FDA for human use. Aiming at finding cures, we tested omaveloxolone in a mouse model of ALD. **Methods:** Female C57B6 mice were subjected to Lieber DeCarli alcohol diet for l0 days + last day binge (NIAAA model) and dosed with either vehicle (peanut butter) or omaveloxolone (24 mg/kg daily orally) for 10 days. At the endpoint, serum ALT and AST levels were evaluated. Liver tissues were processed for histology, and RT- qPCR to assess Nrf2 downstream targets and inflammatory markers. IHC staining for 4-HNE was used to evaluate lipid peroxidation. Western blot was conducted to detect NFκB p65 phosphorylation. STING signaling has been reported to mediate NFκB activation and proinflammatory signaling, hence, STING expression in liver was analyzed by IHC staining and its downstream effector TBK1 by western blot. **Results:** Omaveloxolone significantly reduced ALT and AST levels in alcohol fed mice. The Nrf2 downstream target Nqo1 was dramatically induced. Meanwhile, Lipid peroxidation as shown by 4-HNE staining was suppressed by omaveloxolone. The inflammatory markers TNFα, MCP1, IL-1β and Cxcl1 significantly decreased in the treated mice. The treated mice showed improved liver histology as well. Omaveloxolone reduced NFκB p65 phosphorylation and STING signaling in alcohol fed mice. **Conclusion:** Nrf2 activator omaveloxone is beneficial in a mouse model of ALD by reducing oxidative stress and proinflammatory signaling. As an FDA approved drug, omaveloxolone could be a potential candidate for ALD clinic trial.

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Disclosure information not available at the time of publication: Claire Montgomery, Gino Cortopassi

3583-C | OUTCOMES FROM A SPECIALIST PRE-LIVER TRANSPLANT HIGH INTENSITY ALCOHOL CIRRHOSIS CLINIC

Rebecca O. Kane, Muhammad Azhar Hussain, Neil Rajoriya and Andrew Holt, Queen Elizabeth Hospital

Background: Alcohol-related Liver Disease (ArLD) remains the commonest indication for liver transplantation (LT) in the United Kingdom (UK) but many patients are deemed unsuitable at the time of LT assessment. In 2015 a specialist alcohol cirrhosis high intensity clinic was set up to maximise patient's candidacy for LT. Interim analysis had shown this clinic to be an effective vehicle to optimise previously unsuitable patient groups (entering a palliative pathway), allowing perhaps fairer and equitable access to LT. The aim of this study was review longer term outcomes from this clinic. **Methods:** The multidisciplinary team (MDT) clinic comprised 2 physicians, 2 alcohol nurse specialists and a dietician. All cases were discussed in a mini-MDT meeting after clinic. Patients were seen as new referrals in advance of assessing for LT or following a negative outcome in the listing meeting, requiring further input from the clinic before representation, if appropriate. Electronic data was analysed retrospectively from all patients attending clinic (May 2016- November 2021). **Results:** 508 patients were seen in the MDT clinic (355 male, 153 female), with mean age 53 years (SD+/- 8.82) and median UKELD 54 (SD+/- 5.3). 291 (57%) were presented at the LT listing meeting. 197 (68%) were accepted for listing, with 111 (56%) undergoing LT on follow up. 1 year survival post-LT was 96%, comparable to NHSBT UK figure of 95%. Among those not transplanted (n = 397), 127 (32%) recompensated whilst 73 (18.4%) had relapsed to alcohol during follow up under the clinic. 157 patients (31%) were referred to the clinic after being initially turned down by the LT listing meeting, considered too high risk (medically, psychologically, nutritionally, or any combination). Of these patients, 105 (66.9%) were re-presented after clinic intervention and subsequently listed, with 61 (58.1%) undergoing LT. Of the remaining 44, 9 (8.6%) remained on the waiting list while 35 (33.3%) were removed (15 death/too unwell, 4 alcohol relapse, 16 recompensated). 9/111 (7%) patients had post-LT relapse (as defined by self-admission, blood alcohol level in clinic and trends of LFTs/MCV suggestive of alcohol use). Median follow

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

up post-LT was 47.5 months (range 2-75). **Conclusion:** A specialist high intensity ArLD MDT pre-LT clinic is an effective clinical environment for treating high risk patients and managing their risk factors. Specialist addiction and nutrition-focused MDT management enables patients who were initially deemed unsuitable for LT to be listed and shows low short term relapse in this patient cohort.

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3584-C | OUTCOMES OF LIVER TRANSPLANTATION IN PATIENTS WITH ACUTE ALCOHOLIC HEPATITIS BASED ON WAITLIST DURATION

Omar Alshuwaykh, California Pacific Medical Center, George Cholankeril, Baylor College of Medicine, Donghee Kim, Stanford University Medical Center and Aijaz Ahmed, Stanford University School of Medicine

Background: Acute alcoholic hepatitis is associated with significant short-term mortality and liver transplantation can be a lifesaving option for these patients. We aim to study outcomes of patients with AAH listed for liver transplantation based on their waitlist duration **Methods:** We performed retrospective analysis using the UNOS database of all patients ³ 18 years with primary and secondary diagnosis of AAH from 5/2002 to 12/2020. We categorized patients into those with AAH only and AAH and secondary diagnoses. We calculated MELD score at LT surgery **Results:** We extracted 1028 patients; 727/1028 (71%) were transplanted. 756/1028 (74%) had AAH only and 272/1028 (26%) had AAH in addition to a secondary liver disease diagnosis. We categorized patients into 3 groups based on waitlist durations of £7 days, 8-180 days, and > 180 days. Patients with waitlist duration > 7 days had significantly higher 1-year post transplant survival rates (66%) compared to (45%) for patients with wait list of 7 or less days ($P < 0.0001$). Patients with waitlist duration > 30 days had significantly higher 1-year post transplant survival rates (74%) compared to (50%) for patients with wait list of 30 or less days ($P < 0.0001$). Patients with waitlist duration > 60 days had significantly higher 1-year post transplant survival rates (76%) compared to (51%) for patients with wait list of 60 or less days ($P < 0.0001$). Patients with waitlist duration > 90 days had significantly higher 1-year post transplant survival rates (72%) compared to (58%) for patients with wait list of 90 or less days (P 0.003). Age > 65 years predicted mortality in patients with waitlist duration of < 1 week (HR 11.8, 95% CI 3.4-41.3, $P < 0.001$), whereas male gender (HR 0.4, 95% CI 0.2-0.8, P 0.01) and age 50-65 years (HR 0.4, P 0.2-0.9, P 0.04) both had better survival probability in patients with waitlist duration of 8-180 days **Conclusion:** The encouraging data on the favorable outcomes of early LT for patient is promising. We found that the longer waitlist duration, the better outcomes regarding 1-year survival rates. Patients who were waitlisted for more than 7 days had significantly better survival outcomes compared to those waitlisted for 7 or less days. similarly, patients who were waitlisted for more than 30 days, more than 60 days, and more than 90 days had significantly better survival outcomes compared to those waitlisted for 30 or less days, 60 or less days, and 90 or less days respectively.

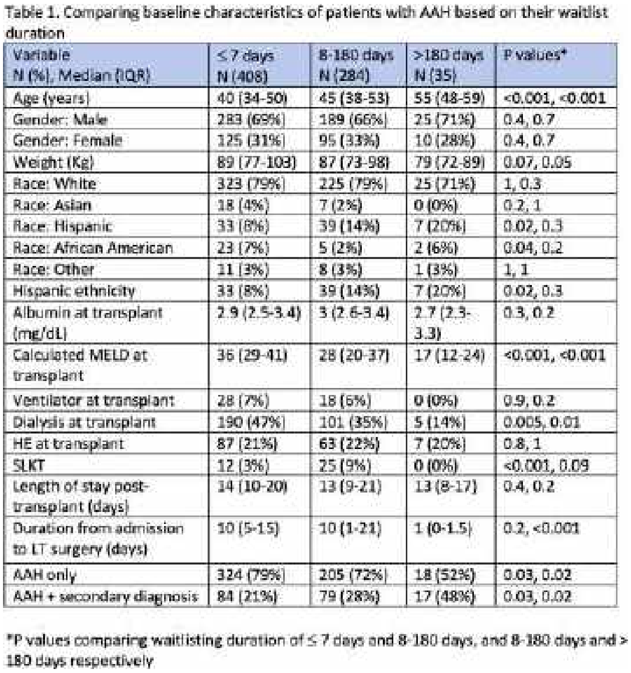

Table 1. Comparing baseline characteristics of patients with AAH based on their waitlist duration

Variable N (%), Median (IQR)	≤7 days N (408)	8-180 days N (284)	>180 days N (35)	P values*
Age (years)	40 (34-50)	45 (38-53)	55 (48-59)	<0.001, <0.001
Gender: Male	283 (69%)	189 (66%)	25 (71%)	0.4, 0.7
Gender: Female	125 (31%)	95 (33%)	10 (28%)	0.4, 0.7
Weight (Kg)	89 (77-103)	87 (73-98)	79 (72-89)	0.07, 0.05
Race: White	323 (79%)	225 (79%)	25 (71%)	1, 0.3
Race: Asian	18 (4%)	7 (2%)	0 (0%)	0.2, 1
Race: Hispanic	33 (8%)	39 (14%)	7 (20%)	0.02, 0.3
Race: African American	23 (7%)	5 (2%)	2 (6%)	0.04, 0.2
Race: Other	11 (3%)	8 (3%)	1 (3%)	1, 1
Hispanic ethnicity	33 (8%)	39 (14%)	7 (20%)	0.02, 0.3
Albumin at transplant (mg/dL)	2.9 (2.5-3.4)	3 (2.6-3.4)	2.7 (2.3-3.3)	0.3, 0.2
Calculated MELD at transplant	36 (29-41)	28 (20-37)	17 (12-24)	<0.001, <0.001
Ventilator at transplant	28 (7%)	18 (6%)	0 (0%)	0.9, 0.2
Dialysis at transplant	190 (47%)	101 (35%)	5 (14%)	0.005, 0.01
HE at transplant	87 (21%)	63 (22%)	7 (20%)	0.8, 1
SLKT	12 (3%)	25 (9%)	0 (0%)	<0.001, 0.09
Length of stay post-transplant (days)	14 (10-20)	13 (9-21)	13 (8-17)	0.4, 0.2
Duration from admission to LT surgery (days)	10 (5-15)	10 (1-21)	1 (0-1.5)	0.2, <0.001
AAH only	324 (79%)	205 (72%)	18 (52%)	0.03, 0.02
AAH + secondary diagnosis	84 (21%)	79 (28%)	17 (48%)	0.03, 0.02

*P values comparing waitlisting duration of ≤ 7 days and 8-180 days, and 8-180 days and > 180 days respectively

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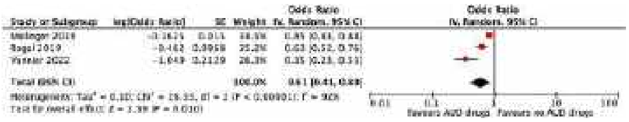
3585-C | PHARMACOLOGICAL THERAPIES FOR ALCOHOL USE DISORDERS REDUCE HEPATIC DECOMPENSATION IN ALCOHOL-RELATED LIVER DISEASE: A GRADE EVALUATION THROUGH A SYSTEMATIC REVIEW AND META-ANALYSIS

Manya Prasad and Mohit Kumar Varshney, Institute of Liver and Biliary Sciences, New Delhi

Background: The role of behavioural therapies for Alcohol Use Disorder (AUD) in alcohol-related liver disease (ALD) patients has been reported but that of pharmacological therapies is yet to be established. A systematic summary of the evidence on the use of pharmacological therapies for AUD in ALD is needed in order to guide formulation of guidelines and recommendations. Therefore, we conducted a systematic review and meta-analysis to study the use of these pharmacological interventions in ALD for patient important outcomes such as abstinence and liver-related patient important outcomes. **Methods:** We searched Medline, Embase, Cochrane database and TRIP database. Title/abstract screening, full text screening and data abstraction were carried out in duplicate. Risk of bias was assessed using the modified version of New Castle Ottawa scale. Pooled effect sizes and 95% confidence intervals were calculated using random effects model meta-analysis. We used adjusted estimates, wherever available, to pool data. The certainty in evidence was rated as high, moderate, low or very low using the GRADE tool. We used detailed GRADE guidance to assess overall risk of bias, imprecision, inconsistency, indirectness and publication bias, and summarized results in an evidence profile. **Results:** Our search yielded 546 titles and abstracts - all were identified from the electronic database search. Altogether, eleven studies (one RCT and 10 cohort studies) were included in the systematic review, and seven studies in the meta-analyses. The mean age of the participants ranged from 16 to 58 years. Meta-analysis of three cohort studies (94,887 participants) showed significantly lesser odds of hepatic decompensation over 6-12 months with use of AUD pharmacotherapy with high statistical heterogeneity (OR 0.61; 95% CI 0.41-0.89; $I^2 = 92\%$). Meta-analysis of one RCT and three cohort studies (303 participants) for the outcome abstinence revealed a pooled proportion of 60.5% (95% CI, 30.6- 90.4; $I^2 = 97.8\%$). The overall rating for certainty in estimates was very low for the outcome hepatic decompensation. The evidence was from observational studies rated down for inconsistency. **Conclusion:** The present systematic review and meta-analysis suggests pharmacological therapies in ALD may reduce incidence of hepatic decompensation and may help in achieving high level of abstinence. Meta-analysis of three retrospective cohort studies revealed a statistically significant and precise reduction in risk of hepatic decompensation in ALD over 6 to 12 months. The body of evidence arises from mostly cohort studies, and overall very few studies have adequately addressed the effect of AUD therapies on long term patient important outcomes. The findings warrant disengagement from a 'liver-centric' management of ALD to one that incorporates a multidisciplinary approach.

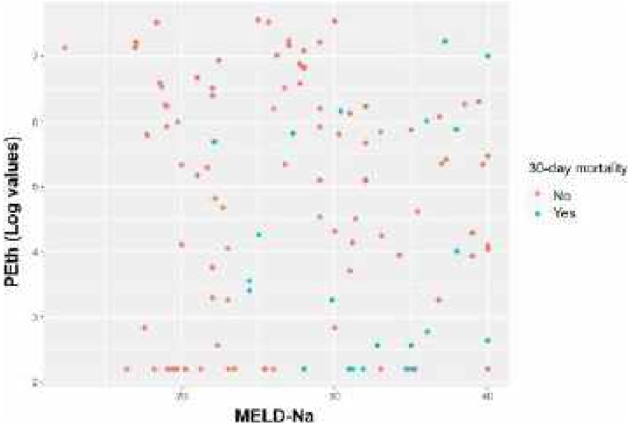


Disclosures: The following people have nothing to disclose: Manya Prasad, Mohit Kumar Varshney

3586-C | PHOSPHATIDYLETHANOL (PETH) LEVELS ARE ASSOCIATED WITH MORTALITY BUT NOT SEVERITY IN ALCOHOL-ASSOCIATED HEPATITIS

Praveena Narayanan[1], Anahita Rabiee[1], Tamar H. Taddei[1,2] and Pramod K. Mistry[1], (1)Yale University, New Haven, CT, (2)West Haven VA Medical Center

Background: Phosphatidylethanol (PEth) is a validated biomarker to detect alcohol use within 21-28 days. While PEth has been studied in the setting of liver transplant evaluation and in chronic liver disease, it has not been studied in alcohol-associated hepatitis (AH). **Methods:** Using a single-center database of patients admitted from 2020 to 2023 with AH, 114 patients were identified with PEth 16:0/18:1 testing within 14 days of hospitalization. We assessed correlations between PEth and demographic factors, established markers of severity with AH, and outcomes from AH, such as mortality at 30 and 90 days. Of those 114 patients, 47 had additional information available regarding their alcohol use history. Categorical variables were compared using chi-squared test; continuous variables were compared using Mann-Whitney U test. Correlations were compared with Spearman's rank correlation coefficient. **Results:** Of 114 patients with AH and PEth testing, 82 (72%) had a positive value (> 20ng/mL) compared to 32 (28%) with a negative value (< 20ng/mL). Between these two groups, there were no significant differences in age (PEth- median 50.22, PEth+ median 46.28), gender (PEth- 75% Male, PEth+ 61% Male), ethnicity (PEth- 97% White, PEth+ 92% White), or MELD-Na (PEth- mean 27.62, PEth+ mean 28.26) (Figure 1). A negative PEth test was significantly correlated with higher mortality at 30 days ($p = 0.036$) and there remained a trend towards higher mortality at 90 days (p = 0.09). There was also a significant difference in AST:ALT (p < 0.001). Self-reports of alcohol consumption and last drink date correlated with PEth testing (n = 44, r = 0.68). **Conclusion:** Significant and sustained alcohol use underlies the development of AH, however PEth is not predictive of measures of AH severity. In our population, PEth correlated with AST: ALT ratio and self-reported alcohol consumption; interestingly, a negative PEth on admission was also associated with higher 30-day mortality. The mechanisms underlying the heterogeneity of PEth test results in the setting of AH should be further investigated to refine our understanding and guide our use of this biomarker in clinical practice.



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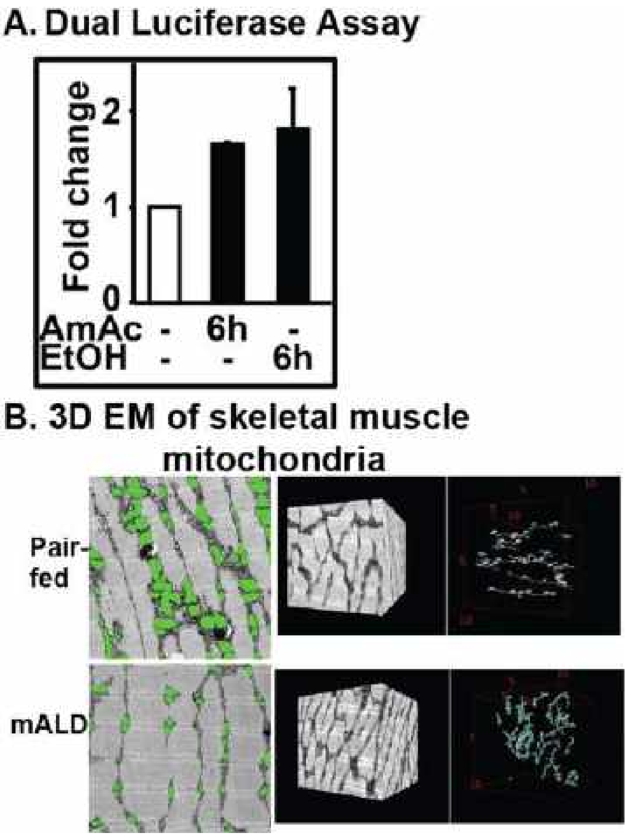
Disclosure information not available at the time of publication: Tamar H. Taddei, Pramod K. Mistry

3587-C | PHYSOXIC HIF1a-REDD1 SIGNALING PERTURBATIONS IN SKELETAL MUSCLE DISRUPT PROTEIN HOMEOSTASIS IN ALCOHOL-ASSOCIATED LIVER DISEASE

Nicole M. Welch[1], Saurabh Mishra[1], Annette Bellar[1], Vandana Agrawal[1] and Srinivasan Dasarathy[2], (1) Cleveland Clinic, (2)Cleveland Clinic Foundation

Background: Loss of skeletal muscle mass and function is frequent and greater in alcohol-associated liver disease(ALD) than in other etiologies of cirrhosis. Alcohol(ethanol,EtOH) impairs hepatocyte ureagenesis with resultant increase in circulating ammonia. In our integrated multiomics analyses studies, we previously identified that hypoxia-inducible factor(Hif)1α signaling was enriched in models of skeletal muscle hyperammonemia. We have also previously shown that skeletal muscle is sensitized by ethanol to the adverse effects of ammonia, but the mechanisms are poorly understood. We therefore sought to determine whether ethanol stabilizes Hif1a under physoxia (physiological partial oxygen pressure) and whether impaired skeletal muscle proteostasis in mouse and human inducible pluripotent stem cell (hiPSC) myotubes and skeletal muscle from humans and mice with ALD(mALD) is mediated by Hif1α. **Methods:** Differentiated C2C12 and hiPSC myotubes were not treated(UnT) or treated with 100mM EtOH for 6 and 24h. Wild-type(WT) mALD were fed an acute on chronic ethanol diet with 6% EtOH. Littermate controls were pair-fed. Assay for transposase accessible chromatin(ATACseq) was performed in C2C12 myotubes. Bulk RNA sequencing (with tissue deconvolution) and untargeted proteomics were performed in EtOH-treated C2C12 and hiPSC-derived myotubes and skeletal muscle from mALD and human patients with cirrhosis. A differentially expressed molecule (DEM) was defined as meeting a pre-defined adjusted or non-adjusted p-value cutoff designed to identify 50-2000 molecules of interest that changed with EtOH compared to UnT. Dual luciferase reporter assay was performed after double transfection of Renilla luciferase and Hif1a luciferase reporter (promoter joined to 3 consecutive hypoxia responsive elements). 3-dimensional electron microscopy (3D EM) was performed in gastrocnemius muscle from pair-fed mice and mALD. **Results:** Integration of DEMs from untargeted data from EtOH-treated models revealed increased expression of HIF1α targets including Vimentin(VIM), Fibronectin 1(FN1), Cbp/P300 Interacting Transactivator With Glu/Asp Rich Carboxy-Terminal Domain 2(CITED2), and DNA Damage Inducible Transcript 4(DDIT4/REDD1). These were experimentally validated in C2C12 myotubes treated with either EtOH or AmAc for 6h. Both treatments increased HIF1α luciferase reporter activity. Protein expression of DDIT4 in myotubes and skeletal muscle was increased with EtOH. 3D EM in mouse skeletal muscle showed changes in mitochondrial network organization with EtOH exposure. **Conclusion:** EtOH-sensitization of skeletal muscle to hyperammonemia stabilizes HIF1α under physoxic conditions and increases DDIT4 expression. DDIT4 is an mTOR inhibitor and has been shown to increase oxidative dysfunction in mitochondria. Targeting HIF1α-DDIT4 signaling may be a potential therapeutic target in ALD to increase skeletal muscle mass.



Disclosures: The following people have nothing to disclose: Nicole M. Welch, Saurabh Mishra, Annette Bellar, Vandana Agrawal, Srinivasan Dasarathy

3588-C | POLYCHLORINATED BIPHENYL 126 ALTERS THE HEPATIC TRANSCRIPTOME TO ENHANCE ALCOHOL-ASSOCIATED LIVER DISEASE

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Background: Alcohol-associated liver disease (ALD) development may be impacted by other lifestyle factors such as tobacco smoking. Previously, environmental pollutants, namely persistent organic pollutants (POPs), have demonstrated to exacerbate dyslipidemia in high-fat diet models. We recently characterized a model for how environmental toxicant, polychlorinated biphenyl (PCB) 126, can disrupt lipid metabolism and exacerbate steatosis in an alcohol feeding model. Because excessive alcohol consumption is a major cause of preventable death and humans are inevitably exposed to POPs, it is important to understand how exposures may modify lifestyle related diseases. The current study's objective is to characterize the hepatic transcriptome in mice exposed to PCB126 followed by ethanol feeding. We hypothesize that PCB126 exposure prior to alcohol feeding will result in unique differentially expressed genes (DEGs) and enriched pathways will implicate altered metabolism and signaling disruption. **Methods:** Male C57BL/6J mice were exposed to 0.2mg/kg PCB126 or corn oil vehicle by oral gavage. Mice were then fed 5% Lieber DeCarli EtOH (EF) or pair fed (PF) diet for ten days followed by 31.5% EtOH binge. Hepatic mRNA was isolated and prepared for RNA sequencing. DEG analysis was performed with DESeq2 for pairwise comparisons for $p \leq 0.05$ and $q \leq 0.05$. **Results:** Hepatic transcriptomic analyses indicated PCB126(PF v EF) had 4832 (2214↑; 2618↓) DEGs while PF(Veh. v PCB126) had 503 (339↑; 164↓) DEGs. Importantly, our EF(Veh. v PCB126) had 907 (536↑;371↓) DEGs. Among the top 20 DEGs in our EF (Veh. v PCB126) comparison, genes included were involved in xenobiotic metabolism, cytoskeleton, and lipid metabolism. Four genes (*Abcb10*, *Slc46a3*, *Tuba8*, and *Ugt1a6b*) were validated by qPCR. In the top 6 of 20 enriched Gene Ontology (GO) processes, 4 processes involved *peptidyl-tyrosine modifications*. This indicates that signaling, *via* altered phosphorylation, may have been disrupted. Other GO processes involved leukocyte regulation, migration, or proliferation, suggesting underlying immune alterations were prevalent. **Conclusion:** These preliminary analyses suggest that PCB126 exposure modifies the hepatic transcriptome to, in part, disrupt cell signaling processes. This study signifies environmental pollutant exposure's ability to enhance ALD. Based on our enriched GO process data, tyrosine modifications may indicate mechanisms related to how PCB126 disrupts signaling in EF mice to enhance ALD.

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The following people have nothing to disclose: Tyler C. Gripshover, Banrida Wahlang, Kimberly Head, Eric C. Rouchka, Jamie Young, Jianzhu Luo, Irina A. Kirpich

3589-C | POLYCOMB REPRESSIVE COMPLEX 2 BINDS AND STABILIZES NANOG TO SUPPRESS DIFFERENTIATION-RELATED GENES TO PROMOTE SELF-RENEWAL OF TICs OF HCCs INDUCED BY CRISPR/Cas9-MEDIATED DRIVER MUTATIONS IN HUMANIZED FRG MICE

Da-Wei Yeh, Cheng Liu, Juan Carlos Hernandez, Stanley M. Tahara, Hidekazu Tsukamoto and Keigo Machida, University of Southern California

Background: The synergistic effect of alcohol and HCV mediated through TLR4 signaling transactivates NANOG, a pluripotency transcription factor important for the stemness of tumor-initiating stem-like cells (TICs). NANOG together with the PRC2 complex suppresses expression of oxidative phosphorylation (OXPHOS) genes to generate TICs. **Methods:** CRISPR KO library screening of ARID1A KO-non-transformed immortalized hepatocytes were tested in humanized FRG hepatocellular carcinoma (HCC) mouse model for tumor size regression phenotypes in response to sorafenib treatment. We generated HCC mice in which liver parenchymal, non-parenchymal and hematopoietic cells are humanized. CRISPR/Cas9 application (*ARID1A* KO and constitutively-active *CTNNB1* knock-in) generates mutations common in HCC patients synergistically generates HCC by alcohol Western diet. This HCC model was used for gene-environment interactions. **Results:** CRISPR KO library screening of ARID1A KO-non-transformed immortalized hepatocytes identified EZH2, EED and SUZ12 as synthetic lethal targets for tumor size regression in response to sorafenib treatment. The phosphodegron sequence PEST domain of NANOG binds EED to stabilize NANOG protein by blocking E3 ligase recruitment and proteasome-dependent degradation, while the tryptophan-rich domain of NANOG binds EZH2 and SUZ12. Human ARID1A gene loss led to the resistance of FAO inhibition therapies due to reduction of mitochondrial ROS levels. Humanized HCC mouse models with mutations and metabolic liver diseases (MLD) provide experimental platforms. CRISPR-Cas9-mediated *ARID1A* knockout and/or constitutively active *CTNNB1* driver mutations promoted tumor development in humanized FRG HCC mouse models. Selective inhibitors targeting of NANOG-PRC2 complex interface efficiently reduced HCC incidence and tumor sizes in several different mouse models and human HCC specimens. FRG mice carrying a double mutation of *ARID1A knockout* and c.a.*CTNNB1* knock-in insertion, but not c.a.*CTNNB1* knock-in insertion alone, showed almost a two-fold higher incidence of tumor formation but exhibited higher sensitivity to the drug treatment. *ARID1A* knockout and constitutively active *CTNNB1* protein levels by immunoblot analyses. The *ARID1A*-knockout humanized livers displayed higher levels of stemness protein levels (including NANOG and OCT4). Use of an interface inhibitor antagonizing PRC2-NANOG binding and/or FAO inhibitor blocked tumor growth. **Conclusion:** The PRC2-NANOG interaction becomes a new drug target for normalizing differentiation by inducing differentiation-related genes, destabilization NANOG protein, and suppressing NANOG activity. This project was supported by NIH grants R01 AA025204-01A1, R21 AA025470-01A1, 1R01AA018857-01, pilot project funding (5P30DK048522-13), P50AA011999 (Animal Core, Morphology Core, and Pilot Project Program) and R24AA012885.

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Disclosure information not available at the time of publication: Da-Wei Yeh, Cheng Liu, Juan Carlos Hernandez, Stanley M. Tahara, Hidekazu Tsukamoto

3590-C | POST-TRANSLATIONAL MODIFICATIONS DRIVE THE EFFECTS OF HMGB1 IN ALCOHOLIC LIVER DISEASE

Xiaodong Ge, Romain Desert, Hui Han, Sukanta Das, Zhuolun Song, Sai Santosh Babu Komakula, Ines Barahona, Daniel Lantvit and Natalia Nieto, University of Illinois at Chicago

Background: high-mobility group box-1 (HMGB1) is a non-histone chromatin-associated protein involved in the pathogenesis of chronic liver disease. We identified that HMGB1 is increased and undergoes post-translational modifications (PTMs) in response to alcohol consumption. Thus, we hypothesized that specific PTMs could drive the pathogenic effects of HMGB1 in alcoholic liver disease (ALD). **Methods:** mice with cell-specific ablation of *Hmgb1* or the *Receptor for advanced glycation end-products* (*Rage*) were generated. Mice were injected with an HMGB1 neutralizing antibody or with the HMGB1 isoforms. The Lieber-DeCarli model of ALD was used. **Results:** *Hmgb1* ablation in hepatocytes ($\mathit{Hmgb1}^{\Delta \mathrm{Hep}}$) or myeloid cells ($\mathit{Hmgb1}^{\Delta \mathrm{Mye}}$) partially protected while ablation in both ($\mathit{Hmgb1}^{\Delta \mathrm{Hep} \Delta \mathrm{Mye}}$) prevented ALD. Neutralization of HMGB1 prevented while injection of [H] HMGB1 promoted ALD, which was worsened by injection of [O] HMGB1. Ablation of [O] HMGB1 protected whereas ablation of [Ac] HMGB1 exacerbated ALD due to inflammatory cell infiltration, which was blocked by ablation of both. Ethanol-fed $\mathit{Rage}^{\Delta \mathrm{Mye}}$ mice were significantly protected, indicating a crucial role of RAGE in myeloid cells for ALD. [O] HMGB1 signaled through RAGE in myeloid cells and was critical for driving steatosis, inflammation, IL1β production, and alcohol-induced liver injury whereas [Ac] HMGB1 was protective by blocking the noxious effects of [O] HMGB1. **Conclusion:** [O] HMGB1 signals through RAGE in myeloid cells to drive the pathogenesis of ALD while [Ac] HMGB1 offsets the effects of [O] HMGB1.

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3591-C | POST-TRANSPLANT ALCOHOL-USE IS MORE COMMON IN RECIPIENTS WITH SHORT-INTERVAL ABSTINENCE

Jessica Ann Musto[1], Geralyn Palmer[1], Mary Nemer[1], Trevor Schell[1], Gabrielle Waclawik[1], Quarshie Glover[1], Michael R. Lucey[2], Fauzia Osman[1] and John P. Rice[1], (1)University of Wisconsin, (2)University of Wisconsin School of Medicine and Public Health, Madison, WI

Background: Early liver transplant for alcohol-associated liver disease (ALD), defined as liver transplant (LT) without a pre-transplant sobriety length mandate, has increased worldwide. Return to drinking is infrequent in short term follow-up but longer-term data is lacking. **Methods:** Single-center retrospective study of adult recipients of primary LT between 2010-2020, with follow-up through July 1, 2022, categorized by indication for LT. Baseline characteristics were compared using chi-square or Fisher's exact and Kruskal-Wallis or ANOVA. Logistic regression was used to identify variables associated with post-LT alcohol use. **Results:** Of 708 patients who underwent LT, 110 (15.5%) had ALD and abstinence <6 months prior to LT (early liver transplant, ELT), 234 (33.1%) had ALD and alcohol abstinence >6 months prior to LT (standard liver transplant, SLT). Median follow-up was 4.6 years (IQR 2.6, 7.3). ELT recipients were younger (median age 46.3 vs 57.5 $p=0.001$) with shorter median abstinence prior to LT (61.5 vs 552 d, $p<0.001$). There was no difference in crude and adjusted post-LT survival. Any alcohol use (40.9 vs 21.8%, $p<0.001$) and potentially harmful alcohol use (31.2 vs 16.0%, $p=0.002$) were more common in ELT recipients. Recurrent decompensated ALD, either by cirrhosis or AH, trended toward more common in ELT recipients (9.1% vs 4.4%, $p=0.09$). By logistic regression, greater than 6 months pre-LT abstinence was associated with a decreased risk of harmful alcohol use (OR 0.40, $p<0.001$), but not in a multivariable model (OR 0.76, $p=0.38$). Multiple previous inpatient AUD treatments (OR 3.25, 95%CI 1.12-9.47, $p=0.03$) was the only factor associated with post-LT alcohol use in the multivariable model. **Conclusion:** Patients with ALD and less than 6-months abstinence have a higher incidence of post-LT alcohol use. Pre-LT abstinence length was associated with post-LT harmful alcohol use on univariate logistic regression, but not in a multi-variable model.

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3592-C | POST-TRANSPLANT SURVIVAL AND ALCOHOL RELAPSE RATES IN LIVER TRANSPLANT RECIPIENTS BEFORE AND AFTER REMOVAL OF A MANDATORY SIX-MONTH ALCOHOL ABSTINENCE PERIOD

Carolyn C. Chang[1], C. Kristian Enestvedt[1], Ali Olyaei[1], Tiana Enos-Dano[1], Susan L. Orloff[2], Erin Maynard[3], Willscott E. Naugler[4], David L. Scott[1], David C. Woodland[1], Alexandra Bolognese[1] and Christopher R. Connelly[1], (1)Oregon Health and Science University, (2) Oregon Health And Science University, (3)Oregon Health & Science University, (4)Oregon Health & Science University, Portland, OR

Background: Alcohol-associated liver disease (ALD) portends a high mortality in patients with high Model for End-Stage Liver Disease (MELD) scores. Six-month mandatory abstinence prior to liver transplant was historically common practice, and many of these patients did not survive to transplant. Paradigms are now shifting. In 2018, our institution adopted a new policy to omit the six-month sobriety period. Our aim was to assess differences in alcohol relapse and survival before and after the policy change. **Methods:** This was a single center, retrospective cohort study of liver transplant recipients with ALD from January 1, 2010 to April 1, 2023. Patients less than 18 years and those with unclear diagnoses were excluded. Transplants were divided into Era 1 (2010-2017) and Era 2 (2018-2023). Patient characteristics, survival, and relapse were compared in patients with and without ALD in the overall cohort, and between eras. Relapse was defined by positive phosphatidylethanol test or chart documentation of relapse. Survival probability was calculated by Kaplan-Meier estimate and compared using the log-rank test. **Results:** 705 patients underwent liver transplantation, 375 in Era 1 and 330 in Era 2. 32% ($n=223$) of liver transplants were performed for patients with ALD, but transplant for ALD was more frequent in Era 2 (42% v. 22%, $p<0.001$).

Overall, recipients with ALD were more likely to be male (81% v. 62%, $p < 0.05$) and younger (51 v. 56 years, $p < 0.001$), but were otherwise similar to non-ALD recipients in terms of MELD, race, and hepatitis C status. Ten-year post-transplant survival was similar between the ALD and non-ALD group (Figure 1A). The overall relapse rate in patients with ALD was 20%, and was significantly higher in Era 2 (23% v. 14%, $p < 0.001$). Characteristics of those with and without relapse were similar. Post-transplant survival was similar between those who experienced relapse and those who did not (Figure 1B). Five-year post-transplant survival was similar between Eras 1 and 2 in patients with ALD (Figure 1C). **Conclusion:** Our study shows an increased rate of transplant for ALD after removal of the mandatory six-month sobriety period. Survival was similar between those with and without ALD. Survival was also similar in those with ALD who did and did not experience relapse. Notably, relapse rates were higher after removal of the six-month sobriety period, but survival was similar before and after removal of this barrier to transplant. These findings suggest that the 6-month abstinence period has no impact on overall patient survival. In fact, it likely prevents otherwise suitable candidates from receiving a life-saving liver transplant.

Figure 1A. Post-transplant survival for patients with diagnosis of ALD versus other etiology (p= 0.219, log-rank)

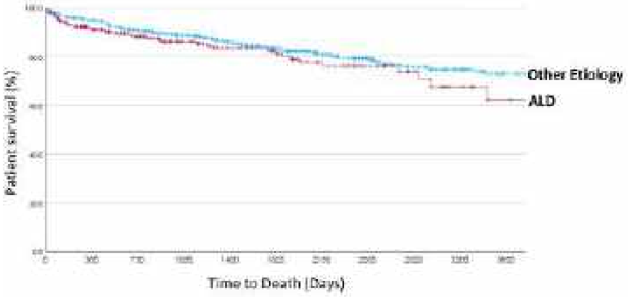


Figure 1B. Post-transplant survival for patients with diagnosis of ALD with or without relapse (p= 0.631, log-rank)

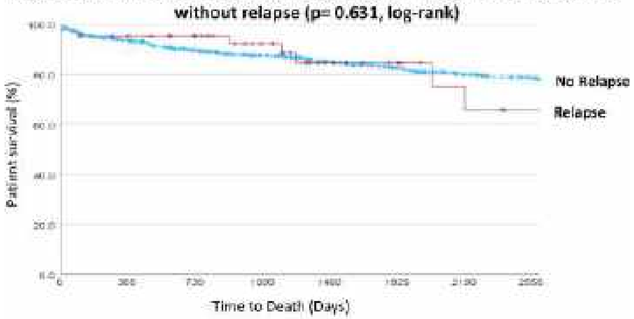
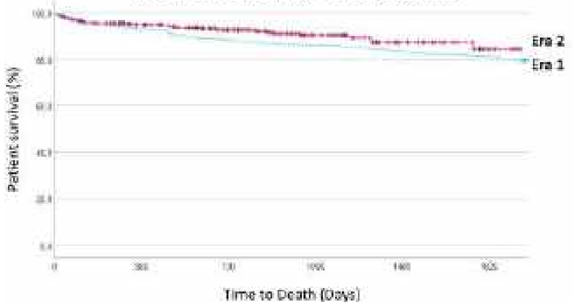


Figure 1C. Post-transplant survival for patients with diagnosis ALD at different Eras (p= 0.135, log-rank)



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3593-C | PRE-AND POST-TRANSPLANT OUTCOMES IN PATIENTS UNDERGOING EXPEDITED AND STANDARD TRANSPLANT FOR ACUTE AND CHRONIC ALCOHOL-RELATED LIVER DISEASE

Olivia Karcis[1], Suzanne S. Chan[2], Michael P. Curry[1], John Messinger[3], Alison Mann[1], Isabelle Iversen[1] and Juan Ramos-Ayes[1], (1)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (2)Beth Israel Deaconess Medical Center, West Newton, MA, (3)Harvard Medical School

Background: Severe alcohol related hepatitis has limited treatment options and a high short term mortality risk with the majority of deaths occurring within months of initial presentation. Liver transplantation has been increasingly used in recent years for this indication requiring expedited assessment in patients with limited sobriety. Expedited evaluation requires rapid medical and psychosocial assessment of the patient and does not allow for the opportunity to demonstrate sobriety. **Methods:** We performed a retrospective study of demographic, psychosocial, and pre- and post-transplant outcomes of patients undergoing expedited workup (n = 65) to those who have undergone standard evaluation (n = 206) at Beth Israel Deaconess Medical Center. Expedited workup was defined by minimal (< 2 weeks) or no outpatient time between transplant evaluation and listing. **Results:** Listed patients were predominantly male (75.8% and 73.8% for expedited and standard listing groups, respectively). Expedited listings were significantly more likely to be younger patients (45.9 vs 54.1 y old, p = 3.29x10^-7). Virtually all patients undergoing standard transplant listing carried a UNOS diagnosis of alcoholic cirrhosis (99%) whereas the expedited group had a higher proportion of acute alcoholic hepatitis (35.4%). Patients who underwent expedited listing had significantly higher peak MELD scores (35.3 vs 28.1, p = 8.61x10^-8), at referral (30.4 vs 20.0, p = 2.07x10^-7), and at listing (31.6 vs 19.4, p = 2.40x10^-19). Those with expedited listings were transplanted at a higher rate (72.3% vs 33.0%) and over a shorter interval from listing to transplant (49.4 vs 402.3 d). Post-transplant relapse rates were higher in the expedited listing group at 1 year (8.5% vs 4.4%) and 3 years (12.8% vs 5.9%). Mortality rates 1 year (4.3% vs 2.9%) and 3 years (6.4% vs 5.9%)

post-transplant were similar for the expedited and standard groups, respectively. **Conclusion:** Patients who underwent expedited listing were more likely to have acute alcoholic hepatitis, which is probably reflective of our center-specific policy allowing for expedited transplantation if the patient did not have prior medical contacts related to alcohol use. Patients who underwent expedited listing had significantly higher illness acuity through the transplant process. The expedited patients also had higher rates of relapse likely due to the limited assessment of sobriety during evaluation. Despite this, mortality rates were similar between groups.

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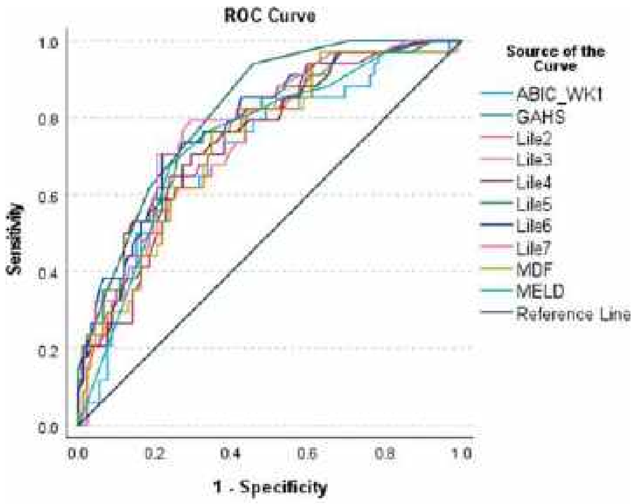
The following people have nothing to disclose: Olivia Karcis

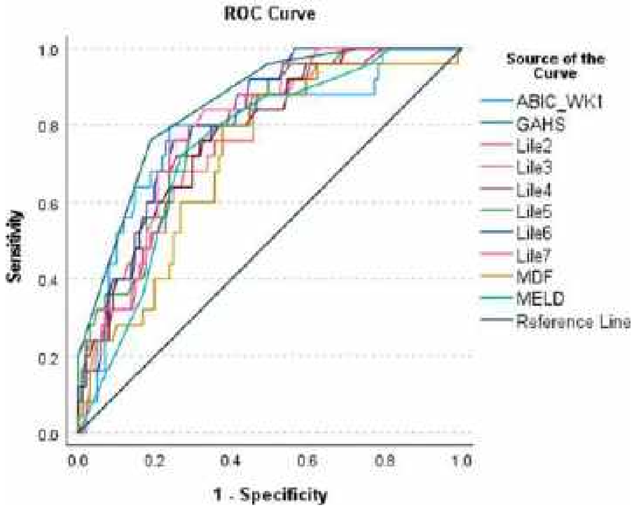
Disclosure information not available at the time of publication: Suzanne S. Chan, John Messinger, Alison Mann, Isabelle Iversen, Juan Ramos-Ayes

3594-C | PROGNOSTIC VALUE OF PRE-DAY 7 LILLE SCORES IN SEVERE ALCOHOLIC HEPATITIS

Kevin Yang, Naren Srinath Nallapeta, Brian Quigley, Alexander Mark Carlson, Nariman Hossein-Javaheri and Thomas Mahl, University at Buffalo

Background: The severe form of alcoholic hepatitis (SAH) confers exceptionally high mortality. These patients are typically started on corticosteroid therapy barring contraindications, and efficacy is assessed at day 7 with the Lille score. We aimed to evaluate prognostic value of pre-day 7 Lille Model scores (LM 2-7) versus other established prognosticators. **Methods:** This retrospective study included all consecutive patients admitted to a tertiary care center with SAH as defined by Maddrey's discriminant function (MDF) > 32. Response to steroid therapy was assessed at day 2 to day 7 of treatment using the Lille score with cutoff value of 0.45. We compared these scores to the Model for End-Stage Liver Disease (MELD), age, bilirubin, international normalized ratio, creatinine (ABIC), and Glasgow Alcoholic Hepatitis Score (GAHS) utilizing receiver operating characteristics (ROC) curves. **Results:** Out of 425 patients admitted with alcoholic hepatitis, 150 patients fit the criteria for SAH. 126 of these patients received corticosteroid therapy. In the steroid arm, average age was 49.17 (SD = 10.95). This sample was 69.8% male, 78.6% white and 7.1% black. The average length of stay (LOS) was 14.44 days (SD = 9.56). 19.8% of the group receiving corticosteroid therapy died at 28 days and 27% at 90 days, compared to the total group of 425 patients with a 28-day mortality of 11.8% and 90-day mortality of 15.3%. The area under ROC curve (AUROC) for LM2 to LM7 for 28-day mortality was 0.777, 0.771, 0.778, 0.791, 0.809, and 0.796 in consecutive order. The AUROC was 0.784 for ABIC, 0.855 for GAHS, 0.719 for MDF, and 0.748 for MELD. The LM2 to LM7 AUROC for 90-day mortality was 0.741, 0.743, 0.756, 0.770, 0.787, 0.779, consecutively. Additionally, the AUROC was 0.713 for ABIC, 0.820 for GAHS, 0.735 for MDF, and 0.744 for MELD. **Conclusion:** In this retrospective study, all LM scores from day 2 to day 7 of treatment showed comparable efficacy in predicting mortality at 28 and 90 days. All prognostic scores showed good predictive power, with MDF having the smallest AUROC at 28 days and ABIC at 90 days. The GAHS had the largest AUROC for both mortality endpoints.





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Disclosure information not available at the time of publication: Brian Quigley

3595-C | PROTECTIVE ROLE OF 17β-ESTRADIOL IN ALCOHOL-ASSOCIATED LIVER DISEASE IS MEDIATED BY SUPPRESSION OF INTEGRIN SIGNALING IN MACROPHAGES

Kruti Nataraj, Michael Schonfeld and Irina Tikhanovich, University of Kansas Medical Center

Background: Alcohol associated liver disease (ALD) is a complex disease regulated by a combination of genetic and environmental factors. Sex is an important variable, and it is known that sex hormone signaling regulate both disease and homeostasis states in the liver. Previously we showed that PRMT6 arginine methyltransferase deficiency controls liver fibrosis development in alcohol fed mice by regulating integrin methylation. However, the increase in fibrosis induced by loss of *Prmt6* was 3-fold lower in females. We hypothesized that PRMT6-intergin signaling is altered in female mice. **Methods:** 6-8 weeks old wild type or *Prmt6* knockout female mice were subjected to gonadectomy, ovaries were removed through an incision just below the rib cage, the muscle layer sutured, and the incision closed with wound clips. In sham-operated mice, incisions were made and closed as above. Mice were then fed a combination of Western diet with alcohol in the drinking water for 18 weeks (WDA model), control mice were given Western diet with plain water. To investigate the role of estrogen, peritoneal macrophages were treated *in vitro* with 10nM, 100 nM or 1μM 17β-estradiol solution. Integrin expression was assessed via qPCR and immunohistochemistry. Fibrosis was assessed using whole liver mRNA of *Col1a1* and Sirius Red staining. **Results:** We found that 17β-estradiol treatment induced *Prmt6* expression and reduced integrin (α4, αx, β1 and β2) expression in a dose dependent manner. In agreement with these data, gonadectomized females showed elevated integrin expression and decreased PRMT6 levels. In addition, 17β-estradiol treatment reduced pro-inflammatory (*Tnf, Il6, Ccl5*) and pro-fibrotic (*Tgfb1*) signaling in macrophages. Later effect was dependent on 17β-estradiol-mediated regulation of integrin expression, since in macrophages lacking integrin α4 or αx, 17β-estradiol treatment failed to reduce pro-inflammatory and pro-fibrotic signaling. Consistent with this, gonadectomized females fed alcohol showed elevated inflammation and fibrosis development (3-fold increase in Sirius Red staining and *Col1a1* expression). Moreover, the increase in fibrosis induced by loss of *Prmt6* was greater in gonadectomized females compared to sham controls suggesting that estrogen contributes to sex differences in knockout mice. **Conclusion:** Our data suggest that estrogen signaling protects mice from alcohol associated liver disease in part through suppression of integrin signaling and induction of *Prmt6* expression.

Disclosures: The following people have nothing to disclose: Kruti Nataraj, Michael Schonfeld, Irina Tikhanovich

f 3596-C | PROTEOMIC PROFILING OF PLASMA AND EXTRACELLULAR VESICLES IN ALCOHOL-ASSOCIATED HEPATITIS PATIENTS: INSIGHTS INTO DISEASE MECHANISMS AND BIOMARKERS

Mrigya Babuta[1], Yanbo Wang[1], Towia Libermann[1], Bruce Barton[2], Srinivasan Dasarathy[3], Craig J. McClain[4], Mack C. Mitchell[5], Laura E. Nagy[3], Svetlana Radaeva[6] and Gyongyi Szabo[1], (1)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (2)University of Massachusetts Memorial Health Care, (3)Cleveland Clinic Foundation, (4)University of Louisville, Louisville, KY, (5)University of Texas Southwestern Medical Center, (6)National Institutes of Health, Bethesda, MD

Background: Extracellular vesicle (EVs) cargo consists of RNA and protein molecules from the cells of origin reflecting the pathophysiological state specific to a disease and thereby, are emerging as potential biomarkers. There is a significant increase in the EV number in plasma of alcohol-associated hepatitis (AH) patients compared to controls. Therefore, in this study we aim to delineate the protein composition of EV cargo and identify the potential biomarkers that distinguish moderate AH (mAH) from severe AH (sAH). **Methods:** The plasma and EV proteome from mAH (MELD > 20) and sAH (MELD < 20) patients enrolled in the DASH consortium ($n = 15$/each group) were analyzed on the SomaScan platform, measuring 1,305 proteins. Statistical analysis identified the proteins significantly associated with mAH or sAH. **Results:** Proteomic analysis identified 209 and 498 proteins in the cargo of EVs of mAH and sAH patients, respectively that were significantly differentially expressed (adj. $p < 0.01$) as compared to healthy controls. Similarly, proteomic analysis identified 366 and 521 proteins in the plasma of human mAH and sAH patients, respectively. Further analysis indicated that 73 proteins were increased by more than two-fold changes in mAH patients and 93 proteins in

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

sAH EV samples compared to control subjects. The proteins detected in the EV cargoes of both mAH and sAH patients involved cellular signaling, metabolic processes and immune system process regulation. Biological functional analysis using Ingenuity Pathway Analysis (IPA) predicted activation of liver inflammation, fibrosis, and liver damage from differentially expressed genes unique to sAH-EVs. The highly upregulated proteins in mAH-EVs compared to control EVs included Latent-transforming growth factor beta-binding protein 4, several Cathepsins, Integrin alpha-beta complex. The significantly upregulated proteins in sAH-EVs compared to control EVs were Heat shock proteins, Tumor necrosis factor receptor superfamily members, and Serine/threonine-protein kinases. There were also a significant number of proteins that were decreased by at least 50% in moderate and severe AH patients as compared to control subjects (27 and 132 proteins respectively). Interestingly, certain signature proteins that were downregulated in the EVs of mAH patients were upregulated in the EVs of sAH patients. **Conclusion:** SomaScan data demonstrate that EV cargo of moderate and severe AH has a unique proteome profile compared to their respective plasma samples. Our data also suggest that EV cargo is selectively enriched in different stages of alcohol-associated hepatitis and, therefore, could be exploited as unique biomarkers while also revealing differences about the underlying biology in moderate and severe AH.

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Disclosure information not available at the time of publication: Towia Libermann, Bruce Barton, Mack C. Mitchell, Svetlana Radaeva

3597-C | PROVIDER ATTITUDES AND PRACTICE PATTERNS IN SCREENING AND MANAGEMENT OF ALCOHOL USE FOLLOWING LIVER TRANSPLANTATION

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Background: Alcohol-associated liver disease (ALD) is the leading indication for liver transplant (LT) though return to alcohol use occurs up to 22% by year 1 and is associated with poor post-LT outcomes. While alcohol screening along with abstinence-promoting behavioral and pharmacotherapy is the foundation in managing alcohol use disorder (AUD), it is underutilized in hepatology. We aim to examine provider attitudes and practice patterns in screening and management of alcohol use in post-LT patients. **Methods**: We conducted a survey of liver transplant providers including (1) gastroenterology, hepatology, and transplant fellows, (2) hepatology and transplant faculty and (3) advanced practice providers (APP) at a single academic transplant center. The survey included 13 questions based on Likert scale to assess provider practice/screening patterns, views and understanding/knowledge of screening and management of AUD. **Results**: Response rate: 57% fellows (16 of 28), 70% faculty (16 of 23), and 71% APP (10 of 14) with an even distribution in years since training: current (38%), <10 years (31%) and >10 years (31%). Although most (96%) felt that screening was important, screening frequency varied among providers with 90% APP screening at most/every visit compared to faculty and fellows (56% vs 50%, $p=0.04$); 31% of faculty reported never/rarely screening. Comfort in screening varied among providers with more APP being very comfortable compared to faculty and fellows (90% vs 69% vs 56%, $p=0.048$). Most (90%) used the unvalidated single question (How often do you have a drink containing alcohol?) compared to validated AUDIT-C (5%, $p=0.04$). 50% felt uncomfortable using DSM-V to diagnose AUD, particularly fellows (63%). Preferred interventions were community support meetings(76%), referral to social work (55%) or addiction medicine (43%), and use of pharmacotherapy (26%), with the latter being highest among faculty compared to fellows/APP (44% vs 25% vs 0%, $p=0.047$). Most preferred that primary care (40%) or addiction medicine (23%) initiate interventions rather than GI/hepatology providers (36%) due to low rates of comfort in AUD counseling (6% vs 13% vs 10%), familiarity with pharmacotherapy (13% vs 6% vs 10%) and discomfort in prescribing pharmacotherapy (38% vs 69% vs 90%, $p=0.05$) among faculty, fellows, and APP, respectively; though most (79%) were interested in learning best practices for treating ALD patients with AUD (Figure). **Conclusion**: Screening for alcohol use in post-LT patients is low with one-third of faculty reporting never/rare screening. Notably, three-fourth of providers did not provide behavioral/pharmacotherapy interventions for AUD due to low rates of comfort in counseling and prescribing pharmacotherapy. This data highlights the need for further efforts in training and empowering gastroenterologyl/hepatology providers to deliver evidenced-based interventions for AUD among post-LT patients.

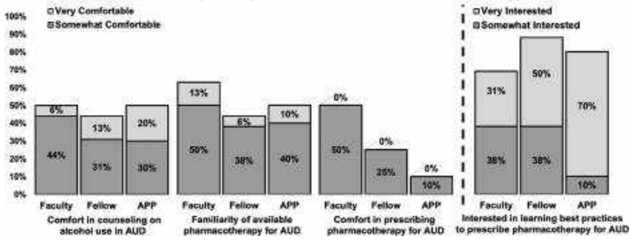
Figure. Providers perspective on counseling and management of alcohol use disorder in the post-transplant setting

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3598-C | RACIAL AND ETHNIC DISPARITIES IN ALCOHOL-ASSOCIATED LIVER DISEASE PREVALENCE AND OUTCOMES IN THE UNITED STATES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Alcohol-associated Liver Disease (ALD), which encompasses alcohol-associated hepatitis (AH), and alcohol-associated cirrhosis (AC) is on the rise in the United States (US). Racial and ethnic disparities are evident within ALD disease; however, the precise nature of these disparities is poorly defined. Therefore, we conducted a systematic review to assess racial and ethnic differences in ALD prevalence, incidence, and mortality in the US. **Methods:** We conducted a search of the PubMed/MEDLINE and EMBASE databases and national conference abstracts to identify studies published from inception through May 8, 2022, that reported ALD, AH, and AC prevalence, incidence, and mortality within the US, stratified by race and ethnicity. We calculated pooled prevalence and incidence by race and ethnicity, including odds ratios (ORs) for ALD, AH, and AC mortality using DerSimonian and Laird method for random effect models. **Results:** We identified 23 studies (18 included in quantitative meta-analysis), comprising 31,764,783 patients, that characterized disparities in ALD prevalence, incidence, or prognosis. Among the general population, ALD prevalence was highest in Hispanics (4.47%; 95%CI: 2.07-9.38), intermediate in Whites (3.13%; 95%CI: 1.53-6.31), and lowest in Blacks (2.12%; 95%CI: 1.29-3.45). Compared to Whites the pooled RR of ALD prevalence were 1.64 (95%CI: 1.12-2.39) and 0.59 (95%CI: 0.34-1.02) for Hispanics and Blacks, respectively. There was no significant difference in risk of AC among Blacks compared to Whites (RR 0.93, 95%CI: 0.77-1.12). Compared with Whites, the pooled risk of AC mortality did not differ for Hispanics (RR 1.02; 95%CI:0.76-1.38) but was significantly lower for Blacks (RR 0.82; 95%CI: 0.74-0.92) and Asians (RR 0.45; 95%CI: 0.45-0.46). Compared with Whites, there were not significant differences in all-cause mortality among Hispanics (OR 1.54, 95%CI: 0.97-2.45), Blacks (OR 1.13, 95%CI: 0.43-2.42), and Native Americans (OR 2.41, 95%CI: 0.42-13.73). Most data were cross-sectional and assessed to be of poor or fair quality. **Conclusion:** Disparities were observed in ALD, including significantly higher prevalence among Hispanics and lower among Blacks, although differences in mortality among those with ALD appear smaller. Current data remains poorly defined regarding disparities in ALD prevalence and outcomes, highlighting a need for improved epidemiological studies in this area.

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Amit G. Singal – Genentech: Consultant, No, No; AstraZeneca: Consultant, No, No; Bayer: Consultant, No, No; Eisai: Consultant, No, No; Exelixis: Consultant, No, No; Boston Scientific: Consultant, No, No; Gycotest: Consultant, No, No; Exact Sciences: Consultant, No, No; Roche: Consultant, No, No; FujiFilm Medical Sciences: Consultant, No, No; GRAIL, LLC: Consultant, Yes, No; Freenome: Consultant, No, No; Histosonics: Consultant, No, No;

The following people have nothing to disclose: Ahmad Anouti, Karim Seif El Dahan, Jeremy Louissaint, Thomas G. Cotter

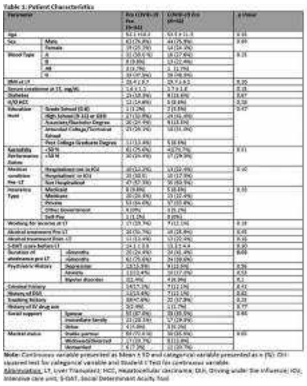
Disclosure information not available at the time of publication: William M. Lee, Mack C. Mitchell

3599-C | RECIDIVISM IN LIVER TRANSPLANT RECIPIENTS WITH ALCOHOLIC LIVER DISEASE IN COVID-19 ERA

Jiten P. Kothadia[1,2], Anwesh Dash[3], Jarrett Rong[3], Tzu-Yu Liu[1,2], Hemnishil Marella[1], Ryan Helmick[1,2], Corey Eymard[1,2], Jason M. Vanatta[1,2] and Satheesh P. Nair[1,2], (1)University of Tennessee Health Science Center, Memphis, TN, USA, (2)Methodist University Hospital, Memphis, TN, USA, (3)The University of Tennessee Health Science Center,Memphis, TN, USA

Background: Liver transplant for alcoholic liver disease (ALD) requires careful evaluation of the patients at risk for recidivism. The COVID-19 pandemic has considerably influenced alcohol use, with an increase in alcohol-related emergencies, alcohol use, and an overall negative impact on patients with alcohol use disorders. We sought to evaluate the impact of COVID-19 on recidivism in LT recipients with ALD. **Methods:** One Hundred forty patients, who underwent liver transplantation (LT) for ALD in our institution were included in the study. Patient were divided into two groups: pre-COVID-19 Era (January 2016- February 2020) and the COVID-19 Era (March 2020-November 2021). Demographics, medical history, alcohol relapse and transplant outcomes were compared between the two groups. **Results:** Among the 140 patients, 82 patients received LT in the pre-COVID-19 Era and 58 patients in the COVID-19 Era. (Table 1). In the pre-COVID-19 Era group, a greater number of patients had abstinence of 6 months or more before liver transplantation (76% vs 58, p = 0.03 %). There were no differences between the groups in overall recidivism rate and recidivism rate within 1-year of LT. Similarly, there were no difference in the length of stay, graft loss, re-admission rate, acute rejection, biliary complications, or vascular complications between the two groups. A lower rate of infection was noted in the COVID-19 Era vs. Pre-COVID Era (10.34 % vs. 25.60 % p = 0.02) (Table 2). **Conclusion:** There was no increased risk of in the alcohol recidivism rate among the patients who underwent liver transplantation during the COVID-19 Era.

Table 1: Patient Characteristics



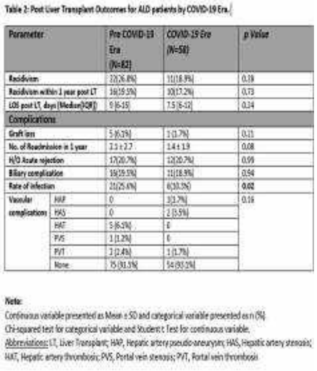


Table 2: Post Liver Transplant Outcomes for ALD patients by COVID-19 Era.

Parameter		Pre COVID-19 Era (N=82)	COVID-19 Era (N=58)	p Value
Recidivism		22(26.8%)	11(18.9%)	0.19
Recidivism within 1 year post LT		16(19.5%)	10(17.2%)	0.73
LOS post LT, days (Median(IQR))		9 (6-15)	7.5 (6-12)	0.14
Complications				
Graft loss		5 (6.1%)	1 (1.7%)	0.21
No. of Readmission in 1 year		2.1 ± 2.7	1.4 ± 1.9	0.08
H/O Acute rejection		17(20.7%)	12(20.7%)	0.99
Biliary complication		16(19.5%)	11(18.9%)	0.94
Rate of infection		21(25.6%)	6(10.3%)	0.02
Vascular complications	HAP	0	1(1.7%)	0.16
	HAS	0	2 (3.5%)	
	HAT	5 (6.1%)	0	
	PVS	1 (1.2%)	0	
	PVT	2 (2.4%)	1 (1.7%)	
	None	75 (91.5%)	54 (93.1%)	

Note:
Continuous variable presented as Mean ± SD and categorical variable presented as n (%)
Chi-squared test for categorical variable and Student t Test for continuous variable.
Abbreviations: LT, Liver Transplant; HAP, Hepatic artery pseudo-aneurysm; HAS, Hepatic artery stenosis; HAT, Hepatic artery thrombosis; PVS, Portal vein stenosis; PVT, Portal vein thrombosis

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3600-C | RESPONSE TO CORTICOSTEROID THERAPY, RECOMPENSATION, AND LONG-TERM SURVIVAL IN PATIENTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS ARE DEPENDENT ON KARNOFSKYS PERFORMANCE STATUS

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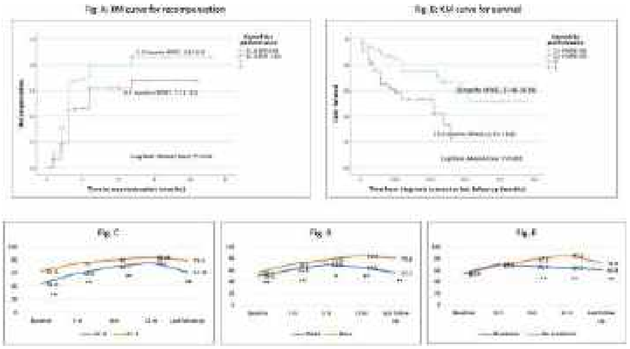
Background: Severity scores, including discriminant function score and MELD score, can predict short-term mortality in patients with severe alcohol-associated hepatitis (SAH). There are no studies evaluating the effect of the Karnofsky performance status (KPS) scores of individual's with SAH on long-term outcomes, which we aimed to assess in the prospective cohort study. **Methods:** Patients with SAH who received medical management and had complete follow-up data were included. Patients who underwent early liver transplantation were excluded. The objective was to compare the baseline characteristics and outcomes, including corticosteroid response, recompensation, and survival of patients with poor KPS (Gr.A: score < 50) vs. good KPS (Gr. B: score > 50) and lastly, to assess the dynamicity of KPS and the predictors of mortality. **Results:** 133 patients with a median follow-up of 10 months (0.5-48 mo) were included. The mean KPS score at baseline was 53.38 ± 11.73. Sixty-four patients (48%) had a score of <50 (Gr. A), and 69 patients (52%) had a score >50 (Gr.B). Severity scores at baseline were higher in Gr. A then Gr. B (MELD: 29.56 ± 4.68 vs. 26.76 ± 5.13; $P = 0.001$ and mDF: 98.87 ± 60 vs. 74.34 ± 38.57 in Gr. B; $P = 0.006$). A higher proportion of patients in Gr. A had ascites (90.6% vs. 63.8%; $P < 0.001$), acute kidney injury (34.4% vs. 7.2%; $P < 0.001$), and hepatic encephalopathy (31.3% vs. 3%; $P < 0.001$) at baseline. A similar proportion of patients received beta-blockers (14.1% vs. 21.7%; $P = 0.25$), antibiotics (norfloxacin and/or rifaximin: 62.5% vs. 55.1%; $P = 0.76$), and corticosteroid therapy (61% vs. 69.6%; $P = 0.36$). However, 60% of patients in Gr. B responded to corticosteroid therapy (Lille's <0.45) compared to only 39.1% in Gr. A ($P = 0.01$). Similarly, only 50% of Gr. A compared 76.8% of patients in Gr. B recompensated ($P = 0.002$). On Kaplan-Meier analysis, the mean time to recompensation was 9.6 months (95%CI, 7.11-12) in Gr. A compared to 6.33 months (95%CI, 4.42-8.25) in Gr. B ($P = 0.01$) (Fig. A). Furthermore, the survival was significantly higher in Gr. B (72.5%) than Gr. A (53.1%; $P = 0.03$). On Kaplan-Meier survival analysis, the mean survival was 15.5 months (95%CI,12.72-18.28) in Gr. A compared to 33 months (95%CI, 27.48-38.54) in Gr. B ($P < 0.001$) (Fig. B). KPS score remained significantly lower in Gr. A than in Gr.B till the last follow-up (Fig. C). Similarly, KPS scores remained lower in those who died (Fig. D) and those who had recidivism (Fig. E). On multivariate Cox regression analysis, poor KPS (HR,1.94 [1.04-3.62]; $P = 0.02$), ascites (HR, 3.07 [1.12-8.33];$P = 0.02$), HE (HR, 4.65 [2.44-8.86];$P < 0.001$), and recompensation (HR, 0.17 [0.9-0.33];$P < 0.001$) predicted long-term mortality. **Conclusion:** Response to corticosteroid therapy, recompensation, and long-term survival in patients with severe alcohol-associated hepatitis are dependent on Karnofsky's performance status.



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3601-C | RIFAXIMIN-Α HAS LIMITED EFFECT ON LIVER AND BRAIN PHENOTYPE IN MURINE MODELS OF EARLY STAGE ALCOHOL-ASSOCIATED AND NON-ALCOHOLIC FATTY LIVER DISEASE

Maximilian Joseph Brol[1], Sabine Klein[1], Robert Schierwagen[1], Mads Israelsen[2], Wenyi Gu[1], Maja Thiele[3], Frank Erhard Uschner[1], Nikolaj Torp[4], Jonel Trebicka[1], Aleksander Krag[5] and Manimozhiyan Arumugam[6], (1)University Hospital Münster, (2)Liver Research Centre, Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark, (3)Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark, Odense C, Denmark, (4)Odense University Hospital, (5)University of Southern Denmark, Odense, Denmark, (6)University of Copenhagen

Background: Alcohol-associated and non-alcoholic fatty liver disease (NAFLD) are rapidly increasing entities and currently the most abundant liver diseases worldwide. Knowledge on pathophysiology is indispensable for the development of therapeutic strategies. Rifaximin-α is a non-absorbable antibiotic and in clinical use in late-stage liver disease for the treatment of hepatic encephalopathy. Many studies were performed in order to evaluate the beneficial effects of Rifaximin-α on alcohol-associated and non-alcoholic fatty liver disease. Here, we aim to investigate the effects of Rifaximin-α on the liver phenotype in different murine models of early stages of fatty liver diseases. **Methods:** 7-week old, C57Bl/6 mice were treated for 7 weeks with either a Methionine-Choline deficient diet (MCD) or Western diet (WD) or standard chow ($n = 20$ per group). Mice were firstly randomized 1:1 on whether to receive Ethanol in the drinking water (stepwise increase up to 16 vol.-%) and whether to receive Rifaximin-α with a dose of 30 μg per mouse per day or not. After sacrifice, livers were phenotyped with regard to fibrosis (hydroxyproline content, Sirius red stain), inflammation (qPCR of Il1b, Tnfa, Ccl2 and F4/80-immunohistochemistry) and steatosis (hepatic triglyceride content, Oil red stain). Brains were analysed by qPCR for inflammatory markers. **Results:** As expected, MCD treatment led to decreased body weight as well as liver steatosis and fibrosis. WD treatment led to an increase in body weight, with very mild steatosis without fibrosis. The addition of ethanol increased fibrosis in MCD-treated animals, but decreased fibrosis in WD-fed mice. Rifaximin-α did not have any significant effect on liver fibrosis, steatosis or inflammation in these models. Tnfa and Il1b-levels in brains were slightly elevated in mice receiving MCD +/- ethanol compared to controls. Rifaximin-α treatment did not alter cytokine levels in brains. **Conclusion:** Ethanol displayed different effects in murine models of NALFD and NASH. Rifaximin-α treatment does not change the liver phenotype of MCD- and WD-induced early NAFLD and alcohol-associated fatty liver disease in mice . The expression of cytokines in the brain remains unchanged in early-stage liver disease and was not further affected by Rifaximin-α treatment.

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The following people have nothing to disclose: Maximilian Joseph Brol, Sabine Klein, Robert Schierwagen, Mads Israelsen, Wenyi Gu, Frank Erhard Uschner, Nikolaj Torp, Manimozhiyan Arumugam

3602-C | RIFAXIMIN-Α REDUCES CIRCULATING CERAMIDES AND INCREASES PHOSPHATIDYLCHOLINES IN PATIENTS WITH ALD: A LIPIDOME ANALYSIS OF THE GALA-RIF TRIAL

Mads Israelsen[1], Tommi Raimo Leo Suvitaival[2], Nikolaj Torp[3], Stine Johansen[3], Maximilian Joseph Brol[4], Camilla D Hansen[5], Andressa de Zawadzki[6], Sönke Detlefsen[3], Peter Andersen[7], Johanne Kragh Hansen[7], Katrine Prier Lindvig[7], Katrine Holtz Thorhauge[8], Morten Karsdal[9], Manimozhiyan Arumugam[10], Peer Bork[11], Jonel Trebicka[12], Maja Thiele[13], Torben Hansen[10], Cristina Legido-Quigley[14], Aleksander Krag[15] and the GALAXY and MicrobLiver Consortia, (1) Odense University Hospital, (2)Steno Diabetes Center Copenhagen, (3)Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, (4)University Hospital Münster, (5)Centre for Liver Research, Department of Gastroenterology and Hepatology, Odense University Hospital, (6)Nordic Bioscience a/S, (7)Liver Research Centre, Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark, (8)Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark, (9)Nordic Bioscience a/S, Denmark, (10)University of Copenhagen, (11)European Molecular Biology Laboratory, Embl, Heidelberg, (12) European Foundation for the Study of Chronic Liver Failure and Grifols Chair, Barcelona, Spain, (13) Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark, Odense C, Denmark, (14)Steno Copenhagen, (15)University of Southern Denmark, Odense, Denmark

Background: Therapeutic targets to halt alcohol-related liver disease (ALD) are highly needed. The GALA-RIF trial showed that rifaximin-α reduced progression of liver fibrosis in patients with ALD, but the mechanism of action remains unknown. The lipid metabolism plays an important role in ALD, and animal models have shown that a pharmacologic reduction of hepatic ceramides can reduce alcohol-induced liver injury. We performed plasma lipidomics from patients of the GALA-RIF trial to assess the effect of rifaximin-α on the lipid profile. **Methods:** We used plasma EDTA from the GALA-RIF trial assessing oral rifaximin-α or placebo for 18 months in a double-blind placebo-controlled 1:1 RCT in patients with biopsy-proven ALD and no previous hepatic decompensation. Plasma was sampled at baseline, after 1 month and after 18 months. Samples were analyzed using an untargeted UHPLC-QTOF/MS lipidomics platform. We performed liver biopsies at baseline and after 18 months and assessed liver fibrosis stage according to the Kleiner fibrosis score. Histological treatment response was classified as “progression”, “stable” or “regression”. Here, we report the results based on the per-protocol population (n = 108) for the completeness of the lipidomic data. **Results:** All 108 patients were Caucasian, 91 (84%) were men and the mean age was 59 (SD 9) years. Distribution of fibrosis stages at baseline was F0/F1/F2/F3/F4 = 5/31/48/18/6. Significantly fewer patients progressed in fibrosis in the rifaximin-α group (n = 13, 24%) compared to placebo (n = 23, 43%). We identified 231 lipid species from 16 lipid classes. After 1 month treatment, rifaximin-α significantly decreased the levels of 4 ceramides (Cers) and 2 phosphatidylcholines (PCs) and increased the levels of 2 phospholipids and 1 sphingomyelin (SM) compared to placebo. At 18 months, rifaximin-α had increased the levels of 7 PCs and 2 SMs while Cers were still decreased but not significant. In the rifaximin-α group, we could stratify patients who progressed in liver fibrosis by a distinctly different lipidome at baseline with significantly elevated levels of lysophosphatidylcholines, sphingomyelins and phosphatidylcholines. **Conclusion:** The beneficial effects of rifaximin-α in patients with ALD may be mediated by the modulation of the lipid metabolism, including reducing the levels of circulating hepatotoxic ceramides. Further, rifaximin-α increases the levels of fibrosis-protective phosphatidylcholines.

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3603-C | ROLE OF HEPATOCYTE MITOGEN-ACTIVATED PROTEIN KINASE PHOSPHATASE 1 (MKP1) IN SEXUAL DIMORPHISM AND SUSCEPTIBILITY TO ALCOHOL INDUCED LIVER INJURY

Mary Nancy Walter, Diego Montoya-Durango, Yali Wang, Walter Rodriguez-Alvarez, Sreelatha Reddy, Jingwen Zhang, Craig J. McClain, Shirish Barve and Leila Gobejishvili, University of Louisville, Louisville, KY

Background: It is well established that females are more susceptible to the toxic effects of alcohol. This sexual dimorphism has been attributed to a range of factors, including baseline differences in immune background and inflammatory response, although the exact mechanisms are still poorly understood. Clinical and animal studies have noted that alcohol reduces the expression of mitogen-activated protein kinase phosphatase 1 (MKP1), a negative regulator of stress MAPK pathways JNK and p38 MAPK, in the liver. However, the role of hepatocyte-specific MKP1 in the pathogenesis of ALD remains uncharacterized. This study aimed to evaluate the role of hepatocyte-specific MKP1 in the susceptibility and sexual dimorphism in alcohol-induced liver injury. **Methods:** Male and female hepatocyte-specific $Mkp1^{-/-}$ knockout (LSKO) and wild type ($Mkp1^{+/+}$ "floxed") mice were subjected to the NIAAA chronic plus binge model. Primary mouse hepatocytes were treated with 50 mM ethanol for 24 or 48 hours. Plasma alanine transaminase (ALT) and aspartate aminotransferase (AST) levels were measured to determine liver injury. Hepatic ER stress and inflammation were evaluated by real-time qPCR and multiplex assays. Statistical analysis was carried out using two- and three-way ANOVA. **Results:** Ethanol treatment resulted in a time-dependent decrease in *Mkp1* mRNA expression in primary hepatocytes in both males and females; however, this effect was significantly more pronounced in hepatocytes from females. Twenty-four hours of ethanol exposure increased mRNA expression of ER stress markers in female *Mkp1* knockout hepatocytes. *In vivo*, *Mkp1* deletion led to increased liver injury in both sexes. Notably, liver injury was significantly higher in wild-type alcohol-fed (AF) female mice when compared to males. Alcohol-mediated ER stress was also higher in LSKO female and male mice, although LSKO females seemed more susceptible to alcohol-induced ER stress than males. Examination of liver inflammatory markers showed that alcohol-fed female LSKO mice had elevated levels of hepatic IL-17, IL-15, MIP-1α (Ccl3), and IL-9 protein levels compared to their pair-fed and wild-type counterparts. **Conclusion:** Hepatocyte MKP1 plays a significant role in alcohol induced liver injury in both male and female mice. However, the disproportionate effect of alcohol on MKP1 expression in female hepatocytes makes them more susceptible to increased alcohol-induced liver injury, ER stress, and hepatic inflammation.

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Disclosure information not available at the time of publication: Yali Wang, Walter Rodriguez-Alvarez, Sreelatha Reddy

3604-C | SARCOPENIA DEFINED WITH L3-SMI IS INDEPENDENT PREDICTOR OF SURVIVAL IN MALE PATIENTS WITH ARLD IN MAINLAND CHINA

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Background: The burden of alcohol-related liver disease (ARLD) is increasing in China. Patients with ARLD are more likely to have comorbid sarcopenia, which may impair the survival of patients with ARLD. The relationship between sarcopenia and prognosis in Chinese patients with ARLD remains unclear. This study aimed to evaluate the relationship between the prognoses of patients with ARLD and sarcopenia, identified using the skeletal muscle index at the third lumbar vertebra level (L3-SMI). **Methods:** Hospitalized patients with ARLD were enrolled retrospectively between 2015 and 2018 and followed up for 24 months to evaluate their survival profiles. Cox proportional hazards regression models were used to estimate patient survival factors. A receiver operating characteristic curve was created to identify the cut-off point of the L3-SMI for predicting the prognoses of Chinese patients with ARLD. **Results:** The study enrolled 168 male patients with ARLD who were followed-up for 24 months or until a study endpoint was met. The overall L3-SMI in patients with ARLD was 42.61 ± 9.15 cm^2/m^2; 42.86% (72 /168) of patients with ARLD were comorbid with sarcopenia. The overall survival in patients with ARLD was 77.38% at 24 months. The survival rate of patients with sarcopenia was lower than that of patients without sarcopenia (66.67% vs. 85.42%, $P = 0.004$). Multiple Cox regression analysis showed sarcopenia, abstinence, and baseline creatinine were independent prognostic factors of 24-month survival with hazard ratios (95% confidence intervals) of 2.022 (1.025–3.991), 0.275 (0.122–0.617), and 1.018 (1.008–1.027), respectively. The cut-off value of the L3-SMI for predicting 24 months of survival was 40.0 cm^2/m^2 for male patients with ARLD. **Conclusion:** Sarcopenia is an independent mortality risk factor in male patients with ARLD in mainland China. Early diagnosis and intervention of sarcopenia are important for optimizing the management of patients with ARLD. Further studies with larger sample sizes are needed to verify the results.

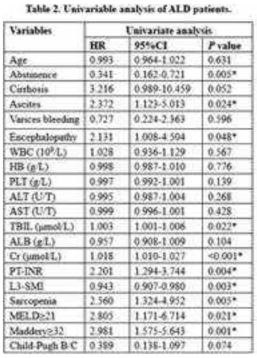

Table 2. Univariable analysis of ALD patients.

Variables	Univariate analysis		
	HR	95%CI	*P* value
Age	0.993	0.964-1.022	0.631
Abstinence	0.341	0.162-0.721	0.005*
Cirrhosis	3.216	0.989-10.459	0.052
Ascites	2.372	1.123-5.013	0.024*
Varices bleeding	0.727	0.224-2.363	0.596
Encephalopathy	2.131	1.008-4.504	0.048*
WBC (10^9/L)	1.028	0.936-1.129	0.567
HB (g/L)	0.998	0.987-1.010	0.776
PLT (g/L)	0.997	0.992-1.001	0.139
ALT (U/T)	0.995	0.987-1.004	0.268
AST (U/T)	0.999	0.996-1.001	0.428
TBIL (μmol/L)	1.003	1.001-1.006	0.022*
ALB (g/L)	0.957	0.908-1.009	0.104
Cr (μmol/L)	1.018	1.010-1.027	<0.001*
PT-INR	2.201	1.294-3.744	0.004*
L3-SMI	0.943	0.907-0.980	0.003*
Sarcopenia	2.560	1.324-4.952	0.005*
MELD≥21	2.805	1.171-6.714	0.021*
Maddery≥32	2.981	1.575-5.643	0.001*
Child-Pugh B/C	0.389	0.138-1.097	0.074

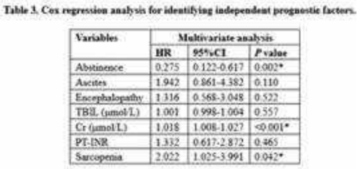

Table 3. Cox regression analysis for identifying independent prognostic factors.

Variables	Multivariate analysis		
	HR	95%CI	*P* value
Abstinence	0.275	0.122-0.617	0.002*
Ascites	1.942	0.861-4.382	0.110
Encephalopathy	1.316	0.568-3.048	0.522
TBIL (μmol/L)	1.001	0.998-1.004	0.557
Cr (μmol/L)	1.018	1.008-1.027	<0.001*
PT-INR	1.332	0.617-2.872	0.465
Sarcopenia	2.022	1.025-3.991	0.042*

Disclosures: The following people have nothing to disclose: Song Yang, Yu Zhang

f 3605-C | SERUM ARYL HYDROCARBON RECEPTOR ACTIVITY IS ASSOCIATED WITH SEVERITY AND MORTALITY IN PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS

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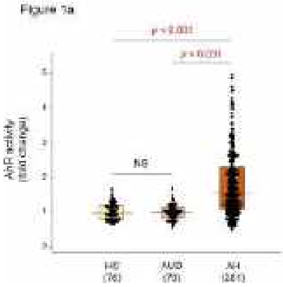
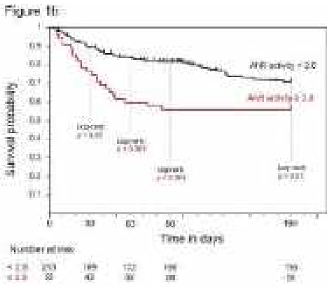
Background: Alcohol-associated hepatitis (AH) is an acute on chronic liver disease that develops in patients with a history of heavy alcohol use. Gut dysbiosis is known to be important for the pathogenesis of this disease. Our and other studies have shown that microbiota-derived tryptophan metabolites are decreased in fecal samples from patients with AH. These metabolites are also known to be ligands for the aryl hydrocarbon receptor (AhR), a transcription factor involved in immunity. The **aim** of this study is to evaluate AhR ligand activity in the serum of patients with AH and to clarify its clinical significance. **Methods:** We measured serum AhR activity of 281 patients with AH, 79 patients with alcohol use disorder (AUD), and 76 healthy controls (HC) at the time of admission to the hospital from two multicenter observational studies, InTeam and AlcHepNet. To evaluate AhR activity, we used an AhR reporter assay; HepG2-Lucia™ AhR cells (InvivoGen) were incubated with each serum sample for 24 hours and luminescence was measured. The activity value for each sample was calculated as a percentage (fold change) of the mean of all healthy samples. **Results:** The median age of AH, AUD, and HC was 45.3 years, 50.0, and 30.9, respectively. Among the AH group, 169 cases (60.4%) were male patients. The median value of the Maddrey discriminant function was 54.5 (IQR 33.2-80.7), and MELD scores was 25 (21-31). The 30, 60, 90, and 180-day mortality rates were 13.1%, 20.9%, 23.1%, and 29.9%, respectively. Patients with AH had significantly higher AhR activity levels compared with AUD and HC (median and IQR: AH 1.56 (1.07-2.28), AUD 0.97 (0.82-1.13), HC 0.96 (0.79-1.16), *p*-value HC vs. AH = < 0.001, *p*-value HC vs. AH = < 0.001, Figure 1a). The AUROC of AhR activity in diagnosing AH was 0.791 (cutoff value = 1.37, sensitivity 59.1%, specificity 94.8%, PPV 95.4%, NPV 56.1%). Within the AH patient cohort, AhR activity was positively correlated with total bilirubin ($r = 0.518$, $p < 0.001$) and MELD score ($r = 0.361$, $p < 0.001$), negatively correlated with albumin ($r = -0.204$, $p < 0.001$). The cumulative 30, 60, 90, and 180-day survival rates for the AhR activity ≥ 2.60 group were all significantly lower than those for the AhR activity < 2.60 group (30day: 76.4 vs 89.6% $p < 0.01$, 60day: 59.9 vs 83.8% $p < 0.001$, 90day: 56.2 vs 81.8% $p < 0.001$, 180day: 56.2 vs 71.0% $p < 0.01$, Log-rank test, Figure 1b). The same optimal cutoff value was used to further stratify severe AH cases with MELD 20 or higher (90-day survival rates: 57.2% (AhR activity ≥ 2.6) vs 77.6% (AhR activity < 2.6) $p < 0.01$, Log-rank test). **Conclusion:** Unlike in the gut, serum AhR activity was significantly higher in patients with AH compared with healthy subjects and patients with AUD, and is associated with increased mortality in AH patients. Serum AhR activity has the potential to serve as a prognostic marker and possibly as therapeutic target.





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The following people have nothing to disclose: Tomoo Yamazaki, Xinlian Zhang, Susan Mayo

3606-C | SEX DIFFERENCES IN LIVER TRANSPLANT OUTCOMES IN PATIENTS WITH ALCOHOL ASSOCIATED LIVER DISEASE (ALD) REFERRED FOR EARLY LIVER TRANSPLANT EVALUATION

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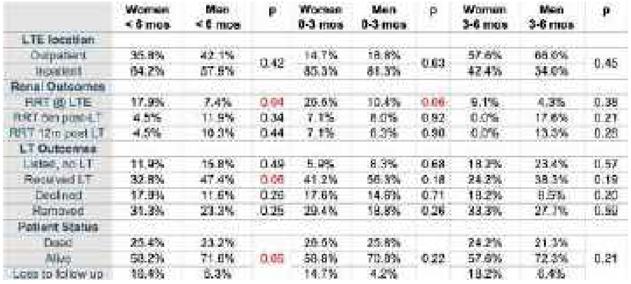
Background: Women experience increased hepatotoxicity from alcohol. Despite this, women with chronic alcohol liver disease (ALD) undergo liver transplant (LT) less than men. To date, no studies have compared outcomes in men versus women with early sobriety. We aimed to compare the impact of sex on LT access and outcomes in patients with early alcohol sobriety. **Methods:** We retrospectively analyzed patients with ALD and early sobriety (≤ 6 mo) who underwent early LT evaluation (eLTE) at our institution over 4 years (2018-2021). Patients were categorized by sobriety period: 0-3 mos vs. 3-6 mos. Pre-LT outcomes were LT candidacy (accepted vs. declined) and use renal replacement therapy (RRT) at time of eLTE. Overall outcomes were LT rate and pre-LT death rate. Variables were compared between sex; sex in this abstract refers to sex assigned at birth (male vs. female), and hereto will be referenced as men and women. Subgroup analyses were completed by sobriety period. Data was compared using Fisher's exact & t-tests. Cox regression was used to determine the effect of patient sex on risk of death up to 2 years; patients were censored at liver transplant date or last known well if lost to follow up. **Results:** 162 patients were analyzed; 67 women (41.4%) and 95 men (58.6%). More women required RRT at the time of eLTE referral than men (17.9% vs. 7.4%, p = 0.04); this difference was rooted in the 0-3 mos group. MELD did not differ by sex for the total cohort (27 women vs. 29 men), but women had a higher MELD in the 3-6 mos cohort (24 vs. 18). Serum creatinine (sCr) did not differ between men and women overall (1.96 vs. 1.91. p = 0.86). Women had higher white blood cell count (WBC) in the 0-3 mos group (17 vs. 13, p = 0.03), but not in the 3-6 mod group (not shown). Days to listing did not differ by sex [14 d in men vs. 15 d in women]. Women with early ETOH sobriety were transplanted less than men (32.8% vs. 47.4%, p = 0.06). In both the 0-3- and 3-6-month groups, LT rate was 15% less in women. When analyzing by eLTE location, the difference in LT rate was more significant in those with outpatient eLTE (12% women vs. 35% men, p = 0.04). Of those who received LT, women had fewer days on the wait list(18 d vs. 39 d). Cox regression controlling for age, sCr, sodium, bilirubin and INR demonstrated a trend between female sex and death through a 2-year period (p = 0.09). **Conclusion:** Our results suggest sex disparities in LT persist in patients with early alcohol sobriety. Despite similar or higher MELD and more severe renal dysfunction as evidenced by increased dialysis, women with early sobriety were transplanted less often than men. Given the increasing number of patients with ALD and the transition to offering earlier LT, more research should be dedicated to mitigating disparities in women who are at elevated risk of severe liver damage from alcohol.



	Women < 6 mos	Men < 6 mos	p	Women 0-3 mos	Men 0-3 mos	p	Women 3-6 mos	Men 3-6 mos	p
LTE location									
Outpatient	35.8%	42.1%	0.42	14.7%	18.8%	0.63	57.6%	66.0%	0.45
Inpatient	64.2%	57.9%		85.3%	81.3%		42.4%	34.0%	
Renal Outcomes									
RRT @ LTE	17.9%	7.4%	0.04	26.5%	10.4%	0.06	9.1%	4.3%	0.39
RRT 6m post-LT	4.5%	11.9%	0.34	7.1%	8.0%	0.92	0.0%	17.6%	0.21
RRT 12m post LT	4.5%	10.3%	0.44	7.1%	6.3%	0.90	0.0%	13.3%	0.28
LT Outcomes									
Listed, no LT	11.9%	15.8%	0.49	5.9%	8.3%	0.68	18.2%	23.4%	0.57
Received LT	32.8%	47.4%	0.06	41.2%	56.3%	0.18	24.2%	38.3%	0.19
Declined	17.9%	11.6%	0.26	17.6%	14.6%	0.71	18.2%	8.5%	0.20
Removed	31.3%	23.2%	0.25	29.4%	18.8%	0.26	33.3%	27.7%	0.50
Patient Status									
Dead	25.4%	23.2%		26.5%	25.0%		24.2%	21.3%	
Alive	58.2%	71.6%	0.05	58.8%	70.8%	0.22	57.6%	72.3%	0.21
Loss to follow up	16.4%	5.3%		14.7%	4.2%		18.2%	6.4%	

Disclosures: Deepika Devuni – Sequana Medical: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Katherine M. Cooper

3607-C | SUCCESSFUL INTEGRATION OF ALCOHOL USE DISORDER TREATMENT INTO A PRIMARY CARE-BASED LIVER CLINIC

Lana Aleuy, Siri Chirumamilla, Shelly-Ann Fluker, Lesley S. Miller and Jennifer E. Lom, Emory University School of Medicine

Background: Alcohol-related liver disease is deadly, and prevalence is increasing in the US. Access to treatment for alcohol-use disorder (AUD) is limited. To address this gap, we launched a novel service line for AUD in our primary care-based liver clinic in 2022. **Methods:** The AUD clinic is embedded in the Grady Liver Clinic (GLC) at Grady Health System, a safety-net health system in Atlanta, GA. The GLC, originally established to treat hepatitis C, is a multidisciplinary clinic, staffed by general internists. Patients are eligible for AUD clinic if they have an AUDIT-C score of 4 or more and are motivated to change their alcohol use. AUD clinic services include structured assessments, motivational interviewing, medication assisted treatment and referral to peer and behavioral health support. We retrospectively collected data on patient demographics and treatment outcomes for patients seen from 1/2022-2/2023. **Results:** Of 89 patients referred 54 unique patients attended at least one visit. Of these, 52% were referred from primary care, 37% from inpatient, 6% from the emergency department, and 6% from gastroenterology. The median age was 56, 72% were male and 87% were black. Patients had public (39%) and private (33%) insurance, and 28% were uninsured. The severity of AUD was categorized into mild (31%), moderate (31%) and severe (37%) using DSM criteria; 28% had liver cirrhosis. 71% of patients had an AUD medication prescribed, of which 68% reported taking the medication. Naltrexone was prescribed most (56%) followed by acamprosate (11%) and gabapentin (4%). In the naltrexone group, 80% had a 2nd refill and 70% had reduced alcohol cravings and decreased alcohol use. All patients within the acamprosate and gabapentin groups had a 2nd refill and reported reduced alcohol cravings and decreased alcohol use. Importantly, hospitalizations for alcohol-related complications decreased. The baseline hospitalization rates for the entire cohort in the 6 months before their first visit was 48%. The hospitalization rate during the study period was 13%. **Conclusion:** Our primary care-based AUD clinic leveraged existing infrastructure to effectively treat motivated patients for AUD. The majority of patients took prescribed medications which led to a significant decrease in alcohol related hospitalizations, supporting that this model could expand access to needed AUD care in similar settings.

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Disclosure information not available at the time of publication: Lesley S. Miller, Jennifer E. Lom

3608-C | SYSTEMIC INFLAMMATION AND LOCAL SIGNALING UPREGULATE PLATELET GALECTIN-3 BINDING PROTEIN WHICH MAY INCREASE PORTAL HYPERTENSIVE EFFECTS OF HEPATIC STELLATE CELLS IN ALCOHOL-ASSOCIATED CIRRHOSIS

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Background: Platelets have been shown to adopt a proinflammatory phenotype in alcohol-associated liver disease, but the detailed mechanisms underlying this phenotype and their role in disease progression remain understudied. **Methods:** Hospitalized patients with alcohol-associated cirrhosis (AC) with portal hypertension ($n = 17$) were compared with healthy controls without known liver disease ($n = 7$). Pure platelets were isolated for RNAseq. Human hepatic stellate cell line (HSC, LX-2 Cells) and a human megakaryocytic cell line (MEG-01 cells) were used for *in vitro* experiments. **Results:** Platelet RNA from AC with portal hypertension vs healthy controls revealed 2021 genes with $|\text{fold-change}| > 1.5$ and $p_{adj} < 0.05$. LGALS3BP (padj $1.21e^{-20}$, 9.23 fold-increase) was one of the most altered genes. This gene encodes galectin-3 binding protein (Gal3BP) which binds its receptor galectin 3 on target cells. A Liver Single Cell Atlas (liveratlas-vilarinholab.med.yale.edu) revealed high expression of galectin-3 in HSCs (7-fold increase relative to other cell clusters, $p_{adj} = 4.11 \times 10^{-154}$, and expressed by 48.8% of HSCs). LX-2 cells treated with recombinant Gal3BP showed significant upregulation of endothelin-converting enzyme 1 expression (1.3 fold-change vs control, $p = 0.02$), which mediates increased active vasoconstrictor endothelin-1 production by HSCs and exacerbates portal hypertension. Ingenuity Pathway Analysis identified TGF-beta and TNF-alpha as potential regulators. Plasma from patients with AC vs healthy controls revealed significant upregulation of TNF-alpha (21.67 pg/mL vs 12.18 pg/mL, $p = 0.02$). Recombinant TNF-alpha upregulated Gal3BP (1.3 fold-change, $p < 0.0001$) in MEG-01 cells. Patient plasma revealed decreased TGF-beta (13.3 vs 57.6 ng/mL, $p = 0.008$), but the platelet RNAseq data revealed increased TGF-beta in platelets themselves in AC vs healthy controls (1.57 fold-change, $FDR = 0.0006$), suggesting potential autocrine signaling. Recombinant TGF-beta significantly upregulated Gal3BP in MEG-01 cells (2.59 fold-change, $p < 0.0001$), and when cultured with lipopolysaccharide (LPS) and ethanol which are key stimuli in alcohol-associated cirrhosis with portal hypertension, MEG-01 cells upregulated both TGF-beta and LGALS3BP in response to LPS and ethanol combined but not either alone. TNF-alpha did not significantly alter TGF-beta in MEG-01 cells. **Conclusion:** Platelets in AC with portal hypertension contain increased Gal3BP, which exacerbates the portal hypertensive effects of HSCs. Gal3BP is regulated in megakaryocytes by potential synergy between systemic inflammation (TNF-alpha) and autocrine signaling in response to alcohol and LPS via TGF-beta. The bone marrow-liver axis may be a novel therapeutic target in portal hypertension and liver fibrosis.

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3609-C | SZN-043, A HEPATOCYTE-TARGETED R-SPONDIN MIMETIC, STIMULATES HEPATOCYTE PROLIFERATION AND IN A HUMANIZED LIVER FRG MOUSE MODEL

Trevor Fisher[1], Mehaben Patel[1], Stella Tran[1], Wen-Chen Yeh[2], Geertrui F Vanhove[2], Jay Tibbitts[3] and Helene Baribault[1], (1)Surrozen, Inc., (2)Surrozen, Inc, (3)Surrozen Inc

Background: Wnt signaling plays a central role in hepatocyte expansion during development and tissue repair. R-spondins (RSPOs) are known enhancers of Wnt signaling, via stabilization of Frizzled and LRP co-receptors. SZN-043 is a bispecific fusion protein and hepatocyte-specific R-spondin mimetic, currently in Phase 1 clinical trial for alcoholic hepatitis. SZN-043 induces hepatocyte-targeted Wnt signaling and hepatocyte proliferation in normal mice. To support the translation of this efficacy to humans, we tested the effects of SZN-043 on human hepatocyte proliferation, using the Fah/Rag2/Il2rg (FRG) humanized liver mouse model. **Methods:** 25 week old FRG triple mutant male mice repopulated with human hepatocytes were obtained from Yecuris (Tualatin, OR). After 3 days acclimation, baseline serum samples were collected on Day 0. Mice were then dosed intraperitoneally with either control antibody, 10 mpk) or SZN-043 (3 or 10 mpk). Liver samples were collected upon termination on Days 1, 2, 3, 5, and 7 for RNA and immunofluorescence analysis. **Results:** SZN-043 induced a dose-dependent increase in the human gene expression of the Wnt/β-catenin targets CYP1A2, CYP2E1, and LECT2 and the proliferation marker, MKI67. Immunofluorescence using double Ki-67 and human ASGR1 staining confirmed that SZN-043 induced a wave of human hepatocyte proliferation, peaking on Days 2 and 3, and reverting to baseline by Day 5. **Conclusion:** These results show that SZN-043 can drive human hepatocyte-proliferation in humanized liver mice. This effect suggests that SZN-043 may have meaningful clinical benefit in human disease states where hepatocyte proliferation is impaired, such as in severe alcoholic hepatitis.

Disclosures: Trevor Fisher – Surrozen: Employee, Yes, No; Surrozen: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Disclosure information not available at the time of publication: Mehaben Patel, Stella Tran, Wen-Chen Yeh, Geertrui F Vanhove, Jay Tibbitts, Helene Baribault

f 3610-C | TELOMERE LENGTH IS SIGNIFICANTLY REDUCED IN ALCOHOL-ASSOCIATED HEPATITIS COMPARED TO ALCOHOL-ASSOCIATED CIRRHOSIS AND HEAVY DRINKERS WITHOUT LIVER DISEASE

Daniel Penrice[1], Nidhi Jalan-Sakrikar[2], Puru Rattan[3], Kamalpreet S. Hara[2], Beatriz Sordi Chara[2], Tejasav Sehrawat[1], Ryan Lennon[1], Blake Kassmeyer[1], Brooke Druliner[1], Kimberly Kossick[1], Anthony Lagnado[1], Lisa Boardman[1], Jean-Pierre Kocher[4], Patrick S. Kamath[1], Vijay Shah[2] and Douglas A. Simonetto[2], (1)Mayo Clinic, (2)Mayo Clinic Rochester, Rochester, MN, (3)Mayo Clinic - Rochester, (4)Division of Biomedical Informatics, Mayo Clinic College of Medicine and Science, Rochester, MN

Background: Telomeres are DNA-protein structures located at the end of chromosomes which prevent DNA degradation and unwanted repair. Telomeres naturally shorten with ageing; however, ineffective maintenance of telomere length has been implicated in many diseases involving organs with high regenerative capacity. Alcohol-associated hepatitis (AAH) is an acute severe form of liver disease which develops in up to 30% of heavy alcohol users and is associated with high mortality. Impaired liver regeneration is one of the hallmarks of AAH and whether telomere shortening may play a role remains unknown. **Methods:** Peripheral blood mononuclear cells (PBMCs) were isolated from blood samples from 88 subjects with AAH, 64 heavy drinkers without liver disease (HD), and 59 healthy controls (HC). All subjects were enrolled in the AlcHepNet Consortium Study. Telomere length was measured in DNA isolated from PBMCs using Monochrome Multiplex Quantitative PCR (MMQPCR) and reported as telomere/single-copy gene (T/S) ratio. Liver FFPE sections were obtained from 9 subjects with AAH, 9 subjects with alcohol-associated cirrhosis (Alc Cirr), and 8 HC. Samples underwent fluorescence *in situ* hybridization with telomere probe (FISH). FISH intensity was calculated as measure of telomere length (~100 hepatocytes/subject) in a blinded fashion. P-values for group comparisons were calculated with one-way ANOVA. **Results:** Median PBMC T/S ratio was 1.29 (Q1: 1.16, Q3: 1.48) in the HC group, 1.23 (1.03, 1.41) in the HD group, and 1.13 (1.00, 1.26) in the AAH group ($P < 0.001$) (Figure 1A). The HC group was younger (mean age 35) and had a lower proportion of males (32%), however HD and AAH groups were similar (64% vs 55% males, and 48 vs 46 median age. The HD group also consumed more alcohol than the AAH group, 140 g/day vs 112 g/day ($P < 0.001$) respectively. No relationship was observed between T/S ratio and lifetime alcohol use ($r = 0.02$, $p = 0.85$). Additionally, no relationship was noted between T/S ratio and MELD score ($r = 0.02$, $p = 0.87$). Median telomere intensity score (TSI) in liver tissue samples was 718 (635.7, 898.2) in the healthy control group, 561 (489.4, 598.5) in the Alc Cirr group, and 491 (428.0, 583.2) in the AAH group ($P = 0.008$) (Figure 1B). The significantly decreased telomere length in the AAH group was seen despite subjects being younger than the cirrhosis group (median age 34.1 in AAH, 46.5 in Alc Cirr, and 49.8 in HC). **Conclusion:** Significantly reduced telomere length was observed in PBMCs and hepatocytes of patients with AAH. These findings suggest global accelerated telomere attrition in AAH rather than an organ-specific phenomenon which may carry diagnostic, prognostic, and therapeutic implications.

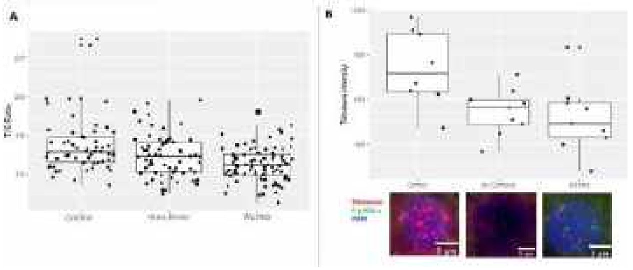
Figure 1 A/B: A. Peripheral (PBMC) cohort characteristics, B. Central (FFPE) staining images and overall telomere intensity

Disclosures: The following people have nothing to disclose: Daniel Penrice, Nidhi Jalan-Sakrikar,

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

Kamalpreet S. Hara, Beatriz Sordi Chara, Tejasav Sehrawat, Jean-Pierre Kocher, Vijay Shah, Douglas A. Simonetto
Disclosure information not available at the time of publication: Puru Rattan, Ryan Lennon, Blake Kassmeyer, Brooke Druliner, Kimberly Kossick, Anthony Lagnado, Lisa Boardman, Patrick S. Kamath

3611-C | THE CHARACTERISTICS OF ALCOHOL USE DISORDER IN PATIENTS AFTER BARIATRIC SURGERY

Robert Gaffey[1], Joel Rosiene[1], Melissa Fazzari[2], Kristina R. Chacko[1] and Clara Tow[1], (1)Montefiore Medical Center, (2)Albert Einstein College of Medicine

Background: Prior studies have shown that bariatric surgery predisposes patients to alcohol use disorder (AUD) and alcohol-associated liver disease (ALD). Multiple studies have demonstrated this link, but there are currently no studies examining time of incident AUD or patient characteristics associated with AUD diagnosis, specifically demographic, diagnostic and laboratory data of these patients. Aims: To determine the time to AUD diagnosis after bariatric surgery and the characteristics and degree of liver dysfunction at time of diagnosis. **Methods:** Using ICD-10 codes, we retrospectively reviewed all patients who underwent bariatric surgery (BS) versus elective cholecystectomy (CCY) at a single urban center between 2015-2020. We excluded those with previously diagnosed AUD, chronic liver disease and those under 21 years of age at time of surgery. We collected sociodemographic information and clinical parameters, including body mass index (BMI), platelets, and liver tests. FIB-4 was calculated when possible. Data were collected prior to surgery, at the time of surgery and at one-year intervals for a maximum of five years. Associations with time to AUD diagnosis were assessed via Cox proportional hazards modeling. **Results:** There were 9335 patients in the cohort: 5696 underwent BS and 3639 underwent CCY. The cohort was diverse with 19% black, 52% Hispanic, and 11% without reported race or ethnicity. There were more women than men (82.2% vs 17.8%). BMI and weight were higher in the bariatric surgery group, as were rates of hypertension, hyperlipidemia, and diabetes. Baseline labs were similar. The average time to AUD diagnosis was 932 days in the BS group and 651 days in the CCY group. There were 169 incident events of AUD in the cohort, 58 post-CCY and 111 post-BS. Univariate analysis showed that female sex, Hispanic ethnicity, and self-identified black race were associated with shorter time to incident AUD for the whole cohort. There was no association between baseline laboratory parameters and time to AUD. Baseline FIB-4 was low and similar between groups. FIB-4 at time of AUD diagnosis was intermediate in the CCY group (mean of 1.9) and low in the BS group (mean of 1.3) ($p = 0.07$). In multivariate analysis, BS was not associated with AUD when compared to the CCY group, but female sex was in both the whole cohort and the BS group. In the bariatric cohort, race, ethnicity, age at surgery, baseline metabolic risk factors, and BMI were not associated with earlier incidence of AUD. **Conclusion:** Our study uniquely examines the characteristics of bariatric surgery patients with incident AUD in a diverse population. Our study does not show an association between BS and AUD when compared to CCY. AUD diagnosis occurs significantly later in BS patients than CCY patients and at higher rates in female patients. Our study did not find laboratory evidence of liver disease at the time of AUD diagnosis.

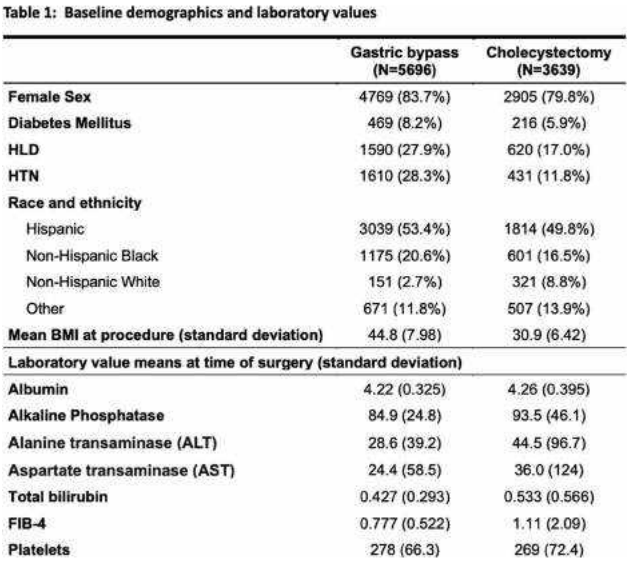

Table 1: Baseline demographics and laboratory values

	Gastric bypass (N=5696)	Cholecystectomy (N=3639)
Female Sex	4769 (83.7%)	2905 (79.8%)
Diabetes Mellitus	469 (8.2%)	216 (5.9%)
HLD	1590 (27.9%)	620 (17.0%)
HTN	1610 (28.3%)	431 (11.8%)
Race and ethnicity		
Hispanic	3039 (53.4%)	1814 (49.8%)
Non-Hispanic Black	1175 (20.6%)	601 (16.5%)
Non-Hispanic White	151 (2.7%)	321 (8.8%)
Other	671 (11.8%)	507 (13.9%)
Mean BMI at procedure (standard deviation)	44.8 (7.98)	30.9 (6.42)
Laboratory value means at time of surgery (standard deviation)		
Albumin	4.22 (0.325)	4.26 (0.395)
Alkaline Phosphatase	84.9 (24.8)	93.5 (46.1)
Alanine transaminase (ALT)	28.6 (39.2)	44.5 (96.7)
Aspartate transaminase (AST)	24.4 (58.5)	36.0 (124)
Total bilirubin	0.427 (0.293)	0.533 (0.566)
FIB-4	0.777 (0.522)	1.11 (2.09)
Platelets	278 (66.3)	269 (72.4)

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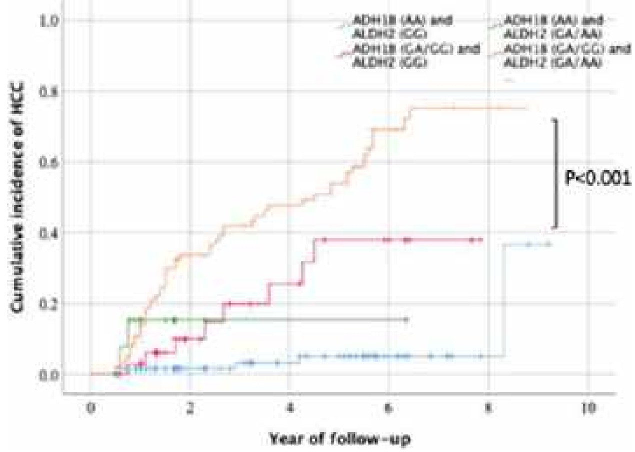
Disclosure information not available at the time of publication: Joel Rosiene, Melissa Fazzari, Kristina R. Chacko, Clara Tow

3612-C | THE CORRELATION OF HEAVY ALCOHOL CONSUMPTION AND ADH1B AND ALDH2 rs671 POLYMORPHISM WITH HEPATOCELLULAR CARCINOMA IN PATIENTS WITH HEPATITIS B VIRUS-RELATED CIRRHOSIS

Chih Wen Lin[1,2], Wen-Lung Wang[1,2], Ming-Chao Tsai[3,4], Sien-Sing Yang[5], Chih-Che Lin[3,4], Yao-Chun Hsu[2,6], Jaw-Town Lin[1], Yaw-Sen Chen[1], Hui-Ting Hu[5], Steven Yu Lin[1,2,7] and Ming-Lung Yu[3,8,9,10], (1)E-Da Hospital, I-Shou University, (2)I-Shou University, (3) Kaohsiung Chang Gung Memorial Hospital,, (4)Chang

Gung University, (5)Cathay General Hospital, Taipei, Taiwan, (6)E-Da Cancer Hospital, I-Shou University, (7) Kaohsiung American School, (8)Kaohsiung Medical University, Kaohsiung, Taiwan, (9)Hepatobiliary Section, Department of Internal Medicine, and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, (10)National Sun Yat-Sen University

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

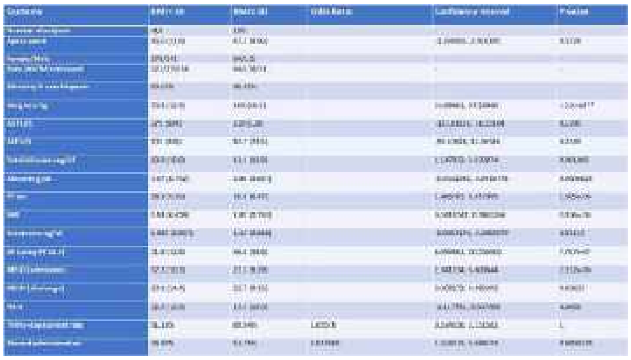


Disclosures: The following people have nothing to disclose: Chih Wen Lin, Wen-Lung Wang, Ming-Chao Tsai, Sien-Sing Yang, Chih-Che Lin, Yao-Chun Hsu, Jaw-Town Lin, Yaw-Sen Chen, Hui-Ting Hu, Steven Yu Lin, Ming-Lung Yu

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

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

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



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

the research grant and manages the funds), No, No; Bristol Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Astra Zeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Marcus Allen Healey, Geetha Ramalingam, Yiwei Hang, Ekaterina Smirnova, Vaishali Patel, Hannah Lee, Scott C. Matherly, Mohammad S. Siddiqui, Joel P. Wedd, Richard K. Sterling

Disclosure information not available at the time of publication: Velimir A. Luketic

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

Wanzhu Tu[1], Lauren D. Nephew[2], Craig J. McClain[3], Samer Gawrieh[4], Srinivasan Dasarathy[5], Vatsalya Vatsalya[3], Douglas A. Simonetto[6], Qing Tang[7], Bruce Barton[8], Gyongyi Szabo[9], Patrick S. Kamath[10], Arun Sanyal[11], Laura E. Nagy[5], Mack C. Mitchell[12], Svetlana Radaeva[13], Vijay Shah[6], Naga P. Chalasani[14], Ramon Bataller[15] and the AlcHepNet Investigators, (1) Department of Biostatistics and Health Data, Indiana University School of Medicine, Indianapolis, in, (2) University of Pennsylvania, Indianapolis, IN, (3) University of Louisville, Louisville, KY, (4)Indiana University School of Medicine, Indianapolis, IN, (5) Cleveland Clinic Foundation, (6)Mayo Clinic Rochester, Rochester, MN, (7)Indiana University, (8)University of Massachusetts Memorial Health Care, (9)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (10)Mayo Clinic, Rochester, MN, (11) Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA, (12) University of Texas Southwestern Medical Center, (13) NIAAA, (14)Indiana University Medical Center, Indianapolis, IN, (15)Barcelona Clinic, Barcelona, Spain

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

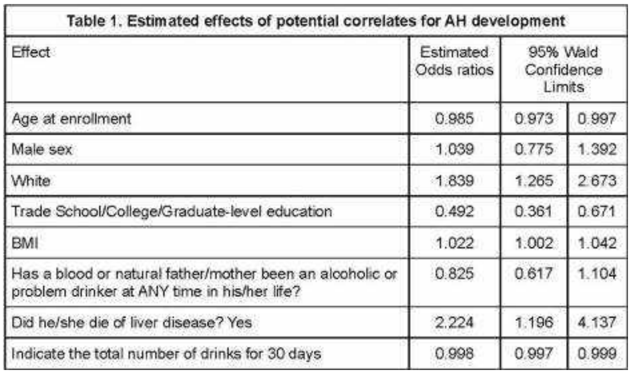

Table 1. Estimated effects of potential correlates for AH development

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

Disclosures: Lauren D. Nephew – Delfi Diagnostics: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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Disclosure information not available at the time of publication: Qing Tang, Bruce Barton, Patrick S. Kamath, Mack C. Mitchell, Svetlana Radaeva

3615-C | THE LANDSCAPE OF INPATIENT ADMISSIONS FOR ALCOHOLIC HEPATITIS IN THE ERA OF EARLY LIVER TRANSPLANTATION

Shahana Prakash, University of Iowa Hospitals and Clinics and Tomohiro Tanaka, University of Iowa Hospitals and Clinics, Iowa City, IA

Background: Liver transplant (LT) is a recent option available in the United States (US) to treat those with severe, refractory alcoholic hepatitis (AH). We examined changes in clinical characteristics of patients admitted with AH and determined how hospital cost, length of stay (LOS), and mortality have changed as practice changes involving LT have shifted. **Methods:** Using the National Inpatient Sample, we performed a cross-sectional analysis of patients admitted with AH during the years 2016-2020 in the US. Differences in clinical characteristics over time were assessed. To compare outcomes between 2016-2017 (when LT was less common) and 2018-2020 (when LT was more common), we conducted linear and logistic regression. Propensity-score matching was used to compare outcomes between patients with and without LT. **Results:** In 2018-2020 (n = 22,072 hospitalizations), compared to 2016-2017 (n = 16,946 hospitalizations), patients admitted with AH tended to have a higher frequency of infection (p = 0.006), hepatorenal syndrome (< 0.001), and ascites (< 0.001). Hospital costs and length of stay (LOS) were highest in transplant hospitals (n = 96 in 2016-2017, n = 274 in 2018-2020), even when LT-related admissions were excluded in years 2018-2020 [LOS: p < 0.001; cost: p = 0.06 compared to non-transplant (NT) teaching hospitals, p < 0.001 compared to NT non-teaching hospitals]. Use of palliative care consult remained low (< 5%), regardless of hospital type. Costs rose over time in both NT teaching (n = 11,090 in 2016-2017 and n = 15,781 in 2018-2020) and non-teaching hospitals (n = 5,760 in 2016-2017 and n = 6,017 in 2016-2017), by on average $4,500 an $3,900, respectively (p < 0.001). Mortality decreased in NT teaching hospitals [aOR 0.7 (95% CI: 0.6-0.8)] and slightly decreased in NT non-teaching hospitals [aOR 0.7 (95% CI: 0.5-1.0)]. In transplant hospitals, there was no change in mortality over time in the unadjusted model. In the propensity-matched cohort involving LT versus non-LT patients (n = 30 in each group), there was a 13% absolute reduction in in-hospital mortality, but this came at about a four-fold higher cost (p < 0.001) and a two-fold longer length of stay (p < 0.001). **Conclusion:** The severity of AH has been increasing over time, yet mortality has declined, after adjusting for severity of disease. All patients who underwent LT survived. However, there is a considerable healthcare burden associated with optimizing patients for potential transplant and performing LT itself.

Disclosures: The following people have nothing to disclose: Shahana Prakash, Tomohiro Tanaka

3616-C | THE MECHANISMS OF ZHIZI DAHUANG DECOTION IN THE TREATMENT OF ALCOHOLIC LIVE DISEASE BY INHIBITING THE OXIDATIVE STRESS IN NEUTROPHILS

Junhua Feng, Yiwen Hou, Jiaxin Tan, Qian Li, Rongjie Zhang, Yueqiu Gao and Man Li, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine

Background: Zhizi Dahuang Decotion (ZZDHD) is a traditional Chinese formula, which have effects on treating alcoholic liver disease(ALD) , but its mechanisms are still poorly understood.We aim to study the mechanisms of ZZDHD in the treatment of alcoholic liver disease by regulating the oxidative stress in neutrophils, and to screen its effective monomers. **Methods:** An ALD model has been established in C57BL/6J mice treated according to the Gao-binge modeling method. We investigated the effects of ZZDHD on regulating levels of inflammation as well as oxidative stress in neutrophils in mice with ALD using biochemical assays, real-time PCR, and Western blot. Effective components in blood and liver tissue were screened by Ultra-High Performance Liquid Chromatography, analysis combined with Network Pharmacology to explore the potential therapeutic monomers for ALD and in mice validation. **Results:** I ZZDHD can alleviate inflammation response, reduce lipid deposition and oxidative stress in mice with ALD. a ZZDHD can alleviate neutrophil infiltration of liver in mice with ALD, and the effect was blocked by neutrophil depletion. b ZZDHD can inhibite expression of NADPH oxidases in neutrophils. c Geniposide can ameliorate liver damage in mice with ALD, as one of the effective components in ZZDHD. **Conclusion:** Our results suggests that ZZDHD can treat ALD by reducing lipid accumulation and oxidative stress in liver, the mechanism is related to inhibiting neutrophil infiltration of liver and expression of NADPH oxidases, Geniposide is an effective monomer in ZZDHD.

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3617-C | THE MELD 3.0 IS NOT SUPERIOR TO THE MELD-NA IN PREDICTING THE SURVIVAL OF CHINESE PATIENTS WITH ALCOHOL-RELATED LIVER DISEASE: A RETROSPECTIVE COHORT STUDY

Chen Liu, Fangfang Duan, Hang Zhai, Min Quan, Jun Cheng and Song Yang, Beijing Ditan Hospital, Capital Medical University, Beijing, China

Background: The model for end-stage liver disease (MELD) 3.0 yields high prognostic performance for patients with end-stage liver disease (ESLD). However, its prognostic performance for patients with alcohol-related liver disease (ARLD) has not been determined. The aim of this study was to perform such an evaluation among Chinese patients. **Methods:** Patients hospitalized with ARLD in one institution from 2015 to 2018 were retrospectively included and followed up for 12 months. The original MELD, MELD-Na, MELD 3.0, and modified Maddrey discriminant function (MDF)

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

scores were calculated for each patient at baseline. Their prognostic performances for 1-year survival were assessed. Time-dependent receiver operating characteristic curves were constructed, and AUCs were calculated for each scoring system. **Results:** Among the 379 patients included in our analysis, 132 patients had alcoholic hepatitis (AH). By the 1-year follow-up, 22.7% (86/379) of all the patients and 38.6% (51/132) of those with AH had died. Overall, patients who had died had higher MELD, MELD-Na, MELD 3.0, and MDF scores (all $P < 0.001$) than those who did not. The same was true in the AH subgroup (MELD: $P < 0.001$, MELD-Na: $P < 0.001$, MELD 3.0: $P = 0.007$, MDF: $P = 0.017$). The AUC of the MELD 3.0 for prediction of 1-year survival among patients with ARLD was 0.704, lower than that of the original MELD (0.743, $P = 0.017$) and MELD-Na (0.751, $P = 0.001$). Moreover, among the AH subgroup, its AUC for prediction of 1-year survival was lower than that of the MELD-Na group (0.639 vs. 0.712, $P = 0.006$). **Conclusion:** The MELD 3.0 was not superior to the original MELD or the MELD-Na in predicting the prognosis of patients with ARLD.

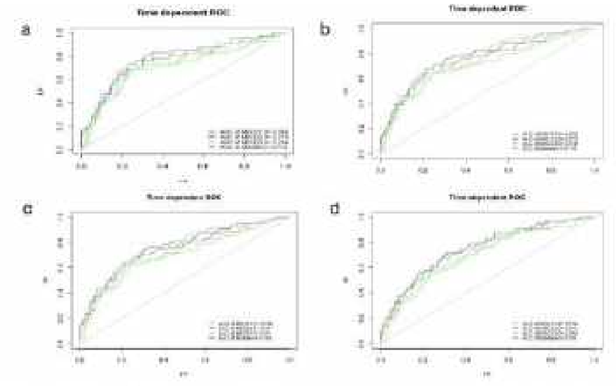

Figure 1. The ROC curves of different score in patients with alcohol-related liver disease. (a) 1-month; (b) 3-month; (c) 6-month; (d) 12-month.

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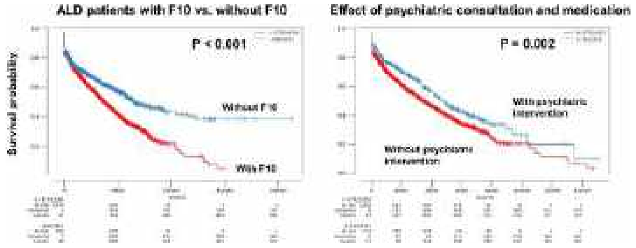
3618-C | THE PROGNOSTIC IMPACT OF PSYCHIATRIC INTERVENTION ON ALCOHOL-ASSOCIATED LIVER DISEASE: A PROSPECTIVE STUDY OF UK BIOBANK COHORT

Keungmo Yang[1], Sunghwan Kim[1,2], Hyun Yang[1] and Si Hyun Bae[1], (1)The Catholic University of Korea, (2) Korea Advanced Institute for Science and Technology

Background: Alcohol-associated liver disease (ALD) is a public health concern, with a high morbidity and mortality rate. Psychiatric comorbidity is common among individual's with ALD and may negatively impact disease progression and outcomes. However, limited evidence exists regarding the prognostic impact of psychiatric interventions on ALD. This prospective study aims to investigate the survival benefits of psychiatric intervention in the treatment of ALD within the UK Biobank cohort. **Methods:** This prospective study included a total of 502370 participants. Among ALD patients, they were divided into two groups: those with psychiatric disorders and those without. Psychiatric disorders were defined based on the inclusion of ICD-10 code F10 (mental and behavioral disorders due to use of alcohol). Psychiatric intervention was determined by the consultation with psychiatrists during hospitalization or the history of medication related to alcohol use disorder (AUD). Survival analysis was performed to examine the prognostic impact of psychiatric intervention on ALD outcomes. **Results:** A total of 2417 ALD patients were included in the final analysis, with 1630 having F10 and 787 without F10. There were no significant differences in baseline characteristics, except for alcohol consumption, between the two groups. Patients with F10 had significantly lower average age of death compared to those without F10 ($P < 0.001$), indicating that having F10 is a poor prognostic factor for ALD patients. Among patients with F10, 221 received consultation for psychiatrists during hospitalization, and 221 had records of medication intake for AUD. Patients who received psychiatric consultation (Median OS 7.5 vs. 4.9 years; $P = 0.033$) and those who took related medications (Median OS 7.0 vs. 5.2 y; $P = 0.002$) presented a significant improvement in long-term overall survival (OS) rates. Psychiatric consultation and antidepressant intake were also identified as favorable prognostic factors in both univariate and multivariate analyses. **Conclusion:** This study demonstrates that psychiatric intervention has a favorable impact in ALD patients with psychiatric comorbidity. These findings emphasize the importance of integrated management for ALD patients, addressing both the medical and psychiatric aspects. The results support the potential benefits of psychiatric interventions in improving outcomes for individual's with ALD.

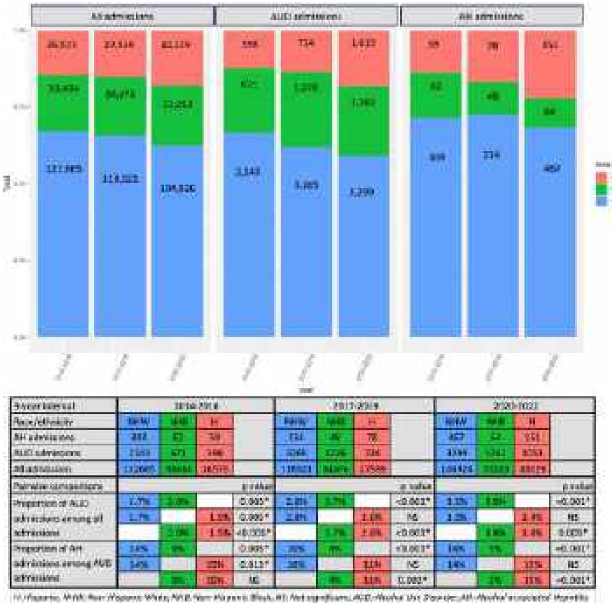


Disclosures: The following people have nothing to disclose: Keungmo Yang, Sunghwan Kim, Hyun Yang, Si Hyun Bae

3619-C | THE ROLE OF RACE AND ETHNICITY ON THE CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS

Anahita Rabiee, Praveena Narayanan, Pramod K. Mistry and Tamar H. Taddei, Yale University, New Haven, CT

Background: Alcohol-associated Hepatitis (AH) is a major cause of alcohol related morbidity and mortality in the United States. Racial and ethnic differences may contribute to the presentation and outcome of AH, through cultural differences influencing alcohol use patterns, social support, access to health care, and genetic predispositions. Our goal was to explore the role of ethnicity and race in the prevalence, characteristics, severity, and outcomes of AH. **Methods:** We conducted a retrospective chart review of all patients with AH who were admitted to a single tertiary health system between 2014 and 2022. Patients had to have an AH ICD code *and* meet clinical criteria for AH (defined as total bilirubin > =3, AST to ALT ratio of > 1.5, AST and ALT < 400). Self-reported race and ethnicity data were used. Patients with no race or ethnicity data, or races representing < 1% of the sample were excluded. To incorporate both race and ethnicity, patients were categorized as: Hispanic, Non-Hispanic White (NHW), and Non-Hispanic Black (NHB). In addition, the total number of all admissions and admissions related to alcohol use disorder (AUD) from 2014 to 2022 were obtained. Continuous variables with non-normal distributions were compared using Kruskal-Wallis rank sum test, and categorical variables were compared using Chi square test. **Results:** From a total of 530,976 admissions to our system between 2014 to 2022, 14,051 (3%) were AUD admissions, of which, 1,566 (11%) were AH admissions. A total of 921 unique patients with AH were identified, among whom, 683 (74%) were NHW, 143 (16%) were Hispanic, and 95 (10%) were NHB. Among Hispanics, 25% identified as White, and 3% as Black. Hispanic patients were significantly younger (median age: Hispanic: 45, NHW: 51, NHB: 55, p= < 0.001) and had lower MELD-Na at presentation (median MELD-Na: Hispanic: 20, NHB: 22, NHW: 25, p= < 0.001). Hispanic patients had significantly lower 30-day mortality (Hispanic: 7%, NHB: 9.5%, NHW: 15.4%, p = 0.014) and 90-day mortality (Hispanic: 14%, NHB: 14.7%, NHW: 21.7%, p = 0.048). There was a statistically significant association between race/ethnicity and AUD and AH admissions. The highest proportion of AUD admissions was among NHB compared to NHW or Hispanics. However, NHB patients had the lowest proportion of AH admissions among AUD admissions across all 3 historic intervals (Figure 1). **Conclusion:** Race and ethnicity are major factors affecting the severity and outcomes of AH, with NHW demonstrating more severe disease at presentation and higher short-term mortality compared to both Hispanics and NHB. The proportion of AUD admissions was highest in NHB compared to NHW and Hispanics in our health system. However, admissions for AH among AUD admissions, disproportionately affected NHW and Hispanic patients compared to NHB. Future research is needed to investigate the underlying reasons for these findings.



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Disclosure information not available at the time of publication: Pramod K. Mistry, Tamar H. Taddei

3620-C | THE SIGNIFICANCE OF FIRST-DEGREE FAMILY HISTORY OF ALCOHOL CONSUMPTION AS A MAJOR PREDICTOR FOR RELAPSE IN PATIENTS ADMITTED FOR ALCOHOL ASSOCIATED HEPATITIS

Adalberto Guzman[1], Evelyn Calderon Martinez[1], Wern Lynn Ng[1], Anas Atrash[1] and Douglas M. Levin[2], (1) UPMC, (2)Ohio State University, Columbus, OH, United States

Background: Alcohol associated hepatitis is characterized by inflammation and liver damage resulting from excessive alcohol consumption. Despite advancements in treatment, the risk of relapse remains high among patients with alcohol associated hepatitis, leading to poor outcomes. Identifying predictors of relapse is crucial for developing effective intervention strategies and improving patient outcomes. **Methods:** This study aimed to

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investigate the significance of first-degree family history of alcohol consumption as a major predictor for relapse in patients admitted for alcohol associated hepatitis. A comprehensive analysis was conducted on a cohort of 47 patients diagnosed with alcohol associated hepatitis and followed up for 3 months after discharge. **Results:** Among the enrolled patients, 33 (70%) who experienced relapse had a first-degree family history of alcohol consumption, revealing a significant association between familial alcohol consumption and a higher likelihood of relapse during the follow-up period. This finding suggests that patients with a positive family history were 2.5 times more susceptible to relapse compared to those without such a family history. Notably, patients with a first-degree family history exhibited a shorter time to relapse, approximately 17 to 23 days, in contrast to patients without such familial influences. These results, derived from a cohort of 47 patients, offer valuable insights into the link between a first-degree family history of alcohol consumption and relapse in alcohol associated hepatitis. The observed shorter time to relapse in patients with a positive family history underscores the importance of targeted interventions and heightened support for this specific subgroup of patients. By recognizing the influence of familial factors on relapse risk, healthcare providers can develop personalized strategies to enhance treatment outcomes and prevent relapses in individual's with alcohol associated hepatitis and a family history of alcohol consumption. **Conclusion:** Further research is warranted to delve into the underlying mechanisms that connect a family history of alcohol consumption to the increased risk of relapse in individual's with alcohol associated hepatitis. Understanding the specific genetic, environmental, and psychosocial factors involved can provide valuable insights into the complex interplay between familial influences and relapse vulnerability. Additionally, investigating the effectiveness of interventions tailored specifically to patients with a positive family history is essential for optimizing relapse prevention strategies and improving the overall management of alcohol associated hepatitis.

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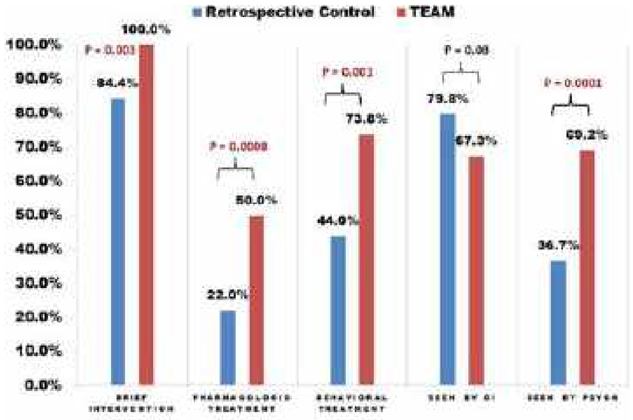
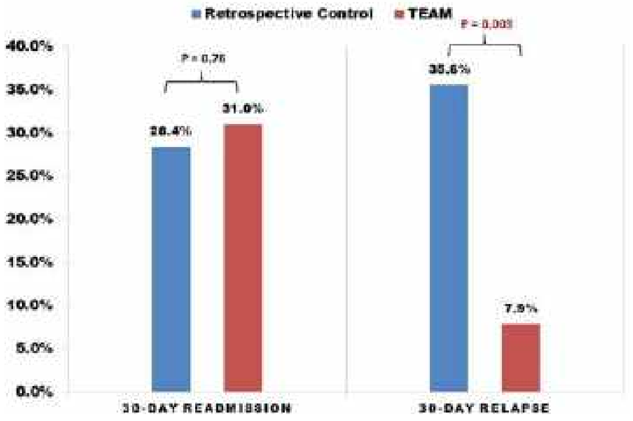
3621-C | THE TREATMENT EDUCATION FOR ALCOHOL MISUSE (TEAM) STUDY: A NOVEL INTERACTIVE VIDEO MODULE ABOUT ALCOHOL USE DISORDER FOR HOSPITALIZED PATIENTS

Patrick Twohig[1], Zachary Benton-Slocum[1], Anna Willet[1], Makayla Schissel[1], Alena Balasanova[1], Kyle Scholten[1], Joshua Warner[1], Tomoki Sempokuya[2,3], Nathalie Khoury[1], Allison Ashford[1] and Thoetchai (Bee) Peeraphatdit[1], (1)University of Nebraska Medical Center, (2)Queen's Medical Center, Honolulu, HI, (3) University of Hawaii

Background: Alcohol-associated liver disease (ALD) accounts for 50% of all liver-related deaths and is the most common reason for liver transplantation in the United States. Despite the availability of efficacious treatment for alcohol use disorder (AUD), very few patients are offered treatment. Providers endorse a lack of knowledge surrounding available treatments and how to prescribe them. **Methods:** Prospective single-center cohort study evaluating the impact of a novel, interactive patient educational video module (EVM) at increasing treatment rates for hospitalized patients with AUD and ALD from December 2022 to March 2023. Patients <18 years old, who declined education, were unable to provide consent, or not hospitalized were excluded. Treatment was defined as receiving medication or participating in behavioral treatment within 30 days of discharge. Primary aim was to improve AUD treatment rates compared to a retrospective control cohort of AUD/ALD patients at our medical center from 2018-2020. AUD treatment rates, alcohol consumption patterns, and 30-day readmission/relapse rates were evaluated within the TEAM group and compared to control. We also received patient feedback on the EVM. **Results:** Of 62 eligible patients, 52 consented to participate (83.8%), and 42 were included in the analysis (5 died, 4 were lost to follow-up, and 1 received a liver transplant). Mean age 45 years, 50% female, mean MELD-Na 15.5. More patients in the TEAM cohort received any AUD treatment compared to control (85.7% vs. 51.3%, $p = 0.0001$). There were no significant differences in AUD treatment rates based on demographics, liver disease severity, or having received prior treatment. AUD treatment rates significantly increased for pharmacologic (22% to 50%, $p = 0.0008$) and behavioral treatment (44% to 73.8%, $p = 0.001$, and thirty-day relapse was significantly lower compared to control (7.9% vs. 35.6%, $p = 0.003$). After viewing the EVM, patients had significant reductions in self-reported number of drinks per day ($p < 0.0001$) and serum pETH levels ($p = 0.008$), and significant increases in pharmacologic ($p = 0.02$) and behavioral ($p = 0.003$) treatment rates at 30-day follow-up. 92.5% of patients found the EVM helpful and 100% would recommend it to others. **Conclusion:** Standardized EVM about AUD treatment can significantly increase treatment rates while reducing 30-day relapse. Most patients consented to participate, found the EVM helpful, and unanimously would recommend it to others. Increased efforts should be made to educate patients about AUD and available treatment options while hospitalized.





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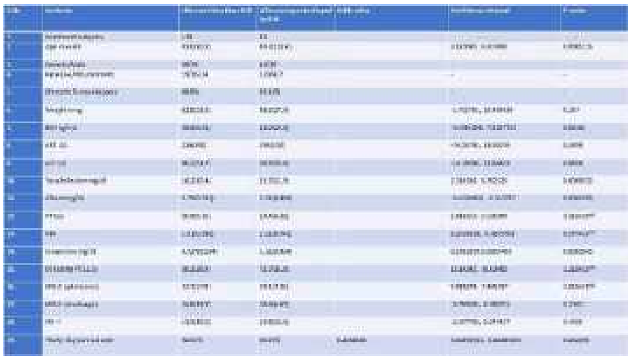
3622-C | THE UTILITY OF LILLE SCORE IN PREDICTING 30-DAY SURVIVAL IN STEROID-TREATED ACUTE ALCOHOLIC HEPATITIS

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

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

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



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

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

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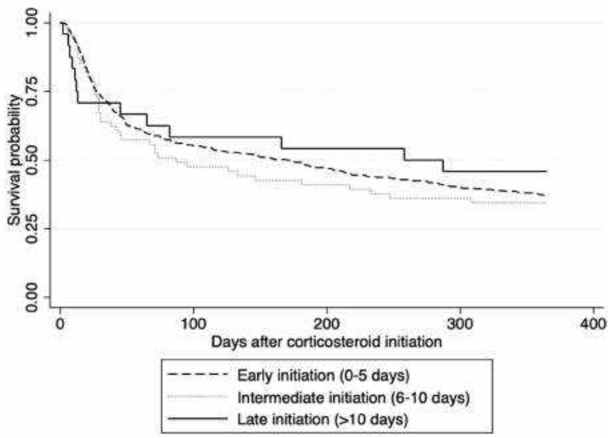
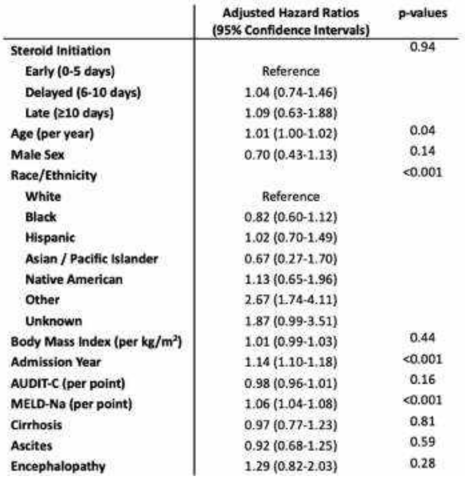
hepatitis (AH) to reduce short-term mortality, few data inform the urgency of steroid initiation. In clinical trials, steroid initiation occurred after 6-14 days, but in clinical practice there is perceived urgency to initiate steroids earlier. No studies to date have compared early versus delayed initiation of steroids on mortality in this population. **Methods:** This was a retrospective cohort study of patients on their first admission for severe AH (Maddrey's Discriminant Function $\geq$ 32) treated with corticosteroids in the Veteran's Health Administration from 1/3/2005-6/1/2022. Admissions were identified via a validated algorithm using International Disease Classification discharge codes and laboratory values. Time-to-event analyses evaluated the association between timing of steroid initiation (early, intermediate, and late initiation starting 0-5, 6-10, and > 10 days after admission, respectively) and overall survival. Multivariable Cox models were adjusted for age, sex, race/ethnicity, body mass index, treatment year, Alcohol Use Disorders Identification Test (AUDIT-C) score, Model for End Stage Liver Disease (MELD-Na) score, cirrhosis, ascites, and hepatic encephalopathy on admission. **Results:** 1,932 patients on their first admissions for severe AH were identified during the study period, of which 843 (43.6%) received corticosteroids. 723 (85.8%), 82 (9.7%), and 38 (4.5%) of these patients had early, intermediate, and late corticosteroid initiation, respectively. Patients with early initiation had significantly higher AUDIT-C scores, lower rates of hepatic decompensation and ascites, and shorter lengths-of-stay compared to those with intermediate or late initiation (all $p < 0.05$). Timing of steroid initiation was not significantly associated with all-cause unadjusted mortality ($p = 0.35$, Figure). Overall survival ranged from 70.8-74.2%, 49.2-58.3%, and 34.4-45.8% at 28-days, 90-days, and 365-days after steroid initiation among the study groups, respectively. Compared to early initiation, intermediate and late initiation were not associated with worse overall survival (adjusted hazard ratio [aHR] 1.04 and 1.09, respectively; $p = 0.94$). Worse survival was associated with older age (aHR 1.01 per year; $p = 0.04$), later admission year (aHR 1.14 per year; $p < 0.001$), and higher MELD-Na score (aHR 1.06 per point; $p < 0.001$). **Conclusion:** In a large multi-center AH cohort, there was no difference in survival related to early, intermediate, or late initiation of corticosteroids. If steroids are associated with a survival benefit, delaying to allow for exclusion of infection and/or optimization of patient selection for corticosteroid treatment has no negative impact.

Figure:

A) Overall survival probability by timing of corticosteroid initiation



B) Multivariable Cox model adjusting for patient characteristics



	Adjusted Hazard Ratios (95% Confidence Intervals)	p-values
Steroid Initiation		0.94
Early (0-5 days)	Reference	
Delayed (6-10 days)	1.04 (0.74-1.46)	
Late (≥10 days)	1.09 (0.63-1.88)	
Age (per year)	1.01 (1.00-1.02)	0.04
Male Sex	0.70 (0.43-1.13)	0.14
Race/Ethnicity		<0.001
White	Reference	
Black	0.82 (0.60-1.12)	
Hispanic	1.02 (0.70-1.49)	
Asian / Pacific Islander	0.67 (0.27-1.70)	
Native American	1.13 (0.65-1.96)	
Other	2.67 (1.74-4.11)	
Unknown	1.87 (0.99-3.51)	
Body Mass Index (per kg/m^2)	1.01 (0.99-1.03)	0.44
Admission Year	1.14 (1.10-1.18)	<0.001
AUDIT-C (per point)	0.98 (0.96-1.01)	0.16
MELD-Na (per point)	1.06 (1.04-1.08)	<0.001
Cirrhosis	0.97 (0.77-1.23)	0.81
Ascites	0.92 (0.68-1.25)	0.59
Encephalopathy	1.29 (0.82-2.03)	0.28

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3624-C | TRANSCRIPTOMIC ANALYSIS IDENTIFIES SENESCENCE-RELATED MECHANISMS ASSOCIATED WITH DISEASE SEVERITY IN ALCOHOL-ASSOCIATED HEPATITIS

Daniel Rodrigo-Torres[1], *Alastair M Kilpatrick*[1,2], *Stephen R Atkinson*[2], *Sofia Ferreira-Gonzalez*[1,3], *Luke D Tyson*[2], *Nikhil Vergis*[2], *Mark R Thursz*[2], *Laura Martinez-Gili*[2] *and Stuart J Forbes*[1], *(1)Centre for Regenerative Medicine, Institute for Regeneration and Repair, the University of Edinburgh, (2)Imperial College London, (3)Centre for Inflammation Research, Institute for Regeneration and Repair, the University of Edinburgh*

Background: Cellular senescence, a state of irreversible cell cycle arrest, has been associated with progression and outcomes in some chronic liver diseases (NASH, PSC, PBC). Its role in alcohol-related liver disease (ALD) and alcohol-associated hepatitis (AH) remains comparatively under-studied. We investigated the role of senescence in AH patients and an *in vitro* model of ethanol-induced toxicity. **Methods:** RNA sequencing (RNA-seq) data of liver biopsies from two ALD cohorts was analyzed: InTEAM (normal $n = 10$; early ALD $n = 12$; AH $n = 18$; AH explants $n = 11$), and a novel RNA-seq dataset of baseline biopsies from patients with severe AH from ISAIAH clinical trial ($n = 30$). Differential expression analysis by disease stage (InTEAM) or Model for End-Stage Liver Disease (MELD) score adjusted for age and sex (ISAIAH) was performed with DESeq2. Gene set enrichment analysis was computed with fgsea and $FDR < 0.05$ was used to define statistical significance. VL-17A cells (HepG2 cell line overexpressing ethanol metabolizing enzymes CYP2E1 and ADH1) were treated *in vitro* with 100mM ethanol for 48h. **Results:** Senescence markers (e.g. CDKN1A [p21], TP53) were significantly upregulated in AH compared to normal liver and early ALD patients in the InTEAM cohort. No additional upregulation was seen in liver explants from patients with AH compared to AH biopsies. In the ISAIAH cohort, whilst expression of these specific senescence markers did not vary significant with MELD the activity of senescence-related genes sets did. Pathways including stabilization of P53, TP53 regulation of metabolic genes, SCF/SKP2 mediated degradation of P27/P21 and mechanistic target of rapamycin complex (mTORC1) were all significantly enriched with worsening AH. Key enrichment drivers significantly downregulated with worsening AH included several subunits of the proteasome and cytochrome c oxidase (e.g. COX6C, COX18), two senescence-related complexes. *In vitro,* we observed a reduction of cell growth in ethanol-treated cells accompanied by an upregulation of senescence markers (e.g. CDKN1A, CDKN2A), and a downregulation of the key enrichment drivers identified in the ISAIAH cohort. **Conclusion:** Severe AH is associated with increased expression of senescence markers. Transcriptomic activation of these pathways correlates with the severity of liver dysfunction and can be recapitulated in vitro using an ethanol-metabolising liver cell line. Cellular senescence may be important in the pathogenesis of severe AH and present a promising target for interventional therapies.

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3625-C | TRANSCRIPTOMIC ANALYSIS OF HIGH-GRADE FIBROSIS IN ALCOHOL-INDUCED LIVER DISEASE

Gopal Krishna R. Krishna Ramadas Dhondalay[1], *Alastair M. Kilpatrick*[1], *Laura Martinez-Gili*[1], *Nikhil Vergis*[1], *Luke D. Tyson*[1], *Stephen R. Atkinson*[1], *Robert C. Glen*[1], *Timothy Md Ebbels*[1], *Ramon Bataller*[2] *and Mark R. Thursz*[1], *(1)Imperial College London, (2) Barcelona Clinic, Barcelona, Spain*

Background: Liver fibrosis is the accumulation of hepatic collagen occurring in response to repeated injury and inflammation. The degree of fibrosis is a key determinant of morbidity and mortality in almost all chronic liver diseases including alcohol-related liver disease. Despite its clinical importance, no therapies exist which successfully modulate hepatic fibrosis necessitating better markers and druggable targets for this aspect of disease. This study aims to delineate the transcriptomic signature of high-grade fibrosis in alcohol-induced hepatitis. **Methods:** Bulk RNA-seq was performed on liver biopsies ($n = 20$) from patients with a clinical diagnosis of severe alcoholic hepatitis. Patients had a median age of 56 years; were predominantly male (14/20) and either fibrosis grade 3 ($n = 4$) or 4 ($n = 16$). Total mRNA was paired-end sequenced using an Illumina HiSeq2000 and mapped to GRCh37/hg19 reference genome using STAR aligner with RSEM for gene expression quantification. A negative binomial model was fitted using DESeq2 to identify genes differentially expressed by fibrosis stage whilst adjusting for age and sex. Genes with log2(fold change) > 1 and adjusted p-value > 0.05 were considered statistically significant. Pathway and gene set enrichment analysis was done using fgsea packages. **Results:** The DE analysis identified 313 genes (51 up-regulated; 262 down-regulated) between grades 3 and 4 fibrosis. Among differentially expressed genes, in high-grade fibrotic samples, the drug metabolism genes (*CYP2A6*. *CYP2A7*, *CYP2C8*, *CYP2C9*, and *CYP39A1*) were found to be significantly downregulated, plasma cell markers like *CD38*, *CD19*, *CD45*, and *CXCR4* were also found to be differentially expressed and immunoglobulin genes (*IGHA1*, *IGHG1*, and *IGHM*) were significantly down-regulated. The fatty acid metabolism (5.57x) and bile acid and bile salt metabolism (16.52x) pathways were significantly enriched in high-grade fibrosis. Furthermore, we also investigated the relation of components of MELD score (Albumin, Bilirubin, and INR) with fibrosis and found cholangiocyte markers and hepatic dysfunction to be highly enriched. **Conclusion:** Gene expression analysis of high-grade fibrotic alcohol-induced liver disease confirms a previously known correlation between bile-acid secretion and reduced drug metabolism. The involvement of plasma cells and immunoglobulins in high-grade fibrosis with other clinical outcomes needs further investigation and could be potential for drug targeting.

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Disclosure information not available at the time of publication: Laura Martinez-Gili, Nikhil Vergis, Luke D. Tyson, Stephen R. Atkinson, Robert C. Glen, Timothy Md Ebbels

3626-C | TRANSIENT ELASTOGRAPHY INCREASES READINESS FOR CHANGE IN INPATIENTS WITH ALCOHOL USE DISORDER: A PROSPECTIVE PILOT STUDY (ELISA)

Stephanie Rutledge[1], *Rohit R Nathani*[2], *Patricia Miguez Arosemena*[2], *Daniel Suter*[3], *David Lehman*[3], *Timothy Brennan*[3] *and Gene Y. Im*[1], *(1)Icahn School of Medicine at Mount Sinai, (2)Mount Sinai Morningside and West Hospital, (3)Mount Sinai West Hospital*

Background: Alcohol use disorder (AUD) is rising, especially with the COVID-19 pandemic. New approaches to the treatment of alcohol use disorder (AUD) are needed for harm reduction or abstinence. Teachable moments (TMs) are health events that can motivate individual's to adopt risk-reducing behaviors. Our aim was to determine the impact of vibration-controlled transient elastography (VCTE) and its interpretation as a TM on psychological scores (PS) in patients with AUD. **Methods:** This is a prospective, investigator-initiated, proof-of-concept pilot study: Evaluating LIver Stiffness and steatosis as a TM in patients with AUD (ELISA). Patients without known liver disease or prior VCTE were enrolled from an inpatient addiction unit at Mount Sinai West. At baseline, four validated PS assessing alcohol use, insight, and readiness to reduce drinking were administered (AUD Identification Test [AUDIT-C], revised Readiness Ruler [RR] (preset value of 0, range –5 to +5), Stages Of Change Readiness And Treatment Eagerness Scale [SOCRATES-8A], and Hanil Alcohol Insight Scale [HAIS]). VCTE was performed with FibroScan™ (Echosens), and results given in real-time via pre-scripted interpretations. PS were repeated immediately after. Follow up was every 3 months for 2 years. The primary endpoint was a change in PS. Secondary endpoints included prevalence of significant fibrosis, return to drinking, heavy drinking days, and linkage to hepatology care when recommended. **Results:** From May 2022, 21 study subjects were enrolled, all providing consent. Mean age was 53 (+/- 13) years, mostly male (76%) and racially diverse (62% White, 19% Black, 5% Hispanic). All had severe AUD, with a mean of 20.4 (+/-9.9) daily drinks for 16.7 (+/-11.2) years. Fourteen (67%) had comorbid psychiatric diagnoses and 16 (76%) had a family history of AUD. Significant fibrosis was detected in 7/21 (33%): three with stage 2 and four with stage 4 fibrosis. Steatosis stages 1, 2 and 3 were present in 11/21 (52%), 2/21 (10%), and 6/21 (28%), respectively. Mean AUDIT-C score was 11.6 (+/- 1.1). Mean scores for SOCRATES-8A (range 19-95), and HAIS (range -20 to +20) were high at baseline, 81.8, and 11.6, respectively with nonsignificant increases of 2.8 and 0.57 after VCTE, respectively. Mean revised RR score increased significantly after VCTE by 3.8 points ($p < 0.001$). No subjects were successfully contacted for follow-up. **Conclusion:** In this prospective pilot study, we demonstrate that VCTE increases readiness for change as measured by revised RR in inpatients with AUD. There was high baseline motivation and existing PS may not capture TM interventions appropriately. One-third had significant fibrosis, but loss to follow-up has concerning implications for linkage to

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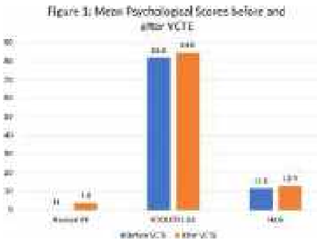
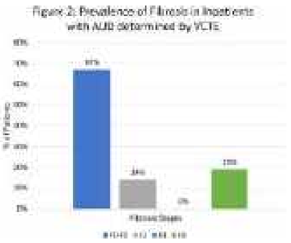
care strategies and longer-term study data.





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3627-C | TRANSPLANTATION OF DYSBIOTIC FECAL MICROFLORA FROM ALCOHOL-ASSOCIATED-HEPATITIS (AAH) PATIENTS, LEADS TO MALLORY-DENK BODY FORMATION AND PATHOGENESIS OF ALCOHOLIC HEPATITIS IN A MOUSE MODEL.

Smita Ghare, Paula Chilton, Manicka Vadhanam, Ben Charpentier, Richa Singhal, Scott Myers, John Greenwell, Jingwen Zhang, Mary Proctor, Leila Gobejishvili, Swati Joshi-Barve, Craig J. McClain and Shirish Barve, University of Louisville, Louisville, KY

Background: Hepatic Mallory-Denk bodies (MDBs) which indicate the histologic severity of alcoholic liver disease are observed with high prevalence in alcohol-associated hepatitis (AAH) patients. Several mechanisms have been proposed in the pathogenesis of MDBs; however, the role of gut microbiota in the development of MDBs has not been investigated. **Methods:** Fecal microbiome transplants (FMT) were performed in conventional mice using well-characterized fecal specimens from AAH patients (AAH-FMT, MELD scores > 22) and controls (N-FMT) 2X/week for 5 weeks. Along with FMT, the mice were pair-fed or 5% ethanol-fed (EF) with the Lieber-DeCarli diet for last 2 weeks. Transplanted microbiome was assessed by 16S rRNA gene sequencing. Histopathological analysis of mouse livers for the presence of MDB along with hepatic steatosis, inflammation, and injury was performed on H&E-stained tissues and were scored by a pathologist blinded to the study. MDB formation was assessed using immunofluorescent staining and mRNA levels of MDB associated proteins in mouse livers were assessed by qPCR. **Results:** Transplantation of dysbiotic fecal microbiome from AAH patients demonstrating a marked loss of butyrate-producing bacteria led to the development of MDBs in livers of recipient mice. Formation of MDBs was further exacerbated upon ethanol-feeding. There was a complementary increase in gene expression levels of MDB components including p62, CK8-18 and transglutaminase-2 in mice receiving AAH-FMT and ethanol. Further, higher aggregation and colocalization of MDB associated proteins was observed by immunofluorescent staining in FMT recipient mice after ethanol feeding. Notably, control mice, either non-FMT or FMT recipient mice given fecal transplants from controls, did not have increased incidence of hepatic MBDs with or without ethanol-feeding. Importantly, intervention with oral supplementation of tributyrin (TB), a butyrate prodrug, remarkably attenuated ethanol induced MDB development along with hepatic steatosis, inflammation, and injury in FMT recipient mice. **Conclusion:** These data strongly suggest that the dysbiotic microflora characterized by a decrease in butyrate producing bacteria plays a causal role in MDB formation and pathogenesis of AAH. Moreover, the data also suggest that TB supplementation could be a significant therapeutic strategy in the management of the alcohol-associated liver disease.

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3628-C | Two hit hypotheses of alcohol-associated hepatitis (AAH): The role of genes in AAH

Anand V. Kulkarni[1], Ravikanth Vishnubotla[2], Govardhan Bale[2], Sameer Shaik[1], Sasikala Mitnala[2], Mithun Sharma[1], Nageshwar D Reddy[1] and Padaki Nagaraja Rao[1], (1)Aig Hospitals, Hyderabad, India, (2) Asian Healthcare Foundation

Background: Progression of liver disease in individual's with similar levels of alcohol consumption is variable, suggesting the contributory role of genetics. Whether such genetic associations exist in patients with alcohol-associated hepatitis (AAH), a disease associated with high mortality, and alcoholic cirrhosis (ALC), a slowly progressive disease, has not been evaluated. **Methods:** In this pilot study, we aimed to compare the genetic

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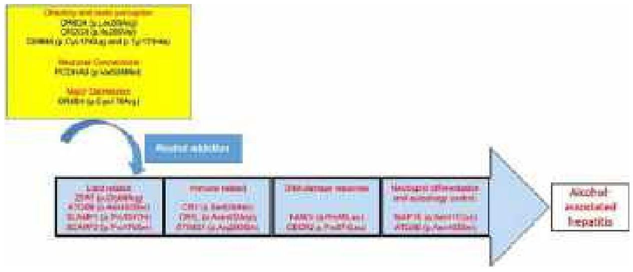
variants of patients with AAH and ALC through whole exome sequencing. The analysis of the samples was performed after alignment using the SSV5UTR panel (74,557,381 bp), which covers 23690 genes. **Results:** 29 patients (ALC-15; AAH-14) were included. The mean age of ALC patients was higher (42.6 ± 5.55 yrs) than AAH patients (37.9 ± 5.9 yrs;P = 0.03). The amount of alcohol consumed (85 ± 28.73 g/d vs. 112.8 ± 51.2 g/d; P = 0.07) and the proportion of patients binging alcohol (26.7% vs. 64.3%;P = 0.06) was lower in ALC group than AAH group. However, the duration of alcohol intake was longer in ALC (12.33 ± 7.11 yrs vs. 4 ± 1.6 yrs; P < 0.001). A total of 10,10,247 variants were identified that predominantly comprised of exonic, intronic, and UTR (3` and 5` UTR) variants. Of these, missense (N = 4020), start loss (N = 7), and 2 kb upstream (N = 34) were identified as damaging and deleterious. Deleterious variants in genes, namely *ZFAT* (p.Gly64Arg; associated with waist-hip ratio in South Asians), *TAS2R19* (p. Leu235Arg-novel variant; sensory perception of taste), *CECR2* (p.Pro674Leu; DNA damage response), *FANCI* (p.Pro55Leu; DNA damage), *ATG9B* (p.Asn493Ser; associated with CT imaging-derived hepatic fat), *OR8D4* (p.Leu55Arg; Olfactory reception) and *PCDHA9* (p.Val508Met; neuronal connections) were exclusively found in AAH group. Higher frequency of variants in the AAH group as compared to the ALC group were identified in genes, namely *OR2G3* (p.Ile289Val; olfactory reception; p = 0.04), *STING1* (p.Arg293Gln; immune-related; p = 0.02), *OR8B4*(p.Cys178Arg; p = 0.04 and p.Tyr131His; p = 0.04; olfactory reception), *MAP1S* (p.Ser411Cys; p = 0.03; neutrophil differentiation and autophagy control). (Figure) **Conclusion:** We propose a two-hit hypotheses that leads to AAH: first hit where individual's with variants in genes related to chemosensory perception (taste and olfaction) tend to consume relatively higher amounts of alcohol and have a risk of addiction, and second hit in the form of variants in genes related to lipid metabolism, apoptosis, autophagy, and neutrophil infiltration leading to impaired functions culminating in alcoholic hepatitis. Further large population-based cohort needs to be assessed to validate the findings.



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3629-C | UNDERUTILIZATION OF PHARMACOLOGIC THERAPY FOR ALCOHOL USE DISORDER (AUD) IN PATIENTS HOSPITALIZED WITH ALCOHOL-ASSOCIATED HEPATITIS

Christine Tien[1], Mimi Xu[1], Niwen Kong[1], David Lehoang[1], Michael Pimienta[2], Divya Ayyala[1], Rachan Narala[1] and Norah Terrault[1], (1)University of Southern California, (2)Stanford University

Background: Abstinence from alcohol plays a key role in reducing mortality in alcohol-associated liver disease, and medication-assisted treatment (MAT) for AUD is recommended to support sobriety. Studies of MAT utilization and efficacy in patients with alcohol-associated hepatitis (AH), a clinical entity with high short-term mortality, are lacking. **Methods**: This was a single-center retrospective study of adults (> 18 y) with an index hospitalization for probable/definite AH (per NIAAA criteria) at an urban safety net hospital from 2016-2022. Primary outcome was MAT prescription on discharge. **Results**: 240 patients were included in this study (median age 42 y, 84% male, 88% Hispanic, MELD-Na 27, IQR 22-31), and 12% (n = 28) were prescribed MAT (TABLE). Gabapentin was prescribed most frequently (64%, n = 18), followed by dual gabapentin/naltrexone therapy (25%, n = 7). The proportion prescribed MAT rose over time (4% 2016-2019 vs 18% 2020-2022, p < 0.001). The MAT group was younger, had lower MELD-Na scores, lower incidence of cirrhosis, fewer median cirrhotic decompensation traits, and were less likely to receive corticosteroids (TABLE). Rate of MAT prescription was higher in patients without decompensated cirrhosis (17% if no traits vs 6% if > 1 trait, p < 0.01) and in those with MELD-Na </= 25 (17% if </= 25 vs 7% > 25, p < 0.02). Apart from total bilirubin values on discharge (8 vs 13 mg/dL, p < 0.01), ALP, AST, and ALT were similar. The MAT group had shorter length of stay (3.5 vs 5 d, p = 0.02) but similar days since last drink (3 vs 5, p = 0.19), social work referral (65% vs 72%, p = 0.48), and hospitalizations within 90 days (1 vs 1). Ninety-day readmission rates (39% vs 42%, p = 0.46) and mortality (4% vs 13%, p = 0.12) rates were not significantly different in MAT vs. no MAT groups. In adjusted multivariable analysis, older age (aOR 0.95, 95% CI 0.90-1.00, p = 0.03), more decompensation traits (aOR 0.30, 95% CI 0.11-0.82, p = 0.02), corticosteroid treatment (aOR 0.35, 95% CI 0.14-0.88, p = 0.03) and higher MELD-Na score (aOR 0.89, 95% CI 0.83-0.96, p < 0.01) were associated with lower odds of MAT therapy. MAT prescription was not associated with 90-day readmission (OR 0.88, 95% CI

0.39-1.96, p = 0.75). **Conclusion**: Pharmacologic therapy for AUD is underutilized in AH patients upon discharge and represents a missed opportunity to support post-discharge sobriety. There is urgent need to identify and address barriers in both provider and patient awareness and enhance utilization of MAT, particularly in this high-risk patient population.

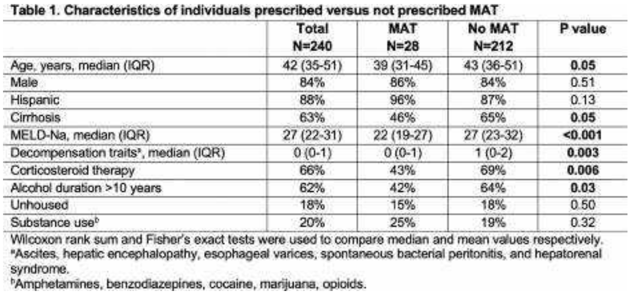

Table 1. Characteristics of individuals prescribed versus not prescribed MAT

	Total N=240	**MAT N=28**	**No MAT N=212**	**P value**
Age, years, median (IQR)	42 (35-51)	39 (31-45)	43 (36-51)	**0.05**
Male	84%	86%	84%	0.51
Hispanic	88%	96%	87%	0.13
Cirrhosis	63%	46%	65%	**0.05**
MELD-Na, median (IQR)	27 (22-31)	22 (19-27)	27 (23-32)	**<0.001**
Decompensation traits[a], median (IQR)	0 (0-1)	0 (0-1)	1 (0-2)	**0.003**
Corticosteroid therapy	66%	43%	69%	**0.006**
Alcohol duration >10 years	62%	42%	64%	**0.03**
Unhoused	18%	15%	18%	0.50
Substance use[b]	20%	25%	19%	0.32

Wilcoxon rank sum and Fisher's exact tests were used to compare median and mean values respectively.

[a] Ascites, hepatic encephalopathy, esophageal varices, spontaneous bacterial peritonitis, and hepatorenal syndrome.

[b] Amphetamines, benzodiazepines, cocaine, marijuana, opioids.

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3630-C | UNRAVELING THE ROLE OF REDUCTIVE STRESS IN HEPATIC TRANSCRIPTIONAL REGULATION OF FATTY LIVER DISEASE

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Background: Hepatic reductive stress, which refers to an elevated cytosolic $NADH/NAD^+$ ratio, is a shared metabolic feature of both alcohol-related and non-alcoholic fatty liver disease, though how it directly affects hepatic fat accumulation is poorly understood. We aimed to investigate possible transcriptional regulation of hepatic fat accumulation by characterizing how direct modulation of reductive stress using a combination of alcohol, which increases reductive stress, and the metabolic tool *Lb*NOX, which decreases reductive stress, influences the hepatic transcriptome. **Methods:** To examine the role of hepatic reductive stress *in vivo*, mice were tail-vein injected with adenovirus either expressing *Lb*NOX or luciferase (control), and gavages with water or ethanol. Total hepatic RNA was isolated, and RNAseq was performed. For cell culture experiments, HEK293T cells were transfected with either plasmid expressing *Lb*NOX, with lowers reductive stress, or *Ec*STH, a new metabolic tool which increases reductive stress. Liquid-chromatography mass-spectroscopy (LC-MS) was used to characterize the metabolite changes, and RNAseq was used to characterize the resulting changes in the transcriptome. A luciferase reporter assay was designed to measure ChREBP activity. **Results:** Hepatic RNASeq showed that modulating reductive stress using alcohol and/or *Lb*NOX significantly altered *de novo* lipogenic gene expression *in vivo*, which was largely mediated by activation of the transcriptional factor Carbohydrate Response Element Binding Protein (ChREBP). Strikingly, *Lb*NOX transfected HEK293T cells, which had decreased reductive stress, showed an 84 % decrease in ChREBP activity, whereas increasing reductive stress using *Ec*STH increased ChREBP activity by 169%. Notably, we found that glyceraldehyde 3-phosphate and glycerol 3-phosphate are among the top metabolites that positively correlate with ChREBP activity and reductive stress. This observation is consistent with previous research, which has suggested that triose-phosphates can stimulate ChREBP and activate *de novo* lipogenesis. **Conclusion:** Our study demonstrates that ChREBP is a reductive-stress responsive transcription factor that contributes to hepatic fat accumulation in both alcohol and non-alcohol related fatty liver disease. Our findings suggest that targeting ChREBP activity via modulating reductive stress might be a novel paradigm for the treatment of fatty liver diseases.

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Disclosure information not available at the time of publication: Valentin Cracan, Russell P. Goodman

3631-C | UPTAKE OF SECONDARY PREVENTIVE DRUGS AFTER MYOCARDIAL INFARCTION IN PATIENTS WITH ALCOHOL-RELATED LIVER DISEASE IS LOW: A NATIONWIDE POPULATION-BASED STUDY

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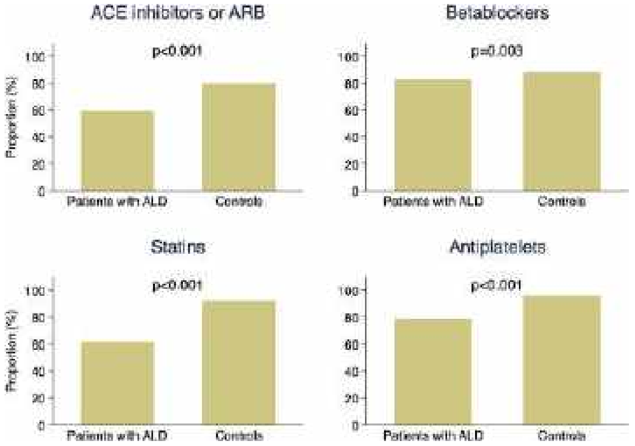
Background: Secondary prevention with antiplatelets, statins, betablockers, and renin-angiotensin inhibitors improves clinical outcomes after myocardial infarction (MI), but the uptake of these therapies in patients with co-existing alcohol-related liver disease (ALD) is unclear. **Methods:** All patients with ALD and a first-time MI between 2006 and 2020 were identified from Swedish national healthcare registers (n = 362) and matched with up to ten controls from the general population with a first-time MI for age, sex, and year of MI (n = 3,155). Adjusted odds ratios (aOR) for filling prescriptions of four-drug secondary prevention (antiplatelets, statins, betablockers, and renin-angiotensin inhibitors) within 30 days after MI were calculated with logistic regression. Adjustments were made for the matching variables, socioeconomic factors, and a range of comorbidities. **Results:** The median age in the patients with ALD was 68 years and 271 (75%) were men. Cirrhosis was present in 189 of the patients with ALD (52%), of whom 78 had decompensated cirrhosis (41%). Complete four-drug secondary prevention was less common in patients with co-existing ALD (39%) compared to controls (67%, p < 0.001) (aOR = 0.30, 95% confidence interval [CI] = 0.23-0.38). The largest difference between patients with ALD and controls was seen for statins (62% vs 92%, p < 0.001, aOR = 0.17, 95%CI = 0.13-0.22). Among individual's who filled prescriptions for four-drug secondary prevention within 30 days and survived the first two years after MI, fewer patients with ALD were still taking their medications at that timepoint compared to controls (52% vs 62%, p = 0.045). **Conclusion:** Patients with ALD had a lower uptake of secondary preventive drugs compared with the general population following MI, in both short- and long-term perspectives. These results suggest that patients with ALD might be undertreated following MI.



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3632-C | UTILITY OF N-ACETYLCYSTEINE IN THE TREATMENT OF ALCOHOLIC HEPATITIS

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Background: Alcoholic hepatitis (AH), the most severe form of alcoholic liver disease, typically carries a very grim prognosis. N-acetylcysteine (NAC) is an antioxidant which counteracts free radicals and can help reduce inflammation, especially in the liver. Studies have shown a modest benefit with the addition of NAC to glucocorticoids for treatment of severe AH. In this study, we investigated the value of NAC in patients with AH. **Methods:** This is a retrospective study performed in a community center between January 2014 and December 2022. Patients older than 18 years admitted to the hospital for acute AH who received intravenous NAC for at least 72 hours were included in this study. The patients' length of hospitalization, mortality rate, and Mayo End-Stage Liver Disease Sodium (MELD-Na) scores were recorded. Mild to moderate AH was defined as a MELD score $\leq$ 20, and severe AH was defined as MELD > 20. We used historical data from prior publications as control groups. Chi square and Fisher exact tests were used to compare categorical variables, and t-test for continuous variables. **Results:** A total of 30 patients admitted to the hospital with AH who received intravenous NAC were identified. Based on the MELD score cutoff of 20, 15 patients of our cohort presented with severe AH and the other 15 presented with mild/moderate AH. The average length of hospitalization in our 30 patients with AH on NAC was 10.7 ± 11.7 days which was significantly longer when compared to 6.5 ± 7.7 days in a historical control cohort of 3,881 subjects with AH, P = 0.003. As expected, on sub-analysis, our patients with severe AH had a longer average length of hospitalization of 15 ± 14.5 days compared to 6.6 ± 5.7 days in patients with mild/moderate AH, P = 0.046. Regarding mortality, the 90 day mortality rate did not differ between our cohort which comprised of 9 out of the 30 patients (30%) when compared to historic control patients (997/3437, 29%), P = 0.1. In the mild to moderate AH cohort, there was only 1 death (6.67%) recorded within 90 days compared to 8 patients (53.3%) with severe AH, P = 0.0053. Only 5 out of the 15 patients with severe AH were prescribed

prednisolone, while other patients did not receive steroids due to contraindications. **Conclusion:** In our study, NAC did not seem to affect length of hospitalization nor 90-day mortality in patients with AH. Patients with AH and MELD score less than 20 had shorter length of stay and lower mortality rates when compared to patients with AH and MELD score of more than 20, while both groups were on NAC therapy. Our next step is to incorporate our control subjects stratified by AH severity in order to further expand this study and clarify utility of NAC in mild/moderate and severe AH.

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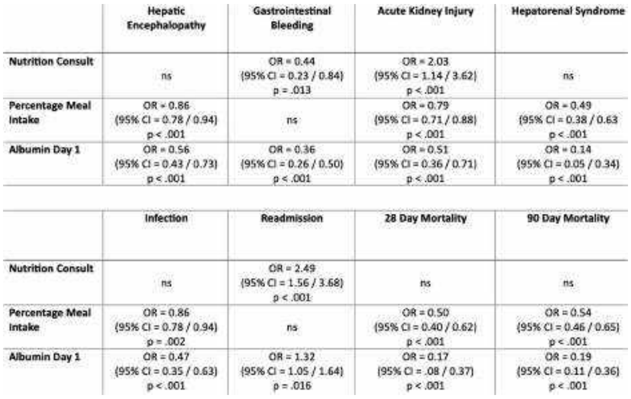
3633-C | VALUE OF NUTRITION AND DIETARY SUPPORT IN ALCOHOLIC HEPATITIS

Kevin Yang, Naren Srinath Nallapeta, Alexander Mark Carlson, Nariman Hossein-Javaheri, Brian Quigley and Thomas Mahl, University at Buffalo

Background: Nutritional status is an often-overlooked component in alcoholic hepatitis. Almost all patients presenting with severe alcoholic hepatitis have a degree of protein calorie malnutrition, which is associated with worse clinical outcomes. Appropriate dietary support in this setting may influence the hospital course. **Methods:** We designed a retrospective study on all patients admitted to a tertiary care center from 2020 to 2022 with a diagnosis of alcoholic hepatitis. Complications and outcomes investigated included hepatic encephalopathy (HE), gastrointestinal bleeding (GIB), acute kidney injury (AKI), hepatorenal syndrome (HRS), bacterial infections, readmissions, and mortality at 28 and 90 days. We conducted a series of logistic regression analyses using a backward step procedure to identify significant predictors of various outcomes. The predictors included nutrition consultation (yes/no), albumin level at day 1 of treatment, and percent meal intake (continuous measure). Linear regression was also used to analyze the relationship between percent meal intake and the predictors. **Results:** The study included 425 patients who fit the criteria for alcoholic hepatitis. In the analysis examining 28-day mortality as the outcome, the significant predictors were percent meal intake and albumin level at day 1. For every 10% increase in meal percent intake, patients were 2 times less likely to die. For every 1 unit increase in albumin, patients were 5.8 times less likely to die. Higher percent meal intake was also a significant predictor for lower rates of HE, AKI, HRS, infection, and 90-day mortality. Higher albumin at day 1 was associated with lower rates of HE, GIB, AKI, HRS, infection, and 90-day mortality, but higher rates of readmission. Nutrition consults were associated with lower rates of GIB (OR = 0.44, 95% CI = 0.23/0.84), higher rates of AKI (OR = 2.03, 95% CI = 1.14/3.62), and more readmissions (OR = 2.49, 95% CI = 1.56/3.68). Patients who received nutrition consultation had higher percentage of meal intake as well (B = 10.51, 95% CI = 5.41/15.62). **Conclusion:** We found that nutritional status, specifically percentage meal intake during hospitalization and day 1 albumin, was significantly associated with lower rates of complications and short-term mortality in alcoholic hepatitis. The mortality benefit of nutrition consults was not evident in this study, perhaps because sicker patients were more likely to require dedicated support.



	Hepatic Encephalopathy	Gastrointestinal Bleeding	Acute Kidney Injury	Hepatorenal Syndrome
Nutrition Consult	ns	OR = 0.44 (95% CI = 0.23 / 0.84) p = .013	OR = 2.03 (95% CI = 1.14 / 3.62) p < .001	ns
Percentage Meal Intake	OR = 0.86 (95% CI = 0.78 / 0.94) p < .001	ns	OR = 0.79 (95% CI = 0.71 / 0.88) p < .001	OR = 0.49 (95% CI = 0.38 / 0.63 p < .001
Albumin Day 1	OR = 0.56 (95% CI = 0.43 / 0.73) p < .001	OR = 0.36 (95% CI = 0.26 / 0.50) p < .001	OR = 0.51 (95% CI = 0.36 / 0.71) p < .001	OR = 0.14 (95% CI = 0.05 / 0.34) p < .001

	Infection	Readmission	28 Day Mortality	90 Day Mortality
Nutrition Consult	ns	OR = 2.49 (95% CI = 1.56 / 3.68) p < .001	ns	ns
Percentage Meal Intake	OR = 0.86 (95% CI = 0.78 / 0.94) p = .002	ns	OR = 0.50 (95% CI = 0.40 / 0.62) p < .001	OR = 0.54 (95% CI = 0.46 / 0.65) p < .001
Albumin Day 1	OR = 0.47 (95% CI = 0.35 / 0.63) p < .001	OR = 1.32 (95% CI = 1.05 / 1.64) p = .016	OR = 0.17 (95% CI = .08 / 0.37) p < .001	OR = 0.19 (95% CI = 0.11 / 0.36) p < .001

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3634-C | VINYL CHLORIDE POTENTIATES LIVER INJURY CAUSED BY CHRONIC ALCOHOL CONSUMPTION IN MICE

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Background: Vinyl chloride, an industrial chemical and environmental contaminant, causes liver injury at high concentrations, but low-level exposure (< 1 ppm) is currently considered safe. The consequences of sub-OSHA exposure on human health are not well understood, especially in the context of VC as a risk-modifying agent. Previous work from this group confirms the role of VC in exacerbating experimental nonalcoholic fatty liver disease (NAFLD) caused by a Western diet. Both NAFLD and alcohol-associated liver disease (ALD) have similar liver pathologies, and the impact of VC exposure in ALD has not been investigated. Moreover, the prevalence of ALD worldwide raises concerns about how VC exposure can enhance disease progression to more severe stages of injury. The purpose of this study was to determine if VC exposure worsens liver damage caused by chronic alcohol (EtOH) consumption. **Methods:** C57Bl/6J mice, pair-fed or fed a Lieber-DeCarli EtOH diet, were exposed to VC (< 1 ppm), or room air for 6 hrs/d, 5 d/wk for 5 weeks. Plasma and liver samples were collected for determination of injury. **Results:** VC exposure exacerbated EtOH-induced liver damage and oxidative stress, and moderately increased inflammation. VC exposure, however, did not affect hepatic lipid content (Oil red-O, triglycerides and cholesterol). Although the increase in lipids caused by ethanol was not impacted by VC exposure, the pattern of steatosis shifted to more micro-vesicular fat, which is often indicative of mitochondrial dysfunction. In line with that VC also changed mRNA expression of genes regulating metabolism. **Conclusion:** Various environmental toxicants are known to modify or enhance liver injury in NAFLD models. Findings from the present study suggest that VC interacts also with other lifestyle factors such as alcohol consumption resulting in exacerbated alcohol-associated liver damage. This emphasizes that environmental chemical exposure, such as to VC, potentially drives inter-individual risk for developing or enhancing disease.

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f 3635-C | VIRAL EXPOSURE PREDICTS MORBIDITY AND MORTALITY IN ALCOHOL-ASSOCIATED HEPATITIS

Cynthia Hsu[1], Limin Wang[2], Evan Maestri[2], Aleesha Jacob[2], Susan Mayo[3,4], Xin Wei Wang[2], Bernd Schnabl[3,4] and AlcHepNet Clinical Investigators, (1) University of California San Diego, La Jolla, CA, (2) National Institutes of Health, (3)University of California San Diego, (4)VA San Diego Healthcare System

Background: Alcohol-associated hepatitis (AH), or severe liver inflammation secondary to heavy alcohol use, is associated with very high mortality even despite abstinence from alcohol; up to forty percent of patients die within 6 months. Patients with AH are especially prone to infections, which can lead to dysfunction of other organs and poorer prognosis. **Methods:** In this study, we performed serological profiling of the viral infection history of 25 healthy controls (HC), 32 patients with alcohol used disorder (AUD) with no apparent liver disease, and 195 patients with AH. AH samples were obtained from two multicenter observational studies, InTeam and AlcHepNet. We used systematic viral epitope scanning by VirScan to comprehensively analyze antiviral antibodies and to better identify serologic biomarkers to predict patient outcomes. Briefly, VirScan is a phage-display immunoprecipitation and sequencing technology that detects the human virome epitopes recognized by antibodies in a serum sample. **Results:** We found significant differences in the serological profiles of these three patient populations, and specifically, we detected a significantly decreased number and diversity of viral antibody targets in the sera of patients with AH (p-value HC vs. AH = 0.002, p-value AUD vs. AH = < 0.001). When the sera of patients with AUD during active alcohol use and after two weeks of abstinence were compared, we detected a significantly increased number of viral epitopes in the sera of abstinent patients (p-value = 0.013), indicating a more robust immune response with abstinence. In patients with AH, a lower number of detectable serum viral antibody targets was correlated with a higher Maddrey's discriminant function score (*p*-value = 0.022) and decompensation events, such as hepatic encephalopathy (*p*-value Control vs. HE Grade 1 = 0.18, p-value Control vs. HE Grade 2 = 0.007, p-value Control vs. HE Grade 3 = 0.008), and a decrease in the diversity of the serum antibody repertoire was correlated with development of ascites (*p*-value < 0.001). Mortality at 30 and 90 days were also associated with a lower number of detectable serum viral antibody targets (p-value mortality at 30 d = 0.018, at 90 d = 0.032). Further, viral exposure to Human herpesvirus 6B and Rhinovirus A was significantly decreased in patients with AH who experienced mortality at 90 days compared to those who survived (*p*-value = 0.041 and 0.0046 respectively). **Conclusion:** We found that abstinence from alcohol is associated with a significant increase in the number of detectable anti-viral antibodies. A decrease in the number of detectable anti-viral antibodies is predictive of decompensation of liver disease and mortality in patients with AH.

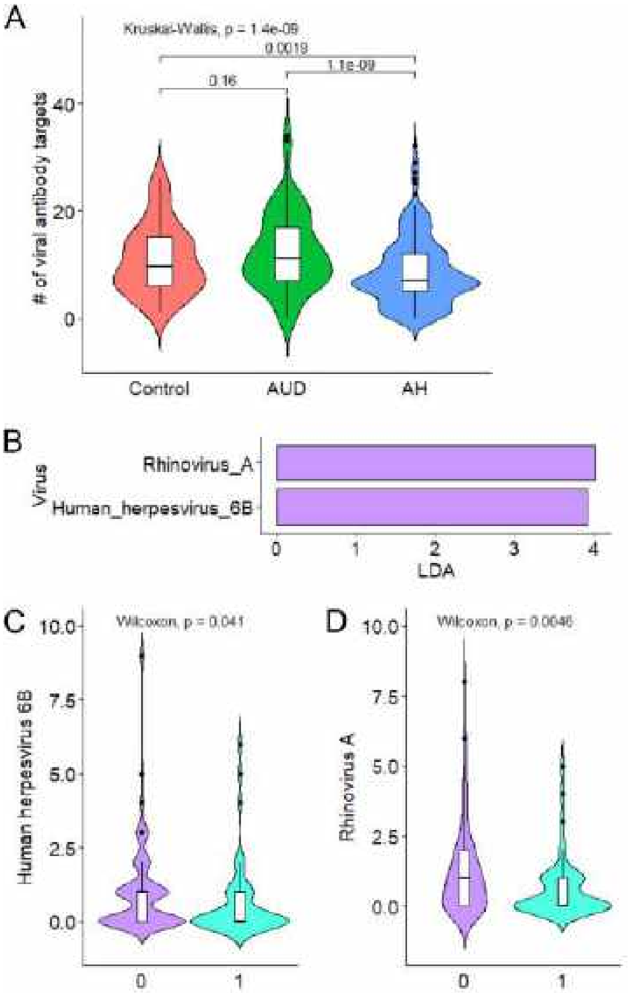

Figure 1. (A) Total number of viral antibody targets in sera of control subjects, patients with alcohol use disorder (AUD), and patients with alcohol-associated hepatitis (AH). (B) Linear discriminant analysis (LDA) of viruses targeted by serum antibodies of patients with AH. (C, D) Total number of epitopes recognized against Human Herpesvirus 6B (C) and Rhinovirus A (D) by serum antibodies of patients with AH.

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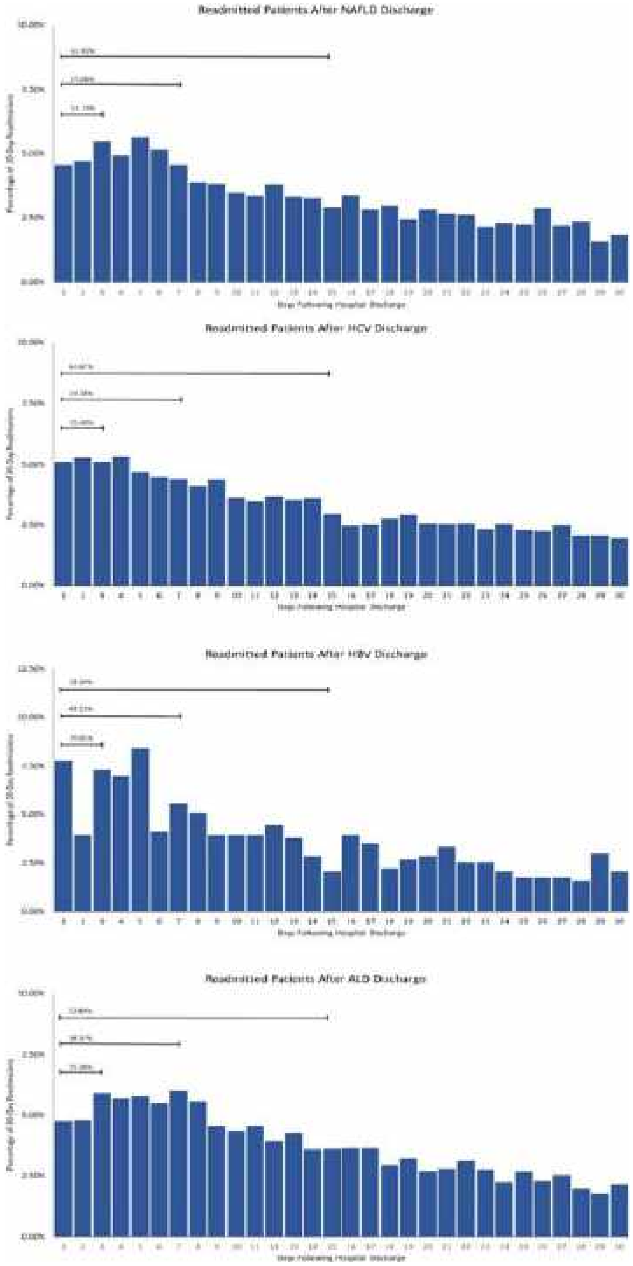
3700-C | ASSESSMENT OF HOSPITAL READMISSION RATES, RISK FACTORS, CAUSES AND COST AFTER DISCHARGE WITH CHRONIC LIVER DISEASE: ANALYSIS OF THE US NATIONWIDE READMISSIONS DATABASE

James M. Paik[1], *Rebecca Cable*[1], *Linda Henry*[1,2,3], *Leyla De Avila*[1], *Huong Pham*[1] *and Zobair M. Younossi*[1,2,3], *(1)Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, (2)Inova Medicine, Inova Health System, Falls Church, VA, (3)Center for Liver Disease, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, VA*

Background: 30-day readmission data for patients with chronic liver disease (CLD) and contribution to healthcare burden are sparse. Aim: To assess trends, predictors, reasons, cost, in-hospital mortality, timing of 30-day readmission after discharged with CLDs. **Methods:** Data from all-adult hospitalizations (all-payer) in Nationwide Readmission Database (NRD, 2010-2017) with a diagnosis of CLD [hepatitis B (HBV) and C (HCV), alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD)] were analyzed. **Results:** During the 2010-2017, the number of patients discharged with NAFLD increased by +103% from 10,638 to 21,544; ALD increased by +82.2% from 16,023 to 29,188; HCV increased by +63.3% from 21,733 to 35,488; and HBV increased by +63.0% from 2,619 to 4,270. The 30-day readmission rate for NAFLD increased (17.8% in 2010 to 19.9% in 2017, $p < 0.001$), whereas those for HCV decreased (18.1% to 16.8%, $p < 0.001$) and those for HBV (18.6% to 16.7%, $p = 0.162$) and ALD (19.7% to 20.5%, $p = 0.128$) leveled off. Multivariable cox model showed that patients with NAFLD had a significantly higher risk of 30-day readmission (Hazard ratio = 1.06, 95%CI: 1.01-1.11). In addition to ascites, hepatic encephalopathy, and higher number of coexisting comorbidities, independent comorbidities associated with a higher risk of 30-day readmission included cirrhosis for NAFLD and HCV; acute kidney injury for NAFLD, HCV, and ALD; HCC for HCV, and peritonitis for ALD. Among readmitted patients, substantial differences in cost and in-hospital mortality between $\leq$30-day and > 30-day readmission were observed ($16,986 vs. $14,648 and 8.2% vs. 5.2% for NAFLD; $16,590 vs. $15,036 and 7.4% vs. 4.3% for HCV; and $19,152 vs. $16,487 and 8.5% vs. 6.3% for HBV; and $17,351 vs. $15,114 and 8.5% vs. 6.3% for ALD). These differences remained significant only for

NAFLD after controlling for patient's demographic, hospital-level and clinical characteristics. Hepatic reasons explained the majority of 30-day readmission. However, a large proportion of patients (43.7% for NAFLD; 28.4% for HCV, 39.0% for HBV, and 29.1%) were readmitted for extrahepatic reasons. Of 30-day readmissions, a disproportionately high number of readmissions occurred during days 1-15 (62.8% for NAFLD, 63.7% for HCV, 74.3% for HBV, and 72.9% for ALD) (Figure). **Conclusion:** Early readmissions for NAFLD were prevalent, causing economic and clinical burden.



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3701-C | EVALUATING HOSPITAL LENGTH OF STAY, READMISSION, AND COST OF CARE IN CIRRHOTICS WITH HEPATIC ENCEPHALOPATHY

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Background: Hospital readmissions are a cause of significant cost burden to the health system. Rifaximin is prescribed to prevent recurrent episodes of Hepatic Encephalopathy in patients with Cirrhosis. The purpose of our study is to compare the hospital length of stay (LOS), re-admission rates, and hospital cost in patients prescribed Rifaximin during hospital stay and on discharge compared to those who were not prescribed Rifaximin. **Methods:** We used the Vizient Clinical Database (VCD) to collect data on patients diagnosed with Hepatic Encephalopathy and Cirrhosis between 2019-2021. The hospital length of stay (in days), re-admission rates, and hospital costs were compared between patients who were treated with rifaximin versus those not treated with rifaximin. Further, we compared the above outcomes in patients with Medicare and Medicaid insurance. Patients younger than 18 years old and those that required hospice, rehabilitation, or nursing facility placement were excluded from our study. Categorical variables were analyzed using the Chi-Square test. All statistical analysis was completed by STATA. P-values < 0.05 was considered statistically significant. **Results:** 29,999 patients with Medicaid were prescribed Rifaximin during hospital stay and on discharge. These patients had a higher mean LOS of 11.88 days as compared to 8.91 days in 22,985 Medicaid patients who were discharged without Rifaximin, and a higher mean direct cost of stay at $31,766 in the Rifaximin cohort versus $27,869 in the cohort not on Rifaximin on discharge. Similarly, the 30-day readmission rate was higher at 28% in the group on Rifaximin compared to the group discharged without Rifaximin at 24%, which is statistically significant ($P = 0.037$). Both groups had a higher observed LOS compared to the expected LOS. During the same period, 29,183 Medicare patients who were prescribed Rifaximin during hospital stay and on discharge had a mean LOS of 8.95 days, a 26% 30-day readmission rate, and a mean direct cost of $17,830. 20,054 Medicare beneficiaries discharged without Rifaximin

had a mean LOS of 8.26 days, 22% 30-day readmission rate, and mean direct cost of $21,702. Medicaid cohort on Rifaximin had a higher 30-day admission (28% vs 22%), mean LOS (11.8 vs 8.95) and higher mean direct hospital cost (31,766$ vs 21,702$) compared to the Medicare cohort. **Conclusion:** Our analysis of the VCD shows that in the Medicaid cirrhotic population, Rifaximin use is associated with a higher LOS, hospital cost, and readmission rates as compared to the Medicare population. This paradox of higher LOS could be explained by the challenges associated with prescription drug coverage and other psychosocial determinants of health. A possible target for reducing the length of stay and readmissions would entail use of dedicated case managers and a less restrictive prior authorization requirements.

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3702-C | FINANCIAL BURDEN AFTER HCC DIAGNOSIS IN A LARGE US NATIONAL PATIENT COHORT

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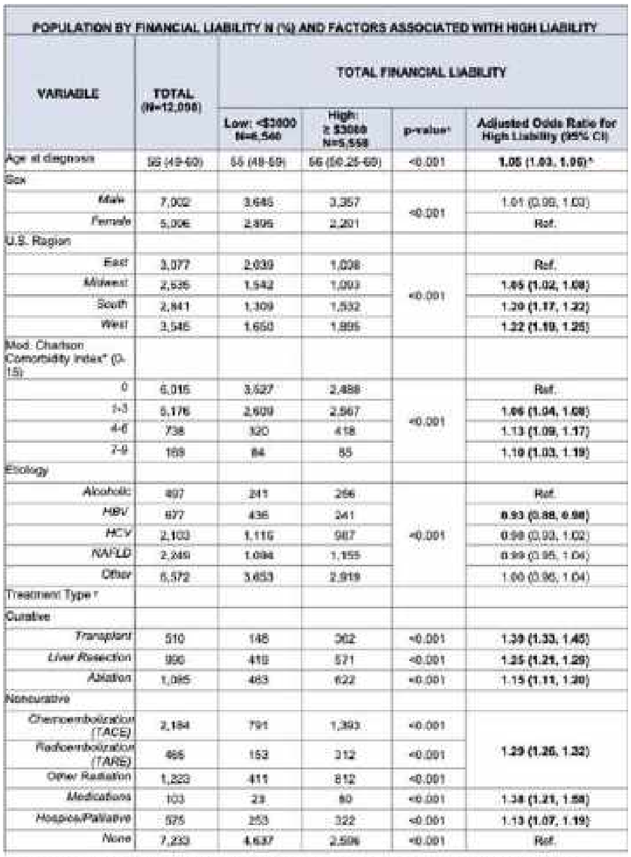
Background: High financial burden of cancer care has been reported for multiple cancer types, although there are fewer data in patients with hepatocellular carcinoma (HCC). We aimed to characterize the financial burden to patients diagnosed with HCC using a large national database and to identify correlates of higher patient financial liability. **Methods:** Adults aged 18-64 diagnosed with HCC (ICD–9/10 codes 155.0, C22.0) from 2006 through 2021 were identified using IQVIA PharMetrics Plus, a nationally representative U.S. database of commercial medical and pharmacy claims. Patients were required to have at least 12 months of continuous medical and pharmacy benefits post diagnosis of HCC. Patient financial liability was defined as the difference between allowed and paid amounts from adjudicated insurance claims. We reported total and HCC-related financial liabilities. Multivariable logistic regression modeling was used to identify variables associated with high ($> = 3000) vs. low (< $3,000) total financial liability post HCC diagnosis. **Results:** We identified 12,098 eligible patients with HCC, with median age 56 years and 58% were male. Of the 40% with at least one HCC therapy during the first year after HCC diagnosis, 18% received TACE or TARE, 10% external beam radiation, 9% ablation, 8% resection, and 4% liver transplantation (Table 1). The median total financial liability during the year after HCC diagnosis was $2,623 (25-75% interquartile range (IQR): $863 - $5,627). Despite all patients having some financial liability, only 15% (n = 1,837) experienced HCC-related liability. Among those with non-zero HCC liability, the median liability was $555 (Q1-Q3: $162 - $1,584). In multivariable analysis, older age, higher comorbidity, having alcohol-related cirrhosis, living in non-East regions, and receiving HCC-related treatment were each significantly associated with high total patient liability (≥ $3,000). **Conclusion:** In this privately insured population, patients' total financial liability after HCC diagnosis was high despite low direct HCC-related costs. There was significant variability in individual financial liability based on patient age, geography, treatments received, HCC etiology, and comorbidity. Patients with a diagnosis of HCC may need financial counseling tailored to their individual risk factors for greater financial liability, especially related to insurance coverage.



POPULATION BY FINANCIAL LIABILITY N (%) AND FACTORS ASSOCIATED WITH HIGH LIABILITY

VARIABLE	TOTAL (N=12,098)	TOTAL FINANCIAL LIABILITY			
		Low: <$3000 N=6,540	High: ≥ $3000 N=5,558	p-value&	Adjusted Odds Ratio for High Liability (95% CI)
Age at diagnosis	56 (49-60)	55 (48-59)	56 (50.25-60)	<0.001	**1.05 (1.03, 1.06)^**
Sex					
Male	7,002	3,645	3,357	<0.001	1.01 (0.99, 1.03)
Female	5,096	2,895	2,201		Ref.
U.S. Region					
East	3,077	2,039	1,038	<0.001	Ref.
Midwest	2,635	1,542	1,093		**1.05 (1.02, 1.08)**
South	2,841	1,309	1,532		**1.20 (1.17, 1.22)**
West	3,546	1,650	1,896		**1.22 (1.19, 1.25)**
Mod. Charlson Comorbidity Index* (0-15)					
0	6,015	3,527	2,488	<0.001	Ref.
1-3	5,176	2,609	2,567		**1.06 (1.04, 1.08)**
4-6	738	320	418		**1.13 (1.09, 1.17)**
7-9	169	84	85		**1.10 (1.03, 1.18)**
Etiology					
Alcoholic	497	241	256	<0.001	Ref.
HBV	677	436	241		**0.93 (0.88, 0.98)**
HCV	2,103	1,116	987		0.98 (0.93, 1.02)
NAFLD	2,249	1,094	1,155		0.99 (0.95, 1.04)
Other	6,572	3,653	2,919		1.00 (0.96, 1.04)
Treatment Type §					
Curative					
Transplant	510	148	362	<0.001	**1.39 (1.33, 1.45)**
Liver Resection	990	419	571	<0.001	**1.25 (1.21, 1.29)**
Ablation	1,095	483	622	<0.001	**1.15 (1.11, 1.20)**
Noncurative					
Chemoembolization (TACE)	2,184	791	1,393	<0.001	**1.29 (1.26, 1.32)**
Radioembolization (TARE)	465	153	312	<0.001	
Other Radiation	1,223	411	812	<0.001	
Medications	103	23	80	<0.001	**1.38 (1.21, 1.58)**
Hospice/Palliative	575	253	322	<0.001	**1.13 (1.07, 1.19)**
None	7,233	4,637	2,596	<0.001	Ref.

& p-value comparing across liability groups; chi-square test used for categorical variables and Kruskal-Wallis test used for continuous variables.* CCI score excluding liver disease and cancer.

^ Adjusted odds ratio for age > 55 (baseline ≤ 55).

§ For purposes of logistic regression, patients were classified by treatment according to a trumping algorithm of Transplant > Resection > Ablation alone > Embolization/Radiotherapy +/- ablation > Medication > Hospice > None; as patients may have received more than one treatment

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3703-C | INCREASE IN POINT-PREVALENCE AND COSTS OF LIVER CIRRHOSIS IN THE NETHERLANDS – A NATIONWIDE HEALTH CLAIMS DATA ANALYSIS

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Background: Chronic liver injury ultimately progresses to the development of cirrhosis. Patients with cirrhosis can be in a compensated or decompensated phase, the latter marked by clinical events such as ascites, hepatic encephalopathy and variceal bleeding. These events are associated with significant morbidity and mortality and the management is challenging and labor-intensive. Due to ongoing unhealthy lifestyle factors resulting in chronic liver injury, the burden of cirrhosis on healthcare systems in Europe is increasing. There is however limited data on the impact of cirrhosis on Dutch healthcare resources. **Methods:** We aimed to determine the point-prevalence and claimed health costs of adults (≥ 18 y) registered as patients with cirrhosis at Dutch hospitals. To this end we extracted health claims data (timeframe 2017-2021) from the records of the Dutch health claims database (Vektis), which covers almost all inhabitants of the Netherlands. We used diagnosis codes 'compensated cirrhosis' and 'decompensated cirrhosis' to identify patients. **Results:** The point prevalence of patients with cirrhosis increased from 48,7 patients per 100.000 adult Dutch inhabitants in 2017 to 75,2 per 100.000 in 2021 (+54%). The point-prevalence for cirrhosis was highest in the province of Limburg with 105,6 patients per 100.000 adult Dutch inhabitants. The annual increase in unique new patients for which hospitals claimed costs was n = 3.725 in 2018, n = 3.840 in 2019 (+3%), n = 3.749 in 2020 (-2%) and n = 3.695 in 2021 (-1%). The largest increase was observed in the province of Zuid-Holland (approximately 5 new patients per 100.000 adult Dutch inhabitants per year). Total number of hospital admissions increased with 19% from 2.443 admissions in 2017 to 2.899 admissions in 2021. The median length of stay for admitted patients with cirrhosis in 2017-2021 was four days [IQR 2-7 d]. The annual reported costs for patients with cirrhosis increased from €35 million in 2017 to €78 million in 2021 (+120%). **Conclusion:** The point-prevalence of Dutch adults registered as a patient with cirrhosis in Dutch hospitals increased by more than fifty percent, with remarkable regional differences. Consequently, the total healthcare costs claimed for these patients more than doubled in less than five years.

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3704-C | TRENDS IN MEDICAID SPENDING ON NUCLEOSIDE/ NUCLEOTIDE ANALOGUES FOR HEPATITIS B: 2012-2010

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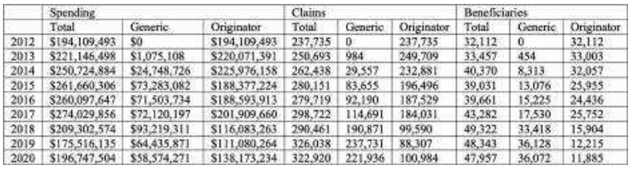
Background: There is no cure for chronic hepatitis B infection and many individual's require expensive, long-term nucleoside and nucleotide analogues (NA) therapy. In the United States, individual's over the age of 65 or who are living with disability are eligible for Medicare and can obtain coverage of their drugs through Medicare Part D. The aim of this study was to assess the number of patients receiving NA monotherapy for HBV in the United States through Medicare and the direct costs associated with coverage. **Methods:** The Centers for Medicare & Medicaid Services Part D database was accessed from 2012-2020 to identify NA used to treat HBV including lamivudine, adefovir, telbivudine, entecavir, tenofovir disoproxil fumarate and tenofovir alafenamide. Emtricitabine/tenofovir was excluded from the analysis as it is often used for treatment of HIV, and the underlying disease being treated could not be determined from this database. Data extracted included the number of beneficiaries, number of claims and amount spent, classified by originator (brand name) and generic versions of each compound. **Results:** In 2012, a total of 32,112 individual's submitted 237,735 claims for NA monotherapy therapy for HBV at an estimated cost of $194 million USD. The number of individual's receiving NA monotherapy has overall increased from 2012 to 2020 by 49% with annual spending growing until 2017 before beginning to decrease related to a drop in the spending on originator drugs. From 2012-2018, the highest annual expenditure for NA was tenofovir disoproxil fumarate representing 58-68% of the annual total spend on NA. From 2019 and beyond, this highest expenditure has shifted to tenofovir alafenamide which represents 65% of NA spending in 2020. There was no payment for telbivudine through the study period. **Conclusion:** There is a significant cost to Medicare for NA monotherapy therapy for HBV, but this economic burden is decreasing despite an increased number of patients treated, likely due to increased access to generic formulations. Understanding how medications are being utilized as well as the impact of generic medications is important for future planning for drug coverage to address and important cause of liver disease in the US.



	Spending			Claims			Beneficiaries		
	Total	Generic	Originator	Total	Generic	Originator	Total	Generic	Originator
2012	$194,109,493	$0	$194,109,493	237,735	0	237,735	32,112	0	32,112
2013	$221,146,498	$1,075,108	$220,071,391	250,693	984	249,709	33,457	454	33,003
2014	$250,724,884	$24,748,726	$225,976,158	262,438	29,557	232,881	40,370	8,313	32,057
2015	$261,660,306	$73,283,082	$188,377,224	280,151	83,655	196,496	39,031	13,076	25,955
2016	$260,097,647	$71,503,734	$188,593,913	279,719	92,190	187,529	39,661	15,225	24,436
2017	$274,029,856	$72,120,197	$201,909,660	298,722	114,691	184,031	43,282	17,530	25,752
2018	$209,302,574	$93,219,311	$116,083,263	290,461	190,871	99,590	49,322	33,418	15,904
2019	$175,516,135	$64,435,871	$111,080,264	326,038	237,731	88,307	48,343	36,128	12,215
2020	$196,747,504	$58,574,271	$138,173,234	322,920	221,936	100,984	47,957	36,072	11,885

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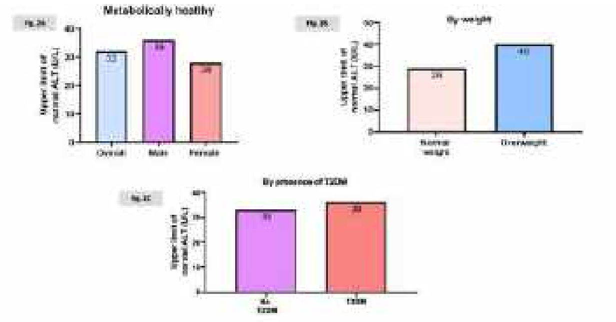
The following people have nothing to disclose: Mayur Brahmania

3705-C | UPPER LIMIT OF NORMAL ALT LEVELS IN HEALTH AND METABOLIC DISEASES: POOLED ANALYSIS OF 484,177 INDIVIDUALS WITH BOOTSTRAP MODELLING

Eunice Tan[1], Daniel Q Huang[2], Natasha Tang Sook Yee[3], Wan Zi Hui[3], Sanjna Nerurkar[3], Justin Yk Chua[3], Kang Shiong Goh[4], Cheng Han Ng[5], Mark Dhinesh Muthiah[2], Yu Zhou[6], Amanda Woodward[7], Michael H Le[7], Yee Hui Yeo[8], Scott D. Barnett[9], Ramsey Cheung[9] and Mindie H. Nguyen[9], (1)Nuhs, (2)National University Health System (NUHS), (3)National University of Singapore, (4)National University Health System, Singapore, (5)Yong Loo Lin School of Medicine, National University of Singapore, (6)Adelaide Medical School, the University of Adelaide, (7)Stanford University, (8)Cedars-Sinai Medical Center, Culver City, CA, (9)Stanford University Medical Center, Palo Alto, CA

Background: At present, physician practice in regards to evaluation for potential liver disease are largely driven by upper limit of normal (ULN) of serum alanine aminotransferase (ALT) by local laboratories, which may not be drawn from a healthy population without liver disease. However, obesity-related metabolic diseases such as type 2 diabetes mellitus (T2DM) have become increasingly prevalent in the recent decades and may affect the "normal" range of ALT. Thus, there remains an unmet need for updated reference ranges of ALT in individual's with no liver disease with and without metabolic diseases. **Methods:** We performed two separate searches of the PubMed, Embase, and Cochrane databases up to March 2020 and April 2021 to identify studies that included individual's with metabolic diseases and those without respectively. We included studies that provided data for mean or median ALT levels and demonstrated absence of hepatic steatosis on ultrasonography. We excluded those with hepatitis B, C infection and/or excessive alcohol consumption. To identify individual's without metabolic diseases, we excluded those who had T2DM, dyslipidemia, and/or were overweight/obese. The mean ALT (U/L) was estimated using a random-effects mixed model and the ULN level (95th-percentile value, U/L) via a bootstrap model with 10,000 resamples. **Results:** 12 articles (349,367 individual's) were included in the analysis for healthy individual's. For studies which included individual's with metabolic disease, 35 articles were included in the analysis: 26 studies by weight status (187,069 normal weight individual's in 13 studies and 85,898 overweight/obese individual's in 13 studies), 15 studies by the presence of T2DM (9,245 individual's with T2DM in 12 studies and 20,904 individual's without T2DM in 3 studies). In healthy individual's, the ALT ULN levels were 32 U/L overall, and higher in males than females: 36 U/L and 28 U/ respectively (Fig 2A). In analyses that included individual's with metabolic diseases, the ALT ULN levels were 40 U/L in overweight/obese compared to 29 U/L in normal weight (Fig 2B); and 36 U/L among those with T2DM compared to 33 U/L in no T2DM (Fig 2C). On meta-regression of study-level factors, body mass index (coefficient 1.49, 95% CI 0.11-2.86, $P = 0.03$), high-density lipoprotein (coefficient -0.47, 95% CI -0.85-(-0.08), $P = 0.02$), and triglycerides (coefficient 0.19, 95% CI 0.12-0.25, $P < 0.0001$) correlated with ALT levels. **Conclusion:** We provide an updated reference ALT ULN levels for healthy individual's without known liver disease and in subgroups of individual's with or without T2DM, and those with normal weight or overweight/obesity. Our updated ALT ULN cutoffs from this study are less stringent than those proposed two decades ago and can inform current practice to streamline investigations of elevated ALT.



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3706-C | A HEPATITIS C (HCV) TEST AND TREAT INITIATIVE IN RESIDENT ASSOCIATED ACADEMIC PRIMARY CARE CLINIC: UPDATES IN AN ERA OF EXPANDED SCREENING GUIDELINES

Eleanor Aubrey Belilos[1], *Zoe Post*[1], *Matthew Eganhouse*[1], *Agnieszka Maniak*[1], *Raeesh Vahora*[1] *and Nancy Reau*[2], *(1)Rush University Medical Center, (2) Rush Medical College, Chicago, IL*

Background: The WHO has tasked health systems to eliminate HCV as a public health threat by 2030, and as such 2020 USPTF guidelines changed to recommend a one-time screen for all adults aged 18-79. Given this, HCV screening responsibility now falls more than ever to primary care. Prior to the expanded guidelines, data from our institution examined resident HCV screening practices and found that consistent care from one primary care physician was associated with improved HCV screening, though rates were still ~50%. Most providers that screen for HCV have little experience in treatment; this new study examined the feasibility and efficacy of teaching residents to both screen and treat HCV in their primary care clinics in an era of expanded screening guidelines. It also explored the utility of a live dashboard in tracking screening rates and treatment practices, with the goal to expand HCV treatment in the primary care setting. **Methods:** A teaching session was held in early 2023 for residents at a single academic center to review updated HCV screening guidelines and teach them to effectively treat HCV in their primary care continuity clinics. A screening and treatment protocol was posted in the resident workroom for reference. A live dashboard was developed to automatically pull EMR data on resident HCV screening and treatment practices from 1/2021-present, to track data prospectively in 3-month intervals. All patient encounters for which HCV screening was incomplete were included. **Results:** From 1/2021-5/2023, 4,121 encounters in resident clinic had HCV screening due; of these, 671 were screened (16.3%) and 12 were HCV antibody positive; 1 had positive RNA and was referred to hepatology (prior to the teaching session). 3 months after the teaching session, the HCV screening rate improved from 14.99% to 21.67% ($p < 0.0001$) and antibody positivity rate increased from 1.53% to 2.56%. Residents also felt significantly more comfortable prescribing HCV treatment if indicated (mean comfort level on a scale of 1-5 increased from 1.7 to 3.9, $p < 0.0001$). **Conclusion:** Educating residents to both identify and treat HCV in their primary care continuity clinics is an easy strategy to increase the provider pool necessary to achieve WHO eradication goals. However, current HCV screening rates are inadequate and have notably decreased since the denominator of patients to be screened was expanded

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in 2020. Residents are amenable to learning how to effectively screen and treat HCV, and implementation of a live tracking dashboard can motivate and hold resident clinicians accountable. Next steps include continuing to monitor the dashboard in regular intervals and implementing additional teaching sessions to include incoming residents, APPs, and precepting attending physicians to further increase comfort with HCV treatment.

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3707-C | A NOVEL HOMELESS HEPATITIS C CARE MODEL: CLINICAL, PATIENT-REPORTED AND HEALTH ECONOMIC OUTCOMES FROM THE END C STUDY

Adele Mourad[1,2], Rona McGeer[1,2], Emma Gray[2], Anna-Marie Bibby-Jones[3], Vikki Charles[2], Natasha Sanderson[2], Thomas Bird[4], Margaret O'Sullivan[2], Lidia Salvaggio[2], Heather Gage[5] and Sumita Verma[1,6], (1) Brighton and Sussex Medical School, Brighton, United Kingdom, (2)University Hospital Sussex NHS Trust, (3) Sussex Partnership NHS Foundation Trust, (4)Royal Surrey NHS Foundation Trust, (5)University of Surrey, (6)University Hospitals Sussex NHS Foundation Trust, Brighton, UK

Background: Approaching hepatitis C virus (HCV) elimination we are left with an increasing complex and marginalised cohort such as people who are homeless (PWAH). We aimed to assess not only clinical but patient reported outcomes (PRO) and health economic outcomes of a novel community-based care model for PWAH. **Methods:** The END C study (2019-2023) based at multiple community homeless sites in southeast England provided point of care HCV testing, transient elastography (TE), onsite direct acting antiviral (DAA) treatment, peer mentor support, and contingency management (supermarket vouchers). Generic (SF-12v2 and EQ-5D-5L) and liver-specific (SFLDQoL) health related quality of life (HRQoL) was assessed before and at end of HCV treatment. Costs/HCV case detected and cured were calculated. Primary outcome measure was sustained virological response (SVR12) (intention to treat ITT). **Results:** A total of 418 individual's were recruited, mean age 44 ± 10.6, 78% male, 74% being homeless at initial assessment. Prevalence of current injecting drug use (IDU), alcohol use and positive HCV RNA were 25% (95% CI 21%-29%), 65% (95% CI 60%-69%) and 28% (95% CI 24%-33%) respectively. Forty-seven percent of the cohort had previously been incarcerated. Of the 344 individual's with a valid TE result, prevalence of cirrhosis ($LSM \geq 12$kpa) was 12 %. Of the $n = 116$ with a positive RNA, $n = 105$ (91%) received DAAs of whom 91% were currently homeless, current IDU and current alcohol use being 88% and 93% respectively. ITT SVR12 rates were 81% (95% CI 72%-88%). The only predictor of non-SVR 12 was $\geq 80\%$ adherence (OR 0.04, 95% CI 0.012-0.148, $p < 0.001$). Reinfection data awaited. HRQoL improved significantly at end of treatment in those with SVR12: SFLDQoL: symptoms ($p = 0.0043$), effect on daily life ($p = 0.0031$), memory ($p = 0.2403$), distress ($p = 0.0155$), loneliness ($p = 0.0126$), hopelessness ($p = 0.2476$), sleep ($p = 0.0164$) and stigma ($p = 0.0055$); SF-12 v2 :physical ($p = 0.0023$) and mental health domains ($p = 0.0374$); and EQ-5D-5L composite profile score ($p = 0.0037$) and visual analogue scale ($p < 0.001$). Cost (British pounds 2022) per case detected was £279; mean cost per cure (excluding DAA costs) being £137. Mortality in the treated cohort was 9.5%, the most common cause being drug overdose. **Conclusion:** With novel engagement strategies, excellent SVR12 rates can be achieved in PWAH at modest costs. In addition, SVR12 is associated with significant improvement in both generic and liver specific HRQoL.

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3708-C | A PROSPECTIVE MULTIMODAL EDUCATION INTERVENTION FOR PROVIDERS TO INCREASE HEPATIC ENCEPHALOPATHY TREATMENT RATES

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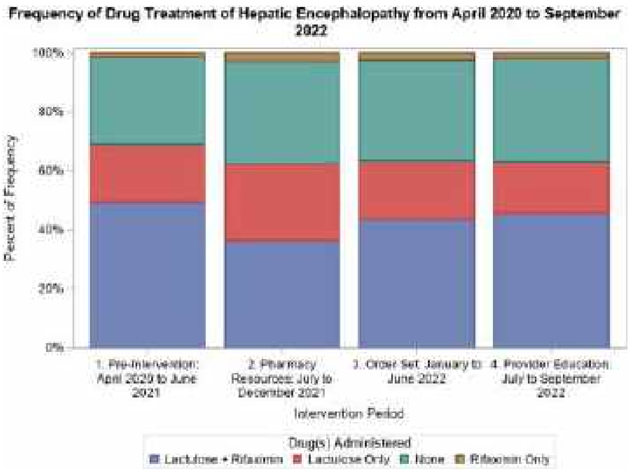
Background: Over 50% of hospitalizations from hepatic encephalopathy (HE) are preventable, but many patients do not receive guideline recommended treatment. Our aim was to use a multimodal education intervention (MMEI) for providers to increase HE treatment rates. We evaluated 1) trends in HE treatment, 2) predictors of receiving treatment, and 3) the impact of HE treatment on hospitalization outcomes. **Methods:** Prospective single-center cohort study of patients hospitalized with HE from July 1, 2021 – September 30, 2022. The MMEI included three phases: 1) Prior authorization resources for HE medication coverage, 2) Standardized electronic order set with suggested HE diagnostic workup and medications, and 3) In-person provider education session on HE treatment and resources from #1 and #2. Treatment was defined as receiving any drug (lactulose or rifaximin), or combination therapy (lactulose and rifaximin) while hospitalized. We compared treatment rates from the 15-month MMEI to a 15-month pre-MMEI control group from April 1, 2020 – June 30, 2021. Adjusted odds ratios (AOR) were generated from logistic regression. **Results:** 471 patients were included - 236 pre-MMEI and 235 during the MMEI. After adjustment, there is a significantly lower odds of receiving any drug post-MMEI compared to pre-MMEI (AOR = 0.61, 95% CI: 0.38, 0.96, $p = 0.03$). There was no significant difference in receiving combination therapy pre- or post-MMEI (AOR = 0.77, 95% CI: 0.46, 1.29, $p = 0.32$). Predictors of receiving any drug included alcohol-related or cryptogenic cirrhosis ($p < 0.001$), and the presence of ascites ($p = 0.005$) and/or portal hypertension ($p = 0.003$), while the only significant predictor of not receiving any drug treatment was having autoimmune cirrhosis ($p < 0.001$). Among those receiving lactulose, patients who were seen by internal medicine ($p = 0.01$) or were intoxicated ($p = 0.02$). Any HE treatment was associated with higher 30-day readmission ($P < 0.001$). **Conclusion:** The MMEI used in our study did not increase HE treatment rates. Despite the benefits of HE treatment, current prescribing patterns at our institution suggest that barriers other than prior authorization resources, standardized electronic order sets, or provider education are limiting the prescription of HE medications. Further efforts are needed to identify and address barriers to drug treatment by providers for patients, especially in subgroups of the population with low treatment rates.



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3709-C | ALCOHOL USE DISORDER AND ALCOHOL RELATED LIVER DISEASE PREVALENCE IN OBSTETRICS AND GYNECOLOGY CLINICS

Mary Thomson, Elizabeth Aby, Thomas M. Leventhal and Nicholas Lim, University of Minnesota

Background: Early identification of alcohol use disorder (AUD) can prevent alcohol related liver disease (ARLD). Young female patients often seek care through an Obstetrician/Gynecologist (OB/GYN), rather than a traditional primary care provider (PCP). The aim of this study is to identify the prevalence of AUD and ARLD in young patients seeking OB/GYN care to better inform AUD screening in this population. **Methods:** A retrospective review of female patients aged 18-45 seen in

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

the University of Minnesota OB/GYN clinics between 10/1/2015-10/1/2021 was conducted. AUD and ARLD were defined using ICD-10 coding. **Results:** 71,853 female patients were included. Median age at first OB/GYN visit was 31 years. The majority (73.8%) were white. The median follow up period was 1,410 days, during which 42.8% had a pregnancy related visit (median 10 visits), and 88.3% had a gynecologic visit (median 2 visits). 4.0% of the cohort had coding for AUD or ARLD (Table 1). Patients with AUD/ARLD were more often white (81.0% v. 73.6%, $p < 0.000$), more likely to have Medicaid insurance (48.3% v. 23.1%, $p < 0.000$), and were older (OR 1.01 (95% CI 1.002-1.014, $p = 0.003$). 6.9% of those with AUD had coexisting ARLD. Patients with ARLD with labs had a median total bilirubin of 0.8 IU/mL (IQR 0.5-1.8) and median AST of 90.9 IU/mL (IQR 44.4-132.8). Median FIB-4 score was 2.0 (IQR 0.9-3.5). Patients with a pregnancy related visit, compared to those only seen for gynecologic issues, were younger, less often white, and more often on Medicaid. They were also less likely to be diagnosed with AUD (2.8% v. 4.0%, $p = 0.000$) and ARLD (0.2% v. 0.4%, $p = 0.000$). 72.4% concurrently saw a PCP. These patients were more likely to have a diagnosis code for AUD (4.1% v. 1.8%, $p < 0.000$) and ARLD (0.3% v. 0.2% $p = 0.003$). They were also older, more often white and on Medicaid compared to those who had not seen a PCP. **Conclusion:** Approximately one in thirty young patients in OB/GYN clinic had evidence of AUD. 6.9% of those with AUD had ARLD; median FIB-4 scores in those with ARLD were concerning for fibrosis. AUD/ARLD were less commonly coded for in those with an obstetrics visit, which may reflect reduced consumption or stigma of alcohol use during pregnancy. AUD and ARLD were more commonly coded for in those with a PCP, indicating these conditions may be under-recognized in OB/GYN clinics. Further work needs to be done to help OB/GYN providers identify harmful alcohol use, particularly in patients who only seek their care.

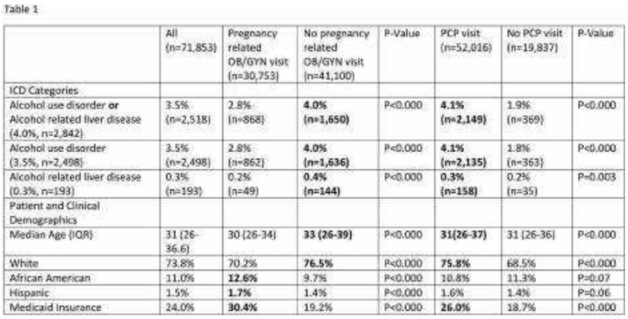

Table 1

	All (n=71,853)	Pregnancy related OB/GYN visit (n=30,753)	No pregnancy related OB/GYN visit (n=41,100)	P-Value	PCP visit (n=52,016)	No PCP visit (n=19,837)	P-Value
ICD Categories							
Alcohol use disorder **or** Alcohol related liver disease (4.0%, n=2,842)	3.5% (n=2,518)	2.8% (n=868)	**4.0% (n=1,650)**	P<0.000	**4.1% (n=2,149)**	1.9% (n=369)	P<0.000
Alcohol use disorder (3.5%, n=2,498)	3.5% (n=2,498)	2.8% (n=862)	**4.0% (n=1,636)**	P<0.000	**4.1% (n=2,135)**	1.8% (n=363)	P<0.000
Alcohol related liver disease (0.3%, n=193)	0.3% (n=193)	0.2% (n=49)	**0.4% (n=144)**	P<0.000	**0.3% (n=158)**	0.2% (n=35)	P=0.003
Patient and Clinical Demographics							
Median Age (IQR)	31 (26-36.6)	30 (26-34)	**33 (26-39)**	P<0.000	**31(26-37)**	31 (26-36)	P<0.000
White	73.8%	70.2%	**76.5%**	P<0.000	**75.8%**	68.5%	P<0.000
African American	11.0%	**12.6%**	9.7%	P<0.000	10.8%	11.3%	P=0.07
Hispanic	1.5%	**1.7%**	1.4%	P<0.000	1.6%	1.4%	P=0.06
Medicaid insurance	24.0%	**30.4%**	19.2%	P<0.000	**26.0%**	18.7%	P<0.000

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3710-C | AMSETY DATABASE: AN AI-POWERED NOVEL WAY TO RECRUIT MOTIVATED LIVER PATIENTS FOR CLINICAL STUDIES

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Background: Recruiting eligible liver subjects for clinical studies faces numerous challenges. Be it for broader diseases like non-alcoholic steatohepatitis (NASH) or for smaller patient populations like liver cancer, finding motivated subjects is difficult, time-consuming, and costly. As a result, completing clinical trials is complicated by marked delays and missed time points. The novel Amsety digital recruiting program consists of the Amsety Database and the Amsety-AI, an Artificial Intelligence for subject selection. This novel recruiting program shows marked benefits towards identifying trial subjects. Amsety-AI introduces an alternative to the liver disease clinical states - enhancing trial recruitment and improving subject retention. **Methods:** Amsety‘s database contains a highly motivated population with liver conditions. Around 500,000 subjects were collected through digital education towards liver health, nutrition, and a liver healthy lifestyle – such as the Liver Health Score, a proprietary instrument to assess lifestyle. The data encompasses vast demographic information, allowing clinical trial networks cursory pre-screening analysis and lowering of screening failure rates. **Results:** We collected Amsety-AI patients across the United States since 2016, including zip codes, age, gender, lifestyle and diet patterns, primary liver conditions as well as comorbidities. The data showed 66% were females, 56% had chronic liver disease; 41% were 50-65 years old and 35% were over 65 years of age. 71% reported some alcohol use on weekly basis and 13% were regular smokers. 21% of the participants had diabetes. Details of their diet is captured as well as level of exercise and self-reported quality of sleep. Attendance of scheduled medical care was self-reported in 90% of individual’s over 65 years versus 65% under 40 years of age. 21% of the participants reported family history of liver disease. More granular data is available. Currently the database grows by around 10,000 individual’s per month. **Conclusion:** Prescreening subjects has shown vast benefits and improvement in screening failure rates, decreasing research networks resources, while markedly reducing time to complete trial recruitment. Amsety-AI is a model for improving subject selections for NASH clinical trials and can help to reach motivated individual’s for Liver Health Care beyond clinical studies.

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The following people have nothing to disclose: Fatma Barakat, Jutta Kurz, Kevin Li

3711-C | ASSESSING ADHERENCE RATES TO QUALITY MEASURES IN HOSPITALIZED PATIENTS WITH CIRRHOSIS

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Background: Cirrhosis is associated with frequent complications and hospitalizations, including hepatic encephalopathy (HE), variceal bleeding, ascites, infection, and renal injury. It is crucial to provide evidence-based care for these complications. In this study, we assessed adherence rates to the AASLD Practice Metrics Committee's cirrhosis quality measures during hospitalizations of cirrhotic patients. **Methods:** We retrospectively reviewed cirrhotic patients admitted to the hospital at a single, academic liver transplant center in a diverse urban neighborhood. We collected admission data for the index admission in 2021, including sociodemographics, characteristics of cirrhosis-related complications, laboratory values, medications, procedures, readmissions, and follow-up appointment data. The primary endpoint was rate of adherence to cirrhosis quality measures. Secondary outcomes were comparison of quality measure adherence in patients with or without subsequent 90-day readmission or death, as well as in patients who did or did not receive hepatology/gastroenterology (GI) consultation. Wilcoxon rank sum, Chi-squared, or Fisher's exact tests were used for the secondary analyses. **Results:** 265 hospitalized cirrhotic patients were included. The median age was 63 years, 58% male, 16% White, 59% Hispanic, and 44% with alcohol related cirrhosis (Table 1). The median MELD-Na was 16. 102 patients (39%) were readmitted or died within 90 days of index admission. Among patients with ascites, 57% were treated with diuretics, 73% were given a low-sodium diet, and paracentesis was performed in 40%. In patients with HE, 80% were given lactulose or rifaximin. In patients with upper GI bleeding, 76% were given antibiotics and 81% had an upper endoscopy (EGD). 37% of patients with varices received band ligation, and 67% were treated with beta-blockers after discharge. Patients who were readmitted or died within 90 days were more likely to have a post-discharge hepatology appointment scheduled ($p = 0.035$); otherwise, there were no differences in quality measure adherence between groups. Inpatient GI/hepatology consultation was associated with higher rates of Hepatitis B testing ($p = 0.005$), rifaximin use ($p = < 0.001$), transplant evaluation ($p = < 0.001$), and hepatology follow-up appointments ($p = < 0.001$). **Conclusion:** In this study of a diverse urban liver transplant center population, adherence to quality measures for hospitalized cirrhotic patients was overwhelmingly poor. While there were no notable differences impacting 90-day readmission/death (likely due to small sample size), we did observe higher quality measure adherence when inpatient GI/hepatology consultation was performed. Further investigation on factors that impact quality measure adherence is warranted in order to develop program improvement initiatives to provide high value care for hospitalized patients with cirrhosis.

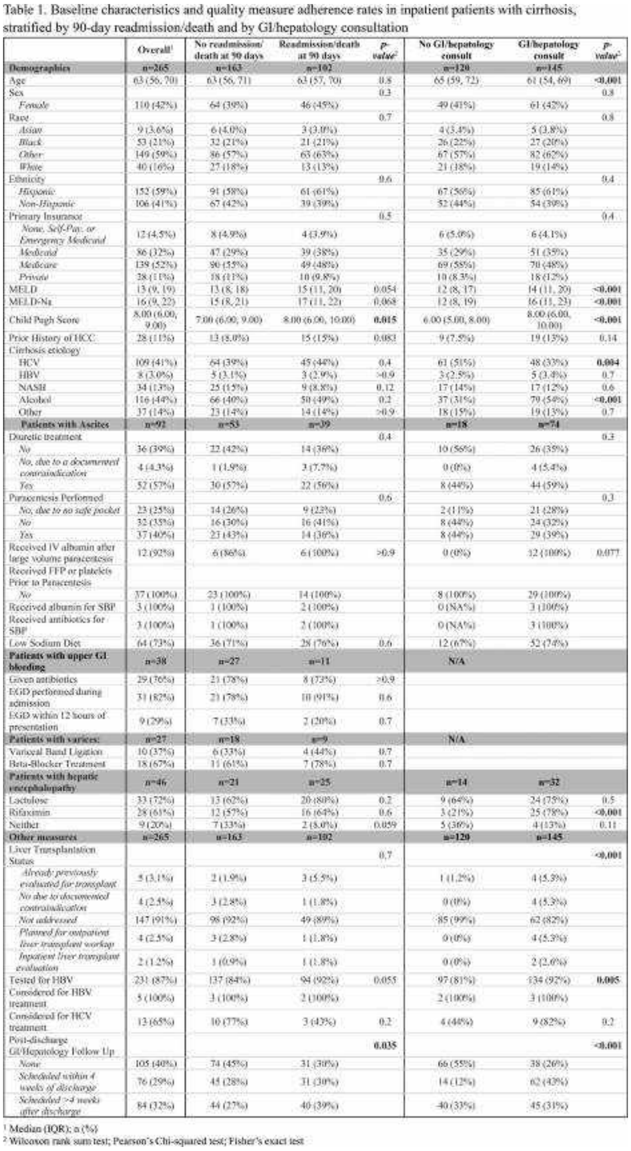

Table 1. Baseline characteristics and quality measure adherence rates in inpatient patients with cirrhosis, stratified by 90-day readmission/death and by GI/hepatology consultation

	Overall[1]	No readmission/ death at 90 days	Readmission/death at 90 days	p-value[2]	No GI/hepatology consult	GI/hepatology consult	p-value[2]
Demographics	**n=265**	**n=163**	**n=102**		**n=120**	**n=145**	
Age	63 (56, 70)	63 (56, 71)	63 (57, 70)	0.8	65 (59, 72)	61 (54, 69)	**<0.001**
Sex				0.3			0.8
Female	110 (42%)	64 (39%)	46 (45%)		49 (41%)	61 (42%)	
Race				0.7			0.8
Asian	9 (3.6%)	6 (4.0%)	3 (3.0%)		4 (3.4%)	5 (3.8%)	
Black	53 (21%)	32 (21%)	21 (21%)		26 (22%)	27 (20%)	
Other	149 (59%)	86 (57%)	63 (63%)		67 (57%)	82 (62%)	
White	40 (16%)	27 (18%)	13 (13%)		21 (18%)	19 (14%)	
Ethnicity				0.6			0.4
Hispanic	152 (59%)	91 (58%)	61 (61%)		67 (56%)	85 (61%)	
Non-Hispanic	106 (41%)	67 (42%)	39 (39%)		52 (44%)	54 (39%)	
Primary Insurance				0.5			0.4
None, Self-Pay, or Emergency Medicaid	12 (4.5%)	8 (4.9%)	4 (3.9%)		6 (5.0%)	6 (4.1%)	
Medicaid	86 (32%)	47 (29%)	39 (38%)		35 (29%)	51 (35%)	
Medicare	139 (52%)	90 (55%)	49 (48%)		69 (58%)	70 (48%)	
Private	28 (11%)	18 (11%)	10 (9.8%)		10 (8.3%)	18 (12%)	
MELD	13 (9, 19)	13 (8, 18)	15 (11, 20)	0.054	12 (8, 17)	14 (11, 20)	**<0.001**
MELD-Na	16 (9, 22)	15 (8, 21)	17 (11, 22)	0.068	12 (8, 19)	16 (11, 23)	**<0.001**
Child Pugh Score	8.00 (6.00, 9.00)	7.00 (6.00, 9.00)	8.00 (6.00, 10.00)	**0.015**	6.00 (5.00, 8.00)	8.00 (6.00, 10.00)	**<0.001**
Prior History of HCC	28 (11%)	13 (8.0%)	15 (15%)	0.083	9 (7.5%)	19 (13%)	0.14
Cirrhosis etiology							
HCV	109 (41%)	64 (39%)	45 (44%)	0.4	61 (51%)	48 (33%)	**0.004**
HBV	8 (3.0%)	5 (3.1%)	3 (2.9%)	>0.9	3 (2.5%)	5 (3.4%)	0.7
NASH	34 (13%)	25 (15%)	9 (8.8%)	0.12	17 (14%)	17 (12%)	0.6
Alcohol	116 (44%)	66 (40%)	50 (49%)	0.2	37 (31%)	79 (54%)	**<0.001**
Other	37 (14%)	23 (14%)	14 (14%)	>0.9	18 (15%)	19 (13%)	0.7
Patients with Ascites	**n=92**	**n=53**	**n=39**		**n=18**	**n=74**	
Diuretic treatment				0.4			0.3
No	36 (39%)	22 (42%)	14 (36%)		10 (56%)	26 (35%)	
No, due to a documented contraindication	4 (4.3%)	1 (1.9%)	3 (7.7%)		0 (0%)	4 (5.4%)	
Yes	52 (57%)	30 (57%)	22 (56%)		8 (44%)	44 (59%)	
Paracentesis Performed				0.6			0.3
No, due to no safe pocket	23 (25%)	14 (26%)	9 (23%)		2 (11%)	21 (28%)	
No	32 (35%)	16 (30%)	16 (41%)		8 (44%)	24 (32%)	
Yes	37 (40%)	23 (43%)	14 (36%)		8 (44%)	29 (39%)	
Received IV albumin after large volume paracentesis	12 (92%)	6 (86%)	6 (100%)	>0.9	0 (0%)	12 (100%)	0.077
Received FFP or platelets Prior to Paracentesis							
No	37 (100%)	23 (100%)	14 (100%)		8 (100%)	29 (100%)	
Received albumin for SBP	3 (100%)	1 (100%)	2 (100%)		0 (NA%)	3 (100%)	
Received antibiotics for SBP	3 (100%)	1 (100%)	2 (100%)		0 (NA%)	3 (100%)	
Low Sodium Diet	64 (73%)	36 (71%)	28 (76%)	0.6	12 (67%)	52 (74%)	
Patients with upper GI bleeding	**n=38**	**n=27**	**n=11**		**N/A**		
Given antibiotics	29 (76%)	21 (78%)	8 (73%)	>0.9			
EGD performed during admission	31 (82%)	21 (78%)	10 (91%)	0.6			
EGD within 12 hours of presentation	9 (29%)	7 (33%)	2 (20%)	0.7			
Patients with varices:	**n=27**	**n=18**	**n=9**		**N/A**		
Variceal Band Ligation	10 (37%)	6 (33%)	4 (44%)	0.7			
Beta-Blocker Treatment	18 (67%)	11 (61%)	7 (78%)	0.7			
Patients with hepatic encephalopathy	**n=46**	**n=21**	**n=25**		**n=14**	**n=32**	
Lactulose	33 (72%)	13 (62%)	20 (80%)	0.2	9 (64%)	24 (75%)	0.5
Rifaximin	28 (61%)	12 (57%)	16 (64%)	0.6	3 (21%)	25 (78%)	**<0.001**
Neither	9 (20%)	7 (33%)	2 (8.0%)	0.059	5 (36%)	4 (13%)	0.11
Other measures	**n=265**	**n=163**	**n=102**		**n=120**	**n=145**	
Liver Transplantation Status				0.7			**<0.001**
Already previously evaluated for transplant	5 (3.1%)	2 (1.9%)	3 (5.5%)		1 (1.2%)	4 (5.3%)	
No due to documented contraindication	4 (2.5%)	3 (2.8%)	1 (1.8%)		0 (0%)	4 (5.3%)	
Not addressed	147 (91%)	98 (92%)	49 (89%)		85 (99%)	62 (82%)	
Planned for outpatient liver transplant workup	4 (2.5%)	3 (2.8%)	1 (1.8%)		0 (0%)	4 (5.3%)	
Inpatient liver transplant evaluation	2 (1.2%)	1 (0.9%)	1 (1.8%)		0 (0%)	2 (2.6%)	
Tested for HBV	231 (87%)	137 (84%)	94 (92%)	0.055	97 (81%)	134 (92%)	**0.005**
Considered for HBV treatment	5 (100%)	3 (100%)	2 (100%)		2 (100%)	3 (100%)	
Considered for HCV treatment	13 (65%)	10 (77%)	3 (43%)	0.2	4 (44%)	9 (82%)	0.2
Post-discharge GI/Hepatology Follow Up				**0.035**			**<0.001**
None	105 (40%)	74 (45%)	31 (30%)		66 (55%)	38 (26%)	
Scheduled within 4 weeks of discharge	76 (29%)	45 (28%)	31 (30%)		14 (12%)	62 (43%)	
Scheduled >4 weeks after discharge	84 (32%)	44 (27%)	40 (39%)		40 (33%)	45 (31%)	

[1] Median (IQR); n (%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

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f 3712-C | ASSESSMENT OF HEPATOCELLULAR CARCINOMA URBAN/RURAL DIFFERENCES IN AFRICA USING SATELLITE SPATIAL SCALING

Erin Mann[1], Manaswita Tappata[2], Joseph Akambase[3], Kelly Searle[1] and Jose D. Debes[1,4], (1)University of Minnesota, (2)University of Minnesota, Minneapolis, Minnesota, Minneapolis, MN, (3)Hennepin Healthcare, Rochester, MN, (4)Erasmus University Medical Center

Background: Sub-Saharan Africa carries one of the highest burdens of hepatocellular carcinoma (HCC) in the world, with hepatitis B (HBV) as the most common cause. Globally, there is evidence that rural communities experience disproportionate cancer morbidity compared to urban ones. However, no study has examined these differences in Africa. **Methods:** We performed a systematic review of studies on HCC in Africa, later completing a meta-analysis using data from those studies to assess mean age, proportion of males, and of HBV positive patients in relation to location of the study. Using land-use/land cover data available from European Space Agency sentinel imagery on Africa, we categorized locations and calculated the distance in kilometers from each study site to the closest rural area (agricultural land). These distances were divided into quartiles. Logistic regression models were fit to estimate 1) the association between distance to the closest rural area and HBV and 2) the association between distance to the closest rural area and gender. Weighted mean age was calculated for each quartile. **Results:** 978 studies were retrieved through electronic database search. After removing duplicates and reviewing for relevance, fifty-seven articles were included. Data on 10,608 patients was used in the meta-analysis across 19 countries in Africa. 74% of patients were male and the weighted mean age was 52.5 years. Proximity to a rural areas was associated with increased odds of HBV after controlling for country, with locations closest to a rural region (<3.2km) having 3.1 times higher odds of HBV-HCC (95% CI 2.65 - 3.60, $p<0.001$) compared to patients in locations furthest from rural areas (>9.5km). When analyzing only studies in West Africa, those in locations closest to rural areas also showed higher odds of HBV-HCC (OR: 1.43, 95% CI 1.15-1.76, $p<0.001$) compared to those furthest from rural areas. However, patients in studies between 6.3 and 9.5km had decreased odds of HBV (OR: 0.42, 95% CI 0.28 – 0.63, $p<0.001$). No association was found between proximity to a rural areas and gender or age (50, 53, 47 and 53 y/o respectively per distance quartile). **Conclusion:** We found an association between proximity to a rural areas and odds of HBV-associated HCC in Africa in a first study of its kind. Further research is needed to understand the burden of HBV-related HCC in Africa across rural and urban areas.

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Disclosure information not available at the time of publication: Joseph Akambase, Kelly Searle

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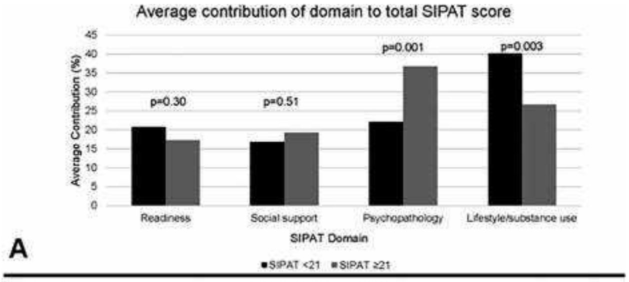
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

3713-C | ASSOCIATION OF PSYCHOSOCIAL RISK FACTORS AND LIVER TRANSPLANT EVALUATION OUTCOMES IN NON-ALCOHOLIC STEATOHEPATITIS

Roy X. Wang[1], Danielle Mirda[1], Jason J. Lee[1], Marina Serper[2] and Therese Bittermann[1], (1)University of Pennsylvania, (2)University of Pennsylvania, Philadelphia, PA, United States

Background: The Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) score is a standardized metric to assess psychosocial risk for transplant candidates. To date, the role of SIPAT in liver transplantation (LT) has largely focused on patients with alcohol-associated liver disease. A recent study demonstrated that SIPAT may also be a useful tool for patients with metabolic syndrome being evaluated for bariatric surgery, in whom issues of surgical readiness, self-care, and social support are equally relevant. This study evaluates the association of SIPAT with metabolic syndrome severity and outcomes in a large cohort of patients with non-alcoholic steatohepatitis (NASH) evaluated for LT. **Methods:** We performed a single-center retrospective cohort study of all patients with NASH evaluated for LT between January 2014-December 2021. SIPAT was obtained at the time of LT evaluation for all candidates. Clinical data from patients' electronic medical record was linked to center-specific transplant registry data. Metabolic syndrome severity was compared descriptively between validated SIPAT score groups: <21 (excellent/good candidate) vs >21 (minimally acceptable/high risk). Multivariable logistic regression, adjusting for demographic and metabolic syndrome factors, evaluated the association of SIPAT score with achieving active LT listing. **Results:** We identified 482 patients with NASH cirrhosis evaluated for LT, among whom 90.5% had SIPAT score <21 and 9.5% SIPAT score >21. The SIPAT >21 group had greater average contribution of the psychopathology domain, while the opposite held true for the lifestyle/substance abuse domain ($p=0.001$ and $p=0.003$, respectively; Figure A). The high SIPAT group was younger (56.8 vs 62.7 y for SIPAT <21; $p<0.001$) and more often female (63.0% vs 41.1%, respectively; $p=0.004$; Figure B). Metabolic factors including composite of cardiovascular disease, uncontrolled diabetes (A1c $>7\%$), uncontrolled hyperlipidemia (LDL >100mg/dL), and class II obesity were not different between groups (all $p>0.05$). Rates of hepatic decompensations and Model for End-stage Liver Disease Sodium score were also not different (all $p>0.05$). Overall, 41% of patients were actively listed, 7% were deferred, and 51% were declined. In multivariable analyses, increasing SIPAT score was independently associated with decreased odds of active LT listing (adjusted OR: 0.82 per 5-point increase, 95% CI: 0.71-0.95, $p=0.009$). **Conclusion:** SIPAT score was not associated with degree of metabolic syndrome or liver disease severity at LT evaluation in the largest cohort to date of patients with NASH cirrhosis. Increasing SIPAT score was associated with reduced odds of active LT listing. Identifying patients with high SIPAT scores may allow for targeted social and behavioral interventions to improve opportunities for LT in the NASH population.



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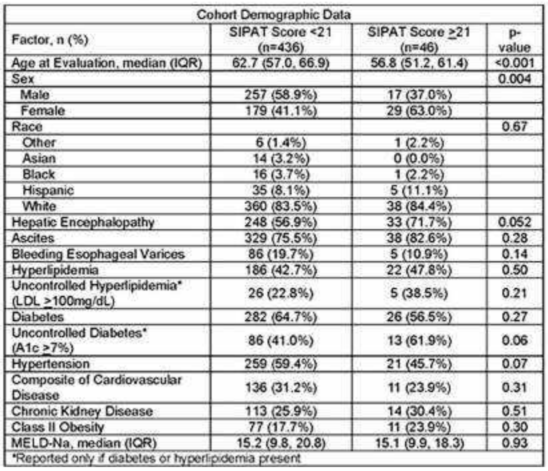

Cohort Demographic Data			
Factor, n (%)	SIPAT Score <21 (n=436)	SIPAT Score ≥21 (n=46)	p-value
Age at Evaluation, median (IQR)	62.7 (57.0, 66.9)	56.8 (51.2, 61.4)	<0.001
Sex			0.004
Male	257 (58.9%)	17 (37.0%)	
Female	179 (41.1%)	29 (63.0%)	
Race			0.67
Other	6 (1.4%)	1 (2.2%)	
Asian	14 (3.2%)	0 (0.0%)	
Black	16 (3.7%)	1 (2.2%)	
Hispanic	35 (8.1%)	5 (11.1%)	
White	360 (83.5%)	38 (84.4%)	
Hepatic Encephalopathy	248 (56.9%)	33 (71.7%)	0.052
Ascites	329 (75.5%)	38 (82.6%)	0.28
Bleeding Esophageal Varices	86 (19.7%)	5 (10.9%)	0.14
Hyperlipidemia	186 (42.7%)	22 (47.8%)	0.50
Uncontrolled Hyperlipidemia* (LDL ≥100mg/dL)	26 (22.8%)	5 (38.5%)	0.21
Diabetes	282 (64.7%)	26 (56.5%)	0.27
Uncontrolled Diabetes* (A1c ≥7%)	86 (41.0%)	13 (61.9%)	0.06
Hypertension	259 (59.4%)	21 (45.7%)	0.07
Composite of Cardiovascular Disease	136 (31.2%)	11 (23.9%)	0.31
Chronic Kidney Disease	113 (25.9%)	14 (30.4%)	0.51
Class II Obesity	77 (17.7%)	11 (23.9%)	0.30
MELD-Na, median (IQR)	15.2 (9.8, 20.8)	15.1 (9.9, 18.3)	0.93

*Reported only if diabetes or hyperlipidemia present

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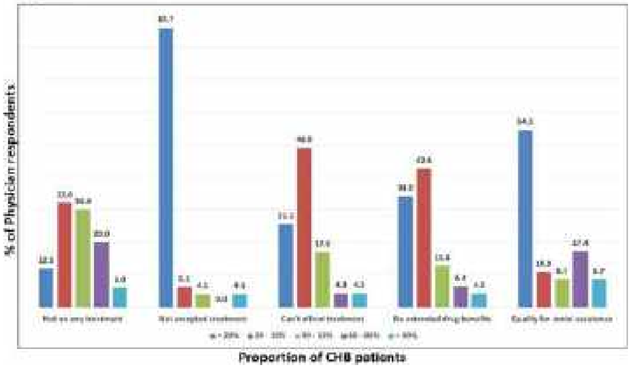
3714-C | BARRIERS TO HEPATITIS B TREATMENT FROM THE PHYSICIAN'S PERSPECTIVES: SURVEY STUDY BY THE CANADIAN HEPATITIS B NETWORK

Hin Hin Ko[1], Curtis Cooper[2], Anna Manko[3], Alnoor Ramji[1], Mang M. Ma[4], Karen E. Doucette[4], Scott K. Fung[5], David Kah Heng Wong[6], Chad Saunders[3,7], Magdy Elkhashab[8], Edward V. Tam[9], Mayur Brahmania[3], Sébastien Poulin[10], Philip Wong[11], Keith

Tsoi[12], Carmine G. Nudo[13], Julie Zhu[14], Carla Osiowy[15], Stephen E. Congly[3], Abdel-Aziz Shaheen[3], Tianyan Chen[11], Giada Sebastiani[16], Vanessa Meier-Stephenson[4] and Carla S. Coffin[3], (1)Division of Gastroenterology, University of British Columbia, BC, Canada, (2)The Ottawa Hospital, Ottawa, ON, Canada, (3)Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, (4)Department of Medicine, University of Alberta, Edmonton, AB, Canada, (5) University Health Network, Toronto, Ontario, Canada, (6)Department of Medicine, University of Toronto, Toronto, ON, Canada, (7)Haskayne School of Business, University of Calgary, AB, Canada, (8)Toronto Liver Center, Toronto, Ontario, Canada, (9)Pacific Gastroenterology Associates, Vancouver, BC, Canada, (10)Cisss Laurentides, St-Jerome, Clinique Médicale Urbaine Du Quartier Latin, QC, Canada, (11) Department of Medicine, McGill University Health Centre, Montreal, QC, Canada, (12)Mcmaster University, Hamilton, on, Canada, (13)Cité-De- La-Santé De Laval, Laval, QC, Canada, (14)Division of Gastroenterology, Health Sciences, Dalhousie University, NS, Canada, (15)National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB, Canada, (16)Department of Medicine, McGill University Health Centre, Westmount, QC, Canada

Background: Although Canada has a universal health care system, this does not include prescription drug benefits and provincial drug coverage formulary is variable. There are systemic factors impacting access to treatment leading to poor outcomes. Our previous study has demonstrated undertreatment in patients with chronic hepatitis B (CHB) who meet treatment guideline criteria. The goal of this survey study was to determine barriers to CHB treatment from the physician's perspectives. **Methods:** An on-line physician survey was sent to members of the Canadian Association for the Study of Liver. Analyses were performed using SPSS. **Results:** Of 50 respondents, 77% (n = 37) were in the 31-50 age group, 54% (n = 27) were male and 52% (n = 26) had been in practice for over 10 years. 32% (n = 16) were gastroenterologists, 30% (n = 15) hepatologists and 30% (n = 15) infectious disease specialists. 38% (n = 19) had more than 200 CHB patients in their practice and 94% (n = 47) had access to transient elastography. 88% (n = 44) followed the Canadian/American treatment guidelines most to all the time, but 70% (n = 35) felt that treatment reimbursement criteria should be broadened especially in those patients with family history for hepatocellular carcinoma. 36% (n = 18) found the provincial medication reimbursement process cumbersome and 20% (n = 10) found that there was a clinically relevant long delay in response from reimbursement authorities. The proportions of CHB patients who were untreated or did not accept treatment and had financial difficulty affording antiviral therapy (Figure 1). 26% (n = 13) of the respondents ranked high medication costs and the need for long-term treatment as the most concerning factors for the patients. Lower medication costs, broadened provincial reimbursement criteria, and improved patient education were identified as the top three strategies that could potentially improve treatment rates among treatment-eligible CHB patients . **Conclusion:** Canadian physicians surveyed report a high proportion of treatment-eligible CHB patients do not receive antiviral therapy due to mediation costs and the need for long-term treatment. Lower drug costs, patient education, and broadened reimbursement criteria could reduce barriers and increase treatment rates for patients with CHB.

Figure 1



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3715-C | BREAKING BARRIERS IN HEPATITIS C – A REAL-WORLD EXPERIENCE IN AN ECONOMICALLY DISADVANTAGED POPULATION

Gregory Churchill[1], Landen Burstiner[1], Abbey Johnston[1], Avni Agrawal[1], Oshin Rai[1], Reshmi Mathew[1], Alexis Kailey Goodman[2], Darby Allison[3] and Maged Peter Ghali[1], (1)University of Florida College of Medicine Jacksonville, (2)University of Florida, (3)Nova Southeastern University College of Osteopathic Medicine

Background: The WHO in 2016 projected global elimination of Hepatitis C by 2030. Despite highly efficacious direct-acting antiviral therapy, 2.3 million Americans remain infected. The United States budgeted 11 billion dollars this year to achieve eradication. It behooves local researchers to identify barriers to treatment, which differ depending on the population targeted. We sought to identify barriers in a frontline safety-net institution treating some of the most economically disadvantaged individual's. **Methods**: We identified all patients at our University hospital

hepatology clinic who were started on treatment for Hepatitis C (46% Medicaid/Uninsured patients). For patients who did not complete the treatment protocol, chart review was employed to identify reasons for discontinuing therapy and to analyze pertinent associations regarding demographics, medication type, and insurance. **Results**: From 2016-2023, 1648 patients were referred to our clinic and 574 patients were enrolled in our treatment program. Of these, 51 (9%) did not complete treatment. The predominant reasons for discontinuation were missed appointments (24), side effects (12), and cost (9). The highest rates of discontinuation were for Epclusa (14.89%), Mavyret (8.95%), then Harvoni (3.75%) (Fisher's Exact Test: $p = 0.003$). There was no clinically significant difference in patients who discontinued due to side effects. ($p = 0.837$). Uninsured completion rate was 97%, Medicare 95%, Medicaid 88%, and private insurance 84% ($p = 0.007$). Neither sex ($p = 0.884$) nor race ($p = 0.282$) significantly influenced the rate of therapy completion. **Conclusion**: In a population with significant healthcare disparities, excellent adherence to treatment protocols can be achieved even in uninsured charity cases. Non-adherence to follow-up is the predominant reason for not completing the treatment protocol. This may reflect challenges in contacting patients. Travel incentives or assistance with communication devices may improve compliance. Epclusa may be inferior to Mavyret due to its longer treatment course and periodic prescription with ribavirin, a medication with a poor side effect profile. Harvoni's lower discontinuation rate may represent an era effect; the most motivated patients sought treatment in the earlier era of therapy. Medicare's superiority over Medicaid may reflect patient level differences in these two populations and deserves further study. Once patients initiate therapy, the majority (89%) complete treatment successfully, but this represents only 35% of those referred. Further study is needed to determine how to better capture those who do not engage in therapy if elimination is to be achieved.

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3716-C | BREAKING THE CHAIN OF TRANSMISSION THROUGH DIAGNOSIS AND CURE OF PWID LIVING WITH HCV IN HARYANA, INDIA

Kanudeep Kaur[1], Rajashree Sen[1], Parveen Boora[2], Usha Gupta[2], Vinod Kumar[2], Sanjay Sarin[1] and Sonjelle Shilton[1], (1)Find, (2)Directorate of Health Services

Background: The World Health Organization (WHO) has set a target of reducing HCV incidence by 80% and mortality by 65% by 2030. The cornerstone of HCV elimination is the availability of highly effective direct-acting antiviral therapy. However, several challenges remain in achieving HCV elimination, including reaching marginalised populations, improving testing and diagnosis rates, and ensuring access to treatment. To achieve HCV elimination, a comprehensive approach is needed, including screening, diagnosis, and treatment, as well as harm reduction efforts for people who inject drugs. In the light of above FIND, in collaboration with the National Viral Hepatitis Control Program and Haryana State AIDS Control Society, initiated a program aimed at eliminating HCV among people who inject drugs (PWIDs) in Haryana. Prior to this, PWIDs had to visit the nearest hospital to avail HCV testing. This program's primary objective is to disrupt the chain of transmission, thereby achieving the goal of HCV elimination in the targeted population. **Methods:** Participants from 10 Oral Substitution Treatment (OST) and 8 Targeted Intervention (TI) sites were enlisted for the study. They underwent screening for Anti-HCV antibody using a rapid diagnostic test (RDT). PWIDs who tested positive for HCV on RDT were requested to provide a blood sample for HCV RNA testing and pre-treatment investigations. The staging of liver disease was determined using the APRI score, where an APRI score below 2 indicated non-cirrhotic status, while a score above 2 indicated cirrhosis. Non-cirrhotic patients were initiated on treatment directly at the OST/TI sites under the supervision of the medical officer, with the medication dispensed by the trained staff nurse. Cirrhotic cases were referred to medical specialists at tertiary hospitals for further evaluation. **Results:** A total of 2830 PWIDs were screened at the 10 OST and 8 TI during the project period, from December 2022 to April 2023. Of the 28.9% ($n = 818$) HCV antibody-positive, 93.8% ($n = 768$) had a confirmatory viral load test, 61.7% ($n = 474$) were HCV RNA-positive. Notably, treatment was initiated in 62.2% ($n = 295$) of the HCV RNA-positive cases, and these individual's are currently receiving ongoing treatment. The treatment initiation for the remaining is ongoing. **Conclusion:** Demonstrated a one stop centre for HCV care at the existing harm reduction service centres among the PWIDs of Haryana through a decentralised approach by setting up treatment centres at the OST /TI facilities.Overall, this approach increased equitable access of HCV care to vulnerable groups reducing risk of transmission and disease burden. The outcomes across the entire care process have been positive, and the decentralization of treatment at the easy-to-approach sites has led to enhanced acceptance and successful completion of treatment among PWIDs. A satisfactory level of patient retention within the HCV care process was reported.

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3717-C | CHARACTERIZING PRACTICE VARIATIONS IN THE CARE OF HOSPITALIZED PATIENTS WITH CIRRHOSIS ACROSS THE UNIVERSITY OF CALIFORNIA HEALTH

Jin Ge[1], Albert Lee[1], Oksana Gologorskaya[1], Chiung-Yu Huang[1], Mark J. Pletcher[1] and Jennifer C. Lai[2], (1) University of California, San Francisco, (2)University of California-San Francisco

Background: Despite publicly available practice guidelines and quality metrics published by AASLD and AGA, cirrhosis care remains highly variable. Investigating variations in guidelines-adherence could identify key opportunities to improve clinical outcomes, but prior studies have largely been based on administrative claims and limited by the lack of patient-level data. We aimed to overcome these limitations by leveraging a novel multicenter EHR database, the University of California Health Data Warehouse (UCHDW), with high-dimensional patient-level data to quantify adherence to national guidelines for inpatient cirrhosis care. **Methods:** UCHDW is an Observational Model Outcomes Partnership (OMOP)-based database with EHR data from the five major medical centers of the University of California Health System (UCH). We identified all adult patients with cirrhosis (based on a well-defined methodology of 1+ concept for chronic liver disease and 1+ concept for cirrhosis or its complications) from 2012 through 2022 in the de-identified version of UCHDW. We evaluated for adherence to five AASLD/AGA quality metrics applicable to inpatients with cirrhosis (Table 1, Column A). To determine pairwise differences between individual UCH sites, we conducted pairwise chi-squared tests with Bonferroni correction. **Results:** We identified 24,628 patients who were hospitalized for cirrhosis or its complications at the five UC Health medical centers. The patient population was gender and racially/ethnically diverse: 40% (9,877) women, 42% (10,448) White, 29% (7,136) Hispanic, 11% (2,620) Asian, 8% (1,864) Black, and 10% (2,555) Other/Unknown. Median (IQR) age was 59 years (IQR 50-67). Adherence to five quality metrics applicable to inpatients with cirrhosis differed significantly between the five UCH sites (Table 1, Column E, $p < 0.01$ for all comparisons). In pairwise comparisons between individual UCH sites (e.g., UC-3 versus UC-5), we found systematic differences between UC-1 versus other sites across all five metrics. When UC-1 is excluded from analyses, we found guideline-adherence rates remained significantly different across all metrics except for Metric 3, which recommends the use of antibiotics/albumin in the treatment of spontaneous bacterial peritonitis (Table 1, Column F). **Conclusion:** We found systematic differences in AASLD/AGA quality metrics across the five UC Health medical centers, and lower apparent quality particularly at one site (UC-1), indicating specific opportunities for improvement. Analyses of high-dimensional EHR data, such as UCHDW, will enable comprehensive evaluations of multi-level factors for potential interventions in the future.

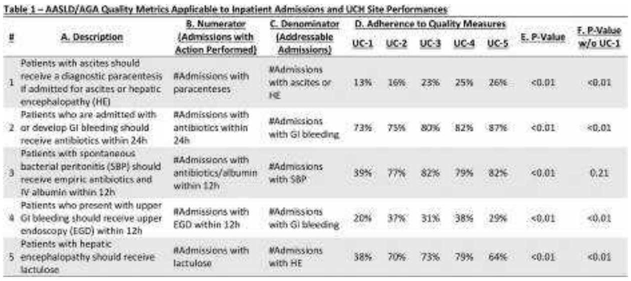

Table 1 – AASLD/AGA Quality Metrics Applicable to Inpatient Admissions and UCH Site Performances

#	A. Description	B. Numerator (Admissions with Action Performed)	C. Denominator (Addressable Admissions)	D. Adherence to Quality Measures UC-1	UC-2	UC-3	UC-4	UC-5	E. P-Value	F. P-Value w/o UC-1
1	Patients with ascites should receive a diagnostic paracentesis if admitted for ascites or hepatic encephalopathy (HE)	#Admissions with paracenteses	#Admissions with ascites or HE	13%	16%	23%	25%	26%	<0.01	<0.01
2	Patients who are admitted with or develop GI bleeding should receive antibiotics within 24h	#Admissions with antibiotics within 24h	#Admissions with GI bleeding	73%	75%	80%	82%	87%	<0.01	<0.01
3	Patients with spontaneous bacterial peritonitis (SBP) should receive empiric antibiotics and IV albumin within 12h	#Admissions with antibiotics/albumin within 12h	#Admissions with SBP	39%	77%	82%	79%	82%	<0.01	0.21
4	Patients who present with upper GI bleeding should receive upper endoscopy (EGD) within 12h	#Admissions with EGD within 12h	#Admissions with GI bleeding	20%	37%	31%	38%	29%	<0.01	<0.01
5	Patients with hepatic encephalopathy should receive lactulose	#Admissions with lactulose	#Admissions with HE	38%	70%	73%	79%	64%	<0.01	<0.01

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Jennifer C. Lai – Novo Nordisk: Advisor, No, No; Genfit: Consultant, No, No; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Vir: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gore: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Flagship Pioneering: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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3718-C | CO-EXISTENT CELIAC DISEASE IN ADULT PATIENTS WITH ALL CAUSE CIRRHOSIS OF THE LIVER

Ankit Agarwal, Aditya Vikram Pachisia, Shubham Mehta, Anam Ahmed, Alka Singh, Sambuddha Kumar, *Shubham Prasad, Bodhisattya Roy Chaudhuri, Lalita Mehra, Rimlee Dutta, Prasenjit Das, Dr Shalimar, Vineet Ahuja and Govind Makharia, All India Institute of Medical Sciences, New Delhi*

Background: Celiac disease (CeD) is emerging as a multisystem disease with involvement of the liver. While patients with CeD have been found to have hypertransaminasemia; patients with cryptogenic hypertransaminasaemia, cryptogenic cirrhosis, and autoimmune liver diseases have also been found to be associated with CeD. We assessed the prevalence of Celiac disease in all-cause cirrhosis. **Methods:** In a prospective study, consecutive patients with cirrhosis, irrespective of the underlying etiology, presenting between March 2022 and February 2023 to Gastroenterology clinic were recruited. All of them were screened for CeD using IgA anti-tissue transglutaminase antibody (anti-tTG Ab) and if found positive, they were subjected to anti-endomysial antibody (EMA) testing and duodenal mucosal biopsy examination. A diagnosis of CeD was established if they had anti-tTG Ab titers > 2 times the ULN in the presence of villous abnormalities of modified Marsh grade > 2 and/or had EMA positive. **Results:** Of 1126 patients with cirrhosis of all causes, 22 (1.9%) had high titers of anti-tTG Ab. EMA was positive in 9 of 15 patients in whom it could be done. Seventeen patients had a villous abnormality of modified Marsh grade ≥ 2. The prevalence of biopsy-confirmed CeD in them was 1.5%. The mean (SD) anti tTG Ab titer fold rise in them was 18.4 + 5.5 folds. Patients with cirrhosis having CeD, when compared to patients with cirrhosis without CeD, were younger, with a higher proportion being males. The median liver stiffness measurement (23.05 vs 29.71 Kpa, P = 0.75), mean CTP (8.9 vs 9.3) and MELD-Na (18.4 vs 19.2), respectively were comparable in patients with and without CeD. The etiology of cirrhosis in patients with associated CeD were alcohol in 7 (31.8%), autoimmune hepatitis in 6 (27.2%), non-alcoholic steatohepatitis in 4 (18.1%), chronic hepatitis B in 2 (9%), Wilson's disease in 1 and a combination of Alcohol+AIH and NASH+AIH in 1 each. The median delay in diagnosis of co-existent CeD was 201 days (range 54 to 886). All patients with co-existent CeD are being followed up prospectively to look for the effect of GFD on liver functions. **Conclusion:** The sero-prevalence and the prevalence of biopsy-confirmed CeD in patients with all-cause cirrhosis were 1.9% and 1.5% which is higher than the prevalence of CeD in the general population. Most of these patients with cirrhosis having CeD already had a known etiology of the cirrhosis. Therefore, all patients with cirrhosis should be screened for CeD as it can result in the diagnostic delay of a potentially reversible cause of chronic liver disease and may improve prognosis.

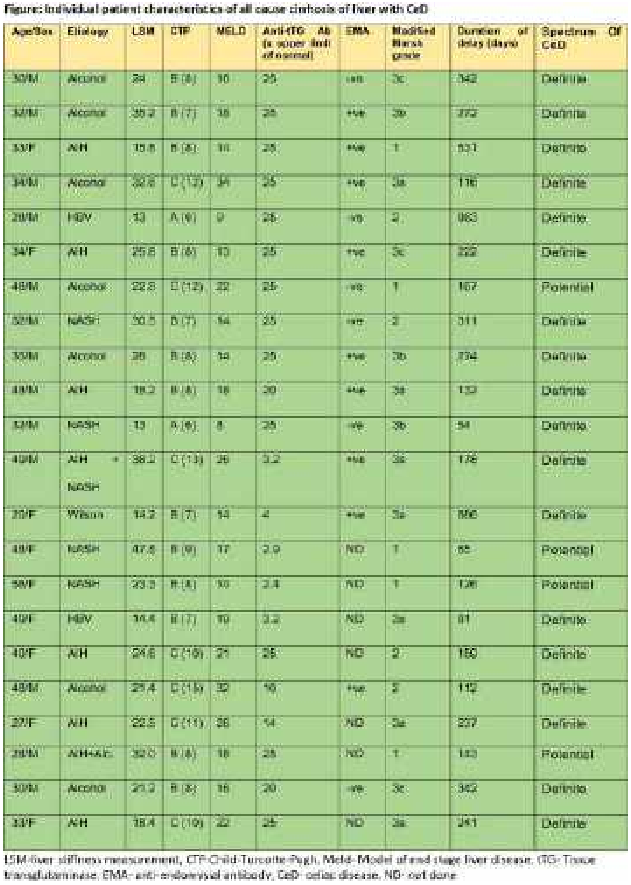

Figure: Individual patient characteristics of all cause cirrhosis of liver with CeD

Age/Sex	Etiology	LSM	CTP	MELD	Anti-tTG Ab (x upper limit of normal)	EMA	Modified Marsh grade	Duration of delay (days)	Spectrum Of CeD
30/M	Alcohol	24	B (8)	16	25	-ve	3c	342	Definite
32/M	Alcohol	35.2	B (7)	18	25	+ve	3b	272	Definite
33/F	AIH	15.8	B (8)	11	25	+ve	1	531	Definite
34/M	Alcohol	32.8	C (13)	24	25	+ve	3a	116	Definite
28/M	HBV	13	A (6)	9	25	-ve	2	863	Definite
34/F	AIH	25.8	B (8)	10	25	+ve	3c	222	Definite
48/M	Alcohol	22.8	C (12)	22	25	-ve	1	167	Potential
52/M	NASH	30.5	B (7)	14	25	-ve	2	311	Definite
30/M	Alcohol	28	B (8)	14	25	+ve	3b	274	Definite
48/M	AIH	18.2	B (8)	18	20	+ve	3a	132	Definite
52/M	NASH	13	A (6)	8	25	-ve	3b	54	Definite
49/M	AIH + NASH	38.2	C (13)	26	3.2	+ve	3a	176	Definite
20/F	Wilson	14.2	B (7)	14	4	+ve	3a	886	Definite
48/F	NASH	47.8	B (9)	17	2.9	ND	1	65	Potential
58/F	NASH	23.3	B (8)	10	2.4	ND	1	126	Potential
49/F	HBV	16.4	B (7)	19	2.2	ND	2a	81	Definite
40/F	AIH	24.8	C (10)	21	25	ND	2	180	Definite
48/M	Alcohol	21.4	C (15)	32	10	+ve	2	112	Definite
27/F	AIH	22.8	C (11)	26	14	ND	3a	237	Definite
28/M	AIH+Alc	32.0	B (8)	18	25	ND	1	143	Potential
30/M	Alcohol	21.2	B (8)	16	20	-ve	3c	342	Definite
33/F	AIH	18.4	C (10)	22	25	ND	3a	241	Definite

LSM-liver stiffness measurement, CTP-Child-Turcotte-Pugh, Meld-Model of end stage liver disease, tTG-Tissue transglutaminase, EMA- anti-endomysial antibody, CeD- celiac disease, ND- not done

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3719-C | COMMUNITY-BASED SCREENING FOR HEPATITIS B VIRUS AND HEPATOCELLULAR CARCINOMA IN RURAL TANZANIA

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Francisco, (3)Arusha Lutheran Medical Center, (4) Erasmus University Medical Center, Netherlands, (5) Hennepin Healthcare, (6)University of Minnesota

Background: Hepatitis B virus (HBV) and hepatocellular carcinoma (HCC) are associated with higher morbidity and mortality in Africa, particularly in rural areas, in part due to lack of identification of patients with HBV and lack of feasible surveillance programs for HCC. In this study, we implemented a community-based combined HBV and HCC screening program in rural Tanzania to increase awareness and early detection. **Methods:** We partnered with regional doctors and public health workers conducting mobile primary care clinics in rural villages in Tanzania at local hospitals and clinics to screen for HBV and HCC between March 2021 and February 2023. Patients who presented to the clinics underwent informed consent and completed a study questionnaire related to HBV. Testing for HBV was conducted with rapid point-of-care (POC) assay requiring a fingerstick which tested for HBsAg (hepatitis B surface antigen). Patients who were HBsAg positive underwent POC ultrasound to screen for HCC, POC for hepatitis C (HCV) antibody, and were referred to HBV clinic for further management. We measured the number of HBV diagnoses (primary outcome) and the number of liver masses (secondary outcome). Data were analyzed with descriptive statistics. **Results:** A total of 501 patients were screened for HBV with rapid antigen testing in four villages, and of these, 63% (n = 303) were female with median age of 40 (IQR 28-55). Only 6% (n = 30) were vaccinated against HBV, 92% (n = 453) were not vaccinated, and 2.4% (n = 12) reported not knowing vaccination status. 73% (n = 310) of respondents reported that they did not know they should get vaccinated against HBV and 3.8% (n = 16) reported that vaccination was too expensive. 41% (n = 182) knew how HBV was transmitted, and 4.1% (n = 18) of patients had at least one household member with HBV. There were 2.4% (n = 11) of patients who were positive for HBsAg, and over half were female (54.5% n = 6) with a median age of 36 years (IQR 34-43). All patients who tested positive were not vaccinated against HBV. All HBsAg positive patients were negative for HCV, and 3 patients were tested for hepatitis B e antigen (HBeAg) with all three being positive. One patient had a mass detected on ultrasound and one patient had ascites detected on ultrasound. **Conclusion:** We found that community-based HBV and HCC screening can be implemented sustainably in Africa with local partnerships. This model could be used in regions with high HBV endemicity and low rates of HCC screening.

Disclosures: The following people have nothing to disclose: Manaswita Tappata, James Ford, Johnstone Kayandabila, Samwel Seth, Jose D. Debes

3720-C | COULD NEW LAWS RESTRICTING RIGHTS AFFECT HEPATOLOGY TRAINING SLOTS IN AREAS OF NEED?

Alan Hutchison, University of Chicago, Medicine, Gautham Reddy, University of Chicago Medicine, Chicago, IL, Anna Mae Diehl, University of Chicago, Medicine, Durham, NC and Sonali Paul, University of Chicago Medical Center

Background: In recent years many states have passed laws limiting reproductive rights such as abortion and access to birth control and rights of transgender individual's to avoid discrimination. This may negatively impact where hepatologists train and live. Given predictions of a shrinking hepatology workforce, it is important to evaluate the impact of these state laws on current disparities and future workforce in hepatology care. **Methods:** We reviewed the Scientific Registry of Transplant Recipients data for centers that performed ≥20 liver transplants (LT) per year and identified if these programs had TH fellowships through manually visiting the websites associated with those centers. We compared this with the list of states that California will not let its employees use state funds to travel to due to a law that "California must take action to avoid supporting or financing discrimination against lesbian, gay, bisexual, and transgender people." (AB 1887). We also compared this with a list of states with active bans on abortion up to 20 weeks after gestation compiled by the New York Times. We compared this data to the hepatology existing workforce predictions from Russo et al. 2020. **Results:** We found that the 16 states with permissive transgender and reproductive laws accounted for 3855 DDLTs and 337 LDLTs across 48 centers with 56 training slots. We found that the 21 states with laws restricting reproductive or transgender rights accounted for 3943 DDLTs and 136 LDLTs across 43 centers with 38 training slots. By regions as defined by Russo et al., the Southeast (SE), Great Lakes (GL), and Northeast regions have the highest projected workforce loss. The SE has 13 centers, 8 centers with 10 TH slots, with all the centers in states with laws restricting both transgender and reproductive rights. The GL has 16 centers, 14 with 16 TH slots in states with permissive laws and 3 with 5 TH slots in states that restrict either transgender or reproductive rights. The NE has 12 centers, 7 with 14 TH slots, all of which are in states with permissive laws. **Conclusion:** New laws restricting reproductive and transgender rights are present in states accounting for half of the national transplant volume and centers and 40% of the training slots. Laws in these states may impact interest in obtaining training or hepatology positions. Workforce

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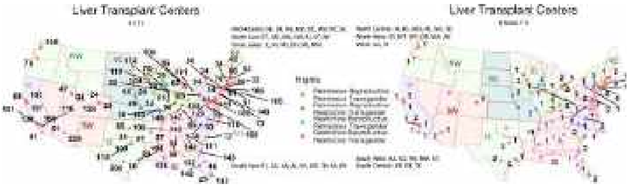
projections show significant shortages in regions heavily impacted and slightly affected by the new laws. Future workforce surveys should incorporate questions about these laws to understand their potential to impact changes in the hepatology workforce.



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The following people have nothing to disclose: Alan Hutchison

3721-C | Creation of a population health disease management strategy for NAFLD in the Veterans Healthcare Administration

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Background: The VA is the largest U.S. provider of liver disease care. In anticipation of ongoing innovation in nonalcoholic fatty liver disease (NAFLD) care and in recognition of disease burden and underdiagnosis, VA hepatology leadership aimed to develop a blueprint for NAFLD population level management. **Methods:** VA hepatology leaders developed a multifaceted approach to address NAFLD as a public health problem in VA. An advisory board of hepatology experts and an interdisciplinary group of providers from across specialties were convened. These stakeholders created an evidence based guidance document for the diagnosis, evaluation and treatment of NAFLD. Simultaneously, a data management plan was developed, evaluating how to extract data about Veterans at risk and the care delivered to this population. Subsequently, we conducted a national survey of resources, knowledge, and current practices to identify and address barriers to providing care. A dashboard was created to track patients with potential NAFLD. **Results:** Over 4 million Veterans had risk factors for NAFLD; 207,529 (4.9%) had a diagnosis of NAFLD and 71,169 (1.7%) had a diagnosis of cirrhosis. Of 124 station survey respondents, most reported that NAFLD patients were managed in hepatology/GI (68, 55%) or in primary care (61, 50%). Patients were followed in GI/liver clinic either long term (14%) or based on having abnormal blood tests (38%) or fibrosis (60%). The most frequent interventions included provider recommendation for weight management and counseling on alcohol abstinence, followed by referral for weight loss or nutrition services. Bariatric services were infrequently used. Vitamin E was the most common pharmacotherapy, followed by pioglitazone, then semaglutide (Table 1). A primary care algorithm for NAFLD diagnosis and risk assessment to guide specialty referral was developed. Ongoing efforts include NAFLD dashboard utilization for case finding, refining data management systems, designation of quality metrics, patient and provider education, and dissemination of resources. **Conclusion:** In preparation for novel pharmacotherapies and rapidly evolving care guidance, VA developed a population management blueprint for NAFLD. This approach began with drafting interdisciplinary consensus guidance, identifying high rates of baseline undiagnosed disease, examining patterns of field-based care, and developing a dashboard to facilitate population management. Interventions underway include dissemination of information addressing NAFLD diagnosis and management, establishing quality metrics for

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NAFLD, and associated monitoring systems.

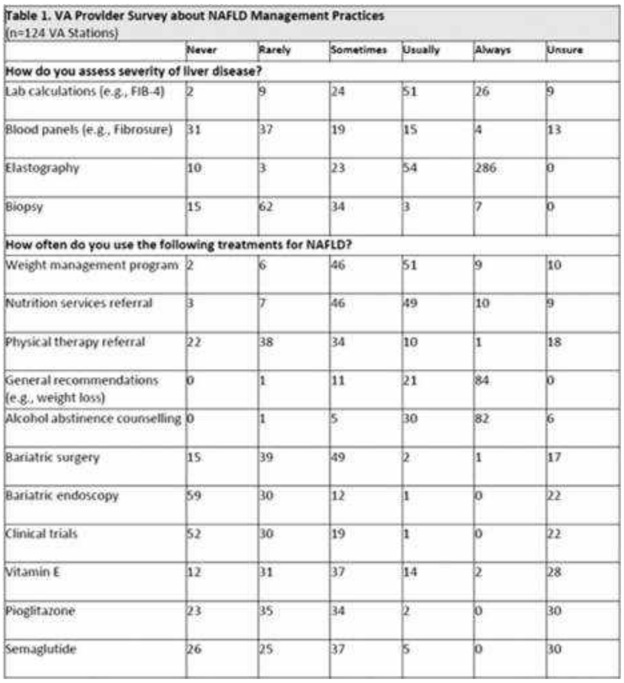

Table 1. VA Provider Survey about NAFLD Management Practices
(n=124 VA Stations)

	Never	Rarely	Sometimes	Usually	Always	Unsure
How do you assess severity of liver disease?						
Lab calculations (e.g., FIB-4)	2	9	24	51	26	9
Blood panels (e.g., Fibrosure)	31	37	19	15	4	13
Elastography	10	3	23	54	286	0
Biopsy	15	62	34	3	7	0
How often do you use the following treatments for NAFLD?						
Weight management program	2	6	46	51	9	10
Nutrition services referral	3	7	46	49	10	9
Physical therapy referral	22	38	34	10	1	18
General recommendations (e.g., weight loss)	0	1	11	21	84	0
Alcohol abstinence counselling	0	1	5	30	82	6
Bariatric surgery	15	39	49	2	1	17
Bariatric endoscopy	59	30	12	1	0	22
Clinical trials	52	30	19	1	0	22
Vitamin E	12	31	37	14	2	28
Pioglitazone	23	35	34	2	0	30
Semaglutide	26	25	37	5	0	30

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Disclosure information not available at the time of publication: Jennifer Anwar, Sandra Gibson, Gyorgy Baffy, Karine Rozenberg-Ben-Dror, Christine M. Hunt, Dawn Scott, Nsikak Ekanem, Yiwen Yao

3722-C | DECREASED COMPLETION OF ORDERED LABS AND IMAGING IN TELEHEALTH COMPARED TO IN-PERSON ENCOUNTERS

Jacqueline B. Henson, Yuval A. Patel, April Wall and Andrew Joseph Muir, Duke University

Background: One important aspect of successful outpatient care is patient completion of ordered testing, including labs and imaging. For telehealth visits, which have become a more routine modality of healthcare delivery since the COVID-19 pandemic, these generally must be performed at a different time and place than the encounter. Whether completion of ordered labs and imaging in telehealth encounters differs from in-person visits, however, is unknown. The aim of this study was to compare order completion in telehealth and in-person encounters and to identify factors associated with lack of completion. **Methods:** Telehealth and in-person encounters in hepatology clinics at our center from 1/1/2021-12/31/2022 were identified. Completion of associated orders for labs and imaging was assessed and compared by visit modality. Encounter- and patient-level factors associated with telehealth order completion were evaluated. Comparisons were performed using chi-square tests or Cochrane-Armitage tests for trend across ordered groups. **Results:** A total of 2489 telehealth visits were conducted, 10.8% of all encounters (23147) for 9925 patients. Telehealth encounters were less likely to have labs (42.2% vs. 69.4%, $p < 0.001$) and imaging ordered (28.4% vs. 40.9%, $p < 0.001$). They were also less likely to have ordered labs completed within 14 days (37.2% vs. 77.8%), 30 days (47.6% vs. 78.1%), and 90 days (59.3% vs. 78.7%; all $p < 0.001$). Ordered imaging was similarly less likely to be performed within one year (57.8% vs. 66.0%, $p < 0.001$), particularly liver ultrasounds (58.9% vs. 67.6%, $p = 0.001$). Among encounters for cirrhosis, liver ultrasounds (55.3% vs. 66.4%, $p = 0.004$) and abdominal computed tomography (52.9% vs. 66.7%, $p = 0.046$) were less likely to be completed after telehealth visits. Return telehealth visits and encounters in patients more remote from the center had a lower proportion of labs completed (Table). When stratified by diagnosis, telehealth encounters for decompensated cirrhosis were most likely to have labs completed, though 43.6% were still not completed within 30 days. Telehealth encounters in patients with Medicaid or without health insurance were less likely to have ordered imaging completed (Table). **Conclusion:** In our population, telehealth encounters had lower completion of ordered labs and imaging compared to in-person visits. More than half did not have labs collected within a month, and liver imaging studies were less likely to be completed in patients with cirrhosis. Though one of the potential benefits of telehealth is improving access for patients more remote from specialty care, increasing distance was associated with decreased lab completion. Further research is needed to better understand the barriers to order completion for telehealth visits and ways to optimize this to improve effectiveness of this visit modality.

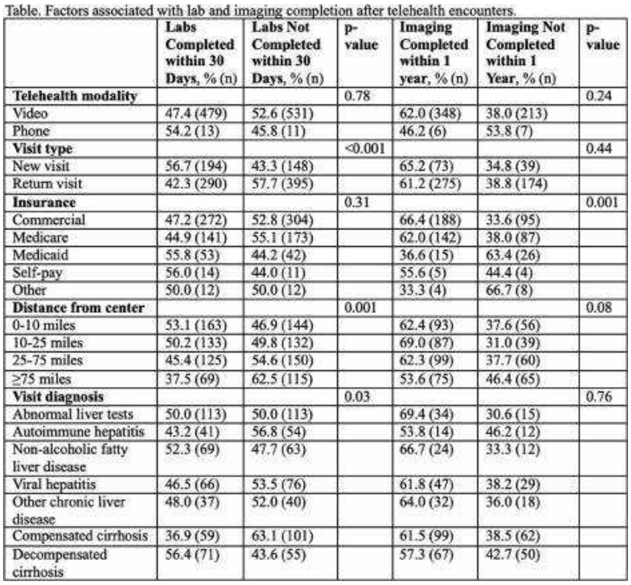

Table. Factors associated with lab and imaging completion after telehealth encounters.

	Labs Completed within 30 Days, % (n)	Labs Not Completed within 30 Days, % (n)	p-value	Imaging Completed within 1 year, % (n)	Imaging Not Completed within 1 Year, % (n)	p-value
Telehealth modality			0.78			0.24
Video	47.4 (479)	52.6 (531)		62.0 (348)	38.0 (213)	
Phone	54.2 (13)	45.8 (11)		46.2 (6)	53.8 (7)	
Visit type			<0.001			0.44
New visit	56.7 (194)	43.3 (148)		65.2 (73)	34.8 (39)	
Return visit	42.3 (290)	57.7 (395)		61.2 (275)	38.8 (174)	
Insurance			0.31			0.001
Commercial	47.2 (272)	52.8 (304)		66.4 (188)	33.6 (95)	
Medicare	44.9 (141)	55.1 (173)		62.0 (142)	38.0 (87)	
Medicaid	55.8 (53)	44.2 (42)		36.6 (15)	63.4 (26)	
Self-pay	56.0 (14)	44.0 (11)		55.6 (5)	44.4 (4)	
Other	50.0 (12)	50.0 (12)		33.3 (4)	66.7 (8)	
Distance from center			0.001			0.08
0-10 miles	53.1 (163)	46.9 (144)		62.4 (93)	37.6 (56)	
10-25 miles	50.2 (133)	49.8 (132)		69.0 (87)	31.0 (39)	
25-75 miles	45.4 (125)	54.6 (150)		62.3 (99)	37.7 (60)	
≥75 miles	37.5 (69)	62.5 (115)		53.6 (75)	46.4 (65)	
Visit diagnosis			0.03			0.76
Abnormal liver tests	50.0 (113)	50.0 (113)		69.4 (34)	30.6 (15)	
Autoimmune hepatitis	43.2 (41)	56.8 (54)		53.8 (14)	46.2 (12)	
Non-alcoholic fatty liver disease	52.3 (69)	47.7 (63)		66.7 (24)	33.3 (12)	
Viral hepatitis	46.5 (66)	53.5 (76)		61.8 (47)	38.2 (29)	
Other chronic liver disease	48.0 (37)	52.0 (40)		64.0 (32)	36.0 (18)	
Compensated cirrhosis	36.9 (59)	63.1 (101)		61.5 (99)	38.5 (62)	
Decompensated cirrhosis	56.4 (71)	43.6 (55)		57.3 (67)	42.7 (50)	

Disclosures: The following people have nothing to disclose: Jacqueline B. Henson

Disclosure information not available at the time of publication: Yuval A. Patel, April Wall, Andrew Joseph Muir

3723-C | DEMOGRAPHIC COMPARISON OF NONALCOHOLIC STEATOHEPATITIS (NASH) PATIENT POPULATIONS IN A LARGE ELECTRONIC MEDICAL RECORDS DATABASE VS. CLINICAL TRIAL POPULATIONS

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Background: Recent Food and Drug Administration (FDA) guidance stressed the importance of studying trial populations that are similar to the patient population likely to use the treatment being developed, if approved. However, the FDA has not provided specific guidance on how to define demographic goals for trial populations. **Methods**: The demographics for age, gender and race were analyzed in the TriNetX Analytics Network database of more than 140 million patients who have received care at 73 health care organizations in the United States within the past two years. Demographic data were assessed for individual's with an ICD-10 K75.81 diagnosis of nonalcoholic steatohepatitis (NASH). **Results**: There were 87,390 individual's in the TriNetX database with an ICD-10 K75.81 diagnosis of NASH, aged 18 or older. The demographic characteristics included age distribution, median age (59 years), gender (58% female; 42% male) and racial distribution (White = 76%, Black or African American = 5%, Asian = 3%, Other or unknown = 16%). Ethnicity data showed that 68% of patients were identified as Not Hispanic or Latino, 22% as Hispanic or Latino and 10% as Unknown. These data were then compared to demographic data from (U.S. only) industry trials available in the clinicaltrials.gov database. There were 35 identified completed NASH trials with gender data on 2,372 subjects, of whom 59% were female and 41% male. Race data were available from 20 studies with 1,884 subjects: White = 87%, Black or African American = 3%, Asian = 3%, Other or unknown = 7%. In terms of Ethnicity, data from 16 studies with 1,432 subjects reported that 64% were Not Hispanic or Latino and 36% were Hispanic or Latino. **Conclusion:** Large electronic medical record databases provide an unprecedented opportunity to rapidly identify the "real world" gender, race and ethnicity demographics of patients receiving health care for conditions such as NASH. These data can be used to guide the appropriate selection of NASH clinical trial study populations, as recommended by the FDA. Based on the current data from completed adult NASH (U.S. only) industry trials, there appears to be a moderate underrepresentation of Black subjects and overrepresentation of Hispanic or Latino subjects in comparison to the "real world" data in the TriNetX database. It is well documented that NASH is more prevalent in the U.S. Hispanic population[1] and therefore we would expect to see a higher proportion of Hispanic patients in the "real world" data. The observed difference in the data set may be due to complex social factors such as lack of understanding and/or willingness to identify with race or ethnic demographics categories, and medical care access. Future studies are needed to investigate the demographic observations. 1. Rich NE, et al. Racial and ethnic disparities in nonalcoholic fatty liver disease prevalence, severity, and outcomes in the United States, Clin Gastroenterol Hepatol 2018;16:198-210.e192

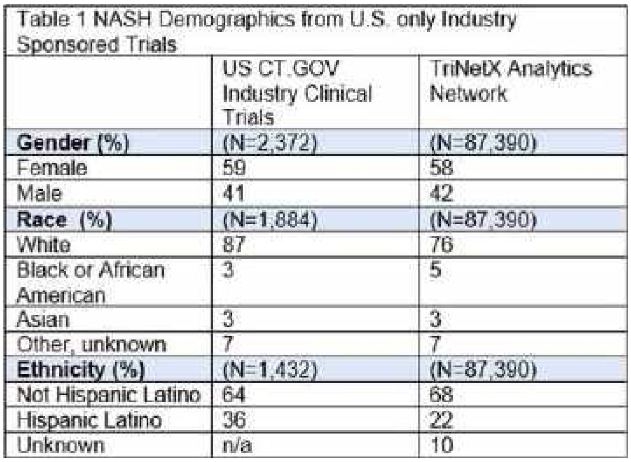

Table 1 NASH Demographics from U.S. only Industry Sponsored Trials

	US CT.GOV Industry Clinical Trials	TriNetX Analytics Network
Gender (%)	(N=2,372)	(N=87,390)
Female	59	58
Male	41	42
Race (%)	(N=1,884)	(N=87,390)
White	87	76
Black or African American	3	5
Asian	3	3
Other, unknown	7	7
Ethnicity (%)	(N=1,432)	(N=87,390)
Not Hispanic Latino	64	68
Hispanic Latino	36	22
Unknown	n/a	10

Disclosures: The following people have nothing to disclose: Paola Figueroa Barojas, Sigrunn Blacoe
Disclosure information not available at the time of publication: Alessandra Vignola, Stephen Peroutka

3724-C | DESIGN OF A CLINICAL DECISION SUPPORT (CDS) SYSTEM FOR CIRRHOSIS MANAGEMENT

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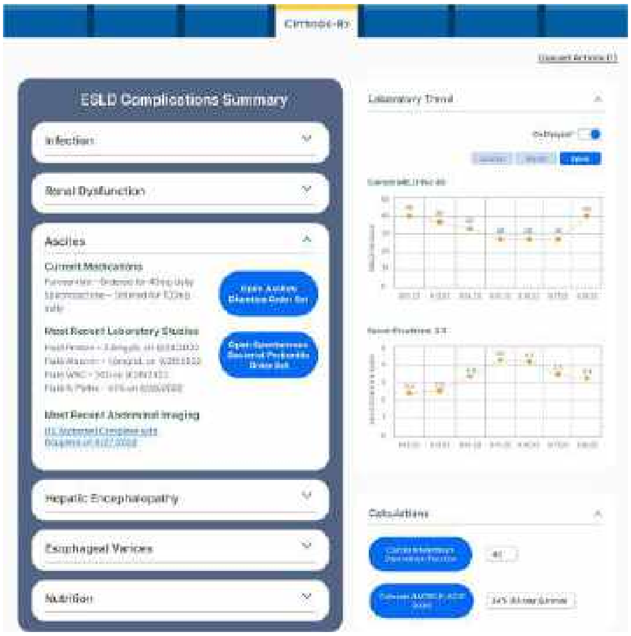
Background: Electronic health record (EHR)-based CDS systems are potentially scalable interventions that could help standardize clinical care. CDS systems, however, have not been extensively investigated in liver disease and cirrhosis management. Human-centered and user-centered design are approaches that systematically engage with potential users in the development of an intervention. In this study, we applied principles from these approaches to design a CDS system for cirrhosis management, called *CirrhosisRx*. **Methods:** We conducted initial focus groups that included clinicians, user-experience designers, informaticists, and programmers to construct a low-fidelity wireframe of the potential CDS system. We then convened six co-design workshops with (N = 4-7 per workshop, and N = 20 total) clinicians from diverse practice background (residents, fellows, hospitalists, gastroenterologists, hepatologists, and advanced practice practitioners) via a snowballing sampling method. Practice settings included a major academic medical center, Veterans Administration hospital, and community-based academic inpatient practice. We elicited approaches and workflows for managing patients with cirrhosis, assessed gaps and needs in existing EHR systems, evaluated potential features, and refined the design prototype for *CirrhosisRx*. At the conclusion of each of the 6 co-design workshops, we analyzed recordings and transcripts for overarching themes. **Results:** Feedback from co-design workshops indicated that aggregation of relevant clinical information into cirrhosis decompensation domains and linkages with prescribed order sets were the most important. Detection of clinical events based on inference from EHR data was not well accepted due to concerns about accuracy. Calculators and visualizations for commonly used risk stratification scores, such as MELD, were helpful but not necessary. The final design for CirrhosisRx is in Figure 1. **Conclusion:** This is one of the first applications of design methods to construct electronic interventions in hepatology. The co-design processes with potential users significantly altered features for *CirrhosisRx*, overall design of the interface, and likely improved the overall usability of the *CirrhosisRx* application. This work provides a framework model for the creation and design of future EHR-based interventions in hepatology care.



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3725-C | DIRECT ACCESS COLONOSCOPY AS A TIME TO CONSIDER HEPATITIS B TRIPLE SCREENING

Eric A. Wien[1], *Catherine Freeland*[2] *and Jonathan M. Fenkel*[1], *(1)Thomas Jefferson University Hospital, (2) Hep B Foundation*

Background: On March 10, 2023, the CDC released new recommendations to offer one-time triple screening for hepatitis B virus (HBV), including HBsAb, HBsAg, and HBcAb total, to all adults age 18+. Patients presenting for the first time to a gastroenterologist/hepatologist (GI/Hep) for colon cancer screening via direct access colonoscopy (DAC) are all age 18+. A possible barrier to implementation of the HBV triple screening recommendation in primary care is that HBV serologies can be difficult to interpret. GI/Hep providers should be able to interpret the results of these tests and provide guidance on management, minimizing the barrier of linkage to care primary care providers may face when implementing HBV screening recommendations. We sought to examine a snapshot of patients coming to our division for DAC over a 2-week period to assess whether a care gap exists and whether DAC may be a time to consider HBV triple screening. **Methods:** All patients presenting for DAC at any of our division's three Pennsylvania-based endoscopy units with any GI/Hep provider during the first two

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

weeks of April 2023 were included in this quality improvement (QI) initiative. The institutional EPIC chart and EPIC's CareEverywhere platform were reviewed for hepatitis B serologies and keyword searched for "HBV" and "hepatitis" to identify any hepatitis B testing obtained prior to the DAC encounter. Descriptive statistics were utilized to measure the outcomes. **Results:** 108 patients underwent DAC during the evaluation period. The cohort was 52.7% female, 50% Caucasian, 37% African-American, 6.5% Asian, and 4.6% Hispanic with a median age of 54 ± 8.99 years. Of the 108 DAC patients, only 9 patients (8.3%) had complete HBV triple screen results for HBsAg, HBsAb, and HBcAb total on their charts. 24 patients (22.2%) had prior HBsAg testing, 24 (22.2%) had prior HBsAb testing, and 12 patients (11.11%) had been tested for HBcAb total. Health disparities in screening could not be assessed due to the small number of patients with complete triple screening in our evaluation cohort. **Conclusion:** Offering HBV triple screening at DAC encounters may offer an excellent QI opportunity to screen patients for HBV. More data is needed to confirm this potential QI care gap and assess potential health disparities in screening, but this snapshot at least suggests this population of patients holds promise for screening.

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The following people have nothing to disclose: Eric A. Wien, Catherine Freeland

3726-C | EFFECT OF PHYSICIAN TURN-OVER IN JULY ON CLINICAL OUTCOMES IN HOSPITALIZED CIRRHOSIS PATIENTS: A US NATIONWIDE STUDY USING DIFFERENCE-IN-DIFFERENCES ANALYSIS

Melis Gokce Celdir[1], Shahana Prakash[1] and Tomohiro Tanaka[2], (1)University of Iowa Hospitals and Clinics, (2) University of Iowa Hospitals and Clinics, Iowa City, IA

Background: Adverse clinical outcomes in US teaching hospitals in July, attributed to the relative inexperience of new trainees, have been referred to as "The July Effect." Studies investigating the July Effect on surgical outcomes and in-hospital myocardial infarction mortality have yielded conflicting results. In this study, our aim was to evaluate the causal effect of physician turnover in July on the clinical outcomes of hospitalized patients with cirrhosis in the United States. **Methods:** Using data from the National (Nationwide) Inpatient Sample (NIS) database from 2016 to 2019, we identified hospitalized cirrhosis patients with and without severe liver-related complications (variceal bleeding, hepatorenal syndrome, or acute-on-chronic liver failure) in both teaching and non-teaching hospitals. We compared the changes in in-hospital mortality and length of stay (LOS) between May and July admissions in teaching hospitals to those in non-teaching hospitals using a Differences-in-Differences analysis with logistic and Poisson regression models. The models included confounders such as sex, age, race, hospital region, and hospital size to account for factors that could have affected the parallel trends assumption. **Results:** Our analysis included 78,373 hospitalizations in teaching hospitals and 23,519 in non-teaching hospitals during May and July. In the analysis of baseline characteristics, we found no significant differences except for age; patients were slightly younger in July (58.1 vs. 57.6 years in teaching hospitals [$p = 0.047$]; 59.0 vs. 58.3 in non-teaching hospitals [$p = 0.12$]). The only cirrhosis-related complication that varied between July and May in teaching hospitals was hepatorenal syndrome (61.8% vs. 63.9% in May vs. July; $p = 0.015$). LOS was longer in teaching hospitals, with a 14% increase in duration (95% CI 13-15%), and in-hospital mortality was higher (odds ratio 1.20; 95% CI 1.12-1.29) compared to non-teaching hospitals. Using the difference-in-difference models, the increase in LOS associated with teaching hospitals was 3% greater (95% CI 2-5%) for all cirrhosis-related admissions and 9% greater (95% CI 6-12%) when only admissions with severe complications were included. No significant "July effect" on mortality was found in teaching hospitals ($p > 0.05$ for adjusted and unadjusted models). **Conclusion:** Our study revealed a significant effect of physician turnover in July on LOS, but not on mortality, in nationwide cirrhosis hospitalizations, particularly when there are complications related to cirrhosis. Appropriate supervision of new trainees may alleviate the healthcare burden associated with the care of hospitalized patients with cirrhosis.

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f 3727-C | ELIMINATING DISPARITIES IN LIVER TRANSPLANT ACCESS THROUGH MARKET ANALYSIS, STRATEGIC DESIGN, AND EXECUTION

Richard Gilroy, Derek Ginos, Joanna Stephens, Sophie Hansen, Nate Peterson and Jean Botha, Intermountain Health

Background: An extensive body of literature and substantial controversy exists regarding disparities in access to a lifesaving liver allograft. Most reports and analyses focus upon socioeconomic factors, OPTN policies, and geography. To date, little has been written on how transplant centers might design their actions to mitigate disparity. This study details how market analysis, strategic design, and a graduated implementation of outreach, with continuous performance review and optimization, can eliminate disparities associated with geographic location. **Methods:** In 2017 a market analysis was completed in 6 regional markets (Utah, Nevada, Idaho, Montana, Wyoming and Colorado). Data sources for these analyses were generated from population charts, physician and gastroenterology demographics, hospital demographics, insurance payer mix data sources and center contracting data. OPTN registry data and SRTR offer and acceptance data were reviewed both within the center and at regional centers. A robust Quality Assessment and Performance Improvement department within the system, with numerous quality dashboard, was then created for each performance domain of interest. Within the program, new policies for organ offer and acceptance, remote patient management tools, and interstate high quality networks of physician partners and institutions were established. Sequentially, markets were then developed based upon internal resources, barriers to market development, and the absolute market potential. **Results:** Between 2008 and 2018 the center averaged 36 transplants per year. Market analysis led to 3 markets being identified for development: Utah, Idaho, and Nevada. The disparity between actual transplant rates were 68, 23 and 46 adult residents in 2019 vs predicted 112, 63, and 106 residents per year (30 transplants/million). Following the initiation of our activities transplant rates, in these states, increased to 107, 52, and 56 were respectively in 2022. Specific to Idaho, a remote location with patients living over 300 miles on average from the center, transplants by this center increased from 3 to 27 patients over the 4 years, while in Nevada the numbers only increased from 2 to 6 patients. Organs derived from donation after cardiac death increased from 5% in 2018 to 29% in 2022. One year patient survival with original allograft (Table 7 SRTR: UTLD) was 96.35% (observed) vs 91.73% (predicted) for January 2023. Center transplant volumes increase from 39 to 104 over 5 yrs. **Conclusion:** While OPTN policies and geography do impact center operational performance and transplant rates, a center's behavior and practices has a clinically significant impact upon transplant rates and a patient's access to transplantable organ offers. Transplant programs must consider their design, internal policies, and practices if we seek to mitigate organ transplant disparities within our communities and between US states.

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f 3728-C | EMERGENCY DEPARTMENT UTILIZATION AND OUTCOMES IN PATIENTS WITH CIRRHOSIS: A NATIONAL COHORT STUDY

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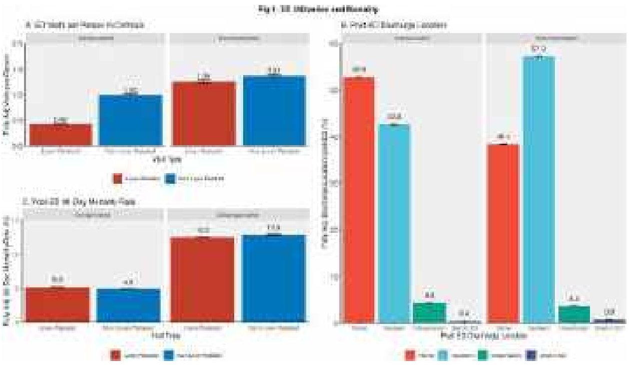
Background: While hospitalizations for cirrhosis are well-characterized, the emergency department (ED) reflects an upstream point of care that is understudied. We aimed to describe the national landscape of ED utilization among patients with cirrhosis, and assess factors associated with ED outcomes. **Methods:** We retrospectively analyzed a large national insurance registry (Optum) between 2015-2019, including adults with at least 180 days of enrollment. Liver transplant recipients were censored at the year of transplant. ED visits (stratified by liver vs. non-liver related) were identified using validated billing code definitions. Negative binomial regression was used to assess ED visits per year and a linear discriminant model was used to assess 90-day mortality rates, with models adjusted for individual-level demographic and clinical characteristics. **Results:** Among 26,190,668 patients, 103,475 were with cirrhosis (median age 65 [IQR 58-72]; 46% female; 62% white). In age-adjusted analysis, ED visits per year were 2.02 [95CI 2.00-2.05] with cirrhosis vs 0.52 [0.52-0.52] without cirrhosis, 1.80 [1.80-1.81] for congestive heart failure (CHF), and 1.43 [1.43-1.44] for chronic obstructive pulmonary disease (COPD). Age-adjusted 90-day mortality rates were 11.1% [11.1-11.2] with cirrhosis vs 4.8% [4.8-4.8] without cirrhosis, 9.0% [9.0-9.0] for CHF, and 6.9% [6.9-6.9] for COPD. The most common diagnoses were abdominal pain (12%), septicemia (10%) and alcohol-related disorders (10%) for liver-related visits; and chest pain (6%), lower respiratory disease (4%), and hypertension (4%) for non-liver visits. Patients with decompensated (vs compensated) cirrhosis had more ED visits, were more likely to have their ED visit be liver-related, to be hospitalized, and had higher 90-day mortality rates after non-liver and liver-related ED visits (summarized in Fig. 1). In multivariable analysis, decompensation [+8.0%, +7.6 to +8.4], dialysis [+3.1%, +1.8 to +4.5], and age [+2.5% per 10 years, +2.3 to +2.7] were associated with increased 90-day mortality. **Conclusion:** In this national study, we show that patients with cirrhosis visit the ED more frequently than those with CHF, COPD, and without cirrhosis, and are often discharged home. Despite visiting the ED, high 90-day mortality rates are seen after both liver-related and non-liver related visits. These findings suggest that the ED may be an important site for high-yield, pre-hospitalization interventions in patients with cirrhosis.



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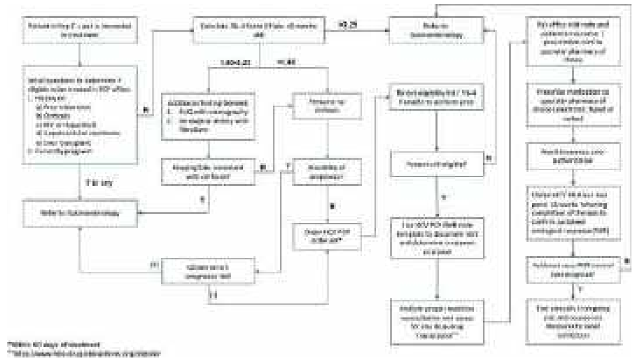
3729-C | EMPOWERING THE FRONTLINE: ENHANCING HEPATITIS C TREATMENT ACCESSIBILITY IN PRIMARY CARE THROUGH PROCESS DESIGN AND RESIDENT EDUCATION

Rita Auro, Michael Schwartz and Alexandra Lane, Cooper University Health Care

Background: In 2022, the World Health Organization (WHO) recommended simplifying the hepatitis C virus (HCV) care pathway to improve treatment access, advocating for diagnosis and management in primary care (PC) settings. Approximately 2.7 million adults in the United States have HCV, with roughly 17,000 new cases annually, particularly among adults with intravenous drug use (IVDU). Despite over 95% of patients being curable with 8-12 weeks of oral direct-acting antiviral (DAA) therapy, treatment rates remain low. Our project aimed to improve treatment access by 1) developing an HCV treatment process in an academic PC clinic and 2) enhancing resident familiarity and confidence in HCV management. **Methods:** The project comprised of two phases. Phase 1 involved specialty pharmacy collaboration, EMR utilization, and content development. DAA therapies, only available at specialty pharmacies, require prior authorization. Hence, coordination with hepatitis C therapy representatives was necessary to identify pharmacies that process authorizations and dispense DAAs. EMR technical specialists assisted in creating an order set encompassing all requisite tests for drug approval. The set coordinates with an EMR template that automatically extracts data for prior authorization, facilitating swift approval processing. Phase 2 entailed education and implementation. After an educational session, residents could commence in-clinic HCV treatment, referring patients to specialists only when necessary. **Results:** Figure 1 demonstrates the comprehensive process flow for HCV treatment, from patient identification through therapy completion. Next steps involve anonymous surveys conducted pre and post-HCV educational session to assess resident confidence in treatment. The results are anticipated this fall. Survey items, rated on a Likert scale, will cover guideline familiarity and comfort with various components of HCV management. The data will undergo descriptive statistical analysis. **Conclusion:** This initiative developed an HCV treatment process in an academic PC clinic, potentially increasing access to timely care. It focused on equipping residents with the resources needed for confident HCV management, especially in an area disproportionately impacted by the virus. This model, effective where HCV infections are typically managed by specialists, may be replicated in other PC clinics to better serve patient populations facing challenges such as active IVDU, economic, or social barriers that can limit access to care.



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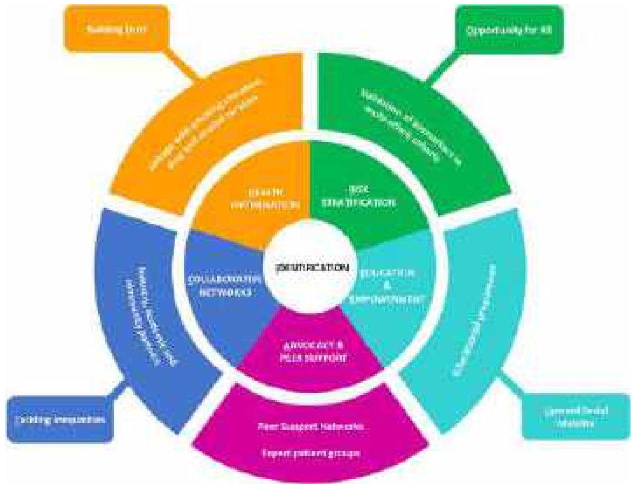
3730-C | EMPOWERING UNDERSERVED HBV COMMUNITIES THROUGH EDUCATIONAL PROGRAMMES, PEER SUPPORT NETWORKS AND COLLABORATIVE ENGAGEMENT (I REACH OUT MODEL)

James Lok[1], Ivana Carey[2], Carlos Moro[2], Saima Ajaz[2], Grace Bottoni[3], Kenneth Kabagambe[4], Chari Cohen[5], Claire Martin[2], Geoffrey M. Dusheiko[6], K Agarwal[6] and

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

HIIT HBV peer consortium, (1)Institute of Liver Studies, King's College Hospital, London, United Kingdom, London, United Kingdom, (2)Institute of Liver Studies, King's College Hospital, London, United Kingdom, (3) NHS South East London Clinical Commissioning Group, (4)National Organisation for People Living with Hepatitis B, (5)Hepatitis B Foundation, (6)King's College Hospital

Background: Hepatitis B virus (HBV) is a global health problem with more than 290 million people affected worldwide. For successive generations, there has been insufficient infrastructure in place to address issues such as inter-sectional stigma and digital misinformation, whilst the focus on health optimisation and education has been unsatisfactory. Over time, this has eroded confidence in healthcare providers, triggering resentment and disengagement with the clinical service. **Methods:** At King's College Hospital, we recognise the limitations of our current system and are pioneering an improved, patient-focused model of care [I REACH OUT (Figure 1)]. This is founded on six core principles, namely Identification of affected individual's, Risk Stratification, Education & Empowerment, Advocacy & Peer Support, Collaborative Networking and Health Optimisation. By mobilising the multidisciplinary team and working closely with our international partners, we anticipate an Opportunity for Upward Social Mobility, Tackling inequalities and building Trust with healthcare professionals. **Results:** Over the past few years, we have invested in local service development and optimised different aspects of this model. From an education perspective, we have delivered content through our Extension for Community Healthcare Outcomes (ECHO) programme and plan to diversify our interfaces with artificial intelligence platforms. We have also secured funding for a full-time HBV peer and their remit will be to share lived experiences and help shape the service from a user's perspective. Additionally, we have strengthened collaborations with other research institutions and built a robust platform for validating prognostic biomarkers. More broadly, we have modernised our non-alcoholic fatty liver disease (NAFLD) service by improving community access to transient elastography and incorporating lifestyle practitioners into the team, and will align these services with the viral hepatitis division. Adherence to a constructivist research paradigm will allow us to evolve this model and sustain high levels of engagement. **Conclusion:** Elimination of viral hepatitis as a global health problem will require a framework of care in which individual's feel empowered to express their autonomy, engage with healthcare providers and embrace a healthy lifestyle. The I REACH OUT model provides a platform to transform care in diverse clinical settings and address underlying social factors.



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3732-C | EVALUATING PROVIDER-LEVEL FACTORS CONTRIBUTING TO SUB-OPTIMAL SURVEILLANCE FOR HEPATOCELLULAR CARCINOMA AMONG PATIENTS WITH CIRRHOSIS ACROSS FOUR SAFETY-NET HEALTH SYSTEMS IN THE UNITED STATES

Robert J. Wong[1,2], Patricia D. Jones[3], Bolin Niu[4], George Therapondos[5], Mae Thamer[6], Onkar Kshirsagar[6], Yi Zhang[6], Paulo Pinheiro[7], Ronnie Fass[8], Mandana Khalili[9] and Amit G. Singal[10], (1)VA Palo Alto Healthcare System, (2)Stanford University School of

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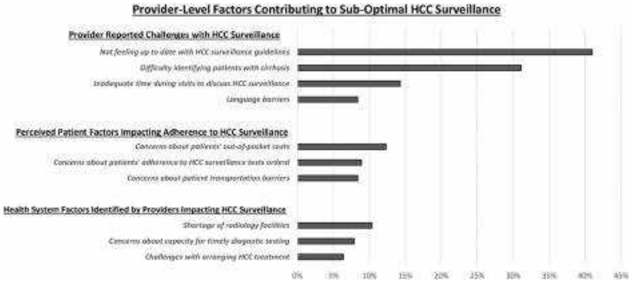
Background: Hepatocellular carcinoma (HCC) surveillance in cirrhosis patients remains under-utilized, particularly among vulnerable safety-net populations, who are mostly ethnic minorities with existing barriers in healthcare access. We evaluated provider-level factors that may contribute to disparities in HCC surveillance across 4 U.S. safety-net health systems. **Methods:** 1,036 providers (attending physicians, advanced practice providers, and residents/fellows) in primary care (PC) and gastroenterology/hepatology (GI-Hep) across 4 safety-net health systems were invited to participate in an anonymous online survey to assess knowledge, attitudes, beliefs, perceived challenges, and COVID-19-related disruptions in HCC surveillance in cirrhosis patients, using a 4-point Likert scale. Knowledge questions were scored from 0 to 6 based on number of questions answered correctly. Multivariable logistic regression models evaluated for predictors of adequate HCC surveillance knowledge (score > 5). **Results:** Of 202 provider respondents (19.5% response rate) (46.0% female, 46.5% white, mean age 42.3 ± 11.7 years, 56.9% PC, 13.1% GI-Hep), only 55.7% had adequate HCC surveillance knowledge, more so among GI-Hep vs. PC (70.0% vs. 52.9%, $p < 0.05$). On multivariable regression, those with perceived barriers or challenges to HCC surveillance had lower odds of adequate HCC surveillance knowledge (OR 0.29, 95% CI 0.10-0.81, $p < 0.01$). Providers reported challenges with HCC surveillance, including not feeling up to date with HCC guidelines (41.0%), difficulty identifying cirrhosis patients (31.1%), inadequate time during visits (14.3%), and language barriers (8.4%). Providers reported perceived patient factors that may impact adherence (12.3% had concerns about patients' out-of-pocket costs, 8.9% about adherence, 8.4% about patient transportation barriers). Health system issues were identified: 10.4% cited shortage of radiology facilities, 7.9% had concerns about capacity for timely diagnostic testing, 6.4% cited challenges with arranging HCC treatment. Pandemic-related disruptions in timely HCC surveillance were reported by 63.8%; over 30% noted persistent delays in HCC surveillance for cirrhosis patients. **Conclusion:** Survey of PC and GI-Hep providers in safety-net health systems identified important provider-level factors contributing to suboptimal HCC surveillance practices in cirrhosis patients, including gaps in knowledge, as well as attitudes, barriers, and persistent disruptions in care due to COVID-19 pandemic.



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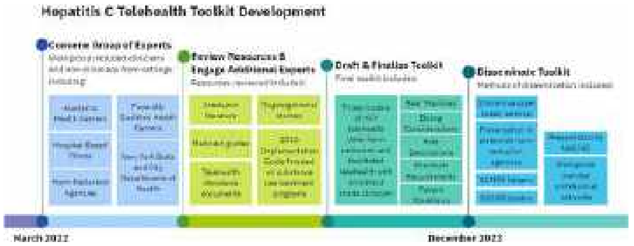
Amit G. Singal – Genentech: Consultant, No, No; AstraZeneca: Consultant, No, No; Bayer: Consultant, No, No; Eisai: Consultant, No, No; Exelixis: Consultant, No, No; Boston Scientific: Consultant, No, No; Gycotest: Consultant, No, No; Exact Sciences: Consultant, No, No; Roche: Consultant, No, No; FujiFilm Medical Sciences: Consultant, No, No; GRAIL, LLC: Consultant, Yes, No; Freenome: Consultant, No, No; Histosonics: Consultant, No, No;

The following people have nothing to disclose: Patricia D. Jones, Bolin Niu, George Therapondos, Mae Thamer, Onkar Kshirsagar, Yi Zhang, Paulo Pinheiro, Ronnie Fass

3733-C | EXPANDING ACCESS TO HEPATITIS C CARE AMONG PEOPLE WHO USE DRUGS: HCV TELEHEALTH TOOLKIT

Lauren Walker[1], Charlotte Miller[1], Linda Wang[2] and Jeffrey Weiss[3], (1)Mount Sinai Institute for Advanced Medicine, (2)Icahn School of Medicine at Mount Sinai, (3)Icahn School of Medicine at Mount Sinai (ISMMS)

Background: The Clinical Education Initiative's Hepatitis C and Drug User Health Center of Excellence (the Center) offers continuing medical education to enhance the capacity of New York State medical providers. Between May 2021 and April 2023, the Center delivered 25 hepatitis C virus (HCV)-focused webinars that trained 566 unique individual's. During the same time period, the Center facilitated HCV-focused ECHO™ sessions, offered a clinical HCV preceptorship program and developed the Hepatitis C Telehealth Toolkit (the Toolkit). **Methods:** The Toolkit was developed in collaboration with the New York Hepatitis Clinical Education Collaborative, a group of organizations dedicated to optimizing viral hepatitis clinician education. In March 2022, the group identified the need for a resource on HCV telehealth to increase access to HCV treatment among persons who inject drugs and convened experts to participate in monthly workgroup meetings to develop the Toolkit. The workgroup consisted of clinicians and non-clinicians from government, academia and harm reduction agencies. To develop the Toolkit, the workgroup reviewed existing resources and engaged additional experts to review specialized content. **Results:** The Toolkit, finalized in December 2022, is a flexible, practical guide that is intended to support both traditional and non-traditional settings interested in providing HCV care via telehealth. The Toolkit describes three models of HCV telehealth (tele-harm reduction and facilitated telehealth with *or* without an onsite clinician), and includes role descriptions, patient workflows, best practices, minimum requirements and billing considerations for each. The Toolkit was disseminated to workgroup members' professional networks and various state- and nation-wide groups. Toolkit dissemination coincided with delivery of a webinar on models of HCV telehealth. Evaluation data from the webinar's attendees demonstrated an increase in self-reported knowledge about models of HCV telehealth, and one attendee stated that they will use learnings from the webinar to implement HCV care in the syringe services program where they work. **Conclusion:** Further evaluation is needed to determine whether and how the Toolkit can best be implemented in clinical settings. With continued dissemination and application, this unique resource for implementing HCV telehealth can serve as a key tool to achieving HCV elimination.



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Disclosure information not available at the time of publication: Charlotte Miller, Linda Wang

3734-C | EXTERNAL VALIDATION OF AN ICD-10 CONSENSUS CODE SET TO IDENTIFY PATIENTS WITH CIRRHOSIS USING ELECTRONIC HEALTH RECORDS IN AN ASIAN POPULATION

Jason Pik Eu Chang[1], Pooi Ling Loi[2], Jeanette Pei-Xuan Ng[1], Hong-Yi Lin[3], Wei Quan Teo[4], Amber Chung[4] and Prema Raj[4], (1)Singapore General Hospital, (2)Department of Gastroenterology & Hepatology, Singapore General Hospital, Singapore, (3) Yong Loo Lin School of Medicine, National University of Singapore, (4)Singhealth-Duke Nus Transplant Centre

Background: Electronic health records (EHR) are commonly used for large, multi-institutional studies in liver cirrhosis. Central to such studies is the development of an algorithm to correctly identify patients with cirrhosis using ICD-10 diagnosis codes. A recent systematic review by Shearer et al proposed a consensus set of nine ICD-10 codes to identify cirrhosis patients. This "9-code set" showed a high positive predictive value (PPV) between 83-89% in European and North American populations. However, its performance in an Asian population has not been studied. We aimed to externally validate the performance of Shearer's 9-code set to identify cirrhosis patients in an Asian population from a tertiary hospital in Singapore, and to explore alternative code sets to improve case-finding. **Methods:** We used an initial algorithm of 25 ICD-10 codes that covered all potential diagnosis codes related to cirrhosis. When applied to the EHRs of all patients admitted to the Singapore General Hospital from 1 January to 31 December 2018, this broad algorithm identified 1733 Asian patients who potentially had liver cirrhosis. We manually reviewed the EHRs of all subjects to confirm the diagnosis of cirrhosis. Next, we evaluated the performance of Shearer's 9-code set in this cohort to determine the sensitivity, specificity, PPV and NPV to identify subjects with cirrhosis. We then examined alternative sets of codes that could potentially improve the identification of cirrhosis patients in our population. **Results:** From the manual review of 1733 subjects' EHRs, 937 (54.1%) were confirmed to have liver cirrhosis. Median age at diagnosis of cirrhosis was 64 years (IQR 55-74), with 65.6% males. The main etiologies of cirrhosis were chronic hepatitis B (30.1%), non-alcoholic fatty liver disease (26.2%) and cryptogenic (15.6%). 59.0% were Child A, 32.7% Child B and 8.3% were Child C. Shearer's 9-code set identified 856 cirrhosis subjects, of which 713 were truly cirrhotic, providing a PPV of 83.3%, NPV 74.5%, sensitivity 76.1%, specificity 82.0%. We identified a set of 10 ICD-10 codes comprising individual and combinations of codes that had marginally better performance compared to Shearer's 9-code set. This "Solidarity-10" code set identified 838 cirrhosis subjects, of which 717 were truly cirrhotic, providing a PPV of 85.6%, NPV 75.4%, sensitivity 76.5%, specificity 84.8%. The replacement of "hepatic failure" with "biliary cirrhosis" and the addition of the combination code of "hepatocellular carcinoma (HCC)" and "ascites" in Solidarity-10 identified an additional 15 cirrhotic patients that were not identified by Shearer's 9-code set. **Conclusion:** The 9 ICD-10 code consensus set proposed by Shearer et al to identify patients with cirrhosis maintains a high PPV of 83.3% in an Asian population. We identified a 10 ICD-10 code set (Solidarity-10) with potentially better performance in populations with high rates of HCC.

Disclosures: The following people have nothing to disclose: Jason Pik Eu Chang, Pooi Ling Loi, Jeanette Pei-Xuan Ng, Hong-Yi Lin, Wei Quan Teo, Amber Chung, Prema Raj

3735-C | FACT OR FICTION: UNDERSTANDING THE QUALITY AND RELIABILITY OF LIVER CIRRHOSIS INFORMATION ON YOUTUBE

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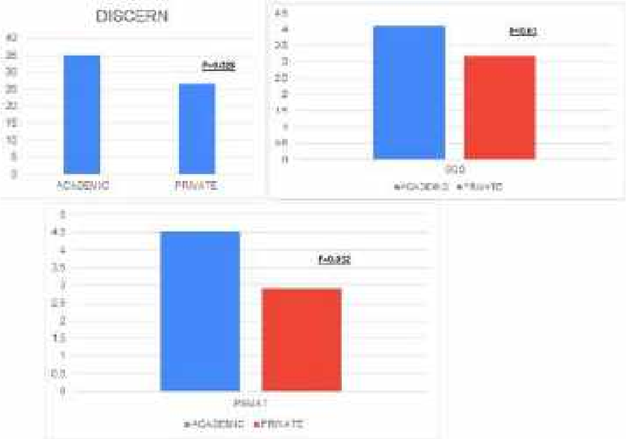
Background: The internet, particularly YouTube, is a popular health information source for many. However, studies suggest that patient information on YouTube is often of poor quality. This study aims to evaluate the content and quality of YouTube videos on fibromyalgia. With over a billion users, YouTube's widespread use doesn't guarantee quality, as videos, including those on liver cirrhosis, aren't subjected to an editorial process. This can lead to misinformation, potentially skewing users' understanding of their health conditions. **Methods:** We searched YouTube for liver cirrhosis videos using "liver cirrhosis" and "alcoholic hepatitis" as keywords. Videos were excluded if they weren't in English, weren't relevant, or lacked audio. We recorded video characteristics such as views, subscriptions, likes, dislikes, comments, and whether they were academic or private. Videos were then categorized as reliable or not based on the accuracy of their scientific information. To assess overall video quality, we used DISCERN, the Global Quality Score (GQS), and the Patient Education Materials Assessment Tool (PEMAT). The level of agreement between seven investigators on DISCERN, GQS, and PEMAT was calculated using intraclass correlation. **Results:** We reviewed 36 YouTube videos that appeared in the search results, of which 16 (44.4%) were academic and 20 (55.5%) were private. Academic videos received higher DISCERN scores than private ones (35 ± 14.5 vs. 26.64 ± 15.07, $p = 0.028$). The Global Quality Score was also higher for academic videos (4.1 vs. 3.2, $p < 0.01$), as was the PEMAT score (4.5 vs. 2.9, $p = 0.032$). Furthermore, academic videos were found to have a positive correlation with the number of likes (OR: 0.65, $P < 0.001$), subscribers (OR:0.78, $P < 0.0001$), and views (OR:1.12, $P < 0.001$). **Conclusion:** Our study shows that the quality of YouTube videos on liver cirrhosis varies widely. Videos from academic sources provided more accurate and high-quality information than private ones, reflected in higher DISCERN, Global Quality Score, and PEMAT ratings. This indicates a positive correlation between academic sources and the number of likes, subscribers, and views. The results underscore the importance of guiding patients toward academically sourced health information, thereby reducing the chance of misinformation.



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

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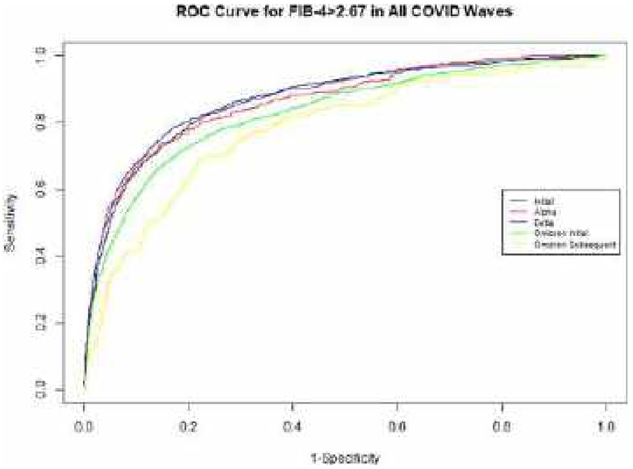
Background: The evolution of the severe acute respiratory syndrome coronavirus has led to new variants of concern that vary in transmissibility, severity or change in clinical presentation. Recent studies of the Omicron variant have shown reduced odds of hospitalization with Omicron vs. the prior Delta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



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

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

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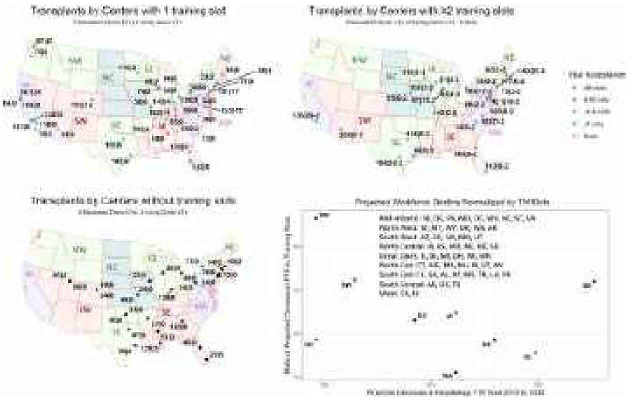
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

data to existing hepatology workforce predictions from Russo et al. 2020. **Results:** Among 107 centers there were 92 TH slots. The median number of LTs was 81, with an inter-quartile range of 50-127, with the most being 226. Among the 64 centers that have the 92 TH slots, a median of 105.5 LTs were performed, with inter-quartile range (IQR) of 73.5-139, with a range of 25-226. Per training slot, the median was 72.25 with IQR of 51-108, with a range of 17-195. Thirty-eight centers with TH slots performed living donor LTs (LDLTs), with median of 7.5 LDLTs, with IQR of 2-16.25 (max 66). Among 27 centers without TH slots, 9 of which do LDLTs and 24 of which have gastroenterology (GI) fellowships, a median of 42 LTs were performed, with IQR of 31-71.5 (max 148). Of the 92 available TH slots, there are 37, 71, and 10 eligible slots for H1B, J1, and E3 visas, respectively. The region with the highest projected workforce loss is the Southeast, losing 352 Full-Time-Equivalent (FTE) hepatology positions from 2018 to 2033. Of its 14 centers, 5 do not have a TH fellowship, though 4 of those have GI fellowships indicating GME infrastructure. These 5 account for 382 deceased donor transplants (DDLT) and 8 LDLTs. Eight centers with 11 TH slots performed 1029 DDLTs and 17 LDLTs; they include 7, 6, and 2 eligible slots for H1B, J1, and E3 visas, respectively. The Great Lakes region has the second highest projected workforce loss of 297 FTE. Of its 16 centers, 3 do not have TH slots, though they have GI programs. Of the 13 training centers that performed 1221 DDLTs and 70 LDLTs with 19 training slots, they include 11, 18, and 2 eligible slots for H1B, J1, and E3 visas, respectively. Projected workforce loss rankings change when normalizing for TH slots. The Southeast has projected losses of 32 FTE per annual TH slot from 2018 to 2033, while the Great Lakes has projected losses of 16 FTE per slot. The Northwest only has a projected loss of 93 FTE, the lowest of the regions, but that translates to a region-high of 46.5 FTE per slot. **Conclusion:** Several opportunities exist to grow the hepatology workforce. Many centers could start or expand TH fellowships still meet ACGME requirements, especially in regions of high need. Finally, visa acceptance among training programs is limited and could be broadened to attract trainees.



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The following people have nothing to disclose: Alan Hutchison

3738-C | HEPATITIS B VIRUS (HBV) AND HEPATITIS D VIRUS (HDV) LABORATORY-BASED REFLEX TESTING CASE STUDIES

Jana Manning[1], Lindsey Hiebert[1], Weiming Tang[2], Philippa Easterbrook[3], Niklas Luhmann[3] and John W. Ward[1], (1)The Task Force for Global Health, (2) University of North Carolina at Chapel Hill, (3)World Health Organization

Background: A global laboratory survey was undertaken by the Coalition for Global Hepatitis Elimination and the University of North Carolina in collaboration with WHO to investigate the scope, use, and implementation experience of reflex viral load for HBV DNA and also reflex HDV serology and RNA testing. **Methods:** A comprehensive web-based survey was conducted using SmartSheet to gather quantitative and qualitative data on HBV DNA and HDV reflex testing. The survey was shared with over 1,000 participants. Reflex laboratory testing was defined as either immediate HBV DNA testing and/or reflex HDV serology testing of persons with positive HBsAg test results using an existing blood specimen, based on a single clinical interaction and one blood sample or immediate testing of positive HDV serology samples for HDV RNA. The survey was in five sections and those that offered reflex testing for either HBV DNA and/or HDV serology addressed reasons for offering reflex testing, specimen collection process, testing protocol, costs, the impact on care, and key challenges in implementation. **Results:** A total of 26 laboratories from 19 countries responded to the survey – 8 (42%) were from high income countries and 11(58%) were from low-middle income countries. Six labs performed HBV DNA reflex testing (China, Ghana, Myanmar, Nigeria,Italy and Spain), and 8 HDV serology reflex testing (USA, China, Egypt, Malawi, Italy, Spain). Of the 6 labs performing HBV DNA reflex testing, all reported initiating this option to improve linkage to care. All six reported securing buy-in from administrators as a key step in implementation, followed by training clinicians (n = 2) and laboratory staff (n = 4). Of the 8 labs performing HDV reflex testing, 3 conducted reflex testing of HBsAg positive specimens, and 4 labs tested for HDV RNA, of which 3 conducted reflex testing of positive HDV serology samples. Of the 5 labs, 3 reported securing a reliable supply of high-quality and approved tests as a challenge. **Conclusion:** Though the number of respondent laboratories is low, our survey demonstrates that laboratories in both high-income and low- and middle-income settings have implemented HBV DNA and HDV reflex testing. More data from diverse settings are needed to guide the implementation of reflex testing. This data can inform planning to scale up HBV and HDV testing and treatment programs.

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3739-C | HEPATITIS C ELIMINATION IN RURAL ARIZONA THROUGH A PHARMACIST-LED TREATMENT MODEL

Katherine Halza[1], Kristen Nelson-Rowan[1], Edmund Evangelista[2], Rhet Pond[3], Richard A. Manch[4], Anthony Santarelli[1], Diana Lalitsasivimol[1] and Linda Williams[1], (1)Kingman Regional Medical Center, (2)Cour College of Pharmacy, (3)Roseman University, (4)Arizona Liver Health, Phoenix, AZ

Background: The World Health Organization (WHO) global hepatitis strategy aims to eliminate Hepatitis C (HCV) by 2030. Innovative models are needed to reach underserved and hard to access patient populations that have historically been undertreated. Mohave County, Arizona is identified as a high priority area, being in the top 5% of United States counties at risk for a HCV outbreak, with an average annual rate of 211 new cases per 100,000 people (2017-2021), but lacks traditional access to HCV care due to the rural health disparities of distance to care, lower median income, and lack of healthcare providers. To address these issues, a pharmacist-led HCV program was implemented via a collaborative practice agreement (CPA) model at the Disease Management Clinic (DMC) within a rural community health system. The purpose of this study is to compare outcomes of the DMC Hepatitis C Program model to the Traditional Care Model (TCM). **Methods:** Our retrospective cohort study of adult patients who were screened for HCV used EMR data from 2020-2023. Patients were stratified into Group A: Referral to the DMC Hepatitis C Program; Group B: Traditional Care Model. We analyzed patients with a positive HCV antibody test, confirmed HCV RNA, and achieved sustained virologic response after 12 weeks post-treatment (SVR12). We compared treatment cascade progression and treatment outcomes among each group. **Results:** Within the DMC treatment cascade, 161 patients were identified HCV antibody+, 147/161 (91%) were connected to care, 107/161 (66%) had a confirmed HCV RNA, 101/161 (63%) were prescribed HCV medication, 86/161 (53%) completed treatment, and 71/161 (44%) achieved SVR12 cure. The average time from outreach to first visit was 31 days, from first visit to start of treatment was 28 days, and from RNA+ to SVR12 was 30 weeks. Within the DMC group, 66% were diagnosed, 63% were treated, and 44% were cured, compared to WHO 2023 targets of 64%, 51%, and 49% respectively. **Conclusion:** This innovative care model can reach WHO HCV elimination goals by improving access and linkage to care, improving time to treatment, and increasing HCV cure rates. Pharmacist-led programs for HCV management leverage the underused group of pharmacists as health care extenders in rural communities to overcome the barriers of difficulty accessing traditional care and provider shortages. Pharmacist CPAs can be used across other populations with health disparities to improve HCV long term outcomes.

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3740-C | HEPATITIS C TREATMENT ACCESS IN ILLINOIS: A LONG AND CIRCUITOUS PATH

Anjana Bairavi Bairavi Maheswaran, Cammeo Mauntel-Medici, Melanie Izquierdo, Heather Lee, Michelle Martin and Janet Lin, University of Illinois at Chicago

Background: Hepatitis C (HCV) is a curable infectious disease that affects over 2.4 million Americans. The CDC reports the number of patients accessing HCV treatment has declined despite favorable policy changes around HCV treatment access. In November 2018, IL Medicaid removed the need for advanced

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

fibrosis of the liver as a criterion for being eligible for HCV treatment. Published data following important policy changes in Illinois is lacking. **Methods:** We retrospectively reviewed charts of the first 100 HCV RNA-positive patients (Jan-Mar 2021). Demographic information (race, ethnicity, sex assigned at birth, insurance type) was collected via EPIC query reports. Manual chart reviews provided data on diagnosis status, care linkage, HCV labs, treatment initiation, substance use, and mental health. Excel (Version 2304) was used for descriptive analysis. We assessed the proportion and demographic composition of patients linked to HCV treatment after a positive HCV RNA test. **Results:** The final sample included 86 treatment-naive HCV patients (avg. age: 57). Most were Male (64%), African American (57%), and publicly insured (Medicaid: 59%, Medicare: 29%). Sixty-five patients (75%) reported ever substance use (excluding alcohol/ tobacco), and 20% reported recent use. Among 59 patients with documented risk factors, 30 reported drug use. Of 86 patients, 71 (83%) underwent liver fibrosis staging, and 53 (62%) initiated treatment. Forty nine patients completed treatment (92%), and 40 achieved sustained virologic response (75%). Most who initiated treatment were Male (64%), African American (60%), Medicaid insured (51%), with F0-F1 fibrosis (75%). Among 33 non-treated patients, 16 (48%) were lost to follow-up, 8 deferred treatment (3 undergoing cancer treatment, 3 awaiting kidney transplantation, 2 with ongoing substance use), 3 were referred elsewhere, 2 deceased, 2 relocated, 1 was denied prior-authorization, and 1 declined treatment. **Conclusion:** The exploratory analysis showed higher treatment uptake in the sample compared to national estimates. A prior study on the hospital's chronic HCV population, demonstrated lower treatment initiation rate (39%) especially among Medicaid recipients (36%). The prior study also highlighted disparities in treatment access ; Medicaid recipients with advanced liver fibrosis were more likely to initiate treatment compared to their counterparts with lower fibrosis scores. In our study, among those who initiated treatment, 55% were Medicaid-insured and 60% of them had little to no liver fibrosis. However, these results are not generalizable. Over 45% of the sample were tested for HCV RNA at a Liver / Infectious Disease specialty clinic indicating care referral. As a nation, we still have significant strides to make and milestones to reach to eradicate HCV. Updating policies and innovating care strategies to align with current HCV trends is crucial towards achieving equitable care nationwide.

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3741-C | HIGH RATES OF NON-INDICATED PROTON PUMP INHIBITOR PRESCRIPTION IN PATIENTS WITH CIRRHOSIS AT A LARGE ACADEMIC MEDICAL CENTER

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Background: The adverse effects of proton pump inhibitor (PPI) use in patients with cirrhosis has been an area of active discussion. While recent studies have demonstrated no association between PPI use and all-cause or cause-specific mortality, a growing body of literature supports a correlation between PPI use and increased rates of serious infection including spontaneous bacterial peritonitis (SBP) and liver related mortality in patients with cirrhosis. These effects are thought to be mediated by alterations in gut microbiome due to acid suppression which can lead to bacterial translocation, subsequent infection, and higher rates of hospital readmission. Our study aims to further characterize the PPI prescription patterns at a large tertiary medical center. **Methods:** All patients with a diagnosis of cirrhosis between August 2020 and August 2022 with an active PPI prescription were included in the study. Demographics, PPI formulation with dose, frequency, and duration were extracted from the Northwestern University Enterprise Data Warehouse (EDW). Prior history of SBP, PPI indication, and etiology of cirrhosis were determined using ICD-10 codes. Appropriate indications for PPI use were determined based on a recent practice update from the American Gastroenterological Association. Chi-squared testing was used to compare the rates of new inpatient PPI prescriptions without appropriate indication. **Results:** Of the 10,863 encounters for 2,538 unique patients

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Symbols: ꬵ , Poster of Distinction; ★, Foundation Award Recipient included in the analysis, 10,070 encounters (92.7%) had a PPI prescription that preceded the study period (Table 1). Pantoprazole was the most commonly prescribed and 193 patients (7.5%) had a prior history of SBP. The indication for PPI use was documented in 6,326 encounters (58.2%) with GERD (n = 5,127, 47.2%), gastric or duodenal ulcer (n-1,453, 13.4%), and multiple indications (n = 1,627, 15.0%) as the most common indications. Of the 793 patients with a new PPI prescription during the study period, only 362 (45.6%) had an appropriate indication for PPI use (Table 1). The median duration of new PPI prescriptions was 161 days. As with analysis of the complete dataset, GERD, gastric or duodenal ulcer, or multiple indications were the most common indications of PPI use. The difference in rates of new inpatient PPI prescriptions without appropriate indication between internal medicine, surgery, and cardiology providers was not statistically significant (p = 0.99). **Conclusion:** Our study highlights both the prevalence and prolonged duration of non-indicated PPI use in patients with cirrhosis at a large tertiary medical center. Future quality improvement initiatives should aim to limit PPI use in patients with cirrhosis to those with clinical indications and educate prescribers on limiting PPI exposure by using the lowest dose and shortest frequency.

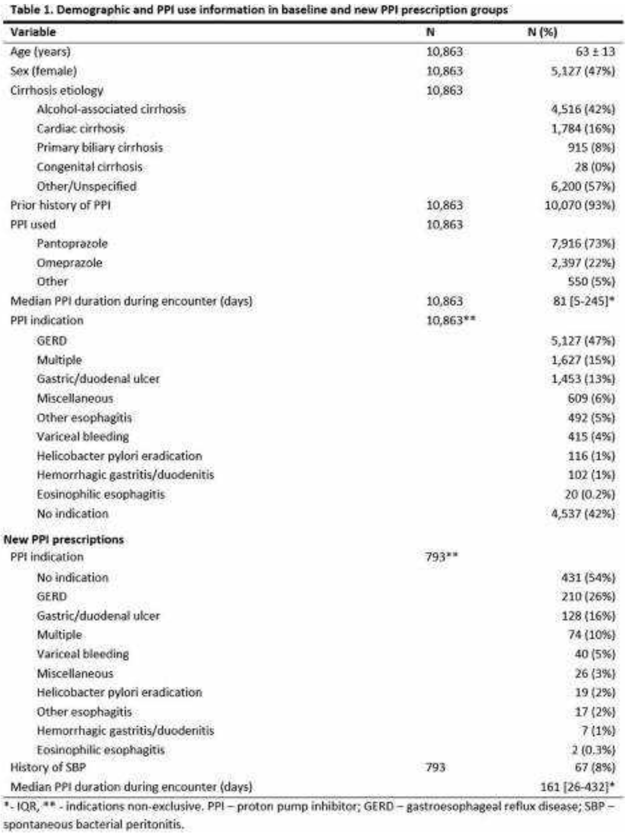

Table 1. Demographic and PPI use information in baseline and new PPI prescription groups

Variable	N	N (%)
Age (years)	10,863	63 ± 13
Sex (female)	10,863	5,127 (47%)
Cirrhosis etiology	10,863	
Alcohol-associated cirrhosis		4,516 (42%)
Cardiac cirrhosis		1,784 (16%)
Primary biliary cirrhosis		915 (8%)
Congenital cirrhosis		28 (0%)
Other/Unspecified		6,200 (57%)
Prior history of PPI	10,863	10,070 (93%)
PPI used	10,863	
Pantoprazole		7,916 (73%)
Omeprazole		2,397 (22%)
Other		550 (5%)
Median PPI duration during encounter (days)	10,863	81 [5-245]*
PPI indication	10,863**	
GERD		5,127 (47%)
Multiple		1,627 (15%)
Gastric/duodenal ulcer		1,453 (13%)
Miscellaneous		609 (6%)
Other esophagitis		492 (5%)
Variceal bleeding		415 (4%)
Helicobacter pylori eradication		116 (1%)
Hemorrhagic gastritis/duodenitis		102 (1%)
Eosinophilic esophagitis		20 (0.2%)
No indication		4,537 (42%)
New PPI prescriptions		
PPI indication	793**	
No indication		431 (54%)
GERD		210 (26%)
Gastric/duodenal ulcer		128 (16%)
Multiple		74 (10%)
Variceal bleeding		40 (5%)
Miscellaneous		26 (3%)
Helicobacter pylori eradication		19 (2%)
Other esophagitis		17 (2%)
Hemorrhagic gastritis/duodenitis		7 (1%)
Eosinophilic esophagitis		2 (0.3%)
History of SBP	793	67 (8%)
Median PPI duration during encounter (days)		161 [26-432]*

*- IQR, ** - indications non-exclusive. PPI – proton pump inhibitor; GERD – gastroesophageal reflux disease; SBP – spontaneous bacterial peritonitis.

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Disclosure information not available at the time of publication: Clare Kane, Daniel R. Ganger

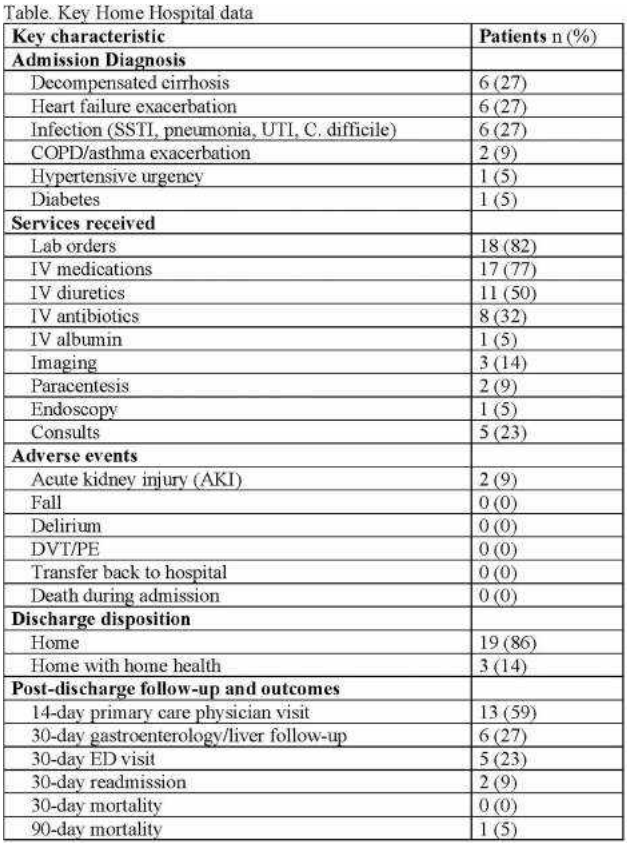
3742-C | HOME HOSPITAL FOR PATIENTS WITH CIRRHOSIS: A CASE SERIES

Olivia Kahn-Boesel[1], Henry Mitchell[2], Lucinda Li[3], Teresa Indriolo[3], Areej El-Jawahri[3], David Levine[2] and Nneka Ufere[3], (1)Harvard Medical School, (2)Brigham and Women's Hospital, (3)Massachusetts General Hospital

Background: Novel care delivery models are needed to address the rising costs and reduce healthcare utilization for patients with cirrhosis. Home hospital (HH) is the delivery of hospital-level care at home, including continuous vital sign monitoring, daily physician and twice daily nurse/paramedic visits. HH reduces cost, utilization, and readmissions for general medical patients, but its feasibility for patients with cirrhosis is unknown. **Methods:** We performed a retrospective case series to describe the experience and outcomes of patients with cirrhosis enrolled in HH at a large tertiary hospital between 2018-2022. We examined patient demographic and clinical characteristics, services provided during HH, and outcomes including adverse events, disposition, readmission and mortality rates. **Results:** 22 patients with cirrhosis (32% male, 45% Hispanic, 27% White, 23% Black) with a median age of 70 (IQR: 60-74) were enrolled in HH. The majority of patients had non-alcoholic steatohepatitis (NASH, 36%) or combination of alcohol-related liver disease and NASH (27%). Median MELD-Na was 12 (IQR: 10-16); 50% of patients had ascites and 36% had hepatic encephalopathy. In total, 59% were admitted to HH directly from the emergency department (ED), 36% from an inpatient floor, and 5% directly from home. The most frequent admission diagnoses were decompensated cirrhosis (27%), heart failure exacerbation (27%), and infection (27%). The most common interventions provided by HH were: monitoring lab chemistries (82%), intravenous medications including diuretics, antibiotics, and albumin (77%), medication reconciliation and teaching (91%), dietary counseling (72%), and specialist consultation (23%). While enrolled in HH, patients could additionally be transported from home to ambulatory facilities for diagnostics/procedures: 3 (14%) had imaging, 2 (9%) underwent serial paracenteses, and 1 (5%) underwent endoscopy. The median length of stay in HH was 7 days (IQR: 4-12). 2 patients (9%)

experienced adverse events (acute kidney injury) that resolved prior to discharge. No patients required escalation of care to the hospital. 2 patients (9%) were readmitted 30 days after discharge, 1 patient (5%) died within 90 days of discharge. **Conclusion:** In this single-site study, we found that HH was safe and effective for patients with cirrhosis and holds promise as a hepatology care delivery model. Future prospective studies are needed to evaluate the quality of HH care for this patient population.

Table. Key Home Hospital data



Key characteristic	Patients n (%)
Admission Diagnosis	
Decompensated cirrhosis	6 (27)
Heart failure exacerbation	6 (27)
Infection (SSTI, pneumonia, UTI, C. difficile)	6 (27)
COPD/asthma exacerbation	2 (9)
Hypertensive urgency	1 (5)
Diabetes	1 (5)
Services received	
Lab orders	18 (82)
IV medications	17 (77)
IV diuretics	11 (50)
IV antibiotics	8 (32)
IV albumin	1 (5)
Imaging	3 (14)
Paracentesis	2 (9)
Endoscopy	1 (5)
Consults	5 (23)
Adverse events	
Acute kidney injury (AKI)	2 (9)
Fall	0 (0)
Delirium	0 (0)
DVT/PE	0 (0)
Transfer back to hospital	0 (0)
Death during admission	0 (0)
Discharge disposition	
Home	19 (86)
Home with home health	3 (14)
Post-discharge follow-up and outcomes	
14-day primary care physician visit	13 (59)
30-day gastroenterology/liver follow-up	6 (27)
30-day ED visit	5 (23)
30-day readmission	2 (9)
30-day mortality	0 (0)
90-day mortality	1 (5)

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3743-C | IDENTIFICATION AND QUANTIFICATION OF JAUNDICE BY TRANS-CONJUNCTIVA OPTICAL IMAGING USING A HUMAN BRAIN-LIKE ALGORITHM: A CROSS-SECTIONAL STUDY

Takuya Kihara, Takaaki Sugihara, Suguru Ikeda, Yukako Matsuki, Hiroki Koda, Takumi Onoyama, Tomoaki Takata, Takakazu Nagahara and Hajime Isomoto, Tottori University

Background: Jaundice is caused by excess circulating bilirubin, known as hyperbilirubinemia. This symptom is sometimes caused by a critical hepatobiliary disorder, and is generally identified as yellowish sclera when bilirubin levels increase more than 3 mg/dL. It is difficult to identify jaundice accurately, especially via telemedicine. This study aimed to identify and quantify jaundice by transconjunctiva optical imaging. **Methods:** Patients with jaundice (total bilirubin ≥ 3 mg/dL) and normal control subjects (total bilirubin < 3mg/dL) were prospectively enrolled from June 2021 to July 2022. We took bilateral conjunctiva imaging with a built-in camera on a smartphone (1st generation iPhone SE) under normal white light conditions without any restrictions. We processed the images using an Algorithm Based on Human Brain (ABHB) (Zeta Bridge Corporation, Tokyo, Japan) and converted them into a hue degree of Hue Saturation Lightness (HSL) color space. **Results:** A total of 26 patients with jaundice (9.57 ± 7.11 mg/dL) and 25 control subjects (0.77 ± 0.35 mg/dL) were enrolled in this study. The causes of jaundice among the 18 male and 8 female subjects (median age 61 yrs.) included hepatobiliary cancer ($n = 10$), chronic hepatitis or cirrhosis ($n = 6$), pancreatic cancer ($n = 4$), acute liver failure ($n = 2$), cholelithiasis or cholangitis ($n = 2$), acute pancreatitis ($n = 1$), and Gilbert's syndrome ($n = 1$). The maximum hue degree (MHD) optimal cutoff to identify jaundice was 40.8 (sensitivity 81% and specificity 80%), and the AUROC was 0.842. The MHD was moderately correlated to total serum bilirubin (TSB) levels ($rS = 0.528$, $p < 0.001$). TSB level (≥ 5 mg/dL) can be estimated by the formula $21.1603 - 0.7371 \times \sqrt{>}(56.3 - \mathrm{MHD})^2$.

Conclusion: The ABHB-based MHD of conjunctiva imaging identified jaundice using an ordinary smartphone without any specific attachments and deep learning. This novel technology could be a helpful diagnostic tool in telemedicine or self-medication.

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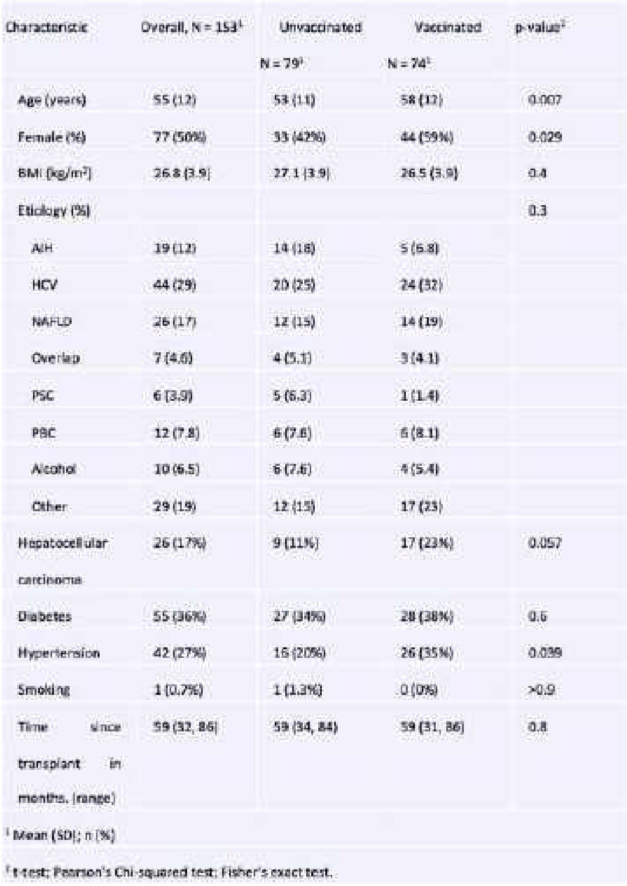
3744-C | IMPACT OF COVID-19 VACCINATION ON LIVER TRANSPLANT RECIPIENTS. EXPERIENCE IN A REFERENCE CENTER IN MEXICO

Daniel Azamar Llamas[1], Josealberto Sebastiano Arenas-Martinez[1], Antonio Olivas-Martínez[2], Eric Kauffman Ortega[1], Jose Victor Jimenez[3], Cristian De Jesús García-Carbrera[1], Fabian Esteban Rivera-Lopez[1], Bruno Papacristofilou-Riebeling[1], Luis Federico Uscanga[1] and Ignacio García Juárez[1], (1)Instituto Nacional De Ciencias Medicas y Nutricion, (2)University of Washington, (3)Yale New Haven Hospital, Stamford, CT

Background: COVID-19 vaccination has proved to be effective to prevent symptomatic COVID-19 infection and severe disease. However, the risk in liver transplant patients has not been widely investigated. We aim to assess the impact of COVID-19 vaccination on the mortality and development of severe and critical disease. **Methods:** A retrospective cohort study where we used the data from LT individual's who attended a reference center between March 2020 and February 2022. Demographic data, cirrhosis etiology, time on liver transplantation, immunosuppressive therapies, and vaccination status were recorded at the time of diagnosis. The primary outcome was death due to COVID-19, and secondary outcomes included the development of severe COVID-19 and intensive care unit (ICU) requirement. **Results:** One-hundred and fifty-three of 324 LT recipients developed COVID-19, in whom the main causes of cirrhosis were HCV infection and metabolic-associated fatty liver disease. The vaccines used were BNT162b2 (48.6%), ChAdOx1 nCoV-19 (21.6%), mRNA-1273 vaccine (1.4%), Sputnik V (14.9%), Ad5-nCoV-S (4.1%) and CoronaVac (9.5%). Case fatality and ICU requirement risk were similar among vaccinated and unvaccinated LT patients who developed COVID-19 (adjusted relative case fatality for vaccinated versus unvaccinated of 0.68, 95% CI 0.14 – 3.24, p = 0.62; adjusted relative risk [aRR] for ICU requirement of 0.45, 95% CI 0.11 – 1.88, p = 0.27). Nonetheless, vaccination was associated with a lower risk of severe disease (aRR for severe disease of 0.32, 95% CI 0.14 – 0.71, p = 0.005). **Conclusion:** Vaccination reduces the risk of severe COVID-19 in LT patients, regardless of the scheme used. Vaccination should be encouraged for all LT recipients.



Characteristic	Overall, N = 153[1]	Unvaccinated N = 79[1]	Vaccinated N = 74[1]	p-value[2]
Age (years)	55 (12)	53 (11)	58 (12)	0.007
Female (%)	77 (50%)	33 (42%)	44 (59%)	0.029
BMI (kg/m²)	26.8 (3.9)	27.1 (3.9)	26.5 (3.9)	0.4
Etiology (%)				0.3
AIH	19 (12)	14 (18)	5 (6.8)	
HCV	44 (29)	20 (25)	24 (32)	
NAFLD	26 (17)	12 (15)	14 (19)	
Overlap	7 (4.6)	4 (5.1)	3 (4.1)	
PSC	6 (3.9)	5 (6.3)	1 (1.4)	
PBC	12 (7.8)	6 (7.6)	6 (8.1)	
Alcohol	10 (6.5)	6 (7.6)	4 (5.4)	
Other	29 (19)	12 (15)	17 (23)	
Hepatocellular carcinoma	26 (17%)	9 (11%)	17 (23%)	0.057
Diabetes	55 (36%)	27 (34%)	28 (38%)	0.6
Hypertension	42 (27%)	16 (20%)	26 (35%)	0.039
Smoking	1 (0.7%)	1 (1.3%)	0 (0%)	>0.9
Time since transplant in months, (range)	59 (32, 86)	59 (34, 84)	59 (31, 86)	0.8

[1] Mean (SD); n (%)

[2] t-test; Pearson's Chi-squared test; Fisher's exact test.

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3745-C | IMPACTING PATIENT RECRUITMENT FOR NASH STUDIES WITH AI-POWERED AMSETY DATABASE

Guy W. Neff[1], Kevin Li[1], Michael Tunkelrott[2], Victoria Aksakovska[2], Jutta Kurz[2], Mustafa Behan[2], Fatma Barakat[3] and Tarek I. Hassanein[3], (1)Covenant Metabolic Specialists, LLC, (2)Amsety Gmbh, (3) Southern California Liver Centers

Background: Recruiting liver subjects for clinical trials is challenging. The Amsety Database, an artificial intelligence (AI) powered recruiting program, offers an effective process to improve recruitment for clinical trials. Developed to market the Amsety Liver Health Nutrition Bar, the self-selected database contains a highly motivated population with liver and related metabolic conditions. Amsety-AI has a growing database of around 500,000 patients across the US, including zip codes, age, gender, lifestyle and diet patterns, primary liver conditions as well as comorbidities. The project aim is to demonstrate Amsety-AI for identifying potential liver trial subjects. **Methods:** From November 2022 to May 2023, a pilot initiative with large clinic research network started to recruit subjects with NASH. Amsety-AI had 30,000 individual's in Florida of whom 2,347 were close to the study center. The initial prescreening survey resulted in 200 individual's that met predetermined qualifications. Candidates were referred to the study center for evaluation and digital pre-screening. **Results:** Of the 200 Amsety candidates, 43 (21.5%) met the criteria of the study and were invited for liver detailed screening. 56% of the respondents were female, and 44% male. The average age is 55 years. Average weight of the female respondents is 166lbs and 194lbs for males. 44% have a family history of liver disease. 13% have cirrhosis; 6% have hepatitis B; 6% have liver cancer. 75% have co-morbidities. 31% have hypertension, 25% are diagnosed with type 2 diabetes, 31% suffer from sleep apnea, 19% have gastroesophageal reflux disease and 13% have cardiovascular problems. Lifestyle habits: 56% exercise less than once/week, 25% consume high density food at least 2-3 times/week, and 13% consume alcohol every day. 31% have experienced recent weight gain. The center is in the process of evaluating the 43 candidates for screening and trial inclusion. The pilot is ongoing and new sites are being added in California and Texas. **Conclusion:** The data shows Amsety-AI creating a highly engaged population database with high potential for clinical trial enrollment. Combining Amsety digital and AI tools will improve speed and decrease costs of patient recruiting in large numbers.

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Victoria Aksakovska – Amsety GmbH: Employee, Yes, No;

Mustafa Behan – Amsety GmbH: Employee, Yes, No; WhoFinance GmbH: Employee, No, No; WhoFinance GmbH: Speaking and Teaching, No, No;

Tarek I. 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Sonic Incytes: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Terns Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Valeant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Kevin Li, Jutta Kurz, Fatma Barakat

f 3746-C | INEQUITIES IN LIVER TRANSPLANT AND LIVER RELATED MORTALITY IN THE UNITED STATES

Anshul Bhatnagar[1], Tzu-Hao (Howard) Lee[2], Ruben Hernaez[2], John A. Goss[1], Abbas Rana[1], Hashem B. El-Serag[1], Fasiha Kanwal[1] and George Cholankeril[1], (1) Baylor College of Medicine, (2)Baylor College of Medicine, Houston, TX

Background: Despite the increasing number of liver transplants (LT) in the U.S. over time, mortality from end-stage liver disease remains disproportionately high. Geographic, racial, sex, and age disparities in access to LT may widen the mortality burden. We aim to measure access to LT and assess disparities within diverse subpopulations using transplant to mortality (TM) ratio, defined by ratio of LT rate to mortality rate. **Methods:** Using population-level data from the United Network for Organ Sharing (UNOS) and Multiple Cause of Death files from the National Vital Statistics System (NVVS), we examined the trends in TM ratios for cirrhosis- and HCC-related mortality for patients with two common chronic liver diseases (hepatitis C (HCV) or alcohol-associated liver disease (ALD)) from 2011 to 2020. Our primary outcome was the TM ratio calculated for each subpopulation and stratified by age, sex, race/ethnicity, geographic region, and number of LT centers within the states. **Results:** There were 36,114 LTs and 181,406 cirrhosis or HCC-related deaths from 2011 to 2020. In the cirrhosis-related mortality group, patients

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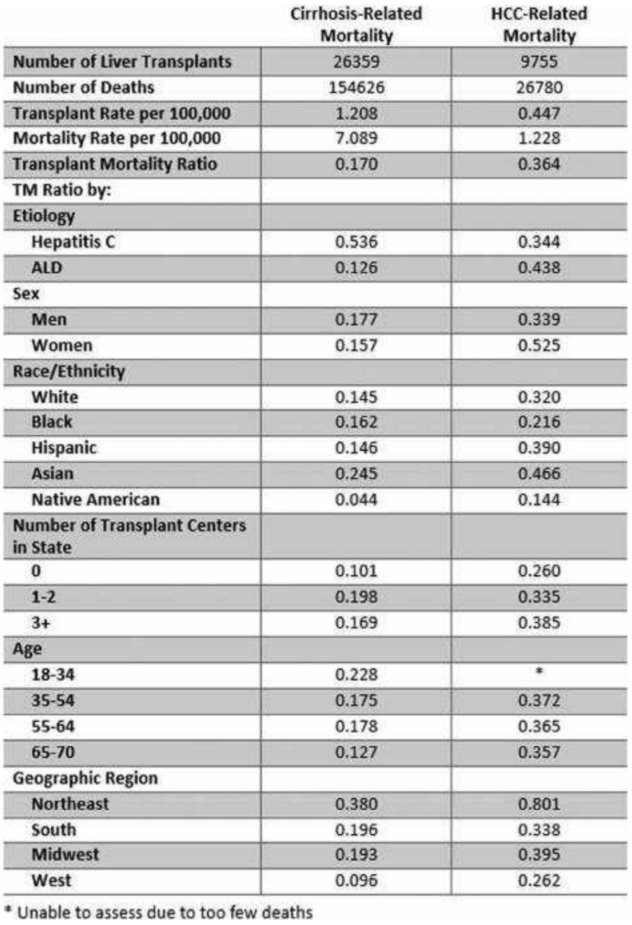
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

with HCV had a higher TM ratio than those with ALD, indicating greater transplant access among HCV patients compared with ALD patients. Regardless of mortality cause, patients living in states with more than 3 LT centers had significantly higher TM ratios than those in states with no LT centers. Patients who lived in the Northeast had the highest TM ratios, while those in the West had the lowest. Asians had the highest TM ratios compared to other races/ethnicities. Native Americans had the lowest TM ratio, followed by Hispanics in the cirrhosis group and Blacks in the HCC group. Women had higher TM ratios in the HCC group, while the opposite was true in the cirrhosis group. For example, black women with ALD in Nevada had a TM ratio of 0.029, indicating a lower chance to transplant and higher mortality compared to Asian men with HCV in New York that had a TM ratio of 1.00. **Conclusion:** There are significant disparities in access to LT in the US. Blacks, Native Americans, and patients living in the South, West, or states without LT centers suffer the greatest challenges in accessing LT. Strategies are needed to mitigate the multi-level barriers to life-saving LT and to better serve vulnerable populations across the country.



	Cirrhosis-Related Mortality	HCC-Related Mortality
Number of Liver Transplants	26359	9755
Number of Deaths	154626	26780
Transplant Rate per 100,000	1.208	0.447
Mortality Rate per 100,000	7.089	1.228
Transplant Mortality Ratio	0.170	0.364
TM Ratio by:		
Etiology		
Hepatitis C	0.536	0.344
ALD	0.126	0.438
Sex		
Men	0.177	0.339
Women	0.157	0.525
Race/Ethnicity		
White	0.145	0.320
Black	0.162	0.216
Hispanic	0.146	0.390
Asian	0.245	0.466
Native American	0.044	0.144
Number of Transplant Centers in State		
0	0.101	0.260
1-2	0.198	0.335
3+	0.169	0.385
Age		
18-34	0.228	*
35-54	0.175	0.372
55-64	0.178	0.365
65-70	0.127	0.357
Geographic Region		
Northeast	0.380	0.801
South	0.196	0.338
Midwest	0.193	0.395
West	0.096	0.262

* Unable to assess due to too few deaths

Disclosures: The following people have nothing to disclose: Anshul Bhatnagar, Tzu-Hao (Howard) Lee, Abbas Rana, Fasiha Kanwal, George Cholankeril

Disclosure information not available at the time of publication: Ruben Hernaez, John A. Goss, Hashem B. El-Serag

3747-C | INPATIENT CLINICAL DIETICIAN IS ASSOCIATED WITH ACHIEVING NUTRITIONAL GOALS AMONG PATIENTS WITH SEVERE ALCOHOLIC-ASSOCIATED HEPATITIS

Tiange Zhang[1], Cara Joyce[2], Stephanie Betcher[1], Fillippa Trikantzopoulou[3] and Steven J. Scaglione[1], (1) Loyola, (2)Loyola University Chicago, (3)Loyola University Medical Center, Chicago, IL

Background: Protein-calorie malnutrition (PCM) is present in nearly all patients with alcoholic hepatitis. An assessment of PCM is simple tool that has prognostic value in patients with severe alcoholic hepatitis (sAH). Nutritional therapy is of likely benefit to patients with sAH. The European Society for Clinical Nutrition and Metabolism (ESPEN) developed evidence based guidelines recommending an energy intake of 35–40 kcal/kg BW/d and protein intake of 1.2–1.5 g/kgBW/d. Adherence to the ESPEN guidelines for total calorie or protein intake remains unclear. Therefore, the aim of this study was to compare clinical characteristics and outcomes of patients with sAH by achievement of ESPEN goals. **Methods:** We used international classification of diseases, 9th and 10th revision codes for alcohol related liver disease and alcohol use disorder between 2012-2021 at three hospitals identifying 1287 potential cases. After detailed chart review, we identified 298 patients that met the NIAAA definition of sAH. Demographic and clinical variables including complications of liver disease, comorbidities, opioid use, and baseline and day 7 nutritional variables were extracted from the EMR. Outcomes of interest were 1) achieving ESPEN guidelines for calorie or protein 2)30 day overall survival. Adjusted odds ratio (aOR) were estimated from multivariable logistic regression analysis. **Results:** The median age of our cohort was 47 +/- 11 years, 62.8% male, 71.5% white, 7.4% African American, and 19.1% Hispanic, 6% other. Chronic opioid use was present in 11.2%. Only 10.4% of patients with sAH achieved ESPEN nutritional goals. Spontaneous recovery occurred in 56.7%, while 16.5% died, and 6.9% received liver transplant. Patients achieving ESPEN goals were more likely to have had a variceal bleed (EVB) (21.4% vs 6.3% ($p < 0.01$), hepatic encephalopathy (58.1% vs 34.5%, $p < 0.010$), and had a dietician involved in their inpatient care (93.5% vs 64.4%, $p < 0.01$). Factors significantly associated with achieving ESPEN goals were a dietician consult (aOR 6.2 95% CI 1.76-39.5, $p < 0.002$) and EVB (aOR 5.4, 95%CI

1.6-16.6, $p > 0.006$), adjusting for age and BMI on admission. Achieving ESPEN goals was not associated with improved 30 day overall survival. **Conclusion:** Nutritional therapy is important therapy in patients with sAH, but achieving well-known goals occurs in only a tenth of patients. Having a dietician involved in the care of patients with sAH is associated with achieving ESPEN goals.

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3748-C | INTEGRATION OF HCV TESTING AND TREATMENT INTO PEER DELIVERED SYRINGE EXCHANGE SERVICES USING TELEHEALTH FOR PEOPLE WHO INJECT DRUGS

Jeffrey Weiss[1], Abigail Hunter[1], David Kalinoski[2], Amanda Clay[2], Caro Bolanos Ordonez[2], Arash Diba[2], Linda Wang[1], Ponni Perumalswami[3], Larissa Wilberschied[4] and Colleen Flanigan[4], (1)Icahn School of Medicine at Mount Sinai, (2)Vocal-NY, (3)VA Ann Arbor Healthcare System, (4)New York State Department of Health

Background: In 2019, VOCAL-NY, a harm reduction agency, and Mount Sinai Hospital expanded their partnership to co-locate hepatitis C virus (HCV) treatment at VOCAL-NY for persons who inject drugs. Due to the COVID pandemic and VOCAL-NY being without a brick and mortar site, co-location of services was delayed until 2023. In the interim, a model of integrating HCV testing into peer delivered syringe exchange services and HCV treatment using telehealth was developed and implemented. **Methods:** VOCAL-NY's HCV point of care testing was integrated into peer delivered syringe exchange community outreach in several neighborhoods in Brooklyn, New York. HCV treatment was conducted via telehealth by a nurse practitioner from Mount Sinai Hospital working collaboratively with the VOCAL-NY team to arrange for laboratory testing, care coordination, treatment visits, and adherence monitoring. HCV testing and treatment were incentivized. De-identified client-level data was reported to the program funder, the New York State Department of Health AIDS Institute, for analysis. **Results:** From July 2019-June 2022, 709 people who use drugs were tested for HCV antibodies using OraQuick® rapid HCV antibody tests and HCV RNA using dry blood spot . Sixty-five of the 709 (9.2%) had detectable HCV RNA. Forty-five of the 65 persons (69.2%) were provided the HCV RNA test results and offered engagement in HCV treatment. Thirty-four clients were interested in treatment and enrolled in the program (70.6% male; 47.1% Hispanic, 32.4% black, 20.6% white; 79.4% injecting drug use in past 12 mo). Twenty-one clients attended the first telehealth visit, 15 initiated treatment, 13 completed treatment, 10 were assessed for SVR12 and 9 achieved SVR12. **Conclusion:** In the context of the COVID pandemic and the absence of a physical site for the harm reduction agency, the feasibility of using a street outreach telehealth model of HCV testing, linkage to care, and treatment was demonstrated with significant drop off at each step of the care cascade. The most significant challenge was remaining in contact with clients who were often (1) unstably housed/street homeless; (2) lacked reliable cell phone service; (3) had multiple competing priorities including food insecurity and inadequately treated medical and psychiatric comorbidities. Lessons learned from the initial phase of the collaboration were used to plan for the co-located model of onsite HCV services to be evaluated in VOCAL-NY's new physical home.

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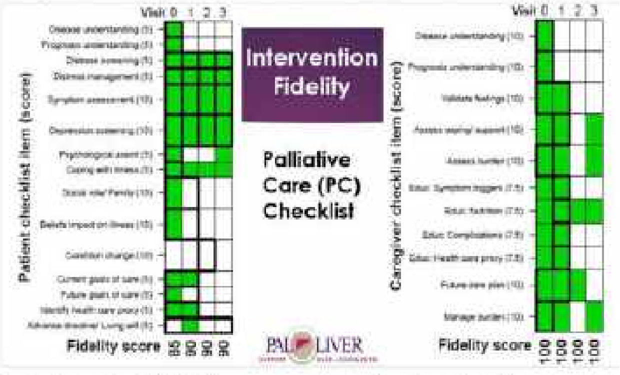
3749-C | INTERVENTION FIDELITY MONITORING FOR PAL LIVER, A COMPARATIVE EFFECTIVENESS TRIAL OF MODELS OF PALLIATIVE CARE DELIVERY FOR END STAGE LIVER DISEASES

Manisha Verma, Einstein Medical Center, Tamar H. Taddei, Yale University, New Haven, CT, Michael Volk, Loma Linda University, Andrzej Kosinski, Duke Clinical Research Institute, Marie Bakitas, University of Alabama at Birmingham and Victor J. Navarro, Md, Albert Einstein Medical Center, Doylestown, PA

Background: Palliative care (PC) comprises multiple elements which may work independently or interdependently to contribute to health outcomes. The generalizability of a PC intervention depends on the fidelity of its implementation. Intervention fidelity (IF) refers to the use of strategies to assess accurate implementation of interventions to maintain their validity, reproducibility, and reliability. PAL LIVER is a comparative effectiveness trial comparing two models: delivered by PC Providers versus Hepatologists trained with primary PC skills. PC delivery is guided by an intervention checklist in both models. This study aims to describe the method of IF monitoring in this ongoing trial, using the first three key domains of the National Institute of Health Behavior Change Consortium 1) intervention design, 2) training providers, 3) delivery of intervention. **Methods:** We developed a PC training program and a PC intervention checklist based on the elements of primary PC using American Society of Clinical Oncology guidelines. All hepatology intervention providers were required to complete the training prior to launch of intervention. All the interventionists (PC providers and Hepatologists) are required to complete the PC checklist after each intervention visit. In addition, clinical notes are documented as a part of standard clinical care. Periodically, selected clinical notes at each site are reviewed and compared to the PC checklist to validate the accuracy of the latter. If there is lack of congruency, the provider is alerted and given additional training. A score is calculated by summing allocated points (Figure). We report the initial visit data as the trial is ongoing. Since the study enrolls dyads, there are separate checklists for patients and caregivers. **Results:** Of the 714 initial patient visits completed, the mean (SD) IF score is 83 (17). Of the 427 initial caregiver visits, the mean (SD) IF score is 77(29). Time spent during the initial visit was between 31-50 min in 50% patients and 21% of caregivers. In > 90% of patient visits, these elements were discussed and documented: assess patients understanding of disease and prognosis; distress; depression and symptom assessment; and assess social support. Health care proxy identification was done during initial visit in 71%, and advance directive discussion in 29%. Caregiver burden assessment was performed in 86% of initial visits. In > 70% of initial visits, caregivers were educated on symptom triggers, complications of liver disease, and role of health proxy. Providers found checklists to be easy to complete and useful at the time of intervention delivery. Completion of checklists was facilitated by integrating checklists within EMRs and by coordinators directly handing checklists to providers following the visit. **Conclusion:** A combination of checklist and clinical note documentation is a feasible and pragmatic approach to maintain IF in multi-site PC intervention trials.

Figure- Elements of Palliative Care Intervention Checklist (Patients and Caregivers)



Legend: All circumferentially bolded boxes are suggested to be addressed at each visit. Boxes not bounded on all sides need to be addressed at one of the three intervention visits within the bolded perimeter.

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3750-C | LIVER TRANSPLANT WAITLISTING IS LOWER AMONG PATIENTS EVALUATED AT SATELLITE CLINICS

Kevin Tang[1], Jason J. Lee[1], Marina Serper[2], Ethan M. Weinberg[1] and Therese Bittermann[1], (1)University of Pennsylvania, (2)University of Pennsylvania, Philadelphia, PA, United States

Background: Satellite liver transplant clinics are increasingly common at transplant centers to improve access to liver transplantation. However, their impact on liver transplant waitlisting is not known. We investigated whether liver transplant evaluation at a satellite clinic was associated with liver transplant waitlisting in a large transplant center. **Methods:** This was a retrospective cohort study of adults evaluated for liver transplant in 2018 and 2021 to compare pre- and post-COVID-19 pandemic characteristics. We abstracted sociodemographic factors, psychosocial risk, comorbidities, liver disease severity, and listing requirements. Covariate adjusted multivariable logistic regression analysis evaluated the association of liver transplant evaluation location and not being waitlisted. **Results:** Of 472 patients evaluated for liver transplant, 19% were evaluated at a satellite clinic. Sex, age, MELD-Na, comorbidities, psychosocial risk, malnutrition, education, and etiology were not different by evaluation location or year. A greater Hispanic (13.2% vs 5.0%) and fewer Black (10.8% vs 4.4%) proportion of patients were seen at satellite clinics ($p = 0.025$ overall). Psychiatric disease was more prevalent in the satellite group (35.2% vs 19.2%; $p = 0.001$). The satellite group had shorter travel distance from home to evaluation location (median 28.5km vs 61.1km; $p < 0.001$) and commute time (median 24min vs 58min; $p < 0.001$). Overall, 43% of the cohort was not waitlisted because of medical/surgical (42%) or psychosocial (14%) contraindications, loss to follow-up (11%), and other (33%), with no difference by location. Patients evaluated at a satellite clinic were more likely to be not waitlisted (57% vs 39%; $p = 0.003$). This difference was most pronounced in 2018 (72% vs 46%; $p = 0.002$) versus 2021 (35% vs 29%; $p = 0.198$). Among patients not waitlisted, time to evaluation decision was shorter at satellite clinics (median 99d vs 166d; $p = 0.002$). There were no differences observed for patients accepted for waitlisting. In multivariable analysis (Table), satellite clinic evaluation was independently associated with higher odds of no waitlisting (OR, 2.31, 95% CI, 1.35-3.94; p = 0.002). **Conclusion:** In a large liver transplant center, patients evaluated at a satellite clinic were less likely to be waitlisted for liver transplant compared to patients evaluated at the main center after adjusting for multiple confounders despite shorter travel distance and commute times. Future studies should examine the factors that guide waitlisting decisions at satellite clinics to inform quality improvement and improve equitable access to liver transplantation.

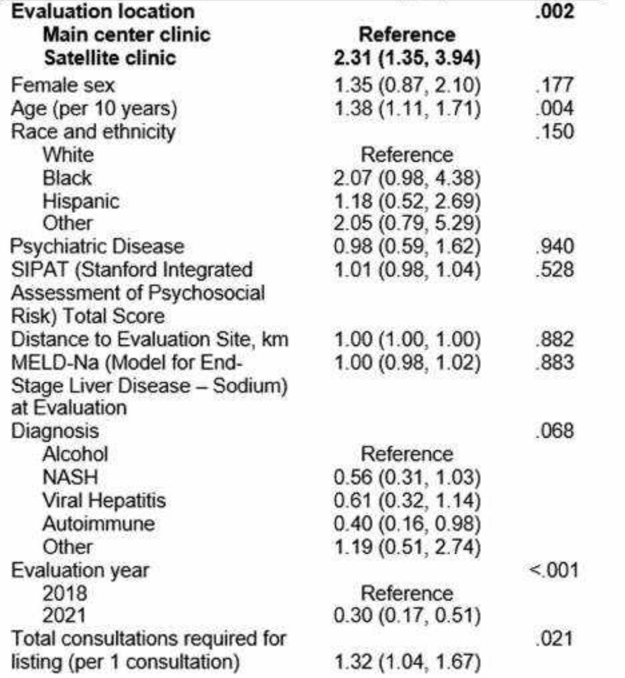

Table. Factors associated with not being listed for liver transplantation

Covariate	OR, (CI)	*P* value
Evaluation location		**.002**
Main center clinic	**Reference**	
Satellite clinic	**2.31 (1.35, 3.94)**	
Female sex	1.35 (0.87, 2.10)	.177
Age (per 10 years)	1.38 (1.11, 1.71)	.004
Race and ethnicity		.150
White	Reference	
Black	2.07 (0.98, 4.38)	
Hispanic	1.18 (0.52, 2.69)	
Other	2.05 (0.79, 5.29)	
Psychiatric Disease	0.98 (0.59, 1.62)	.940
SIPAT (Stanford Integrated Assessment of Psychosocial Risk) Total Score	1.01 (0.98, 1.04)	.528
Distance to Evaluation Site, km	1.00 (1.00, 1.00)	.882
MELD-Na (Model for End-Stage Liver Disease – Sodium) at Evaluation	1.00 (0.98, 1.02)	.883
Diagnosis		.068
Alcohol	Reference	
NASH	0.56 (0.31, 1.03)	
Viral Hepatitis	0.61 (0.32, 1.14)	
Autoimmune	0.40 (0.16, 0.98)	
Other	1.19 (0.51, 2.74)	
Evaluation year		<.001
2018	Reference	
2021	0.30 (0.17, 0.51)	
Total consultations required for listing (per 1 consultation)	1.32 (1.04, 1.67)	.021

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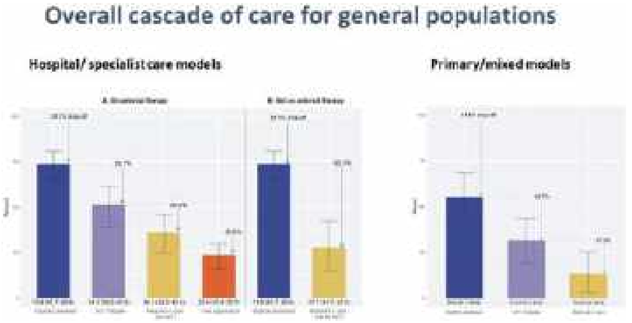
Ethan M. Weinberg – Mallinckrodt Pharmaceuticals: Consultant, Yes, No; Mallinckrodt Pharmaceuticals: Advisor, Yes, No; PharmaIN: Consultant, No, No; Biovie: Consultant, No, No;
The following people have nothing to disclose: Kevin Tang, Jason J. Lee, Therese Bittermann

3751-C | MODELS OF CARE OF PEOPLE LIVING WITH CHRONIC HEPATITIS B: SYSTEMATIC REVIEW AND META-ANALYSIS

Alexander J. Stockdale[1], Bethany Holt[2], Ajeet Bhadoria[3], Daniel Ikeda[2], David Duong[2], Todd Pollack[2], Gibril Ndow[4], Vy H. Nguyen[2], Janus Ong[5], Thuy Pham[6], Abhishek Sadasivan[7], Roger Chou[8] and Philippa Easterbrook[9], (1) Malawi-Liverpool-Wellcome Trust Clinical Research Programme, (2)Harvard Medical School, (3)All India Institute of Medical Sciences, Rishikesh, (4)Lshtm, (5) National Institute of Health, Manila, Philippines, (6)Health Advancement in Vietnam (HAIVN) and Beth Israel Deaconess Medical Center, Hanoi, Vietnam, (7)AIIMS Rishikesh, (8)Oregon Health & Science University, (9) World Health Organization

Background: Globally, less than 10% of 296 million with chronic hepatitis B virus (HBV) infection had been diagnosed and only 2% treated. Increasing access to HBV care and treatment requires simplified service delivery models. A global systematic review and meta-analysis was conductedidentify range of service delivery models for HBV testing, care, and treatment, and compare outcomes achieved across the HBV care continuum. **Methods**: We searched PubMed, Embase, and Scopus for studies published in last 10 years that evaluated service delivery models and care cascade for HBV. Models were categorised as hospital-based, primary care/co-managed, integrated with HIV/NCD/ harm reduction sites, or for other special populations. Key outcomes across the HBV care cascade (linkage to care, treatment uptake, viral load suppression, adherence and retention to care) were pooled using random-effects meta-analysis and nested elements confidence intervals calculated using parametric bootstrapping. **Results**: Our search identified 3989 reports; 69 met the eligibility criteria. 17 (25%) were from LMICs. Most were observational (41 or 61%) or non-randomized interventional designs (24 or 35%), with very few RCTs (3 or 4%). In total, 9 (13%) described hospital/specialist-based models (Hosp), 22 (32%) were primary care/co-managed or screening only (Prim), and the remainder related to integrated models (e.g., harm reduction, PLHIV) or tailored for special populations (e.g., migrants, pregnancy). Only 4% of studies reported outcomes across the complete cascade of care; 33% on early outcomes (testing and linkage) and 6% across late cascade outcomes (treatment and retention). Among those reporting late cascade outcomes, antiviral treatment initiation among eligible patients was 37%, viral suppression 9%, and retention in care 16%. There were higher rates of treatment eligibility assessment following diagnosis for Hosp vs Prim care (74% [95% CI 66–81] vs 55.5% [41.7–68.6]), and for treatment initiation (69.3% [54.1–81.2] *vs* 57.3% [39.3–73.5]. Retention in care was similar (~42%) between models, but greater in those on antiviral therapy (70.3% [58.7–79.7]) than those only monitored (37.5% [21.0–57.6]). Adherence to treatment and DNA suppression rates were rarely reported. **Conclusion**: We identified a wide range of hospital and primary care-based service delivery models for HBV care and treatment in high and low income settings. Few reported data across the full cascade of care, especially for assessing treatment response. Linkage to care, uptake

of treatment and retention in care was sub-optimal, and especially for reported primary-care based models. Interventions to improve adherence and retention in care are urgent across all models. Future studies should capture data across the cascade of care and utilize standardised definitions for linkage, eligibility assessment and retention.



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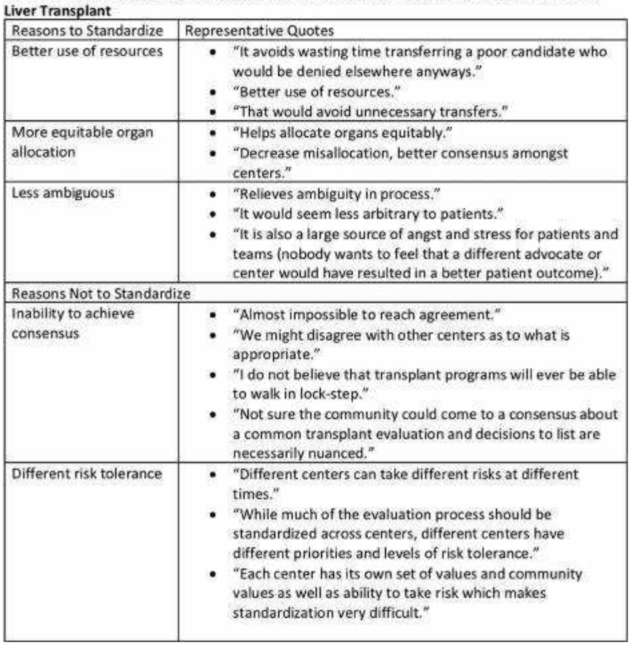
Disclosure information not available at the time of publication: Roger Chou

3752-C | NATIONAL SURVEY OF SECOND OPINIONS FOR HOSPITALIZED PATIENTS IN NEED OF LIVER TRANSPLANTATION

Alyson Kaplan[1], Grace Lee-Riddle[2], Yael R. Nobel[3], Lorna M. Dove[2], Akhil Shenoy[2], Russell Rosenblatt[4], Benjamin Samstein[5], Jean C. Emond[6] and Robert S. Brown Jr[7], (1)Weill Cornell Medical Center, (2)Columbia University Medical Center, New York, NY, (3)Columbia University Irving Medical Center, New York, NY, (4)Weill Cornell Medicine, NY, (5)Newyork-Presbyterian/Weill Cornell Medical Center, (6)Columbia University, New York, NY, (7)Cornell University

Background: Decisions by liver transplant (LT) centers about patient candidacy can be the difference between life or death. Center practices of receiving and referring for second opinion for inpatients declined for LT is not well understood. We aimed to survey LT centers across the United States (US) to assess their perceptions of and barriers to second opinion referrals for this population. **Methods:** The medical and surgical directors of 100 unique LT programs that had done > 20 LTs in the year 2021 were surveyed with a 33-item questionnaire including both multiple choice and free response questions. **Results:** The response rate was 60% (60 LT centers) and included 28 large (≥ 100 LTs in 2021) and 32 small volume programs (< 100 LTs in 2021). 62% of responses were from hepatologists and 38% from surgeons. The top 3 reasons for inpatient denial for LT included lack of social support (20.9%), too physically frail (20.3%), and too short remission from alcohol (11.3%). The most common etiology of liver disease for which patients were referred for a second opinion was alcohol-associated hepatitis (38%). 25% of programs reported "frequently" facilitating a declined inpatient for a second opinion, 51.8% of programs reported "sometimes" doing so, and 6.67% of programs reported never doing so. The most common barriers to referral identified were that other centers had similar psychosocial criteria (20.2%), insurance limitations (19.0%), and patients being too sick for transfer (18.4%). 100% of programs reported that they receive referrals for second opinions, but only 25% reported transplanting these referrals over 20% of the time. Neither program size nor program location statistically impacted the findings. When asked if centers would be in favor of standardizing the medical and psychosocial evaluation process for inpatients to eliminate the need for second opinions, 37.5% of centers would be in favor, 39.3% would not be, and 23.2% were unsure for varied reasons (Table 1). **Conclusion:** Practices and perceptions of second opinions for hospitalized patients evaluated for LT varied widely across the US. Centers report ambivalence regarding the next step towards facilitating referrals. Working to achieve equity in LT, while still maintaining individual program autonomy, seems to be a goal of many programs. Policy development for second opinions of inpatient evaluations will require further stakeholder engagement if there is to be community consensus on optimizing LTs for this particular population.

Table 1. Themes Regarding Standardization of the Medical and Psychosocial Evaluation for Liver Transplant



Reasons to Standardize	Representative Quotes
Better use of resources	• "It avoids wasting time transferring a poor candidate who would be denied elsewhere anyways." • "Better use of resources." • "That would avoid unnecessary transfers."
More equitable organ allocation	• "Helps allocate organs equitably." • "Decrease misallocation, better consensus amongst centers."
Less ambiguous	• "Relieves ambiguity in process." • "It would seem less arbitrary to patients." • "It is also a large source of angst and stress for patients and teams (nobody wants to feel that a different advocate or center would have resulted in a better patient outcome)."
Reasons Not to Standardize	
Inability to achieve consensus	• "Almost impossible to reach agreement." • "We might disagree with other centers as to what is appropriate." • "I do not believe that transplant programs will ever be able to walk in lock-step." • "Not sure the community could come to a consensus about a common transplant evaluation and decisions to list are necessarily nuanced."
Different risk tolerance	• "Different centers can take different risks at different times." • "While much of the evaluation process should be standardized across centers, different centers have different priorities and levels of risk tolerance." • "Each center has its own set of values and community values as well as ability to take risk which makes standardization very difficult."

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

3753-C | NATIONWIDE SURVEY OF THE IMPACT OF COVID-19 ON THE CLINICAL PRACTICE AND CARE OF PATIENTS WITH LIVER DISEASE IN JAPAN★

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Background: The COVID-19 pandemic has had various effects on medical care, including changes in care-seeking behavior and postponement of tests and surgeries. Comprehensive investigation into the pandemic's effects on liver disease care is also necessary. Since 2017, we have been developing clinical indicators for hepatitis and cirrhosis care at regional core centers for the management of liver disease as a part of the Policy Research for Hepatitis Measures of the Ministry of Health, Labor and Welfare in Japan. In this study, we used these indicators to assess the impact of the pandemic on liver disease care at regional core centers nationwide. **Methods:** The survey regarding 29 clinical indicators (hepatitis CIs) was conducted with 71 regional core centers. The hepatitis CIs consisted of 6 indicators related to general hepatitis and cirrhosis, 10 related to hepatitis C, 6 related to hepatitis B, 3 related to cirrhosis, and 4 related to subsidy systems. Results of surveys from 2018 to 2022 were compared to assess changes in indicators between the pre- (2018) and the pandemic periods (Early phase: 2020,2021, Late phase: 2022). We also analyzed the association between trends in these indicators and the data related with COVID-19 infection such as the number of severe cases and deaths due to COVID-19, vaccination rate and policy responses to the pandemic. **Results:** From 2018 to 2022, 17,707-20,960 patients/year (average 19,517) were enrolled for the analysis in 71 institutions in Japan. In the early phase of the pandemic period, compared to pre-pandemic period, there was a downward trend in many hepatitis CIs, with particularly large changes in indicators related to imaging and endoscopy. 16 indicators showed improvement in the 2022 survey, most of them related to hepatitis C and hepatitis B. In the evaluation using standardized scores, indicators related to antiviral treatment for hepatitis C and hepatitis B increased compared to 2021 (hepatitis C: -0.79 to 0.19, hepatitis B: -0.22 to -0.07), suggesting that the impact of the COVID-19 is being overcome. In addition, improvements in these indicators were more associated with the government stringency index and the proportion of vaccinated persons than with the number of severe cases or deaths. **Conclusion:** Trends in each indicator over time allowed us to evaluate the impact of COVID-19 on hepatitis care in Japan. Our survey showed that the spread of the COVID-19 infections has adversely affected liver disease treatment, however, the impact of pandemic on antiviral therapy for hepatitis B and C is reducing. The fluctuation in hepatitis clinical indicators were associated with vaccination coverage and policy responses to the pandemic.

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Tatsuya Kanto – Abbvie: Speaking and Teaching, No, Yes; Gilead Sciences: Speaking and Teaching, No, Yes;

The following people have nothing to disclose: Hiroko Setoyama, Noriko Oza, Tetsuro Shimakami, Junko Tanaka

3754-C | OBSTETRICIAN AND GYNECOLOGIST PERSPECTIVES ON SCREENING FOR AND MANAGEMENT OF ALCOHOL USE DISORDER AND ALCOHOL RELATED LIVER DISEASE

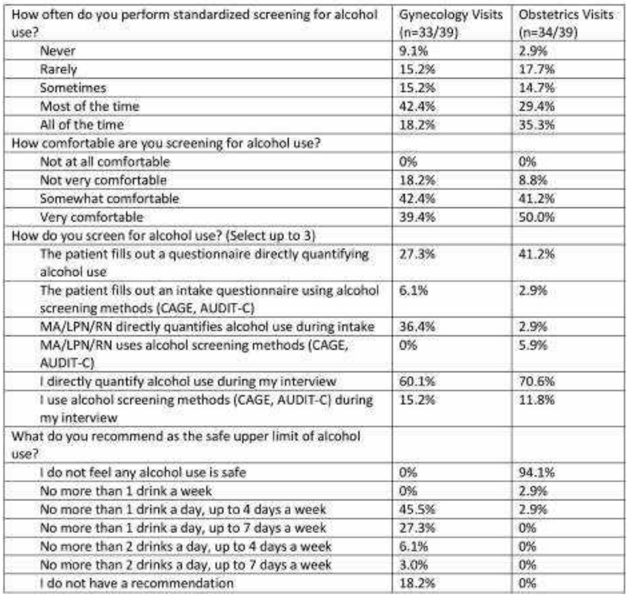
Mary Thomson, Cresta Jones and Nicholas Lim, University of Minnesota

Background: There has been a dramatic rise in female mortality due to alcohol-related liver disease (ARLD). Early identification and treatment of alcohol use disorder (AUD) could reduce future development of ARLD in these patients. Female patients may only see an Obstetrics/Gynecology (OB/GYN) provider for their health needs, providing a unique opportunity to screen for AUD and ARLD. **Methods:** An anonymous survey was distributed to 143 OB/GYN providers at the University of Minnesota and affiliated sites who participate in routine outpatient care to understand their experience and comfort with screening for and management of AUD and ARLD. **Results:** 39 (27.3%)

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

eligible providers completed this survey: median age, 41; 53.8% were MD/DO, 43.6% were certified nurse midwives; 35.9% were within 5 years of training. More than 90% of providers reported routinely screening for diabetes mellitus, colon cancer, breast cancer, and tobacco use. 59% cared for someone with ARLD and 28.2% had cared for someone who died from this. More than 60% reported screening for harmful alcohol use in both OB and GYN visits (Table 1). Reasons for not screening for harmful alcohol use during GYN visits included inability to effectively screen (28.6%), counsel (28.6%), or refer (28.6%) patients with harmful alcohol use. Reasons for not screening for harmful alcohol use at OB visits included time constraints (33.3%), worries about legal consequences for the patient (33.3%), and not feeling able to effectively refer patients with harmful use (33.3%). In patients identified with harmful alcohol use, 89.8% providers counseled on safe alcohol use, 41.0% referred to an addiction specialist, 41.0% recommended discussing with their primary care provider, and 35.9% referred to a social worker. A minority had ordered labs (41.0%) or imaging (25.6%) on patients suspected of having ARLD. Only 30.8% felt they received adequate education on harmful alcohol use and ARLD during their training, 41.0% felt there were adequate resources on ARLD for OB/GYNs while 92.3% were interested in learning more about ARLD **Conclusion:** Almost all OB/GYNs provide aspects of traditional primary care, but have limited comfort with screening and management of patients with AUD or ARLD. Improving education on AUD and ARLD for OB/GYN providers can potentially boost screening and early intervention in female patients with AUD and ARLD.

Table 1:



How often do you perform standardized screening for alcohol use?	Gynecology Visits (n=33/39)	Obstetrics Visits (n=34/39)
Never	9.1%	2.9%
Rarely	15.2%	17.7%
Sometimes	15.2%	14.7%
Most of the time	42.4%	29.4%
All of the time	18.2%	35.3%
How comfortable are you screening for alcohol use?		
Not at all comfortable	0%	0%
Not very comfortable	18.2%	8.8%
Somewhat comfortable	42.4%	41.2%
Very comfortable	39.4%	50.0%
How do you screen for alcohol use? (Select up to 3)		
The patient fills out a questionnaire directly quantifying alcohol use	27.3%	41.2%
The patient fills out an intake questionnaire using alcohol screening methods (CAGE, AUDIT-C)	6.1%	2.9%
MA/LPN/RN directly quantifies alcohol use during intake	36.4%	2.9%
MA/LPN/RN uses alcohol screening methods (CAGE, AUDIT-C)	0%	5.9%
I directly quantify alcohol use during my interview	60.1%	70.6%
I use alcohol screening methods (CAGE, AUDIT-C) during my interview	15.2%	11.8%
What do you recommend as the safe upper limit of alcohol use?		
I do not feel any alcohol use is safe	0%	94.1%
No more than 1 drink a week	0%	2.9%
No more than 1 drink a day, up to 4 days a week	45.5%	2.9%
No more than 1 drink a day, up to 7 days a week	27.3%	0%
No more than 2 drinks a day, up to 4 days a week	6.1%	0%
No more than 2 drinks a day, up to 7 days a week	3.0%	0%
I do not have a recommendation	18.2%	0%

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3755-C | OPPORTUNITIES TO REDUCE HBV-RELATED DISPARITIES THROUGH HARM REDUCTION ORGANIZATIONS

Amy B. Jessop, Heptrec, Melissa Lam, University of Pennsylvania and Catherine Freeland, Hepatitis B Foundation

Background: Approximately 40% of new hepatitis B (HBV) infections in the U.S. occur among people who inject drugs (PWID). To meet hepatitis elimination goals and reduce HBV's impact, we must prevent infections and identify and care for existing infections in PWID. Harm reduction organizations (HROs) engage this "hard-to-reach" group regularly with trusted, low barrier services and are obvious, positive partners for public health and healthcare systems. HROs, however, have not been key players in these efforts. This study examines HBV-related interests and actions of select U.S.-based HROs and identifies opportunities for engagement with traditional healthcare systems and providers. **Methods:** We conducted semi-structured interviews with 20 leaders of HROs in the Northeast (8), South (4), Midwest (3), Southwest (1), Northwest (4) regions of the U.S. using an interview guide developed through consideration of published manuscripts and expert consultation. Researchers reviewed transcripts with an inductive thematic analysis. A code book was developed (> 80% agreement) and data were analyzed with NVivo software. **Results:** Few HROs conducted HBV activities and few considered HBV as a priority, even though HIV and HCV are primary concerns. Legal statutes and relationships with public health agencies positively and negatively influenced actions. Among HROs with HBV activities, there was strong collaboration with healthcare centers and with providers dedicated to serving PWID. HBV testing was rare, generally only at HROs with onsite medical providers (reportedly due to need for phlebotomy and lab orders) and is often limited to participants with HIV or HCV. Vaccination occurred more frequently but still limited to on-site medical services or through public health outreach. To improve HBV actions, HROs need increased staff education, prioritization at health departments, culturally appropriate materials, revised government and insurance policies for vaccination, point-of-care testing, and engagement of more healthcare providers. **Conclusion:** To improve HBV actions, HROs need increased staff education, prioritization at health departments, culturally appropriate materials, revised government and insurance policies for vaccination, point-of-care testing, and engagement of more healthcare providers.

Engagement of healthcare providers is essential to reduce HBV transmission, infection and related hepatocellular carcinoma. To address the identified gaps in HBV within HROs healthcare providers are needed for engagement for vaccination, testing, and follow up care. Provider support is also necessary for advocacy efforts to revise immunization policies, push point-of-care testing approval, reduce insurance-related barriers to treatment and monitoring, reduce PWID-related stigma and to expand capacity for treatment of PWID.

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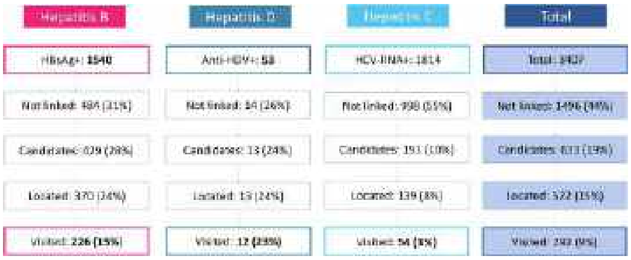
3756-C | PATIENTS WITH HEPATITIS B AND D ARE MORE OFTEN LINKED TO MEDICAL CARE THAN PATIENTS WITH HEPATITIS C

Elena Vargas-Accarino[1], Anna Feliu-Prius[2], Adriana Palom[1], Ariadna Rando[1], Ana Barreira[1], Joan Martínez Camprecios[3], Judit Vico-Romero[1], Juan Carlos Ruiz Cobo[3], Jordi Llaneras[3], Mar Riveiro[3], Francisco Rodriguez-Frias[1], Rafael Esteban-Mur[4] and Maria Buti[5], (1)Vall D'hebron Research Institute (VHIR), (2)Hospital Universitari Vall D'hebron, (3)Vall D'hebron University Hospital, (4)Hospital Universitario Vall D'hebron, (5)Hospital Universitari Vall d'Hebron, Department of Medicine of the UAB (Universitat Autònoma de Barcelona), Spain

Background: To achieve the WHO goals for viral hepatitis elimination is crucial to identify people living with hepatitis B and C. The objective of this study was to retrieve individual's with hepatitis B, C and D lost to follow-up and to deepen the reasons why they were not linked to care. **Methods:** Retrospective and prospective search of serum samples with hepatitis C (HCV-RNA+), hepatitis B (HBsAg+) and hepatitis D (anti-HDV+) from the microbiology database of the northern area of Barcelona (450,000 inhabitants). Individual's with a positive serum sample were identified and their medical records were reviewed to identify those lost to follow-up and the reasons of lack of linkage to care. Candidates to contact were telephoned a maximum of five times to offer them a medical visit. **Results:** A total of 3,407 medical records were reviewed between January 2019 and June 2022. Among them, 1,540 (45%) were HBsAg+, 53 (2%) anti-HDV+, and 1,814 (53%) HCV-RNA+. A total of 433 patients (28%) of the HBsAg+, 13 (24%) of the anti-HDV and 191 (10%) of those HCV-RNA+ were not linked to care. The reasons why the patients were not linked to care were: poor adherence to treatment, not attending the medical visit, treatment rejection and patients that were lost by the system. The main reasons of non-previously linked to care differs in relation to the type of viral hepatitis infection; the percentage of patients that rejected treatment and with poor adherence to treatment was higher in patients with hepatitis C (28% and 18% respectively) than in patients with hepatitis B (8% and 5%) or D (0 and 8%). Moreover, individual's with hepatitis C had significantly more advanced age or comorbidities (703 patients (23%)), compared to patients with hepatitis B or D (17 (1%) and 1 (2%)) ($p < 0.0001$) (median age of patients with hepatitis C, B and D was 60, 43 and 40 y old respectively). After the telephone calls, 226 HBsAg+ patients, 12 anti-HDV+ (2 of them HDV-RNA+) and 54 HCV-RNA+ were finally linked and treated; being HCV-RNA+ patients significantly less linked to care ($p < 0.0001$). 670 (20%) out of the 3,407 patients reviewed could not be contacted due to missing personal data. **Conclusion:** 292 (19%) patients have been linked to care, suggesting this is an effective strategy. Patients with hepatitis D are more linked and predisposed to be linked to care than patients with hepatitis C. The primary reasons for non-prior linkage to care vary depending on the type of viral hepatitis infection and the biggest challenge of this strategy has been the lack of contact details.



Hepatitis B	Hepatitis D	Hepatitis C	Total
HBsAg+: 1540	Anti-HDV+: 53	HCV-RNA+: 1814	Total: 3407
Not linked: 484 (31%)	Not linked: 14 (26%)	Not linked: 998 (55%)	Not linked: 1496 (44%)
Candidates: 429 (28%)	Candidates: 13 (24%)	Candidates: 191 (10%)	Candidates: 633 (19%)
Located: 370 (24%)	Located: 13 (24%)	Located: 139 (8%)	Located: 522 (15%)
Visited: 226 (15%)	Visited: 12 (23%)	Visited: 54 (3%)	Visited: 292 (9%)

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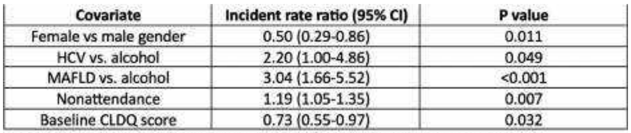
Maria Buti – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, Yes; GSK: Advisor, Yes, No;

The following people have nothing to disclose: Elena Vargas-Accarino, Anna Feliu-Prius, Adriana Palom, Ariadna Rando, Ana Barreira, Joan Martínez Camprecios, Judit Vico-Romero, Juan Carlos Ruiz Cobo, Jordi Llaneras, Francisco Rodriguez-Frias

3757-C | PREDICTING LIVER-RELATED EMERGENCY ADMISSIONS IN CIRRHOSIS: A MULTI-CENTRE STUDY

Alan J. Wigg[1,2], Peter D. Rose[1,2], Sumudu Narayana[2], Richard J Woodman[1] and ALFIE Investigator Group, (1) Flinders University, (2)Southern Adelaide Local Health Network

Background: Rates of hospital readmission for patients with cirrhosis is high. These patients have increased overall mortality and contribute to significant healthcare costs. Many liver-related emergency admissions (LREA) are potentially preventable, thus identifying predictors of LREA may provide a target for intervention. There is currently no Australian multicentre data looking at LREA in cirrhosis. The primary aim of this study was therefore to determine predictors of LREA in cirrhosis across a multicentre, multi-state Australian database. **Methods:** The patient cohort studied was from the ALFIE dataset. This was a multicentre (5 centres across SA, WA and NSW) randomised controlled trial occurring between 2018 and 2022, with 1:1 randomization between a nurse coordination model and standard of care. All patients were recruited following an inpatient admission with a complication of chronic liver failure (CLF) (including ascites, encephalopathy, variceal bleeding, SBP, AKI-HRS, and alcohol-related acute on chronic liver failure) with planned follow up of 2 years. Baseline covariates studies included: randomization group, age, gender, aetiology, MELD and Child Pugh score, type of index cirrhosis complication, site, Charlson Comorbidity Index, SEIFA score, ARIA score, presence at baseline of carer or GP, dietician and pharmacy reviews and attendance rates at planned outpatient care. A variety of baseline scores assessing patient knowledge, self-management ability and quality of life were also used as covariates. Multivariate analysis was performed using negative binomial regression to identify covariates associated with LREA. LREA were defined as readmissions due to one or more complications of cirrhosis. **Results:** A total of 146 patients were analysed. The cohort had the following characteristics: mean age 54.9 years, 68% male, median MELD score 19.0 and median Child-Pugh score 9.0. The main causes of CLF were alcohol (68%), MAFLD (16%) and HCV (11%). A total of 384 LREA admissions occurred over a median follow up of 2.0 years, with a mean of 2.63 LREA per patient. 116 patients (79%) had at least one LREA over the study period. Table 1 shows the covariates that were significant predictors of LREA on multivariate analysis. **Conclusion:** Cirrhotic patients who are male, with HCV or MAFLD, who miss follow-up appointments and with lower baseline quality of life scores are more likely to have LREA. Interventions targeting cirrhotic patients with these higher risk features may help reduce LREA.



Covariate	Incident rate ratio (95% CI)	P value
Female vs male gender	0.50 (0.29-0.86)	0.011
HCV vs. alcohol	2.20 (1.00-4.86)	0.049
MAFLD vs. alcohol	3.04 (1.66-5.52)	<0.001
Nonattendance	1.19 (1.05-1.35)	0.007
Baseline CLDQ score	0.73 (0.55-0.97)	0.032

Table 1: Covariates significant for prediction of LREA on multivariant analysis.

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3758-C | PREDICTION MODELS OF EARLY READMISSIONS IN CIRRHOSIS: A SCOPING REVIEW

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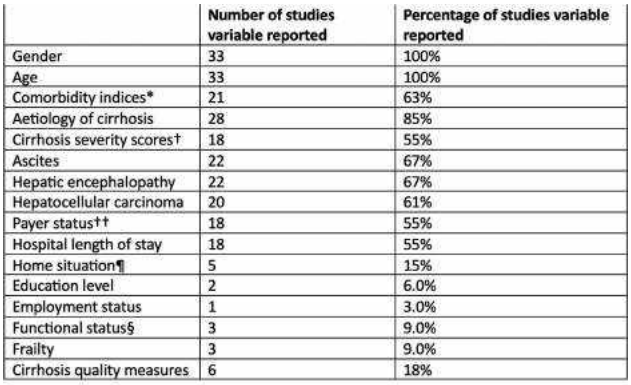
Background: Patients hospitalised with cirrhosis have high rates of early readmissions within 30 days. These patients have increased overall mortality and represent a significant cost to healthcare systems. Many of these readmissions are potentially preventable, thus prediction of patients at high risk of early readmission may provide an opportunity for quality improvement and intervention. Our aim was to perform a scoping review of the literature predicting early readmissions in cirrhosis to determine which variables are incorporated into prediction models, the type of prediction models used and the performance of these models. **Methods:** Relevant literature from electronic references databases were searched from inception to March 2023. A total of 33 studies were incorporated into the final review. All variables included in univariate and multivariate analyses were examined. Prediction models were analysed for model type, presence of a validation and derivation cohort, and discrimination ability. **Results:** Out of the 33 studies, there were 13 nationwide databases, 4 multi-centre studies and 16 single centre studies. There were 30 retrospective studies and 3 prospective studies. Regarding patient cohort, 13 studies only included patients with decompensated cirrhosis, including 3 with specifically hepatic encephalopathy. The pooled early readmission rate was 22.7%. Table 1 demonstrates the frequency of major variables reported. Models of prediction were proposed in 11 studies, with 10 of these incorporating linear regression models and 1 incorporating Cox regression models. Only 5 studies provided both a derivation and validation cohort, 2 of which were externally validated. Only 3 studies yielded a derivation model with at least reasonable discrimination (concordance index greater than 0.7) and no study yielded a validation model with at least reasonable discrimination. Machine learning was used as a prediction tool in one study, however it did not demonstrate reasonable discrimination, and no social, functional, frailty or quality measure variables were incorporated. **Conclusion:** Social, functional, frailty, and quality measure variables are underrepresented in models predicting early readmission in cirrhosis and these models demonstrate suboptimal discrimination. Incorporation of these important variables into a machine learning model may enhance its performance and better identify cirrhotic patients at high risk of early readmission who may benefit from further intervention.



	Number of studies variable reported	Percentage of studies variable reported
Gender	33	100%
Age	33	100%
Comorbidity indices*	21	63%
Aetiology of cirrhosis	28	85%
Cirrhosis severity scores†	18	55%
Ascites	22	67%
Hepatic encephalopathy	22	67%
Hepatocellular carcinoma	20	61%
Payer status††	18	55%
Hospital length of stay	18	55%
Home situation¶	5	15%
Education level	2	6.0%
Employment status	1	3.0%
Functional status§	3	9.0%
Frailty	3	9.0%
Cirrhosis quality measures	6	18%

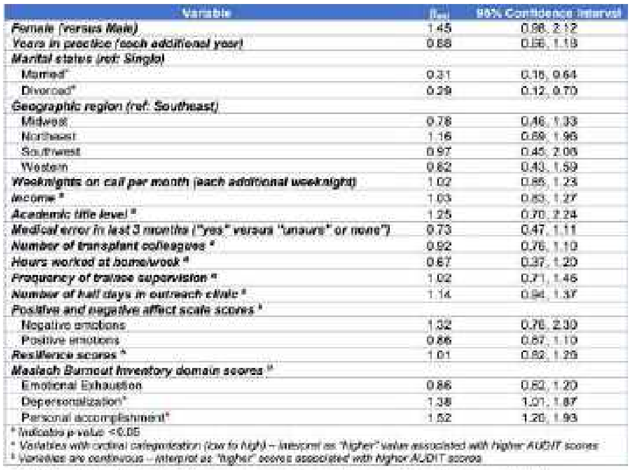
Table 1: Key variables analysed in scoping review and frequency they were analysed.
*Including Charlson Comorbidity Index or Elixhauser Comorbidity Index
†Including MELD, MELD-Na and Child Pugh scores
††Including Medicare funded, privately funded and on Medicaid
¶Including homelessness status, home alone, number of other adults at home and children at home
§Including dependence on activities of daily living, functional status questionnaire score and chronic liver disease questionnaire score

Disclosures: Alan J. Wigg – Astra Zeneca: Speaking and Teaching, No, Yes;
The following people have nothing to disclose: Peter D. Rose, Richard J. Woodman

3759-C | PREVALENCE AND PREDICTORS OF PROBLEMATIC ALCOHOL USE AMONG TRANSPLANT HEPATOLOGISTS

Christopher L. Coe[1], Nicole Prause[1], Jihane N. Benhammou[1,2], Jasleen Singh[1], Akshay Shetty[1], Hirsh Trivedi[3], Beshoy Yanny[1], Kamron Pourmand[4] and Arpan Arun Patel[1,5], (1)University of California, Los Angeles, (2)VA Greater Los Angeles Healthcare System, (3)Cedars-Sinai Medical Center, Los Angeles, CA, (4)Mount Sinai Hospital, (5)Greater Los Angeles VA Healthcare System

Background: In the United States (U.S.), problematic alcohol use is common not only among the adult population but also physicians, 15.3% of whom screen positive for alcohol abuse/dependence. Male and younger physicians may be at higher risk, and specialty-specific estimates of use vary widely. The aim of this study is to describe the prevalence and predictors of problematic alcohol use among transplant hepatologists in the U.S., which is not known. **Methods:** This was a secondary analysis of a 69-item survey sent to practicing transplant hepatologists in the United States in 2019, which assessed prevalence and predictors of burnout. It included 22 items from the Maslach Burnout Inventory, as well as items related to demographics, practice characteristics, and psychological factors, including the 3-item Alcohol Use Disorders Identification Test-Concise (AUDIT-C). We used well-established cutoffs to define problematic drinking (3 or higher for women; 4 or higher for men) and alcohol abuse/dependence (4 or higher for women; 5 or higher for men). A working group of transplant hepatologists narrowed predictors in our analysis to those hypothesized to be associated with problematic alcohol use. We used generalized linear models to describe associations between predictors and AUDIT-C scores (Table). **Results:** A total of 185 responses were analyzed. Forty-seven (25.4%) respondents met criteria for problem drinking and 20 (10.8%) screened positive for alcohol abuse/dependence. There was no difference in sex, age, or career stage between those with negative or positive screens for problematic drinking. Our final model demonstrated that having higher feelings of personal accomplishment (standardized beta coefficient [β_{std}]: 1.52, 95% confidence interval [CI]: 1.20-1.93) and depersonalization (β_{std}: 1.38, 95% CI: 1.01-1.87) were independently associated with higher AUDIT-C scores. Compared with being single, being married or divorced (β_{std}: 0.8, 95% CI: 0.67-0.95) was independently associated with lower AUDIT-C scores. **Conclusion:** One in four surveyed transplant hepatologists in the U.S. screened positive for problematic alcohol use. Traditional risk factors, such as age and sex, were not associated with greater alcohol use; however, transplant hepatologists who experience depersonalization, report being high-achieving, or have never been married may be at a higher risk. This should inform efforts to destigmatize problematic alcohol use and ensure access to substance use resources for hepatologists. For interested colleagues, a list of confidential physician health programs is published online (http://www.fsphp.org/state-programs).



Variable	β_{std}	95% Confidence Interval
Female (versus Male)	1.45	0.98, 2.12
Years in practice (each additional year)	0.88	0.56, 1.19
Marital status (ref: Single)		
Married*	0.31	0.15, 0.64
Divorced*	0.29	0.12, 0.70
Geographic region (ref: Southeast)		
Midwest	0.78	0.46, 1.33
Northeast	1.16	0.69, 1.96
Southwest	0.97	0.45, 2.06
Western	0.82	0.43, 1.59
Weeknights on call per month (each additional weeknight)	1.02	0.85, 1.23
Income ª	1.03	0.83, 1.27
Academic title level ª	1.25	0.70, 2.24
Medical error in last 3 months ("yes" versus "unsure" or none")	0.73	0.47, 1.11
Number of transplant colleagues ª	0.92	0.76, 1.10
Hours worked at home/week ª	0.67	0.37, 1.20
Frequency of trainee supervision ª	1.02	0.71, 1.46
Number of half days in outreach clinic ª	1.14	0.94, 1.37
Positive and negative affect scale scores ᵇ		
Negative emotions	1.32	0.76, 2.30
Positive emotions	0.86	0.67, 1.10
Resilience scores ᵇ	1.01	0.82, 1.25
Maslach Burnout Inventory domain scores ᵇ		
Emotional Exhaustion	0.86	0.62, 1.20
Depersonalization*	1.38	1.01, 1.87
Personal accomplishment*	1.52	1.20, 1.93

* Indicates p-value <0.05
ª Variables with ordinal categorization (low to high) – interpret as "higher" value associated with higher AUDIT scores
ᵇ Variables are continuous – interpret as "higher" scores associated with higher AUDIT scores

Table. Predictors of higher AUDIT scores among survey participants– Generalized Linear Model.

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3760-C | PREVALENCE OF VIRAL HEPATITIS AND SEROLOGIC EVIDENCE OF IMMUNITY AMONG INJECTION DRUG USERS IN US ADULTS FROM 2009 TO 2018

Javeria Khalid[1], Yinan Huang[2] and Rajender Raj Aparasu[1], (1)University of Houston, (2)University of Mississippi

Background: In the United States (US), illicit drug users continue to rise, with an estimated 43.5 million people (19.4%) exposed to illicit drugs. Globally, viral hepatitis (A, B, C, D & E) among illegal drug users is a public health concern due to concerns of disease transmission through social and sexual interactions. Moreover, there are limited data on the recent prevalence of viral hepatitis in US adults who inject illicit drugs. Therefore, this study aims to analyze the prevalence and predictors of viral hepatitis and hepatitis-B immunization among adults in the US who inject illicit drugs from 2009 to 2018. **Methods:** This retrospective, cross-sectional study used the National Health and Nutrition Examination Survey (NHANES) from 2009-2018. The study included adults aged 18 to 69 who filled out questionnaires for drug use information (including heroin, amphetamines, buprenorphine, benzodiazepines, barbiturates, cocaine, and methamphetamine). Viral hepatitis (A, B, C, D & E) infections among these populations were identified based on serological laboratory tests. Adults were considered immunized for HBV if serological HBV-antibody titer was > 10mIU/Ml. Trend analysis evaluated prevalence trends of viral hepatitis and vaccine-induced immunity among injection drug users across five survey-year cycles. **Results:** According to NHANES (2009-2018) survey, an estimated 18.23% (95%CI:15.64%-20.04%) injection drug users had HBV infection, and 33.02% (95%CI:30.96%-34.45%) had HCV infection, while infection rate for HBV and HCV was 3.9% and 1.13% among non-injection drug users, respectively. Among all injection drug users, the prevalence of HBV infection has increased significantly from 16.7% in 2009-2010 (95%CI: 9.23%-20.6%) to 24.46% in the 2017-2018 cycle (95% CI:15.1%-28.3%) ($P < 0.001$). However, the prevalence of HCV infection did not change significantly during the study period (HCV infection: 2009-2010 cycle (35.9% [95% CI, 33.5%-37.15%]) to the 2017-2018 cycle (34.48% [95% CI, 18.59%-41%]; P-value = 0.56). Moreover, the odds for HCV infection were 26.79 (95% CI:17.07-42.2) among injection drug users and 7.2 (95%CI:5.2-10.1) for HBV infection. The odds for HBV vaccination were similar for injection drug users (high-risk adults) compared to non-injection drug users (OR: 1.05, 95%CI: 0.8-1.378). **Conclusion:** Despite periodic releases of guidelines for controlling blood-borne infection, viral hepatitis is still high among injection drug users, while vaccine-induced immunity remains low. Concerted efforts are needed to maintain the rate of blood-borne diseases and improve the HBV immunization rate among injection drug users in the U.S.
Disclosures: The following people have nothing to disclose: Javeria Khalid, Yinan Huang, Rajender Raj Aparasu

3761-C | PRIMARY CARE AND ENDOCRINE SPECIALTY CLINICIAN KNOWLEDGE AND PERSPECTIVES ON SCREENING FOR NON-ALCOHOLIC FATTY LIVER DISEASE IN AN URBAN, SAFETY-NET SETTING

Arpan Mohanty, Kathryn Fantasia, Kirsten Austad, Allan J. Walkey and Mari-Lynn Drainoni, Boston Medical Center, Boston, MA

Background: Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent cause of chronic liver disease and a public health problem. Even though the incidence of NAFLD and related complications such as cirrhosis and liver cancer are rising, it remains underdiagnosed in primary care and endocrinology clinics. The aim of this study is to understand clinician perspectives on the current status of NAFLD screening and risk stratification so as to inform future implementation strategies to improve NAFLD care. **Methods:** In 2022, we conducted a sequential exploratory mixed-methods study at a large, urban US safety-net hospital. A survey was deployed to 299 clinicians from adult primary care and related subspecialties (geriatrics, infectious disease/HIV primary care) and endocrinology. A subset participated in semi-quantitative interviews. Survey and interview questions were on knowledge, attitude, and practice around NAFLD screening and risk stratification. The interviews were designed to gain a deeper understanding on barriers and facilitators and perspectives on electronic health record (EHR) integrated tools to improve NAFLD screening. **Results:** Survey response was 36.5% (109 respondents). Survey findings indicate that most clinicians (83%) recognize NAFLD as a significant health problem though most underestimate its prevalence (69%). Only 34% of the respondents reported using fibrosis prediction scores such as FIB-4 and 47% reported using transient elastography for

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

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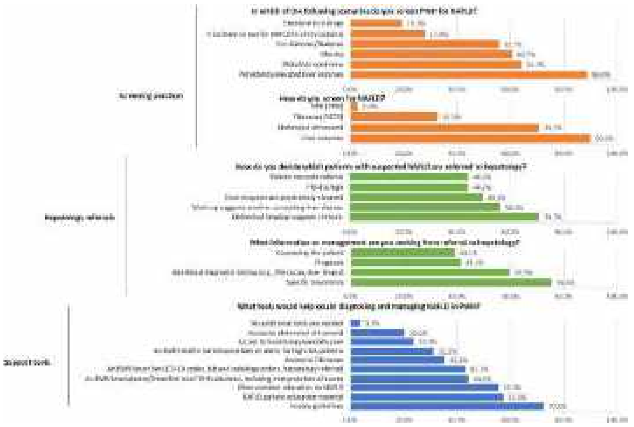
Disclosure information not available at the time of publication: Kathryn Fantasia, Kirsten Austad, Allan J. Walkey, Mari-Lynn Drainoni

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

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

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



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

Andreas Zori[1], Maya Jordan[2], Ismael Media[2], Juan Gonzalez[2], Divya Devabhaktuni[2], Calvin Kiani[2] and Roniel Cabrera[2], (1)University of Florida, Gainesville, FL, (2)University of Florida

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

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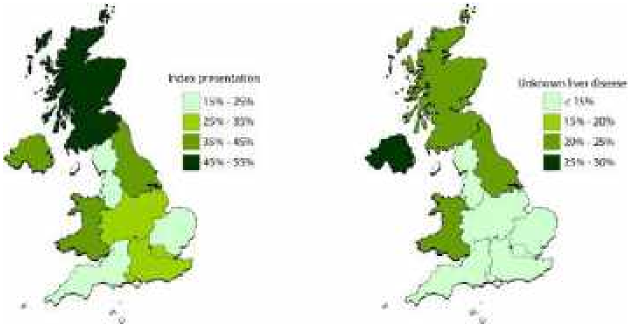
3764-C | PUBLIC HEALTH STRATEGIES AND EARLY DETECTION PROGRAMS SHOULD FOCUS ON INDIVIDUALS AT RISK OF ALCOHOL RELATED HARM TO REDUCE MORBIDITY AND MORTALITY FROM DECOMPENSATED CIRRHOSIS IN THE UK

The Trainee Collaborative for Research and Audit in Hepatology UK, Torch-UK

Background: In the natural history of chronic liver disease (CLD), the onset of decompensation is associated with a significant increase in patient mortality. However, strategies aiming to reduce the prevalence of CLD and complications of advanced disease have had limited success to this point. We aimed to characterise index presentations of decompensated cirrhosis to hospitals in the United Kingdom (UK) and understand differences between those with known and unknown liver disease. **Methods:** Patients admitted to hospitals with decompensated cirrhosis between 1/11/2019-30/11/2019 from across the UK were included in this analysis. Admission clinical, demographic and laboratory data were collected with outcome and trust-specific data. Data regarding the presence of a local community early detection program was also supplied. Univariable and multivariable analyses were performed. **Results:** 1224 admissions from 104 hospitals across the UK were included. There were regional variations in the proportion of admissions with index presentations and with unknown liver disease (Figure 1). Index presentations were more likely to consume alcohol regularly (67.78% v 49.67%, $p < 0.0001$*), present with jaundice (24.38% v 10.58%, $p < 0.0001$*) and less likely to present with encephalopathy (9.2% v 21.17%, $p < 0.0001$*) than patients with established disease. No other differences were reported in demographic, aetiological, deprivation or clinical data between these cohorts. Patients with index presentations of previously unknown liver disease were more likely to regularly drink alcohol (75.16% v 61.36%, $p = 0.01$*) and had significant worse prognostic scores than index presentations with known liver disease. No other differences were reported in demographic, aetiological, deprivation or clinical data between these cohorts. The presence of a local community early detection program was not associated with a significantly lower proportion of admissions with index presentations or unknown liver disease. Inpatient mortality was high in index presentations (17.77%) and highest in the those with unknown liver disease (19.89%) but this was not significant when adjusted for patient age, critical care admissions and MELD score. **Conclusion:** Public health strategies are required to reduce alcohol use across the UK in order to reduce morbidity and mortality from decompensated cirrhosis. These likely include Minimum Unit Pricing and increased funding for alcohol services. Early detection programs should focus on identifying those at risk of alcohol related harm.



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3765-C | RAPID HEPATITIS B VIRUS TESTING AND HEPATOCELLULAR CARCINOMA SCREENING THROUGH AN EMERGENCY DEPARTMENT IN TANZANIA

Manaswita Tappata[1], James Ford[2], Johnstone Kayandabila[3], Joseph Morrison[4], Samwel Seth[3], Aliasghar Mukhtar[3], Michael Schick[4], Larissa May[4] and Jose D. Debes[1,5], (1)University of Minnesota, (2) University of California, San Francisco, (3)Arusha Lutheran Medical Center, (4)University of California Davis, Sacramento, CA, (5)Erasmus University Medical Center, Netherlands

Background: Africa suffers from a high burden of hepatitis B virus (HBV) and hepatocellular carcinoma (HCC). Novel screening strategies are needed to achieve The World Health Organization goal of detecting 90% of global cases of HBV by 2030. In this study, we assessed the utility of an emergency department (ED)-based combined HBV and HCC screening program in Tanzania. **Methods:** We conducted a study in a combined HBV and HCC screening program at an ED in Arusha, Tanzania at a regional referral hospital between April and June 2022. All patients who presented to the ED (primary or from clinic) were approached for enrollment, underwent informed consent, and completed a study questionnaire with the aid of study staff. HBV testing was conducted via fingerstick using a rapid point-of-care assay to detect HBV surface antigen (HBsAg). Patients who were HBSAg positive underwent point of care ultrasound to screen for HCC, and were referred to HBV clinic for further management. We trained local ED and critical care providers who had prior ultrasound experience on how to systematically screen the liver for masses. We measured the number of HBV diagnoses (primary outcome) and the number of liver masses (secondary outcome). Data were analyzed with descriptive statistics. **Results:** A total of 846 patients were tested for HBV during the study period (primary ED: 761, clinic-referral: 85). Median age of patients was 44 ± 15 years, and 66% were female. Only 15% of patients reported having a primary care doctor. 13% of patients had been previously vaccinated for HBV. 65% of patients did not know how HBV is transmitted. 6% of patients had a family member with a known HBV infection. There were 17 new HBV diagnoses (primary ED: 16, clinic-referral: 1), which corresponds to a seroprevalence of 2.0% [95% CI 1.2, 3.2]. No patients had liver masses detected on point of care ultrasound. **Conclusion:** We found that an ED-based, combined HBV and HCC screening protocol can be feasibly implemented with short-interval training of local providers and minimal time. This study could serve as a model for HBV/HCC screening in regions with high HBV endemicity and low rates of community screening.

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3766-C | REPEATED EMERGENCY DEPARTMENT UTILIZATION BY INDIVIDUALS WITH CIRRHOSIS IS PREDICTABLE AND MAY BE AVOIDABLE WITH HEALTHCARE DELIVERY REFORM

Swetha Parvataneni[1], Yara Sarkis[2], Brittany Baker[2], Michelle Haugh[1], Qing Tang[1], Lauren D. Nephew[1], Marwan S. Ghabril[1], Naga P. Chalasani[3], Raj Vuppalanchi[2], Nicholas Eric Harrison[1], Eric S. Orman[1] and Archita Parikh Desai[1], (1)Indiana University, (2) Indiana University School of Medicine, (3)Indiana University Medical Center, Indianapolis, IN

Background: Emergency Department (ED) care is often required to manage cirrhosis related complications and utilization of the ED by individual's with cirrhosis has not been well described. We aimed to describe ED care utilization and compared the outcomes of high ED utilizers versus not in individual's with cirrhosis. **Methods:** We retrospectively reviewed charts for adults with cirrhosis without prior liver transplant (LT) presenting to any ED from 01/2021 – 12/2021 in a large, state-wide healthcare system (16 EDs) associated with a LT center. Patient characteristics and features of the first ED visit during 2021 as well as 90-day health-care use and outcomes were collected. Charts were adjudicated to determine if the ED visit could have been avoided based on pre-determined criteria. Predictors of being a high ED utilizer (HEDU, >2 visits during 90-day follow-up) were assessed using multivariable logistic regression models. **Results:** The study cohort ($n = 1850$) is described in the Table. Return visits were common (41%, mean visits 1.9 ± 1.3) with 19% of the cohort being a HEDU. Compared to non-HEDUs, HEDUs were younger, were more likely to have active alcohol use, complications of cirrhosis and a higher MELD score (Table). Rates of ED interventions were not significantly different between the groups, including receipt of paracentesis (Table). Upon expert review, 20% of initial visits could have been avoided, of which 33% deemed avoidable with an urgent visit in hepatology, urgent paracentesis (24%), improved medical management at home (23%) and/or non-emergent weekend/holiday services (16%). In those with a repeat ED visit, 32% were deemed avoidable. The 5 most frequent reasons for initial ED visit were: abdominal pain, 19%; shortness of breath, 16%; fall/generalized weakness, 13%; altered mental status, 12%; and ascites, 10%. In those with a subsequent visit for these top reasons, presentation for the same symptom occurred in 12-23% of non-HEDU vs. 13-23% of HEDUs ($p > 0.05$ for each). Considering 90-day outcomes by HEDU status, HEDUs returned sooner than non-HEDUs (Table). While HEDUs had a similar risk of 90-day mortality (16.7% vs. 13.4%, $p = 0.131$), they were more likely to undergo LT within 90-days (0.8% vs. 2.3%, $p = 0.038$). Independent predictors of being a HEDU were: weekday presentation (OR 0.74, 0.56, 0.98), lack of clear etiology of cirrhosis (OR 3.05, 95% CI: 1.81, 5.16), ascites (OR 1.5, 95% 1.13, 1.94), higher number of prior ED visits (1.22, 95%CI: 1.12-1.32) and prior hospitalizations (1.18, 95% CI: 1.07-1.31). **Conclusion:** Individual's with cirrhosis seek ED care, often for liver-related conditions, of which 1 out of 5 can be prevented. Furthermore, these individual's are at high-risk for repeated ED use, hospitalization and mortality. Prior health-care use is an important predictor of HEDU and should be incorporated discharge planning to prevent subsequent returns to the ED, possibly through improved outpatient services.

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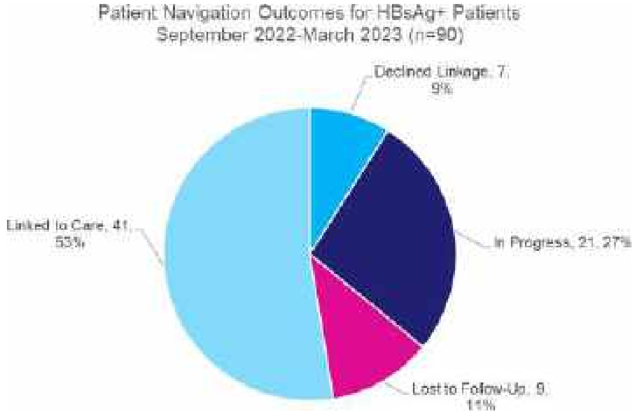
3767-C | RESULTS OF A UNIVERSAL HEPATITIS B SCREENING AND LINKAGE TO CARE PROGRAM IN A LARGE, URBAN HEALTH SYSTEM

Anna Mageras[1], Caroline Romano[1], Tasnim Bhuiyan[1], Francina R. Collado[1], Brooke Wyatt[2], Rebecca Roediger[1], Eric Woods[1] and Douglas T. Dieterich[3], (1) Icahn School of Medicine at Mount Sinai, (2)Icahn School of Medicine at Mount Sinai (ISMMS), (3)Icahn School of Medicine at Mount Sinai, New York, NY

Background: In March 2023, the CDC updated its screening guidelines for hepatitis B virus (HBV) from risk-factor-based to universal one-time screening for adults. In anticipation of this change, in October 2022 we implemented universal one-time HBV screening for adults in our multi-center hospital system serving metro-NYC, where HBV prevalence is 2.9%. We describe modifications to the electronic medical record (EMR), changes in screening rates, and the cohort of patients identified as HBsAg+. **Methods:** We met with population health, ambulatory, EMR IT, and laboratory teams to build the EMR modification and provider education materials. The screening consists of three lab orders: HBsAg, anti-HBs, and anti-HBc (all with one click), in line with updated CDC guidance. To complement the EMR alert, we conducted outreach to PCPs and implemented navigation for patients who tested HBsAg+, with the goal of connecting them to care. HBsAg+ cohort demographics were summarized descriptively and compared using chi square tests across patients already versus not yet receiving care. **Results:** Since implementation of the EMR alert, the average HBV screening rate has increased from 4% at baseline in September 2022 to 23% in March 2023 across our pilot clinics that received education (n = 3) and from 3% to 15% in clinics that did not (n = 2). From September 2022 to March 2023, we identified 231 HBsAg+ patients who were screened or had an encounter at one of our pilot clinics. Of these, 24 (10%) were screened for the first time during this period, and 207 (90%) had a previous HBsAg+ test on record. Of these patients, 90 (39%) were not engaged in HBV care. Among these, 54% attended at least one liver appointment by May 19, 2023, largely due to patient navigation; 27% were still being engaged by our navigators; and 19% declined care or were lost to follow-up. The HBsAg+ cohort was 50% male; 73% < 65 years old; 22% born in a country with ≥ 2% HBV prevalence; 35% Black, 28% Asian, 12% Latino, 10% White, and 15% unknown race. There were no statistically significant differences across these demographics when comparing patients already in care to those not yet linked. **Conclusion:** Many patients with HBV are undiagnosed or diagnosed but not receiving liver care. Policy changes, automatic prompts in the EMR, and outreach to providers can promote universal HBV screening and diagnosis. Preliminary results indicate that provider engagement and patient navigation enhance the positive effect of EMR alerts on screening rates and linkage to care for patients with chronic HBV. Future directions include investigating barriers to care.



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f 3768-C | SHORT-TERM VARIATION IN TRANSIENT ELASTOGRAPHY MEASUREMENTS WHEN USED AS A POPULATION SCREENING TOOL

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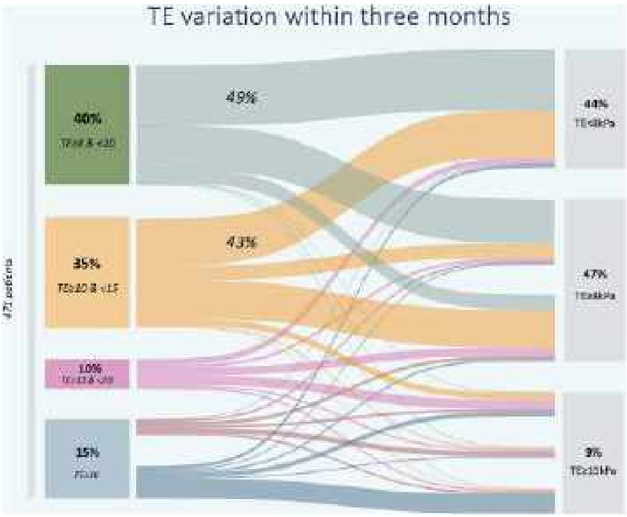
Background: Chronic liver disease is a leading global cause of death and disability. To improve prognosis, several recent studies focus on population screening for liver fibrosis to enable early detection and timely intervention to halt disease progression. Liver stiffness by transient elastography (TE) above 8 kPa is considered the reference screening cut-off value. Yet, the variability of TE is unknown when used in low-prevalence populations. We, therefore, aimed to investigate short-term variation in TE measurements in a screening setting. **Methods:** We included screening positive participants from two screening cohorts: The European LiverScreen project which screens for fibrosis using TE in a general population aged 40 or above, and the Danish DECIDE project which screens an at-risk population with excessive use of alcohol, obesity or type 2 diabetes, aged 30-75. All those screening positive (TE ≥ 8 kPa) were offered a second visit with a repeated TE within three months. We tested absolute and relative changes in TE from the first to second visit, and intervals of TE 8, 10, 15, 20, and 25 kPa. Finally, we explored potential causes for short-term variation including time between measurements, transaminases, BMI, probe size, and lifestyle changes. **Results:** We included 294 subjects from the general population and 177 subjects at-risk (median age 60 y (IQR 53-66), 67% male, 88% Caucasian, 62%, BMI ≥ 30 kg/m^2). The median TE was 10.7 kPa (IQR 9.1-15.2) at screening and 8.9 kPa (IQR 6.5-12.9) at the second visit after an average of 32 days. At screening, 186 (40%) had a TE 8-9.9 kPa, 166 (35%) had a TE 10-14.9 kPa, 46 (10%) had a TE 15-19.9 kPa and 73 (15%) had a TE ≥ 20 kPa. At the second visit, 44% dropped below 8 kPa with 43% dropping from TE ≥ 10 kPa at screening (figure). Almost half (46%) of the study population dropped more than 20% in TE measurements between the first and second visits. In a multivariable regression analysis, delta-TE did not correlate with age, gender, ALT/AST ratio, high BMI or probe size. **Conclusion:**

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

Elevated transient elastography is prone to significant variation in populations where fibrosis prevalence is low. Lifestyle changes between the first and second visit may have an influence on the observed changes. Yet although known predictors can explain a small degree of short-term TE variance, regression towards the mean plays an important role in the selection of screening positives. High liver stiffness should be confirmed with a second measurement when used as a screening tool.



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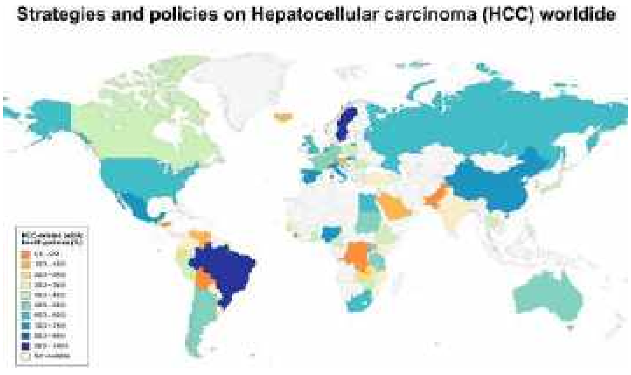
3769-C | SUB-OPTIMAL GLOBAL PUBLIC HEALTH POLICIES AND STRATEGIES TO TACKLE HEPATOCELLULAR CARCINOMA

Luis Antonio Diaz[1], Eduardo Fuentes-López[1], Blanca Norero[2], Oscar Corsi[1], Gustavo Ayares[1], Francisco Javier Idalsoaga[1], Javier Uribe[1], Sergio García[1], Valeria Vázquez[3], Lucas Lacalle[1], Katherine Maldonado[4], Gonzalo Pizarro[5], Jorge Arnold[6], Mariana Lazo[7], Catterina Ferreccio[8], Manuel Mendizabal[9], Federico Piñero[9], Juan Ignacio Marin[10], Ifeorah Ijeoma[11], Anand V. Kulkarni[12], Thomas G. Cotter[13], Salvatore Piano[14], Alexandre Louvet[15], Mayur Brahmania[16], Vincent Wai-Sun Wong[17], Winston Dunn[18], Helena Cortez-Pinto[19], Patrick S. Kamath[20], Ashwani K. Singal[21], Jose D. Debes[22], Maria Reig[23], Rohit Loomba[24], Ramon Bataller[25], Jeffrey V. Lazarus[26], Marco Arrese[1], Juan Pablo Arab[27] and On behalf of the Observatorio Multicéntrico de Enfermedades Gastrointestinales (OMEGA) collaborators, (1)Pontificia Universidad Católica De Chile, (2)Hospital Sotero Del Río, (3) Instituto Tecnológico De Monterrey, (4)Hospital Roosevelt, (5)Centro De Estudios Clínicos Bradford Hillcentro De Estudios Clínicos Bradford Hill, (6) Pontificia Universidad Catolica, (7)Drexel University School of Public Health, (8)Advance Center for Chronic Diseases, Accdis, (9)Hospital Universitario Austral, (10) Hospital Pablo Tobón Uribe, (11)University of Nigeria, (12)Aig Hospitals, Hyderabad, India, (13)University of Texas Southwestern Medical Center, Dallas, TX, (14) Unit of Internal Medicine and Hepatology, Department of Medicine, University of Padova, Padova, Italy, (15) CHU De Lille, (16)University of Calgary, (17)The Chinese University of Hong Kong, (18)University of Kansas Medical Center, Kansas City, KS, (19) Universidade De Lisboa, (20)Mayo Clinic, Rochester, MN, (21)Department of Medicine, University of South Dakota Sanford School of Medicine, Vermillion, SD, USA, (22)University of Minnesota, (23)Hospital Clinic Barcelona, (24)University of California, San Diego, San Diego, CA, (25)Barcelona Clinic, Barcelona, Spain, (26) Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Barcelona, Spain, (27)University of Western Ontario, London, ON, Canada

Background: Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide. The aims of the study were to explore HCC-related population-wide public health policies (PHP) in terms of prevention, treatment availability, epidemiological surveillance, and awareness campaigns worldwide. **Methods:** We conducted a 43-item survey about HCC: policies and civil society (18 questions), clinical guidelines (5 questions), epidemiology (7 questions), and care management (13 questions). We invited 249 gastroenterologists, hepatologists, oncologists, surgeons, radiation therapists, and public health experts from 74 countries/territories. The survey was carried out using an electronic form between May 2022 and January 2023. Data were collected in a spreadsheet, revised by two independent reviewers, and verified with governmental institutions, regulatory agencies, scientific societies, and scientific publications. We classified policies into eight dimensions, including criteria for low, moderate, and strong PHP establishment. We estimated an index using multiple correspondence analysis. **Results:** We obtained 134 responses from 66 countries/territories (Africa N = 16, the Americas N = 18, Asia N = 10, Europe N = 21, and Oceania N = 1). The median index was 43.7 [IQR: 30.9–59.3]. The lower scores were observed in Sierra Leone (0), Lebanon (5.5), and Pakistan (5.5), while Italy (79.7), Brazil (94.1), and Sweden (100) obtained the highest scores (Figure). In particular, 46 (69.7%) countries had a written national cancer strategy or action plan, but only 5 (7.6%) had a specific written national strategy or action plan on HCC. Thirty-two (48.5%) countries had national clinical practice guidelines on HCC and 54 (81.8%) countries had a national disease registry that included HCC. The most common strategies for staging of HCC were Barcelona Clinic Liver Cancer (BCLC) (85%) and TNM classification (10%). The survey reflects important differences in the availability of treatments, including surgery (98.4%), tyrosine kinase inhibitors (95.1%), chemoembolization (85.2%), radiofrequency or alcohol ablation (82%), immunotherapy plus anti-VEGF (82%), liver transplant (74.2%), stereotactic body radiation therapy (42.6%), and radioembolization (36.4%). **Conclusion:** Existence of PHP on HCC is insufficient worldwide. The most common strategy for staging is BCLC, but there are important differences in treatment availability across countries, especially regarding curative therapies.


Strategies and policies on Hepatocellular carcinoma (HCC) worldide

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3770-C | THE EFFECT OF IMPLEMENTING GAMIFICATION IN HEPATOLOGY CURRICULUM FOR MEDICAL STUDENTS

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Background: Gamification, or the incorporation of game theory into curriculum, has been correlated with improved knowledge retention compared to standard didactics. Gamification appeals to current medical students given their technical savvy and desire for a diverse educational experience. Application of gamification to a hepatology curriculum has not yet been studied. Our study aims to determine the impact of gamified hepatology modules on medical student knowledge retention and exam performance. **Methods:** We created 3 web-based, gamified hepatology modules on liver anatomy, evaluation of jaundice, and elevated liver function tests (LFTS) with 15 question pre and post-tests. Differences in each module's pre and post test scores were compared using paired t-tests, with students serving as internal controls. We also compared medical school exam scores in students who did and did not complete the modules using independent 2 sample t-tests. Both total exam score (n = 120 items) and hepatology item specific exam scores (n = 11 items) were assessed. **Results:** In total 13% of students (n = 36) completed the modules and 87% of students (n = 240) did not use the modules. Module users scored 1.2 points higher on the total exam score and 2 points higher on hepatology exam score. However, there was no significant difference in total exam score between module users (M = 86%, SD = 8.67) and non-module users ((M = 84.8%, SD = 8.04); t(274) = [-0.85], p = 0.4). There was also no difference in hepatology score between module users (M = 88.1%, SD = 11.25) and non-module users (M = 86.1%, SD = 10.68; t(274) = [-1.02], p = 0.31, Table 1). Module completion yielded significant increases in pre to post test scores for the Jaundice (Mean Pre-test = 57% vs. Mean post-test = 69%, SD = 3.02; t(37) = [-3.42], p = 0.002) and Anatomy modules (Pre-test = 61% vs. post-test = 72%, SD = 2.57; t(50) = [-4.31], p = < 0.001), but score improvement was not significant in the LFT module (p = 0.06, Table 2). When evaluating a combined module score, module completion demonstrated significant improvement in pre vs post test scores (Pre-test = 59% vs. post-test = 68%, SD = 2.82; t(107) = [-5.09], p < 0.001). **Conclusion:** Compared to non-module users, module users had higher hepatology exam and total exam scores, yet this difference was not statistically significant. However, the lack of difference in exam scores may be due to a type 2 error, as module pre and post test scores were significantly improved overall and in all modules except the LFT module. Students who chose to participate in the modules may have a common characteristic that is inherently different than students who chose not to complete the modules. This study suggests that gamification may be beneficial in aiding hepatology knowledge recall. Larger sample studies and investigation of student characteristics are needed to further define the role of a gamified hepatology curriculum.

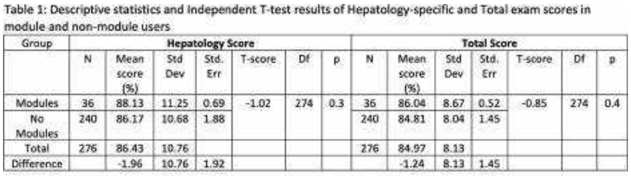

Table 1: Descriptive statistics and Independent T-test results of Hepatology-specific and Total exam scores in module and non-module users

Group	Hepatology Score							Total Score						
	N	Mean score (%)	Std Dev	Std. Err	T-score	Df	p	N	Mean score (%)	Std Dev	Std. Err	T-score	Df	p
Modules	36	88.13	11.25	0.69	-1.02	274	0.3	36	86.04	8.67	0.52	-0.85	274	0.4
No Modules	240	86.17	10.68	1.88				240	84.81	8.04	1.45			
Total	276	86.43	10.76					276	84.97	8.13				
Difference		-1.96	10.76	1.92					-1.24	8.13	1.45			

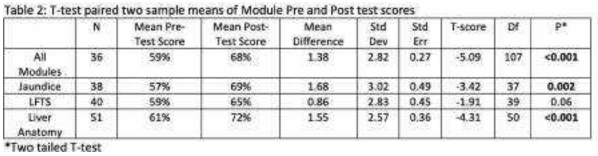

Table 2: T-test paired two sample means of Module Pre and Post test scores

	N	Mean Pre-Test Score	Mean Post-Test Score	Mean Difference	Std Dev	Std Err	T-score	Df	P*
All Modules	36	59%	68%	1.38	2.82	0.27	-5.09	107	**<0.001**
Jaundice	38	57%	69%	1.68	3.02	0.49	-3.42	37	**0.002**
LFTS	40	59%	65%	0.86	2.83	0.45	-1.91	39	0.06
Liver Anatomy	51	61%	72%	1.55	2.57	0.36	-4.31	50	**<0.001**

*Two tailed T-test

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

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3771-C | THE ENHANCED LIVER FIBROSIS TEST IMPROVES EARLY DIAGNOSIS OF ALCOHOL RELATED LIVER DISEASE IN COMMUNITY SETTINGS

Charlotte Turner[1], Alexander J. Hung[1,2], Freya Rhodes[2], Jennifer M. Ryan[2] and William M. Rosenberg[2,3], (1)University College London, (2)Royal Free Hospital, (3)University College London, United Kingdom

Background: Alcohol-related liver disease (ArLD) is a leading cause of cirrhosis and death, but affects a minority of people with alcohol use disorder (AUD). Early detection of ArLD allows specialists to intervene and alter disease trajectory, whilst those without ArLD may be best served by community alcohol services. We assessed the effectiveness of a primary care referral pathway using the enhanced liver fibrosis (ELF) test to stratify patients with AUD and facilitate specialist referral of those with ArLD. **Methods:** The ELF ArLD pathway was established in January 2020, and evaluated over the subsequent 3 years. Patients assessed using the pathway were compared to those referred to the Royal Free Hospital using standard care (SC). Laboratory ELF tests for AUD were used to identify patients assessed in primary care, and their outcomes determined from primary care and hospital electronic medical records. The clinical status of all patients assessed in specialist liver clinics was determined using a composite clinical judgement (examination, blood tests, elastography, imaging and biopsy if performed) from electronic records. An “appropriate” referral was deemed to constitute the presence of at least steatosis. **Results:** Using SC, 132 patients were referred, of which 98.5% (n = 130) were appropriate. At least advanced fibrosis was present in 68.9% (n = 91), 56.5% (n = 74) had cirrhosis, and 30.3% (n = 40) were decompensated at referral. On the ELF pathway, 30 patients (29.1%) with AUD avoided referral. Of the 69 patients referred using ELF, 89.9% (n = 62) were appropriate; 29% (n = 20) had advanced fibrosis and 10.1% (n = 7) were cirrhotic. Patients referred via SC were 91% more likely to be cirrhotic (OR = 0.088; CI = 0.038-0.201) and 82% more likely to have advanced fibrosis (OR = 0.184;CI = 0.097-0.348). **Conclusion:** The majority of patients referred using SC had established cirrhosis when first seen compared to 10% of ELF referrals, indicating that use of the pathway facilitated specialist intervention before liver damage was irreversible. Use of ELF avoided unnecessary specialist referral in 30% of cases. In patients with AUD, the ELF pathway may be used for early detection of ArLD to permit specialist intervention and avoid unnecessary referral of people with AUD without ArLD. The low uptake of the pathway has been attributed to poor dissemination of the pathway impacted by the COVID-19 pandemic, necessitating better implementation.

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3772-C | THE IMPACT OF COVID-19 OUTBREAK BETWEEN FEBRUARY AND JUNE 2022 ON MANAGEMENT OF CHB OUTPATIENTS IN SHANGHAI:A CROSS-SECTIONAL STUDY

Shaowen Jiang, Simin Guo and Qing Xie, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine

Background: An outbreak of coronavirus disease 2019 (COVID-19) caused by Omicron BA.2 variant occurred from February to June 2022 in Shanghai, China, which severely disrupted citizens' daily life and work. However, little is known about the impact of this COVID-19 outbreak on the management of outpatients with chronic hepatitis B(CHB). **Methods:** A structured questionnaire was designed to learn about the continuity of antiviral treatment and HCC surveillance during the pandemic. CHB outpatients in our hospital were invited to answer this questionnaire online via WeChat app or in a face-to-face interview from November to December 2022. **Results:** Totally 487 responders were included in our analysis, comprising 394 on NA (nucleos/tide analogs) monotherapy, 40 on IFN (interferon)+NA therapy, 5 on IFN monotherapy and 48 without any antiviral therapy. From February to June 2022, interruption of NA occurred in 13.4% (58/434) of responders on NA therapy, 31% of whom suffered from > 4 weeks of NA discontinuation. Internet hospital was the main source of accessing NA during the lockdown phase, accounting for 43.5% (189/434). Interruption of IFN occurred in 57.8% (26/45) of responders on IFN ± NA therapy, 57.6% of whom suffered from > 4 weeks of IFN discontinuation. Multivariate logistic regression analysis showed that interferon-containing treatment and age were independently associated with interruption of antiviral therapy during this special period (OR = 8.338, 95%CI: 4.170-16.672, $p < 0.001$; OR = 0.964, 95%CI: 0.939-0.989, $p = 0.005$). Movement restriction ranked first (63.0%, 307/487)in all reasons for delayed or unmet medical needs (accessing antivirals and outpatient review). 48.4% (236/487)of responders had an interval of > 6 months between two liver ultrasonic examinations, and COVID-19 pandemic was the top reason (34.7%, 82/236) for a delayed HCC surveillance. After the lockdown measure was lifted, 3.7% (18/487) of responders were found to develop HCC, 4.1% (20/487) had an abnormal liver function test, 5.1% (25/487) had a HBV-DNA rebound and 9.2% (45/487) have not performed any outpatient review so far. **Conclusion:** COVID-19 outbreak between February and June 2022 caused by Omicron BA.2 variant had a negative impact on management of CHB outpatients in Shanghai. Some measures should be taken to maintain the continuity of antiviral treatment and HCC surveillance in the future pandemic of COVID-19 and other diseases.

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3773-C | THE LIVER TRANSPLANT CASCADE OF CARE AMONG PATIENTS REFERRED FROM A SAFETY NET HOSPITAL

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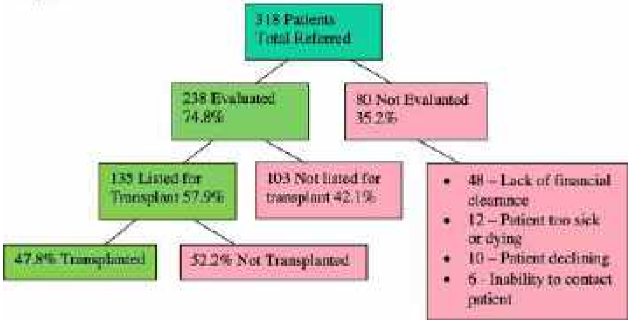
Background: Safety-net hospitals provide essential care to low-income adults in the United States (US), who have high burden of end-stage liver disease yet face significant barriers to accessing life-saving liver transplantation (LT). We aimed to describe the LT cascade of care in a large US safety-net system and determine predictors of completing an initial evaluation. **Methods:** This was a multi-site retrospective study of adult patients with end-stage liver disease who received outpatient hepatology care at LA General (LAG) Medical Center (2nd largest county hospital in the US) and were referred to USC or UCLA transplant centers for LT evaluation between 2016-2022. Primary outcome was completing a LT evaluation defined as an initial visit with a transplant hepatologist. Logistic regression was performed to determine clinical and sociodemographic predictors of outcome. Covariates with univariate $p < 0.1$ were included in multivariate models, with additional adjustment for age, race and ethnicity, and LT evaluation site. **Results:** Results: 318 patients were referred from LAG for LT evaluation. The mean age was 58 years; 64% were male, 81% Hispanic, 75% foreign born; 33% reported English as primary language, and 80% had Medicaid insurance. 55% had ETOH-assoc. cirrhosis, 17% had HCV, and 14% had NASH cirrhosis. The mean MELD-Na was 16. 80% had history of clinical decompensation. 238 (75%) were evaluated; 135 (58%) were listed, and 64 (48%) were transplanted (Figure 1). Of 80 patients not evaluated, most were due to lack of financial clearance followed by death (Figure 1). Per univariate analysis, patients completing evaluation were more likely to be married, have NASH vs. HCV, prior variceal hemorrhage or SBP; less likely to have unstable housing or shorter than 6-months sobriety. NASH cirrhosis (OR 5.60, 95% CI 1.47-21.34), over 6 months sobriety (OR 3.60, 95% CI 1.39-9.34) and unstable housing (OR 0.30, 95% CI 0.10-0.93) were significant predictors of completing LT evaluation. Patients who were evaluated had higher 1-year (84.4% vs. 67.0%) and 5-year (52.3% vs. 36.8%) survival ($p < 0.001$). **Conclusion:** One out of four safety-net patients referred for LT did not complete an initial evaluation, over half of which were due to financial clearance. Our data suggest optimizing insurance pathways in safety-net systems is critical to tackling referral drop-offs for LT and improving survival.

Figure 1



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3774-C | THE NUTRITION IN CIRRHOSIS GUIDE AND ITS POTENTIALLY BENEFICIAL IMPACT ON PATIENTS WITH CIRRHOSIS

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Background: Liver disease affects 1 in 4 Canadians. One of the most common complications of chronic liver disease is malnutrition, associated with decreased quality of life. Very few studies have focused on nutritional education resources for this population rendering their development and evaluation essential. The general objective is to assess the potential impact of the evidence-based *Nutrition in Cirrhosis Guide* on cirrhotic patients followed at the CHUM's liver outpatient clinic. The first specific objective is to quantitatively assess nutritional knowledge, quality of life and nutritional status. The second is to qualitatively assess the patients' satisfaction of the *Guide*. **Methods:** A randomized controlled study including 100 cirrhotic patients in 2 groups: Guide+ (n = 50) and Guide- (n = 50), is on-going. All patients are assessed for nutrition knowledge, quality of life and presence of malnutrition at baseline, 3 and 6 months. The *Guide* is taught to Guide+ patients for 6 months. Guide- patients do not use the *Guide*. The qualitative part evaluates patients' satisfaction of the *Guide* through 5 focus groups 3 patients) to assess general appreciation, complexity and applicability of the *Guide*. A patient-partner participates in focus groups. Preliminary **Results:** To date, 23 patients have completed the study: Guide+ (n = 12) and Guide- (n = 11). The preliminary results show a trend of improvement of nutrition knowledge for Guide+ patients (from 76.0% to 80.4%) after 3 months, not maintained at 6 months (down to 76.4%; $p > 0.05$). The Guide- patients' knowledge remains unchanged throughout the study. There is a trend of improvement in malnutrition in the group Guide+ (58.3% of patients initially malnourished, 41.7% at 3 months and 20.0% at 6 months; $p > 0.05$), which worsened in the group Guide- (from 36.4% to 54.5% at 3 months, to 45.5% at 6 months). Preliminary results from focus groups suggest an overall satisfaction towards the content, but a need to lighten and better divide the concepts. **Conclusion:** A trend of improvement is denoted in patients' nutritional knowledge over 3 months, not maintained at 6 months, and a decrease in the presence of malnutrition after 6 months. The results of this project will help optimize the quality of care for cirrhotic patients.

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3775-C | TRAVEL TIME TO LIVER TRANSPLANTATION CENTERS IN THE UNITED STATES

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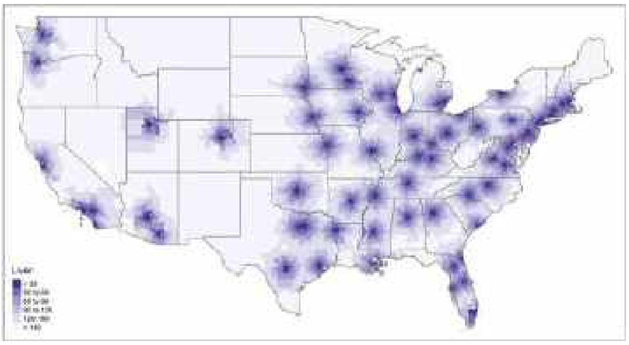
Background: Currently, over 11,000 patients are waiting to have a liver transplant (LT) in the United States. Despite recent emphasis on improving equity in access to LT, gender, racial, and socioeconomic disparities persist. One additional contributor to unequal access is geographic distance; increased distance from liver transplant centers (LTCs) is associated with lower transplant rates and increased mortality. However, travel time has emerged as a more accurate measure of geographic access. To our knowledge, this is the first study to examine geographic access to LTCs in the US using travel-time. **Methods:** Organ Procurement & Transplantation Network was queried for LTCs. Population and coordinates of every census block in the Continental US were extracted from the 2020 US census. Travel-times were computed using an Open-Source Routing Machine server built on Open Street Network data. For map representations, we computed population-weighted mean travel-times for each census tract. **Results:** In the US, 143 LTCs performed 9,236 total transplants in 2021. 55.4% of the US population lives within 60 minutes of the nearest LTC, and 67.3% and 76.8% live within 90 and 120 minutes, respectively. 23.2% (76.5 million people) live more than 2 hours away from the nearest LTC. (Figure 1) On a state level, Connecticut is the only state where over 90% of the population resides within 60 minutes of the nearest transplant center, and 6 additional states have more than 75% of the population living within 60 minutes. In nine states, more than 75% of the population lives beyond 120 minutes from the nearest center, including six where more than 75% of inhabitants lives further than 180 minutes. Of the ten most populous states, New York (69.0%) has the highest percentage of its population living within 60 minutes of the nearest LTC, while North Carolina (41.2%) has the lowest percentages. **Conclusion:** While proximity to LTC by travel time appears adequate on a national level, state-to-state variability is profound. Given the highly specialized and resource-heavy nature of liver transplantation, it is not feasible to reduce geographic disparities by establishing new LTCs. Alternative solutions must be explored; one possible solution is to expand telemedicine infrastructure, as access to virtual care has been demonstrated to reduce wait time between initial referral and formal evaluation. Additionally, it is crucial to strengthen partnerships between LTCs and local primary care specialist providers.

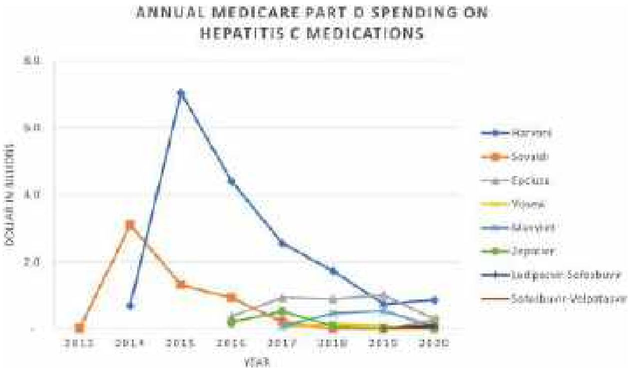


Disclosures: Arun Jesudian – Salix Pharmaceuticals: Speaking and Teaching, Yes, No; Salix Pharmaceuticals: Consultant, Yes, No;
Brett Fortune – W L Gore and Associates: Consultant, No, No;
The following people have nothing to disclose: Xiaohan Ying, Russell Rosenblatt
Disclosure information not available at the time of publication: Walter Mathis, Emily Smith, Peter Kahn

3776-C | TRENDS IN ORAL MEDICATIONS FOR HEPATITIS C IN MEDICARE POPULATION FROM 2013 TO 2020

Xiaohan Ying, Emily Smith, Rochelle Wong, Nicole Palmer, Russell Rosenblatt and Arun Jesudian, Weill Cornell Medicine, NY

Background: Chronic hepatitis C (CHC) is a major cause of liver-related morbidity and mortality globally, and there are an estimated 2.4 million people in the United States living with CHC. Since 2013, the FDA has approved numerous oral medications for CHC with curative intent. We aim to analyze Medicare Part D utilization and spending on oral antiviral medications for CHC. **Methods:** We used publicly available Medicare Part D data (2013-2020) to determine the number of beneficiaries who received these medications and the associated total annual spending. JoinPoint Regression was used for annual percent change (APC) and trends analysis. **Results:** Eight medications were included in our study: Solvaldi®, Harvoni®, Epclusa®, Zepatir®, Mavyret®, Vosevi®, generic ledipasvir-sofosbuvir, and generic sofosbuvir-velpatasvir. Between 2013 and 2020, total Medicare spending was \$29.8B; \$18B (60.4%) was spent on Harvoni®, followed by \$5.8B (19.6%) for Sovaldi®, and \$3.5B (11.8%) for Epclusa. Total Medicare spending increased significantly from 2013 to 2015 (APC 1868%, 95% CI: 1450% to 2399%, $p < 0.001$) followed by a steady decline after 2015 (APC -35.7%, 95% CI: -39.1% to -32.2%, $p < 0.001$). Figure 1. Within the same period, a total of 412,680 Medicare beneficiaries received these medications with similar observable trends over time (2013-2015: APC: 1059%, 95% CI: 709% to 1561%, $p < 0.001$; 2015-2020: APC -23.7%, 95% CI -29.6% to -17.3%, $p = 0.002$). Over the study period, Medicare spending was ~\$70,000 per person treated, with Sovaldi® costing ~\$90,000 per person and Harvoni® ~ \$83,000. In 2019, two generic medications were introduced (ledipasvir-sofosbuvir, sofosbuvir-velpatasvir) both costing ~\$22,000 per person. Medicare spending on Sovaldi® and Harvoni ® within the first two full years of their respective approval accounted for over 50% of total Medicare Part D spending on CHC medications during our 2013 – 2020 study period. **Conclusion:** The introduction of highly effective oral medications has revolutionized CHC treatment. It is estimated that approximately half of the CHC infected Medicare population was treated between 2013 and 2016. While a significant number of Medicare beneficiaries with CHC has been treated, reduced cost of treatment with the introduction of generic medications has the potential to expand access considerably.



Disclosures: Arun Jesudian – Salix Pharmaceuticals: Speaking and Teaching, Yes, No; Salix Pharmaceuticals: Consultant, Yes, No;
The following people have nothing to disclose: Xiaohan Ying, Russell Rosenblatt
Disclosure information not available at the time of publication: Emily Smith, Rochelle Wong, Nicole Palmer

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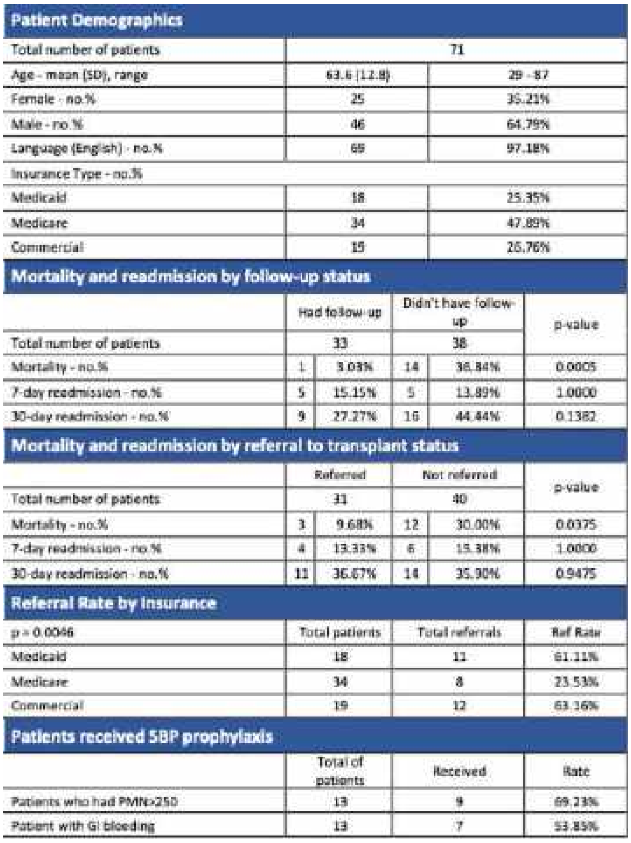
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

3777-C | UNLOCKING THE POWER OF LIVER TRANSPLANT REFERRALS: A JOURNEY THROUGH A PENNSYLVANIA COMMUNITY HOSPITAL

Adalberto Guzman[1], Evelyn Calderon Martinez[1], Wern Lynn Ng[1], Anas Atrash[1] and Douglas M. Levin[2], (1) UPMC, (2)Ohio State University, Columbus, OH, United States

Background: Cirrhosis accounts for about 34,000 deaths annually in the United States. Access to Liver transplantation (LT) has shown a profound improvement in the management of advanced liver disease. Liver transplant is indicated for severe acute or advance chronic liver diseases when the limits of medical therapy have been reached. About 95% of patients with end stage liver disease are not referred for transplant evaluation, even when the criteria are met. We present the results of the retrospective phase of a quality improvement project to increase liver transplant referral rates in our hospital. **Methods:** Using Epic's SlicerDicer function, patients admitted during November and December of 2022 with a diagnosis of cirrhosis of any type were identified using ICD-10 codes. Those with incomplete information or duplicated were excluded obtaining a total of 71 patients. We used chi-square test to analyze between group differences for mortality and readmission analysis. The Fisher exact test was employed when any of the expected frequencies was five or less. We used the Wilcoxon rank-sum test or Kruskal-Wallis test to analyze the differences in length of stay, as appropriate. A p value less than 0.05 was considered statistically significant. All the analyses were done by SAS 9.4 (SAS Institute, Cary NC). **Results:** From the 71 patients, 46 (64.7%) were male. More than 70% had either Medicare or Medicaid as primary insurance. The readmission rate at 7 days was 14% and at 30 days was 35.2%. In our population the mortality rate for 3 months was 21%. There was a statistically significant difference in mortality when comparing patients that were referred to a liver transplant center (independent from transplant status) vs those who were not referred ($p = 0.0375$). The mortality rate was higher in patients that had an outpatient follow-up (with either PCP or GI/hepatology specialist) in comparison with those who did not ($p = 0.0005$). **Conclusion:** The access to a liver transplantation referral, a close follow-up after discharge can make a significant difference in mortality in patients with end-stage liver disease. Multiple reasons have been identified for a lack of referrals. This project aims to create a medical health record order set for clinicians to refer potential liver transplant candidates based on the American Association of Liver diseases



Patient Demographics					
Total number of patients	71				
Age - mean (SD), range	63.6 (12.8)		29 - 87		
Female - no.%	25		35.21%		
Male - no.%	46		64.79%		
Language (English) - no.%	69		97.18%		
Insurance Type - no.%					
Medicaid	18		25.35%		
Medicare	34		47.89%		
Commercial	15		26.76%		
Mortality and readmission by follow-up status					
	Had follow-up		Didn't have follow-up		p-value
Total number of patients	33		38		
Mortality - no.%	1	3.03%	14	36.84%	0.0005
7-day readmission - no.%	5	15.15%	5	13.89%	1.0000
30-day readmission - no.%	9	27.27%	16	44.44%	0.1382
Mortality and readmission by referral to transplant status					
	Referred		Not referred		p-value
Total number of patients	31		40		
Mortality - no.%	3	9.68%	12	30.00%	0.0375
7-day readmission - no.%	4	13.33%	6	15.38%	1.0000
30-day readmission - no.%	11	36.67%	14	35.90%	0.9475
Referral Rate by Insurance					
p = 0.0046	Total patients		Total referrals		Ref Rate
Medicaid	18		11		61.11%
Medicare	34		8		23.53%
Commercial	19		12		63.16%
Patients received SBP prophylaxis					
	Total of patients		Received		Rate
Patients who had PMN>250	13		9		69.23%
Patient with GI bleeding	13		7		53.85%

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3778-C | "HAVING ANOTHER OUTLET TO DISCUSS THEIR DISEASE, THEIR WORRIES, THEIR FEARS…WITH SOMEBODY WHO ISN'T THEIR HEPATOLOGIST" PALLIATIVE CARE CLINICIANS' EXPERIENCE FROM THE PAL LIVER STUDY

Nicholas Hoppmann[1], Manisha Verma[2], Stephanie Ford[3], Margaret Armstrong[3], Macy Stockdill[4], Victor J. Navarro, Md[5] and Marie Bakitas[3], (1)Columbia VA Healthcare System, Columbia, SC, (2)Einstein Healthcare Network, (3)University of Alabama at Birmingham, (4)National Institute of Health, (5)Albert Einstein Medical Center, Doylestown, PA

Background: Palliative care (PC) is an integral part of managing patients with chronic illness and high symptom burden including end-stage liver disease

(ESLD). Given the limited PC workforce, as a part of the Pal-Liver comparative effectiveness trial, we compared ESLD patient outcomes between patients who received PC provided by PC-trained hepatologists vs. PC specialists (PCORI-NCT03540771). As part of a larger qualitative interview study of patients, caregivers and clinicians participants, we describe PC specialists' experiences caring for patients with ESLD and their caregivers as part of the Pal-Liver study. **Methods:** We conducted qualitative interviews with PC specialist participants within the 18-institution cluster-randomized comparative effectiveness trial of PC delivered by PC-trained hepatologists (10 sites) vs PC specialists (8 sites) to ESLD patients and caregivers. Trained interviewers used a semi-structured guide to interview hepatologists (n = 13) and PC specialist (n = 15) participants to explore pre- and post-study experiences, challenges, and benefits, in providing specialty PC for patients with ESLD. Phone interviews were digitally-recorded, transcribed verbatim, coded, and analyzed aided by NVIVO 12 software. We constructed a consensus-driven code book of emergent manifest and latent themes. Here we report preliminary analysis of PC specialist's perspectives. **Results:** PC specialist participants (n = 15) from the 8 PC specialist-provided institutions had a mean age of 49.8 years and were mostly female (93.3%) and white (86.6%). Main themes included: 1) patients and caregivers appreciated having a non-transplant clinician with whom to discuss their concerns 2) patients and caregivers lacked awareness of the role of PC 3) early PC referral and increased collaboration occurs with PC-minded hepatologists; 4) the study raised PC clinicians' awareness and desire for hepatology and transplant-specific education; 5) true primary PC integration in ESLD requires hepatologists' training as well as additional time for implementation during patient encounters. **Conclusion:** Pal-Liver PC clinician participants identified patient and caregiver's appreciation of communication with a non-transplant clinician, the need to clarify the role of PC, the value of hepatologists PC champions, but also recognized that primary PC training alone will not increase PC implementation until additional time is available during patient encounters. Future analysis will compare hepatology and PC specialist perspectives to inform pragmatic PC delivery models.

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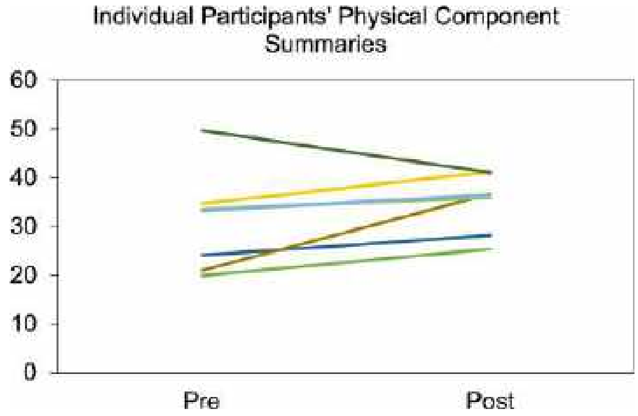
3779-C | A REMOTE INTERACTIVE EXERCISE PROGRAM FOR PATIENTS WITH CIRRHOSIS AND FRAILTY: THE FITNESS IMPROVEMENT WITH TELEHEALTH (FIT) PILOT EXPERIENCE

Eric S. Orman[1], Andrea Burkhardt[1], Kelsey Green[2], Archita Parikh Desai[1], Niharika R. Samala[3], Naga P. Chalasani[4] and Malaz Boustani[1], (1)Indiana University, (2)Indiana University School of Medicine, (3)Indiana University, Indianapolis, IN, (4)Indiana University Medical Center, Indianapolis, IN

Background: Individual's with cirrhosis are often physically frail and may benefit from exercise. However, in-person supervised programs may have limited reach, and home-based self-directed programs have been plagued by poor adherence. We developed a video telehealth-based exercise program for patients with cirrhosis and frailty to overcome obstacles limiting previous programs. **Methods:** Patients with cirrhosis seen in outpatient hepatology clinics at Indiana University were screened for frailty. Those with frailty (Liver Frailty Index [LFI] $\geq$ 4.5) were invited to participate in a 12-week interactive two-way video telehealth exercise program (Fitness Improvement with Telehealth [FIT]), consisting of 45-minute seated exercise sessions three times weekly. Pre- and post-program LFI, quality of life (SF-36), anxiety (GAD-7), depression (PHQ-9), and feedback (Net Promoter Score [NPS]) were compared. **Results:** 90 patients were screened, of whom 24 were frail. Eight participated, 6 completed all sessions, and 7 provided end-of-study measures. The median participant age was 60, 50% were female, and 63% were members of a racial or ethnic minority group. 75% were on Medicare and/or Medicaid, and none were employed (3 disabled). The median BMI was 36 kg/m^2, median Charlson comorbidity score was 5, 38% had impaired basic ADLs, and 63% had impaired instrumental ADLs. Comparing scores pre- and post-intervention, LFI did not change (pre 5.2 vs. post 5.1), and there were no significant differences in SF-36 scores: vitality (pre 17.5 vs. post 35, p = 0.62), physical function (27.5 vs. 50, p = 0.73), bodily pain (46 vs. 75, p = 0.13), general health (37.5 vs. 47, p = 0.80), physical role (75 vs. 75, p = 0.44), emotional role (100 vs. 100, p = 0.86), social role (68.8 vs. 76, p = 0.97), mental health (84 vs. 84, p = 0.13), physical component score (28.7 vs. 36.6, p = 0.18; Figure), and mental component score (56.3 vs. 55.6, p = 0.24). GAD-7 was also unchanged (pre 5 vs. post 2, p = 0.63), as was PHQ-9 (10 vs. 8, p = 0.80). On

the NPS, 4 rated FIT a “10,” and the overall NPS was 28.6. **Conclusion:** Patients with cirrhosis and frailty who participated in the FIT program had high completion rates and satisfaction with the program. However, initial participation rates were low. Future work is needed to identify ways to spur initiation of behavior change in those with cirrhosis and frailty. After initiation, the FIT program may be a scalable and sustainable way to maintain physical exercise in this population.



Disclosures: Eric S. Orman – Biovie: Advisor, No, No; Salix: Independent contractor (including contracted research), No, No;

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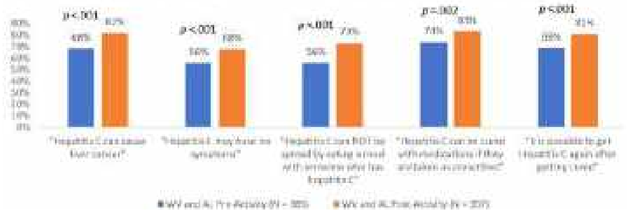
Disclosure information not available at the time of publication: Andrea Burkhardt, Kelsey Green, Archita Parikh Desai, Malaz Boustani

3780-C | ADDRESSING HEPATITIS C (HCV) MICRO-ELIMINATION GOALS: AN IMPLEMENTATION SCIENCE INITIATIVE IN PARTNERSHIP WITH STATE AND LOCAL HEALTH DEPARTMENTS

Ricardo A. Franco[1], Seema Gupta[2], Jeffrey Carter[3], Melissa Rodriguez[3], Laura Simone[3] and Leah Molloy[3], (1)University of Alabama at Birmingham, (2)Marshall University Joan C Edwards School of Medicine, (3) PRIME Education

Background: The elimination of Hepatitis C virus (HCV) infections is a national priority. State and local health departments play critical roles in HCV prevention and treatment, but setbacks in outreach activities related to the COVID-19 pandemic have restricted the availability and accessibility of these services. To support HCV micro-elimination goals, we partnered with state and county departments of health in two states - West Virginia (WV) and Alabama (AL) - to improve healthcare professional (HCP) and patient engagement in the HCV care cascade through education designed to identify and close local and regional gaps in HCV awareness, knowledge, screening, and linkage to care. **Methods:** Between September 2021 and December 2021, 6 live patient education programs were led by HCPs in community centers and clinics in West Virginia. Surveys were administered before and after each session. The initiative was scaled up to deliver three additional sessions in Alabama in April 2022. **Results:** Surveys were conducted amongst the 385 participating patients. 13% of the 71 patients in WV and 55% of the 314 patients in AL reported a past diagnosis of HCV. Patient knowledge about HCV and hepatocellular carcinoma, symptoms, cure, and reinfection improved after the sessions (Figure). Amongst the 61 participating HCPs (23 in WV and 38 in AL), confidence in counseling patients improved following the program. More providers felt confident in counseling patients on HCV test results (**p = 0.009**; 100% in WV; 78% in AL) and linking newly diagnosed patients (**p = 0.003**; 95% in WV; 89% in AL) than at baseline (76% in WV; 58% in AL and 76% in WV; 61% in AL, respectively). When asked what they thought would keep patients from starting or adhering to HCV treatment, HCPs identified inability to pay (37%) or patient perceptions that medications are not effective or necessary (21%), while patients reported fear of negative judgment (23%) and uncertainty of where to get medication (23%) as their top barriers. Following the programs, HCPs identified increasing patient awareness and access to HCV screening as their top goal to improve care (84% in WV and 78% in AL). **Conclusion:** Patient knowledge and attitudes about HCV varied, as did provider perceptions about patients’ barriers to care. Educational sessions can help to narrow knowledge gaps among patients and improve provider confidence in patient counseling, increasing the potential for changes in behavior related to HCV awareness and management.

Figure. Patient Knowledge about HCV Before and After the Educational Sessions: Percent of Patients that Selected the Correct Response to True/False Questions



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The following people have nothing to disclose: Leah Molloy

Disclosure information not available at the time of publication: Seema Gupta, Jeffrey Carter, Melissa Rodriguez, Laura Simone

3781-C | ADVANCED CARE PLANNING FOR PATIENTS WITH CIRRHOSIS, THE FIRST EXPERIENCE OF TERTIARY LIVER UNIT

Daniel Ján Havaj[1], Karolina Kristina Sulejova[1], Jana Vnencakova[1], Beáta Škvarková[1], Simona Zemanová[2], Svetlana Adamcova Selcanova[1] and Lubomir Skladaný[1], (1)University Hospital of F. D. Roosevelt, (2)No

Background: Cirrhosis is a leading cause of mortality and morbidity across the world. The clinical trajectory is unpredictable and the development of acute decompensation with complications is associated with a significant lowering of median survival in the absence of liver transplantation. These barriers impair the patient's ability to participate in decision-making, leading to invasive life-sustaining therapies during their end-of-life. Advanced care planning represents the process over the course of illness trajectory involving the assessment of goals, values, and preferences, designation of a surrogate decision-maker, and documentation of patient will. The aim of this pilot study is to evaluate the portrait of patient goals of care in our register of cirrhosis, including end-of-life. **Methods:** In the following period, we evaluated patient goals of care by the validated ACP questionnaire in all patients first time hospitalized in our liver unit and enrolled into the local register of cirrhosis. **Results:** The questionnaire was proposed to 268 patients between May 2022 and 2023, 237 patients (88%) were accepted to participate (140 men (59%), 97 women (41%), mean age 55,4 years, CHP 8,6, MELD-Na 19,3). 41% were admitted because of acute decompensation and nearly half of them (49%) because of ACLF. 19% were evaluated as candidates for liver transplantation. The mean quality of life was 8,1 (EQ-5D), the mean LFI was 4,1 and overall mortality was approximately 20% (28 d 12,7%, 90 d 17,8%, 365 d 20,76%). The majority of patients in case of acute deterioration prefer an active approach, only 7% don't want to be admitted and approximately 7% don't want to receive antibiotics and intravenous therapy. More than a quarter of patients disagree with artificial feeding via a tube through the nose (30%) or into the stomach (25%). 4% of patients don't want to be resuscitated. The majority of patients prefers to spend their last few days at home, and only 11% prefer hospital or hospice care. 98% of patients identified a surrogate decision maker, and 15% gave someone a power of attorney. 10% of patients were assigned a decision to refuse treatment. The majority of patients (97%) made the decision to formally share goals of care with healthcare providers. 70% of patients would like to discuss their wishes for future care in the end stage of their life. When we looked at the different attitudes on the questions about don't resuscitate, identification of a surrogate decision maker, and readiness for discussion about end-of-life, there was no difference in terms of age, sex, etiology, disease severity, quality of life, and frailty index. **Conclusion:** ACP is crucial for providing healthcare consistent with patient goals and values, especially at the end of life. This study described the first experiences with advanced care planning in our tertiary liver unit and reveals the patient's wishes for health care.

Disclosures: The following people have nothing to disclose: Daniel Ján Havaj, Karolina Kristina Sulejova, Jana Vnencakova, Beáta Škvarková, Simona Zemanová, Svetlana Adamcova Selcanova, Lubomir Skladaný

3782-C | ALCOHOLIC LIVER DISEASE AND NON-ALCOHOLIC FATTY LIVER DISEASE WERE THE MAIN DRIVERS OF CIRRHOSIS RELATED DEATHS BEFORE AND DURING THE COVID-19 PANDEMIC IN THE UNITED STATES

James M. Paik[1,2,3], Dipam Shah[4], Katherine Elizabeth Eberly[4], Pegah Golabi[1,2,3], Linda Henry[1,2,4] and Zobair M. Younossi[1,2,3], (1)Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, (2)Center for Liver Disease, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, VA, (3)Inova Medicine, Inova Health System, Falls Church, VA, (4)Inova Health Systems Medicine Service Line, Falls Church, VA

Background: Although liver mortality increased during the COVID-19 pandemic, the impact may differ according to the etiology of liver disease [hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease (ALD), and non-alcoholic liver disease (NAFLD). **Aim:** To assess changes in liver-specific deaths attributable to HBV, HCV, ALD, and NAFLD after the COVID-19 Pandemic start. **Methods:** We assessed liver-specific deaths in the U.S. using death data (2011-2021) obtained from National Vital Statistics System (NVSS). The average annual percentage change (AAPC) from the models selected by Joinpoint regression analysis over the pre-pandemic (2011-2019) and then from 2019-2021 were reported because non-linear trend in death rates were observed over the 2011-2021. Liver-specific death was defined as an underlying cause of death. **Results:** During the pre-pandemic, age-standardized hepatocellular carcinoma (HCC)- and cirrhosis-related death rates increased by AAPC = +1.18% (95% confidence interval, 0.34% to 2.03%) and AAPC = +1.95% (1.56% to 2.35%). In this context, during the 2019-2021, the AAPC in age-standardized cirrhosis-related death rate (per 100,000) accelerated: AAPC = +11.25% (15.23 in 2019 to 18.86 in 2021) whereas that in age-standardized HCC-related death rate slowed down to AAPC = -0.39% (-1.32% to 0.54%). According to the etiology of liver disease, during the 2019-2021, the age-standardized cirrhosis-related death rates from ALD and NAFLD increased by AAPC = +17.29% (12.21% to 20.38%) and AAPC = +8.21% (3.52% to 10.42%). In contrast, the age-standardized cirrhosis-related death rates from HCV and HBV decreased: AAPC = -3.07% [-4.83% to -1.53%]) and AAPC = -0.88% [-2.98% to 1.31%]).After pandemic start to 2021, ALD was responsible for 47.32% of the increase in cirrhosis-related deaths followed by NAFLD (40.85%), HCV (2.51%); and HBV (0.16%). Interestingly, a differential increase in ALD-cirrhosis deaths and NAFLD-cirrhosis deaths were observed according to age: ≥65 years (ALD 69.86% and NAFLD 53.32%), 45-64 years (29.35% ALD and 39.13% NAFLD), and 20-44 years (ALD 0.79% and NAFLD 7.55%). **Conclusion:** Increases in cirrhosis-related deaths were driven by ALD and NAFLD. ALD predominantly affected patients ≥65 years old while NAFLD affected the younger population.

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The following people have nothing to disclose: James M. Paik, Pegah Golabi, Linda Henry

Disclosure information not available at the time of publication: Dipam Shah, Katherine Elizabeth Eberly

3783-C | ASSOCIATION BETWEEN CIRRHOSIS AND SEVERE COVID-19 OUTCOMES: A POPULATION-BASED COHORT STUDY IN CANADA

Héctor Alexander Velásquez García[1,2], Prince Adu[2], Dahn Jeong[1], Jean Damascene Makuza[1,2], Georgine Cua[2], Mawuena Binka[1,2], James Wilton[2], Hind Sbihi[2] and Naveed Zafar Janjua[1,2,3], (1)University of British Columbia, (2)British Columbia Centre for Disease Control, (3)St. Paul's Hospital

Background: Population-level evidence for the association between cirrhosis and COVID-19 severe outcomes remains an important knowledge gap. We assessed the association between cirrhosis and COVID-19-related severe outcomes (hospitalization and intensive care unit [ICU] admission) among individual's who have tested positive for COVID-19. **Methods:** We used data from the British Columbia (BC) COVID-19 Cohort, a population-based surveillance platform that integrates data on all individual's tested for COVID-19, with data on hospitalizations, medical visits, emergency room visits, prescription drugs, chronic conditions, and deaths in the Canadian province of BC. We included all individual's aged 18 or above who tested positive for SARS-CoV-2 by real-time reverse transcription-polymerase chain reaction, from January 01 to December 31, 2021. Multivariable logistic regression models were used to assess the associations between cirrhosis status and COVID-19 related hospitalization and ICU admission, adjusting for age, sex, variant of concern, comorbidities, area-level income, geographic area, and vaccination status. Cirrhosis was identified with a validated algorithm using relevant ICD-9/10 codes. Hospitalization was defined as admission to a BC acute care facility within 14 days after a positive SARS-CoV-2 test, and ICU was defined as admittance to ICU during hospitalization. **Results:** This analysis included 162,509 individual's of whom 768 (0.5%) had cirrhosis. Compared to individual's without cirrhosis, those with cirrhosis had a higher rate of ICU (12.8% v. 1.5%) and hospital (17.2% v. 3.6%) admission. In the adjusted models, cirrhosis was associated with increased odds of hospitalization (excluding ICU cases, aOR = 1.97, 95%CI: 1.58–2.47; including ICU cases, aOR = 2.55, 95%CI: 2.11–3.08) and ICU admission (aOR = 3.33, 95%CI: 2.56–4.35). Cirrhosis was also associated with increased odds of ICU admission among individual's who were already hospitalized (aOR = 1.84, 95%CI: 1.38–2.46). Stratified analyses by age showed increased odds of hospitalization and ICU among people with cirrhosis across all age-groups (18-49, 50-69 and ≥70 y). **Conclusion:** Cirrhosis is associated with greater odds of hospitalization and ICU admission among COVID-19 patients. These findings emphasize the importance of timely monitoring, prioritization of COVID-19 vaccination, and early treatment for people living with cirrhosis to prevent and mitigate severe COVID-19 outcomes.

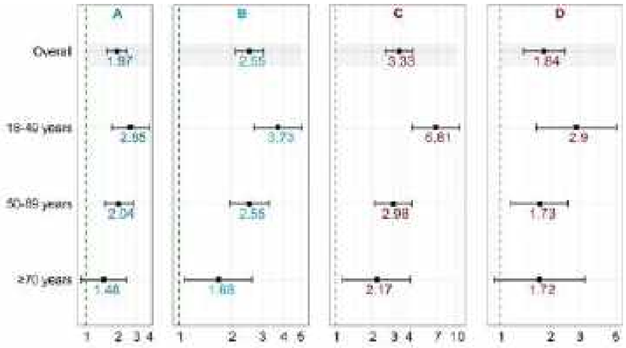


Figure 1. Cirrhosis overall and age-stratified adjusted odds ratios for COVID-19-related hospitalization and ICU admission.

A: Outcome hospitalization: Hospitalization (excludes ICU admissions) vs. non-hospitalization.
B: Outcome hospitalization: Hospitalization (includes ICU admissions) vs. non-hospitalization.
C: Outcome ICU: ICU admissions vs. non-hospitalization.
D: Outcome ICU: ICU admissions vs. hospitalization.

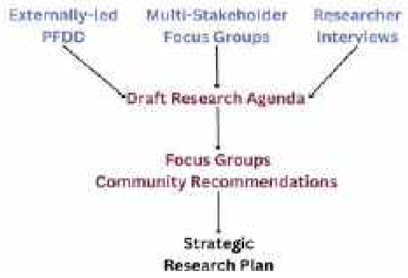
Disclosures: The following people have nothing to disclose: Héctor Alexander Velásquez García, Prince Adu, Dahn Jeong, Jean Damascene Makuza, Georgine Cua, Mawuena Binka, James Wilton, Hind Sbihi, Naveed Zafar Janjua

3784-C | CENTERING THE PATIENT VOICE IN MULTI-STAKEHOLDER ENGAGEMENT TO DEVELOP A STRATEGIC RESEARCH PLAN FOR THE PSC COMMUNITY

Jessie D. Kirkpatrick[1,2], Mahesh Krishna[1,3], Sarah Curup Callif[1], Mary Pressley Vyas[4], Rachel Gomel[1], Matthew McMurtry[1], Willie McKinney[1], Christopher L. Bowlus[5], Daniel S. Pratt[6], Joshua R. Korzenik[7], Ricky Safer[1], Joanne Hatchett[1], Stephen J Rossi[1] and Ruth-Anne Pai[1], (1)PSC Partners Seeking a Cure, (2) Massachusetts Institute of Technology, (3)Johns Hopkins Medical School, (4)PSC Partners Seeking a Cure Canada, (5)University of California Davis, Sacramento, CA, (6)Massachusetts General Hospital, (7)Brigham and Women's Hospital

Background: Primary sclerosing cholangitis (PSC) is a rare, progressive immune-mediated liver disease with no Food Drug and Administration (FDA) approved treatments available. Drug development is limited due to poor understanding of the pathophysiology of PSC, with no surrogate endpoints or validated patient-reported outcomes. PSC Partners Seeking a Cure aimed to generate an organizational research plan with patient and researcher input to better understand and address these gaps. **Methods:** Our interdisciplinary team of PSC Partners representatives and clinical researchers led a two-year process to develop a strategic research plan (SRP) with 4 stages: 1) Organization of an externally-led patient-focused drug development (EL-PFDD) meeting with the FDA. 2) A series of focus groups to discuss symptoms, patient-reported outcomes, research, natural history, and drug development. 3) Review of the scientific literature and interviews with 9 PSC researchers to capture gaps in understanding of PSC. The first three steps informed the development of the draft research agenda. 4) Discussion of the draft research agenda within focus groups at the PSC Partners Annual Conference in 2022. Participants provided research recommendations which were analyzed by our interdisciplinary team and scored using a standardized rubric. Both qualitative and quantitative data guided generation of the SRP. **Results:** These efforts incorporated the voices of more than 500 unique PSC patients and caregivers. More than 100 patients and caregivers participated in 15 focus groups and contributed 65 community recommendations across 6 diverse topics for future research directions. PSC researchers contributed 59 recommendations for future research directions, 22 of which (37%) aligned with the 65 community recommendations. Assessment of multi-stakeholder recommendations formed 4 pillars of focus for PSC Partners and the structure of the SRP: 1) Improve understanding of the mechanisms contributing to the development and progression of PSC, 2) Further understanding of the gut-liver connection in PSC, 3) Develop safe and effective treatments to slow progression and reduce symptom burden for those with PSC, and 4) Provide support and education through patient engagement and knowledge translation. **Conclusion:** This initial round of prioritization resulted in PSC Partners' efforts to develop surrogate endpoints and patient-reported outcome measures for clinical trials. Future support and new partnerships will further work across the 4 pillars as PSC Partners plays an active role in research and drug development to find a cure for PSC.

Figure 1: Novel approach to generating a strategic research plan consolidating researcher and patient priorities led by PSC Partners Seeking a Cure.



Disclosures: Christopher L. Bowlus – Cymabay: Advisor, No, Yes; GSK: Advisor, No, Yes; Invea: Advisor, No, Yes; Ipsen: Advisor, No, No; Boston Scientific: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Calliditas: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; ChemoMab: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; COUR Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Cymabay: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GSK: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Hanmi: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Ipsen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Mirum: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Novo Nordisk: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Viking: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; BMS: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;

Joshua R. Korzenik – Thetis: Consultant, No, No; ClostraBio: Consultant, No, No; Corevitas: Consultant, No, No; Promakhos: Consultant, No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; ColonaryConcepts: Executive role , No, No; Bilayer Therapeutics: Executive role , No, No;

Stephen J. Rossi – PSC Partners Seeking a Cure: Consultant, No, No;

The following people have nothing to disclose: Jessie D. Kirkpatrick, Mahesh Krishna, Sarah Curup Callif, Mary Pressley Vyas, Rachel Gomel, Matthew McMurtry, Willie McKinney, Daniel S. Pratt, Ricky Safer, Joanne Hatchett, Ruth-Anne Pai

3785-C | CIRRHOSIS INCIDENCE AMONG YOUNG ADULTS (18-44) AND IN FEMALES - A POPULATION-BASED STUDY FROM 2010 TO 2019

Nabiha Faisal[1], Lisa Lix[1], Randy Walld[1], Alexander Singer[1], Eberhard Ludwig Renner[1], Harminder Singh[1], Leanne Kosowan[1] and Alyson Mahar[2], (1)University of Manitoba, (2)Queen's University

Background: The past decade has witnessed significant changes in the risk factors associated with cirrhosis that underscore the importance of ongoing efforts to prevent and manage this critical and potentially life-threatening condition. To facilitate the development of these strategies, our study aimed to investigate the temporal trends of cirrhosis incidence in Manitoba, Canada, as well as assess changes in these estimates across different age groups and between males and females. **Methods:** Individual level administrative healthcare data from Manitoba was used to identify individual's with cirrhosis between 2010-2019 using a validation algorithm (≥ 1 hospitalization or ≥ 1 physician claims; sensitivity, specificity, positive and negative predictive values include 68%,98%,19% and 99% respectively). To establish incident cases, we used a five-year look back window. Annual incidence rates were estimated using a generalized linear model and generalized estimating equations with a negative binomial distribution adjusting for age and sex. Linear trends of incidence by calendar year, overall and by age and sex, were tested using linear regression models. **Results:** Between 2010-2019, a total of 24,303 incident cases of cirrhosis were identified. Mean age at diagnosis was 50 years SD 15.8 and 51% were males. Age and sex adjusted incidence increased by 50% between 2010-2019 (264 vs 389/100,000). Incidence increased by 2-fold over the study period for aged 18-44 (144 vs 289/100,000) more among females than males (Figure 1). Cirrhosis incidence increased on average per year by 6% (95% confidence interval (CI) 5% to 7%, ($p<0.001$), with the largest increase of 8% per year (95% CI 7% to 9%) $p<0.0001$ in those aged 18-44 years. The youngest age group (ages 18-44 y) also exhibited the highest rate of increase in the incidence of cirrhosis compared to other age groups ($P<0.001$). The incidence of cirrhosis showed a greater annual increase in females, with a rate of 7% per year (95% CI 5% to 8%), compared to males, who had a rate of 5% per year (95% CI 4% to 6%) ($p<0.0001$). In addition, females demonstrated a significantly higher rate of change in cirrhosis incidence compared to males ($p=0.0025$).

Conclusion: The incidence of cirrhosis substantially increased over the study period, signaling an alarming shift in the disease burden towards younger individual's and females. Public health action is required to implement an effective multi-faceted approach encompassing prevention, early detection, and the provision of high-quality healthcare.

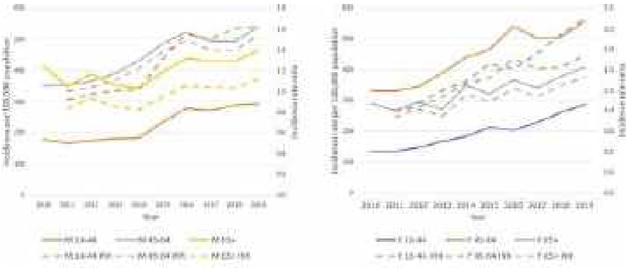


Figure 1. Trends of incidence rate and incidence rate ratio (IRR) by age group and sex

Disclosures: The following people have nothing to disclose: Nabiha Faisal, Randy Walld, Leanne Kosowan

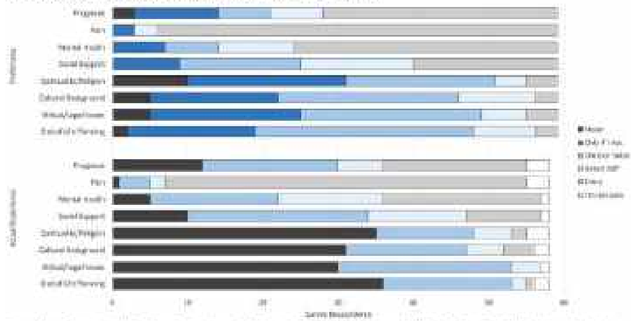
Disclosure information not available at the time of publication: Lisa Lix, Alexander Singer, Eberhard Ludwig Renner, Harminder Singh, Alyson Mahar

f 3786-C | CIRRHOSIS PATIENT PERSPECTIVES ON PALLIATIVE CARE: A SURVEY PROJECT

Alan Noll[1], Rachel Hannum[1], Shalini Sivathasan[2], Nneka Ufere[3], Jennifer C. Lai[4] and Shari S. Rogal[2,5], (1) University of Pittsburgh Medical Center, (2)University of Pittsburgh, (3)Massachusetts General Hospital, (4) University of California, San Francisco, (5)VA Pittsburgh Healthcare System

Background: Despite a high physical and psychological symptom burden, patients with cirrhosis underutilize specialty palliative care (PC) services. When used, PC is often introduced late in the disease course, limiting potential benefit. While there has been an increasing call for earlier integration of PC into cirrhosis care, patients' preferences and needs have not been fully explored. We therefore aimed to understand the physical and psychological symptom burden, PC needs, and preference for PC among an outpatient cohort of patients with cirrhosis. **Methods:** From November 2022 to April 2023, patients with cirrhosis at a tertiary care center were recruited to complete a one-time survey. Survey items included: the Edmonton Symptom Assessment Scale (ESAS), questions about how often the 8 domains of PC (see Fig. 1) are addressed in hepatology clinic, and their preferences for PC. **Results:** N = 59 patients responded to survey questions ($M_{age} = 57 \pm 12$ y, 42% women, $M_{MELD} = 11 \pm 5$). Over half (61%) had decompensated cirrhosis, 5% had hepatocellular carcinoma, and none had previously seen PC. Top etiologies of liver disease were: Alcohol = 36%, NASH = 32%, hepatitis C = 8% and primary biliary cholangitis = 8%. Patients with decompensated cirrhosis reported more severe pain, lack of appetite, difficulty falling asleep, itchiness, leg swelling and overall symptoms ($ps < 0.05$). Patients universally wanted hepatology providers to ask about each of the 8 domains of PC at least once (Fig. 1). Prognosis and mental health were addressed significantly *less* than respondents preferred ($p < 0.05$). While most patients wanted hepatology providers to address the various domains of their PC needs, only 19% of respondents wanted to see specialists in PC; 35% reported that the most appropriate time to refer to PC was only once they were too sick to care for themselves. Older age was significantly associated with desire for PC ($p < 0.01$) among those with compensated cirrhosis, while female sex ($p = 0.007$) and higher symptom burden ($p < 0.01$) were significantly associated with desire for PC among patients with decompensated cirrhosis ($p = 0.01$). **Conclusion:** Almost all patients with cirrhosis wanted their hepatology providers to address the various domains of PC. While relatively few wanted to see PC specialists, those who did were more likely to be women, older, and those with higher symptom burdens.

Figure 1. Frequency of PC Domains* being addressed in clinic: Preferred versus Actual Experience



Note. *As per the National Coalition for Hospice and Palliative Care's *Clinical Practice Guidelines for Quality Palliative Care 4th edition*

Disclosures: Jennifer C. Lai – Novo Nordisk: Advisor, No, No; Genfit: Consultant, No, No; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Vir: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gore: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Flagship Pioneering: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's

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

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The following people have nothing to disclose: Alan Noll, Rachel Hannum, Shalini Sivathasan, Nneka Ufere, Shari S. Rogal

3787-C | COINCIDENT LIVER DISEASE INCREASED THE RATE OF ICU CARE, ENDOTRACHEAL INTUBATION AND IN-HOSPITAL DEATH IN PATIENTS HOSPITALIZED WITH COVID-19

Jessica Ann Musto[1], *Thomas M. Piasecki*[1], *Wendy S Slutske*[1] *and Michael R. Lucey*[2], *(1)University of Wisconsin, (2)University of Wisconsin School of Medicine and Public Health, Madison, WI*

Background: The interaction of liver disease with COVID-19 infection has not been well elucidated. This study employed a national multi-center prospective database of patients with COVID-19 to compare mortality rates in hospitalized COVID-19 patients with and without liver disease. **Methods:** Data from all patients with COVID-19 who were hospitalized at 21 participating healthcare systems between February 1, 2020 and January 31, 2022 were recorded. Subjects were followed until hospital discharge or death. The main outcome of interest was in-hospital mortality. Secondary outcomes of interest were endotracheal intubation and ICU admission. The analyses used generalized linear mixed model logistic regression including random intercepts to account for the clustering of patients within healthcare systems. **Results:** Among 145,940 patients hospitalized for COVID-19, 48.9% male, ages 18-90+ years-old with median age 63 years-old, 7,217 (4.9%) had some form of liver disease. The presence of liver disease was associated with increased odds of all tested adverse outcomes in patients hospitalized with COVID-19. Of those patients with liver disease, 1,519 (21%) died while hospitalized with COVID-19 compared to 11,517 (8.3%) without liver disease (aOR 3.58, 95% CI 3.35, 3.82, $p < 0.001$). The presence of liver disease was also associated with increased odds of endotracheal intubation (aOR 3.03, 95% CI 2.87, 3.21, $p < 0.001$) and ICU admission (aOR 2.30, 95% CI 2.18, 2.42, $p < 0.001$). There was a clear gradient of mortality according to severity of liver disease (fibrosis OR < cirrhosis OR < decompensated cirrhosis OR) and each category of liver disease was associated with adverse outcomes compared to no liver disease. On multivariable analysis, liver disease, male gender, increasing age, higher BMI and former smoking status were all associated with increased mortality from COVID-19. **Conclusion:** In this large, observational cohort of hospitalized patients with COVID-19, mortality in patients with liver disease was triple that seen in patients without liver disease, and the rate of severe complications such as transfer to the ICU and endotracheal intubation were significantly more common in liver patients.

Disclosures: Michael R. Lucey – target. Pharmasolutions: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Novartis: Advisor, No, Yes;
The following people have nothing to disclose: Jessica Ann Musto
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3788-C | COMPREHENSIVE CARE OF PATIENTS WITH CIRRHOSIS DECREASES LIVER DECOMPENSATION AND NEED FOR LIVER TRANSPLANTATION

Tarek I. Hassanein[1], *Julian Diaz-Moreno*[2], *Noora Alqassim*[2], *Ahmed Atalla*[2], *Abdul Rahman Khan*[2], *Fatma Barakat*[2], *Anna Marie Hefner*[2] *and Deanna Oliver*[1], *(1)Gateway Comprehensive Medical Group, APC, (2)Southern California Liver Centers*

Background: Chronic liver injury results in progressive fibrosis and ends in cirrhosis with decompensation and/or HCC. The primary goal in caring for patients with cirrhosis is to eliminate the primary liver injury and control other co-morbidities to prevent liver decompensation. In 2010, our Center deployed a systematic program of care for patients with cirrhosis. **Methods:** Between January 2010 and December 2022, 5352 patients (pts) with cirrhosis were seen. Primary liver disease, co-morbidities, medications, vital signs, outpatient visits, hospital admission, disposition, laboratory and imaging results amongst other variables were retrieved for all the patients. **Results:** The initial analysis included 750 consecutive cirrhotic patients and shows the following: 398 (53.1%) females. Mean age was 65.8 ± 10.6 years. 63% Hispanics and 89% whites. Visits: Median follow-up: 67 (1-156) months. Median number of outpatient visits at Hepatology practice is 21.5 visits (1-201) Underlying etiology of liver disease was primarily history of HCV (60%), Alcoholic liver disease (30%), and NASH (25%). Classification: Refer to table for Child Pugh classification and MELD changes from initial visit to last visit. Platelets count: 75% had platelets count < 150 at the initial visit versus 68% at their last visit. Disposition: 71.6% alive. 17% received a liver transplant. **Conclusion:** Eliminating primary liver injury, supported by managing co-morbidities in a closed intense care program results in 1) minimizing liver decompensation, 2) prolonging survival, 3) decreases rates of hospitalization, 4) decreases need for liver transplantation and ultimately decreases cost of cirrhosis care. Further analysis of the data is underway.

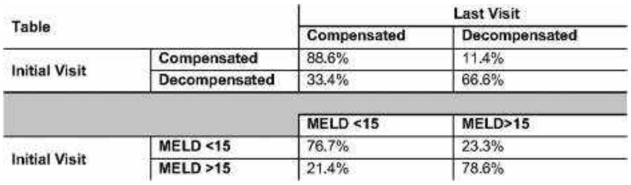

Table		Last Visit	
		Compensated	Decompensated
Initial Visit	Compensated	88.6%	11.4%
	Decompensated	33.4%	66.6%
		MELD <15	MELD>15
Initial Visit	MELD <15	76.7%	23.3%
	MELD >15	21.4%	78.6%

Disclosures: Tarek I. Hassanein – AbbVie: Advisor, No, No; Bristol-Myers Squibb: Advisor, No, No; Gilead: Advisor, No, No; Mallinckrodt: Advisor, No, No; Merck: Advisor, No, No; Orgonovo: Advisor, No, No; AbbVie: Speaking and Teaching, No, No; Bristol-Myers Squibb: Speaking and Teaching, No, No; Gilead: Speaking and Teaching, No, No; AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Allergan: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Amgen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; 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The following people have nothing to disclose: Julian Diaz-Moreno, Noora Alqassim, Ahmed Atalla, Abdul Rahman Khan, Fatma Barakat, Anna Marie Hefner, Deanna Oliver

f 3789-C | CROSS-SECTIONAL AND LONGITUDINAL ASSESSMENT OF THE EDMONTON SYMPTOM ASSESSMENT SYSTEM IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

John Donlan[1], Chengbo Zeng[2], Teresa Indriolo[3], Lucinda Li[3], Joyce Zhou[3], Kedie Pintro[3], Nora Horick[3], Maria Edelen[2], Areej El-Jawahri[3] and Nneka Ufere[4], (1) Harvard Medical School, (2)Brigham and Women's Hospital, (3)Massachusetts General Hospital, (4) Massachusetts General Hospital, Boston, MA

Background: Understanding the symptom burden of patients with decompensated cirrhosis (DC) is critical for improving their health-related quality of life (HRQOL). The Edmonton Symptom Assessment System (ESAS) is a simple 10-item measure assessing physical and psychological symptoms that has been validated in patients with serious illnesses. This prospective longitudinal study aims to assess the face validity of the ESAS among outpatients with DC who concurrently completed the Short-Form Liver Disease Quality of Life (SF-LDQOL) questionnaire. **Methods:** Outpatients with DC were prospectively recruited from a single liver transplant center and completed the ESAS and SF-LDQOL at baseline and at 3 months. For both scales, we calculated the total scores for each timepoint and change in scores from baseline. We examined the correlations in total scores and change in scores between ESAS and SF-LDQOL. We employed regression analysis to examine whether change in ESAS scores was associated with change in SF-LDQOL scores, with adjustment for age, baseline MELD-Na, etiology of DC, transplant status, and history of ascites, hepatic encephalopathy (HE), variceal bleeding (EVB) and hepatocellular carcinoma (HCC). **Results:** From 7/2018-9/2022, we enrolled 218 patients with DC (median age 60 [IQR 51-65], median MELD-Na 16 [IQR 11-22], 48% alcohol-related liver disease, 50% listed for transplant, 92% ascites, 74% HE, 33% history of EVB, 12% HCC). At baseline, the mean total ESAS score was 37.7 (SD 19.9). The total ESAS score was significantly and negatively correlated with the SF-LDQOL total score ($r = -0.65$, $p < 0.01$) but was not correlated with MELD-Na score. At 3 months, 83 patients were unavailable for analysis due to death, liver transplant, or loss to follow-up. Of the remaining 135 patients, the change in SF-LDQOL scores was moderately correlated with changes in ESAS scores at 3 months ($r = -0.47$, $p < 0.01$) but not baseline MELD-Na scores. In bivariate analysis, the change of ESAS score explained 23% of the change of SF-LDQOL. In multivariable analysis, the change in total ESAS score was a significant predictor of the change in SF-LDQOL ($\beta = -0.34$, $p < 0.001$) (Table). **Conclusion:** The ESAS is a simple tool for longitudinally assessing symptom burden among patients with DC. The change in ESAS total score can account for the change in SF-LDQOL at 3 months. Future directions include implementation of ESAS in research and clinical practice as a key outcome measure in cirrhosis care.

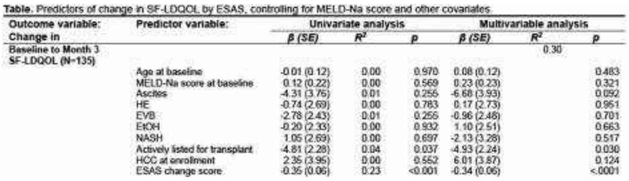

Table. Predictors of change in SF-LDQOL by ESAS, controlling for MELD-Na score and other covariates

Outcome variable: Change in	Predictor variable:	Univariate analysis			Multivariable analysis		
		β (SE)	R^2	p	β (SE)	R^2	p
Baseline to Month 3 SF-LDQOL (N=135)						0.30	
	Age at baseline	-0.01 (0.12)	0.00	0.970	0.08 (0.12)		0.483
	MELD-Na score at baseline	0.12 (0.22)	0.00	0.569	0.23 (0.23)		0.321
	Ascites	-4.31 (3.76)	0.01	0.256	-6.68 (3.93)		0.092
	HE	-0.74 (2.69)	0.00	0.783	0.17 (2.73)		0.951
	EVB	-2.78 (2.43)	0.01	0.256	-0.96 (2.48)		0.701
	EtOH	-0.20 (2.33)	0.00	0.932	1.10 (2.51)		0.663
	NASH	1.05 (2.69)	0.00	0.697	-2.13 (3.28)		0.517
	Actively listed for transplant	-4.81 (2.28)	0.04	0.037	-4.93 (2.24)		0.030
	HCC at enrollment	2.35 (3.96)	0.00	0.552	6.01 (3.87)		0.124
	ESAS change score	-0.35 (0.06)	0.23	<0.001	-0.34 (0.06)		<.0001

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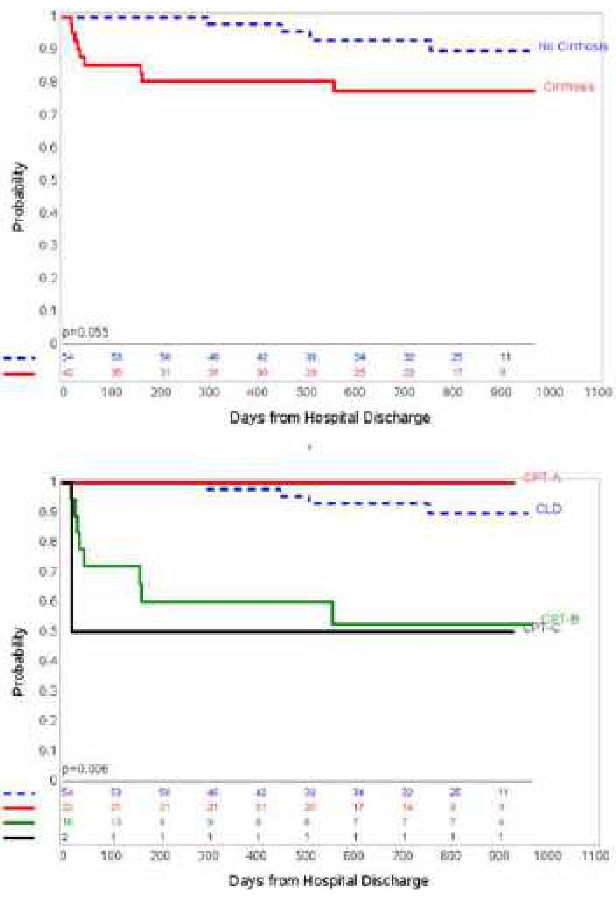
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

3790-C | DECOMPENSATED CIRRHOTICS WITH COVID-19 INFECTION HAVE A HIGHER POST HOSPITALIZATION MORTALITY COMPARED TO COMPENSATED CIRRHOTICS OR THOSE WITHOUT CIRRHOSIS

Ethan Berman[1], Alexa Giammarino[1], Jeffrey Lowell[1], Pratik Patel[2], Hassam Ali[3], Maham Ghani[1], Akash Singh[4], Edgewood Warner[1], Salima Makhani[1] and Sanjaya Kumar Satapathy[5], (1)Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, (2) Northwell Health, Forest Hills, NY, (3)East Carolina University, (4)Einstein Healthcare Network, (5)Division of Hepatology, Northwell Health, and Donald and Barbara Zucker School of Medicine at Hofstra/ Northwell, Hempstead, NY, USA.

Background: The COVID-19 pandemic had a profound and immediate worldwide effect resulting in significant mortality. Over three years from the first COVID-19 diagnosis in the United States, we are beginning to see the long term effects of the disease. There is an array of short term data published on the mortality of patients with chronic liver disease (CLD) and COVID-19; however, we lack sufficient long term follow-up information for CLD patients who survived COVID-19 infection. **Methods:** We retrospectively analyzed 192 patients admitted to any Northwell Health hospital in the state of New York for a COVID-19 infection who also had an ICD-10 diagnosis of chronic liver disease. We included 96 of the 143 patients with confirmed COVID-19 infection who survived their hospitalization and were discharged between March 2020 through April 2020. Of this final cohort of CLD patients, 87 had cirrhosis and 56 did not have cirrhosis. Patients without known follow up data were excluded ($n = 47$). Follow up was censored on November 22, 2022. Post hospitalization follow up data was analyzed to assess survival probability using Kaplan-Meier survival curves. **Results:** In patients with COVID-19 infection, those with CLD with cirrhosis had significantly higher age ($p = 0.053$) at admission, bilirubin ($p = < 0.001$), AST ($p = 0.009$), ALP ($p = < 0.001$), lactate ($p = 0.028$), INR ($p = < 0.001$), MELD ($p = < 0.001$) and lower platelet count ($p = < 0.001$) and albumin ($p = 0.001$) than patients with CLD without cirrhosis. Patients with cirrhosis had significantly lower ferritin ($p = 0.053$) and d-dimer ($p = 0.023$) compared to patients without cirrhosis. When evaluating follow up data, cirrhotic patients had higher post-hospitalization mortality than non-cirrhotic patients ($p = 0.055$). Patients with Child-Pugh class A cirrhosis had no mortality at day 900 post- hospitalization, which is similar to the mortality rate of chronic liver disease patients without cirrhosis. Survival probability in patients with Child-Pugh class A cirrhosis (100.00%) and no cirrhosis (89.71%) were significantly higher than those with Child-Pugh classes B (52.66%) and C cirrhosis (50.00%) ($p = 0.006$) (Graph 1). **Conclusion:** Patients with CLD (well compensated cirrhosis or no cirrhosis) who survived a COVID-19 hospitalization had significantly better post hospitalization survival than patients with decompensated cirrhosis. Greater efforts should be made to ensure adequate follow up for patients with CLD who are hospitalized with COVID-19, particularly in decompensated cirrhosis.

Graph 1: Survival among COVID-19 patients with chronic liver disease with and without varying degrees of cirrhosis



Disclosures: The following people have nothing to disclose: Ethan Berman, Alexa Giammarino, Jeffrey Lowell, Pratik Patel, Hassam Ali, Maham Ghani, Akash Singh, Salima Makhani, Sanjaya Kumar Satapathy

Disclosure information not available at the time of publication: Edgewood Warner

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

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Somaya Albhaisi, Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA, Ekaterina Smirnova, Virginia Commonwealth University, Richmond, VA and Arun Sanyal, Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

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

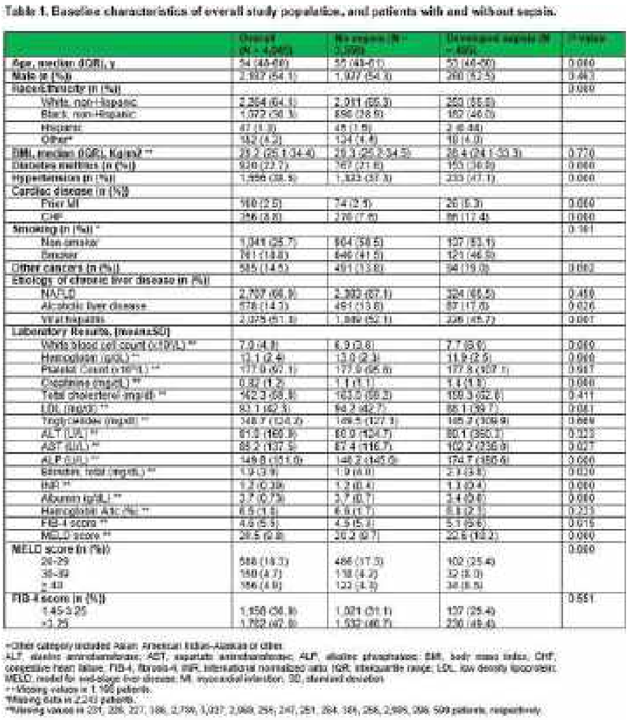
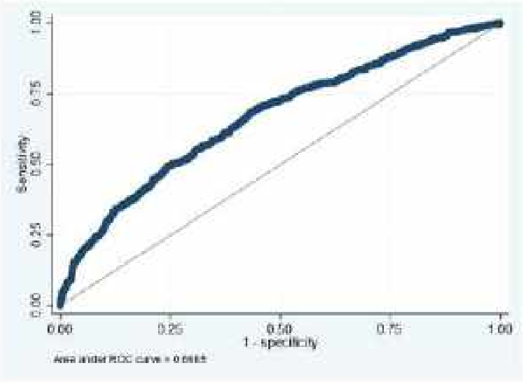


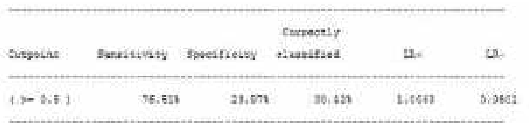
Table 1. Baseline characteristics of overall study population, and patients with and without sepsis.

	Overall (N = 4,045)	No sepsis (N = 3,550)	Developed sepsis (N = 495)	P value
Age, median (IQR), y	54 (46-60)	55 (48-61)	53 (46-59)	0.000
Male n (%)	2,187 (54.1)	1,927 (54.3)	260 (52.5)	0.463
Race/Ethnicity (n (%))				0.000
White, non-Hispanic	2,264 (64.1)	2,011 (65.3)	253 (55.8)	
Black, non-Hispanic	1,072 (30.3)	890 (28.9)	182 (40.2)	
Hispanic	47 (1.3)	45 (1.5)	2 (0.44)	
Other*	152 (4.3)	134 (4.4)	18 (4.0)	
BMI, median (IQR), Kg/m2 **	28.2 (25.1-34.4)	28.3 (25.2-34.5)	28.4 (24.1-33.3)	0.770
Diabetes mellitus (n (%))	920 (22.7)	767 (21.6)	153 (30.9)	0.000
Hypertension (n (%))	1,556 (38.5)	1,323 (37.3)	233 (47.1)	0.000
Cardiac disease (n (%))				
Prior MI	100 (2.5)	74 (2.1)	26 (5.3)	0.000
CHF	356 (8.8)	270 (7.6)	86 (17.4)	0.000
Smoking (n (%)) *				0.161
Non-smoker	1,041 (25.7)	904 (58.5)	137 (53.1)	
Smoker	761 (18.8)	640 (41.5)	121 (46.9)	
Other cancers (n (%))	585 (14.5)	491 (13.8)	94 (19.0)	0.002
Etiology of chronic liver disease (n (%))				
NAFLD	2,707 (66.9)	2,383 (67.1)	324 (65.5)	0.458
Alcoholic liver disease	578 (14.3)	491 (13.8)	87 (17.6)	0.026
Viral hepatitis	2,075 (51.3)	1,849 (52.1)	226 (45.7)	0.007
Laboratory Results, [mean±SD]				
White blood cell count (x10⁹/L) **	7.0 (4.8)	6.9 (3.8)	7.7 (8.0)	0.000
Hemoglobin (g/dL) **	13.1 (2.4)	13.0 (2.3)	11.9 (2.5)	0.000
Platelet Count (x10⁹/L) **	177.9 (97.1)	177.9 (95.6)	177.8 (107.1)	0.987
Creatinine (mg/dL) **	0.82 (1.2)	1.1 (1.1)	1.4 (1.8)	0.000
Total cholesterol (mg/dL) **	162.3 (58.8)	163.5 (58.2)	159.3 (62.6)	0.411
LDL (mg/dL) **	93.1 (42.3)	94.2 (42.7)	88.1 (39.7)	0.061
Triglycerides (mg/dL) **	148.7 (124.2)	149.5 (127.1)	185.2 (309.9)	0.669
ALT (U/L) **	81.8 (169.8)	80.9 (124.7)	80.1 (360.3)	0.323
AST (U/L) **	88.2 (137.5)	87.4 (116.7)	102.2 (236.8)	0.027
ALP (U/L) **	149.8 (151.0)	148.2 (145.0)	174.7 (180.6)	0.000
Bilirubin, total (mg/dL) **	1.9 (3.9)	1.9 (4.0)	2.3 (3.8)	0.020
INR **	1.2 (0.39)	1.2 (0.4)	1.3 (0.4)	0.000
Albumin (g/dL) **	3.7 (0.73)	3.7 (0.7)	3.4 (0.8)	0.000
Hemoglobin A1c (%) **	6.5 (1.6)	6.5 (1.7)	6.8 (2.1)	0.223
FIB-4 score **	4.6 (5.5)	4.5 (5.4)	5.1 (6.6)	0.015
MELD score **	20.5 (9.8)	20.2 (9.7)	22.6 (10.2)	0.000
MELD score (n (%))				0.000
20-29	588 (16.3)	486 (17.3)	102 (25.4)	
30-39	150 (4.7)	118 (4.2)	32 (8.0)	
≥ 40	156 (4.8)	122 (4.3)	34 (8.5)	
FIB-4 score (n (%))				0.551
1.45-3.25	1,158 (30.8)	1,021 (31.1)	137 (25.4)	
>3.25	1,762 (47.0)	1,532 (46.7)	230 (49.4)	

*Other category included Asian, American Indian-Alaskan or other.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BMI, body mass index; CHF, congestive heart failure; FIB-4, fibrosis-4; INR, international normalized ratio; IQR, interquartile range; LDL, low density lipoprotein; MELD, model for end-stage liver disease; MI, myocardial infarction; SD, standard deviation
+ Missing values in 1,198 patients.
*Missing data in 2,243 patients.
**Missing values in 231, 226, 227, 186, 2,759, 3,037, 2,969, 294, 247, 251, 284, 181, 266, 2,986, 206, 509 patients, respectively.

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





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                                          Correctly
Cutpoint      Sensitivity   Specificity   classified        LR+      LR-
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( >= 0.5 )         76.51%        28.07%       30.43%     1.0640   0.8361
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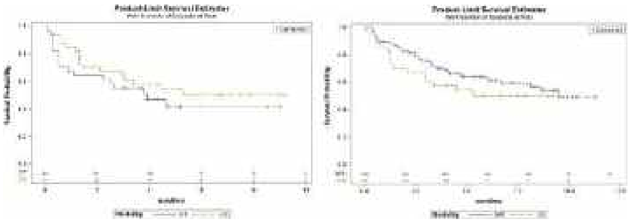
3792-C | EFFECT OF DIFFERENT RADIOLOGIC MODALITIES FOR SURVEILLANCE OF HEPATOCELLULAR CARCINOMA ON SURVIVAL OF HIGH RISK CIRRHOTIC PATIENTS.

Ahmed El Sabagh[1,2], Islam Mohamed[1,2], Megha Bhongade[1], Nikita Rao[1], Eunji Jo[3], Susan G. Hilsenbeck[3] and Prasun K. Jalal[1], (1)Baylor College of Medicine, (2)Faculty of Medicine, Ain Shams University, (3)Dan L Duncan Comprehensive Cancer Center at Baylor St. Luke's Medical Center

Background: American Association for the Study of Liver Diseases (AASLD) recommends that patients with high risk of developing hepatocellular carcinoma (HCC) undergo regular surveillance with ultrasonography (US) every 6 months with or without Alpha-feto protein (AFP). However, compared to cross-sectional imaging modalities -Computed tomography (CT) and Magnetic resonance imaging (MRI) - US has lower efficacy for detection of early HCC. To our knowledge, there are no studies evaluating the overall survival and receipt of curative treatment for patients who received surveillance using the different imaging modalities. **Methods:** We retrospectively reviewed all patients who were diagnosed with HCC at Baylor Saint Luke's Medical Center Hospital between January 2011 and June 2021. Patients who underwent regular surveillance were identified. Data retrieved from electronic medical records and radiology reports included demographic and laboratory features, surveillance modality, tumour characteristics, treatments received and survival data. We estimated survival using the Kaplan-Meier method and compared the different modalities using the Log Rank test. We used univariate and multivariate Cox model to evaluate factors affecting survival. **Results:** A total of 183 patients developed HCC while on biannual surveillance program (115 with MRI, 34 with CT and 34 with US). Patients were similar regarding with respect to age, sex, comorbid diseases. However, our cohort shoed statistically significant differences regarding race and ethnicity, with more African American and Hispanic population undergoing surveillance with US. Moreover, Race and ethnicity were associated with lower survival rates. The initial survival analysis showed that compared to other modalities MRI had statistically significant association with longer survival (p-value = 0.034). However, cox-multivariate regression model with adjustment for race, ethnicity, MELD score and total tumor size at time of diagnosis shows that surveillance modality has no statistically significant association with survival (MRI: HR 1.80, p-value = 0.095) (CT: HR 0.71, p-value = 0.26). **Conclusion:** For cirrhotic patients with high risk for HCC, surveillance with MRI or CT was not associated with higher survival rate compared. This result shed the light on importance of adherence to surveillance irrespective of modality. Additionally, racial and ethnic disparities may affect the access to the HCC surveillance.



Disclosures: The following people have nothing to disclose: Ahmed El Sabagh, Islam Mohamed, Megha Bhongade, Nikita Rao, Eunji Jo, Susan G. Hilsenbeck, Prasun K. Jalal

3793-C | IMPACT OF ATEZOLIZUMAB + BEVACIZUMAB THERAPY ON HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

Masako Shomura[1], Haruka Okabe[1], Emi Sato[2], Koichi Shiraishi[3], Yoshitaka Arase[3], Kota Tsuruya[3], Yusuke Mishima[2], Shunji Hirose[3] and Tatehiro Kagawa[3], (1) Faculty of Nursing, Tokai University School of Medicine, (2)Department of Advanced Medical Science, Tokai University Graduate School of Medicine, (3)Division of Gastroenterology, Department of Internal Medicine, Tokai University School of Medicine

Background: Health-related quality of life (HRQoL) is an essential consideration for patients with hepatocellular carcinoma (HCC) and is becoming an important endpoint in evaluating new therapies such as atezorizumab+bevacizumab (Atez+Bev) for advanced HCC. HRQoL can be affected by cancer symptoms and adverse events (AEs) of therapies. This study aimed to identify factors associated with treatment efficacy, treatment duration, and overall survival (OS) in HCC patients receiving Atez+Bev, based on their characteristics, including AEs and HRQoL at 3 months. **Methods:** The consecutive HCC patients who received Atez+Bev from Nov 2020 to Apr 2023 were followed up until Apr 21, 2023, or death. Treatment efficacy was assessed according to modified RECIST at 6-9 weeks. HRQoL was monitored every month by EORTC-QLQ C30. The relationship of baseline characteristics, AEs, and HRQoL with efficacy, OS, and treatment duration was analyzed by multivariate logistic regression models and Cox's hazards models with a landmark method. A nursing intervention program was provided to all patients, including education regarding self-monitoring and AEs management, and telephonic consultations. **Results:** A total of 52 patients were enrolled; the majority of patients were men (87%), aged 70 years or older (50%), and had a Child-Pugh score of 5 (48%) and Barcelona Clinic Liver Cancer Stage C (44%). The disease control and response rate (RR) were 78.4% and 37.3%, respectively, with a median treatment duration of 10.8 and OS of 17.9 months. The commonest AEs (all grades) were hypoalbuminemia (90%), fatigue (86%), and thrombocytopenia (75%). HRQoL scores of five functional domains such as general health, physical function (PF), role function, emotional function, and cognitive function (CF), and seven symptoms such as fatigue, nausea, pain, dyspnea, insomnia, and financial difficulties significantly worsened during the first three months. CF < 80 (Odds ratio [OR] 0.16, 95% confidence interval [CI]: 0.03–0.87, $p = 0.03$) at month 3, extrahepatic invasion (OR 0.11, 95% CI: 0.02–0.58, $p < 0.00$) and TNM stage IV (OR 0.24, 95%CI: 0.07–0.83, $p = 0.02$) were associated with lower RR. History of liver resection (OR 4.35, 95%CI: 1.09-16.67) and grade $\geqq 2$ skin toxicities (OR 10.00, 95%CI: 1.03-100.00, $p < 0.05$) contributed to higher RR. Factors predictive of shorter OS were PF < 80 (Hazard ratio [HR] 2.52, 95%CI: 1.05-6.03, $p = 0.04$), grade $\geqq 2$ hypoalbuminemia (HR 4.37, 95% CI: 1.50–12.76, $p = 0.01$), and DCP value $>$ 1000 (HR 2.81, 95% CI: 1.22–6.51, $p = 0.02$). **Conclusion:** The HRQoL scores significantly deteriorated at month 3 after the beginning of Atez+Bev therapy in HCC patients. Declining CF and PF scores were associated with poor prognosis. Thus, maintaining HRQoL during anticancer therapy by appropriately managing AEs with multidisciplinary team support would contribute to a better prognosis.

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The following people have nothing to disclose: Masako Shomura, Haruka Okabe, Emi Sato, Koichi Shiraishi, Yusuke Mishima, Shunji Hirose

3794-C | MENSTRUAL AND REPRODUCTIVE HEALTH IN LIVER TRANSPLANT CANDIDATES: A CROSS SECTIONAL SURVEY

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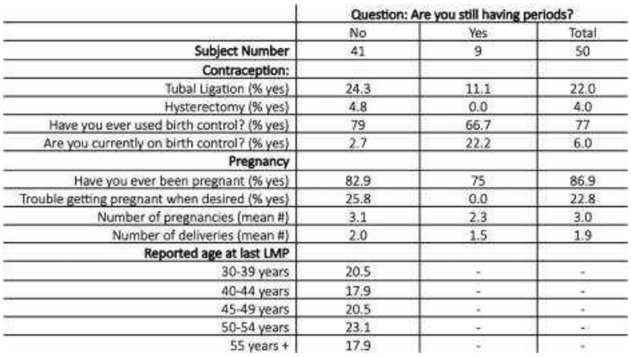
Background: Menstrual and reproductive health is affected by chronic liver disease (CLD). Patients with advanced CLD often become oligo- or amenorrheic, which typically resolves after liver transplant (LT). There are limited gynecologic and obstetric data in LT candidates that would inform appropriate reproductive health counseling in transplant clinics. Thus, we designed a cross-sectional women's health survey for patients presenting for pre-LT clinical care. **Methods:** We distributed a 25-question survey querying gynecologic and obstetric history to all pre-LT patients assigned female gender at birth (hereto called women) between 1/16/23-5/2/23. Menstrual status was determined by the response to the following yes or no question: "Are you still having menstrual periods?". Subgroup analysis was reported by age at time of survey (≤ 50 vs > 50 y) and by menstrual status. Data are reported as: percentage, (# or positive responses/# of total answers for specific question). **Results:** The survey was completed by 50 of 56 patients. Mean age of respondents was 55 +/-12 years; 16 patients were $\leq$ 50 years of age. Of those who reported disease etiology, most had alcohol-related liver disease (62%, 22/36), followed by NAFLD (16%, 6/36), PBC or AIH (16%, 6/36) and HCV (6%, 2/36). Most patients (82%, 36/50) reported amenorrhea (100% of those > 50 vs. 43.8% ≤ 50 y). On a Likert scale characterizing menstrual regularity, 36% (16/44) selected always normal periods, 30% (13/44) selected fairly normal periods, and 34% (15/44) selected irregular periods; 58% and 44% reported prior heavy or painful menses, respectively. Of those no longer menstruating, 20.5% (8/39) and 17.9% (7/39) reported last menstrual period at age < 40 and between 40-45, respectively. Regarding why menses stopped, 70% (29/41) reported menses stopped at random, 10% (4/41) reported menses stopped due to a medication or procedure, and 20% (7/41) did not know why menses stopped. The majority (77%, 36/47) reported prior contraceptive use (27 oral contraception, 7 intrauterine device, 2 not specified). Of the menstruating, 22% (2/9) were using contraception at time of visit. 86% of patients (47/50) reported a prior pregnancy of which 60% (28/47) reported more pregnancy events than deliveries. The average age of first and last pregnancy were 23 and 30, respectively. Approximately one quarter (23%, 8/35) reported difficulty conceiving when desired. **Conclusion:** Women with CLD experience irregular and painful menses. Further, 40% of participants reported LMP < age 45, compared to the nationwide prevalence of 12%. Importantly, self-reported menopause in these young women likely reflects secondary amenorrhea, a condition which typically resolves following transplant. This population is thus at risk for early and unplanned pregnancy if reproductive counseling is not conducted throughout the pre and post-transplant time periods.



	Question: Are you still having periods?		
	No	Yes	Total
Subject Number	41	9	50
Contraception:			
Tubal Ligation (% yes)	24.3	11.1	22.0
Hysterectomy (% yes)	4.8	0.0	4.0
Have you ever used birth control? (% yes)	79	66.7	77
Are you currently on birth control? (% yes)	2.7	22.2	6.0
Pregnancy			
Have you ever been pregnant (% yes)	82.9	75	86.9
Trouble getting pregnant when desired (% yes)	25.8	0.0	22.8
Number of pregnancies (mean #)	3.1	2.3	3.0
Number of deliveries (mean #)	2.0	1.5	1.9
Reported age at last LMP			
30-39 years	20.5	-	-
40-44 years	17.9	-	-
45-49 years	20.5	-	-
50-54 years	23.1	-	-
55 years +	17.9	-	-

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Disclosure information not available at the time of publication: Anita Krishnarao, Mary Flynn, Monika Sarkar

f 3795-C | OUTCOMES OF CIRRHOSIS PATIENTS ADMITTED FOR INFLUENZA COMPARED TO SARS-Cov2 ADMISSIONS IN THE UNITED STATES

Yasmeen Obeidat[1], Renuka Verma[2], Kamleshun Ramphul[3], Hemamalini Sakthivel[4] and Tejas Joshi[1], (1) Marshall University, (2)Guru Gobind Singh Medical School, (3)Independent Researcher, (4)One Brooklyn Health System/Interfaith Medical Center Program

Background: Several studies have highlighted the impact of cirrhosis on the immune system, contributing to a weaker response and poorer prognosis following infections. We wanted to compare the outcomes and healthcare burden these now endemic viruses have on adult cirrhosis patient population. We conducted an in-depth retrospective analysis via one of the largest hospitalization databases from the United States, with a primary objective of understanding the differences in characteristics, complications and outcomes among adults with a diagnosis of cirrhosis that were admitted for either Influenza or COVID-19. **Methods:** Patients who also had a diagnosis of influenza were included from the 2016-2019 NIS. For the 2020 NIS, we included patients with a diagnosis of COVID-19. A diagnosis of cirrhosis was also identified. We proceeded to evaluate for potential complications and outcomes during their hospitalization (death, non-invasive ventilation, mechanical ventilation, septicemia, acute kidney injury), and the adjusted odds ratios (aOR), while considering for confounders, were estimated via different logistic regression models. Completed propensity matched analysis, set at a 1:1 ratio and caliper width of 0.20. The various outcomes were further compared and a secondary logistic regression model was also used to estimate the events in cirrhosis patients. **Results:** In 2020, there were an estimated 1628110 cases of COVID-19 in the United States. A total of 48810 (3.0%) cases also had cirrhosis. 4690 (9.6%) of cirrhosis patients required non-invasive ventilation (aOR 1.460, 95% CI 1.413-1.508, $p < 0.01$), 17850 (36.6%) needed mechanical ventilation (aOR 4.375, 95% CI 4.286-4.467, $p < 0.01$), 23200 (47.5%) developed septicemia (aOR 2.705, 95% CI 2.653-2.757, $p < 0.01$), and 26180 (53.6%) reported Acute kidney injury (aOR 2.983, 95% CI 2.922-3.045, $p < 0.01$). Unfortunately, 18305 (37.5%) of cirrhosis patients did not survive their hospitalization for COVID-19 (aOR 4.265, 95% CI 4.176-4.356, $p < 0.01$) (table 1, figure 1). **Conclusion:** Cirrhosis patients have various physiological changes which can alter their immune response to infection. Our study confirms that they are at higher risk for several complications and poor outcomes, including death, compared to those without cirrhosis. Several differences were noted in outcomes between cirrhosis patients with COVID-19 as compared to influenza, as highlighted by our study. Better understanding these outcomes can help tailor our vigilance and management approach when managing cirrhosis patients with each specific viral infection.

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

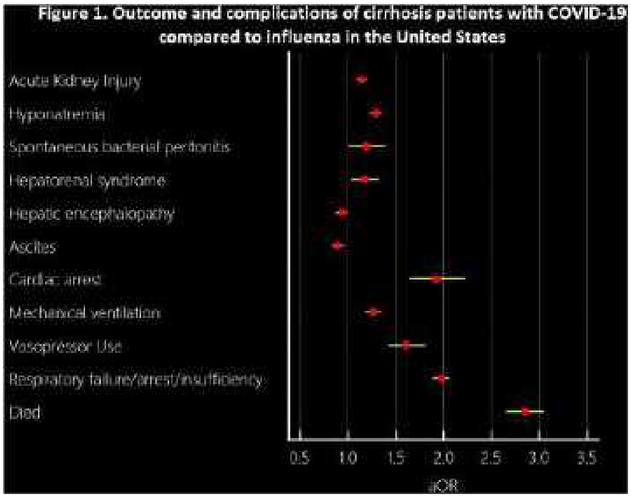

Figure 1. Outcome and complications of cirrhosis patients with COVID-19 compared to influenza in the United States

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3796-C | OVERVIEW OF INTERIM FINDINGS FROM A SURVEY ON PATIENT ATTITUDES TOWARD CLINICAL TRIAL PROCESSES IN CHRONIC LIVER DISEASES

Shavonne Temple[1], Frhaan Zahrawi[2], Farzaneh Dashti[2], Tamar H. Taddei[2], Joseph K. Lim[2], Wajahat Z. Mehal[2] and Bubu A Banini[2], (1)LSU Health Shreveport, (2)Yale University, New Haven, CT

Background: Chronic liver disease (CLD) affects 1.5 billion people worldwide and over 30 million people in the United States. However, there is insufficient information about patients' knowledge of clinical trials in CLD. We aimed to achieve a better understanding of patient awareness of clinical trials in CLD by surveying a diverse patient population with various etiologies of CLD. **Methods:** A 26 questions survey was designed and administered to adult patients aged ≥ 18 years with a diagnosis of CLD. The study was reviewed and approved by local Review Board (IRB). A bilingual (English and Spanish) recruitment message was sent through the Electronic Medical Record (EMR). The survey included questions on: general information (8 questions [Q]); current health status (2Q); clinic accessibility (2Q); and clinical research knowledge and opinions (14Q). The QR code for the survey was also distributed outside of the EMR via social media. **Results:** Between June 2022 and May 2023, a total of 299 responses were obtained comprising 61% women and 39% men. Respondents were 86% Caucasian, 4% African American, 2% Asian American, 1% American Indian, and 7% Other. Respondents identified as 9% Hispanic and 91% non-Hispanic. The etiology of CLD was 38% NAFLD, 13% ALD, 11% HCV, 11% autoimmune hepatitis, 6% primary biliary cholangitis, 4% HBV, 1% primary sclerosing cholangitis, and 16% other liver diseases. Only (41%) indicated that their medical provider had informed them about clinical trials. The majority of respondents (88%) were very likely or likely to participate in clinical trials if given the opportunity. The commonest motivating factors for clinical trial participation were: desire to contribute to medical science (28%); help others (28 %); and receive treatment (21%). The majority (61%) of respondents strongly agreed or agreed that they preferred in-person visits over video or telephone visits. Regarding frequency of imaging procedures, 27% thought monthly liver ultrasound was reasonable; 25% preferred every 3 months. For MRI, 24% indicated a preference for yearly imaging; 20% indicated every 6 months. For liver biopsy, 29% indicated yearly;16% indicated every 6 months. For liver stiffness measurement, almost half (47%) of respondents were not sure or had no opinion regarding preferred frequency. **Conclusion:** Our interim report from a bilingual system-wide electronic survey of patients with CLD indicates that the majority of patients are interested in clinical trial participation due to the potential to improve their health or those of others. Areas for improvement include providing more education and information to patients regarding ongoing clinical trials, efforts to disseminate information to diverse patient populations, and increased patient education on liver-related procedures such as liver stiffness measurement.

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Joseph K. Lim:

Disclosure information not available at the time of publication: Shavonne Temple, Farzaneh Dashti, Tamar H. Taddei, Bubu A Banini

3797-C | PAIN IN US ADULTS WITH LIVER DISEASE: INSIGHTS FROM THE NATIONAL HEALTH INTERVIEW SURVEY

Grace Zhang[1], Aly Cortella[1], Jennifer C. Lai[2] and Jessica Beth Rubin[3,4], (1)UCSF, (2)University of California-San Francisco, San Francisco, CA, (3) University of California, San Francisco, San Francisco, CA, (4)San Francisco VA

Background: Pain is common in patients with chronic liver disease, impairing their daily functioning and quality of life. However, our limited understanding of patterns of pain in this population, as well as differences compared to patients with other chronic conditions, hinders the development of effective cirrhosis-specific pain management strategies. **Methods:** Using cross-sectional data from 2016-2021 National Health Interview Survey, we examined pain rates, severity, and functional limitations due to pain in respondents with self-reported liver disease (i.e. viral hepatitis, cirrhosis, or liver cancer), compared to the general population and those with other chronic conditions associated with pain (arthritis, diabetes, chronic kidney disease [CKD]). We defined pain and functional limitation outcomes by report of symptoms on most or all days. Categorical and continuous variables were compared by χ^2 and t-test, respectively. **Results:** Our liver disease cohort comprised of 5330 participants (63% viral hepatitis, 49% cirrhosis, 2% liver cancer), among whom 42% reported pain, 42% severe pain, and 28% functional limitations by pain. Only 22% of non-liver disease patients reported pain, 30% severe pain, and 13% functional limitations by pain. Compared to liver disease respondents without pain, those with pain were older (60 y vs 57 y old), more often female (52% vs 46%), less often Asian (2% vs 8%) or Hispanic (10% vs 16%), and had lower levels of education (40% vs 33% high school or less) and employment (71% vs 52% unemployed) ($p < 0.001$ for all). The proportion of liver disease respondents reporting pain remained stable over the study period. Liver disease respondents were less likely to have pain than those with CKD or arthritis ($p < 0.001$ for both) but had similar rates as those with diabetes ($p = 0.8$) (Figure). Liver disease respondents had similar rates of *severe pain* compared to all 3 other chronic conditions and were more likely to be functionally limited by pain than those with arthritis ($p < 0.001$). **Conclusion:** The prevalence of pain in liver disease is higher than in the general population, and the prevalence of severe pain and resulting functional limitations is similar to or higher than among those with other painful chronic conditions. Future research should focus on elucidating mechanisms of this disproportionately severe pain in liver disease patients to develop safe and effective treatment options that improve their quality of life.

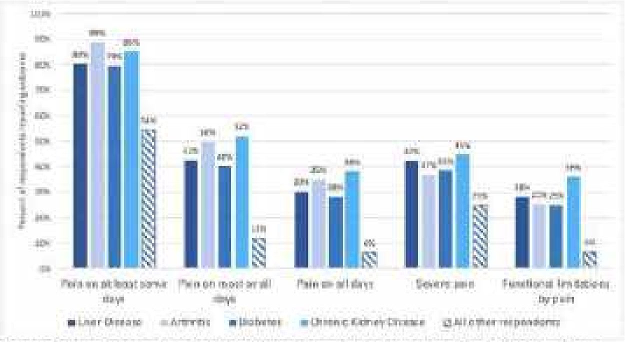

Figure. Comparing reports of pain frequency, severity, and functional limitations for liver disease and other chronic conditions including arthritis, chronic kidney disease, diabetes mellitus, and the general population.

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3798-C | PATIENT EXPERIENCE WITH A SMARTPHONE-ENABLED INTERACTIVE CARE PLAN FOR MANAGEMENT OF CIRRHOSIS

Kathryn A. Schmidt[1], *Daniel Penrice*[1], *Sarah Harper*[2], *Jordan Coffey*[2], *William Harmsen*[2], *Julianne Lunde*[2], *Barbara Copeland*[2], *Rachel Gullerud*[2], *Winnie Fan*[2], *Hugo E. Vargas*[3], *Blanca Lizaola-Mayo*[3] *and Douglas A. Simonetto*[1], *(1)Mayo Clinic Rochester, Rochester, MN, (2)Mayo Clinic, (3)Mayo Clinic Arizona, Phoenix, AZ*

Background: Patients with cirrhosis are at increased risk for disease-related hospitalizations and reduced quality of life. An interactive care plan (ICP) – a smartphone-enabled self-care application for monitoring and managing cirrhosis – was developed and implemented at Mayo Clinic. We sought to understand the impact of this novel interactive digital platform by evaluating patients' willingness to engage, usage, satisfaction, and potential barriers. **Methods:** Patients 18 or older who receive longitudinal care for cirrhosis at Mayo Clinic in Rochester and Arizona were enrolled. The ICP delivered daily flowsheets, questionnaires, and self-management education to the online patient portal over 12 months. Cirrhosis-related symptom tracking and educational content were developed by the hepatology team. Surveys using a 5-point Likert scale were sent to participants at the midway point (6 mo) of their care plan. **Results:** Of the 98 participants (47% male, median age 66 (range 30-83), 60% in Rochester, 40% in Arizona) enrolled in the ICP for 1 year, 26 completed the mid-point survey. Themes include patient communication with the care team, education/understanding of their condition, and usefulness/accessibility of educational materials. Communication: Most patients felt confident using the ICP (85%) and interacting with the care team (96%). A majority also felt that the app was easy to use (88%), and that it improved communication with their care team (85%). Education/understanding of condition: Most patients felt the ICP helped them to better understand their condition (73%), how to care for themselves (69%), and what steps they could take to improve their health (69%). Quality of Educational Materials: Most patients agreed that the educational materials were easy to understand (88%). Fewer patients felt that the materials matched their personal needs (58%) or information they received from their care team (62%). Most were comfortable with how often they received educational materials (79%) and were able to find the materials when needed (69%). Overall, most patients would recommend the ICP to others with similar conditions (73%) and were satisfied with the ICP (88%) underscoring the need for and benefit of a care plan in high-risk patient populations. **Conclusion:** Tailoring an ICP program to the unique needs of patients with cirrhosis has the potential to improve satisfaction with their care. Most patients had a positive experience, benefitting from the communication and education as well as empowering them to be more engaged in their cirrhosis care. With additional surveys upon completion of the program, we will better characterize unique phenotypes and tailor educational content to specific needs.

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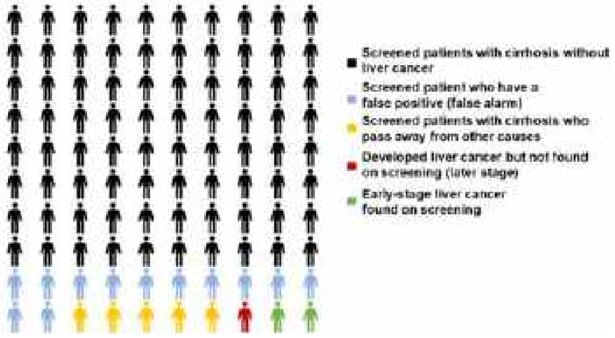
3799-C | PATIENT KNOWLEDGE AND ATTITUDES ABOUT VALUE OF HEPATOCELLULAR CARCINOMA (HCC) SURVEILLANCE

Darine Daher[1], Karissa D. Kao[2], Karim Seif El Dahan[1], Dala Eloubeidi[2], Austin J. Fobar[2], Lisa Quirk[1], Nishi Patel[3], Megha Bhongade[4], Islam Mohamed[4], Ahmed El Sabagh[4], Sean Woolen[5], Jonathan P Troost[2], Prasun Jalal[4], Maarouf A. Hoteit[6], Amit G. Singal[1] and Neehar Dilip Parikh[2], (1)University of Texas Southwestern Medical Center, (2)University of Michigan, (3)University of Pennsylvania, (4)Baylor College of Medicine, (5) University of California San Francisco, (6)Hospital of the University of Pennsylvania

Background: Society guidelines recommend HCC surveillance for patients with cirrhosis and chronic hepatitis B; however, suboptimal adherence in clinical practice impairs effectiveness. Patient knowledge and attitudes regarding the value of HCC screening can contribute to underuse of surveillance so are essential to understand as potential intervention targets. **Methods:** We administered a survey evaluating knowledge and attitudes about HCC surveillance practices and value among patients with cirrhosis at four medical centers in the US. We included adult patients with Child-Pugh A or B cirrhosis (defined by histology, imaging, elastography, or laboratory indices) who were eligible for HCC surveillance. We excluded patients with a history of HCC, liver transplantation, or Child Pugh C cirrhosis. **Results:** Participants ($n = 175$) had a median age of 60 years, 51% were female, 77% White, 10% Black, and 19% Hispanic. Patients' knowledge of surveillance logistics was high, with > 75% of patients correctly answering knowledge questions. Self-assessment of HCC risk varied widely, with 39% believing they had a less than 1% annual risk and 18% believing they had an annual risk exceeding 5%. Most (75%) reported their provider had discussed benefits of HCC screening, but only 59% reported a discussion of potential harms. Respondents largely agreed that surveillance improves early detection (79%), curative therapy (84%), and survival (75%), although over half (55%) believed surveillance prevented HCC from developing. Early detection was a priority for 83% of patients, independent of improved survival. However, most respondents (> 80%) acknowledged that a discussion of potential harms was important and that false positive results would cause anxiety. Two-thirds (66%) also believed that financial harms should also be considered when considering HCC screening. Over half of patients (52%) reported tolerating false positives in less than 20% of cases over a time frame where HCC risk approached 10%. When presented with the pictogram (Figure), 91% of respondents indicated they would undergo HCC surveillance. **Conclusion:** Patients with cirrhosis undergoing HCC screening displayed high levels of knowledge about HCC screening but have misconceptions that are potential educational targets. Patients acknowledge the importance of screening harms but prioritize early detection as the primary driver of surveillance value.

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

Figure 1. Pictogram depicting HCC screening benefits, harms, and competing risks



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Maarouf A. Hoteit – HepQuant, LLC: Consultant, No, No;
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The following people have nothing to disclose: Darine Daher, Karissa D. Kao, Karim Seif El Dahan, Dala Eloubeidi, Austin J. Fobar, Lisa Quirk, Nishi Patel, Megha Bhongade, Islam Mohamed, Ahmed El Sabagh, Sean Woolen, Jonathan P. Troost

3800-C | PATIENT PREFERENCES FOR HEPATOCELLULAR CARCINOMA SCREENING ATTRIBUTES

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Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer related mortality in patients with cirrhosis. Ultrasound and alpha fetoprotein (AFP) are the most commonly recommended surveillance tools; however, several alternate emerging modalities have been proposed, including imaging- and blood-based strategies, each with its own performance and logistical attributes. Understanding patient preferences regarding surveillance attributes can help identify which strategies will be well accepted when implemented in practice. **Methods:** We conducted a choice-based conjoint survey among patients with cirrhosis undergoing HCC surveillance at 4 medical centers in the US. Participants were provided 15 scenarios in which they were asked to choose surveillance modalities based on six test attributes: benefits (i.e., sensitivity for early HCC), physical harms (i.e., false positives requiring additional testing), financial harms (i.e., out-of-pocket costs), test logistics (i.e., blood draw vs. imaging), test location (i.e., in-clinic vs. separate appointment) and duration of testing (Table). Hierarchical Bayes discrete choice conjoint analysis was used to derive attribute importance. **Results:** We surveyed 255 patients, with a median age of 60 years, 51% male, 82% White, 8% Black, and 15% Hispanic. The highest priority attribute was surveillance benefits (42.9%; 95%CI: 40.6-45.1%), followed by financial harms (19.4%; 95%CI: 18.1-20.7%). Patients placed less priority on test logistics (12.3%; 95%CI: 11.5-13.2%), test location (9.2%; 95%CI: 8.5-10.0%), time duration (8.3%; 95%CI: 7.8-8.7%), and physical harms (7.9%; 95%CI: 7.2-8.6%). In subgroup analyses, Black and Hispanic patients placed lower importance on sensitivity and more on financial harms than White ($p = 0.01$) and non-Hispanic ($p < 0.001$) patients, respectively. Hispanic participants prioritized convenient testing locations compared to non-Hispanic patients ($p = 0.03$). Participants with less than a high school education ($p = 0.004$) and annual income less than $25,000 ($p = 0.001$) placed higher importance on financial harms. **Conclusion:** Patients with cirrhosis prioritize high test sensitivity and low financial harms, while placing less importance on test logistics and risk of physical harms; however, preferences significantly differed by race, ethnicity, and socioeconomic status. These data suggest patient acceptance of and adherence to surveillance may improve with increased options for surveillance modalities.

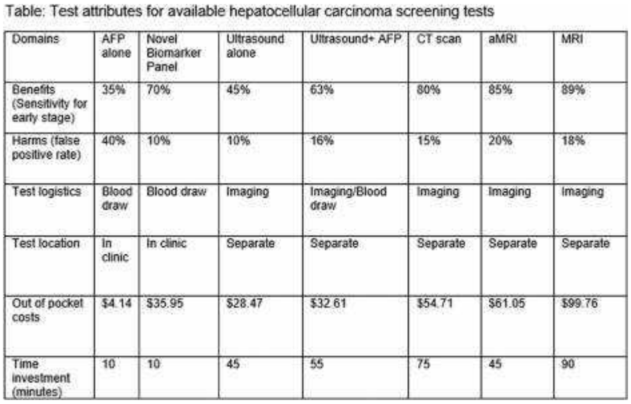
Table: Test attributes for available hepatocellular carcinoma screening tests

Domains	AFP alone	Novel Biomarker Panel	Ultrasound alone	Ultrasound+ AFP	CT scan	aMRI	MRI
Benefits (Sensitivity for early stage)	35%	70%	45%	63%	80%	85%	89%
Harms (false positive rate)	40%	10%	10%	16%	15%	20%	18%
Test logistics	Blood draw	Blood draw	Imaging	Imaging/Blood draw	Imaging	Imaging	Imaging
Test location	In clinic	In clinic	Separate	Separate	Separate	Separate	Separate
Out of pocket costs	$4.14	$35.95	$28.47	$32.61	$54.71	$61.05	$99.76
Time investment (minutes)	10	10	45	55	75	45	90

Disclosures: Maarouf A. Hoteit – HepQuant, LLC: Consultant, No, No;

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Amit G. Singal – Genentech: Consultant, No, No; AstraZeneca: Consultant, No, No; Bayer: Consultant, No, No; Eisai: Consultant, No, No; Exelixis: Consultant, No, No; Boston Scientific: Consultant, No, No; Gycotest: Consultant, No, No; Exact Sciences: Consultant, No, No; Roche: Consultant, No, No; FujiFilm Medical Sciences: Consultant, No, No; GRAIL, LLC: Consultant, Yes, No; Freenome: Consultant, No, No; Histosonics: Consultant, No, No;

Neehar Dilip Parikh – Eisai: Advisor, No, Yes; Exact Sciences: Consultant, No, Yes; Gilead: Advisor, No, Yes; Fujifilm Medical: Consultant, No, Yes; Freenome: Consultant, No, Yes; Exelixis: Consultant, No, No;

The following people have nothing to disclose: Karissa D. Kao, Jonathan P. Troost, Dala Eloubeidi, Karim Seif El Dahan, Darine Daher, Austin J. Fobar, Lisa Quirk, Nishi Patel, Megha Bhongade, Islam Mohamed, Ahmed El Sabagh, Sean Woolen

3801-C | PATIENT-REPORTED FUNCTIONAL STATUS AND PHYSICAL FUNCTION HAVE WEAK CORRELATIONS WITH PHYSICAL MEASURES AND MAY NOT IMPROVE PREDICTION OF SHORT-TERM OUTCOMES IN CIRRHOSIS

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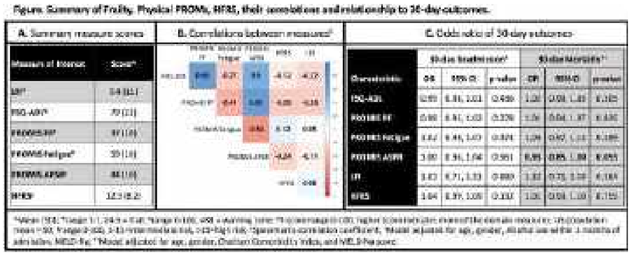
Background: Physical frailty can be measured by batteries of physical tests such as the Liver Frailty Index (LFI), but these require physical capacity and specialized equipment. Patient-reported outcome measures (PROMs) of physical function and electronic health record (EHR) data may be used as surrogates for physical frailty. We aimed to measure the correlations between these different measures and assess their ability to predict 30-day outcomes in hospitalized individual's with cirrhosis. **Methods:** From a prospective inpatient cirrhosis cohort, 191 adults enrolled from 7/2020-4/2023 completed the Functional Status Questionnaire, FSQ; Patient-Reported Outcomes Measurement Information System, PROMIS Profile-29 v2.1; and LFI. The Hospital Frailty Risk Score (HFRS) was calculated using EHR data. Scores range from 0-100 for all measures except LFI which ranges from 1-7. Spearman's correlation coefficients were assessed between these measures. Predictors of 30-day readmission and mortality were assessed using multivariable logistic regression models. **Results:** The cohort had a mean age of 53.5 ± 12.5 years and was 55% male, 80% White, and 10% Hispanic. Mean Charlson comorbidity index of 5.6 ± 2.5 and mean MELD-Na score of 23 ± 8. Primary reasons for admissions were ascites/volume overload (37%), abdominal pain (26%), and acute kidney injury (23%). Figure A summarizes LFI, PROMIS physical function (PF), fatigue, and ability to participate in social roles (APSR) and HFRS scores. The correlations between LFI, PROMs and HFRS were weak ($r \leq 0.30$, Figure B). There were moderate correlations between FSQ and PROMIS PF ($r = 0.66$) and APSR ($r = 0.50$). Median days between LFI assessment and PROMs was 0 days (IQR: 0). Those with a 30-day readmission (34%) were not significantly different from those not re-admitted except for active alcohol use (79% vs. 64%, $p = 0.05$). Those who died within 30-days ($n = 18$, 9.4%) were older (59 vs. 53, $p = 0.055$), less likely to have hepatitis C (0% vs 18%, $p = 0.47$) and had a higher MELD-Na (29 vs. 22, $p = 0.002$) compared to survivors. LFI, PROM scores and HRFS were not significantly different between these groups. In multivariable models, LFI, PROMs and HRFS did not independently predict 30-day readmission or mortality (Figure C) although PROMIS APSR was marginally associated with 30-day mortality (OR 0.93, 95% CI 0.85, 1.00). **Conclusion:** In patients with decompensated cirrhosis, patient report of physical functions is poor, comorbidity is high and physical frailty is common; however, there is poor correlation between these measures. Further, these measures have limited value in predicting 30-day readmissions beyond markers of liver disease in advanced cirrhosis. Future work should assess if change in PROs overtime can predict cirrhosis-related outcomes.



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The following people have nothing to disclose: Archita Parikh Desai, Thomas Cerri, Naga P. Chalasani
Disclosure information not available at the time of publication: Timothy Stump, Jake McCarty, Janeth Castano, Patrick Monahan, Marwan S. Ghabril

3802-C | PATIENTS WITH CIRRHOSIS RAPIDLY REVIEW POTENTIALLY ABNORMAL HCC SURVEILLANCE RESULTS VIA THE PATIENT PORTAL

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Background: Patients with cirrhosis have an increased risk of hepatocellular carcinoma (HCC) and undergo surveillance every six months. Historically, abnormal imaging findings were first communicated to patients via direct patient-provider communication in clinic or by telephone. However, since implementation of the 21st Century Cures Act, patients can immediately review test results through the electronic patient portal. We investigated how often and how rapidly patients view ambulatory liver imaging results through the patient portal. **Methods:** We identified patients with cirrhosis who were enrolled in the patient portal and had at least one ambulatory ultrasound or triphasic CT/MRI between 1/1/2021 and 5/1/2023. Reasons for exclusion included a history of liver transplantation or history of HCC. Patient follow-up was censored at time of HCC diagnosis or liver transplantation. We extracted dates and times that imaging results were released to patients via the patient portal and times that results were viewed by the patient. For each result, we calculated the median (IQR) time between result release and patient review. **Results:** The cohort (n = 169) was demographically diverse (median age 62.2 years, 41% female, and 25.4% Hispanic ethnicity). Of 346 ambulatory imaging studies performed during the study period, abnormal imaging findings were reported in 58 (16.8%): 14 on ultrasound (5 US-2 and 9 US-3) and 44 on CT or MRI (24 LR-3, 9 LR-4, 10 LR-5, and 1 LR-M). Over 90% (n = 312; 90.2%) of results were viewed by the patient. Only 12 (7.1%) patients (comprising 19 imaging studies) never viewed their results via the portal. Overall, the median time from result release to patient review was 3.6 (IQR 0.79-27.9) hours. **Conclusion:** Most patients with cirrhosis enrolled in the patient portal view their HCC imaging results via the patient portal, typically within a few hours of release. Given the risk of abnormal imaging findings, our study highlights a potential source of distress for patients accessing high-risk imaging results prior to result-related provider communication.

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The following people have nothing to disclose: Jeremy Louissaint, Jonathan Melendez-Torres, Elliot B. Tapper
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3803-C | PERSONALIZING HEPATOLOGY: THE ROLE OF CHATBOTS IN TAILORED TREATMENT PLANS IN THE FIELD OF HEPATOLOGY

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Background: Chatbot's like ChatGPT and Google Bard have significantly impacted healthcare, particularly hepatology, enhancing liver disease diagnosis and treatment. These advanced solutions interpret ultrasound images, analyze various samples, streamline administrative tasks, and aid in medical imaging and device automation. By enabling personalized treatments and side-effect predictions, they have considerably improved hepatology disorder management. Integrating these AI tools provides patients with tailored treatment evaluations, promoting informed decision-making. However, the effectiveness of these chatbots still warrants further scrutiny. **Methods:** The study set out to evaluate the precision of two prominent Chat Bots - Chat GPT and Google BARD - in addressing medical management queries. Both bots were tasked with a series of questions, and their responses were evaluated on a 1-10 Likert scale, with 1 indicating utmost accuracy. Two unbiased evaluators examined each bot's responses to ensure objective evaluation. The research aimed to provide insight into these Chat Bots' capabilities via a structured performance appraisal, focusing on accuracy and dependability. The dualevaluator system and the Likert scale approach helped minimize possible bias, thereby lending credibility to the findings. **Results:** Our research contrasted the effectiveness of Chat GPT and Google BARD in the realm of liver disease management. Chat GPT excelled, scoring 74% in the accuracy of information compared to Google BARD's 49% ($p = 0.015$) and 48% vs.29% in medical information reliability ($p = 0.032$). This study emphasizes the critical role of accuracy, and dependability, in developing liver disease-oriented chatbots. While Chat GPT displayed impressive performance, indicating its potential as a reliable tool, it also underscored the necessity for continued research and development in this field. **Conclusion:** This research revealed the relative strengths of Chat GPT and Google Bard in liver disease management, with Chat GPT outperforming in both accuracy and reliability. As AI technologies continue to permeate healthcare, ensuring their accuracy is crucial. While Chat GPT demonstrated promising potential as a reliable hepatology tool, it also highlighted the continuous need for research and development in this domain. The significant disparity in performance emphasizes the importance of rigorous testing and validation before integrating AI tools into medical practice.

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3804-C | PHASE ANGLE NEGATIVELY CORRELATES WITH LIVER FRAILTY INDEX AND MAY HELP PREDICT LIKELIHOOD OF DISCHARGE HOME AFTER LIVER TRANSPLANT

Nabeel Wahid, Northwestern Medicine, Fawzy Barry, University of California-San Francisco, Pamela M. Bloomer, University of Pittsburgh Medical Center, Jennifer C. Lai, University of California-San Francisco, San Francisco, CA and Andres Duarte-Rojo, Northwestern University Feinberg Scho

Background: Liver frailty index (LFI) is a clinical tool consisting of 3 performance-based tests (grip strength, chair stands, and balance) used to assess frailty in liver transplant (LT) candidates and has been associated with pre- and post-transplant mortality. Phase angle (PhA) from bioimpedance spectroscopy is an easily measured composite of tissue resistance and reactance to an electric current, which directly reflects muscle mass. Although PhA has been associated with frailty, it is unclear how well PhA correlates with LFI and whether the association is affected by outpatient (OP) or inpatient (IP) status. We examined the correlation of PhA with LFI in both OP and IP settings and explored their association with post-LT disposition. **Methods:** We utilized a prospective cohort of OP/IP being evaluated for LT at two transplant centers in the United States with available LFI and PhA measurements. LFI and PhA were measured between April 2021 and October 2022, and patients were followed until May 2023. Associations between PhA and LFI was assessed using Spearman rank or Mann-Whitney U tests. **Results:** A total of 82 patients, including 51 OP and 31 IP, were included in the study with a total of 36 patients (44%) proceeding to LT. Compared to IP, OP tended to have a higher BMI (27 vs 30, $p = 0.05$), lower MELD (15 vs 21, $p > 0.001$) and were more likely to identify as Hispanic (48% vs 2%, $p < 0.001$). PhA negatively correlated with LFI overall (Spearman's rho -0.34, $p = 0.003$) though this was driven by OP (Spearman's rho -0.57, $p < 001$) (Table). When broken down by LFI components, PhA correlated with grip strength in both OP and IP but only correlated with chair stands in OP. Although 55% of IP could not complete all the components of LFI (i.e., the chair stands/balance sections), there were no differences in PhA between those who completed and did not complete the chair stands/balance sections (median PhA 4.8 [IQR 3.4-5.4] vs 5.0 [IQR 3.9-6.8], respectively, $p = 0.35$). Yet, a patient's inability to complete the chair stands/balance sections conferred higher LFI scores (6.0 [5.9-6.4] vs 3.6 [3.3-4.6], $p < 0.001$). Neither LFI nor PhA were associated with LT ($p = 0.95$ and $p = 0.30$). However, lower OP LFI and higher OP PhA were observed in patients who were discharged home after LT vs. discharged elsewhere (median LFI 2.9 [IQR 2.3-3.4] vs 3.8 [IQR 3.4-4.8] respectively, $p = 0.008$; median PhA 5.3 [IQR 4.4-5.3] vs 3.2 [IQR 2.7-4.6] respectively, $p = 0.009$), with no relationship observed in IP. **Conclusion:** Expectedly, PhA negatively correlated to LFI, reflecting how higher muscle mass corresponds with a less frail profile. Both PhA and LFI were predictive of post-LT discharge when measured in the ambulatory setting. The association between PhA and LFI in IP was likely affected by assumptions made for patients unable to complete all LFI components. Further studies are needed to assess if PhA and LFI may be used as complementary metrics for prognosticating inpatients with severely impaired mobility.

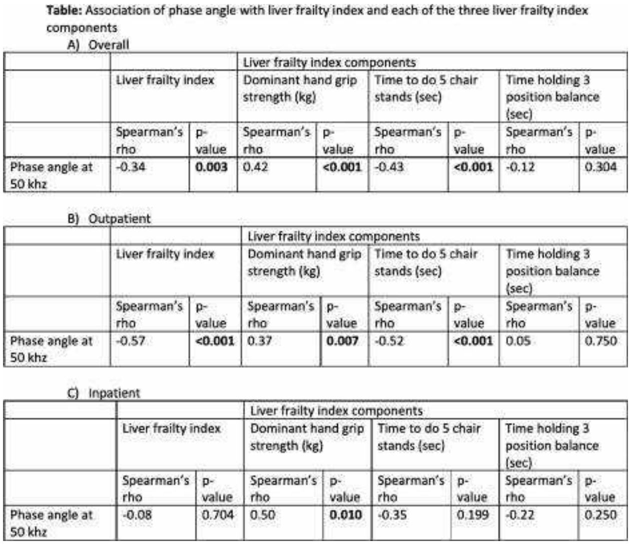

Table: Association of phase angle with liver frailty index and each of the three liver frailty index components

A) Overall

	Liver frailty index		Liver frailty index components					
			Dominant hand grip strength (kg)		Time to do 5 chair stands (sec)		Time holding 3 position balance (sec)	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
Phase angle at 50 khz	-0.34	**0.003**	0.42	**<0.001**	-0.43	**<0.001**	-0.12	0.304

B) Outpatient

	Liver frailty index		Liver frailty index components					
			Dominant hand grip strength (kg)		Time to do 5 chair stands (sec)		Time holding 3 position balance (sec)	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
Phase angle at 50 khz	-0.57	**<0.001**	0.37	**0.007**	-0.52	**<0.001**	0.05	0.750

C) Inpatient

	Liver frailty index		Liver frailty index components					
			Dominant hand grip strength (kg)		Time to do 5 chair stands (sec)		Time holding 3 position balance (sec)	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
Phase angle at 50 khz	-0.08	0.704	0.50	**0.010**	-0.35	0.199	-0.22	0.250

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3805-C | PREDICTING 90-DAY MORTALITY IN PATIENTS WITH DECOMPENSATED CIRRHOSIS USING THE "SURPRISE QUESTION": A PROSPECTIVE COHORT STUDY

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Background: The Surprise Question (SQ) has been previously used to predict mortality in patients with serious illnesses such as cancer and congestive heart failure. We aimed to assess the predictive accuracy of the SQ for hospitalized patients with decompensated cirrhosis (DC). **Methods:** We conducted a prospective cohort study of consecutive patients with DC admitted to a large academic medical center between 2/2022-1/2023. Internal medicine (IM) and/or hepatology clinicians (attendings and/or trainees/advanced practice providers [APP]) were approached within the first 72 hours of patients' admission. Clinicians were asked to provide a "surprised" (SQ+) or "not surprised" (SQ-) response to the following question: "would you be surprised if this patient were to die in the next 90 days?". To assess the performance of the 90-day SQ in predicting 90-day mortality, we calculated the sensitivity, specificity, positive and negative predictive values (PPV/NPV), positive and negative likelihood ratios (LR+/LR-), and accuracy. **Results:** The full cohort included 80 hospitalized patients with DC (mean age 58 (SD 13), median MELD-Na 21 [IQR 14-27], 13% on liver transplant waitlist). Response rates were 77% (54/70) among hepatology clinicians and 65% (110/168) among IM clinicians. Hepatology clinicians provided responses to the SQ for 35 patients of whom 12 (34%) had died by 90 days. IM clinicians provided responses for 79 patients of whom 19 (24%) had died by 90 days. Among hepatology clinicians, the 90-day SQ had the following test characteristics: sensitivity (8% [95%CI: 0-24%]), specificity (65% [95%CI: 46-85%]), PPV (11% [95%CI: 0-32%]), NPV (58% [95%CI: 39-77%]), LR+ (0.24 [95%CI: -0.23-0.71]), LR- (1.41 [95%CI: 0.92-1.89]), and accuracy (46% [95%CI: 29-62%]). Among IM clinicians, the 90-day SQ had the following test characteristics: sensitivity (26% [95%CI: 7-46%]), specificity (38% [95%CI: 26-51%]), PPV (12% [95%CI: 2-22%]), NPV (62% [95%CI: 47-78%]), LR+ (0.43

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

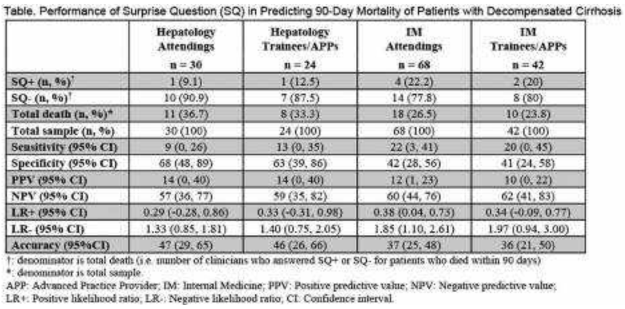

Table. Performance of Surprise Question (SQ) in Predicting 90-Day Mortality of Patients with Decompensated Cirrhosis

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

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

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Disclosure information not available at the time of publication: Chengbo Zeng, Teresa Indriolo, Nancy Mason, Michaela Rowland, Kirsten Engel, Dio Kavalieratos, Kedie Pintro, Nora Horick, Maria Edelen, Areej El-Jawahri, Kei Ouchi

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

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Background: Patients with cirrhosis are at risk for developing complications which are associated with high mortality. Prognostic tools estimating a patient's risk of adverse liver outcomes based on cirrhosis etiology could inform disease management. The aims of our study were to investigate predictors of adverse liver outcomes and to develop simplified prognostic models by disease etiology among patients with cirrhosis. **Methods:** Six prognostic models were developed using proportional hazards regression, classified by cirrhosis etiology, after identifying meaningful predictors of 5-year risk of ascites, hepatic encephalopathy (HE), and variceal bleeding (VB) among patients with cirrhosis due to nonalcoholic steatohepatitis (NASH) or viral hepatitis (table 2). The predictors for each model were selected via LASSO regression. **Results:** A total of 4045 adult patients with cirrhosis were included in the analysis from a single U.S. center retrospective cohort. The 5-year rates were 31.6%, 22.9%, and 30.7% for ascites, HE, and VB, respectively. Baseline characteristics of study population are summarized in table 1. Multivariable analyses showed that independent predictors in cirrhosis due to NASH and viral hepatitis were: (a) ascites: albumin and international normalized ratio (INR); (b) HE: albumin, INR, total bilirubin, platelet count; (c) VB: albumin, platelet count, hemoglobin. No variables were significantly associated with outcomes in patients with alcohol-associated liver disease. Validation analyses based on 30-day risk showed that these models were reasonably predictive (table 3). **Conclusion:** Our new, simplified models accurately and consistently predicted 5-year risk of ascites, HE, and VB among patients with cirrhosis due to NASH or viral hepatitis using simple routinely available variables measured at baseline. These models could be employed to identify high-risk patients who might benefit from greater attention and more aggressive treatments.

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

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Background: Liver fibrosis may lead to hepatocellular carcinoma (HCC). Hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, metabolic syndrome, and alcohol use disorder (AUD) are risk factors for fibrosis. Early screening for fibrosis using serum biomarkers in community settings is not well established. **Methods:** Adult patients at the HOPE Clinic, a federally qualified health care center in Houston, were enrolled from January 2021 through May 2023 and surveyed about risk factors for liver fibrosis. We measured vital signs and waist circumference, calculated body mass index (BMI), and performed blood testing. We defined chronic HBV infection as positivity for hepatitis B surface antigen; chronic HCV infection as detectable HCV RNA; metabolic syndrome as the presence of at least 3 of 4 conditions: hyperglycemia, hypertension, dyslipidemia, and obesity; and AUD as an AUDIT-C score of ≥ 4 for men and ≥ 3 for women. Transient elastography was performed to assess for fibrosis, with scores ≥ 8 kPa indicating $\geq$F2 fibrosis. Serum biomarkers of fibrosis were defined as Fibrosis-4 (FIB-4) score ≥ 2.67 (based on ALT, AST, platelets, age); NAFLD Fibrosis Score (NFS) ≥ 0.675 (based on ALT, AST, platelets, albumin, age, BMI, diabetes); and Fatty Liver Index (FLI) ≥ 30 (based on triglycerides, gamma-glutamyl transferase, waist circumference, BMI). We described the prevalence of fibrosis risk factors and tested the associations of risk factors and serum biomarkers with $\geq$F2 fibrosis using Fisher's exact test. Logistic regression was used to model the outcome of $\geq$F2 fibrosis. **Results:** We enrolled 977 patients, 409 men (42%) and 568 women (58%). The median age was 48 years (IQR = 22). A total of 483 patients (50%) were White, 252 (27%) were Asian, and 210 (22%) were Black. Among all patients, 394 (41%) were Hispanic. Forty-three percent of patients (n = 416) had BMI ≥ 30. Six percent of patients (57/944) had chronic HBV infection, < 1% (1/939) had chronic HCV infection, 48% (440/912) had metabolic syndrome, and 13% (125/971) had AUD. Of 891 patients who completed transient elastography, 86 (10%) had $\geq$F2 fibrosis. Among patients with metabolic syndrome, FIB-4 score ≥ 2.67 (OR 26.2, 95% CI 5.3-129.7) and NFS ≥ 0.675 (OR 8.9, 95% CI 2.3-34.3) were predictive of $\geq$F2 fibrosis, but FLI ≥ 30 (OR 4.5, 95% CI 0.7-27.6) was not. The receiver operating characteristic curve for the model was 0.74 (95% CI 0.68-0.80). After controlling for age and sex, we found that metabolic syndrome (1.89, [95% CI 1.09-3.26]), AUD (1.15 [95% CI 1.02-1.30]), NFS ≥0.675 (1.54 [95% CI 1.21-1.96]), and FIB-4 ≥2.67 (1.33 [95% CI 1.07-1.66]) were statistically significant predictors of fibrosis > F2 (see Table). **Conclusion:** In this community-based study, 1 in 10 patients had fibrosis. Metabolic syndrome and AUD were significant predictors of ≥F2 fibrosis, along with FIB-4 and NFS. Incorporating these predictors into clinical algorithms will be useful to prevent HCC.

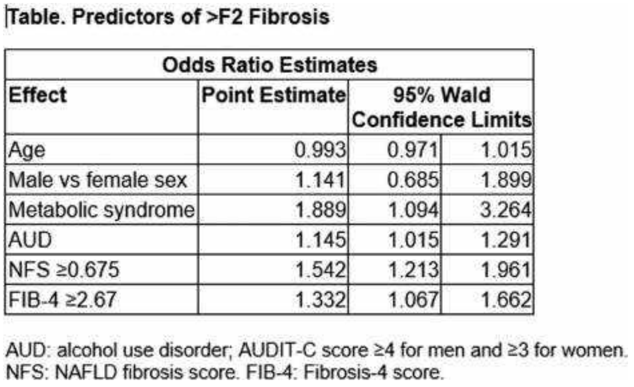

Table. Predictors of >F2 Fibrosis

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
Age	0.993	0.971	1.015
Male vs female sex	1.141	0.685	1.899
Metabolic syndrome	1.889	1.094	3.264
AUD	1.145	1.015	1.291
NFS ≥0.675	1.542	1.213	1.961
FIB-4 ≥2.67	1.332	1.067	1.662

AUD: alcohol use disorder; AUDIT-C score ≥4 for men and ≥3 for women.
NFS: NAFLD fibrosis score. FIB-4: Fibrosis-4 score.

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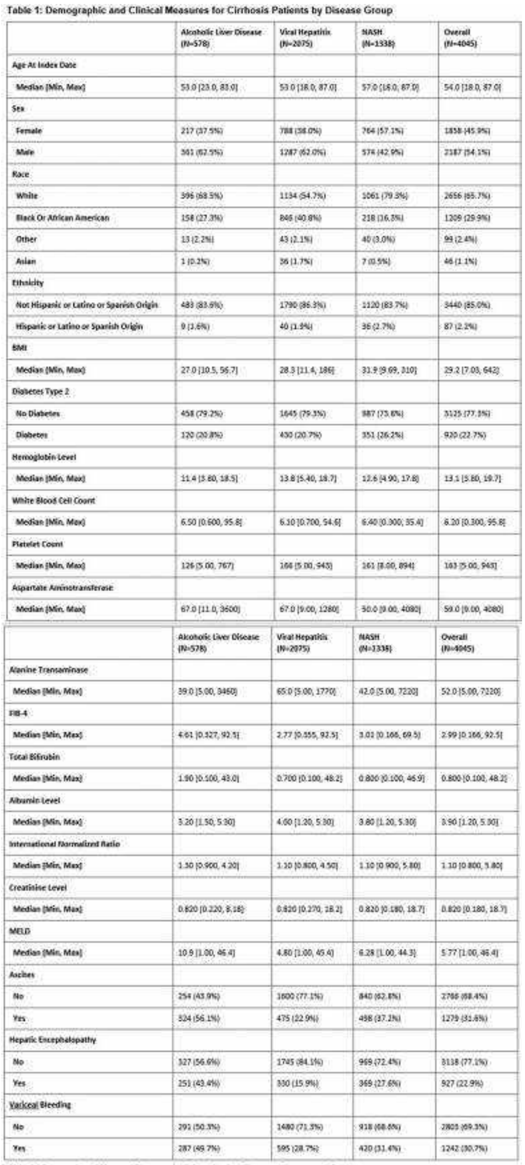

Table 1: Demographic and Clinical Measures for Cirrhosis Patients by Disease Group

	Alcoholic Liver Disease (N=578)	Viral Hepatitis (N=2075)	NASH (N=1338)	Overall (N=4045)
Age At Index Date				
Median [Min, Max]	53.0 [23.0, 83.0]	53.0 [18.0, 87.0]	57.0 [16.0, 87.0]	54.0 [18.0, 87.0]
Sex				
Female	217 (37.5%)	788 (38.0%)	764 (57.1%)	1858 (45.9%)
Male	361 (62.5%)	1287 (62.0%)	574 (42.9%)	2187 (54.1%)
Race				
White	396 (68.5%)	1134 (54.7%)	1061 (79.3%)	2656 (65.7%)
Black Or African American	158 (27.3%)	846 (40.8%)	218 (16.3%)	1209 (29.9%)
Other	13 (2.2%)	43 (2.1%)	40 (3.0%)	99 (2.4%)
Asian	1 (0.2%)	36 (1.7%)	7 (0.5%)	46 (1.1%)
Ethnicity				
Not Hispanic or Latino or Spanish Origin	483 (83.6%)	1790 (86.3%)	1120 (83.7%)	3440 (85.0%)
Hispanic or Latino or Spanish Origin	9 (1.6%)	40 (1.9%)	36 (2.7%)	87 (2.2%)
BMI				
Median [Min, Max]	27.0 [10.5, 56.7]	28.3 [11.4, 186]	31.9 [9.69, 310]	29.2 [7.03, 642]
Diabetes Type 2				
No Diabetes	458 (79.2%)	1645 (79.3%)	987 (73.8%)	3125 (77.3%)
Diabetes	120 (20.8%)	430 (20.7%)	351 (26.2%)	920 (22.7%)
Hemoglobin Level				
Median [Min, Max]	11.4 [3.80, 18.5]	13.8 [5.40, 18.7]	12.6 [4.90, 17.8]	13.1 [3.80, 19.7]
White Blood Cell Count				
Median [Min, Max]	6.50 [0.600, 95.8]	6.10 [0.700, 54.6]	6.40 [0.300, 35.4]	6.20 [0.300, 95.8]
Platelet Count				
Median [Min, Max]	126 [5.00, 767]	166 [5.00, 943]	161 [8.00, 894]	163 [5.00, 943]
Aspartate Aminotransferase				
Median [Min, Max]	67.0 [11.0, 3600]	67.0 [9.00, 1280]	50.0 [9.00, 4080]	59.0 [9.00, 4080]
Alanine Transaminase				
Median [Min, Max]	39.0 [5.00, 3460]	65.0 [5.00, 1770]	42.0 [5.00, 7220]	52.0 [5.00, 7220]
FIB-4				
Median [Min, Max]	4.61 [0.327, 92.5]	2.77 [0.555, 92.5]	3.01 [0.166, 69.5]	2.99 [0.166, 92.5]
Total Bilirubin				
Median [Min, Max]	1.90 [0.100, 43.0]	0.700 [0.100, 48.2]	0.800 [0.100, 46.9]	0.800 [0.100, 48.2]
Albumin Level				
Median [Min, Max]	3.20 [1.50, 5.30]	4.00 [1.20, 5.30]	3.80 [1.20, 5.30]	3.90 [1.20, 5.30]
International Normalized Ratio				
Median [Min, Max]	1.30 [0.900, 4.20]	1.10 [0.800, 4.50]	1.10 [0.900, 5.80]	1.10 [0.800, 5.80]
Creatinine Level				
Median [Min, Max]	0.820 [0.220, 8.18]	0.820 [0.270, 18.2]	0.820 [0.180, 18.7]	0.820 [0.180, 18.7]
MELD				
Median [Min, Max]	10.9 [1.00, 46.4]	4.80 [1.00, 45.4]	6.28 [1.00, 44.3]	5.77 [1.00, 46.4]
Ascites				
No	254 (43.9%)	1600 (77.1%)	840 (62.8%)	2766 (68.4%)
Yes	324 (56.1%)	475 (22.9%)	498 (37.2%)	1279 (31.6%)
Hepatic Encephalopathy				
No	327 (56.6%)	1745 (84.1%)	969 (72.4%)	3118 (77.1%)
Yes	251 (43.4%)	330 (15.9%)	369 (27.6%)	927 (22.9%)
Variceal Bleeding				
No	291 (50.3%)	1480 (71.3%)	918 (68.6%)	2803 (69.3%)
Yes	287 (49.7%)	595 (28.7%)	420 (31.4%)	1242 (30.7%)

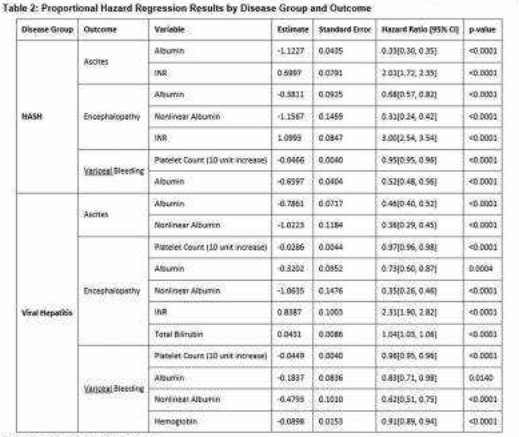

Table 2: Proportional Hazard Regression Results by Disease Group and Outcome

Disease Group	Outcome	Variable	Estimate	Standard Error	Hazard Ratio [95% CI]	p-value
NASH	Ascites	Albumin	-1.1227	0.0435	0.33[0.30, 0.35]	<0.0001
		INR	0.6997	0.0791	2.01[1.72, 2.35]	<0.0001
	Encephalopathy	Albumin	-0.3811	0.0925	0.68[0.57, 0.82]	<0.0001
		Nonlinear Albumin	-1.1567	0.1459	0.31[0.24, 0.42]	<0.0001
		INR	1.0993	0.0847	3.00[2.54, 3.54]	<0.0001
	Variceal Bleeding	Platelet Count (10 unit increase)	-0.0466	0.0040	0.95[0.95, 0.96]	<0.0001
		Albumin	-0.6597	0.0404	0.52[0.48, 0.56]	<0.0001
Viral Hepatitis	Ascites	Albumin	-0.7861	0.0717	0.46[0.40, 0.52]	<0.0001
		Nonlinear Albumin	-1.0223	0.1184	0.36[0.29, 0.45]	<0.0001
	Encephalopathy	Platelet Count (10 unit increase)	-0.0286	0.0044	0.97[0.96, 0.98]	<0.0001
		Albumin	-0.3202	0.0952	0.73[0.60, 0.87]	0.0004
		Nonlinear Albumin	-1.0635	0.1476	0.35[0.26, 0.46]	<0.0001
		INR	0.8387	0.1003	2.31[1.90, 2.82]	<0.0001
		Total Bilirubin	0.0431	0.0086	1.04[1.03, 1.06]	<0.0001
	Variceal Bleeding	Platelet Count (10 unit increase)	-0.0449	0.0040	0.96[0.95, 0.96]	<0.0001
		Albumin	-0.1837	0.0836	0.83[0.71, 0.98]	0.0140
		Nonlinear Albumin	-0.4793	0.1010	0.62[0.51, 0.75]	<0.0001
		Hemoglobin	-0.0898	0.0153	0.91[0.89, 0.94]	<0.0001

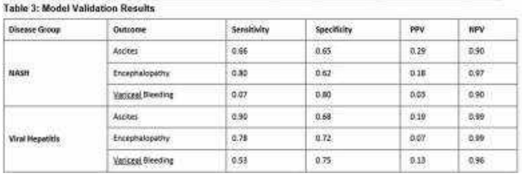

Table 3: Model Validation Results

Disease Group	Outcome	Sensitivity	Specificity	PPV	NPV
NASH	Ascites	0.66	0.65	0.29	0.90
	Encephalopathy	0.80	0.62	0.18	0.97
	Variceal Bleeding	0.07	0.80	0.03	0.90
Viral Hepatitis	Ascites	0.90	0.68	0.19	0.99
	Encephalopathy	0.78	0.72	0.07	0.99
	Variceal Bleeding	0.53	0.75	0.13	0.96

3808-C | PSYCHOSOCIAL PREDICTORS OF REQUIRING EXPEDITED INPATIENT LIVER TRANSPLANT EVALUATION

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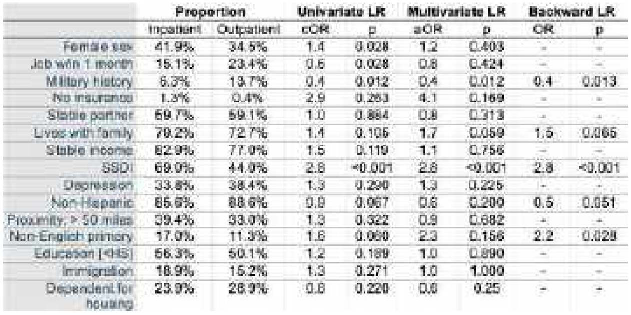
Background: Failure to refer for liver transplant evaluation (LTE) in a timely manner may lead to expedited LTE in the setting of acute decompensation. It has been historically difficulty to identify risk factors for late referral, particularly psychosocial risk factors. We analyzed patients undergoing inpatient LTE (I-LTE) versus outpatient LTE (O-LTE) to identify psychosocial risk factors for expedited LTE at our center. **Methods:** Patients completed LTE for cirrhosis over a 4-year period were included. Psychosocial data was collected from social work and psychiatry LTE assessments. 15 variables were compared between I-LTE and O-LTE: age, sex, education, proximity to center > 50 miles (proximity) marital status (MS), insurance status (IS), living with family, being dependent on others for housing (housing dependent), military history (military), employment within 1-month, stable income, social security income (SSDI), depression history, English as a second language (ESL), and birthplace (in vs. out of US). Univariable logistic regression (LR) was used to identify psychosocial variables associated with I-LTE. A multivariate LR model was built and backward LR was used to identify potential independent predictors of transplant; probability to enter = 0.05 and probability to remove = 0.10. Models were assessed using Hosmer Goodness of Fit (GoF). **Results:** 624 patients were included (25.6% I-LTE vs 74.3% O-LTE). I-LTEs were more likely to be women, Hispanic, and to have autoimmune or genetic liver disease. Death was more common and transplant less common in I-LTE. Multivariate LR using all factors had excellent GoF (0.97). Potential independent predictors of LTE location on backward LR included military, SSDI, ethnicity, ESL and living with family (right panel). Adding disease etiology did not affect these findings. Predictors differed between men and women. Predictors of I-LTE in men included: military (OR 0.41), MS (OR 0.47), SSDI (OR 3.0), and housing dependent (OR 1.8). Predictors in women included MS (2.6), SSDI (2.4), Hispanic ethnicity (1.6), proximity (2.4), ESL (3.6). Models had higher GoF in men than women (0.75 vs. 0.40). **Conclusion:** Expedited LTE is associated with increased risk of mortality in men and women. Psychosocial variables may strengthen models aiming to identify patients at risk for expedited LTE at individual centers. Housing situation and SSDI were strongly associated with increased risk of I-LTE for men and women at our center. However, having a stable relationship was protective against I-LTE in men but not in women. Psychosocial factors differ by sex in patients seeking LT and should be considered when referring patients for LTE.



	Proportion		Univariate LR		Multivariate LR		Backward LR	
	Inpatient	Outpatient	cOR	p	aOR	p	OR	p
Female sex	41.9%	34.5%	1.4	0.028	1.2	0.403	-	-
Job w/in 1 month	15.1%	23.4%	0.6	0.028	0.8	0.424	-	-
Military history	6.3%	13.7%	0.4	0.012	0.4	0.012	0.4	0.013
No insurance	1.3%	0.4%	2.9	0.263	4.1	0.169	-	-
Stable partner	69.7%	69.1%	1.0	0.884	0.8	0.313	-	-
Lives with family	79.2%	72.7%	1.4	0.105	1.7	0.059	1.5	0.065
Stable income	82.9%	77.0%	1.5	0.119	1.1	0.756	-	-
SSDI	69.0%	44.0%	2.8	<0.001	2.8	<0.001	2.8	<0.001
Depression	33.8%	38.4%	1.3	0.290	1.3	0.225	-	-
Non-Hispanic	85.6%	88.6%	0.9	0.067	0.6	0.200	0.5	0.051
Proximity: > 50 miles	39.4%	33.0%	1.3	0.322	0.9	0.682	-	-
Non-English primary	17.0%	11.3%	1.6	0.080	2.3	0.156	2.2	0.028
Education (<HS)	56.3%	50.1%	1.2	0.189	1.0	0.890	-	-
Immigration	18.9%	15.2%	1.3	0.271	1.0	1.000	-	-
Dependent for housing	23.9%	26.9%	0.8	0.220	0.8	0.25	-	-

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3809-C | QUALITY OF LIFE, SYMPTOM BURDEN, PSYCHOLOGICAL DISTRESS, AND PROGNOSTIC PERCEPTIONS AMONG PATIENTS WITH DECOMPENSATED CIRRHOSIS

Nneka Ufere[1], Lucinda Li[1], John Donlan[2], Teresa Indriolo[1], Joyce Zhou[1], Alyson Kaplan[3], Alan Noll[4], Nancy Mason[1], Michaela Rowland[1], Kirsten Engel[1], Jennifer C. Lai[5], Maria Edelen[6], Chengbo Zeng[6], Kedie Pintro[1], Nora Horick[1] and Areej El-Jawahri[1], (1) Massachusetts General Hospital, (2)Harvard Medical School, (3)New York-Presbyterian/Weill Cornell Medical Center, (4)University of Pittsburgh Medical Center, (5) University of California-San Francisco, San Francisco, CA, (6)Brigham and Women's Hospital

Background: Patients with decompensated cirrhosis (DC) struggle with a life-limiting illness course. Yet, data describing patients' quality of life (QOL), symptom burden, psychological distress, and illness and prognostic understanding in this population are lacking. **Methods:** We conducted a cross-sectional study in which outpatients with DC completed assessments of quality of life (Short-Form Liver Disease Quality of Life scale, SF-LDQOL, range 0-100, higher scores = higher QOL), symptom burden (Revised Edmonton Symptom Assessment Scale, ESAS-r), depression (Patient

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

Health Questionnaire 9, PHQ-9) and anxiety symptoms (Hospital Anxiety and Depression Scale, HADS-A). Patients also completed the Prognostic Treatment Perceptions Questionnaire to assess their readiness to discuss prognosis and self-reported health status. We used linear regression analyses to examine the associations of patients' self-reported health status (terminally ill vs. not terminally ill) and their quality of life, symptom burden, and psychological distress. **Results:** Between July 2018 and September 2022 we prospectively enrolled 66% (218 of 330) of eligible outpatients with DC (mean age 57.5 [SD 10.2], median MELD-Na 16 [IQR 11-22], 50% listed for transplant). To date, the cohort has had 1-year and 2-year mortality rates of 12.3% (27/218) and 19.3% (42/218), respectively. Mean SF-LDQOL score was 57.8 (SD 16.4). Patients reported a high frequency of moderate-to-severe tiredness (77%), drowsiness (68%), pain (50%) and muscle cramps (48%). In total, 42% reported moderate-to-severe depression and 44% reported clinically significant anxiety symptoms. Almost all (93%) indicated that knowing their prognosis was "extremely important" or "important". However, 81% had never discussed their end-of-life care wishes with their hepatologist. Overall, 34% self-reported a terminally ill health status. Patients who reported a terminally ill health status had worse quality of life (SF-LDQOL; B = -7.27, p = 0.002), symptom burden (ESAS; B = 8.54, p = 0.003), anxiety (HADS-A; B = 1.89, p = 0.002) and depression (PHQ-9; B = 2.64, p = 0.001). **Conclusion:** Patients with DC struggle with poor QOL and immense symptom burden and psychological distress. Despite patients reporting the importance of knowing their prognosis, self-reported terminally ill health status was associated with lower QOL and mood. Interventions to improve patients' prognostic understanding while providing adequate psychosocial support are warranted.

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3810-C | SERIOUS ILLNESS COMMUNICATION SKILLS TRAINING FOR GASTROENTEROLOGY FELLOWS: A PILOT STUDY

Nilofar Najafian[1], Anne Walling[1], Karen Spritzer[1], Janet Gripshover[2], Shirley Otis-Green[1], Lin Chang[1], Neil Wenger[1] and Arpan Arun Patel[3], (1)University of California-Los Angeles, (2)Geisinger Medical Center, (3)Greater Los Angeles VA Healthcare System

Background: Patients with decompensated cirrhosis and their treating clinicians rarely engage in goals of care discussions, despite recommendations. Participation in serious illness communication skills training may help clinicians improve their confidence and skills for such discussions, but gastroenterologists (GIs) and hepatologists lack training opportunities individualized to their practice. Investment in such training during GI fellowship is ideal, as standardized assessments show deficiencies in end-of-life communication among GI fellows, and GIs/hepatologists cite insufficient training as a major barrier to conversations. Normalization of such conversations among GIs/hepatologists can help ensure that care delivered is more patient and caregiver-centered. Our aim is to report the results of a pilot training program on serious illness communication skills for GI fellows. **Methods:** The 2.5-hour training included didactics on advance care planning and serious illness communication (1 hour) and practice delivering serious news to standardized patients (1.5 hours, sharing with a patient with cirrhosis that they are not a transplant candidate). Adaptation of training materials, development of cases, and training of standardized patients were conducted by the interdisciplinary UCLA Advance Care Planning Program (https://www.uclahealth.org/programs/advance-care-planning). Fellows were asked to complete surveys pre- and post-training, which included questions about demographics and prior training [pre-, N = 6], session feedback [post-, N = 7], and validated items assessing self-reported clinician barriers to goals of care communication [pre- and post-, N = 36]. We analyzed results using descriptive statistics and performed paired *t*-tests to assess the relationship between communication skills training and self-reported barriers. **Results:** A total of 21 fellows (20 GI, 1 transplant hepatology) completed training and the assessments. Little over half (12/21 = 57%) reported

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prior training consisting of observation and structured feedback. Domains that significantly improved after training included: self-reported knowledge, skills, beliefs about capabilities, attitudes about organizational support and social/professional role regarding having discussions. All fellows reported the program format and selection of topics as very good or excellent. Qualitative feedback supported these findings (Figure). Conclusion: A 2.5-hour serious illness communication training was highly acceptable and significantly improved multiple domains, including GI fellows' self-reported knowledge, skills, capabilities for communication, and attitudes about organizational support and social/professional role. Such programs should be adapted using trainee feedback, scaled, and disseminated.

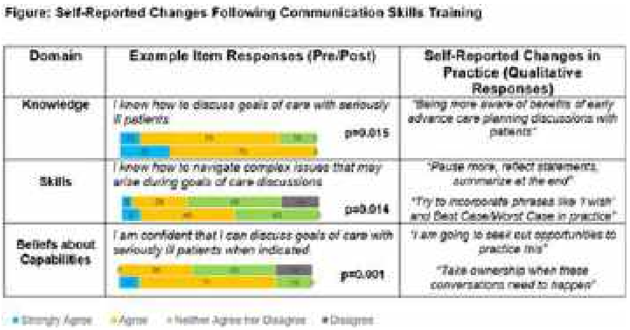
Figure: Self-Reported Changes Following Communication Skills Training

Domain	Example Item Responses (Pre/Post)	Self-Reported Changes in Practice (Qualitative Responses)
Knowledge	*I know how to discuss goals of care with seriously ill patients* p=0.015	*"Being more aware of benefits of early advance care planning discussions with patients"*
Skills	*I know how to navigate complex issues that may arise during goals of care discussions* p=0.014	*"Pause more, reflect statements, summarize at the end"* *"Try to incorporate phrases like 'I wish' and Best Case/Worst Case in practice"*
Beliefs about Capabilities	*I am confident that I can discuss goals of care with seriously ill patients when indicated* p=0.001	*"I am going to seek out opportunities to practice this"* *"Take ownership when these conversations need to happen"*

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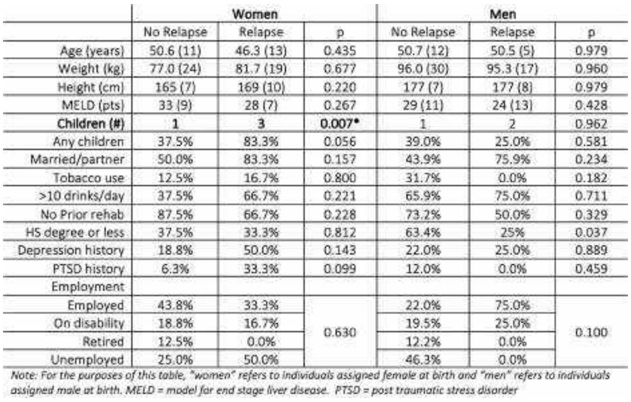
f 3811-C | SEX DIFFERENCES IN POST LIVER TRANSPLANT ALCOHOL RELAPSE IN PATIENTS EVALUATED WITH EARLY SOBRIETY

Katherine M. Cooper[1], *Alessandro Colletta*[2] *and Deepika Devuni*[1], *(1)UMass Chan Medical School, (2) UMass Chan Medical School, Worcester, MA*

Background: Alcohol associated liver disease (ALD) is an increasingly prevalent transplant indication in the United States for both acute and chronic forms of liver failure. Risk factors for alcohol relapse have been studied but are poorly understood, particularly in patients with early liver transplant evaluation (e-LTE) after alcohol cessation We aimed to assess risk factors for relapse in patients with e-LTe with a focus on identifying sex differences in risk factors for relapse. **Methods:** We retrospectively analyzed patients with ALD and early alcohol sobriety (<6 mo) who completed e-LTE between 2018 and 2021 ($n=162$). Patients were further categorized by 0-3 mos (very early) and 3-6 mos sobriety (early). Clinical, demographic, and psychosocial factors were collected at time of LTE. Psychosocial predictors of post LT alcohol relapse were evaluated in the total cohort and by patient gender. Backward logistic regression was used to identify potential predictors of relapse amongst all variables in the total group (See table 1 for list). Subsequently, data was compared by relapse status in men and in women using Fishers Exact and Students t-tests. Odds ratios were calculated with logistic regression. A trend was evaluated at $p=0.10$ and significance was evaluated at $p=0.05$. **Results:** 162 patients were identified (82 very early LTE and 80 early LTE). 67 patients (42.1%) underwent LT and this was more common in very early sobriety group (50.0% vs. 32.1%, $p=0.02$). Post LT relapse rate was 10% overall; the strongest potential predictors of relapse were sex (0.05), marital status (0.11), and number of standard drinks per day ($p=0.05$). Of note, there were no differences in post-LT treatment for alcohol use disorder (not shown). Relapse was 3.5x more common in women overall (27.3% vs. 8.9%, $p=0.05$). On subgroup analysis, this relationship persists in the very early sobriety group (35.7% vs. 7.4%, $p=0.02$), but does not in the early group (12.5% vs. 11.1%, $p=0.91$). Women with post LT relapse were younger, but not significantly, than those without relapse. Marriage status, employment, depression and PTSD history, prior alcohol use treatment, and number of daily drinks were similar by relapse status for men and women. However, women with post LT relapse were more likely to have children than women without relapse ($p=0.05$). Further, women with relapse had more children under the age of 18 years on average than those without post-LT relapse. This relationship was generally persevered when controlling for age, race, and education status on multivariate logistic regression (OR 3.8, $p=0.07$). **Conclusion:** Women with ALD who have children, particularly younger children, may be at increased risk of relapse. The more negative effect on women compared to men may be due to increased caregiving responsibility. There is significant opportunity to better understand this relationship and improve interventions to reduce relapse in this high-risk population.



	Women			Men		
	No Relapse	Relapse	p	No Relapse	Relapse	p
Age (years)	50.6 (11)	46.3 (13)	0.435	50.7 (12)	50.5 (5)	0.979
Weight (kg)	77.0 (24)	81.7 (19)	0.677	96.0 (30)	95.3 (17)	0.960
Height (cm)	165 (7)	169 (10)	0.220	177 (7)	177 (8)	0.979
MELD (pts)	33 (9)	28 (7)	0.267	29 (11)	24 (13)	0.428
Children (#)	**1**	**3**	**0.007***	1	2	0.962
Any children	37.5%	83.3%	0.056	39.0%	25.0%	0.581
Married/partner	50.0%	83.3%	0.157	43.9%	75.9%	0.234
Tobacco use	12.5%	16.7%	0.800	31.7%	0.0%	0.182
>10 drinks/day	37.5%	66.7%	0.221	65.9%	75.0%	0.711
No Prior rehab	87.5%	66.7%	0.228	73.2%	50.0%	0.329
HS degree or less	37.5%	33.3%	0.812	63.4%	25%	0.037
Depression history	18.8%	50.0%	0.143	22.0%	25.0%	0.889
PTSD history	6.3%	33.3%	0.099	12.0%	0.0%	0.459
Employment						
Employed	43.8%	33.3%	0.630	22.0%	75.0%	0.100
On disability	18.8%	16.7%		19.5%	25.0%	
Retired	12.5%	0.0%		12.2%	0.0%	
Unemployed	25.0%	50.0%		46.3%	0.0%	

Note: For the purposes of this table, "women" refers to individuals assigned female at birth and "men" refers to individuals assigned male at birth. MELD = model for end stage liver disease. PTSD = post traumatic stress disorder

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3812-C | STIGMA IS A PREDICTOR OF IMPAIRMENT OF HEALTH RELATED QUALITY OF LIFE AMONG PATIENTS WITH NAFLD

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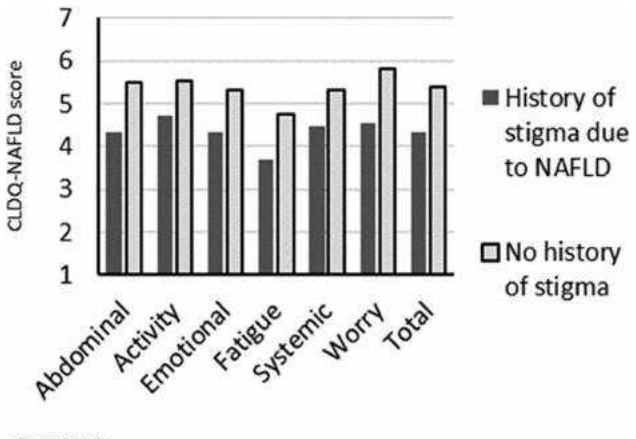
Background: Stigma can be associated with impairment of patients' quality-of-life. Aim: Evaluate the association between stigma and HRQL among NAFLD patients. **Methods:** NAFLD patients were invited to complete the Chronic Liver Disease Questionnaire-NAFLD (CLDQ-NASH; 36 items, 6 domains, range 1-7,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



All p values<0.05

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3813-C | SYMPTOM BURDEN, QUALITY OF LIFE, AND PALLIATIVE CARE IN END-STAGE LIVER DISEASE

Joel P. Wedd[1], Danielle Noreika[1], Irma Hashmi[1], Stephanie Taylor[1] and Richard K. Sterling[2], (1)Virginia Commonwealth University, (2)Virginia Commonwealth University Health System

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

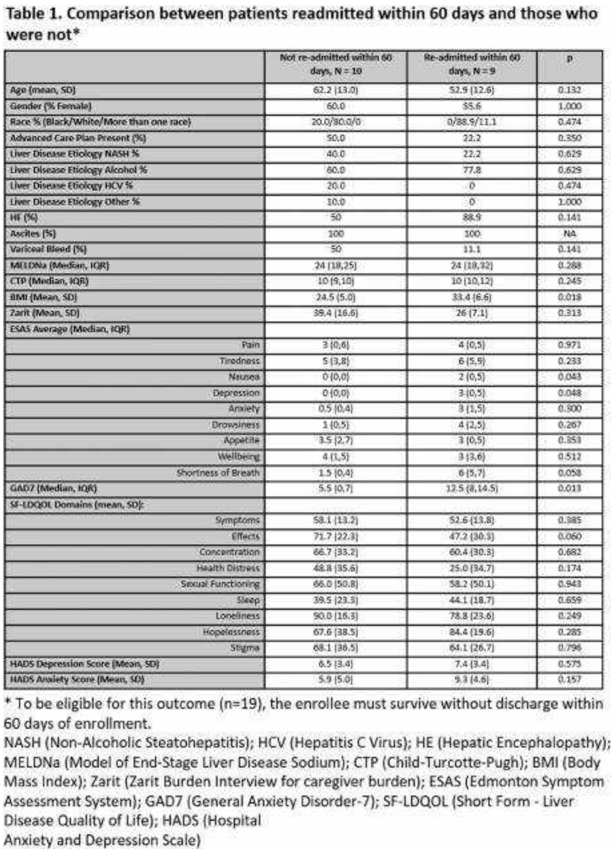

Table 1. Comparison between patients readmitted within 60 days and those who were not*

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

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

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

Masaaki Korenaga[1]*, Chieko Ohe*[2]*, Keiko Kamimura*[2]*, Keiko Korenaga*[3]*, Tatsuya Ide*[4] *and Tatsuya Kanto*[5]*, (1) The Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, (2) Japan Health Insurance Association, (3)National Center for Global Health and Medicine, (4)Kurume University School of Medicine, (5)The Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Ichikawa, Japan*

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

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3815-C | The associations between MELD, CTP and Quality of Life scores for patients with End Stage Liver Disease.

Manisha Verma[1], *Alfred Sidney Barritt IV*[2], *Maya Balakrishnan*[3], *Marina M. Roytman*[4], *Binu V John*[5], *Andrzej Kosinski*[6], *Yang Yue*[6] *and Victor J. Navarro, Md*[7], *(1)Einstein Medical Center, (2)University of North Carolina, (3)Baylor College of Medicine, Houston, TX, (4)UCSF Fresno, (5)University of Miami and Miami VA, (6)Duke Clinical Research Institute, (7)Albert Einstein Medical Center, Doylestown, PA*

Background: Patient reported quality of life (QoL) has increasingly been recognized as an important clinical parameter and research end point in palliative care (PC) and hepatology research. This study investigates 1) the associations between baseline liver function (MELD, CTP scores) and QoL measures (Patient Reported Outcomes Measurement Information System/ PROMIS-29 domain scores and FACT-Hep total score), and 2) provides estimates of PROMIS-29 domain scores for ESLD patients participating in the ongoing PAL LIVER trial. **Methods:** PAL-LIVER is a multi-site cluster randomized PC intervention trial enrolling patients with decompensated cirrhosis, and/or Hepatocellular Cancer (HCC). Pearson correlation coefficient was used to summarize the association between the baseline MELD, CTP and FACT-Hep total scores. To identify any moderation effect of HCC on the MELD and FACT-Hep association, linear regression with FACT-Hep as an outcome, and covariates including HCC status, MELD, as well as interaction between these two variables was done. In addition, we evaluated the relationship between FACT-Hep total score and PROMIS-29 domain scores, as well as HCC moderation effect on this relationship in the same way as described above. **Results:** Recruitment into this study is ongoing. 821 patients have been enrolled (mean age 62.8, 28% females, 79% Caucasians), with 29% having HCC. Mean baseline MELD score is 11.4 (SD 6.1), CTP score 8.3 (1.9) and FACT-Hep total score 116.2 (SD 28.1) respectively. There is a statistically significant correlation between MELD and FACT-Hep total score at baseline, although the magnitude is small (r = -0.13, p < 0.001). CTP score correlates better with FACT-Hep (-0.19, p < 0.001). Mean (SD) PROMIS- 29 T scores are- Physical function 38.4 (9.6), Anxiety 53.5 (10.9), Depression 53.3 (10.7), Fatigue 57.6 (11.5), Sleep disturbance 54.4 (10.8), Social roles 45.4 (10.6), and Pain interference 57.0 (11.0). Among all domain scores, physical function scores are the worst when compared to general population mean of 50 (SD = 10). All PROMIS-29 domain T scores correlate strongly with FACT-Hep total score (Table). The relationship between MELD and baseline FACT-Hep total score was stronger for HCC when compared to patients without HCC, but this differential effect was not statistically significant (interaction p = 0.058). Patients without HCC showed differential relationship of the FACT-Hep total score with Depression (interaction p < 0.001) and Fatigue (interaction p = 0.029) scores as compared to those with HCC. **Conclusion:** The correlation between MELD, CTP scores and QoL is moderate. CTP correlates better with QoL than MELD scores. FACT-Hep total score correlates strongly with all PROMIS-29 domains, thus future research can utilize either one. Given moderate correlation between liver function and QoL, there's probably other factors that contribute to QoL. There are differences in relationships in HCC Vs. no HCC patients.

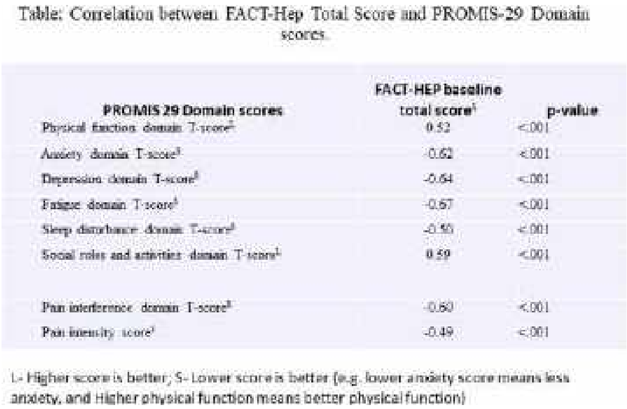

Table: Correlation between FACT-Hep Total Score and PROMIS-29 Domain scores.

PROMIS 29 Domain scores	FACT-HEP baseline total score[L]	p-value
Physical function domain T-score[L]	0.52	<.001
Anxiety domain T-score[S]	-0.62	<.001
Depression domain T-score[S]	-0.64	<.001
Fatigue domain T-score[S]	-0.67	<.001
Sleep disturbance domain T-score[S]	-0.55	<.001
Social roles and activities domain T-score[L]	0.59	<.001
Pain interference domain T-score[S]	-0.60	<.001
Pain intensity score[S]	-0.49	<.001

L- Higher score is better; S- Lower score is better (e.g. lower anxiety score means less anxiety, and Higher physical function means better physical function)

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3816-C | THE HOSPITAL FRAILTY RISK SCORE IDENTIFIES LIVER CIRRHOSIS PATIENTS AT RISK OF FRAILTY AND MORTALITY

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Background: Frailty in older adults and in liver cirrhosis is a predictor of worse outcomes and high resource utilization.[1] Validated assessments of frailty in liver cirrhosis include tests on physical function which may not be carried out routinely in real world clinical practice.

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

The hospital frailty risk score (HFRS)[2] uses administrative data from a set of weighted ICD10 codes to identify frailty. While the HFRS was originally designed as a geriatric assessment tool, our study aims to validate the HFRS in the cirrhotic population as a prognostic predictor of mortality and hospital readmissions. **Methods:** Patients with liver cirrhosis and at least 1 hospital admission in 2018 from 2 large public hospitals in Singapore were identified using ICD-10 codes. The diagnosis of cirrhosis was confirmed using imaging, liver stiffness measurement or histology. A 2-year lookback period, as utilized in the Gilbert study, was used to calculate the HFRS using the cumulative sum of a weighted ICD10 code set. Patients were categorized into low risk (HFRS < 5) or higher risk (HFRS ≥ 5). Patient outcomes were tracked from 2016-2020. **Results:** A total of 1037 patients with liver cirrhosis and at least 1 hospital admission or emergency department (ED) visit in the year 2018 were included. During the two-year lookback period for the 1037 patients, there were 8965 hospital admissions or ED visits where 286 distinct patients had visits with ICD-10 codes identified in the Gilbert study. Based on the weighted HFRS calculation, only 2.3% patients in the study cohort were in the higher risk (HFRS ≥ 5) group. However, these patients had a significantly higher mortality rate (79.2% vs. 35.1% HFRS < 5; $p = 0.008$). Additional subgroup analysis by age (< 65, 65-75, age > 75) was performed and showed a trend of increased mortality with each age category when comparing the two groups. The mortality data are as follows: Age < 65 (57.1% vs. 41.9% HFRS < 5); age 65-75 (75% vs. 55.7% HFRS < 5; Age > 75 (92.3% vs. 59% HFRS < 5). **Conclusion:** Our study shows that a Hospital Frailty Risk Score ≥ 5 is a significant predictor of frailty and mortality among patients with cirrhosis. Early identification of at-risk patients is necessary to implement interventions known to improve frailty, especially as we care for a globally aging population living with chronic disease. The HFRS is a useful cost-effective tool that can be leveraged using administrative data to identify at-risk patients with cirrhosis to help improve health outcomes.

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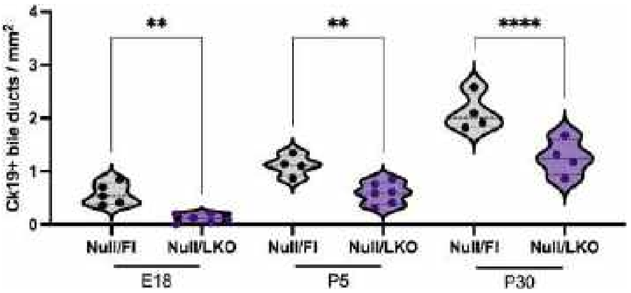
Disclosure information not available at the time of publication: Kalki Rajamanickam Chandrasekaran, Hiang Keat Tan, Rahul Kumar, Kevin Kim Jun Teh, Chanda Kendra Ho

f 3900-C | ABSENCE OF BILIARY ATRESIA CANDIDATE GENE PKD1L1 IMPAIRS BILIARY DEVELOPMENT

Dominick Hellen[1], Ashley Bennett[1], Caroline Klindt[1], David Lee[1], Paul A. Dawson[1] and Saul Karpen[2], (1) Division of Pediatric GI/Hepatology, Children's Healthcare of Atlanta & Emory University School of Medicine, (2)Children's Healthcare of Atlanta & Emory University School of Medicine, Atlanta, GA

Background: Biliary atresia (BA) is the most prevalent serious liver disease of infancy, yet limited progress has been made in understanding the causes and contributors to its etiopathogenesis. Recently, applying data acquired from human BA DNA analyses, a liver-restricted deletion of the BA candidate gene *Pkd1l1* in mice led to histologic features akin to that seen in BA livers including ciliopathy, ductal plate expansion, and enhanced peribiliary fibroinflammation. To better delineate *Pkd1l1*'s role in developing cholangiocytes, we studied embryonic, postnatal, and isolated cholangiocytes from a developmentally-focused *Pkd1l1* knockout line. **Methods**: We generated $Pkd1l1^{null/Fl}$ (null/Fl), and *null/Pkd1l1*-deficient mouse (null/LKO) models, respectively. From embryonic day 18 (E18) through postnatal day 30 (P30), null/Fl and null/LKO mice were evaluated with standard serum chemistries, and whole slide liver histology, with a focus on developmental biliary structures, junctional complexes, and transcription factors. At P30, bile duct ligation (BDL) was performed for 7 days of null/Fl and null/LKO mice followed by standard serum and liver analytics. Isolated intrahepatic $Pkd1l1^{Fl/Fl}$ (CTL) and *Pkd1l1-deficient* (KO) cholangiocytes were studied in vitro for structural features and reactive phenotype. **Results**: Histological analyses at ages E18, P5, and P30 revealed delayed biliary maturation, a significant increase in immature *Sox9*+ cholangiocytes, and a reduction of mature Ck19+ cholangiocytes and bile ducts in null/LKO compared to null/Fl livers (see Figure). Disordered tight junctional complexes were evident at ages P5 and P30 by disordered ZO-1 and β-catenin staining in null/LKO vs null/Fl cholangiocytes. Following BDL, peribiliary fibroinflammation, and necrosis were markedly increased in null/LKO compared to null/Fl livers. Isolated KO cholangiocytes revealed perturbed tight junctions, reduced cilia, altered β-catenin signaling, and decreased rates of proliferation in contrast to CTL. **Conclusion**: Developing cholangiocytes deficient in *Pkd1l1* exhibit ductal immaturity, with tight junction and intracellular structural disturbances. The absence of *Pkd1l1* in young cholangiocytes leads to enhanced susceptibility to obstructive damage from BDL. In sum, the null/LKO mouse provides a novel and useful model to explore the consequences of absent *Pkd1l1* with indication that its absence can induce the developmental cholangiopathy that leads to the BA phenotype. Figure: Delayed and reduced Ck19+ bile ducts at all time points throughout development in null/LKO compared to null/Fl livers. N = 4-6/group. $^{**}p < 0.01$, $^{****}p < 0.0001$.



Disclosures: Paul A. Dawson – Albireo Pharma, Inc.: Speaking and Teaching, No, No;

Saul Karpen – Albireo/Ipsen: Consultant, No, No; Mirum: Consultant, No, No; HemoShear: Consultant, No, No; Intercept: Consultant, No, No;

The following people have nothing to disclose: Dominick Hellen

Disclosure information not available at the time of publication: Ashley Bennett, Caroline Klindt, David Lee

3901-C | IL-17 SIGNALING IN PRIMARY SCLEROSING CHOLANGITIS PATIENT-DERIVED ORGANOIDS

Ana Sofia Garcia Moreno[1], Gregory J. Gores[1], Maria Eugenia Guicciardi[1], Erik Jessen[1], Alexander Q. Wixom[1], Filippo Pinto E Vairo[1], Jingchun Yang[1], Sumera I. Ilyas[2], Jackie K Bianchi[1] and Konstantinos N. Lazaridis[1], (1)Mayo Clinic, (2)Mayo Clinic, Rochester, Rochester, MN

Background: IL-17 signaling has been implicated in the pathogenesis of Primary Sclerosing Cholangitis (PSC). However, a direct assessment of IL-17 signaling in PSC cholangiocytes is lacking. **Methods:** Cholangiocytes obtained from bile and brushing samples collected during endoscopic retrograde cholangiography (ERC) from PSC (n = 9) and non-PSC (n = 7) patients were cultured as organoids. These extrahepatic cholangiocyte organoids (ECO) were treated with vehicle or IL-17A (100 ng/mL for 24 hours) and analyzed by NanoString and single cell RNA sequencing (scRNA-seq). In addition, ECO from 9 PSC patients were subjected to whole genome sequencing (WGS), to determine if somatic mutations are implicated in IL-17 signaling dysregulation. **Results:** ScRNA-seq analysis confirmed the ECO were cholangiocytes and were not contaminated by hepatocytes or fibroblasts. The ECO abundantly expressed the IL-17 receptors A, C, and E. Unsupervised clustering identified 8 cholangiocyte clusters in the ECO; however, there were no differences between PSC and non-PSC ECO. PSC ECO respond differently to IL-17 stimulation as compared to non-PSC ECO. When comparing PSC to non-PSC ECO after IL-17 treatment, there was an enhanced expression of 33 genes such as TLR2, KLRB1, BTLA, FCGR2A/C and IL22. In particular, PSC ECO had a robust response to IL-17 in all of the clusters, with the differential expression of genes associated with protein processing, prion, and Huntington diseases, bladder cancer, rheumatoid arthritis, AGE-RAGE, and HIF-1 signaling pathway. After rigorous filtering, WGS identified the presence of somatic mutations on the RUNX and MAPK pathways that were shared between 3 and 4, respectively in the 9 PSC patients. However, no somatic mutations dysregulating genes in the IL-17 pathway were identified. **Conclusion:** PSC- as compared to non-PSC derived ECO respond differently to IL-17A stimulation suggesting dysregulation of this pathway in PSC, implicating IL-17 signaling in PSC disease modulation.

Disclosures: Sumera I. Ilyas – AstraZeneca: Consultant, No, No;

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Disclosure information not available at the time of publication: Maria Eugenia Guicciardi, Erik Jessen, Filippo Pinto E Vairo, Jingchun Yang, Jackie K Bianchi, Konstantinos N. Lazaridis

f 3902-C | MRP9 IS A NOVEL REGULATOR OF CHOLANGIOCYTE MITOCHONDRIA METABOLISM

Anit Shah[1], Ramesh Kudira[1], Hannah Nartker[1], Bryan Donnelly[1], Wujuan Zhang[1], Manavi Singh[1], Maria E. Moreno-Fernandez[1], Alexander G. Miethke[1] and Chunyue Yin[1,2], (1)Cincinnati Children's Hospital Medical Center, Cincinnati, OH, (2)University of Cincinnati

Background: In an effort to discover new genes causal for cholestatic liver disease, we recently reported a biallelic frameshift variant in *ABCC12* in a patient with intrahepatic cholestasis and bile duct paucity. *ABCC12* encodes the ATP-binding cassette protein MRP9, whose function is poorly understood. Studies conducted on zebrafish and mice have demonstrated that MRP9 loss renders cholangiocytes susceptible to bile acid-induced apoptosis, but the underlying mechanism is unclear. MRP9 has been implicated to mediate sperm mitochondrial function in mice. Its role in cholangiocyte mitochondria remains unknown. **Methods:** We performed immunofluorescent staining to investigate the subcellular localization of MRP9 in the H69 human cholangiocyte cell line. *Abcc12-/-* mice and zebrafish show progressive abnormalities in bile duct profiles during juvenile and adult stages. To determine the initial cause of bile duct defects, we focused on larval zebrafish and neonatal mice. We compared transcriptomes of cholangiocytes isolated from wildtype and *abcc12-/-* neonatal mice. We examined the ultrastructure of zebrafish and mouse cholangiocytes using transmission electron microscopy. We assessed mitochondrial energetic metabolism in neonatal mouse

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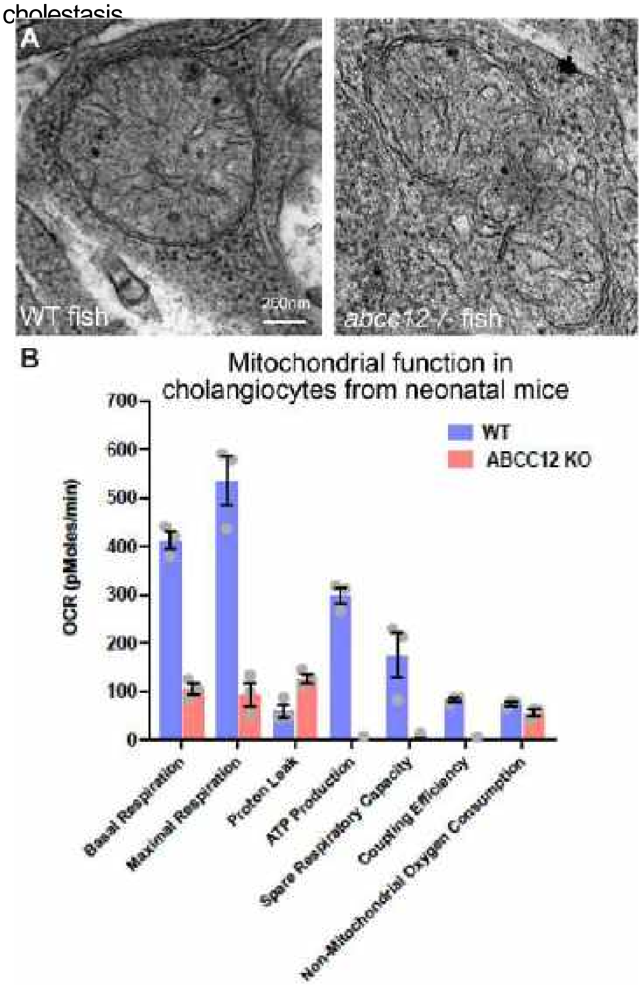
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

cholangiocytes through Seahorse assay. **Results:** In human H69 cells, MRP9 was localized in proximity to the plasma membrane and mitochondria. Bulk RNAseq analysis showed that pathways associated with cholangiocyte development during the embryonic stages were upregulated in *Abcc12-/-* neonatal mice, indicating a less mature phenotype compared to wildtype cells. The mutant cholangiocyte transcriptome indicated increased lipid and glucose metabolism, as well as dysregulated mitochondrial metabolism. Ultrastructural analyses of larval zebrafish and neonatal mice revealed vacuolization, loss of cristae, and mitophagy in the mitochondria of mutant cholangiocytes (Fig. A). Seahorse mito stress test demonstrated impaired mitochondrial energetic metabolism in the mutant cholangiocytes, as evidenced by decreased basal respiration, maximal respiration, ATP-linked respiration, and non-mitochondrial respiration, along with increased proton leak compared to controls (Fig. B). **Conclusion:** These findings identify mitochondria dysfunction as a potential cause for apoptosis in *Abcc12-/-* cholangiocytes. They connect MRP9 to cholangiocyte mitochondria metabolism for the first time, highlighting the link between cell-specific mitochondrial function and susceptibility to bile duct paucity and neonatal cholestasis.



Disclosures: Alexander G. Miethke – Mirum Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Mirum Pharmaceuticals: Consultant, Yes, No;
The following people have nothing to disclose: Bryan Donnelly, Chunyue Yin
Disclosure information not available at the time of publication: Anit Shah, Ramesh Kudira, Hannah Nartker, Wujuan Zhang, Manavi Singh, Maria E. Moreno-Fernandez

f 3903-C | OVEREXPRESSION OF OSTEOPONTIN (SPP1) IN BILIARY EPITHELIAL CELLS CAUSES DUCTULAR REACTION

Sai Santosh Babu Komakula, Xiaodong Ge, Zhuolun Song, Hui Han, Sukanta Das, Ines Barahona, Daniel Lantvit and Natalia Nieto, University of Illinois at Chicago

Background: Osteopontin (OPN, encoded by *SPP1*) is implicated in chronic liver disease. OPN expression increases in chronic liver disease including, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), fibrosis, and hepatocellular carcinoma (HCC). Biliary epithelial cells (BECs) maintain the structural integrity of the bile ducts (BDs) and form a continuous barrier between hepatocytes and bile. Moreover, BECs play a major role in bile acid (BA) composition and secretion, which in turn influences intestinal physiology. Proliferation of BECs occurs in cholangiopathies. OPN is highly expressed in BECs, however the role of BEC-derived OPN is still unknown. **Methods:** we analyzed publicly available human liver scRNAseq data sets. We generated mice with BECs-specific OPN overexpression (*Spp1*$^{\mathrm{KI\ BEC}}$) or ablation (*Spp1*$^{\Delta\mathrm{BEC}}$) using *Sox9-Cre*^{ER} mice and injecting tamoxifen (75 mg/kg body weight) at 8 weeks of age. Mice were sacrificed 1 and 4 weeks later. Histology of liver and intestine was performed. Intestinal transit rate was analyzed using the carmine red assay. **Results:** *SPP1* expression increased in BECs from NAFLD and ALD patients compared to healthy subjects. Homozygous *Spp1*$^{\mathrm{KI\ BEC}}$ mice died 10 days after tamoxifen injection, indicating that overexpression of OPN in BECs is deleterious. *Spp1*$^{\mathrm{KI\ BEC}}$ mice had significant body weight loss (~25%) and the ratio of liver-to-body weight decreased. Moreover, *Spp1*$^{\mathrm{KI\ BEC}}$ mice had significantly increased intestinal transit rate. Histological analysis of liver revealed greater number of bile ducts per portal triad, indicating ductular reaction. H&E staining showed damaged duodenal epithelium. Since homozygous *Spp1*$^{\mathrm{KI\ BEC}}$ mice died early, we then used heterozygous (*Spp1*$^{\mathrm{KI\ (+/-)\ BEC}}$) mice for further analyses along with *Spp1*$^{\Delta\mathrm{BEC}}$ and *Sox9-Cre*^{ER} mice and they were sacrificed 4 weeks after tamoxifen injection. H&E staining showed increased ductular reaction in liver from *Spp1*$^{KI\ (+/-)\ BEC}$ compared to control (*Sox9-Cre*^{ER}) mice. Of note, the intestinal transit rate significantly increased in *Spp1*$^{KI\ (+/-)\ BEC}$ mice and decreased in *Spp1*$^{\Delta BEC}$ mice compared to control mice. **Conclusion:** expression of OPN in BECs is elevated in NAFLD and ALD patients. Overexpression of OPN in BECs increases ductular reaction, alters the intestinal epithelium, and lengthens the intestinal transit rate.

Disclosures: The following people have nothing to disclose: Sai Santosh Babu Komakula, Xiaodong Ge, Zhuolun Song, Hui Han, Sukanta Das, Ines Barahona, Daniel Lantvit, Natalia Nieto

3904-C | REGNASE-1 DYSFUNCTION PROMOTES INTRAHEPATIC CHOLANGIOCARCINOMA DEVELOPMENT VIA MYELOID CELL-MEDIATED HEPATOCYTE TRANSDIFFENTIATION

Yu Sato[1], Takahiro Kodama[2], Shuhei Yamamoto[1], Yuto Shiode[3], Hayato Hikita[1], Tomohide Tatsumi[1] and Tetsuo Takehara[2], (1)Osaka University, Graduate School of Medicine, (2)Osaka University Graduate School of Medicine, (3)National Cancer Institute Laboratory of Human Carcinogenesis

Background: Etiology of Intrahepatic cholangiocarcinoma (ICC) is still unclear, but chronic liver inflammation is considered as the risk factor. An endoribonuclease Regnase-1(Reg1) controls inflammation by degrading mRNAs of inflammatory mediators. Herein, we investigated the role of Reg1 in ICC. **Methods:** We analyzed spontaneous ICC models including the liver-specific Pten/Traf3 double knockout (DKO) mice and wild-type mice with hydrodynamic injection of transposon-based Yap and Akt expression vectors. We generated liver-specific Reg1 KO mice, liver-specific Reg1/Pten DKO (LDKO), hepatocyte-specific Reg1/Pten DKO (HDKO) and chorangiocyte-specific Reg1/Pten DKO (CDKO) mice. They were also crossed with ROSA-LacZ mice for lineage tracing. We performed scRNA-seq of the liver of WT and Reg1 KO mice and tumor and non-tumor liver tissue of an ICC patient. Association of intratumor Reg1 expressions and prognosis was evaluated in 40 ICC patients. **Results:** Reg1 expression levels were lower in tumors than in non-tumor liver tissues in two ICC models. Reg1 KO mice showed cholangiocyte hyperplasia with CD11b^{+} cell infiltration, resulting in spontaneous ICC development. Liver-specific Reg1 deletion also significantly accelerated ICC formation in the absence of Pten. ICC developed in HDKO but not in CDKO mice. Lineage tracing of HDKO mice showed that proliferative cholangiocytes were derived from hepatocytes. scRNA-seq analysis revealed a predominant intrahepatic immune cell cluster expressing CD11b and TNF not in WT mice but Reg1 KO mice. Similar unique cluster was also found only in tumor sites but not in non-tumor liver tissue of ICC patients. Antibody-mediated depletion of CD11b^{+} cells or genetic TNF deletion suppressed the cholangiocyte neoplastic growth in Reg1 KO mice, suggesting that TNF secreted from CD11b^{+} cells was responsible for ICC formation by Reg1 loss. Mechanistically, Reg1 deletion in hepatic cells upregulated expressions of CXC chemokines important for CD11b^{+} cell recruitment and RIP-Seq analysis showed direct binding of Reg1 to these mRNAs. Reg1 deletion in hepatic cells promoted migration of co-cultured CD11b^{+} cells and upregulated their TNF expressions. Conversely, CD11b^{+}TNF^{+} cells upregulated cholangiocyte markers of co-cultured Reg1-deficient hepatocytes. Lastly, intratumor Reg1 expression was negatively correlated with the number of infiltrated CD11b^{+} cells and poor prognosis in ICC patients. **Conclusion:** Regnase-1 dysfunction promotes myeloid cell-mediated ICC development.

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3905-C | TRANSCRIPTOME ANALYSIS REVEAL CONJUGATED BILE ACID INDUCED DUCTAL PROLIFERATION VIA YAP1-PITX1-NRAS AXIS IN BILIARY ATRESIA

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Background: Biliary atresia (BA) is a severe inflammatory and fibrosing cholangiopathy of neonates. Despite successful hepatoportoenterostomy, the liver continues to progress with fibrosis and cirrhosis towards liver failure requiring organ transplantation. We hypothesize that elevated levels of conjugated bile acids in BA livers augments pathologic activation of *YAP1*, loss of *PITX1*, and *NRAS* induction to abnormally proliferate intrahepatic bile ducts. **Methods:** To identify gene signature responsible for elevated conjugated bile acids in BA, first, we analyzed publicly available curated gene expression datasets (GSE46960, GSE122340, GSE136270) of liver biopsies collected from normal and BA patients. Next, we compared gene datasets (GSE186444) of cholangiocyte organoids (CO) generated from livers of normal donor (ND) and BA patients at diagnosis (Dx) or transplant (Tx) to identify pathways that would induce ductular proliferation. **Results:** Bile acid-CoA:amino acid N-acyltransferase (*BAAT*), an enzyme producing conjugated bile acids was found elevated in BA livers compared to normal controls (0.33 ± 0.9 vs -0.47 ± 0.49; $p < 0.001$), (164.9 ± 68.7 vs 93.7 ± 67.6; $p < 0.05$), and (4841 vs 1888; $p < 0.05$) in all three data sets. Analyzing dataset of CO, we found an increased expression of *YAP1* in Tx compared to Dx (89.9 ± 17 vs 54.2 ± 24.5; $p < 0.05$) along with its downstream targets *TEAD1* (36.2 ± 5.8 vs 18.8 ± 10; $p < 0.01$), and *SMAD2* (87.2 ± 23.3 vs 47.8 ± 15.8; $p < 0.05$). This increased expression of *YAP1* could be a direct effect of increased conjugated bile acids or an indirect effect with loss of *CRB3,* an inhibitor of *YAP1,* in Tx compared to Dx (45.6 ± 10.3 vs 58.7 ± 5.9; $p < 0.05$). Identifying a pathway that induces cholangiocyte proliferation with disease progression, we found loss of *PITX1* in Dx and Tx (ND, 7.3 ± 5.6 vs Dx, 0.45 ± 0.6, $p < 0.05$; vs Tx, 0.74 ± 0.8, $p < 0.05$) that could be a result of *YAP1* activation. Following the loss of *PITX1,* a suppressor of *RAS* further analysis revealed activation of *NRAS* pathway in Tx compared to Dx (*NRAS*, 18.5 ± 4.3 vs 11.7 ± 2.9, $p < 0.05$; *RAF1*, 58.2 ± 7.1 vs 45.2 ± 6.4, $p < 0.05$; *p38*, 39.7 ± 5.8 vs 27.1 ± 7.7, $p < 0.05$; *ERK2*, 96.1 ± 12 vs 49.5 ± 21.2, $p < 0.01$). Finally, proliferation of cholangiocytes can be confirmed with activation of *NOTCH2* in Tx compared to Dx (19.3 ± 3 vs 12.8 ± 5.9, $p < 0.05$). **Conclusion:** Based on the bioinformatic analysis and published data we conclude that activation of *YAP1* by conjugated bile acids results in stimulation of *NRAS,* potentially via loss of *PITX1* that would uncover a novel mechanism in abnormal bile duct proliferation with disease progression in BA (Figure 1). However, this remains to be experimentally/functionally tested.

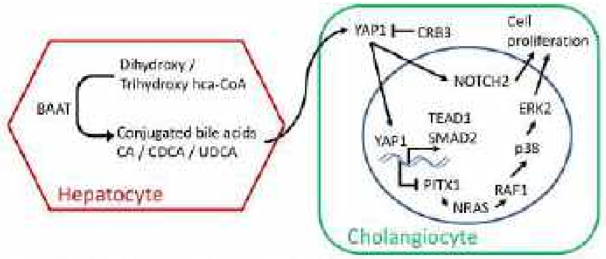

Figure 1. Schematic representation of intrahepatic bile duct proliferation with disease progression in Biliary atresia. BAAT, bile acid-CoA:amino acid N-acyltransferase; CA, cholic acid; CDCA, chenodeoxycholic acid; UDCA, ursodeoxycholic acid; YAP1, Yes1 associated transcriptional regulator; CRB3, crumbs cell polarity complex component 3; TEAD1, TEA domain transcription factor 1; SMAD2, SMAD family member 2; PITX1, paired like homeodomain 1; NRAS, NRAS proto-oncogene, GTPase; RAF1, Raf-1 proto-oncogene, serine/threonine kinase; p38, mitogen -activated protein kinase 14; ERK2,mitogen-activated protein kinase 1.

Disclosures: The following people have nothing to disclose: Surya Amarachintha, Arul Thason, Anh-Hue Tu
Disclosure information not available at the time of publication: Stacey S. Huppert

3906-C | VANISHING BILE DUCT SYNDROME (VBDS): HOW DO DUCTS DISAPPEAR?

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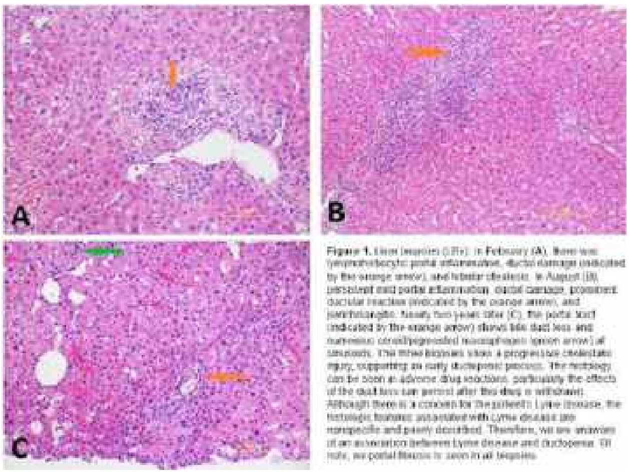
Background: Vanishing Bile Duct Syndrome (VBDS) is an acquired condition characterized by prolonged cholestasis and more than 50% progressive loss of bile ducts on liver biopsy (LBx). Common causes of VBDS are antibiotics (Abx) and herbal intake. Reported cases of VBDS have been scarce, leading to a poorly understood pathophysiology thought to be immune-mediated cholangiolar damage in response to direct injury by drugs, metabolites, and prolonged stagnant bile salt exposure. We aim to provide evidence to clarify VBDS pathophysiology further. **Methods:** A 63-year-old woman with recurrent Lyme arthritis was treated, in November, with Cefdinir (CFD), minocycline (MNC), and Flagyl (FLG) for ten days. A week later, her symptoms were unresolved, and she took Bactrim and Lamictal for five days. Unfortunately, her symptoms continued, and she started Malarone and Artemisinins in addition to resuming CFD, MNC, and FLG. Finally, in February, she saw her provider for fatigue, nausea, constipation, pruritus, icterus, jaundice, and abdominal pain. **Results:** Routine biochemistry (BCH) showed elevated liver enzymes (LFTs) and bilirubin (TB) of 4.9, and she was sent to the hospital (H), where new BCH showed an alkaline phosphatase (ALP) of 488 and TB of 11. The ABx were stopped after a suspected drug-induced injury and started Ursodiol with tapered steroids. Imaging (IMG), autoimmune, and viral serology were all normal. She was discharged to a specialized liver clinic, where a LBx showed lymphohistiocytic portal inflammation and ductal damage (Figure 1A). In March, her ALP was 515, TB was 32.1, and IMG showed hepatosteatosis, no obstruction, and cholestatic inflammation, resolved on repeat IMG in May. In August, ALP was 510, TB was 3.9, and repeat LBx showed persistent inflammation, worsened ductal damage, and pericholangitis (Figure 1B). Nearly two years after stopping ABx, the LFTs were normal, except ALP was 341, and repeat LBx showed ductopenia with numerous sinusoidal macrophages (Figure 1C). **Conclusion:** Progressive cholestatic injury supporting an early ductopenic process is seen in adverse drug reactions, particularly persistent ductal loss without portal fibrosis, despite withdrawing the offending drug (Figure 1). Furthermore, our findings demonstrate that chronic T-cell-mediated cholestatic injury, bile duct destruction by circulating leukocytes, and hepatic repair and resolution by Kupffer cells, maintaining hepatic homeostasis, were the driving forces for the emergence of VBDS. The highlighted case and objective data provide evidence for the natural history of VBDS, prompting further research.



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3907-C | A HIGH FAT DIET MODULATES BILE ACID COMPOSITION AND GUT MICROBIOTA LEADING TO SEVERE CHOLANGITIS AND CIRRHOSIS IN A MURINE MODEL OF PBC

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Background: The obesity epidemic has increased the number of patients with primary biliary cholangitis (PBC) suffering from metabolic syndrome. Indeed, the complication of fatty liver disease complicates the pathology of PBC and reduces the efficacy of ursodeoxycholic acid. We hypothesized that alterations in bile acid (BA) composition and gut microbiota by a high-fat diet (HFD) would influence cholangitis and hepatic fibrosis in PBC. **Methods:** We took advantage of a unique PBC hepatic fibrosis mouse model, Cyp2c70/Cyp2a12 double knockout (DKO) mice, which have human-like BA composition, and develop progressive PBC following immunization with a PDC-E2 mimic, 2-octynoic acid (2OA). We serially studied 2OA-treated DKO mice or control mice, each of which was fed an HFD (60% kcal from fat) or a normal diet (ND) for 10 weeks by comparing pathological changes, hepatic expression of inflammatory cytokines, chemokines, and fibrosis markers, BA composition, and gut microbiota. **Results:** 2OA-treated DKO mice fed an HFD had significantly exacerbated portal and lobular inflammation and bile duct damage, and cirrhotic change compared with those mice fed ND. Hepatic expression of Th1 cytokines/chemokines and fibrotic markers were predominantly induced in 2OA-treated DKO mice fed an HFD. The ratio of chenodeoxycholic acid + lithocholic acid (LCA) to cholic acid (CA) + deoxycholic acid and the BA hydrophobicity index in the liver were significantly increased by an HFD, which was associated with reduced expressions of Cyp8b1, a key enzyme in the CA biosynthetic pathway, and Cyp3a11 and Sult2a1, enzymes metabolizing LCA. In addition, there was a higher relative abundance of secondary BA-producing bacteria with 7α-dehydroxylation activity (*Bacteroides*, *Acetatifactor*) in 2OA-treated DKO mice fed an HFD, correlating with the increase in LCA. **Conclusion:** Increased hepatic BA hydrophobicity associated with the alteration of hepatic BA metabolism and gut microbiota by an HFD exacerbated cholangitis and critically progressed to cirrhosis in this murine PBC model. These data demonstrate that diet-induced changes in gut microbiota and BA composition influence cholangitis and the progression of hepatic fibrosis. These features have the potential for understanding not only hepatic pathology in patients with PBC suffering from metabolic syndrome but also the natural history and role of diet-induced inflammation in all patients with PBC.

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f 3908-C | A NOVEL MODEL TO STUDY MECHANISMS OF CHOLESTASIS IN HUMAN CHOLANGIOCYTES REVEALS A ROLE FOR THE SIPR2 PATHWAY

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Background: After injury, cholangiocytes develop a reactive phenotype involving secretion of cytokines and chemokines which recruit immune cells that promote inflammation and biliary fibrosis. The underlying mechanisms are not completely understood and may involve the bile acid-activated Sphingosine-1-phosphate receptor 2 (S1PR2). To better model the molecular pathogenesis of human cholangiopathy and S1PR2, we developed a human extrahepatic cholangiocyte organoid (ECO) injury model that mimics the cholestatic microenvironment. We explored ECO responses to hydrophobic bile acids and cytokines, and focused on the role of S1PR2 signaling in injury and rescue with therapeutic bile acids NorUDCA and UDCA. **Methods:** Human ECOs were exposed to 1 mM TCA, 1 mM GCA or 0.5 mM GCDCA ± 20 ng/ml TNFα for 24 hours to initiate injury. Treatment with 250 μM NorUDCA or 62.5 μM UDCA were initiated 8 hours after injury induction. Outcome measures included ECO diameter change, cell proliferation, LDH activity and mRNA quantitation of reactive phenotype markers MCP-1, IL-8, TNF-α, Vimentin and TGF-β1. To test the role of S1PR2 pathway, S1PR2 agonist Sphingosine-1-phosphate (S1P), antagonist JET-013 (JET), and ERK-1/2 inhibitor were utilized. **Results:** Exposure to TCA, GCA or GCDCA with TNF-α had synergistic effects; with combined exposure ECO diameters were reduced 3.5 ± 0.6, 4.8 ± 0.6 and 5.4 ± 0.6 fold; cell proliferation decreased $29 \pm 3.8\%$, $27.4 \pm 3.8\%$ and 30.2 ± 3.8 %; while LDH activity increased $5.9 \pm 0.4\%$, $4.6 \pm 0.5\%$ and $12.3 \pm 0\%$; respectively compared to control ($P < 0.05$), together with marked increase in all reactive phenotype marker mRNAs. Both NorUDCA and UDCA treatments improved all measured ECO effects from the bile acid TCA +TNF-a treatment and suppressed reactive phenotype marker mRNAs. S1P stimulation reproduced cholangiocyte injury and reactive phenotype, which was inhibited by JET, ERK1/2 inhibitor, and NorUDCA and UDCA. S1PR2 inhibition with JET partially suppressed cholangiocyte reactive phenotype after injury. S1PR2 downstream mediators ERK1/2 phosphorylation and COX2 expression were suppressed by JET and by NorUDCA and UDCA treatment after injury. **Conclusion:** We modeled the reactive state in human ECOs. In response to cholestatic conditions we demonstrated a contributory role of S1PR2 in injury and therapeutic response via NorUDCA and UDCA. This new cholangiocyte injury model provides a valuable tool to further understand the role of bile acids in human cholangiopathies.

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3909-C | ABLATION OF OSTEOPONTIN (SPP1) IN HEPATOCYTES AND BILIARY EPITHELIAL CELLS PROTECTS FROM PRIMARY SCLEROSING CHOLANGITIS

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Background: primary sclerosing cholangitis (PSC) is a rare chronic cholestatic liver disease characterized by strictures of the intrahepatic or extrahepatic biliary system, inflammation, and portal fibrosis, all of which lead to impaired bile formation, cirrhosis, and liver failure. Osteopontin (OPN, encoded by *SPP1*), is highly expressed in hepatocytes and biliary epithelial cells (BECs), regulates extracellular matrix (ECM) turnover, and increases in cholestatic disorders, however the role of OPN in PSC is unknown. Our aim was to investigate the effect of OPN from hepatocytes and BECs in PSC. **Methods**: we analyzed *SPP1* expression in publicly available RNA-seq datasets and in liver biopsies from PSC patients. To investigate the role of OPN from hepatocytes and BECs, we ablated *Spp1* in these cells in $\mathit{Mdr2}^{-/-}$ mice, a mouse model of PSC, and sacrificed them at 1 month of age. **Results**: *SPP1* mRNA and OPN protein expression were higher in patients with advanced PSC. $\mathit{Mdr2}^{-/-}\mathit{Opn}^{\Delta \mathrm{Hep}}$ and $\mathit{Mdr2}^{-/-}\mathit{Opn}^{\Delta \mathrm{BEC}}$ had reduced liver injury (ALT and AST) compared to $\mathit{Mdr2}^{-/-}$ mice. H&E staining, immunohistochemistry and qPCR analyses demonstrated that $\mathit{Mdr2}^{-/-}\mathit{Opn}^{\Delta \mathrm{Hep}}$ and $\mathit{Mdr2}^{-/-}\mathit{Opn}^{\Delta \mathrm{BEC}}$ showed less DR, number of bile ducts per portal triad, atrophied bile ducts, SOX9 expression, and *Krt19, Epcam,* and *Krt7* mRNAs compared to $\mathit{Mdr2}^{-/-}$ mice. Sirius red/fast green staining revealed that $\mathit{Mdr2}^{-/-}\mathit{Opn}^{\Delta \mathrm{Hep}}$ and

$Mdr2^{-/-}Opn^{\Delta BEC}$ had less fibrotic onion-like structures compared to $Mdr2^{-/-}$ mice. Immunohistochemistry, flow cytometry, and qPCR analyses unveiled that $Mdr2^{-/-}Opn^{\Delta Hep}$ and $Mdr2^{-/-}Opn^{\Delta BEC}$ mice had decreased portal inflammation (F4/80^{+} cells, CD8^{+} T-cells, CD4^{+} T-cells, and B-cells) and lower expression of proinflammatory genes (*Il6, Ifn, Tnfa*) compared to $Mdr2^{-/-}$ mice. **Conclusion**: ablation of *Spp1* from hepatocytes and BECs decreases DR, fibrosis, and inflammation in livers from $Mdr2^{-/-}$ mice and protects from PSC.

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3910-C | AGGRAVATING EFFECT OF LCA ADMINISTRATION ON CHOLANGITIS OCCURRING IN A MOUSE MODEL WITH HUMAN-TYPE BILE ACID COMPOSITION

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Background: Fibrosis around the large intrahepatic bile ducts characterized as the onion-skin lesion is a typical lesion of sclerosing cholangitis. Bile acids (BAs) might be involved in the pathogenesis, but still not well understood because no mouse models have been established to evaluate the role of BAs. One reason for this is the species difference in BA metabolism between humans and mice. In mice, a human-type hydrophobic BA, chenodeoxycholic acid (CDCA), is metabolized to mouse-specific BAs (muricholic acids; MCAs) by Cyp2c70, and also, the secondary BAs (lithocholic acid and deoxycholic acid; LCA and DCA) are converted back to the primary BAs by Cyp2a12, and consequently, the hydrophilic BAs as cholic acid (CA) and MCAs are the predominance. The present study evaluated the frequency of cholangitis and its possible onset factors in the mouse model with human-type BA composition by gene double knockouts (DKO) of *Cyp2c70* and *Cyp2a12* as well as the influences of LCA (the most hydrophobic BA) treatment. **Methods:** Wild-type (WT) C57BL/6J and DKO mice (5 weeks of age) were treated with or without LCA solution (75 mg/L) for 15 weeks in drinking water (Male/Female = 8/8 in each group). We evaluated hepatic BA profile, histological images, and gene and protein expressions of integrins (Itg) β6 and αV. ItgαVβ6 activates TGFβ and highly expresses in the epithelial cells in the colon with ulcerative colitis, which is often concurrent with primary sclerosing cholangitis. **Results:** The BA composition in the DKO livers changed to the human-type BAs (CA, CDCA, DCA, LCA) from the WT livers mainly occupied by CA and MCAs. Particularly, LCA content in the DKO livers was significantly increased by the LCA treatment. In histological observations, the frequency of onion-skin lesions with inflammatory cells around the large intrahepatic bile ducts was 88% (severe 63%; mild 25%) in the DKO livers and increased to 100% (severe 100%) by the LCA treatment, while no observations in the WT livers with and without LCA treatment. However, severe inflammation and damage in the parenchymal cells were not observed in WT and DKO groups and by LCA treatment. The mRNA expressions of *Itgβ6* and *ItgαV* were significantly higher in the DKO livers than in the WT livers, and the highly expressed Itgβ6 protein was observed in the portion of the fibrotic bile duct in the DKO livers by the immunohistochemical stain. **Conclusion:** Severe fibrosis with inflammation around the large intrahepatic bile ducts was induced in the DKO livers, and further aggravated by LCA administration at a low dose that does not cause acute and serious liver damage. The human-type hydrophobic BAs, particularly in LCA, are strongly suggested to be related to the onset of sclerosing cholangitis associated with Itg αVβ6.

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3911-C | CHOLESTATIC DECREASE OF BILE SHEAR STRESS PROMOTES AKT ACTIVATION AND AGGRESSIVE FEATURES IN CHOLANGIOCARCINOMA

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Background: Cholestasis, altered or absent bile flow, is associated with poor survival in patients with cholangiocarcinoma, an aggressive cancer of the biliary epithelium. Changes in bile flow often result from remodeling of bile duct geometry due to strictures or obstruction. Experimental cholestasis promoted tumor growth and progression. However, studies are needed that directly assess the mechanical interaction between bile flow, or bile shear stress, and cancer signaling. We hypothesized that cholestasis and absent bile shear stress increases cancer signaling and aggressive cellular behavior. **Methods:** KMCH cells, a human cholangiocarcinoma cell line, were used. Fluid shear stress was applied by orbital plate method approximating shear from bile flow and compared to identical culture conditions without media flow. Kinase activation in shear versus early and late stasis was assessed by sandwich-ELISA for phosphokinase activity. Subcellular fractionation and immunoblot were used to identify protein localization and levels. Migration was assessed with wound-closure where the scratch was positioned at 0, 45, and 90 degrees to the direction of shear stress. Proliferation was assessed by cell count. **Results:** Transition of cells from shear stress pre-treatment to stasis (2 hours) increased levels of PRAS40 and β-catenin, proteins associated with cancer cell survival and epithelial-to-mesenchymal transition (EMT). Longer stasis increased β-catenin and it's regulators phospho-GSK3β and phospho-Akt. Consistently, intracellular and nuclear β-catenin increased with increased time in stasis. Tumor cells showed increased migration and proliferation with time in stasis providing additional evidence of mechanical responsiveness. Migration was not dependent on the direction of shear stress **Conclusion:** We demonstrated the regulation of cholangiocarcinoma by mechanical forces modeling cholestasis, activating Akt and increasing nuclear β-catenin. Restoring mechanosensory responses to cholestatic environments provides a novel therapeutic approach in cholangiocarcinoma and new understanding of mechanical interaction between bile and the biliary epithelium.

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3912-C | CLAUDIN-1 IS A MEDIATOR AND THERAPEUTIC TARGET FOR CHOLANGIOPATHIES

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Background: Cholangiopathies are biliary diseases progressing to end-stage liver disease, fibrosis, and hepatobiliary cancers. Clinical care of most cholangiopathies lacks effective therapeutic strategies other than liver transplantation. Claudin-1 (CLDN1) is a transmembrane protein expressed in tight junctions. CLDN1 is also expressed non-junctionally mediating cell plasticity and signaling. We have previously developed a monoclonal antibody (mAb) targeting CLDN1 outside the tight junctions exhibiting an excellent safety profile (Roehlen et al. Science Transl. Med. 2022). The aim of this study was to investigate the functional role of CLDN1 as a mediator and therapeutic target for cholangiopathies. **Methods:** CLDN1 expression in liver tissues of patients with cholangiopathies was analysed using RNAseq, multicolor immunofluorescence, and spatial transcriptomics. Proof-of-concept studies using CLDN1-specific mAb H3L3 were performed in state-of-the-art mouse models for cholangiopathies. The HepaRG progenitor cell model and primary human cholangiocytes were used to study cell plasticity and signaling. **Results:** CLDN1 expression is significantly upregulated in primary sclerosing cholangitis (PSC), primary biliary cholangitis, biliary atresia, and the Alagille syndrome. Expression analysis of PSC patient-derived liver tissues revealed CLDN1 expression in cholangiocytes, reactive ductular biliary epithelial cells, and peri-portal hepatocytes, as well as fibroblasts and macrophages. scRNA analyses showed that CLDN1 is highly expressed by EPCAM+ progenitor cells and cholangiocytes. CLDN1 expression in PSC co-localizes with other known disease drivers at the periphery of scar lesions, such as p21, NF-kB, EGFR, and IL-8 in spatial transcriptomics analyses of patient tissues. Proof-of-concept studies showed that monoclonal anti-CLDN1 mAb H3L3 improved survival, cholestasis and liver function in the bile duct ligation mouse model and markedly and significantly reduced hepatobiliary fibrosis and its porto-portal progression without detectable adverse effects in the DDC biliary fibrosis model. Mechanistic studies showed that anti-CLDN1 mAb induced maturation of liver progenitor cells and inhibited NF-kB and MAPK signaling in vivo and cell-based models including human cholangiocytes. **Conclusion:** Our results uncover a previously unknown role of CLDN1 in the pathogenesis of cholangiopathies and provide preclinical proof-of-concept for a CLDN1 as a target to treat PSC and cholangiopathy-induced liver fibrosis.

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f 3913-C | CONDITIONAL LOSS OF Β-CATENIN LOWERS TOXIC BILE-INDUCED HEPATIC INJURY AND IMPROVES CHOLESTATIC OUTCOME IN MURINE MODEL★

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Background: Primary sclerosing cholangitis is a chronic fibrosing cholangiopathy partly attributed to toxic bile insults for which there is no medical treatment with proven efficacy. A high concentration of lithocholic acid (LCA) in primary sclerosing cholangitis patients is associated with hepatotoxicity and adverse clinical outcomes. We previously reported that conditional loss of β-catenin prevents the development of cholestatic liver injury after bile duct ligation by decreasing bile acid synthesis. To ascertain our findings, we tested if loss of β-catenin can elicit protection in toxic bile acid model of hepatobiliary injury. **Methods:** Age-matched wild-type control (Con) and liver-specific β-catenin knockout (KO) mice were fed LCA-supplemented diet. Mice were euthanized and liver tissues analyzed by histology, qPCR, RNAseq, immunostaining, Western blot and liquid chromatography-mass spectrometry. Serum biochemistry was measured to assess liver injury parameters. **Results:** Morphological comparison depicted significant necrotic lesions in Con livers following LCA diet which were remarkably reduced in the β-catenin KO livers. Serum analysis showed significant decrease in hepatic and biliary injury in KO compared to Con. Gene expression evaluation by qPCR revealed decreased bile acid uptake transporters, increased apical and basolateral efflux transporters, and increased expression of detoxifying cytochrome P450 enzymes in the KO group with the net result of decreased accumulation of toxic bile acid in KO livers. Additionally, bile acid composition was slightly altered in KOs after LCA diet, with a predominance of TbMCA over TMDCA. Pancytokeratin immunostaining showed increased ductular response in KO livers, likely as a compensatory mechanism for mediating enhanced bile clearance. RNA-seq analysis showed decreased proinflammatory genes in the KO livers compared to Con. Immunostaining analysis further confirmed significant activation of IL-33 in the hepatocytes of Con but not in KO. **Conclusion:** As observed previously in our bile duct ligation model, our current study in toxic bile acid model further supports that loss of β-catenin reduces hepatotoxicity and offers protection from hepatobiliary injury. This is achieved through increased transport and hydroxylation of toxic bile acid. IL-33 seems to be an important target of β-catenin and its secretion from hepatocytes may contribute to hepatic injury induced by the toxic bile LCA.

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Disclosure information not available at the time of publication: Rong Zhang, Silvia Liu, Pamela Cornuet, Xiaochao Ma

f 3914-C | DEFINING THE WNT SIGNALING LANDSCAPE OF THE EXTRAHEPATIC BILE DUCT AT HOMEOSTASIS AND IN OBSTRUCTIVE CHOLANGIOPATHY★

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Background: Understanding the mechanisms that drive quiescent cholangiocytes to become proliferative in acute injury and chronic biliary diseases such as primary sclerosing cholangitis and cholangiocarcinoma are necessary for the discovery of new therapeutic targets. WNT signaling has been implicated in cell fate determination, proliferation, and disease progression in GI organs, including liver; however, its role in cholangiocyte biology is not as well understood. WNT ligands can activate canonical (β-catenin mediated) or non-canonical pathways with antagonists (secreted frizzled-related protein, sFRP), and potentiators (R-spondins, Rspo) modulating WNT signaling. We aim to understand the WNT signaling landscape in the extrahepatic bile duct (EHBD) in homeostasis and injury. **Methods:** To investigate these questions, we performed single-cell (scRNA-seq) and bulk RNA-seq of the EHBD in mice and bulk RNA-seq in human biliary organoids. We used bile duct ligation (BDL) to model acute obstructive injury. We interrogated samples of cholangiocarcinoma (CCA) from The Cancer Genome Atlas (TCGA) for WNT signaling. We used mouse organoids to examine WNT effects on cholangiocyte proliferation and a porcupine (PORC) inhibitor to prevent WNT secretion. **Results:** Our transcriptomic analysis of mouse EHBD and human organoids revealed *WNT7B* as the predominant ligand in cholangiocytes. Both *Wnt4/7b* (canonical or non-canonical)

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

were upregulated and *Wnt5a* (noncanonical) was downregulated post-BDL. Upregulated WNT target genes (*Birc5*, *Ccnd1*, etc.) and *β-catenin* are expressed in cholangiocytes. WNT antagonists sFRP 1/5 are downregulated post-BDL. Fibroblasts are the primary source of sFRPs and Rspos. While organoids can be maintained in WNT-free media, loss of endogenous WNT secretion (via PORC inhibitor) resulted in decreased organoid growth. Similar to BDL, human CCA samples (TCGA) show increased proliferation (*KI67*) and *WNT7B*. **Conclusion:** These data indicate that 1) *WNT7B* is upregulated in acute and chronic biliary diseases. 2) WNT signaling enhances cholangiocyte growth *in vitro*. 3) sFRP1/5 may attenuate WNT effects at homeostasis. 4) Fibroblasts secrete both inhibitors and potentiators of WNT signaling. 5)The opposing expression of WNT ligands in biliary injury indicates a potential interplay between canonical and non-canonical signaling. Further studies elucidating the role of WNT signaling may provide further insight into the mechanisms driving cholangiocyte proliferation in biliary diseases and provide new therapeutic targets.

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3915-C | DELETION OF INTERLEUKIN-17A AUGMENTS PORTAL FIBROSIS IN A MOUSE MODEL OF CHOLESTATIC LIVER INJURY

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Background: The underlying mechanism contributing to cholestatic liver injury remains unclear. The proinflammatory cytokine interleukin-17A (IL-17A) has been implicated in human cholestatic liver injury. However, mechanistic insights on how IL-17A modulates cholestatic liver injury are lacking and require further exploration in preclinical models. Herein, we examined the effects of IL-17A genetic deletion in a mouse model of cholestasis. **Methods:** Age- and gender-matched littermate WT and *Il-17a*$^{-/-}$ were fed intermittently on 0.1% 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet or control diet (n = 10, each) and standard diet for 21 days to induce cholestatic liver injury. We assessed liver inflammation, ductular reaction, and fibrosis using complementary approaches. **Results:** DDC-fed mice displayed significant increases in liver weight/body weight ratio and histological and serological characteristics of cholestatic liver injury compared to control-diet-fed mice in both WT and *Il-17a*$^{-/-}$ mice; however, there were no differences between WT and *Il-17a*$^{-/-}$ DDC-fed mice. Immunofluorescence staining for Desmin and Collagen I and Sirius red indicated portal fibrosis was significantly increased in DDC-fed *Il-17a*$^{-/-}$ mice compared to DDC-fed WT mice. Immunofluorescence staining for IBA1 (a pan macrophage marker) and myeloperoxidase (a neutrophil marker) displayed an increase in macrophages and neutrophils in DDC-fed *Il-17a*$^{-/-}$ mice vs. DDC-fed WT mice. Mass cytometry (CyTOF) on intrahepatic leukocytes confirmed this observation. Gene expression profiling and pathway analysis of intrahepatic leukocytes subjected to Nanostring analysis displayed upregulation of multiple profibrogenic genes and enrichment of fibrosis-relating pathways in both WT and *Il-17a*$^{-/-}$ mice. Compared to DDC-fed WT mice, the profibrotic gene *Tnfsf14* was significantly upregulated in DDC-fed *Il-17a*$^{-/-}$ mice. Taken together, these data suggest deletion of *Il-17a* in the mouse model of cholestatic liver injury results in upregulating profibrogenic pathways and alteration of immune cell populations within the liver, promoting fibrosis. **Conclusion:** IL-17A appears to restrain liver inflammation and fibrosis by suppressing *Tnfsf14* expression.

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3916-C | INHIBITION OF THE RENAL APICAL SODIUM DEPENDENT BILE ACID TRANSPORTER PREVENTS CHOLEMIC NEPHROPATHY

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Background: Cholemic nephropathy (CN) is a severe complication of cholestasis-associated liver diseases, and no specific treatment is available. We revisited the pathophysiology to investigate the role of bile acids (BAs) and test new therapeutic strategies. **Methods:** The liver-kidney axis was time-dependently analysed in wild type (WT) mice for up to 12 weeks after bile duct ligation (BDL) or sham operation. BA flux in kidneys and livers was spatio-temporally visualized by intravital imaging, and further quantified by MALDI-MSI and LC-MS/MS. AS0369, a systemically bioavailable apical sodium-dependent bile acid transporter (ASBT) inhibitor was synthesized and its specificity and pharmacokinetic properties characterized in mice. AS0369 was administered twice daily after BDL and its effects on liver and kidney were quantified using RNA-sequencing, histological, and serum and urine biochemistries. Translational relevance was evaluated by ASBT immunostaining in kidney biopsies from two cohorts of CN patients. **Results:** Enhanced reabsorption of BAs from the renal tubular lumen into proximal renal tubular epithelial cells (TEC) and a progressive increase in kidney BA tissue levels is observed after BDL. BA enrichment in TEC is followed by cell death, damage of peritubular capillaries, massive leakage of BA into the renal interstitium, and increased kidney fibrosis. Renal ASBT expression is restricted to the TEC and maintained after BDL. ASBT inhibition by AS0369 blocked BA uptake in renal TEC, massively increased urinary nonsulfated BA excretion, prevented BDL-associated mortality, and almost completely prevented kidney injury up to 6 weeks after BDL as evidenced by intravital imaging and MALDI-MSI, kidney histology, transcriptomics, urine and serum biomarkers (urea and NGAL). Preserved ASBT expression in human TEC was demonstrated in renal biopsies from CN patients, including at late-stage disease, highlighting the translational potential of treating CN by targeting ASBT. **Conclusion:** BA enrichment in TEC followed by cell death is an early key event in CN and consistent with an impaired kidney adaptive response to cholestasis. Inhibiting renal ASBT preserves the TEC and prevents CN even under conditions where serum and urinary BA concentrations are massively increased.

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The following people have nothing to disclose: Michael Trauner
Disclosure information not available at the time of publication: Daniela González, Ute Hofmann, Maiju Myllys, Reham Hassan, Tom Lüdde, Hanns-Ulrich Marschall, Guido Stirnimann, Peter Boor, Karolina Edlund

3917-C | LEUKEMIA INHIBITORY FACTOR (LIF) AS TRIGGER SIGNAL TO IMMUNE ACTIVATION IN AUTOIMMUNE CHOLESTATIC DISEASE

Cristina Di Giorgio[1], Ginevra Urbani[1], Martina Bordoni[1], Michele Biagioli[1], Carmen Massa[1], Silvia Marchianò[1], Rachele Bellini[1], Eleonora Distrutti[2], Angela Zampella[3] and Stefano Fiorucci[1], (1)University of Perugia, (2) Azienda Ospedaliera Di Perugia, (3)University of Naples, Federico II

Background: Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) represent primary autoimmune cholestatic liver diseases characterized by the chronic inflammation and progressive loss of the hepatic bile ducts. The pathogenesis of the disease is still unclear, although autoimmune mechanisms have been partially elucidated. The interaction between self-reactive immune cells, hepatic stellate cells (HSCs), sinusoidal endothelial cells (SECs) and cholangiocytes contributes to the perpetuation of chronic inflammation and fibrosis development. Recent evidence demonstrates that the Leukemia inhibitory factor (LIF) is expressed at low levels in normal human liver, whereas is greatly increased in fibrotic liver, suggesting its role in liver disease and immune response. LIF exerts its biological function through its binding to a heterodimeric receptor complex, LIFR and is expressed by several type of differentiated cells such as immune cells, epithelial cells, endothelial cells and fibroblasts. However, the role of LIF in PBC is highly debated. **Methods:** In vitro

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

assays were performed on a normal human cholangiocyte cell line (NHC). In vivo, Abcb4$^{-/-}$on C57BL/6 background and C57BL/6 congenic littermates, were monitored for for 16 weeks. At the time of sacrifice, liver were excised and analyzed. **Results:** LIFR and LIF, mRNA and protein expressions, were detected in NCH. LIF and IL-6 was upregulated by 100 ng/ml LPS, while LIFR appeared downregulated. Abcb4$^{-/-}$ mice, which spontaneously developed PBC/PSC-like disorders, showed an increment of biochemical parameters across time compared to Abcb4$^{+/+}$ mice, the fibrosis score (Syrius red) and the expression of pro-fibrotic markers Tgfβ and Col1a1 mRNA. Consistent with in vitro results, Lif and Il-6 expression were increased, while showed low levels of Lifr and Il-10 mRNA expression. RNAseq analysis of liver samples revealed high dissimilarities between Abcb4$^{+/+}$ and Abcb4$^{-/-}$. Finally, we have demonstrated that NHC exposure to 10 ng/ml LIF exacerbated the effect of LPS trigger, upregulating the expression the pro-inflammatory markers and LIF and downregulating the expression of the LIFR in activated NHC. **Conclusion:** Our data demonstrated that LIF exert an additive effect to that LPS, exacerbating the inflammatory pattern. In this contest the antagonism of LIFR might mitigate the LPS-induced NHC activation.

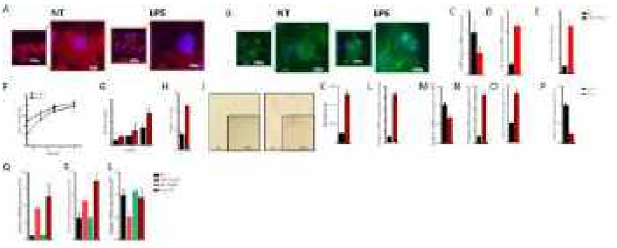

Figure 1. LIF was upregulated in vitro and in vivo models of PBC, moreover LIF exposure exacerbated the effect promoted by LPS challenge on normal human cholangiocytes. NHC cells were exposed to 100 ng/ml LPS alone or left untreated for 24h. Data presented are immunofluorescence analysis of **(A)** LIFR (red) and **(B)** LIF (green) in left untreated (on left) and LPS-challenged (on right) NHC cells. Relative mRNA expression levels of **(C)** LIFR **(D)** LIF and the pro-inflammatory cytokine **(E)** IL-6. Data are normalized to GAPDH mRNA. Results are the mean±SEM of 5 samples per group. *p<0.05. Abcb4-/- male mice spontaneously develop biliary damage and liver fibrosis. They were monitored for 16 weeks. At the time of sacrifice, liver was excised and analyzed. **(F)** Body weight (g) changes across time. **(G)** Bilirubin (mg/dL) changes. **(H)** Number of circulating White Blood Cells (WBC) (10³/µL). **(I)** Syrius-Red staining of liver sections (5x and 10x Magnification) with **(K)** fibrosis score in arbitrary units and relative liver mRNA expression of the pro-fibrotic marker gene, **(L)** Col1a1 **(K)**, **(M)** Lifr; **(N)** Lif; **(O)** Il-6; **(P)** Il-10. Data are normalized to Gapdh mRNA. Results are the mean±SEM of 5 mice per group. *p<0.05. NHC cells were exposed to 100 ng/ml LPS, 10 ng/ml LIF alone or in combination of both, or left untreated for 24 h, then RNA was extracted and analyzed. Relative mRNA expression of the pro-inflammatory cytokines **(Q)** IL-6; **(R)** LIF and **(S)** LIFR. Data are normalized to GAPDH mRNA. Results are the mean±SEM of 5 samples per group. *p<0.05.

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Disclosure information not available at the time of publication: Eleonora Distrutti, Angela Zampella, Stefano Fiorucci

3918-C | MODULATION OF GPBAR1 ATTENUATES LIVER FIBROSIS IN A MOUSE MODEL OF AUTOIMMUNE CHOLESTATIC LIVER DISEASE

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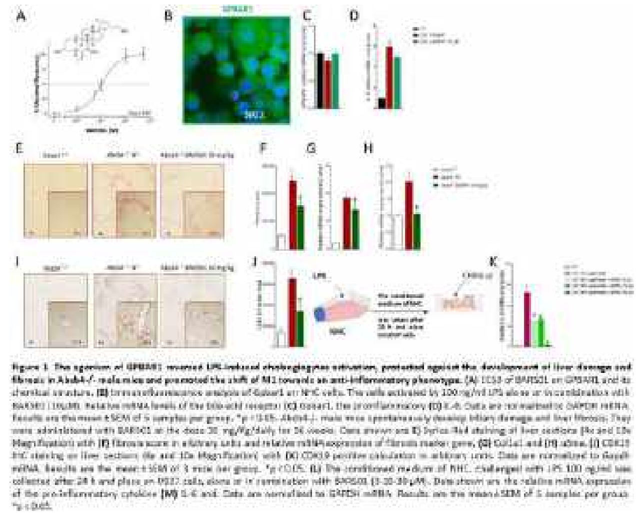
Background: Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) represent the main forms of autoimmune cholestatic liver characterized by chronic inflammation and progressive bile ducts loss. The etiology of PBC and PSC results from complex interactions between a genetic background, environmental trigger and immune dysregulation. Macrophages play a role in the pathogenesis of autoimmune cholestasis at the interface between the innate and adaptive immunity. The GPBAR1 (also known as TGR5) is a cell membrane receptor for secondary bile acids. GPBAR1 is highly expressed in Kupffer cells, liver endothelial cells and cholangiocytes and its expression is reduced PBC patients. Whether GPBAR1 plays a mechanistic role in PBC, however, remains poorly defined. BAR501 is a GPBAR1 agonist that exerts anti-inflammatory effects. **Methods:** In vitro assays were performed on a normal human cholangiocytes (NHC) cell and U937, a monocyte line. In vivo, Abcb4 $^{-/-}$ male mice were administered with BAR501 (10 mg/Kg) for 16 weeks. ANIT model on Il10$^{-/-}$ mice adminestred with BAR501 (10 mg/Kg). **Results:** GPBAR1 expression, mRNA and protein, was detected in NCH, and its activation with BAR501 (10 μM) reverted the pro-inflammatory phenotype promoted by LPS (100 ng/ml) as demonstrated by downregulation of pro-inflammatory markers. Administered in vivo to Abcb4$^{-/-}$, BAR501 attenuated hepatic damage as documented by reduced of AST, ALT and bilirubin plasma levels and the number of plasmatic WBC counts. BAR501 reduced the severity of liver fibrosis and expression of the Col1a1 and αSMA mRNAs. Moreover, BAR501 decreased the CDK19 positive area, as well the expression of Il-6 and Gpbar1 mRNAs. RNAseq analysis of liver samples reveal major dissimilarities between Abcb4$^{-/-}$ left untreated or administered with BAR501, downregulating the expression of many genes belonging to inflammatory and pro-fibrotic pathways. BAR501 reversed the developed of a pro-inflammatory phenotype induced by challenging U937 cells with NHC supernatants (LPS induction), reversing the M1 phenotype and IL-6 production. Because of Abcb4$^{-/-}$ mice showed reduced levels of Il-10 mRNA, Il-10$^{-/-}$ mice were challenged with ANIT and the administration of BAR501 didn't revert the disease. **Conclusion:** GPBAR1 agonism, counter-regulates the development of a pro-inflammatory phenotype of liver macrophages, this reducing development of inflammation, fibrosis and bile duct damage in models of cholestasis.



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Disclosure information not available at the time of publication: Eleonora Distrutti, Angela Zampella, Stefano Fiorucci

3919-C | OVEREXPRESSION OF TNFα CONTRIBUTES TO INCREASED HEPATIC INFLAMMATION AND CHOLANGIOCYTE PROLIFERATION IN MICE

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Background: Intestinal inflammation is common factor in approximately 70% patients diagnosed with Primary Sclerosing Cholangitis. The $TNF^{\Delta ARE}$ mouse carry mutations that result in nearly 20-fold increases in circulating TNFα. These mice spontaneously develop ileitis early after weaning and intestinal fibrosis by 24 weeks of age. The impact of genetic TNFα overexpression on the liver has not been explored. The aim of this study was to examine the influence of TNFα overexpression on hepatic injury, fibrosis, inflammation and bile acid synthesis in mice. Furthermore, the impact of increased intestinal inflammation and fibrosis on ileal FXR signaling was examined. **Methods:** Using serum, hepatic and ileal tissue isolated from 24-week old C57BL/6 and $TNF^{\Delta ARE+/-}$ ($N = 4$-6 per condition) mice, fibrosis, inflammation, ductal proliferation and regulation of bile acid synthesis was assessed by immunohistochemical and quantitative PCR methods. **Results:** Compared to age matched C57BL/6mice, $TNF^{\Delta ARE+/-}$ mice exhibited increased biochemical injury as evidenced by increased serum AST (2.00 ± 0.30-fold increase) which corresponded to increased hepatic picrosirius red staining and an increase in mRNA expression of *Timp1, Col1a1* and *Mmp9* supporting induction of fibrosis. Examining inflammation, immunohistochemical staining revealed a significant periportal increase in MPO+ neutrophils and a panlobular increase in F4/80+ macrophages and CD3+ lymphocytes. Importantly, periportal inflammation corresponded to a significant increase in Cytokeratin 7 staining supporting increased ductular proliferation. In the liver, mRNA expression of *Nr0b2* (Shp) and *Abcc2* (Mrp2) correlating with suppression of *Cyp7a1*, *Cyp7b1*, *Cyp27a1* but no significant differences were evident in the bile acid transporter *Abcb11* expression supporting dysregulation of bile acid homeostasis. In the ileum, increased inflammation correlated with increased *Fgf15* and *Nr0b2* mRNA expression, supporting a role for intestinal injury-dependent changes in FXR signaling. **Conclusion:** Increased TNFα expression is sufficient to promote both intestinal and hepatocellular fibrotic injury and contributes to hepatic dysregulation of FXR signaling and bile acid homeostasis. Overall, these results suggest that the $TNF^{\Delta ARE}$ mouse may be a useful model for studying inflammatory cholangiopathies such as human PSC.

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3920-C | PARENTERAL NUTRITION UNCOUPLES ILEAL TO HEPATIC CIRCADIAN EXPRESSION IN MICE

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Background: We have developed a mouse model of Parenteral Nutrition Associated Liver Disease in which PN infusion results in increased liver injury. In the liver, the master genes Clock and Arntl/Bmal drive rhythmic gene expression and regulate circadian expression of hepatic functions including bile acid synthesis. Once activated, Bmal/Clock are negatively regulated by several transcription factors including Nr1d1, Dbp, Dec1/2, Cry1/2 and Per1/2. The aim of this study was to examine the effect of PN on expression of ileal and hepatic of circadian regulatory (CR) genes, FXR signaling and bile acid synthesis in mice. **Methods:** First, WT mice were exposed to continuous soy oil lipid emulsion based PN infusion through a central venous catheter for 4 days (PN). Water was provided ad libitum, but no nutrients were provided enterally. On d4, mice were sacrificed, serum harvested, and ileal and hepatic tissue obtained at 7AM and 7PM. From tissue samples, gut permeability, relative expression of circadian transcription factors and FXR signaling was assessed. **Results:** Administration of 4d PN increased hepatic injury, inflammatory cytokine expression and gut permeability as evidenced by increased serum AST, TNFa mRNA expression and FITC dextran fluorescence. In the ileum, increased expression of the FXR target genes *Fgf15*, *Nr0b2*, *Slc51a* (OSTα) corresponded to suppression of *Slc10a2* (ASBT) supporting ileal FXR activation. Interestingly, ileal FXR expression decreased suggesting a feedback inhibition of FXR expression. In the liver, hepatic expression of *Abcb11* was increased whereas *Abcc2* decreased following 4d PN. Although *Abcb11* mRNA was increased, no significant differences were evident in hepatic *Nr0b2* or *Nr1h4* mRNA expression supporting dysregulation of FXR signaling. Marked hepatic and ileal desynchrony of mRNA expression of circadian transcription factors was evident. Finally, a comparison of ileal with hepatic circadian transcription factor expression demonstrated significant uncoupling following PN administration. **Conclusion:** Dysregulation of circadian regulatory machinery is in part due to uncoupling of the gut-liver circadian axis. Pharmacologic targeting of CR as a therapeutic strategy for PNAC thus deserves further investigation.

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3921-C | ROLE OF OSTEOPONTIN (SPP1) IN BILIARY ATRESIA ONSET AND PROGRESSION

Zhuolun Song, Hui Han, Xiaodong Ge, Sukanta Das, Sai Santosh Babu Komakula, Ines Barahona, Romain Desert, Dipti Athavale, Wei Chen, Daniel Lantvit and Natalia Nieto, University of Illinois at Chicago

Background: biliary atresia (BA) is a devastating neonatal cholangiopathy that leads to cholestasis and progressive hepatic failure. Our poor understanding of the onset and progression of BA results in compromised transplant-free survival. Osteopontin (OPN, encoded by *SPP1*), is highly expressed in biliary epithelial cells (BECs) and is involved in chronic liver disease, however whether OPN participates in BA is unknown. Here we investigated the role of OPN in the onset and progression of BA. **Methods:** *SPP1* gene expression in BA patients was analyzed using publicly available datasets of scRNA-seq, RNA-seq, and microarrays. OPN protein expression in BA livers was analyzed by immunohistochemistry. OPN concentration in serum was measured by ELISA. To induce BA in mice, we inoculated i.p. rhesus rotavirus (RRV) to BALB/c pups as well as pups with *Spp1* depletion in the liver within 24 hours of birth. Symptoms of BA were monitored after RRV inoculation and mice were sacrificed on day 11. Growth rate was evaluated, activity of transaminases and levels of total bilirubin were measured in serum, and histopathological changes were assessed. **Results:** in humans, *SPP1* is predominantly expressed in BECs in healthy individual's and is highly increased in cirrhosis. Notably, *SPP1* gene expression is significantly higher in livers from BA patients compared to non-BA cholestatic liver disease or control pediatric liver donors (GSE122340, GSE46960). *SPP1* gene expression highly correlates with *KRT7*, *KRT19* and *MMP7*, all markers of BECs. BA patients with fibrosis exhibit higher *SPP1* expression than those with inflammation only (GSE15235). Liver tissue from BA patients shows prominent expression of OPN. The OPN concentration in serum is significantly higher in BA patients compared with patients with other cholestatic liver diseases. BALB/c mice with BA show delayed development, jaundice and acholic stools. Moreover, they have increased transaminases and higher levels of total bilirubin. H&E staining reveals massive ductular reaction and hepatic inflammation. The concentration of OPN in serum and urine and the hepatic expression of OPN are significantly increased in mice with BA compared to controls. Mice lacking *Spp1* in the liver exhibit significant body weight reduction as well as more inflammatory response in liver tissue 11 days after RRV injection compared with control littermates. **Conclusion:** hepatic *SPP1* gene expression and serum OPN concentration differentiate BA from patients with other cholestatic liver disease. OPN is highly expressed in serum, urine, and liver tissue in a mouse model of BA. Depletion of *Spp1* from liver results in significant grow retardation and an inflammatory response after RRV injection.

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Disclosure information not available at the time of publication: Dipti Athavale, Wei Chen

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

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

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

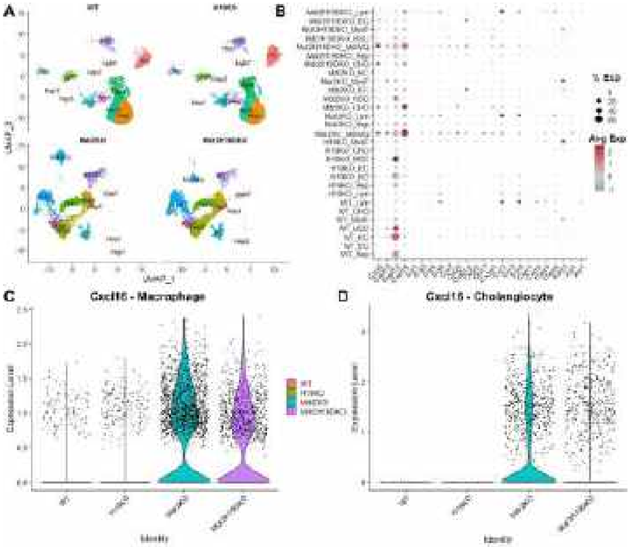

Fig 1. (A)Uniform Manifold Approximation And Projection (UMAP) of all identified cell types from all samples. (B)Dotplot of important chemokine signaling related genes in all cell types across all samples. (C)Violin plot of Cxcl16 expression in macrophage (KC & Md-MQ) populations cross all samples. (D)Violin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

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

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

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

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

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

thermodynamic stability, we have carried out in-cell thermal shift (CETSA) measurements for 13 different PFIC2 mutations, including the most prevalent BSEP mutations E297G and D482G. Using a novel split luciferase detection method, shifts in aggregation temperature (T_{agg}) could be classified into three groups based on the degree of thermal destabilization, 1) no effects on T_{agg}, 2) mildly destabilizing thermal shifts of -2-4 °C, and 3) severe destabilization of 9-11°C. Furthermore, to support the structural basis for BSEP protein destabilization, we determined the cryo-EM structure of wild-type BSEP to 3.0 Å resolution. **Results:** All group 3 variants were localized to the NBD2-ICL2 interface of BSEP. Confocal microscopy indicated cytoplasmic versus plasma membrane localization in HEK293 cells, confirming that these mutations result in defective protein trafficking. Focusing on mutations in NBD and ICL2, our high-resolution cryo-EM model provided a structural framework for rationalizing the thermal destabilization of these mutants, suggesting a novel, NBD2-localized mechanism through which the most severe missense patient mutations drive severe cholestatic disease. **Conclusion:** These data provide critical insight into the molecular dysfunction of 13 PFIC2-associated trafficking mutations. Moreover, our novel CETSA approach and cryo-EM models support a rationalized drug discovery approach for the development of small molecule PFIC2 precision therapeutics that would address the underlying cause of disease.

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Disclosure information not available at the time of publication: Clemence Gruget, Bharat Reddy, Patrick Stoiber

3924-C | HEPATIC INSULIN RESISTANCE INCREASES RISK OF GALLSTONE DISEASE IN SOUTHWESTERN INDIGENOUS AMERICANS

Beyza N Aydin, Nih

Background: Recent animal models indicate that hepatic insulin resistance directly promotes cholesterol gallstones. Gallstone disease (GSD) is linked with surrogate markers of whole-body insulin resistance, but the impact of insulin resistance specifically within the liver is unclear. Thus, we sought to determine whether hepatic and whole-body insulin resistance in humans, both measured with reference methods, are associated with the development of GSD in a prospective cohort. **Methods:** Healthy Southwestern Indigenous American adults without GSD and diabetes at baseline were included ($n = 450$). At baseline, participants had a 2-step hyperinsulinemic-euglycemic clamp with ^{3}H-labelled glucose tracer at submaximal and max insulin stimulation (240 and 2400 pmol/m^2/min) for measurement of whole-body insulin sensitivity (M-low and M-high; submaximal and max insulin stimulation, respectively) and hepatic glucose production (HGP) before and during the submaximal insulin infusion (HGP-basal and HGP-insulin). Body composition and glucose area under the curve (AUC) from a 3-h oral glucose tolerance test were also measured. Incident GSD was identified by clinical history and chart review during follow-up visits conducted at ~2-year intervals. The separate associations of HGP (basal, insulin, and % suppression), M-low, and M-high (per 1-SD change) with risk of GSD were assessed by Cox regression models adjusted for age, sex, body fat (%), glucose AUC, and plasma insulin (corresponding to time of HGP or M). **Results:** During median follow-up of 11.6 years, 60 participants (13%) developed GSD. Participants who developed GSD were of similar age (26 ± 6 vs. 27 ± 6 y) and whole-body insulin sensitivity (M-low: 2.5 ± 0.7 vs. 2.8 ± 1.2; M-high: 8.3 ± 1.9 vs. 8.6 ± 2.2; mg/kg-metabolic body size/min) as those who did not develop GSD, but were more likely to be female (82% vs. 32%, $p < 0.0001$), have higher body fat (37 ± 7 vs. 31 ± 8%), higher HGP-basal and HGP-insulin (1.99 ± 0.27 vs. 1.90 ± 0.24, $p = 0.01$; 0.50 ± 0.41 vs. 0.35 ± 0.42 $p = 0.01$; mg/kg-metabolic body size/min), and lower % suppression of HGP (74 ± 22 vs. 82 ± 22, $p = 0.01$). In separate adjusted models, higher HGP-insulin and lower % suppression of HGP (i.e., hepatic insulin resistance) were associated with increased risk for GSD (hazard ratio [HR] per SD: HR 1.38, 95% CI 1.12, 1.69, $p = 0.002$; HR 1.41 95% CI 1.16-1.72, $p = 0.0007$). HGP-basal, M-low, and M-high were not associated with GSD in adjusted models (p's > 0.22). **Conclusion:** Using a direct measure of HGP, higher absolute HGP during insulin infusion and lower suppression were associated with development of GSD, but whole-body insulin resistance was not associated. Insulin resistance within the liver may have a specific role in the pathogenesis of GSD and is a potential therapeutic target for prevention of the disease.

Disclosures: The following people have nothing to disclose: Beyza N Aydin

3925-C | HEPATIC NONVESICULAR CHOLESTEROL TRANSPORT IS CRITICAL FOR SYSTEMIC LIPID HOMEOSTASIS

Xu Xiao, UCLA

Background: In cell models, changes in the ‘accessible’ pool of plasma membrane (PM) cholesterol are linked with the regulation of endoplasmic reticulum sterol synthesis and metabolism by the Aster family of

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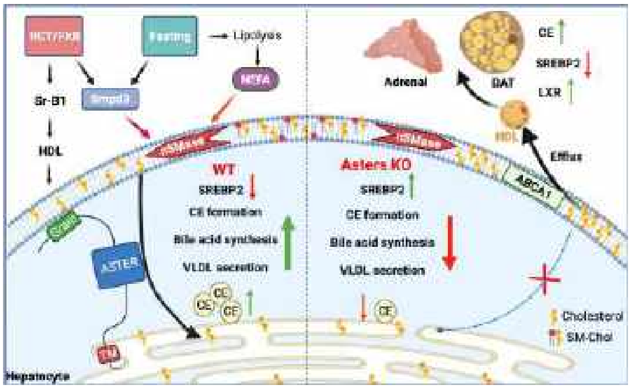
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

nonvesicular transporters; however, the relevance of such nonvesicular transport mechanisms for lipid homeostasis in vivo has not been defined. **Methods:** To study Aster function in the liver, we generated mice with hepatocyte-specific deletion of either Aster-A (L-A knockout (KO)), Aster-C (L-C KO) or both (L-A/C KO) and conducted lipidomic analysis with in vivo tracer studies with [14C]cholesterol. **Results:** Here we reveal two physiological contexts that generate accessible PM cholesterol and engage the Aster pathway in the liver: fasting and reverse cholesterol transport. During fasting, adipose-tissue-derived fatty acids activate hepatocyte sphingomyelinase to liberate sequestered PM cholesterol. Aster-dependent cholesterol transport during fasting facilitates cholesteryl ester formation, cholesterol movement into bile and very low-density lipoprotein production. During reverse cholesterol transport, high-density lipoprotein delivers excess cholesterol to the hepatocyte PM through scavenger receptor class B member 1. Loss of hepatic Asters impairs cholesterol movement into feces, raises plasma cholesterol levels and causes cholesterol accumulation in peripheral tissues. **Conclusion:** These results reveal fundamental mechanisms by which Aster cholesterol flux contributes to hepatic and systemic lipid homeostasis.



Disclosures: The following people have nothing to disclose: Xu Xiao

3926-C | INOSITOL-REQUIRING ENZYME 1a/X-BOX BINDING PROTEIN 1 (IRE1a/XBP1) PATHWAY REGULATES HEPATIC BILE ACID METABOLISM

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Background: Cholestasis causes hepatic ER stress that can activate the IRE1α/XBP1 pathway of the unfolded protein response and can regulate bile acid synthesis. We developed liver-specific tet-on, TRE promoter-IREα (TG-IRE1α) mice which have doxycycline (DOX)-induced increases in hepatic IRE1a and XBP1. The aim of this study is to use TG-IRE1α mice to determine the regulation of hepatic IRE1α/XBP1 signaling on bile acid metabolism. **Methods:** Male 8-12 wk old TG-IRE1α mice were treated with ip DOX (50 mg/kg) or saline for 4 or 48 hrs; or were fed DOX-supplemented chow (200mg/kg) or chow-alone for 48 hrs. Gene and protein expression were measured with qPCR and western blotting, and bile acid concentrations were measured spectrophotometrically. **Results:** TG-IRE1α mice treated with ip DOX for 4 hrs had a 2.6-fold increase in hepatic IRE1α gene expression ($P < 0.001$). Hepatic pIRE and XBP1s protein expression increased 1.25- and 2-fold ($P < 0.04$ and $P < 0.01$, respectively) versus saline controls. Gene expression for the XBP1 downstream target *ERdj4* also increased 2-fold ($P = 0.02$). DOX-treated mice had > 90% reduction in hepatic gene expression of *Cyp7a1* from 1.13+/-0.63 to 0.1+/-0.06 ($P < 0.003$), and 33% and 29% reductions of *FXR* ($P < 0.005$) and *Abcb11* ($P < 0.03$), respectively. Hepatic gene expression of the bile acid synthesis genes *Cyp8b1* and *Cyp27a1*, *PERK* and *ATF6* pathways, and RIDD targets (*Blocs1, Angptl3)* were unchanged. In contrast, 48 hrs of ip DOX treatment resulted in a 2.1-fold increase of CYP7A1 protein ($P < 0.03$), and all other above changes resolved. Ileal FGF15 gene expression was unaltered at 4 and 48 hrs. 4 hrs of ip Dox reduced hepatic bile acid concentrations from 256+/-135 to 92+/-50 nmol/g liver ($P < 0.02$), which normalized at 48 hours. Feeding Dox-supplemented chow for 48 hours increased *Cyp7a1* hepatic protein expression 1.8-fold ($P < 0.05$), and gene expression of *Cyp8b1*, *Cyp27a1* and *Abcb11* 5-, 2.5-, and 2.2-fold, respectively ($P < 0.03$ for all). Hepatic bile acids were higher in DOX-fed mice (803+/-1125 to 222+/-288 nmol/g), but this did not reach significance. **Conclusion**: TG-IRE1α mice treated with ip DOX for 4 hrs have hepatic IRE1α/XBP1 pathway activation, markedly reduced Cyp7a1 gene expression and lower hepatic bile acids, which normalize by 48 hrs. In contrast, DOX-chow feeding for 48 hrs increases expression of bile acid synthesis genes and Abcb11. We speculate that IRE1α/XBP1 signaling is important in the pathogenesis of cholestatic liver disease.

Disclosures: The following people have nothing to disclose: Mahmoud Khalafalla, Andrew Benintende, Xiaoying Liu, Alyssa Kriegermeier, Brian LeCuyer, Richard M. Green

3927-C | TAUROCHOLATE ADMINISTRATION TO PIGS ENHANCES PORTAL VENOUS BLOOD FLOW AND HEPATIC OXYGEN CONSUMPTION, BUT NOT PREHEPATIC SPLANCHNIC OXYGEN CONSUMPTION

Susanne Keiding[1,2], Kim Frisch[3], Frank Viborg Mortensen[1], Aage Kristian Olsen Alstrup[1], Ole L Munk[1] and Michael Sørensen[4], (1)Aarhus University, (2) Department of Nuclear Medicine and PET Center, Aarhus University, (3)University of Aarhus, Health, (4) Viborg Regional Hospital

Background: In a placebo-controlled study of patients with PBC, administration of the synthetic bile acid obeticholic acid enhanced hepatic blood flow (*Kjærgaard, J Hepatol 2021*). In the present study in anaesthetized pigs, we examined if administration of the natural bile acid taurocholate increases blood flows in the portal vein and/or hepatic artery – and hepatic and/or prehepatic oxygen consumption. **Methods:** Eight 40-kg propofol-anaesthetized female pigs were used. Taurocholate was given as IV bolus and infusion of 0−0.2 mmol/min via a catheter in a femoral vein. Oxygen concentration was measured in blood sampled from catheters in a femoral artery, a hepatic vein (via a jugular vein) and in portal vein via a 30-cm long incision below the right curvature. This incision was also used to place ultrasound transit-time flow meter probes around the portal vein and hepatic artery/arteries for continuous blood flow rate measurements. Hepatic oxygen consumption was estimated as the sum of portal vein and hepatic arterial blood flow rates multiplied with the difference between flow-weighted oxygen concentration in arterial and portal vein blood and oxygen concentration in hepatic vein. Prehepatic splanchnic oxygen consumption was estimated as portal venous blood flow multiplied with difference between oxygen concentration in arterial and portal venous blood. **Results:** Hepatic oxygen consumption was increased by taurocholate and in experiments with high doses of taurocholate, it was 2−3 times higher than in experiments with no taurocholate (mean 2 mmol/min versus 0.7 mmol/min; $P < 0.01$). There was no significant effect of taurocholate on prehepatic splanchnic oxygen consumption (mean 1.4 mmol/min). Portal venous blood flow was increased by taurocholate and in experiments with high doses of taurocholate, it more than doubled compared to experiments with no taurocholate (mean 1.9 L/min versus 0.8 L/min; $P < 0.01$) with no significant effect on hepatic arterial blood flow (mean 0.22 L/min). **Conclusion:** The main findings of this study are instant and big enhancements in hepatic oxygen consumption and portal venous blood flow by high-dose infusion of the bile acid taurocholate. We ascribe these effects to energy-requiring transport of taurocholate through the liver, leading to increase in the hepatic oxygen consumption, and portal venous blood flow. These effects may be ascribed to the so-called "metabolic requirement," the mechanism of which is an exciting subject for further investigation.

Disclosures: The following people have nothing to disclose: Susanne Keiding, Kim Frisch, Frank Viborg Mortensen, Aage Kristian Olsen Alstrup, Ole L Munk, Michael Sørensen

3928-C | THE ADDITION OF OMEGA-3 TO FIBRATES: A PROMISING WAY TO REDUCE HEPATIC BILE ACID

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Background: The accumulation of toxic bile acids (BA) in the liver is a key factor in the pathogenesis of primary biliary and sclerosing cholangitis (PBC and PSC), two autoimmune liver diseases deprived of any curative options. While PBC and/or PSC treatment are currently limited to Ursodiol® (UDCA) and Ocaliva® (OCA), fibrates, such as fenofibrate and bezafibrate, are currently tested in off-labeled trials. Since we already reported that omega-3 polyunsaturated fatty acids, such as the eicosapentaenoic (*EPA*) and docosahexaenoic acids (DHA), improve the response to UDCA and OCA, we sought to test the possibility that similar improvement also occurs with fenofibrate and bezafibrate. **Methods:** Human HepG2 cells were treated for 24H with vehicle (DMSO-ethanol 0.01%/0.01% v/v), 100μM fenofibrate and 100μM bezafibrate, in the presence or absence of EPA/DHA (50:50μM). Total RNA was purified, and the expression of essential genes related to BA transport, synthesis and detoxification was quantified by qRT-PCR. **Results:** When used alone fenofibrate and bezafibrate caused 37% and 34% reduction in CYP7A1 transcript levels, respectively. While in the presence of EPA/DHA mRNA levels of this rate-limiting enzyme for BA synthesis were 58% and 52% reduced by the same dosage of fenofibrate and bezafibrate. Similarly, the addition of EPA/DHA to fenofibrate reinforced the overexpression of the export gene MRP2 from 1.5 to 29-fold over control. Interestingly, the combinations EPA/DHA+fenofibrate ($p < 0.001$) and +bezafibrate ($p < 0.01$) caused 58% and 47% reduction of CYP27A1 transcripts a BA-synthesizing enzyme. When used alone the 2 drugs failed to modulate this gene expression. A similar inhibition was also observed for the Ntcp transcript but only with the EPA/DHA+bezafibrate combination. **Conclusion:** The addition of EPA/DHA to fibrates seems to be a promising way to reduce the hepatic BA concentration. Further analysis is, however, required to validate this hypothesis.

Disclosures: The following people have nothing to disclose: Audrey-Anne Lavoie, Olivier Barbier

3929-C | THE BIOACTIVE OMEGA-3 DERIVATIVE, PROTECTIN DX, IMPROVES THE ABILITY OF LOW DOSES OCALIVA TO REDUCE BILE ACID SYNTHESIS AND SECRETION IN LIVER CELLS.

Audrey-Anne Lavoie[1,2,3], Mélanie Verreault[4], Jocelyn Trottier[4], René Maltais[5], Jean-Yves Sancéau[5], Donald Poirier[6], André Marette[7] and Olivier Barbier[4], (1) Université Laval, (2)CHU De Québec - Université Laval, (3)Nutriss Center - Nutrition, Health and Society, (4) Université Laval, Faculty of Pharmacy, Québec, Canada, (5)CHU De Québec Research Center, (6) Université Laval, Faculty of Medicine, Québec, Canada, (7)Centre De Recherche De L'institut Universitaire De Cardiologie Et De Pneumologie De Québec

Background: The toxic bile acids (BA) that accumulate in the liver during cholestasis play a crucial role in the destruction of epithelial cells and hepatocytes in patients with cholestatic autoimmune liver diseases, such as primary biliary and sclerosing cholangitis (PBC and PSC). Their reduction is therefore a major drug target for PBC and PSC treatments. Ocaliva® (OCA) is an FDA-approved treatment with limited clinical use due to the occurrence of severe dose-related side effects. In the presence of omega-3 fatty acids such as EPA and DHA, the OCA dose allowing an optimal reduction of BA toxicity is reduced by 20 times in liver cells. The present study aimed at investigating whether the bioactive omega-3 derivative, protectin DX (PDX), is also an improver of Ocaliva's ability to reduce the hepatic BA concentration. **Methods:** Human hepatoma HepG2 cells were treated with vehicle (DMSO/ethanol; 0.01%/0.01% v/v), and 1µM OCA in the presence or absence of EPA/DHA (50:50µM) or PDX (5µM) for 24 hours. Total RNA was purified, and gene expression was analyzed by qRT-PCR. Experiments were performed twice in quadruplicates. BA secretion was also assessed by liquid chromatography with tandem mass spectrometry (LC-MS/MS) in culture media. **Results:** In the presence of EPA/DHA and PDX, liver cells exhibited a stronger response to Ocaliva 1µM when compared to the drug alone. Indeed, OCA 1µM caused a 54.3% reduction in CYP7A1 transcript levels, a gene coding for the rate-limiting enzyme in BA synthesis, while in the presence of PDX, the same amount of drug led to a stronger ($p < 0.05$) reduction of this transcript to 64.7%. PDX also significantly enhanced the ability of OCA to increase the mRNA expression of BA export transporters such as OSTα and β, MRP2 and 3 ($p < 0.001$). Interestingly, both combinations of OCA with EPA/DHA ($p < 0.01$) and PDX ($p < 0.05$) led to a stronger reduction of chenodeoxycholic acid (CDCA) secretion in cell media. **Conclusion:** These experiments indicate that, as EPA/DHA, protectin DX improves the ability of a low OCA dose to inhibit BA synthesis and export in HepG2 cells. Considering the toxic and pro-inflammatory roles played by bile acids during cholestatic autoimmune liver diseases such as PBC and PSC, the use of PDX+low OCA dose combinations may provide an alternative pharmacological option for these diseases. Further analyses are, however, required to validate this hypothesis.

Disclosures: The following people have nothing to disclose: Audrey-Anne Lavoie, Mélanie Verreault, Jocelyn Trottier, André Marette, Olivier Barbier

Disclosure information not available at the time of publication: René Maltais, Jean-Yves Sancéau, Donald Poirier

3930-C | THE LOSS OF INTESTINAL MICROBIOME IMPACTS BILE ACID SYNTHESIS, TRANSPORT, AND METABOLISM IN THE GUT-LIVER AXIS

Elena Maria Haddad, Mélanie Verreault, Jocelyn Trottier and Olivier Barbier, Université Laval, Faculty of Pharmacy, Québec, Canada

Background: Bile acids (BAs) are steroid acids synthetized in the liver, with essential roles in the control of lipid and vitamin absorption in the intestines. These molecules undergo an enterohepatic cycle, with 95% of BA being reabsorbed in the ileum and sent back to the liver. The remaining 5% are metabolized by intestinal bacteria of the large intestine. To fully grasp the systemic impact of this bacterial metabolism on BAs homeostasis, we investigated how the expression and/or activity of key genes is affected in the liver and intestine of germ-free (GF) mice. **Methods:** GF mice were generated using Swiss Webster strain at the animal facility of the CHU de Québec-Université Laval research centre (Québec, Canada). Samples from 8-month-old GF male and female mice were analyzed in comparison to sex- and age-matched conventionally raised (CONV-R) SP1 Elite animals. Hepatic BA levels were quantified using LC-MS/MS. Tissular transcript and protein levels involved in synthesis (*Cyp7a, 27a1, 8b1, and 2c70*), metabolism (*Cyp3a11, Sult2a1, Ugt1a1, Fxr, Vdr*), transport (*Asbt, Bsep, Ostα, Ostb, Mrp2, Mrp3, Ibabp, Ntcp*) and regulation of BAs were determined using qRT-PCR and western-blotting, respectively. Sulfonation assays were performed using liver homogenates and the lithocholic acid as a substrate. **Results:** In the liver, male GF animals exhibited higher total, unconjugated and primary BAs levels ($p < 0.001$). These parameters remained unchanged in female GF mice when compared to control animals. *Cyp8b1* mRNA and proteins were increased ($p < 0.01$) in livers from male GF, but not in female, while the same gender specificity also applied to the reduction of *Cyp3a11* mRNA levels in GF male livers ($p < 0.01$). In contrast to that, the mRNA, protein, and activity levels of the BA-sulfonating enzymes *Sult2a1* were increased only in female livers. The same applies to transcript levels of *Ugt1a1, Bsep, Ntcp, Ostb, Mrp2, Mrp3* and *Fxr*. In the intestine similar gender- and gene-, and tissue-specific regulatory events were observed. For example, *Asbt* mRNA expression was up-regulated in small and large intestine of male GF mice ($p < 0.01$), while *Vdr* mRNAs were increased in both male and female samples, but only in the duodenum **Conclusion:** These analyses reveal that the loss intestinal microbiome affects both hepatic and intestinal determinants of BA homeostasis, thus supporting the idea that microbial activities exert systemic impacts. Such regulatory events display a major gender-related sexual dimorphism.

Disclosures: The following people have nothing to disclose: Elena Maria Haddad, Mélanie Verreault, Jocelyn Trottier, Olivier Barbier

3931-C | THE X-BOX BINDING PROTEIN 1 (XBP1s) AGONIST IXA4 REGULATES HEPATIC BILE ACID METABOLISM

Andrew Benintende[1], Mahmoud Khalafalla[1], Micaela Naibryf[1], Xiaoying Liu[2], Alyssa Kriegermeier[3], Enrique Saez[4], R. Luke Wiseman[4] and Richard M. Green[5], (1) Northwestern University Feinberg School of Medicine, (2)Feinberg School of Medicine, Northwestern University, (3)Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, (4)Scripps Research, (5)Feinberg School of Medicine, Northwestern University, River Forest, IL

Background: Cholestasis can cause increased hepatic bile acid concentrations and ER stress, with activation of the unfolded protein response IRE1α/XBP1 signaling pathway. Furthermore, the hepatic IRE1α/XBP1 pathway can also regulate bile acid metabolism. However, the complex regulation of ER stress and bile acid synthesis and metabolism is not fully understood. IXA4 is a newly developed XBP1s agonist that activates liver XBP1s signaling and has been shown to be beneficial in murine models of fatty liver disease. In this study we aimed to use IXA4 to determine the regulation of XBP1 signaling on bile acid metabolism. **Methods:** 8-12 week old C57BL/6J mice were treated with IXA4 (50 mg/kg ip) or vehicle-alone (DMSO/EtOH/Kolliphor El) for 2 or 48 hrs. Hepatic gene expression was measured with RNASeq and qPCR and serum C4 levels were measured using LC-MS/MS. **Results:** Two hours after IXA4 treatment, there was a 1.7-fold increase in hepatic gene expression of the XBP1s downstream targets ERDJ4 ($P < 0.05$) and HRD1 ($P < 0.06$). Hepatic Cyp7a1 gene expression was decreased by over 55% in IXA4 treated mice compared to vehicle controls (0.49 +/- 0.31 vs. 1.13 +/- 0.49, respectively, $P < 0.05$). Cyp7a1 bile acid synthesis enzymatic activity measured by serum C4 was also reduced with IXA4 treatment, being 12.5 +/- 5.9 ng/mL vs. 25.7 +/- 1.5 ng/mL in IXA4 treated and control mice ($P < 0.05$). The hepatic gene expression of SHP, Cyp8b1, and HNF4-alpha were reduced by 42% ($P = 0.01$), 36% ($P = 0.03$) and 46% ($P = 0.01$), respectively. Hepatic FXR, Abcb11, and NTCP expression were unaffected. Liver ASBT gene expression increased 2-fold ($P < 0.005$), while there was no difference in ileal ASBT nor FGF15 gene expression. Hepatic bile acid concentrations were similar in both groups. After 48 hours of IXA4 treatment, hepatic SHP expression remained decreased ($P < 0.05$), while expression of the above suppressed genes returned to baseline. **Conclusion:** Treatment with the XBP1s agonist IXA4 for two hours reduced hepatic Cyp7a1 gene expression and Cyp7a1 bile acid synthesis activity. IXA4 administration also resulted in decreased expression of hepatic Cyp8b1, SHP, and HNF4-alpha. The reduction in Cyp7a1 gene expression resolved by 48 hours, although SHP expression remained lower. These data suggest that the UPR has an important role in bile acid synthesis and metabolism and is regulated, at least in part, by activation of hepatic XBP1s.

Disclosures: R. Luke Wiseman – Protego Biopharma: Advisor, Yes, No;

The following people have nothing to disclose: Andrew Benintende, Mahmoud Khalafalla, Micaela Naibryf, Xiaoying Liu, Alyssa Kriegermeier, Enrique Saez, Richard M. Green

3932-C | VALIDATION OF THE MICE AS AN EXPERIMENTAL MODEL FOR STUDYING BILE ACID GLUCURONIDATION AND ITS POTENTIAL AS A TREATMENT TARGET IN AUTOIMMUNE AND CHOLESTATIC HEPATO-BILIARY DISEASES

Elena Maria Haddad, Jordan Grondin, Sarra Beji, Justine Chouinard, Mathilde Mouchiroud, Mélanie

Verreault, Jocelyn Trottier, Alexandre Caron and Olivier Barbier, Université Laval, Faculty of Pharmacy, Québec, Canada

Background: Glucuronidation is a phase II conjugation reaction involved in the detoxification of numerous exogenous and endogenous compounds such as bile acids (BAs). These acids play important roles for cholesterol, lipids and glucose metabolism and absorption. But their accumulation, as it occurs in cholestatic diseases such as primary biliary and sclerosing cholangitis (PBC and PSC), is toxic for liver cells and promotes inflammatory processes ultimately leading to liver failure, if not pharmacologically prevented. While the mechanisms governing human BA glucuronidation are well understood, this process occurring in mice has received less attention, thus limiting the access to well-known animal models for studying BA glucuronidation formation *in vivo*. **Methods:** Glucuronidation assays were conducted using recombinant Udp-glucuronosyltransferase (Ugt) enzymes and tissue homogenates from male and female CD1-Elite mice (n = 4/group). The enzymatic assays were performed at 37°C in presence of the UDP-glucuronic acid co-substrate with various BA substrates, and the formation of BA-Glucuronides (BA-G) was quantified using LC-MS/MS. LC-MS/MS was also used to profile BA-G in murine feces, intestinal contents, liver, and plasma. How environmental factors affect BA glucuronidation were investigated by exposing male C3H/HeJ mice (n = 8/group) fed with control or high fat diets to different temperatures (10°C and 30°C). **Results:** The β-muricholic acid (β-MCA)-24G was the most frequently detected BA-G in mice, while the murine Ugt2b34, 2b35 and 2b37 were the most reactive enzymes for BA-G formation. The most reactive tissues were the liver and colon, and female organs exhibited higher activity levels than male ones. HFD-fed mice livers exhibited significantly higher rates of glucuronidation of β-MCA. In contrast, the same diet caused a significant reduction in β-MCA-24G formation in the colon. **Conclusion:** These experiments revealed the BA-, Ugt-, tissue- and sex-dependent manner in which bile acids are glucuronidated in mice. We also demonstrated that the BA glucuronidation activity is regulated in a tissue- and stimuli (i.e diet or temperature factor)-dependent way. Overall, these observations support the idea that mice could be an adequate model for studying the role of BA glucuronidation in the context of PBC and PSC treatment.

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The following people have nothing to disclose: Elena Maria Haddad, Jordan Grondin, Sarra Beji, Justine Chouinard, Mathilde Mouchiroud, Mélanie Verreault, Jocelyn Trottier, Olivier Barbier

4000-A | A META-ANALYSIS OF CUMULATIVE INCIDENCE OF HEPATOCELLULAR CARCINOMA AFTER THE FONTAN OPERATION

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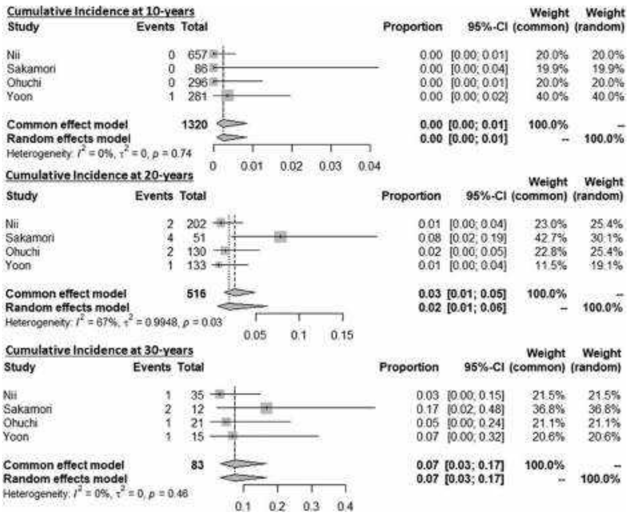
Background: Hepatic complications are increasingly recognized after the Fontan operation. The development of hepatocellular carcinoma (HCC) is one of the most feared complications with high mortality when diagnosed,[1] but its incidence and risk factors are poorly understood. We conducted a systematic review and meta-analysis of the incidence of HCC after Fontan. **Methods:** We searched PubMed, CINAHL, and MEDLINE databases for articles reporting the incidence of HCC after the Fontan operation on March 21, 2023. We excluded cross-sectional studies, case reports, case series, or review articles. Studies were required to be retrospective or prospective cohort studies and report the cumulative incidence of HCC after Fontan. Two reviewers independently reviewed studies for inclusion and extracted variables of interest. A single-arm random effects meta-analysis was conducted in RStudio (version 1.3.1093). Meta-regression analysis was conducted to evaluate study-level effect of variables on the development of HCC. **Results:** We identified four studies including a total of 1,980 patients that met criteria for inclusion. The cumulative incidence of HCC at 10, 20, and 30 years after Fontan was 0% (95% CI 0.00-0.01), 2% (0.01-0.06), and 7% (0.03-0.17) respectively (Figure 1). Heterogeneity was low at 10 and 30 years ($I^2 = 0\%$), but moderate at 20 years ($I^2 = 67\%$). On metaregression, only duration of follow-up was significantly associated with HCC incidence (OR 1.31, 95% CI 1.1-1.57). Gender, manner of HCC diagnosis, prevalence of cirrhosis, anticoagulation use, Fontan type, and congenital anatomical diagnosis were not associated with HCC incidence. **Conclusion:** By 30 years after Fontan, cumulative incidence of HCC is high (7%). The only identifiable risk factor is duration of follow-up and not underlying cirrhosis or heart disease characteristics indicating screening should be considered based on time after the Fontan operation. Our findings are limited by an inconsistent definition used for HCC and cirrhosis in the literature and further research and cost-effectiveness analysis is needed to determine the optimal timing and modality for HCC screening in this population.



Disclosures: Richard Gilroy – Abbvie: Speaking and Teaching, No, No; Salix: Speaking and Teaching, No, No;
The following people have nothing to disclose: Sophie Hansen, Christopher Danford
Disclosure information not available at the time of publication: Ian Lindsay, John Doty, Ross Butschek

4001-A | A NATIONWIDE STUDY ON THE CURRENT TREATMENT STATUS AND NATURAL PROGNOSIS OF HEPATOCELLULAR CARCINOMA IN ELDERLY

Jeong-Ju Yoo[1], Dong Ah Park[2] and Jayoun Lee[2], (1) Soonchunhyang University Bucheon Hospital, (2)National Evidence-Based Healthcare Collaborating Agency

Background: The aim of this study was to identify the treatment status and natural prognosis of hepatocellular carcinoma (HCC) patients aged 65 years or older in South Korea. **Methods**: We analyzed 3,492 patients' data from linking the liver cancer stage data of the Central Cancer Registry of National Cancer Center (2011-2016) and the death data of the National Statistical Office. **Results**: The average age of the patients was 72 years. The most common etiology of HCC was hepatitis B (32.7%), followed by hepatitis C (18.9%). Among a total of 3,492 elderly patients, 2,624 patients (69.2%) received first-line active treatment for HCC, The most frequently selected treatment was transarterial chemoembolization (TACE), followed by surgical resection and radiofrequency ablation (RFA). The proportion of patients receiving supportive care increased with increasing age. Second-line treatment was performed in only 36.7% of cases, with all others choosing supportive care. Among the various treatments, liver transplantation was found to have the greatest effect in reducing the risk of death (HR 0.164, 95% CI 0.061-0.444), followed by resection (HR 0.231), RFA (HR 0.296), radioembolization (HR 0.447), and TACE (HR 0.503). The median survival for untreated HCC in BCLC stage 0/A/B/C/D was 3.7 years, 2.3 years, 7.9 months, 3.9 months, and 2.9 months, respectively. **Conclusion**: This study highlights the current status of elderly patients with HCC in South Korea. While the proportion of patients receiving supportive care is high among the elderly, effective treatment can improve their survival rate.

Disclosures: The following people have nothing to disclose: Jeong-Ju Yoo, Dong Ah Park, Jayoun Lee

4002-A | A PHASE II STUDY OF AUTOLOGOUS NATURAL KILLER CELLS WITH HEPATIC ARTERIAL INFUSION CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED HEPATOCELLULAR CARCINOMA

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Background: Patients with locally advanced HCC who were refractory to the standard treatment have a limited treatment option. We aimed to evaluate the efficacy and safety of autologous NK cell therapy combined with the hepatic artery infusion chemotherapy (HAIC) in patients with intermediate and/or locally advanced HCC. **Methods:** This was an open-label, multi-center, prospective Phase II study done at four centers in South Korea. Patients were eligible if they were aged 19 years or older and had locally advanced HCC unresectable and/or refractory to the standard treatments, macrovascular invasion, and no extrahepatic spread. Patients who had achieved SD or better after 2nd cycle of HAIC with 5-fluorouracil and cisplatin received Vax-NK/HCC therapy for 5 consecutive days every 4 weeks for up to 2 cycles (dose: 1×10^9 NK cells/injection) through hepatic arterial infusion following 2 additional cycles of HAIC. The primary endpoint was the objective response rate (ORR), and the secondary endpoints were disease control rate (DCR), time to progression (TTP), overall survival (OS), and safety. The clinical response was evaluated by modified Response Evaluation Criteria in Solid Tumors (mRECIST). **Results:** As of May 2023, 16 out of 17 patients enrolled were evaluable for the primary and secondary outcomes. The investigator-assessed ORR was 62.5% (complete response [CR]: 37.5%, partial response [PR]: 25%). Stable disease

(SD) was observed in six (37.5%) patients, resulting in a disease control rate (DCR) of 100%. There were no incidences of decompensation or severe adverse events during HAIC, and no adverse events related to NK cell infusion were noted. **Conclusion:** Although this phase II study is still in progress, its preliminary data suggest that the locoregional infusion of NK cells with cytotoxic chemotherapy is safe and feasible for locally advanced HCC refractory to the standard treatment. This result warrants further development of this novel treatment to establish its efficacy in this type of disease.

Disclosures: The following people have nothing to disclose: Woo Kyun Bae, Byung Chan Lee, Yang Hyun Baek, Jung Gil Park, Jeong Won Jang, Je Jung Lee, Sung Bum Cho, Yangseok Koh

4003-A | A SINGLE CENTER ANALYSIS OF PATIENTS UNDERGOING LIVER RESECTION FOR INTRAHEPATIC CHOLANGIOCARCINOMA

Begum Ozturk and Laith H. Jamil, Beaumont Hospital, Royal Oak

Background: Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer with increasing rates of incidence and mortality. Surgical resection with negative margins and regional lymphadenectomy is the mainstay of the treatment for patients with resectable-iCCA. Because of its rarity and low resectability rate of iCCA, prognostic markers and outcomes of patients who undergo liver resection are not well defined. We aimed to evaluate the characteristics of patients undergoing liver resection for iCCA at our institution over ten years. **Methods:** All patients with iCCA who had liver resection between 3/2013-3/2023 at our institution were included in the study. An institutional review board approval was obtained by our institution. Patients who had neoadjuvant therapy prior to resection and patients with a history of malignancy were excluded. Demographic, clinical, radiological, and histological data were collected. Continuous variables are reported as median (interquartile range, IQR), and categorical variables by counts and percentages. **Results:** A total of 68 patients (36 female, 32 male) were included in the final analysis. The median age at resection was 66 years (57.2-74). Liver cirrhosis was present on histology in four patients (5.8%), of which three had non-alcoholic steatohepatitis, and one had primary sclerosing cholangitis. Of all patients, 52.9% had hypertension, 22% had diabetes mellitus, 8.8% had inflammatory bowel disease, 25% had clinically significant alcohol use history, and 47% had former or current tobacco use for more than 5 pack-years. The median pre-operative BMI was 27.84 kg/m^2 (25-32). Pre-operative values of albumin, total bilirubin, AST, ALT, ALP, CA19-9, CEA, and AFP are shown in table 1. The median tumor size was 4.2 cm (3.1-5.9), and 16.1% of the patients had satellite lesions. 36.7% of the patients had lymph node invasion, 30.8% had perineural invasion, and 16.1% had vascular invasion on liver histology. Positive surgical margins were present in 19.1% of patients. Progression of disease or recurrence was seen in 58.8% of patients in a median of 1.1 years (0.7-1.7), and 25% of the patients died during follow-up. Duration from liver resection to last follow-up or death was 1.5 years (0.8-2.9). **Conclusion:** Our results show that iCCA has a high risk of progression/recurrence despite curative resection. Predictive markers of recurrence and survival in patients vary in the literature and remain to be validated.

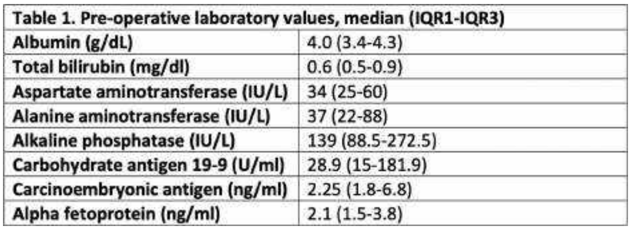


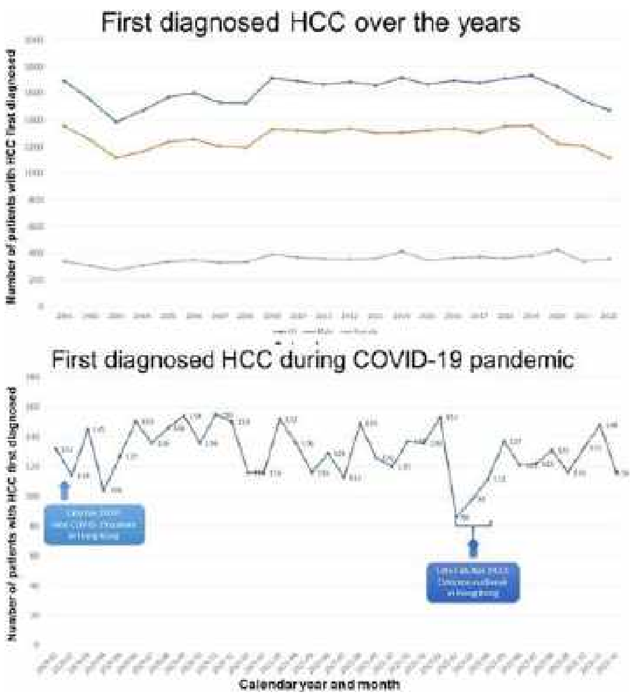
Table 1. Pre-operative laboratory values, median (IQR1-IQR3)	
Albumin (g/dL)	4.0 (3.4-4.3)
Total bilirubin (mg/dl)	0.6 (0.5-0.9)
Aspartate aminotransferase (IU/L)	34 (25-60)
Alanine aminotransferase (IU/L)	37 (22-88)
Alkaline phosphatase (IU/L)	139 (88.5-272.5)
Carbohydrate antigen 19-9 (U/ml)	28.9 (15-181.9)
Carcinoembryonic antigen (ng/ml)	2.25 (1.8-6.8)
Alpha fetoprotein (ng/ml)	2.1 (1.5-3.8)

Disclosures: The following people have nothing to disclose: Begum Ozturk, Laith H. Jamil

4004-A | ABRIDGED NEW DIAGNOSIS OF HEPATOCELLULAR CARCINOMA (HCC) AMID COVID-19 OUTBREAKS: A TERRITORY-WIDE STUDY IN HONG KONG

Grace Lai-Hung C Wong[1], Vicki Wing Ki Hui[1], Yee-Kit Tse[1], Vincent Wai-Sun Wong[2] and Terry Cheuk-Fung Yip[3], (1) The Chinese University of Hong Kong, (2)The Chinese University of Hong Kong, Hong Kong, China, (3)The Chinese University of Hong Kong, Hong Kong, 91, China

Background: In the US, two national emergency declarations dealing with the COVID-19 pandemic are going to end on May 11, 2023. Over the last three years of COVID-19 pandemic, medical services had been seriously disturbed and had led to delays in achieving the goals set by the World Health Organization (WHO) of reducing of chronic viral hepatitis mortality by 65% by 2030. We aimed to evaluate the numbers of newly diagnosed hepatocellular carcinoma (HCC) from 2001 to 2022, with special interest amid the time of COVID-19 pandemic. **Methods:** This was a territory-wide retrospective observational cohort study in Hong Kong. We identified subjects who had newly diagnosed HCC based on diagnosis codes of the electronic database, Clinical Data Analysis and Reporting System (CDARS) of Hospital Authority which serves all public hospitals in Hong Kong. **Results:** We identified 35,647 subjects (78.3% men, mean age 63 y) who had HCC first diagnosed in 2001-2022. The median annual number of new HCC increased from 1,563 (range 1,384-1,716) in 2001-2010, to 1,689 (range 1,662-1,736) in 2011-2019. This dropped dramatically during COVID-19 pandemic, from 1,649 in 2020 to 1,546 in 2021 and 1,473 in 2022 (Figure 1A). The monthly number of new HCC was time-sensitive to COVID-19 outbreaks; it dropped from approximately 140-150 to 114 right after the first COVID-19 case in February 2020. The drop was even more dramatic during the omicron outbreak in early 2022, with the monthly number of new HCC dropped down to 86 in February 2022, 98 in March 2022 and 112 in April 2022. It gradually increased to the close-to-usual numbers (range 116-148) in the 2nd half of 2022 (Figure 1B). **Conclusion:** COVID-19 pandemic significantly reduced the number of newly diagnosed HCC in the public healthcare system. Further studies are warranted to investigate if such reduction had led to delayed HCC diagnosis, or shift of medical service from public the private sector. Resumption of HCC surveillance programme is pivotal for early HCC diagnosis and hence higher chances of curative treatments in order to meet the WHO goal of reducing of chronic viral hepatitis mortality by 65% by 2030 Figure. Number of newly diagnosed HCC in A. 2001-2020 annually and B. 2020-2022 monthly during the COVID-19 pandemic.



Disclosures: Vincent Wai-Sun Wong – Sagimet: Consultant, No, Yes; Pfizer: Consultant, No, Yes; Novo Nordisk: Speaking and Teaching, Yes, Yes; Novo Nordisk: Consultant, Yes, Yes; Inventiva: Consultant, No, Yes; Intercept: Consultant, No, Yes; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead Sciences: Speaking and Teaching, No, No; Gilead Sciences: Consultant, No, Yes; Echosens: Consultant, Yes, Yes; Boehringer Ingelheim: Consultant, No, Yes; AbbVie: Speaking and Teaching, No, Yes; AbbVie: Consultant, No, Yes; Abbott: Speaking and Teaching, No, Yes; TARGET PharmaSolutions: Consultant, No, No; Unilab: Speaking and Teaching, No, Yes; Illuminatio Medical Technology Limited: Stock – privately held company (individual stocks and stock options), No, No;

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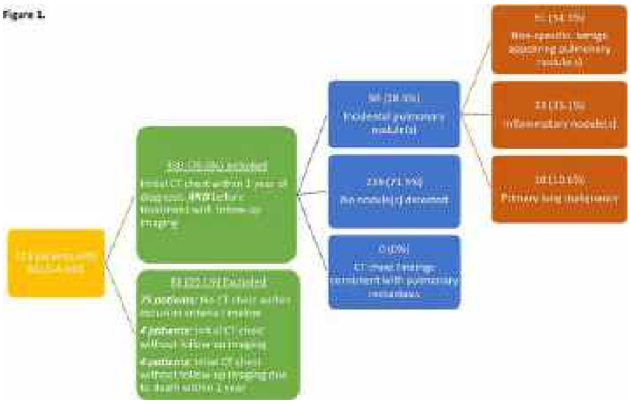
4005-A | ABSENCE OF PULMONARY METASTASIS ON CHEST CT IN BCLC-A HCC

Thuy-Duyen Nguyen[1], Shanna Cheng[1], Melissa Chai[1], Christopher E. Slatore[2], Willscott E. Naugler[1] and Janice Jou[1], (1)Oregon Health & Science University, (2) VA Portland Hospital

Background: Barcelona Clinic Liver Cancer (BCLC) system is often used to stage hepatocellular carcinoma (HCC). Current AASLD guidelines recommend obtaining a CT chest regardless of BCLC stage. Recent studies suggest early stage or BCLC-A HCC pulmonary metastasis rates are low. This study's aim was to determine pulmonary metastasis incidence in BCLC-A HCC patients and assess utility in obtaining a CT chest. **Methods:** We conducted a retrospective study of patients with cirrhosis and newly diagnosed HCC, confirmed on imaging/biopsy, using Oregon Health & Science University's Multidisciplinary Liver Tumor database between January 2015–December 2021. The primary outcome was pulmonary metastasis detection rate on CT chest within 1 year of BCLC-A diagnosis and prior to HCC treatment. The secondary outcome was the identification of other pulmonary nodules. **Results:** We identified 413 patients with BCLC-A HCC. There were 330 patients (79.9%) who had a CT chest within 1 year of diagnosis of HCC and a minimum of 1-year follow-up after the initial CT. We excluded 75 patients (18.1%) with no CT chest within inclusion criteria timeline and 8 patients (1.9%) with no follow-up imaging to confirm nodule identification after initial CT chest showed incidental pulmonary nodules. The median age was 64.4 (±8.6) years and 94 (28.5%) were female. Cirrhosis etiologies were HCV 51.2% (n = 169), alcohol-associated 16.0% (n = 53), NAFLD 13.0% (n = 43), HCV/HBV 7.6% (n = 25), HBV 3.0% (n = 10), AIH 0.6% (n = 2) and other 8.5%

(n = 28). The median MELD 3.0 score was 11.0 (± 4.3). At time of diagnosis, 28.2% (n = 93) never smoked tobacco, 50.6% (n = 167) formerly smoked, and 21.2% (n = 70) were actively smoking at the time of diagnosis. 70.3% (n = 322) had one HCC lesion, 20.9% (n = 69) had two, and 8.8% (n = 29) had three. The median lesion size was 2.1 cm (± 1.6). Median AFP was 7.1 (range 0–3917.3). Of the 330 patients, none had findings consistent with pulmonary metastasis on CT chest. 71.5% (n = 236) did not have any lung nodules. 28.5 % (n = 94) had incidental pulmonary nodules. Of patients with pulmonary nodules, 54.3% (n = 51) had resolved/stable nodules suggesting a benign etiology, 35.1% (n = 33) were inflammatory nodules, and 10.6% (n = 10) were primary lung malignancies. **Conclusion:** In our study, no patients with BCLC-A HCC had pulmonary metastasis on CT chest within 1 year of diagnosis. Future studies are warranted to assess the cost effectiveness of routine CT chest at time of diagnosis of BCLC-A HCC and to examine potential predictors of pulmonary metastasis.



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Disclosure information not available at the time of publication: Shanna Cheng, Melissa Chai, Christopher E. Slatore, Willscott E. Naugler

4006-A | ACHIEVEMENT OF COMPLETE RESPONSE AND DRUG-FREE STATUS BY ATEZOLIZUMAB PLUS BEVACIZUMAB COMBINED WITH LOCOREGIONAL THERAPY IN PATIENTS WITH TRANSARTERIAL CHEMOEMBOLIZATION-UNSUITABLE, INTERMEDIATE-STAGE HEPATOCELLULAR CARCINOMA: A MULTICENTER PROOF-OF-CONCEPT STUDY

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Background: Atezolizumab plus bevacizumab therapy is extremely effective in the treatment of intermediate-stage hepatocellular carcinoma (HCC), with a response rate of 44%, as reported in the IMbrave150 trial. When tumor shrinkage is obtained, achieving complete response (CR) is possible in many cases using curative conversion with resection, ablation, or super selective transarterial chemoembolization (TACE) with curative intent. This concept, *i.e.*, curative conversion by combining systemic therapy and locoregional therapy, has not been reported before. This multicenter proof-of-concept study was conducted to show the value of curative conversion in immunotherapy-treated intermediate-stage HCC meeting TACE-unsuitable criteria. **Methods**: This study included 110 consecutive Child-Pugh A patients who received atezolizumab plus bevacizumab as first-line treatment for unresectable and TACE-unsuitable intermediate-stage HCC at seven centers in Japan. CR rate, drug-free rate, time to CR, change in liver function, efficacy in positron emission tomography (PET)-positive HCC, progression-free survival (PFS), and overall survival (OS) were assessed in patients who achieved CR using resection, ablation, super selective TACE with curative intent following atezolizumab plus bevacizumab or atezolizumab plus bevacizumab alone. **Results**: Clinical or pathological CR was achieved in 38 patients (35%) (median observation period: 21.2 mo). The modalities of curative conversion in 35 patients were as follows: resection, 7; ablation, 13; and superselective TACE, 15. Three patients achieved clinical CR with atezolizumab plus bevacizumab therapy alone. Among the 38 CR patients, 25 achieved drug-free status. PFS was not reached, and three patients experienced recurrence after reaching CR. Regarding OS, there were no deaths in any of the CR patients. The albumin-bilirubin score did not deteriorate after locoregional therapy or resection. Of seven PET-positive patients who achieved CR with atezolizumab plus bevacizumab followed by curative conversion, five achieved drug-free status. **Conclusion**: The achievement of CR rate by curative conversion in patients treated with atezolizumab plus

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

bevacizumab as the preceding therapy for unresectable and TACE-unsuitable intermediate-stage HCC was 35%. Overall, 23% of patients achieved drug-free status and no recurrence was observed from this patient subgroup with CR and drug free status. Thus, achieving CR and/or drug-free status should be a therapeutic goal for patients with intermediate-stage HCC without vascular invasion or extrahepatic spread.

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4007-A | ADVERSE EVENTS AS PREDICTIVE FACTORS OF THERAPEUTIC ACTIVITY IN PATIENTS WITH HCC TREATED WITH ATEZOLIZUMAB PLUS BEVACIZUMAB

Yuri Tsujimoto[1], Toshifumi Tada[2], Takashi Kumada[3], Atsushi Hiraoka[3], Masashi Hirooka[3], Kazuya Kariyama[4], Ei Itobayashi[3], Tsuji Kunihiko[3], Toru Ishikawa[3], Hidenori Toyoda[5], Takeshi Hatanaka[6], Satoru Kakizaki[7], Hideko Ohama[8], Fujimasa Tada[9], Kazuhiro Nouso[3] and Yoichi Hiasa[10], (1)Japanese Red Cross Society Himeji Hospital, (2)Japanese Red Cross Himeji Hospital, Himeji, Japan, (3)Relpec Study Group and HCC 48 Group, (4)Okayama City Hospital, (5) Ogaki Municipal Hospital, (6)Gunma Saiseikai Maebashi Hospital, (7)National Hospital Organization Takasaki General Medical Center, Takasaki, Gunma, Japan, (8)Takarazuka City Hospital, (9)Ehime Prefectural Central Hospital, (10)Ehime, Toon-shi, Ehime, Japan

Background: To investigate the possible correlation between the occurrence of adverse events (AEs) and outcome in patients with unresectable hepatocellular carcinoma (HCC) treated with atezolizumab plus bevacizumab (Atezo/Bev). **Methods:** A total of 286 patients with unresectable HCC who were treated with Atezo/Bev as first-line systematic therapy were included. **Results:** For treatment-related AEs, decreased appetite of any grade, proteinuria of any grade, and fatigue of any grade were present more frequently than 20% of the time. In a multivariate Cox proportional hazards model adjusted for immune-related liver dysfunction, immune-related endocrine dysfunction, proteinuria, fatigue, decreased appetite, and hypertension, decreased appetite (hazard ratio [HR], 1.745; 95% confidence interval [CI], 1.093-2.786; $p = 0.020$) and hypertension (HR, 0.596; 95 CI, 0.373-0.954; $p = 0.031$) were independently associated with progression-free survival. Multivariate Cox proportional hazards modeling adjusted for the same AEs showed that fatigue (HR, 2.055; 95% CI, 1.092-3.869; $p = 0.026$) was independently associated with overall survival. Median progression-free survival was 8.3 months (95% CI, 6.6-not available (NA)) for patients with no appetite loss and

4.8 months (95% CI, 3.4-7.4) for those with appetite loss (p = 0.006). Median progression-free survival was 6.6 months (95% CI, 5.5-8.3) for patients without grade IV hypertension and 12.6 months (95% CI, 6.7-NA) for patients with grade IV hypertension (p = 0.041). For radiological best response rate, the disease control rate was significantly higher in patients who developed treatment-related hypertension (94.2%) than in those who did not (79.1%) (p = 0.009).

Conclusion: Treatment-related hypertension is associated with good outcomes in patients with unresectable HCC treated with Atezo/Bev.

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4008-A | AGE DISPARITIES IN CLINICAL OUTCOMES AND TREATMENT UTILIZATION IN HEPATOCELLULAR CARCINOMA

Olgert Bardhi[1], Karim Seif El Dahan[1], Nicole E. Rich[1], Sarah Rosanna Lieber[1], Jeremy Louissaint[1], Thomas G. Cotter[2], Lisa B. VanWagner[1], Neehar Dilip Parikh[3], Anna Mae Diehl[4], Laura M. Kulik[5], Ju Dong Yang[6], Purva Gopal[1], Amit G. Singal[1] and Darine Daher[1], (1) University of Texas Southwestern Medical Center, (2) University of Texas Southwestern Medical Center, Dallas, TX, (3)University of Michigan, (4)University of Chicago, (5)Northwestern University, (6)Cedars-Sinai Medical Center, Los Angeles, CA

Background: Hepatocellular carcinoma (HCC) is the leading cause of cancer-related mortality in patients with cirrhosis. Prognosis significantly differs by tumor stage and treatment type; 5-year survival exceeds 70% for patients with early-stage HCC that undergo curative surgical therapy compared to < 10% for those with larger tumor burden treated with palliative therapies. Understanding the impact of older age on treatment eligibility and outcomes, including overall survival, is important to inform optimal surveillance and treatment recommendations. **Methods:** We performed a search of MEDLINE and EMBASE databases and national conference abstracts from January 2000 to July 2022 to identify studies reporting tumor stage, curative treatment receipt, or overall survival among patients with HCC, stratified by age category (younger vs. older) thresholds. Curative treatment was defined as liver transplant (LT), surgical resection, and ablative therapies; we excluded studies that only looked at non-curative therapies. We calculated pooled risk ratios (RR) and hazard ratios (HR) with the corresponding 95% confidence interval (CI) stratified by age using the DerSimonian and Laird method for random effects models. **Results:** We identified 139 studies (n = 191,582 patients) that investigated treatment receipt in young vs. old patients with HCC. Across all studies, curative therapy did not significantly differ between younger and older patients (RR 1.01, 95% CI 1.00 – 1.02), although age thresholds varied. However, in subgroup analyses, younger patients were more likely to undergo curative treatment among studies using an age cutoff of 65 years (RR 1.07, 95% CI 1.03 – 1.12) and 75 years (RR 1.10; 95% CI 1.00 – 1.21). Among the subset studies (n = 6) with 65-year age threshold that reported receipt of LT, younger patients were more likely to undergo transplantation (RR 2.81; 95% CI 0.89 – 8.87). Among all studies, younger patients had reduced mortality compared to older patients (HR 0.88; 95% CI 0.82 – 0.93). **Conclusion:** Patients > 65 years appear less likely to undergo curative treatment, particularly liver transplantion, and experience higher hazards of mortality. Studies need to identify underlying reasons for this disparity, including possible differences in tumor burden, liver dysfunction, comorbidities, or patient preferences. Improved selection tools are needed to identify elderly patients who can most benefit from surveillance programs and curative therapies.

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Ju Dong Yang – AstraZeneca: Consultant, No, No; Eisai: Consultant, No, No; Exact Sciences: Consultant, No, No; Exelixis: Consultant, No, No; Fujifilm Medical Sciences: Consultant, No, No; Merck: Consultant, No, No;

Purva Gopal – Genentech: Consultant, No, No; AstraZeneca: Consultant, No, No; Bayer: Consultant, No, No; Eisai: Consultant, No, No; Exelixis: Consultant, No, No; Boston Scientific: Consultant, No, No; Gycotest: Consultant, No, No; Exact Sciences: Consultant, No, No; Roche: Consultant, No, No; FujiFilm Medical Sciences: Consultant, No, No; Freenome: Consultant, No, No; GRAIL, LLC: Consultant, Yes, No;

Amit G. Singal – Genentech: Consultant, No, No; AstraZeneca: Consultant, No, No; Bayer: Consultant, No, No; Eisai: Consultant, No, No; Exelixis: Consultant, No, No; Boston Scientific: Consultant, No, No; Gycotest: Consultant, No, No; Exact Sciences: Consultant, No, No; Roche: Consultant, No, No; FujiFilm Medical

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Disclosure information not available at the time of publication: Laura M. Kulik

4009-A | ARTIFICIAL INTELLIGENCE MODEL TO PREDICT DE NOVO HEPATOCELLULAR CARCINOMA AFTER 5 YEARS OF ANTIVIRAL THERAPY

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Background: Patients with chronic hepatitis B (CHB) receiving potent antiviral agent, such as entecavir (ETV) or tenofovir (TFV), achieve virological and biochemical stability after long-term (>5 y) therapy. Prediction of de novo hepatocellular carcinoma (HCC) in these patients is particularly important considering limited medical resources and relatively lower incidence of HCC compared with those treated for <5 years. Therefore, we aimed to construct an individualized artificial intelligence (AI) model to predict de novo HCC after 5 years of ETV/TFV therapy. **Methods:** From retrospective registry data from two university hospitals, 5,908 and 562 patients with CHB who were treated with ETV/TFV for >5 years and were not diagnosed with HCC during the first 5 years of therapy were selected, respectively. A total of 37 variables including baseline characteristics (age, sex, cirrhosis, and type of antiviral agent), laboratory parameters (albumin, bilirubin, prothrombin time, transaminases, platelet counts, HBeAg, HBV DNA, and Child-Pugh score) at baseline and at 5 years, aspartate aminotransferase to platelet ratio at 5 years, and derived time-varying variables (change in laboratory parameters) were used as input variables. From the training set (n = 4,726), we applied five machine learning algorithms based on 100 datasets derived from repeated 5-fold cross-validation, including adaptive boosting, extreme gradient boosting, light gradient boosting machine, logistic regression, and random forest classifier. Internal validation was performed in a split dataset (n = 1,182). The final model was tested in patients from another university hospital as external validation (n = 562). **Results:** In the training set, logistic regression showed the highest area under the receiver operating curve (AUROC) of 0.803 and balanced accuracy of 0.735, which outperformed other AI algorithms (AUROC, 0.775-0.802 and balanced accuracy, 0.701-0.729). The sensitivity and specificity were 75.3% and 71.6%, respectively. An ensemble approach by soft voting technique demonstrated that the combined model with logistic regression and random forest classifier provided the best performance (AUROC, 0.811 and balanced accuracy, 0.754). The results derived from the test set also showed good performance metrics (AUROC, 0.784 and balanced accuracy, 0.712). In the external validation, our model showed an AUROC of 0.862 and balanced accuracy of 0.771. A web-based calculator was developed. **Conclusion:** Our AI model combining logistic regression and random forest classifier provides good performance in predicting de novo HCC occurrence after 5 years of ETV/TFV therapy. It can compute the estimated risk of HCC and facilitate individualized HCC surveillance based on risk stratification.
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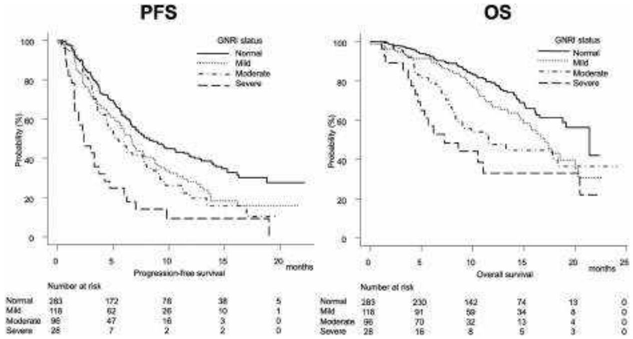
Disclosure information not available at the time of publication: Joo Ho Lee, Kwan Sik Lee, Jinseok Lee

4010-A | ATEZOLIZUMAB PLUS BEVACIZUMAB THERAPY FOR HEPATOCELLULAR CARCINOMA – GERIATRIC NUTRITIONAL RISK INDEX AS A CONVENIENT PROGNOSTIC EVALUATION TOOL

Atsushi Hiraoka[1], Toshifumi Tada[2], Hideko Ohama[1], Masashi Hirooka[2], Fujimasa Tada[1], Kazuya Kariyama[2], Ei Itobayashi[2], Tsuji Kunihiko[2], Toru Ishikawa[2], Hidenori Toyoda[2], Takeshi Hatanaka[2], Satoru Kakizaki[2], Atsushi Naganuma[2], Tomomitsu Matono[2], Kazuhiro Nouso[2], Yoichi Hiasa[2] and Takashi Kumada[2], (1)Ehime Prefectural Central Hospital, (2)Relpec Study Group and HCC 48 Group

Background: The geriatric nutritional risk index (GNRI) is an easy-to-use tool for assessing nutritional status based on body weight and serum albumin. This study aimed to evaluate the prognostic predictive ability of the GNRI for patients with hepatocellular carcinoma (HCC) treated with atezolizumab plus bevacizumab (Atz/Bv). **Methods:** The GNRI was used to evaluate prognosis of 525 HCC patients who received Atz/Bv as first-line systemic chemotherapy (median age = 74 years, male = 420, HCV:HBV:HBV+HCV:alcohol:others = 187:88:2:104:144, Child-Pugh A:B:C = 484:40:1, BCLC 0:A:B:C:D = 7:25:192:283:18). They were classified into normal, mild-, moderate-, and severe-decline GNRI groups, with muscle volume decline (MVD) used for sub-analysis. **Results:** Prognoses [median progression-free survival (mPFS)/median overall survival (mOS)] were stratified according to GNRI status (normal vs. mild- vs. moderate- vs. severe-decline = 8.3/21.4 vs. 6.7/17.0 vs. 5.3/11.5 vs. 2.4/7.3 months) ($P < 0.001$). mPFS and mOS according to Child-Pugh A, B, and C were 7.0/19.1, 4.3/6.4 and 0.4/

1.1 months, respectively (P < 0.001), and according to albumin-bilirubin (ALBI) grade 1, 2, and 3 were 9.3/21.4, 6.0/14.5 and 3.0/7.3 months, respectively (P < 0.001). For predicting PFS and OS, GNRI c-index values were higher than those of Child-Pugh class and ALBI grade (0.574/0.632 vs. 0.527/0.570 vs. 0.565/0.629). Time-dependent receiver operating characteristic curve (ROC) analysis was used to evaluate the area under the curve (AUC) for PFS and OS at 6 and 12 months. The AUC at 6 and 12 months for PFS was 0.616 and 0.594 for GNRI, 0.533 and 0.533 for Child-Pugh class, and 0.607 and 0.591 for ALBI grade, respectively, and for OS was 0.669 and 0.667 for GNRI, 0.622 and 0.580 for Child-Pugh class, and 0.654 and 0.661 for ALBI grade, respectively. MVD frequency increased as GNRI value declined (GNRI status: normal vs. mild- vs. moderate- vs. severe-decline = 17.6% vs. 29.2% vs. 41.2% vs. 57.9%, P < 0.001), with a GNRI value of 97.8 predictive of occurrence (AUC 0.715, 95%CI 0.649-0.781, specificity/sensitivity = 0.644/0.688). There was a significant relationship of GNRI with SMI for both genders (male: r = 0.42, 95%CI 0.302-0.526, P < 0.001, female: r = 0.438, 95%CI 0.169-0.646, P = 0.002) **Conclusion:** The present results suggest that GNRI is a useful prognostic tool for predicting both prognosis and MVD in HCC patients treated with Atz/Bv.



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The following people have nothing to disclose: Atsushi Hiraoka, Toshifumi Tada, Hideko Ohama, Masashi Hirooka, Fujimasa Tada, Kazuya Kariyama, Ei Itobayashi, Tsuji Kunihiko, Toru Ishikawa, Hidenori Toyoda, Satoru Kakizaki, Atsushi Naganuma, Tomomitsu Matono, Kazuhiro Nouso, Yoichi Hiasa, Takashi Kumada

4011-A | BODY MASS INDEX IS NOT ASSOCIATED WITH POST-LIVER TRANSPLANT HEPATOCELLULAR CARCINOMA RECURRENCE

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Background: The number of patients undergoing liver transplantation (LT) for hepatocellular carcinoma (HCC) continues to rise. Post-LT HCC recurrence occurs in 15-20% of patients, with median survival of less than one year. Prior studies have suggested that obesity and increased visceral adipose tissue increase risk for HCC recurrence. However, the impact of body mass index (BMI) on risk of HCC recurrence after liver transplantation has not been studied in a large dataset in the setting of the current HCC-related Model for End Stage Liver Disease (MELD) exception pathway that includes a 6-month observation period. **Methods**: We performed an analysis of patients who underwent LT for HCC in the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) with a waitlist registration date starting October 8, 2015 (marking the implementation of mandated 6-month waiting period for HCC exception points) and LT date through March 31, 2020 (to allow for minimum three years post-LT follow-up time). We assessed for patient and tumor characteristics associated with HCC recurrence after transplantation. **Results**: A total of 7,502 patients with HCC underwent LT in the study period, of whom 521 (6.9%) had post-LT HCC recurrence. The median age was 62 years, and the majority were male (77.2%) and non-Hispanic White (66.1%). Median BMI was 28.6, and most patients were normal weight (BMI 18.5-24.9, 22.6%), overweight (BMI 25-29.9, 35.8%), or obese (BMI 30-34.9, 26.2%). In univariable analysis, neither median BMI nor BMI category (compared to normal) was significantly associated with risk for HCC recurrence (Table 1). Alcohol-associated liver disease and nonalcoholic fatty liver disease (NAFLD) were associated with decreased risk for HCC recurrence. HCC identified on explant, increased number of tumors on explant, lymph node involvement, extrahepatic spread, vascular invasion, and poor tumor differentiation were all associated with increased risk for post-LT HCC recurrence. In multivariable analysis adjusting for patient and tumor characteristics, tumor characteristics including greater number of tumors on explant ($p < 0.001$) and the presence of vascular invasion ($p = 0.02$) were both associated with increased risk for post-LT HCC recurrence. BMI did not have a significant association with risk for post-LT HCC recurrence. **Conclusion**: Among patients who underwent LT for HCC after implementation of the mandated 6-month waiting period for HCC exception points, increased tumor burden and high risk tumor characteristics were associated with increased risk for HCC recurrence. Patient BMI and metabolic syndrome factors such as NAFLD or the presence of diabetes were not significantly associated with risk for recurrence in this large dataset.

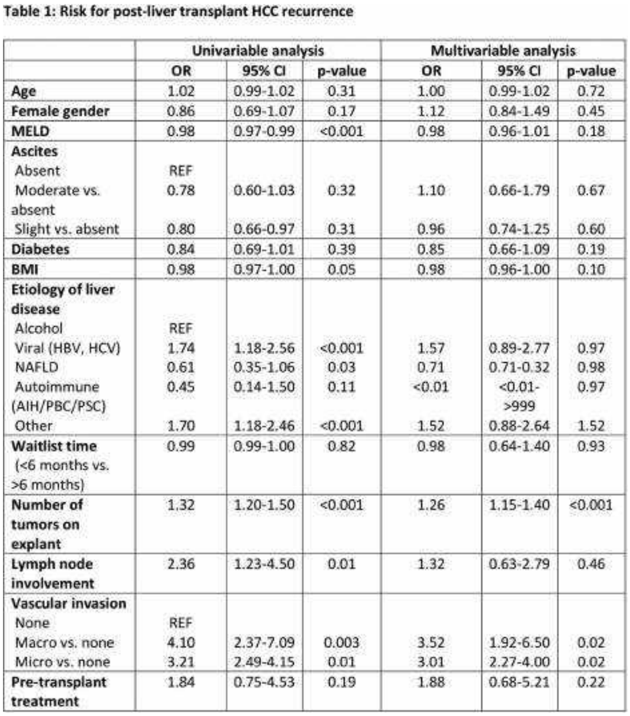

Table 1: Risk for post-liver transplant HCC recurrence

	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.02	0.99-1.02	0.31	1.00	0.99-1.02	0.72
Female gender	0.86	0.69-1.07	0.17	1.12	0.84-1.49	0.45
MELD	0.98	0.97-0.99	<0.001	0.98	0.96-1.01	0.18
Ascites						
Absent	REF					
Moderate vs. absent	0.78	0.60-1.03	0.32	1.10	0.66-1.79	0.67
Slight vs. absent	0.80	0.66-0.97	0.31	0.96	0.74-1.25	0.60
Diabetes	0.84	0.69-1.01	0.39	0.85	0.66-1.09	0.19
BMI	0.98	0.97-1.00	0.05	0.98	0.96-1.00	0.10
Etiology of liver disease						
Alcohol	REF					
Viral (HBV, HCV)	1.74	1.18-2.56	<0.001	1.57	0.89-2.77	0.97
NAFLD	0.61	0.35-1.06	0.03	0.71	0.71-0.32	0.98
Autoimmune (AIH/PBC/PSC)	0.45	0.14-1.50	0.11	<0.01	<0.01->999	0.97
Other	1.70	1.18-2.46	<0.001	1.52	0.88-2.64	1.52
Waitlist time (<6 months vs. >6 months)	0.99	0.99-1.00	0.82	0.98	0.64-1.40	0.93
Number of tumors on explant	1.32	1.20-1.50	<0.001	1.26	1.15-1.40	<0.001
Lymph node involvement	2.36	1.23-4.50	0.01	1.32	0.63-2.79	0.46
Vascular invasion						
None	REF					
Macro vs. none	4.10	2.37-7.09	0.003	3.52	1.92-6.50	0.02
Micro vs. none	3.21	2.49-4.15	0.01	3.01	2.27-4.00	0.02
Pre-transplant treatment	1.84	0.75-4.53	0.19	1.88	0.68-5.21	0.22

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4012-A | BRIDGING THERAPY FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA AWAITING LIVER TRANSPLANTATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Liver transplantation (LT) is the curative treatment of choice for patients with early-stage hepatocellular carcinoma (HCC) and liver dysfunction. However, LT is limited by organ shortage and increasing wait times, so bridging therapy is recommended to reduce the risk of waitlist dropout. Given the association between viable tumor on explant and recurrence, bridging therapy may also improve post-transplant outcomes. However, data evaluating this association have been conflicting. **Methods:** We conducted a systematic review using the Medline and EMBASE databases of studies published between database inception and July 31, 2022, which reported post-transplant outcomes, stratified by receipt of locoregional therapy. Studies that investigated downstaging therapy were excluded. The exposure of interest was bridging therapy for HCC within Milan criteria. Primary outcomes were post-LT recurrence-free and overall survival. Pooled hazard ratios were calculated for each outcome using the DerSimonian and Laird method for random effects models. **Results:** We identified 34 studies, including 16,545 patients with and 19,280 patients without bridging therapy. Patients with bridging therapy had a larger pre-treatment tumor burden and longer wait times vs. those without bridging therapy. Overall, bridging therapy was not associated with post-LT recurrence-free survival (HR 0.91; 95%CI 0.77 – 1.08) or overall survival (HR 1.09; 95%CI 0.95 – 1.24). In subgroup analyses by study period, bridging therapy was associated with worse overall survival (HR 1.23; 95%CI 1.04 – 1.45), but no difference in recurrence-free survival (HR 0.85; 95%CI 0.58 – 1.24), among studies published between 2005 and 2014. Conversely, in latter studies, bridging therapy was not associated with overall survival (2015 – 2019: HR 1.08; 95%CI 0.83 – 1.41, and after 2019: HR 0.90; 95%CI 0.67 – 1.20), or recurrence-free survival (2015 – 2019: HR 0.96; 95%CI 0.76 – 1.21, and after 2019: HR 0.79; 95%CI 0.25 – 2.46). Most studies had a high risk of bias due to lack of adjusting for tumor burden, degree of liver dysfunction, or differences in transplant waiting times. **Conclusion:** Beyond known benefits of reducing risk of waitlist dropout, bridging therapy is not associated with improved post-transplant recurrence-free or overall survival in patients with HCC within Milan criteria. Bridging therapy may not be beneficial for patients in whom risk of waitlist dropout is low, such as those in regions with short wait times.

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Anna Mae Diehl – Exelixis: Advisor, No, No; AstraZeneca: Advisor, No, No; Genentech: Advisor, No, No; Replimune: Advisor, No, No; Eisai Inc: Advisor, No, No;

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Disclosure information not available at the time of publication: Laura M. Kulik

4013-A | CENTER EXPERIENCE AND OUTCOMES IN TRANSPLANTATION FOR CHOLANGIOCARCINOMA

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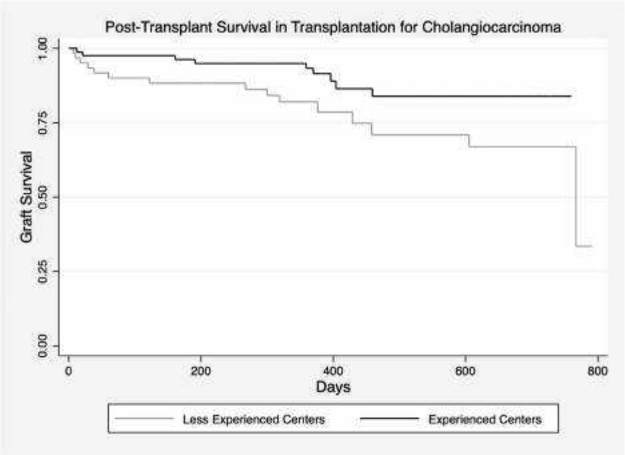
Background: Liver transplantation has been offered as a treatment for select patients with unresectable hilar cholangiocarcinoma since the 1990s at one center, and with UNOS approval of an exception point pathway, at a few centers nationally since 2009. With the implementation of the national liver review board in 2019, qualification for exception points was based on a standardized approval process of the selection criteria rather than regional review board review. It has previously been suggested that transplant centers who perform a higher volume of transplants for cholangiocarcinoma have improved patient outcomes. However, these studies were performed in the era of regional exception points. The goal of this study is to investigate the association between center experience and patient outcomes since the national standardization of exception point approval. **Methods:** Patients listed for transplantation using cholangiocarcinoma exception points from 5/2019-12/2022 were identified in the UNOS database. Transplant centers were grouped based on volume. Experienced centers were defined as having done at least 10 transplant during the time period. The remaining centers were grouped as less experienced. Recipient and donor characteristics, one-year graft survival, and hospital length of stay were compared between these groups using Wilcoxon ranksum, Fisher's exact, and log-rank tests were used where appropriate. **Results:** 166 patients listed based on cholangiocarcinoma exception points and were transplanted. Of these, 98 (59%) were performed at experienced centers (5) and 68 (41%) at less experienced centers (32). The groups did not differ in recipient age, BMI, gender, or MELD score. Donors at experienced centers were older (51.5 [39-62] vs 43.5 [31-50.5], p = 0.002), had higher BMI (29.6 [24.1-34.9] vs 26.7 [23.8-30.5], p = 0.02), and were more likely to be expanded criteria (55.9% vs 11.2%, p = 0.008). However, experienced centers had higher one-year survival. (91.8% vs 74.4%, p = 0.02). Hospital length of stay did not differ. Log-rank test showed experienced centers had improved post-transplant survival rate (p = 0.03). (Figure 1) **Conclusion:** These data suggest that more experienced with transplantation for cholangiocarcinoma is associated with improved outcomes, which is concordant with the current literature. However, it is unclear if this is driven by better patient selection for a complex protocol, or by added surgical or medical expertise in more experienced centers. Improved availability of explant pathology data from recipients of transplant for malignant disease would allow for further research in this field.



Disclosures: Maarouf A. Hoteit – HepQuant, LLC: Consultant, No, No;
Matthew H. Levine – Eurofins USA: Advisor, No, No;
The following people have nothing to disclose: Omar Bushara, Therese Bittermann, Tarek Araji

4014-A | CHALLENGES IN HEPATOCELLULAR CARCINOMA DURING COVID-19 PANDEMIC

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

University of Medicine and Pharmacy "Carol Davila" Bucharest, (3)County Clinical Emergency Hospital of Sibiu

Background: Hepatocellular carcinoma (HCC) is one of the most aggressive neoplasms and a leading cause of cancer-related deaths worldwide with an incidence that continues to increase. Data regarding epidemiology is heterogeneous worldwide. Even if viral hepatitis is known as an important risk factor for HCC development, non-alcoholic fatty liver disease (NAFLD) became a leading cause of HCC in developed countries. Despite the considerable improvements in diagnosis and therapy, the overall outcomes of HCC are still far from satisfactory. Data regarding epidemiology of HCC in Romanian population is scarce. This study aims to investigate HCC etiology, risk factors, the clinical impact of tumor location, and management of these patients. **Methods:** In this retrospective study, we used medical coding data to identify patients with a diagnosis of HCC from Central Military Emergency Hospital Dr. Carol Davila who were hospitalized between March 2020 and February 2023. Statistical analyses were carried out using SPSS 29.0.1.0. Continuous variables were compared using an analysis of variance (ANOVA) while the categorical variables were compared using the Chi-square test. **Results:** A total of 74 patients with a mean age of 65.29 (SD +/- 8.04) were diagnosed with HCC out of which 67.6% were males. Hepatitis C was the main cause of HCC (28.4%), followed by hepatitis B (25.7%) and alcoholic liver disease associated with hepatitis B (10.8%). Half of the patients found with HCC were known with cirrhosis. Furthermore, at the moment of the diagnosis, 25.7% of the patients were already stage IV, lung metastasis being the most frequent site of dissemination. The most frequent location of the tumor was the right liver lobe (64%). There was no association between the etiology of HCC and the location of the tumor. The sensitivity of AFP levels in detecting HCC with a cut-off value of 20 ng/ml was only 56.9%. **Conclusion:** Our analysis revealed that in Romania viral hepatitis is still a major health problem in comparison with the actual trend. HCC is still diagnosed in advanced stages, despite the screening programs for patients at risk. Difficulty regarding optimal management could have been determined by Covid-19 Pandemic. Data highlights that we should develop better prevention strategies and that we need to implement better monitoring programs for the early diagnosis of HCC.

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4015-A | CHANGING EPIDEMIOLOGY OF HCC IN MELBOURNE, AUSTRALIA: PRIMARY OUTCOMES OF THE PROSPECTIVE HOMER-2 COHORT

Joan Ericka Flores[1], Alexander J. V. Thompson[1], Sheng Wei Lo[2], Thai Hong[1], Stuart Keith Roberts[3], Amanda J. Nicoll[4], Diana Lewis[2], Zina Valaydon[5], Siddharth Sood[6], Gauri Mishra[7], William W. Kemp[3], Ammar Majeed[3], James Haridy[6] and Jessica Howell[1], (1)St Vincent's Hospital Melbourne, Australia, (2) Northern Health, (3)Alfred Health, (4)Eastern Health, (5) Footscray Hospital, Footscray, Victoria, Australia, (6) Royal Melbourne Hospital, (7)Monash Health

Background: Surveillance for hepatocellular carcinoma (HCC) with six monthly ultrasounds for at-risk patients with cirrhosis or chronic hepatitis B is recommended is recommended, however rates of uptake remain unacceptably low internationally. With the HOMER-2 cohort, we aimed to describe the uptake of surveillance and the changes in HCC epidemiologic profile. **Methods:** HOMER-2 is a prospective, multi-site cohort of all incident adult HCC cases from Greater Melbourne, Australia identified through HCC multidisciplinary team meetings at the eight tertiary centres with HCC specialist units between 18 Oct 2021 and 17 Oct 2022. Surveillance uptake occurred where patients were known to health services, receiving follow up and scans in the two years preceding HCC diagnosis, to account for COVID-19 disruptions to care. Optimal surveillance was defined as completion of two scans in the preceding year, and suboptimal surveillance completed less. Variables were compared to the similar HOMER cohort of HCC cases from 1 July 2012 and 30 June 2013 using Chi square or Wilcoxon rank-sum test. **Results:** There were 202 incident HCC cases identified, 78% were male (n = 159), median age of 68 years (IQR 60-74 y), 61% born overseas (n = 116). Established cirrhosis was known in 47% (n = 96), 33% (n = 66) newly diagnosed with cirrhosis at time of HCC diagnosis, 20% (n = 41) non-cirrhotic. Early-stage HCC (BCLC 0-A) occurred in 47% (n = 95). Surveillance uptake occurred in 39% (n = 79). Of these, 53 % (n = 42) had optimal surveillance and 47% (n = 39) had suboptimal surveillance. In patients with known cirrhosis, 67% (n = 66) were undergoing surveillance and 45% (n = 21) of eligible patients with chronic hepatitis B. Having at least one abdominal scan in the preceding 12 months for any indication was associated with increased odds of early-stage HCC (OR 2.99, 95% CI 1.68-5.32, $p < 0.0001$). Surveillance through imaging +/- AFP was the most common mode of presentation at

37% (n = 75), then symptomatic disease (pain/decompensation) 34% (n = 69), clinician investigation of liver test derangement 16% (n = 32) and incidental findings 13% (n = 27). Compared to the original HOMER cohort (2012-13), there was an overall decrease in crude HCC incidence estimates from 6.57 to 4.11/100 000, a significant decrease chronic hepatitis C as a risk factor and increase in MAFLD; a higher proportion diagnosed with early-stage HCC, although there was no improvement in surveillance uptake over time (Table 1). **Conclusion:** The incidence of HCC in Melbourne, Australia has reduced between 2012-13 and 2021-22, temporally associated with the introduction of DAAs for HCV in 2016, and an increase in MAFLD-HCC reflecting the obesity epidemic. Early-stage HCC at diagnosis was more common in 2021-22, but rates of diagnosis in surveillance remained sub-optimal, highlighting the need for programs to promote community diagnosis of liver disease and enrolment in HCC surveillance.

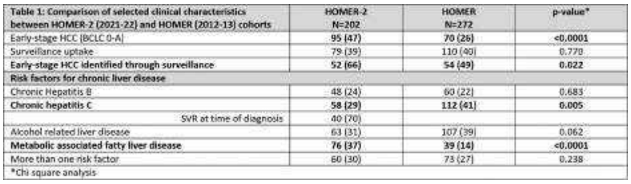

Table 1: Comparison of selected clinical characteristics between HOMER-2 (2021-22) and HOMER (2012-13) cohorts	**HOMER-2 N=202**	**HOMER N=272**	**p-value***
Early-stage HCC (BCLC 0-A)	95 (47)	70 (26)	<0.0001
Surveillance uptake	79 (39)	110 (40)	0.770
Early-stage HCC identified through surveillance	**52 (66)**	**54 (49)**	**0.022**
Risk factors for chronic liver disease			
Chronic Hepatitis B	48 (24)	60 (22)	0.683
Chronic hepatitis C	**58 (29)**	**112 (41)**	**0.005**
SVR at time of diagnosis	40 (70)		
Alcohol related liver disease	63 (31)	107 (39)	0.062
Metabolic associated fatty liver disease	**76 (37)**	**39 (14)**	**<0.0001**
More than one risk factor	60 (30)	73 (27)	0.238
*Chi square analysis			

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4016-A | CHARACTERISTICS AND OUTCOMES OF HEPATOCELLULAR CARCINOMA IN THE FONTAN SURVIVOR: A MULTICENTER RETROSPECTIVE STUDY EXAMINING LIVER OUTCOMES

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Background: The Fontan operation is a surgical procedure to palliate single ventricle congenital heart disease. Hepatocellular carcinoma (HCC) is a rare and potentially fatal complication of Fontan-associated liver disease (FALD). We aim to describe tumor characteristics, including stage, treatment, and outcomes of HCC occurring in the context of FALD. **Methods:** This is a multicenter, retrospective case series of adult Fontan patients diagnosed with HCC between 2005 and 2022. Descriptive statistics were used to compare groups. Patient survival was evaluated using Kaplan-Meier curves and log-rank tests. **Results:** Fifty-eight patients (43% female, 79% White) were diagnosed with HCC at median age 31 (interquartile range 26, 38) years. Diagnoses were made by biopsy (45%), imaging (38%), explant/resection (16%), or autopsy (2%). Twenty-five (43%) patients had a single lesion and median tumor size was 3.9 cm. Metastatic disease was present in 3 patients (5%) and vascular invasion in 6 patients (10%). There were 42 patients (72%) classified as Child-Turcotte-Pugh class A, 16 (28%) as class B, and none in class C. Nine patients (16%) were Barcelona Clinic Liver Cancer (BCLC) stage 0, 30 patients (54%) stage A, 8 patients (14%) stage B, 6 patients (11%) stage C, and 3 patients (5%) stage D. Treatment modalities included surgery in 18 patients (31%, 9 resection, 9 combined heart-liver transplant), liver-directed therapy in 28 patients (48%, 6 percutaneous ablation, 22 transarterial chemoembolization, transarterial radioembolization or external radiotherapy), systemic therapy 3 patients (5%) and palliative care only in 9 patients (16%). Forty-four percent of BCLC stage 0 or A patients had surgical therapy and 15% had percutaneous ablation, while 13% of BCLC stage B patients had surgery and none had percutaneous ablation (p = 0.001). One- and 3-year survival were 79% and 64%, respectively. Three-year survival was higher in patients who received surgery or ablation (80%) compared to other liver directed therapy (64%), systemic therapy (0%), and palliative care (17%, p = 0.004; Figure). There was no recurrence or evidence of viable tumor after treatment following liver transplant or ablation, compared to 4 patients (44%) after surgical resection and 13 patients (59%) after non-ablation liver-directed therapy (p = 0.001). **Conclusion:** This is the largest case series describing staging, therapy and outcome of HCC in the context of FALD. More than two-thirds of the cases were diagnosed at an early stage, of whom slightly more than half received potentially curative surgery or ablation. We demonstrate higher survival rates among patients who received these treatments. Survival was worse in the remaining one-third who were diagnosed at later stages and did not undergo curative therapy. Our findings underscore the importance of HCC screening for early detection in Fontan patients.

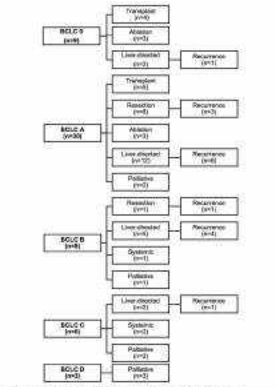
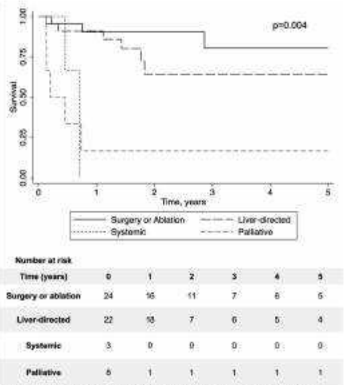


Figure A: Barcelona Clinic Liver Cancer (BCLC) stage, treatment and recurrence for patients with hepatocellular carcinoma (HCC) after Fontan palliation. BCLC stage was missing for two patients; one was treated with liver-directed therapy and had evidence of active tumor at last follow-up.



Time (years)	0	1	2	3	4	5
Surgery or ablation	24	16	11	7	6	5
Liver-directed	22	18	7	6	5	4
Systemic	3	0	0	0	0	0
Palliative	6	1	1	1	1	1

Figure B: Survival of patients with hepatocellular carcinoma after Fontan palliation stratified by most definitive treatment received (n=58). For example, patients who received liver-directed therapy followed by surgical therapy were categorized in the surgery group as most definitive treatment. Number at risk table and log rank p-value are shown.

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4017-A | CHARACTERIZING THE IDENTIFYING MODALITY OF INELIGIBLE PATIENTS WHO PRESENTED FOR LIVER TRANSPLANTATION EVALUATION FOR COLORECTAL LIVER METASTASES

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Background: Liver transplantation is a novel therapy for patients with unresectable colorectal liver metastases (CRLM). 5-year survival using liver transplantation appears to be significantly better than systemic chemotherapy in selected patients. Despite strict criteria for transplantation, there is little guidance on the required workup prior to full transplant evaluation; as a result, most referred patients do not proceed to transplantation. The purpose of this study is to identify the necessary screening tests for patients with CRLM referred for liver transplant evaluation and describe the reasons many do not progress to transplantation. **Methods:** 23 patients were referred for CRLM evaluation for liver transplantation from 2018 to 2022. Demographic and transplant evaluation data was collected for all patients throughout evaluation. **Results:** The population was 91% male with median age 53.8 years at diagnosis. 52% had their primary intact at referral and the Sigmoid colon was the most common site of primary tumor. Number of liver metastases ranged from 3 to > 20 with a median of 10; 43% of patients had a largest tumor size > 5.5cm. 57% of patients had prior liver resection, ablation, or HAI pump. 30% of patients had CEA at referral > 80 and 22% had progression of disease on chemotherapy. 13% of patients had an Oslo Score of 0; 52% an Oslo score of 1, 30% an Oslo score of 2, and 4% an Oslo score of 3. 22% of patients had a KRAS mutation. Of the 23 patients that presented for evaluation, 6 were listed for transplant, and 4 received a liver transplant; 1 is currently in evaluation. For the 18 patients who are no longer eligible, we identified the reason evaluation was ended and how this was discovered in Table 1. Of the 11 patients determined to be ineligible by CT Chest, 27% were ruled out on their first CT Chest and did not have prior high resolution CT Chest. Follow-up data at 1 year was available for 10 of the patients ineligible for transplant and overall survival at 1 year for these patients was 60%. **Conclusion:** It is important to streamline the appropriate imaging and procedural screening among patients referred for liver transplantation for CRLM. Most patients referred were ruled out due to extra-hepatic disease during the evaluation. Employing the use of CT chest, PET/CT imaging, and lymphadenectomy appears essential to understanding why many do not progress to transplantation and is critical to refining referral criteria to improve access to transplantation for appropriate patients with unresectable CRLM.

Table 1: Reasons for ineligibility – patients no longer eligible for transplant (n=18)

Reason for ending evaluation, n (%)	
Metastasis outside the liver	16 (89)
Rendered NED on imaging	1 (6)
Patient opted against transplant	1 (6)
Scan to identify ineligibility, n (%)	
CT chest	11 (61)
PET/CT skull base to thigh	4 (22)
Lymphadenectomy	1 (6)
Peritoneal metastases on colonic resection	1 (6)

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

Disclosure information not available at the time of publication: Ellie Brandon, Mateo Noriega, Pashtoon Murtaza Kasi, Manish Shah, Juan P Rocca

4018-A | CLINICAL CHARACTERISTICS AND RISK FACTORS OF EXTRAHEPATIC RECURRENCE AFTER HEPATECTOMY OF HEPATOCELLULAR CARCINOMA WITHOUT INTRAHEPATIC HEPATOCELLULAR CARCINOMA: A MULTI-INSTITUTIONAL 15-YEAR OBSERVATIONAL STUDY

Jae Hyun Yoon[1]*, Ga Ram You*[2]*, Sung Bum Cho*[2] *and Sung Kyu Choi*[1]*, (1)Chonnam National University Hospital, (2)Hwasun Chonnam National University Hospital*

Background: Extrahepatic recurrence (EHR) is a well-known poor prognostic factor regarding hepatocellular carcinoma (HCC). Although EHR after hepatectomy of HCC may occur in high risk group of patients, little is known about EHR when there are no intrahepatic HCC. We investigated the clinical features and risk factors regarding EHR without remnant intrahepatic HCC at the time of EHR diagnosis. **Methods:** Among 1,069 treatment-naive patients who underwent curative hepatectomy for HCC at four tertiary academic hospitals from January 2004 to December 2019, 569 patients were enrolled. Multivariate analysis via Cox-regression was performed to identify the variables associated with EHR. **Results:** Thirty-eight patients developed EHR after hepatectomy without remnant intrahepatic HCC during median follow-up duration of 1.04 years. (Figure 1) Patients with EHR demonstrated significant early initial HCC recurrence than the patients without EHR; 1.73 vs. 4.43 years, respectively. On multivariate analysis, compared to patients without EHR, patients with EHR (without IHR) showed higher portion of venous/lymphatic involvement (HR 2.418, $p = 0.020$), tumor necrosis (HR 2.592, $p = 0.009$) and initial tumor stage beyond Milan criteria ($HR = 3.008$, $p = 0.001$). Also on analysis of factors related to survival after surgical resection of HCC, EHR was strongly associated with poor survival on multivariate analysis via Cox-regression ($HR = 14.044$, $p < 0.001$) (Figure 3). Not only the cumulative rates of EHR correlated with the numbers of risk factors but also the survival rates also exhibited step-wise relationship (Figure 2, and 3). **Conclusion:** EHR without remnant viable HCC may occur in considerable number of patients after hepatectomy for HCC. Patients with high risk for EHR are warranted for meticulous postoperative surveillance for timely EHR detection and positive clinical outcomes despite no intrahepatic HCC.

Figure 1.

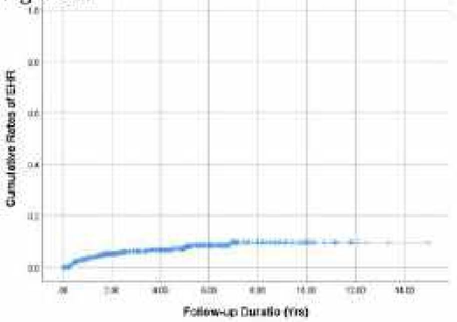


Figure 2.

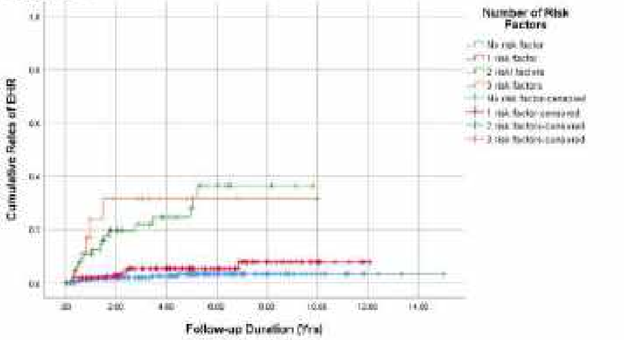
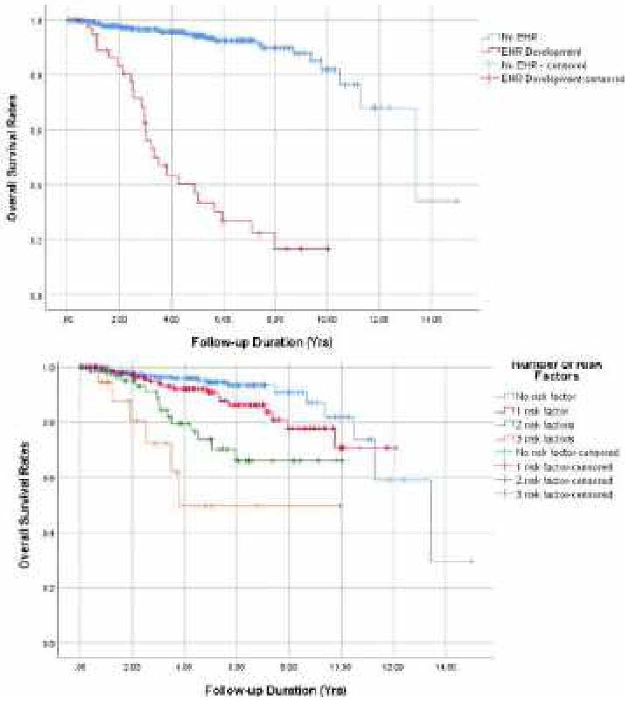


Figure 3.



Disclosures: The following people have nothing to disclose: Jae Hyun Yoon, Ga Ram You, Sung Bum Cho, Sung Kyu Choi

4019-A | CLINICAL FACTORS ASSOCIATED WITH THE THERAPEUTIC EFFICACY OF ATEZOLIZUMAB PLUS BEVACIZUMAB IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA: A MULTICENTER PROSPECTIVE OBSERVATIONAL STUDY

Kazuki Maesaka[1], Hayato Hikita[1], Machiko Kai[1], Yuki Tahata[2], Kazuma Shinkai[1], Akira Doi[2], Kazuyoshi Ohkawa[3], Masanori Miyazaki[4], Hisashi Ishida[5], Kengo Matsumoto[6], Yasutoshi Nozaki[7], Takayuki Yakushijin[8], Ryotaro Sakamori[9], Takahiro Kodama[2], Tomohide Tatsumi[2] and Tetsuo Takehara[2], (1)Osaka University, Graduate School of Medicine, (2)Osaka University Graduate School of Medicine, (3)Osaka International Cancer Institute, (4)Osaka Police Hospital, (5)Ikeda Municipal Hospital, (6)Toyonaka Municipal Hospital, (7) Kansai Rosai Hospital, (8)Osaka General Medical Center, (9)National Hospital Organization Osaka National Hospital

Background: The treatment efficiency and predictors of atezolizumab plus bevacizumab therapy for unresectable hepatocellular carcinoma (uHCC) in real-world practice have not been established. This study aimed to assess the therapeutic efficacy of atezolizumab plus bevacizumab and investigate the clinical factors associated with progression-free survival (PFS) and overall survival (OS). **Methods:** Patients with uHCC treated with atezolizumab plus bevacizumab in 19 hospitals were registered before the treatment and observed prospectively. Of this prospectively observational cohort, the outcomes of 222 patients were analyzed. The therapeutic responses were assessed according to the Response Evaluation Criteria in Solid Tumor version 1.1. **Results:** The median age of study patients was 73 years. One hundred and forty-seven (66.2%) patients were treated as their first systemic chemotherapy, whereas 75 (33.8%) had received another regimen before the treatment. One hundred and sixteen (47.7%) patients had more than four intrahepatic tumors, 37 (16.7%) patients had macrovascular invasion, and 88 (39.6%) patients had extrahepatic metastasis. The hepatic etiologies were as follows: viral, $n = 120$ (54.1%); non-viral, $n = 102$ (45.9%). The median NLR was 2.44 (IQR 1.78–3.55). The objective response rate and disease control rate were 22.0% and 70.6%, respectively. The median PFS was 5.7 months and 7.8 months in all patients and in the first-line systemic treatment group, respectively. Independent risk factors for the shortened PFS were younger age (< 75) (3.9 mo vs. 8.6 mo; $p = 0.008$), a higher number of intrahepatic tumors (≥ 5) (4.0 mo vs. 7.9 mo; $p < 0.001$), macrovascular invasion (2.3 mo vs. 6.7 mo; $p < 0.001$), and higher NLR (≥ 3.03) (3.0 mo vs. 7.8 mo; $p < 0.001$). On the other hand, non-viral etiology of hepatitis and the presence of prior systemic therapy were not risk factors for the shorten PFS. The median OS was not reached; however, independent risk factors for the shortened OS were a higher number of intrahepatic tumors (≥ 5), macrovascular invasion, higher α-fetoprotein level (≥ 400), worse Child-Pugh score (≥ 6), and higher NLR (≥ 3.03). **Conclusion:** Patients with older age, a lower number of intrahepatic tumors, the absence of macrovascular invasion, and lower NLR were expected to have the prolonged PFS in atezolizumab plus bevacizumab therapy for uHCC.

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4020-A | CLINICAL IMPACT OF DIRECT ACTING ANTIVIRALS ON PROGNOSIS OF PATIENTS WITH HEPATOCELLULAR CARCINOMA DUE TO HEPATITIS C VIRUS IN JAPAN

Hideko Ohama[1,2], Atsushi Hiraoka[1,2], Toshifumi Tada[2], Masashi Hirooka[2], Kazuya Kariyama[2], Ei Itobayashi[2], Tsuji Kunihiko[2], Toru Ishikawa[2], Hidenori Toyoda[2], Takeshi Hatanaka[2], Satoru Kakizaki[2], Atsushi Naganuma[2], Tomomitsu Matono[2], Fujimasa Tada[2], Kazuhiro Nouso[2], Yoichi Hiasa[2] and Takashi Kumada[2], (1)Ehime Prefectural Central Hospital, (2)Relpec Study Group and HCC 48 Group

Background: Direct acting antivirals (DAAs) capable of eliminating hepatitis C virus (HCV) sustained virological response SVR at a higher rate than interferon therapy has been available in Japan since 2014. This study examined the clinical impact of DAAs for hepatocellular carcinoma (HCC) due to HCV before and after the advent of these drugs. **Methods:** Enrolled were 1982 patients with HCC due to HCV treated at our institutions in Japan from January 2000 to January 2023. They were divided into two groups based on before and after DAA availability: pre-DAA (before 2013, $n = 1181$) and post-DAA (after 2014, $n = 801$). Changes in clinical features and prognoses were evaluated in a retrospective manner. **Results:** The groups did not show significant differences for Liver Cancer Study Group of Japan tumor node metastasis stage or Japan integrated staging (JIS) score. However, the post-DAA group had higher frequencies of patients with SVR from anti-viral treatments (45.9% vs. 10.1%), elderly age (73 vs. 69 y old), lower AST (40 vs. 56 IU/L), ALT (31 vs. 46 IU/L), and AFP (11.2 vs. 23.6 ng/mL) levels, higher platelet count (13.6 vs. 10.8 x10^{4}/µL), longer prothrombin time (88.0% vs. 81.9%), better ALBI score (-2.53 vs. -2.36), and higher rate of curative treatment (surgical resection or radio frequency ablation) (73.7% vs. 65.0%) ($p < 0.001$, for all). Also, recurrence-free survival (RFS) after curative treatment was significantly better in the post-DAA group (median 2.9 vs. 2.1 y) as was overall survival (OS) [median: not applicable (NA) vs. 5.5 y) ($p < 0.001$, for all). After inverse probability weighting (IPW) adjustment using propensity scores based on multivariate analysis, OS was also better in the post-DAA group (median 7.0 vs. 5.7 y, $p < 0.001$). As a sub-analysis, comparisons of prognosis among three groups after dividing the post-DAA group into non-SVR ($n = 307$), pre-SVR (HCC developed after SVR, $n = 368$), and post-SVR (SVR developed after HCC, $n = 126$) showed that OS for the non-SVR group was significantly shorter (median 3.2 y vs. NA vs. NA, $P < 0.001$), with no significant difference noted between the pre- and post-SVR groups ($p = 0.19$). **Conclusion:** The prognosis of patients with HCC due to HCV was greatly improved after introduction of DAAs, with the resultant high rate of HCV elimination dramatically changing clinical practice for HCV-related HCC cases.

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4021-A | CLINICAL OUTCOMES OF POROUS GLASS MEMBRANE PUMPING EMULSIFICATION DEVICE IN TRANSARTERIAL CHEMOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA

Fumitaka Mizuno, Norihiro Imai, Shinya Yokoyama, Kenta Yamamoto, Takanori Ito, Yoji Ishizu, Takashi Honda, Masatoshi Ishigami and Hiroki Kawashima, Nagoya University Graduate School of Medicine

Background: A porous glass membrane pumping emulsification device (GMD) enables the formation of a high-percentage water-in-oil emulsion with homogeneous and stable droplets. Although GMD is expected to improve local therapeutic effects in transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC), the clinical outcomes of GMD in TACE are limited to a few reports to date. **Methods:** From 2019 to 2023, 57 patients with unresectable HCC were treated with 72 TACE sessions using GMDs. All TACE procedures were performed according to the standard treatment protocol. Ethiodized oil was mixed with epirubicin solution using a GMD. The ratio of epirubicin solution to ethiodized oil was 1:2. The emulsion was injected into the tumor-feeding artery, followed by embolization. The treatment efficacy was evaluated by contrast-enhanced computed tomography 1–3 months after TACE using a GMD and every 2–3 months thereafter. Based on changes in the maximum diameter of viable lesions, the treatment responses of target tumor were categorized by the modified Response Criteria in Solid Tumors. The changes in liver function after the treatment and the treatment-related adverse events were analyzed retrospectively. **Results:** There were 47 males and 10 females; the median age was 73 years (range 45-89). Child–Pugh scores were A (score 5) in 36 patients, A (score 6) in 14 patients, B (score 7) in five patients, and B (score 8) in two patients. The Barcelona Clinic Liver Cancer stages were 0 (very early stage) in 13 patients, A (early stage) in 33 patients and B (intermediate stage) in 11 patients. The median size of treated HCCs was 23.5 (range 6–61) mm, and 44 nodules were solitary. The median dosage of ethiodized oil mixed with epirubicin solution was 3.0 (range 0.7–12) ml. Treatment effects of target tumors were complete response in 76% and partial response in 17%. The local recurrence rates at 6 months and 12 months were 84.2% and 59.2% respectively. The median time to recurrence after the treatment was 581 days. During the observation period, no major treatment related complications were observed. Multivariate Cox proportional hazards model analysis including emulsion dosage, localization, and enhancement pattern revealed that the number of HCC and first TACE were significantly associated with better local control. **Conclusion:** The use of GMD in TACE enables the tumor to accumulate ethiodized oil more densely, resulting in effective local control.

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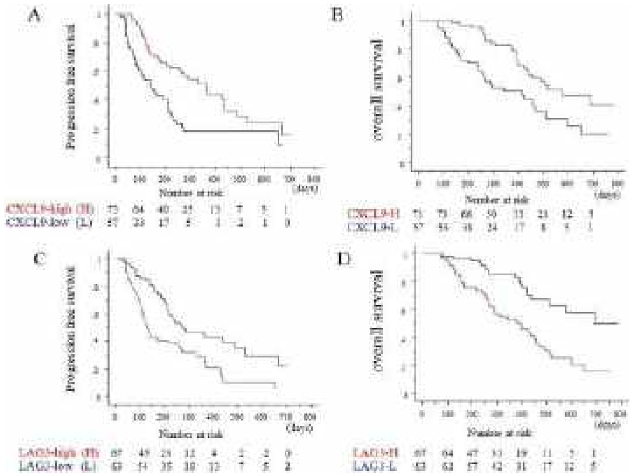
4022-A | CLINICAL SIGNIFICANCE OF CIRCULATING IMMUNE MOLECULE BIOMARKERS FOR PREDICTING THE EFFICACY OF ATEZOLIZUMAB PLUS BEVACIZUMAB THERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA

Makoto Chuma[1], Haruki Uojima[2], Hidenori Toyoda[3], Atsushi Hiraoka[4], Masanori Atsukawa[5], Tomomi Okubo[6], Toshifumi Tada[7], Yoshitaka Arase[8], Hisashi HIdaka[2], Takashi Kumada[9], Tatehiro Kagawa[8] and Shin Maeda[10], (1)Yokohama City University Medical Center, (2)Kitasato University School of Medicine, (3)Ogaki Municipal Hospital, (4)Ehime Prefectural Central Hospital, (5)Nippon Medical School Hospital, (6)Nippon Medical School Chibahokusoh Hospital, (7)Japanese Red Cross Himeji Hospital, Himeji, Japan, (8)Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokai University School of Medicine, (9)Gifu Kyoritsu University, (10)Yokohama City University

Background: Atezolizumab plus bevacizumab (ATZ+BV) therapy has become a first-line therapy for unresectable hepatocellular carcinoma (u-HCC), but predictive biomarkers of the response of this therapy have not yet been clarified. The aim of this study was to identify clinically significant biomarkers of the response to ATZ+BV therapy in u-HCC. **Methods:** First, for the potential of cell-free DNA/circulating tumor DNA (ctDNA) as biomarkers for predicting the therapeutic outcome, we have extracted cell-free DNA from serum in 24 u-HCC patients treated with ATZ+BV therapy and AmpliSeq for Illumina Cancer Hotspot Panel v2 was used to detect and analyze mutations. Second, levels of specific immune-related cytokines reported in sera from HCC patients (i.e., CD274; LAG3; CCL2, 4, 5, and 20; CXCL1, 9, 10, 11, 12, and 13; CX3CL1, CCR5, IFNγ; and IL-6 and 8) were measured using enzyme-linked immunosorbent assays in blood samples from 130 u-HCC patients treated with ATZ+BV therapy. **Results:** Variant read frequency (VRF) mutations in TP53 (12.6%), APC (8.4%), PICK3CA (8.4%), and VHL (4.2%) were found as pathologically malignant genes at a VRF of ≥ 1%, but there was no correlation between these mutations and treatment response. CTNNB1 was also detected in two stable disease (SD) cases and two progressive disease (PD) cases, but at a low VRF of 0.5%. We measured 16 chemokines in 130 cases and found significant differences in expression among OR, SD, and PD cases, for CXCL9 and LAG3 which are related to recruitment of CD8 T-cell or CD8 T-cell exhaustion. Receiver-operating characteristic curve analyses of CXCL9 (402 mg/ml) and LAG-3 (3864 pg/ml) indicated areas of 0.739 and 0.707, respectively, to differentiate OR from non-OR and to differentiate PD from non-PD. The patients with high serum CXCL9 (CXCL9-H) exhibited significantly longer progression-free survival (PFS) and overall survival (OS) compared to patients with low serum CXCL9 (CXCL9-L) (adjusted hazard ratio [aHR] = 0.43, 95% confidence interval [CI] = 0.28-0.66, $P < 0.001$, and aHR = 0.42, 95% CI = 0.25-0.70, $P < 0.001$, respectively) (Figure A, B). Furthermore, patients with low serum LAG-3 (LAG-3-L) exhibited significantly longer PFS and OS compared to patients with serum LAG-3-H (aHR = 0.43, 95% CI = 0.28-0.66, $P = 0.001$, and aHR = 0.42, 95% CI = 0.25–0.70, $P < 0.001$, respectively) (Figure C, D). **Conclusion:** Although no ctDNA mutations were found to be related to the efficacy of ATZ+BV therapy, serum levels of CXCL9 and LAG-3 were associated with the efficacy of ATZ+BV therapy and both PFS and OS, suggesting the importance of CD8 T-cell function in predicting the effectiveness of this treatment in patients with unresectable hepatocellular carcinoma.



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Sumitomo Pharma: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Mitsubishi Tanabe Pharma: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Eisai: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Abbvie: Grant/ Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; EA pharma: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Otsuka Pharmaceutical: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Kyowa Kirin: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Teijin: Grant/ Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Japan Blood Products Organization: Grant/ Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Chugai-pharma: Speaking and Teaching, No, Yes; Sumitomo Pharma: Speaking and Teaching, No, Yes; Eisai: Speaking and Teaching, No, Yes; Abbvie: Speaking and Teaching, No, Yes; Gilead Sciences: Speaking and Teaching, No, Yes; Takeda Pharmaceutical Company: Speaking and Teaching, No, Yes; MSD: Speaking and Teaching, No, Yes; Kowa Company: Speaking and Teaching, No, Yes; EA pharma: Speaking and Teaching, No, Yes; Otsuka Pharmaceutical: Speaking and Teaching, No, Yes; Kyowa Kirin: Speaking and Teaching, No, Yes; AstraZeneca: Speaking and Teaching, No, Yes; Nobelpharma: Speaking and Teaching, No, Yes; Eli Lilly: Speaking and Teaching, No, Yes; Miyarisan: Speaking and Teaching, No, Yes; ASKA Pharmaceutical: Speaking and Teaching, No, Yes;

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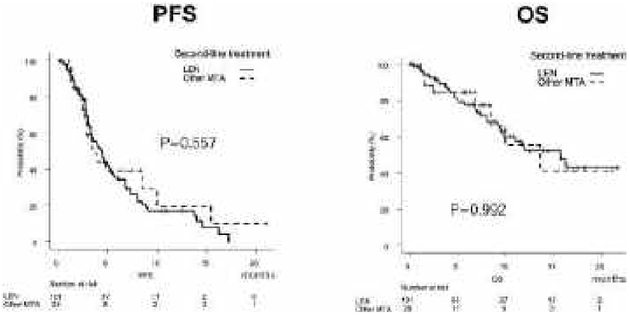
4023-A | CLINICAL USEFULNESS OF LENVATINIB AS SECOND-LINE TREATMENT FOR HEPATOCELLULAR CARCINOMA FOLLOWING ATEZOLIZUMAB PLUS BEVACIZUMAB FAILURE

Atsushi Hiraoka[1], Toshifumi Tada[2], Masashi Hirooka[2], Kazuya Kariyama[2], Ei Itobayashi[2], Tsuji Kunihiko[2], Toru Ishikawa[2], Hidenori Toyoda[2], Takeshi Hatanaka[2], Satoru Kakizaki[2], Atsushi Naganuma[2], Tomomitsu Matono[2], Hideko Ohama[1], Fujimasa Tada[1], Kazuhiro Nouso[2], Yoichi Hiasa[2] and Takashi Kumada[2], (1)Ehime Prefectural Central Hospital, (2)Relpec Study Group and HCC 48 Group

Background: Atezolizumab plus bevacizumab (Atez/ Bev) is a standard first-line treatment for advanced hepatocellular carcinoma (HCC), though effective methods for post-progression systemic treatment have yet to be established. The present study investigated the potential of lenvatinib as second-line treatment after Atez/Bev failure. **Methods:** A total of 101 patients who received lenvatinib as second-line treatment between 2020 and 2022 were included. Median age was 72 years and the majority were male (77%). Most patients had Child-Pugh A (82%), while BCLC staging was A:B:C: D = 1:35:61:4. As controls, 29 patients who received another molecular targeting agent (MTA) as second-line treatment during the same period (sorafenib 14, ramucirumab 11, cabozantinib 4) were also enrolled. The therapeutic efficacy of lenvatinib given as second-line treatment was retrospectively evaluated. **Results:** Median progression-free survival (PFS) and median overall survival (OS) for all patients were 4.4 and 15.7 months, respectively. For those with Child-Pugh class A, median PFS was 4.7 months and median OS was not reached. When compared with patients who received another MTA, there were no significant differences in terms of PFS (3.5 months, $P = 0.557$) or OS (13.6 months, $P = 0.992$), and also no significant differences for clinical background factors. Modified RECIST findings revealed that objective response and disease control rates for patients treated with lenvatinib were 23.9% and 70.4%, respectively (CR:PR:SD:PD = 3:14:33:21), while those shown by RECIST ver. 1.1 were 15.4% and 66.2%, respectively (CR:PR:SD:PD = 1:10:36:24). The most common adverse events (any grade $\geq 10\%$) were appetite loss (26.7%), general fatigue (21.8%), proteinuria (16.8%), and hypertension

(13.9%). **Conclusion:** Lenvatinib treatment may not provide a pseudo-combination immunotherapy effect after Atez/Bev treatment failure, though the present results suggest that it can be an effective second-line treatment option for advanced HCC patients following such failure. These results provide important insights into the therapeutic potential of lenvatinib for this patient population and highlights the need for further research to optimize treatment strategies.



Disclosures: Takeshi Hatanaka – Eisai: Speaking and Teaching, Yes, No;
The following people have nothing to disclose: Atsushi Hiraoka, Toshifumi Tada, Masashi Hirooka, Kazuya Kariyama, Ei Itobayashi, Tsuji Kunihiko, Toru Ishikawa, Hidenori Toyoda, Satoru Kakizaki, Atsushi Naganuma, Tomomitsu Matono, Hideko Ohama, Fujimasa Tada, Kazuhiro Nouso, Yoichi Hiasa, Takashi Kumada

4024-A | CLINICOPATHOLOGIC AND TREATMENT OUTCOME DATA FROM 165 FIBROLAMELLAR CARCINOMA PATIENTS

Shadi Chamseddine[1], Sunyoung Lee[1,2] and Ahmed Kaseb[1], (1)The University of Texas MD Anderson Cancer Center, (2)Severance Hospital, Yonsei University College of Medicine

Background: Fibrolamellar carcinoma (FLC) is a rare subtype of liver cancer that primarily affects young adults and adolescents. The main objective of this study is to evaluate the association between survival outcomes and clinical factors of patients with FLC. **Methods:** We retrospectively collected clinicopathologic and treatment outcome data from 88 male and 77 female patients with a pathologic diagnosis of FLC. Median overall survival (OS) and progression-free survival (PFS) were calculated using Kaplan-Meier curves. Log rank test, univariable and multivariable Cox models were applied to evaluate the association between clinical outcomes and patients' characteristics. **Results:** Mean age at diagnosis was 27.4 years (age range: 9, 76), median OS was 42.6 months (95% CI: 36.5, 59.2). 50.3% of patients in our study were AJCC Stage IV at the time of presentation, with 67.5% having vascular invasion at diagnosis. 5% of patients had liver cirrhosis. 68.5% of patients received surgery, including metastasectomy. 30.9% received radiation therapy, and 77.5% received systemic therapy. Combination of 5-fluorouracil and interferon-alpha2 was the most frequently used systemic therapy (83 patients), with 45 patients receiving other forms of chemotherapy. The median OS of patients who underwent surgery was 59.2 months (95% CI [49.51, 89.68]) versus 20.34 months (95% CI [15.37, 26.02] in patients who did not. Of those who did not have surgery, 94.2% (49 patients) had AJCC stage > II. Higher tumor stage(> II) (HR = 2.841; 95% CI [1.309, 6.165]), lack of surgery (HR = 3.47; 95% CI [2.193, 5.488]) and lack of receipt of radiation therapy (HR = 1.685; 95% CI [1.059, 2.68]) were positively associated with worse OS. **Conclusion:** We identified prognostic factors in FLC. The associations of receipt of surgery and radiation with prolonged OS suggest that local control and cancer debulking in this disease is paramount.

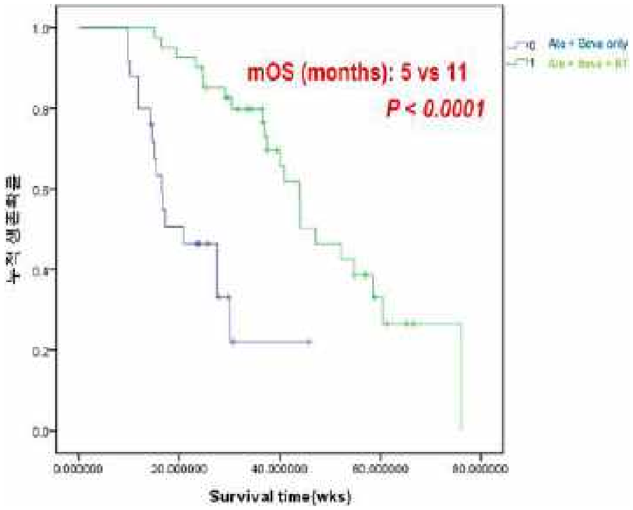
Disclosures: The following people have nothing to disclose: Shadi Chamseddine, Sunyoung Lee, Ahmed Kaseb

4025-A | COMBINATION OF RADIATION THERAPY IMPROVE EFFICACY OF ATEZOLIZUMAB PLUS BEVACIZUMAB (ATE+BEVA) THERAPY IN ADVANCED HEPATOCELLULAR CARCINOMA WITH HIGH RISK FACTOR (HUGE TUMOR, BILIARY AND MAIN PORTAL VEIN INVASION)

Sangyoun Hwang, Wan Jeon, Hyung Jun Kim, Jung Woo Im, Ki Jeong Jeon and Beom Jin Shim, Dongnam Institute of Radiological & Medical Sciences

Background: Atezolizumab plus bevacizumab (Ate +Beva) proved better efficacy compared to sorafenib as a first line systemic therapy for advanced hepatocellular carcinoma (HCC). However, there is unmet need in the so called "high risk population" (huge tumor, bile duct invasion, main portal vein invasion) because efficacy of Ate+Beva is worse in those group. Radiation therapy (RT) with immunotherapy could be expected synergic effect by immune stimulation. Therefore we describe the efficacy and safety of RT with immunotherapy in high risk population of advanced HCC. **Methods:** The clinical course of patients with advanced HCC who received Ate+Beva therapy in single cancer center from September 2020 to December 2021 was assessed until May 2022. Overall response rate (ORR) and disease control rate (DCR) per RECIST v1.1 and mRECIST, median overall survival (OS), and safety were analyzed.

Especially we divided two groups (RT vs non-RT) in high risk population and analyzed OS of two groups. **Results:** 163 patients were treated with Ate+Beva therapy, Child A:B:C patients were 147:16:1, BCLC stage B:C patients were 23:140. Median OS of total patients was 10.2 months, ORR & DCR of total patients were 20.8%, 72.4%. Severe adverse event (AE) beyond grade 3 was 12.9%, AE of Grade 5 (hemoptysis, pneumonitis, variceal bleeding, duodenal ulcer perforation, autoimmune hepatitis) was 3.1%. Median OS of RT group and non-RT group in total patients were 10.7 vs 11.7 months ($p = 0.597$), however those of two groups in high risk population were 11 vs 5 months ($p < 0.0001$). SAE of two groups was not different significantly. **Conclusion:** This study demonstrates that RT combined with Ate+Beva could improve efficacy about 2 times ompared to Ate+Beva without RT in high risk population of HCC without difference of AE. Further validation with large cohort in prospective study are needed to prove efficacy of Ate +Beva combined with RT in high risk population.



Disclosures: The following people have nothing to disclose: Sangyoun Hwang, Wan Jeon, Hyung Jun Kim, Jung Woo Im, Ki Jeong Jeon, Beom Jin Shim

4026-A | COMPARATIVE ANALYSIS OF ATEZOLIZUMAB PLUS BEVACIZUMAB AND HEPATIC ARTERY INFUSION CHEMOTHERAPY IN UNRESECTABLE HEPATOCELLULAR CARCINOMA: A MULTI-CENTER, PROPENSITY SCORE STUDY

Si Hyun Bae[1], Jae-Sung Yoo[2], Pil Soo Sung[2], Jeong Won Jang[2], Jong Choi[2], Seung Kew Yoon[2] and Department of Gastroenterology and Hepatology, Seoul St Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea, (1)The Catholic University of Korea, (2)Seoul St Mary's Hospital, the Catholic University of Korea, Seoul, Republic of Korea

Background: Patients who are not feasible for or cannot afford the first-line systemic chemotherapy, hepatic artery infusion chemotherapy (HAIC) may be proposed and can be used for treatment. Up to date, to our knowledge, there has been no study regarding the comparison between combination therapy, atezolizumab and bevacizumab, and hepatic artery infusion chemotherapy in advanced hepatocellular carcinoma (HCC) patients. The purpose of this study was to compare the prognosis and characteristics of the advanced HCC patients treated with the first-line combination therapy and hepatic artery infusion chemotherapy. **Methods:** We retrospectively assessed 174 patients treated with HAIC and 77 patients treated with atezolizumab/bevacizumab combination therapy between 2018 and 2022 in 5 university-affiliated hospitals in Korea. Firstly, we assessed the overall survival (OS), progression free survival (PFS), objective response rate (ORR) and disease control rate (DCR) between atezolizumab/ bevacizumab combination therapy and hepatic artery infusion chemotherapy. Due to baseline characteristic differences between the two groups, we also analyzed results with propensity score matching (PSM) method **Results:** When we compared the baseline characteristics of the enrolled patients, we found that there were significant differences in age, tumor numbers, portal vein invasion and Child Pugh scores. HAIC treated patients were significantly younger, had significantly more single number of tumors, had more portal vein invasions and had worse Child-Pugh scores. Despite the fact that HAIC-treated patients had more portal vein invasions and worse Child-Pugh scores, however, there was no significant difference in overall survival or progression-free survival between the two groups. After adjusting for bias that could occur due to confounding variables by PSM method, patients treated with Ate/beva therapy has a significantly longer OS than patients treated with HAIC ($P < 0.05$), although there were no significant differences in progression-free survival and objective responses. **Conclusion:** According to our multi-center, propensity score study, patients treated with Ate/beva therapy has a significantly longer OS than patients treated with HAIC.

Disclosures: The following people have nothing to disclose: Si Hyun Bae, Jae-Sung Yoo, Pil Soo Sung, Jeong Won Jang, Jong Choi, Seung Kew Yoon

4027-A | COMPARATIVE ANALYSIS OF ATEZOLIZUMAB PLUS BEVACIZUMAB AND LENVATINIB ON LIVER FUNCTION IN HEPATOCELLULAR CARCINOMA PATIENTS: A MIXED-EFFECTS REGRESSION MODEL

Takeshi Hatanaka[1], Satoru Kakizaki[2], Atsushi Hiraoka[3], Toshifumi Tada[4], Masashi Hirooka[5], Kazuya Kariyama[6], Ei Itobayashi[7], Tsuji Kunihiko[8], Toru Ishikawa[9], Hidenori Toyoda[10], Atsushi Naganuma[2], Tomomitsu Matono[11], Hideko Ohama[12], Fujimasa Tada[3], Yutaka Yata[13], Kazuhiro Nouso[6], Yoichi Hiasa[5], Takashi Kumada[14] and The Real-life Practice Experts for HCC (RELPEC) Study Group, and HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan), (1)Gunma Saiseikai Maebashi Hospital, (2)National Hospital Organization Takasaki General Medical Center, (3) Ehime Prefectural Central Hospital, (4)Japanese Red Cross Himeji Hospital, (5)Ehime University Graduate School of Medicine, (6)Okayama City Hospital, (7)Asahi General Hospital, (8)Teine Keijinkai Hospital, (9) Saiseikai Niigata Hospital, (10)Ogaki Municipal Hospital, (11)St. Mary's Hospital, (12)Takarazuka City Hospital, (13)Hanwa Memorial Hospital, (14)Gifu Kyoritsu University

Background: The aim of the retrospective study was to compare the impact of atezolizumab plus bevacizumab (Atez/Bev) and lenvatinib (LEN) on liver function in patients with hepatocellular carcinoma. **Methods:** Between March 2018 to July 2022, we included 526 patients receive Atez/Bev and 731 patients received LEN in this study. We conducted a 1:1 propensity score matching analysis and identified 324 patients in each group for inclusion in the present analysis. We used non-linear mixed-effects regression models to compare the rate of ALBI score, serum albumin and total bilirubin in Atez/Bev and LEN group. **Results:** After the propensity score matching, the median age of the Atez/Bev and LEN groups were 74.0 [68.0-80.0] and 74.0 [69.0-79.0] years old, respectively. In the Atez/Bev group, 276 (85.2%) were male, while in the LEN group, 276 (85.2%) were male. There was no significant difference in the performance status between the two groups, with 274 (84.6%) having a status of 0, 41 (12.7%) having a status of 1, and 9 (2.8%) having a status of ≥ 2 in the Atez/Bev group, and 262 (80.9%), 54 (16.7%), and 8 (2.5%) in the LEN group, respectively ($p = 0.4$). The serum level of albumin was 3.8 (interquartile range [IQR] 3.4-4.1 g/dL) in the Atez/Bev group and 3.8 (IQR 3.4-4.0 g/dL) in the LEN group, showing no significant difference ($p = 0.9$). Similarly, the serum total bilirubin was 0.8 (IQR 0.6-1.0 mg/dL) in the Atez/Bev group and 0.8 (IQR 0.5-1.0 mg/dL) in the LEN group, with no significant difference observed ($p = 0.1$). The mean ALBI score in Atez/Bev and LEN groups were -2.41 ± 0.40 and -2.44 ± 0.42 at baseline, and -2.17 ± 0.56 and -2.19 ± 0.58 at 12 weeks, respectively. Although the ALBI score significantly worsened during treatment in both groups ($p < 0.001$), there was no significant difference in the rate of ALBI score deterioration between the two groups ($p = 0.06$). There was also no significant difference in the rate of decreasing serum albumin and increasing total bilirubin levels ($p = 0.5$ and 0.07). Subgroup analyses showed that LEN-treated patients with BCLC advanced stage ($p = 0.02$) and those who initially received the full dose ($p < 0.001$) had a significantly greater worsening of ALBI score compared to Atez/Bev treatment. **Conclusion:** There was no significant difference in the trend of liver function deterioration between both groups. Caution should be exercised for LEN-treated patients with BCLC advanced stage or those receiving a full dose of LEN.

Disclosures: Takeshi Hatanaka – Eisai: Speaking and Teaching, Yes, No;

The following people have nothing to disclose: Satoru Kakizaki, Atsushi Hiraoka, Toshifumi Tada, Masashi Hirooka, Kazuya Kariyama, Ei Itobayashi, Tsuji Kunihiko, Toru Ishikawa, Hidenori Toyoda, Atsushi Naganuma, Tomomitsu Matono, Hideko Ohama, Fujimasa Tada, Yutaka Yata, Kazuhiro Nouso, Yoichi Hiasa, Takashi Kumada

4028-A | COMPARISON OF ATEZOLIZUMAB PLUS BEVACIZUMAB AND LENVATINIB FOR HEPATOCELLULAR CARCINOMA WITH PORTAL VEIN TUMOR THROMBOSIS

Jeayeon Park[1], Hyunjae Shin[1], Moon Haeng Hur[2], Min Kyung Park[1] and Yun Bin Lee[2], (1)Seoul National University College of Medicine, (2)Seoul National University Hospital

Background: Atezolizumab plus bevacizumab and lenvatinib are currently available as first-line therapy for the treatment of unresectable hepatocellular carcinoma (HCC). However, studies comparing the efficacy of atezolizumab plus bevacizumab and lenvatinib are still scarce. This study aimed to investigate the effectiveness of these treatments in HCC patients with portal vein tumor thrombosis (PVTT). **Methods:** We retrospectively included consecutive patients who received either atezolizumab plus bevacizumab or lenvatinib as first-line systemic therapy for the treatment of HCC with PVTT between October 2020 and July 2022 at a tertiary referral center. Primary endpoint was overall survival (OS), and secondary endpoints included progression-free survival (PFS) and disease control rate (DCR) determined by Response Evaluation Criteria in Solid Tumors, version 1.1. **Results:** A total of 52 patients were included: 30 received atezolizumab plus bevacizumab and 22 received lenvatinib. The median follow-up duration was 6.4 months (interquartile range,

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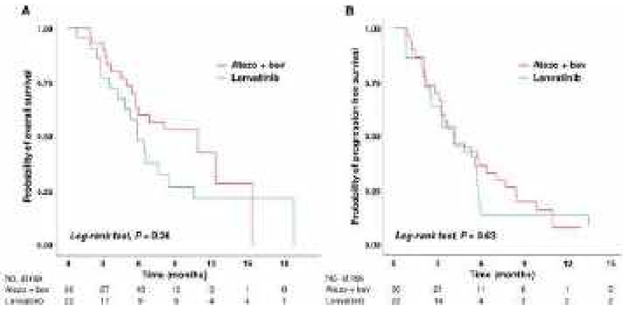
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

3.9–9.8). The median OS was 10.8 months (95% confidence interval [CI], 5.7–not estimated) with atezolizumab plus bevacizumab and 5.8 months (95% CI, 4.8–not estimated) with lenvatinib ($P = 0.26$ by log-rank test; Figure 1A). There was no statistically significant difference in OS between patients treated with atezolizumab plus bevacizumab and those treated with lenvatinib (atezolizumab plus bevacizumab versus lenvatinib; adjusted hazard ratio [aHR], 0.53; 95% CI, 0.22–1.26; $P = 0.15$). The median PFS was similar between the two treatments ($P = 0.63$ by log-rank test; Figure 1B), with 4.1 months (95% CI, 3.3–7.7) for atezolizumab plus bevacizumab and 4.3 months (95% CI, 2.6–5.8) for lenvatinib (atezolizumab plus bevacizumab versus lenvatinib; aHR, 0.70; 95% CI, 0.34–1.56; $P = 0.34$). HRs were similar after balancing with inverse probability treatment weighting. The DCRs were 23.3% and 18.2% in patients receiving atezolizumab plus bevacizumab and lenvatinib, respectively ($P = 0.89$). **Conclusion:** The effectiveness of atezolizumab plus bevacizumab and lenvatinib was comparable for the treatment of HCC with PVTT.



Disclosures: The following people have nothing to disclose: Jeayeon Park, Hyunjae Shin, Moon Haeng Hur, Min Kyung Park, Yun Bin Lee

4029-A | COMPARISON OF CLINICAL OUTCOME BETWEEN NIVOLUMAB AND REGORAFENIB AS SECOND-LINE SYSTEMIC THERAPY AFTER SORAFENIB FAILURE IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

Jae Seung Lee[1,2], Hong Jun Lee[1], Hye Won Lee[1,2], Beom Kyung Kim[1,2], Seung Up Kim[1,2], Jun Yong Park[1,2], Sang Hoon Ahn[1,2] and Do Young Kim[1,2], (1) Yonsei University College of Medicine, Seoul, Republic of Korea, (2)Severance Hospital, Seoul, Republic of Korea

Background: Nivolumab and regorafenib are used as second-line therapies for patients with advanced hepatocellular carcinoma (HCC). We aimed to compare the effectiveness of nivolumab to regorafenib. **Methods:** We retrospectively reviewed HCC patients treated with nivolumab or regorafenib after sorafenib failure. Progression-free survival (PFS) and overall survival (OS) were analyzed. Inverse probability of treatment weighting (IPTW) using the propensity score (PS) was conducted to reduce treatment selection bias. **Results:** Among the recruited 189 patients, 137 and 52 patients received regorafenib and nivolumab after sorafenib failure, respectively. Nivolumab users showed higher Child-Pugh B patients (42.3% vs. 24.1%) and shorter median sorafenib maintenance (2.2 vs. 3.5 mo) compared to regorafenib users. Compared to regorafenib users, nivolumab users showed shorter median OS (4.2 vs. 7.4 mo, $P = 0.045$) and similar median PFS (1.8 vs. 2.7 mo, $P = 0.070$), respectively. However, median OS and PFS were not different between the two treatment groups after 1:1 PS matching yielded 34 pairs (log-rank $P = 0.810$ and 0.810, respectively), and after stabilized IPTW (log-rank $P = 0.445$ and 0.878, respectively). In addition, covariate-adjusted Cox regression analyses showed that the nivolumab (vs. regorafenib) use was not significantly associated with the PFS and OS after 1:1 PS matching and stabilized IPTW (all $P > 0.05$). **Conclusion:** Clinical outcomes in patients treated with nivolumab and regorafenib after sorafenib failure did not differ significantly.

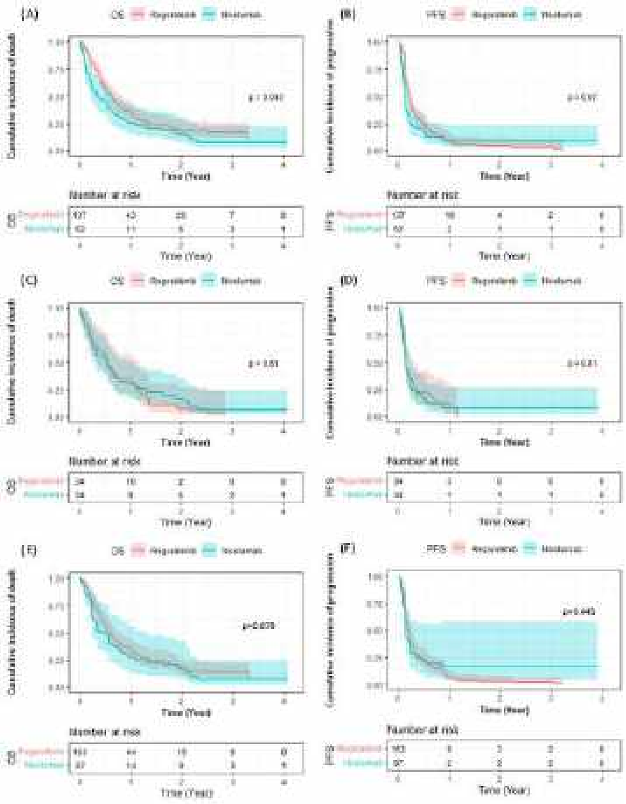


Figure. Kaplan–Meier curves with survival analysis for regorafenib and nivolumab users. (A) OS and (B) PFS of the unmatched cohort, (C) OS and (D) PFS of the 1:1 propensity score-matched cohort, and (E) OS and (F) PFS of the covariate-adjusted cohort after the stabilized inverse probability of treatment weighting. Abbreviation: OS, overall survival; PFS, progression-free survival.

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Advisor, No, Yes; Gilead Sciences Inc.: Advisor, Yes, No; GreenCross: Advisor, No, Yes; GSK: Advisor, No, Yes; Ildong: Advisor, No, Yes; Inovio: Advisor, No, Yes; Janssen: Advisor, No, Yes; Roche: Advisor, No, Yes; Samil: Advisor, No, Yes; SL Vaxigen: Advisor, No, Yes; Yuhan: Advisor, No, Yes;

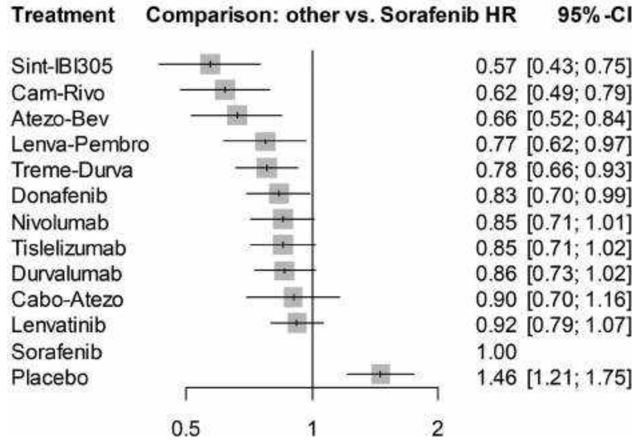
The following people have nothing to disclose: Jae Seung Lee, Hong Jun Lee, Hye Won Lee, Beom Kyung Kim, Seung Up Kim, Jun Yong Park, Do Young Kim

4030-A | COMPARISON OF FIRST-LINE SYSTEMIC THERAPIES FOR ADVANCED HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Moon Haeng Hur[1], Youngsu Park[1], Yunmi Ko[1], Hyunjae Shin[1], Jeayeon Park[1], Ju Yeon Kim[1], Yun Bin Lee[1], Su Jong Yu[1], Yoon Jun Kim[2], Jung-Hwan Yoon[1] and Jeong-Hoon Lee[3], (1)Seoul National University College of Medicine, (2)Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, South Korea, (3)Seoul National University College of Medicine, Seoul, South Korea

Background: Recently, several novel systemic therapies and their combinations have shown favorable outcomes in patients with advanced hepatocellular carcinoma (HCC). We performed a systemic review and network meta-analysis (NMA) to compare the efficacies of these treatments in relation to the current standards of care. **Methods:** A systematic literature search was conducted from inception to December 2022 on PubMed, EMBASE, Web of Science, and the Cochrane Controlled Register of Trials to identify phase III randomized controlled trials assessing the efficacy of systemic agents used as first-line therapies among patients with unresectable HCC. Studies investigating locoregional treatment or conventional cytotoxic chemotherapy were excluded. To focus on recently introduced systemic therapies, treatment regimens presented prior to 2018 (i.e., the year of lenvatinib introduction) were also excluded, except for sorafenib. Hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival (OS) and progression-free survival (PFS) were pooled and *P* score was calculated to rank treatment regimens. **Results:** A total of 5,038 studies were identified after duplicates removal and 12 trials (13 regimens) were included for NMA. Low level of heterogeneity ($I^2 = 0\%$) and inconsistency (Cochran's $Q = 0.01$, $P = 0.93$) was confirmed. Compared to sorafenib, sintilimab plus a bevacizumab biosimilar (Sint-IBI305) showed the greatest OS benefit (HR = 0.57, 95% CI = 0.43–0.75, *P* score = 0.944), followed by camrelizumab plus rivoceranib (Cam-Rivo; HR = 0.62, 95% CI = 0.49–0.79, *P* score = 0.892) and atezolizumab plus bevacizumab (Atezo-Bev; HR = 0.66, 95% CI = 0.52–0.84, *P* score = 0.834; Figure). The superiority of Sint-IBI305 was maintained in the subgroup of HCC with macrovascular invasion and/or extrahepatic spread and hepatitis B virus-related HCC. Regarding PFS, Cam-Rivo ranked first (HR = 0.52, 95% CI = 0.41–0.65, *P* score = 0.927), followed by Sint-IBI305 (HR = 0.56, 95% CI = 0.45–0.69, *P* score = 0.863) and lenvatinib plus pembrolizumab (Lenva-Pembro; HR = 0.57, 95% CI = 0.46–0.72, *P* score = 0.848). **Conclusion:** Novel systemic therapies including Sint-IBI305 and Cam-Rivo demonstrated promising results compared to the current standard regimens (sorafenib, lenvatinib, and Atezo-Bev); however, further validation is warranted.

Figure



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4031-A | COMPARISON OF GAAD VERSUS GALAD SCORES FOR THE SURVEILLANCE OF HEPATOCELLULAR CARCINOMA – A PROSPECTIVE STUDY

Chee-Kiat Tan, Wei Lun Liou, Si-Yu Tan, Kaina Chen, Thinesh Krishnamoorthy, Jason Pik Eu Chang and Chin-Pin Yeo, Singapore General Hospital

Background: Hepatocellular carcinoma (HCC) is the 6th most common cancer and the 3rd leading cause of cancer death globally. HCC surveillance has been shown to improve outcomes. Alpha-fetoprotein (AFP) is traditionally used in HCC surveillance but has suboptimal sensitivity. Hence, newer biomarkers, lectin-reactive AFP (AFP-L3) and des-γ-carboxy prothrombin (DCP), have been combined with AFP as a HCC risk algorithm, GALAD (gender/age/AFP-L3/AFP/DCP). Recently, GAAD (gender/age/AFP/DCP) which has the advantage of not having to do an additional AFP-L3 assay, has also been proposed as HCC risk algorithm. Our study aims to compare the performance of the GAAD and GALAD scores in a prospective cohort of at-risk individual's undergoing HCC surveillance. **Methods:** Patients undergoing HCC surveillance with 6-monthly ultrasonography (US) and AFP assay in Singapore General Hospital Department of Gastroenterology and Hepatology were enrolled between Dec 2017 and Oct 2018. Study sera were collected on the day of US for up to 3 consecutive visits. All the patients continued to receive HCC surveillance with 6-monthly US and AFP assay. The study sera were assayed by the Roche Elecsys® DCP and AFP kits, as well as the μTASWako® DCP, AFP and AFP-L3 kits, to calculate the GAAD and GALAD scores respectively using the algorithms provided by the manufacturers. The manufacturer's cut-off value for the GAAD score was 2.57 and -1.95 for the GALAD score (Japanese cut-off value). The study was IRB approved. **Results:** There were 180 patients. The median age was 59 years with 107 (59.4%) males. Hepatitis B was the most common chronic liver disease (83.9%). The median follow-up period was 49.6 months. By Feb 2023, 20 patients had developed HCC and they were all early stage disease. Median time between study sera and HCC was 20.5 months. The positive and negative predictive values for HCC detection by the GAAD (55.6%, 91.2%) and GALAD (45.5%, 93.7%) scores were similar. The GALAD score was able to predict 75% of HCCs developing within the next 1 year compared to 25% by the GAAD score. AUROC was 0.815 (95%CI: 0.713-0.916) for the GALAD score with an optimal cut-off value of -2.04 and 0.786 (95%CI: 0.679-0.893) for the GAAD score with an optimal cut-off value of 0.93. Thus, the performance of the GALAD score in our cohort was similar to the manufacturer's recommended cut-off value of -1.95, unlike that of the GAAD score (manufacturer's recommended cut-off value is 2.57). **Conclusion:** In our prospective study, the GALAD score performed better for HCC surveillance in our population compared to the GAAD score as it is better able to portend the development of HCC within a year using the manufacturer's recommended cut-off value.

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The following people have nothing to disclose: Wei Lun Liou, Si-Yu Tan, Kaina Chen, Thinesh Krishnamoorthy, Jason Pik Eu Chang, Chin-Pin Yeo

4032-A | COMPARISON OF PROGNOSTIC IMPACT OF ATEZOLIZUMAB PLUS BEVACIZUMAB VERSUS LENVATINIB AS FIRST-LINE SYSTEMIC THERAPY IN PATIENTS WITH INTERMEDIATE-STAGE HCC

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Background: The study goal was to compare the outcomes of patients with intermediate-stage (Barcelona Clinic Liver Cancer [BCLC]-B) hepatocellular carcinoma (HCC) who received atezolizumab plus bevacizumab (Atezo/Bev) or lenvatinib (LEN) as first-line systemic therapy. **Methods:** A total of 358 patients with BCLC-B HCC treated with Atezo/Bev (n = 177) or LEN (n = 181) as first-line systemic therapy were included. **Results:** The median progression-free survival (PFS) times in the Atezo/Bev and LEN groups were 10.8 months (95% confidence interval [CI], 7.8–12.6) and 7.3 months (95% CI, 6.3–8.5), respectively (p = 0.019). In the propensity score–matched cohort, the median PFS times in the Atezo/Bev (n = 151) and LEN (n = 151) groups were 10.2 months (95% CI, 7.0–12.3) and 6.9 months (95% CI, 5.9–8.1), respectively (p = 0.020). Restricted mean survival times of PFS were significantly higher in the Atezo/Bev group than in the LEN group at landmarks of 12 and 18 months (p = 0.031 and 0.012, respectively). In a subgroup analysis of patients with HCC beyond the up-to-seven criteria, the median PFS times in the Atezo/Bev (n = 134) and LEN (n = 117) groups were 10.5 months (95% CI, 7.0–11.8) and 6.3 months (95% CI, 5.5–7.3), respectively (p = 0.044). In addition, among patients with non-viral hepatitis (non-B, non-C), the median PFS times in the Atezo/Bev (n = 100) and LEN (n = 85) groups were 10.6 months (95% CI, 7.0–19.1) and 6.9 months (95% CI, 5.4–8.5), respectively (p = 0.022). **Conclusion:** The use of Atezo/Bev as first-line systemic therapy in patients with BCLC-B HCC is expected to result in good outcomes.

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The following people have nothing to disclose: Toshifumi Tada, Takashi Kumada, Atsushi Hiraoka, Masashi Hirooka, Kazuya Kariyama, Ei Itobayashi, Tsuji Kunihiko, Toru Ishikawa, Hidenori Toyoda, Satoru Kakizaki, Fujimasa Tada, Hideko Ohama, Kazuhiro Nouso, Tomomitsu Matono, Yutaka Yata, Yoichi Hiasa, Masatoshi Kudo

4033-A | COMPARISON OF TREATMENT OUTCOMES BETWEEN LENVATINIB AND ATEZOLIZUMAB PLUS BEVACIZUMAB FOR HEPATOCELLULAR CARCINOMA IN PATIENTS AGED 80 YEARS OR OLDER: A MULTICENTER STUDY

Satoru Kakizaki[1,2], Takeshi Hatanaka[2,3], Atsushi Hiraoka[2,4], Toshifumi Tada[2,5], Masashi Hirooka[2,6], Kazuya Kariyama[2], Ei Itobayashi[2,7], Tsuji Kunihiko[2,8], Toru Ishikawa[2,9], Hidenori Toyoda[2,10], Atsushi Naganuma[1,2], Tomomitsu Matono[2,11], Hideko Ohama[2,12], Fujimasa Tada[2,4], Kazuhiro Nouso[2,13], Yoichi Hiasa[2,6] and Takashi Kumada[2,14], (1)National Hospital Organization Takasaki General Medical Center, (2)Relpec Study Group and HCC 48 Group, (3) Gunma Saiseikai Maebashi Hospital, (4)Ehime Prefectural Central Hospital, (5)Japanese Red Cross Himeji Hospital, (6)Ehime University Graduate School of Medicine, (7)Asahi General Hospital, (8)Teine Keijinkai Hospital, (9)Saiseikai Niigata Hospital, (10) Ogaki Municipal Hospital, (11)St. Mary's Hospital, (12) Takarazuka City Hospital, (13)Okayama City Hospital, (14)Gifu Kyoritsu University

Background: The optimal treatment strategy for older patients with hepatocellular carcinoma (HCC) is still controversial. In this study, we compared the treatment outcomes of lenvatinib (LEN) and atezolizumab plus bevacizumab (Atez/Bev) for HCC in patients aged 80 years and older. **Methods:** Between March 2018 and July 2022, there were 861 LEN-treated patients and 518 Atez/Bev-treated patients in our hospitals. Of these, 170 cases in the LEN group and 92 cases in the Atez/Bev group were aged 80 years or older and receiving first-line treatment. **Results:** The median ages of the LEN and Atez/Bev groups were 83 (81-86) years and 83 (82-86) years, respectively (p = 0.3); 119 cases (70.0%) and 64 cases (69.4%) were male, respectively (p = 1.0). There were no significant differences in background liver disease (p = 0.9), BCLC stage (p = 0.3), or Child-Pugh class (p = 0.8). The ALBI scores were -2.46 (-2.70 to -2.11) and -2.42 (-2.66 to -2.12) for the LEN and Atez/Bev groups, respectively (p = 0.5). The mALBI grades (1/2a/2b/3) were 65 (38.2%)/ 49 (28.8%)/ 51 (30.0%)/ 5 (2.9%) and 32 (34.8%)/ 25 (27.2%)/ 35 (38.0%)/ 0 (0.0%), respectively (p = 0.3). There were no significant differences in AFP levels (p = 0.4) or DCP levels (p = 0.3). Therefore, there were no significant differences in patient background. The best treatment effect evaluated by mRECIST (CR/PR/SD/PD/NE) was 4 (2.4%)/ 57 (33.5%)/ 46 (27.1%)/ 31 (18.2%)/ 32 (18.8%) in the LEN group versus 7 (7.6%)/ 24 (26.1%)/ 27 (29.3%)/ 14 (15.2%)/ 20 (21.7%) in the Atez/Bev group (p = 0.2); response rates were 35.9% and 33.7%, respectively (p = 0.8), and disease control rates were 62.9% and 63.0%, respectively (p = 1.0), with no significant differences. The median progression-free survival (PFS) was 6.3 (95% CI 4.3-7.3) months in the LEN group versus 7.2 (95% CI 4.8-10.6) months in the Atez/Bev group, which was not significantly different (p = 0.2). In multivariate analysis, only mALBI grade 2b or 3 (HR 1.43, 95% CI 1.05-1.95, p = 0.02) contributed to PFS. Treatment (LEN or Atez/Bev) was not a significant factor. Adverse events were similar in both groups, including anorexia, fatigue and malaise, increased blood pressure, and proteinuria. **Conclusion:** The outcomes and adverse events were generally similar between LEN and Atez/Bev in the elderly. It was suggested that LEN may be one of the treatment options for patients with autoimmune diseases and those at high risk of esophageal varices rupture.

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4034-A | COMPLEMENTING LOCOREGIONAL THERAPIES WITH IMMUNE CHECKPOINT INHIBITORS IN ADVANCED HCC IMPROVES DISEASE-FREE SURVIVAL AND DECREASES DROP-OUT FROM THE LIVER TRANSPLANT LIST

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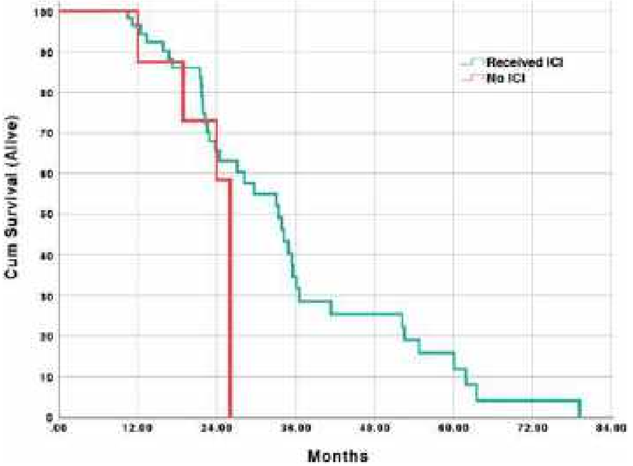
Background: The incidence and mortality of HCC continues to be on the rise in the US. Although liver transplantation is considered the curative therapy, a significant number of HCC cases are identified beyond MILAN criteria. Various Immune Checkpoint Inhibitors (ICI) have been recently approved as a treatment of advanced unresectable HCC. We report on the significant impact of complementing locoregional therapies (LRT) with ICIs ± VEGF Inhibitors. **Methods:** Between May 2018 and May 2023, 323 patients (pts) were diagnosed with HCC and managed by a liver cancer clinic. 197 pts were not prescribed ICI because it was not indicated, contraindicated, or pts had metastatic cancer. 126 pts were prescribed ICI as adjunctive therapy to LRT (primarily TACE ± RFA and Y-90). Of the 126 pts, 35 did not start ICI because of insurance denials, pt refusal, or referral to hospice. Of the 91 pts who started ICI, 72 received at least 2 doses and are the subjects of this analysis. ICI was infused per the package insert and pts were followed per standard of care. Labs, imaging, further locoregional interventions, disease progression, transplantation candidacy, and survival were analyzed. **Results:** Median follow-up was 27 (3-91) months. 73.6% were males. 70.2% Hispanic, 92.3% white. Mean age was 65.7 ± 8.5 years. Main underlying liver disease etiology was History of HCV. All were Child-Pugh A or B. BCLC classification pre-ICI: 32.6% A3, 15.4% A4, 33.8% B, and 18.2% C. ICI treatment: 52 pts (57.1%) were treated with nivolumab (nivo) only, 26 pts (28.6%) with nivolumab/ipilimumab (nivo/ipi), and 13 pts (14.3%) with atezolizumab/bevacizumab (ate/bev). Safety and Tolerability: Liver enzymes and MELD score were stable throughout treatment. 11 pts on nivo experienced controllable adverse events. In the nivo/ipi group, 4 pts discontinued ICI due to rash and 3 pts due to severe immune reaction. All pts who received ate/bev permanently discontinued treatment due to side effects including bleeding. Efficacy: 66.2% are still alive. Only 56% required LRT post-starting ICI. Recurrence was seen in 4 pts while on ICI and 8 pts after treatment discontinuation. 5% received a liver transplant. 15% of pts became MILAN eligible post ICI. Median duration on ICI was 13 (1-46) months. There was a statistically significant (p-values < 0.05) decrease in the average number of viable lesions as well as the average size of viable lesions post ICI treatment. Survival: Median survival from HCC diagnosis was 16 months in pts who did not receive ICI versus 35 months in those who did receive ICI (figure). **Conclusion:** In patients with advanced HCC the combination of LRT and ICI is: 1) safe and well-tolerated, 2) more effective than LRT alone, 3) patients required fewer LRT sessions after initiation of ICI, 4) had prolonged disease stability and overall transplant-free survival, and 5) maintained their status within MILAN criteria and decreased the dropout rate from the transplant list.



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4035-A | COMPLIANCE OF HEPATOCELLULAR CARCINOMA SCREENING IN PATIENTS WITH CHRONIC VIRAL HEPATITIS

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Background: This study aimed to investigate the compliance of the screening for hepatocellular carcinoma (HCC) in patients with chronic viral hepatitis. **Methods**: A cross-sectional study was conducted based on nationally representative samples from the Korean National Health and Nutrition Examination Survey 2007-2012. Of 50,405

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

participants, a total of 1,275 patients with chronic hepatitis B or chronic hepatitis C were included in the final analysis. We investigated compliance of HCC screening using ultranonography and serum alpha-protein. Univariable and multivariable logistic regression analyses were performed to evaluate the screening compliance associated risk factors such as age, sex, marital status, residential area, self-rated health status, education level, income status, private insurance for health care, alcohol and smoking. **Results**: The mean age of 1,275 patients was 49.4 years and male was 51% (n = 618). The compliance of HCC screening was observed in 508 patients (40%): within 6 months before the survey, 12 % (n = 155); 6-12 months, 11% (n = 134); > 12 months, 17% (n = 219). The multivariable analysis showed that compliance of HCC screening was significantly associated with age: 40-60 years (odds ratio [OR] 3.06 with 95% confidence interval [CI]: 2.26-4.15, $p < 0.001$), age: > 60 years (OR 2.92 with 95% CI: 1.93-4.42 $p < 0.001$), self-rated health status: moderate (OR 1.42 with 95% CI: 1.07-1.89, $p = 0.016$), self-rated health status: poor (OR 152 with 95% CI: 1.08-2.13, $p = 0.015$), education: university or higher (OR 1.37 with 95% CI: 1.04-1.81, $p = 0.025$), income: > 50 percentile (OR 1.95 with 95% CI: 1.49-2.56, $p < 0.001$) and private insurance for health care (OR 1.40 with 95% CI: 1.02-1.91, $p = 0.038$). **Conclusion**: Compliance of HCC screening was favorable in patients with older age, poor health status, higher education level, high income and private insurance for health care in Korea. These findings may be helpful to increase HCC screening and surveillance rate in patients with chronic viral hepatitis.

Disclosures: The following people have nothing to disclose: Byung Ik Kim, Ju-Yeon Cho, Yong Kyun Cho, Won Sohn

f 4036-A | CONCURRENT MULTI-ARM COMPARISONS OF PERCUTANEOUS ABLATION, OPEN OR LAPAROSCOPIC LIVER RESECTION FOR PATIENTS WITH BCLC STAGE 0-A HEPATOCELLULAR CARCINOMA

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Background: Liver resection and ablation remain the most common therapeutic options for BCLC stage 0-A hepatocellular carcinoma (HCC), but there is a lack of evidence to show which is the most suitable therapy. This study aimed to make multi-arm comparisons of the short-term and long-term outcomes of percutaneous ablation (PA), open (OLR) or laparoscopic liver resection (LLR) for these patients. **Methods:** This was a retrospective observational cohort study. Multiple generalized propensity score methods were performed to concurrently compare the clinical outcomes of these three treatment options to balance potential confounders. **Results:** Of 1778 patients included, 1237, 307 and 234 underwent OLR, LLR and PA, respectively. After overlap weighting, patients in the minimally invasive group (LLR and PA groups) had few postoperative complications and short postoperative hospital stays (both $P < 0.001$). The 5-year recurrence-free survival (RFS) rate was significantly higher in the LLR group when compared with the OLR and PA groups (56.2% vs. 47.2% vs. 28.3%, $P < 0.001$) while there were no significant differences in the 5-year overall survival (OS) rate among the three groups (86.5% vs. 82.4% vs. 78.9%, $P = 0.083$). Multivariable Cox analysis showed that LLR was an independent factor for better RFS. In subgroup analysis, the long-term outcomes of patients with BCLC stage A HCC were consistent with the whole population. **Conclusion:** In the observational study using various covariate adjustment analysis, LLR is not only minimally invasive, but also provides better RFS and equivalent OS for patients with BCLC stage 0-A HCC when compared with OLR and PA.

Disclosures: The following people have nothing to disclose: Zhihang Chen, Qian Zhou, Zebin Chen, Shunli Shen, Ming Kuang

f 4037-A | CONVENTIONAL AND MACHINE-LEARNING BASED RISK SCORE REFLECTING INFLAMMATORY, FIBROSIS AND NUTRITIONAL STATUS FOR PATIENTS WITH EARLY STAGE HEPATOCELLULAR CARCINOMA – THE CATS-INF SCORE

Chun-Ting HO[1], Chien-Wei Su[1,2], Elise Chia-Hui Tan[3], Wei-Yu Kao[4], Yi-Hsiang Huang[1,2], Teh-Ia Huo[1,2], Ming-Chih Hou[1,2] and Jaw-Ching Wu[1], (1)National Yang Ming Chiao Tung University, (2)Taipei Veterans General Hospital, (3)China Medical University, (4)Taipei Medical University Hospital

Background: Field factors such as inflammatory, fibrosis and nutritional status play important roles in tumor microenvironment and determine the prognoses of patients with hepatocellular carcinoma (HCC). Machine-learning (ML) has become a promising method to identify significance of factors and predict outcomes of patients. We aimed to develop a risk score by combining conventional methods and ML according to serum biomarkers reflecting the field factors and stratify patients with early-stage HCC into different prognostic groups. **Methods:** A total of 1411 HCC patients within Barcelona Clinic Liver Cancer classification (BCLC)

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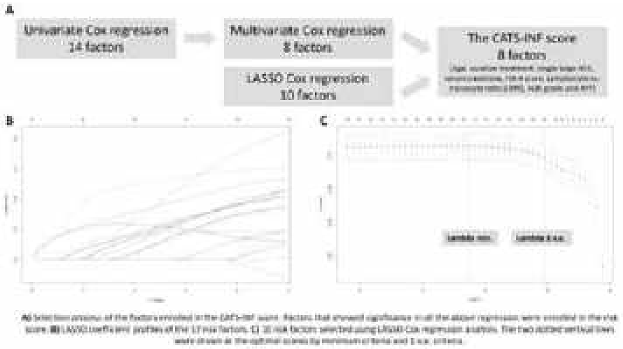
stage 0 to A HCC diagnosed at Taipei Veterans General Hospital from 2012 to 2021 were retrospectively enrolled in the study and divided into training cohort (n = 988) and validating cohort (n = 423) randomly. Serum biomarkers and prognostic scores determining poor overall survival (OS) of the training cohort were first analyzed by conventional method (Cox proportional hazards model) and then validated by ML based methods (LASSO Cox regression). Factors that showed significance in all the above regression models were enrolled in the risk score. The risk score (CATS-INF score) was computed by utilizing coefficients from the multivariable Cox proportional hazard model and were standardized to a score ranging from 0 to 100. The total score of each patient was calculated and grouped into three categories (high, medium, and low risk) based on the 33rd and 66th percentiles. The CATS-INF score was then validated on the validation cohort. **Results:** After a median follow-up of 38.0 months (interquartile range IQR 18.0-57.0 mo), 368 patients died, and the 5-year OS rate was 67.5%. Age, curative treatment, solitary large HCC (SLHCC), serum creatinine, fibrosis-4 (FIB-4) score, Lymphocyte-to-monocyte ratio (LMR), albumin bilirubin (ALBI) grade and alpha fetoprotein (AFP) level were selected as factors of the risk score due to their significance in both Cox proportional hazards model and LASSO Cox regression. The formula of the CATS-INF score according to their coefficient is: CATS-INF score = 50×(Age > 65 y) + 77×(No curative treatment received) + 100×SLHCC + 46×(Serum Creatinine > 1.2 mg/dL) + 77×(FIB-4 > 3.25) + 47×(LMR < 3.62) + 68×(ALBI grade 2 or 3) + 60×(AFP > 20 ng/mL). The cut-off value between low, intermediate, and high-risk groups were 55 and 154, respectively. For patients in the validation cohort, the 5-year OS rates were 77.0%, 62.5% and 45.4% in the low, intermediate, and high-risk groups, respectively ($p < 0.001$). **Conclusion:** The CATS-INF score developed by non-invasive serum biomarkers reflecting field factors can efficiently stratify patients with early-stage HCC into different prognostic groups.



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4038-A | COULD STEREOTACTIC RADIOSURGERY AS A PALLIATIVE MANAGEMENT OF HEPATOCELLULAR CARCINOMA LEAD TO IMPROVED SURVIVAL?

Khaled Abdel Karim[1], Waleed Abdel Atty Hamed[1], Gamal Esmat[2], Mohamed ElGharib[1] and Mohamed M Darwish[1], (1)Ain Shams University, (2)Cairo University

Background: The survival and treatment options for patients with hepatocellular carcinoma HCC presented with portal vein thrombosis are far from being satisfactory. The efficacy and safety of stereotactic radiosurgery SRS as a palliative treatment for those patients were proven earlier and we are here presenting our longer-term results. **Methods:** Between January 2020 and Jan 2023, we examined and followed up patients who were ineligible for local treatment of HCC and are having portal vein thrombosis PVT. SRS was offered to those patients as palliative treatment in a dose of 40 Gy in 5 fractions. The patient who showed radiological disease control or recanalization of the PVT were re-challenged for other treatment modalities. **Results:** Twenty-eight patients were enrolled, 23 were males, and only 5 were females. The median age of those patients was 62 years (range 44 to 73 y). They were having Child- Pugh B or early C (7-9). All the patients suffered from PVT (main portal vein or one of its branches). The 6, 12, and 24-months overall survival OS were 89%, 68%, and 40% respectively. Radiological response (stable disease and decreased tumour size) was found in 74% of cases (20/28) by the 3 months' first follow up. The thrombosed portal vein showed radiological signs of recanalization in 57% of treated patients. Those responding patients showed reduced levels of alpha fetoprotein and improved levels of local pain. No grade 4 adverse events were recorded. By the time of data analysis (February 2023) 12 patients were still alive (12 to 30 mo), 8 of those were re-challenged for sorafenib and/or TACE. **Conclusion:** SRS as a palliative treatment for advanced HCC could lead to improved survival in patients with good performance status. Larger size multicentre randomized studies with longer follow up are needed to solidify such results.

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4039-A | CURRENT PATTERN AND FUTURE PROJECTIONS OF PRIMARY LIVER CANCER IN THE GULF COOPERATION COUNCIL COUNTRIES: ANALYSIS FROM GLOBOCAN 2020 DATABASE

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Background: Liver cancer is among the leading causes of cancer morbidity and mortality globally, but the rates vary between countries. Little is known about the current pattern and future burden of liver cancer in the GCC countries (Saudi Arabia, Qatar, United Arab Emirates, Bahrain, Oman, and Kuwait). **Methods:** We used incidence estimates from the GLOBOCAN 2020 database developed by the International Agency for Research on Cancer, France. We provided the incidence and mortality estimates (numbers and with age-standardized incidence rates, ASRs) in 2020 and future projections for 2040. **Results:** Liver cancer was the seventh most common type of cancer in terms of incidence in the GCC countries in 2020, but the fourth leading cause of cancer deaths. Overall, the GLOBOCAN 2020 estimates indicate that new liver cancer cases (n = 1580) and deaths (n = 1,510) occurred in the GCC countries with ASRs (5.2/100,000) and (5.1/100,000), respectively. Liver cancer in 2020 was more common among males than females across the GCC countries, with the overall incidence ASR (5.9 VS 3.2) and mortality (5.8 VS 3.1), respectively. Saudi Arabia accounted for almost 73% of all cases and (72%) of all deaths from GCC countries and had the highest ASR incidence of liver cancer (5.2) and mortality (5.1) for both genders. By 2040, the number of liver cancer cases in the GCC is estimated to increase by 230%(n = 5205) from current estimates, while mortality will increase by 234% (n = 5059). **Conclusion:** Future cancer control policies in the GCC countries should comprehensively emphasize liver cancer risk factors from viral and nonviral etiologies to address the increasing burden of liver cancer.

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4040-A | DECREASED RISK OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC HEPATITIS B TREATED WITH BESIFOVIR

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Background: Besifovir dipivoxil maleate (BSV) is a new potent antiviral agent approved in Korea. The favorable antiviral effect of BSV may lower the risk of HCC in patients with CHB. Nevertheless, there is currently a lack of information concerning the impact of BSV treatment on the occurrence of HCC. We aimed to assess the incidence of HCC under BSV therapy using clinical trial and real-world BSV data and to compare it with that observed during entecavir (ETV) or tenofovir disoproxil fumarate (TDF) therapy. **Methods:** We combined the phase 3 clinical trial data of BSV which was conducted for 8 years and retrospective data which was collected in the real-world. The retrospective cohort consisted of patients who initiated ETV, TDF, or BSV as a first treatment between 2007 and 2022 at five tertiary hospitals. Incidences of HCC under these antiviral therapies were compared. To further validate, we conducted propensity score matching with an optimal variable ratio of 1:2 or 1:1 for the ETV or TDF treatment groups, respectively. This approach allowed us to create matched cohorts and enabled a more meaningful comparison of HCC incidences between the groups. We performed the log-rank test to evaluate any significant differences. **Results:** A total of 385, 1139, and 688 patients were treated with BSV, ETV, and TDF, respectively. The incidence of HCC was significantly lower in the BSV group compared with ETV or TDF groups (BSV vs ETV, $P = 0.007$; BSV vs. TDF, $P = 0.015$). After propensity score matching, we observed that the incidence rate of HCC remained significantly lower in the BSV group in comparison to the ETV group ($P = 0.016$). However, there was no significant difference in HCC incidence rates between the BSV and TDF groups ($P = 0.253$). Further analysis using multivariable analysis within this matched cohort indicated that BSV significantly reduced the risk of developing HCC when compared to ETV. **Conclusion:** BSV therapy may improve prognosis of patients with CHB by decreasing the incidence of HCC.

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The following people have nothing to disclose: Seong Hee Kang, Young Kul Jung, Jin Mo Yang, Jae Young Jang, Yong Kyun Cho, Yoon Jun Kim, Joo Hyun Sohn, Jin-Woo Lee, Sung Jae Park, Yim Sun Young, Seung Kak Shin, Ji Hoon Kim, Yeon Seok Seo
Disclosure information not available at the time of publication: Won Kim, Young-Oh Kweon, Gun Young Hong, Jin Kyung Park, Soonho Um

4041-A | DIFFERENTIALLY REGULATED IMMUNE EXHAUSTION TARGETS BETWEEN HCC AND ICCA ARE POTENTIAL DIAGNOSTIC AND PREDICTIVE BIOMARKERS IN LIVER CANCER

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Background: Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) are increasingly important tumor entities, especially in young patients. Previous studies have looked at distinct methylation patterns in HCC. With the shift in etiologies and an increasing amount of patients at risk for developing de novo HCC without cirrhosis and an increasing incidence in iCCA, it is vital to develop safe and accurate biomarkers for the diagnosis and prognosis in these patients. While established markers for immunohistochemistry and serum markers are helpful in the diagnosis, they're neither specific, nor predictive. **Methods:** All tests were carried out based on formalin-fixed and paraffin-embedded (FFPE) tissue from resected liver lesions before treatment and with consistent follow-up data including post-surgical treatments, recurrence, survival data and other clinical conditions and risk factors. Total RNA and DNA was extracted from these tissues. The extracted RNA was used for a gene expression analysis with the nCounter® NanoString system and nCounter® Immune Exhaustion Panel. DNA methylation patterns were analysed using the Human Methylation EPIC array (Illumina) of all samples. **Results:** HCC cases clearly separated from iCCA cases in the unsupervised hierarchical clustering of gene expression and the DNA methylation pattern analysis. Several significantly dysregulated targets in HCC compared to iCCA were identified and correlated with clinical data. While established markers were also included in the analysis, new markers, i.e. ITGB8 and ALDH3A1 were identified as immune-modulatory target transcripts. Immunohistochemistry showed significant expression in HCC cases and expression of ALDH3A1 was significantly associated with lower recurrence free survival ($p < 0.05$). **Conclusion:** Our data shows that differentially regulated immune exhaustion targets between HCC and iCCA are of high interest in the development of clinical and therapeutic targets in liver cancer. Metabolite interconversion enzymes, such as ALDH3A1, are discussed to be essential for the activation or inactivation of anticancer drugs and could potentially affect drug treatment outcome, thereby representing potential biomarkers. Immunohistochemistry proved to be a valid diagnostic tool for ALDH3A1 expression and clinical data suggests prognostic value. Further validation studies need to be conducted to assess clinical relevance.
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4042-A | DISPARITIES IN SURVIVAL OF PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC) BY LIVER DISEASE ETIOLOGY AND TIME PERIODS: A U.S. POPULATION-BASED STUDY FROM 2000 TO 2017

Elizabeth Garcia[1], Nicholas Chien[2], Yee Hui Yeo[3], Mindie H. Nguyen[4] and Ramsey Cheung[4], (1)Mountain

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

View High School, (2)Stanford University, (3)Cedars-Sinai Medical Center, Culver City, CA, (4)Stanford University Medical Center, Palo Alto, CA

Background: HCC is the 6th greatest mortality rate of all cancers in the USA with an upward trend in nonviral HCC from alcohol-associated and nonalcoholic fatty liver disease. Despite progress in early HCC detection, HCC treatment, and antiviral therapies for viral hepatitis, it is unclear if survival rates have improved in the recent decade and whether survival has improved consistently for both viral and nonviral HCC. **Methods:** To investigate the survival trends of patients with HCC, stratified by etiologies and HCC diagnosis year, between 2000 and 2017, the SEER-Medicare linked database was analyzed. HCC was diagnosed according to the International Classification of Diseases-Oncology-3 codes, site: C22.0 and histology: 8170-8175. Patients with HCC prior to Medicare coverage, prior malignancies, and without death certificates were excluded. **Results:** A total of 52,698 patients with HCC between 2000 and 2017 were included. Viral HCC patients were more likely to be Asian (18.0% vs. 10%) or Black (17.9% vs. 7.0%) with higher percentage of early HCC stage I/II (52.0% vs. 43.0%), all $P < 0.001$. Compared to HCC patients diagnosed 12/2013 and before, those diagnosed after 12/2013 were more likely to be obese (29.0% vs. 14.0%) and with early HCC stage I/II (35.0% vs. 26.1%), all $P < 0.001$. The 5-year cumulative survival were higher in viral vs. nonviral HCC (16.4% vs. 12.0%) and after 12/2013 vs before (17.1% vs. 12.1%), both $P < 0.001$. In stratified analysis by both etiology and time, survival was higher in viral HCC compared to nonviral patients during the pre as well as post 12/2013 periods (Figure 1A). Survival also increased significantly for both the viral and nonviral groups over time with rising median survival yearly (Figure 1B) and 5-year survival pre and post 12/2023 (Figure 1A, viral HCC increasing by 6.5% from 14.7% to 21.2% [a 44.2% increase] and nonviral increasing by 3.6% from 10.7% to 14.3% [a 33.6% increase]). On multivariable Cox's regression analysis adjusting for age, sex, race and ethnicity, tumor stage, cirrhosis status, HCC treatment, and time period, viral etiology was independently associated with higher survival as compared to non-viral etiology (adjusted hazard ratio [aHR] = 1.25, 95%CI 1.23-1.28), while HCC diagnosis after 12/2013 was also associated with higher survival compared to earlier time (aHR = 1.27, 95%CI 1.24-1.30), both $P < 0.001$. **Conclusion:** HCC were diagnosed in earlier stages in recent time, and HCC survival rates have improved over time but more for viral than nonviral etiology. However, overall 5-year survival was still low at only 14.3% for nonviral and 21.2% for viral etiology. Further efforts are needed to improve HCC surveillance and treatment.

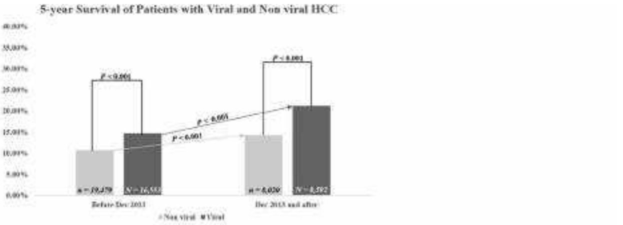

Figure 1A: 5-year survival of patients with viral and non viral HCC before and after Dec 2013

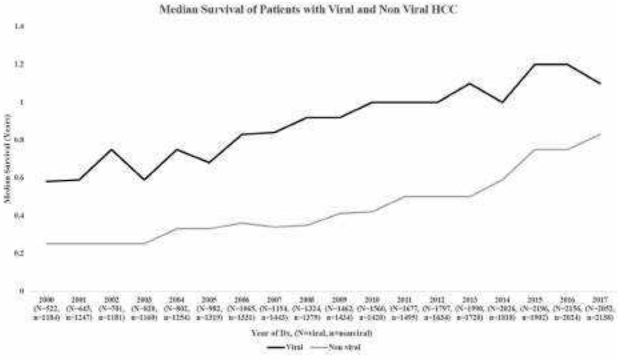

Figure 2A: Median survival of patients with viral and non viral HCC from 2000-2017

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4043-A | DRAMATIC INCREASE IN USE OF IMMUNOTHERAPY FOR HEPATOCELLULAR CARCINOMA (HCC) – A TERRITORY-WIDE STUDY FROM 2015-2022

Terry Cheuk-Fung Yip, The Chinese University of Hong Kong, Hong Kong, 91, China, Vincent Wai-Sun Wong, The Chinese University of Hong Kong, Hong Kong, China, Stephen Lam Chan, State Key Laboratory of Translational Oncology, Department of Clinical Oncology, Sir Yue-Kong Pao Center for Cancer, the Chinese University of Hong Kong and Grace Lai-Hung C Wong, The Chinese University of Hong Kong

Background: Immunotherapy is an established treatment for many malignancies including hepatocellular carcinoma (HCC). We aimed to determine the change in the usage of various immunotherapies since their availability in 2015 in Hong Kong. **Methods:** This was a territory-wide cohort study of HCC patients who had received at least one kind of targeted therapies (cabozantinib, regorafenib, sorafenib, ramucirumab) or immunotherapies (atezolizumab combined with bevacizumab, ipilimumab combined with nivolumab, or pembrolizumab) from 2015 to 2022 in Hong Kong. The secular trend of new prescriptions of these immunotherapies was analyzed. **Results:** We identified 3,013 HCC patients (mean age 61.0 ± 11.9 y, 71.9% male,

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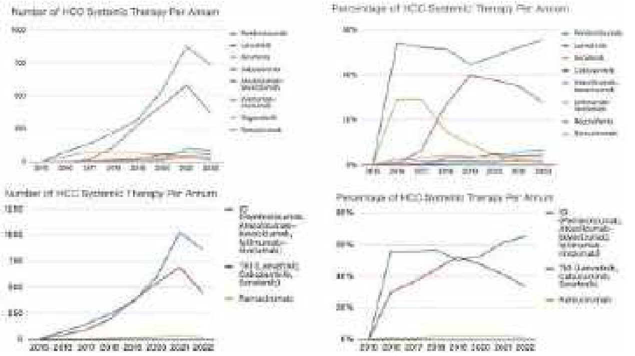
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

43.5% had chronic hepatitis B) who had received at least one line of systemic therapy, with 224 (7.4%) patients having received more than one line of systemic therapy. The usage of atezolizumab-bevacizumab combination has increased dramatically from 2020 (n = 10, 0.9%) to 2021 (n = 101, 6.0%). The prescription of ipilimumab-nivolumab combination has gradually increased from 2016 (n = 2, 1.4%) to 2021 (n = 49, 2.9%), then dramatically from 2022 (n = 38, 2.9% in the first 5 mo) onwards. Pembrolizumab use has increased noticeably from 2016 onwards and peaked in 2021 (Figure). **Conclusion:** We report a dramatic increase in the newly approved immunotherapy regimens atezolizumab-bevacizumab and ipilimumab-nivolumab combinations since their approval in 2020, and use of pembrolizumab peaked in 2021, whereas tyrosine kinase inhibitors dropped since 2019 likely because of the wide use of newly approved regimens. Figure. Secular trends on the relative representation of immunotherapy regimens and other systemic therapies for HCC patients in Hong Kong 2015-2022



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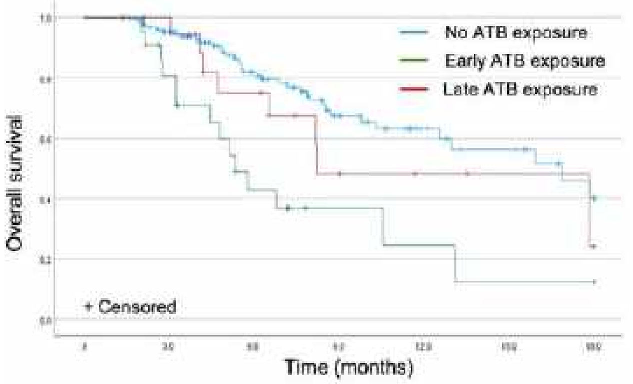
4044-A | EARLY ANTIBIOTIC EXPOSURE, BUT NOT LATE EXPOSURE, DURING THE COURSE OF IMMUNOTHERAPY NEGATIVELY AFFECTS OUTCOMES IN PATIENTS RECEIVING FIRST-LINE ATEZOLIZUMAB PLUS BEVACIZUMAB FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA

Aryoung Kim, Byeong Geun Song, Myung Ji Goh, Wonseok Kang, Dong Hyun Sinn, Geum-Youn Gwak, Yong-Han Paik, Moon Seok Choi and Joon Hyeok Lee, Samsung Medical Center

Background: Immunotherapy with atezolizumab plus bevacizumab (atezo/bev) represents the new standard of care in first-line systemic therapy of unresectable hepatocellular carcinoma (uHCC). While antibiotic (ATB) exposure may affect the therapeutic efficacy of immunotherapy through perturbation of gut microbiome, few studies have addressed the effect of early and late antibiotic exposure during the course of immunotherapy on the outcomes of uHCC patients receiving first-line atezo/bev therapy. **Methods:** In this single institution retrospective cohort study, patients with uHCC receiving atezo/bev as a first-line therapy between August 2020 and December 2022 were analyzed. Early ATB exposure was defined as exposure within 30 days of initiation of atezo/bev. Late ATB exposure was defined as exposure during the course of atezo/bev except for the initial 30 days. ATB exposure was correlated with outcomes in terms of progression-free survival (PFS) and overall survival (OS). Multivariable analysis was performed with the Cox proportional hazards model. Propensity score (PS) matching was performed in a 1:5 ratio of covariates including age, Child-Pugh score, model for end-stage liver disease score, albumin-bilirubin grade, and neutrophil-to-lymphocyte ratio. **Results:** A total of 177 patients with uHCC were included in the final analysis. Early ATB exposure (n = 22, 12.5%) was associated with shorter PFS (2.3 mo in early exposure vs. 6.3 mo, Log rank $p = 0.015$; HR 1.95, 95% CI 1.10-3.45, $p = 0.022$) and OS (5.4 mo in early exposure vs. 16.9 mo, Log rank $p < 0.001$; HR 2.10, 95% CI 1.10-4.02, $p = 0.024$). Similar results were observed in PS-matched analysis of PFS (2.3 mo in early exposure vs. 6.2 mo, Log rank $p = 0.024$) and OS (5.4 mo in early exposure vs. 15.9 mo, Log rank $p = 0.007$). Compared with no ATB exposure throughout the course of atezo/bev therapy, late ATB exposure showed similar PFS (6.1 mo in late exposure vs. 6.5 mo, Log rank $p = 0.71$; HR 0.78, 95% CI 0.40-1.52, $p = 0.46$) and OS (8.2 mo in late exposure vs. 16.9 mo, Log rank $p = 0.29$; HR 1.18, 95% CI 0.54-2.57, $p = 0.68$). Interestingly, compared to early ATB exposure, late ATB exposure was associated with longer PFS (6.1 mo in late exposure vs. 2.3 mo, Log rank $p = 0.035$) and OS (8.2 mo in late exposure vs. 5.4 mo, Log rank $p = 0.09$). **Conclusion:** Early ATB exposure, but not late exposure, is associated with worse PFS and OS in patients with uHCC receiving first-line atezo/bev therapy. Prospective clinical and translational studies are necessary to understand the mechanisms underlying ATB-mediated alterations of gut microbiome and treatment response to atezo/bev therapy in patients with uHCC.



Antibiotics exposure	Log-rank p-value
None vs. Early exposure	<0.001
None vs. Late exposure	0.29
Early vs. Late exposure	0.09

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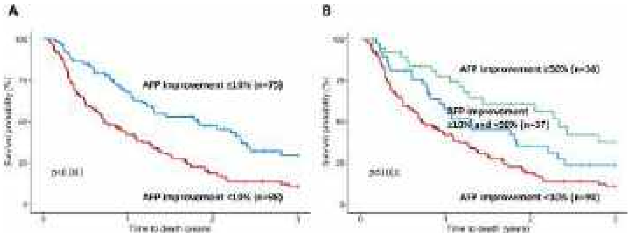
4045-A | EARLY CHANGES IN ALPHA-FETOPROTEIN ARE ASSOCIATED WITH TREATMENT RESPONSE AND OVERALL SURVIVAL IN A REAL-WORLD COHORT OF HEPATOCELLULAR CARCINOMA PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS

Michael Li[1], Kate Kelley[1], Neil Mehta[1], Francis Yao[1], Lawrence Fong[1] and Jennifer C. Lai[2], (1)University of California, San Francisco, (2)University of California-San Francisco

Background: Multiple immune checkpoint inhibitor (ICI) regimens are now first-line therapy in advanced hepatocellular carcinoma (HCC), but there is limited data regarding early predictors of treatment response. **Methods:** We conducted a single-center retrospective cohort study of all HCC patients who received ICI therapy from 2016 onwards. The primary outcome was treatment response (complete or partial response as clinically assessed by the treating provider). The secondary outcome was time to all-cause death. **Results:** In the 173 study patients with available treatment response data, the median MELD was 10 [IQR 9, 16] and the median AFP was 138 [8, 1995]. 47 patients (27%) experienced treatment response. Median time from pre-treatment AFP to on-treatment AFP was 42 [29, 55] days. The median percent change in AFP was significantly different comparing patients with and without treatment response (-39% [-92%, -8%] vs 11% [-16%, 74%], respectively, $p < 0.001$). As a single predictor of treatment response, percent change in AFP had a c-statistic of 0.80. The optimal cutoff for percent change in AFP was -9.7% based on maximizing the J statistic; this cutoff had a sensitivity of 75% and a specificity of 71% for treatment response. After adjusting for ICI regimen, Child-Pugh class, and tumor burden, percent reduction in AFP was associated with treatment response (OR 1.21 for each 10% reduction in AFP, 95% CI 1.11-1.33, $p < 0.001$). Similar results were produced when a binary AFP variable using the cutoff of $\geq 10\%$ reduction was substituted for the continuous AFP variable in the model (OR 5.33 for patients who had $\geq 10\%$ early AFP improvement, 95% CI 2.42-11.74, $p < 0.001$). Patients with $\geq 10\%$ early AFP improvement also had improved overall survival compared to those with $< 10\%$ improvement (median 1.82 vs 0.73 y, log-rank $p < 0.001$; Figure A). Improved overall survival was also seen with further stratification of AFP improvement (median 2.34 vs 1.30 vs 0.73 years, log-rank $p < 0.001$; Figure B). After adjusting for ICI regimen, Child-Pugh class, and tumor burden using Cox regression, $\geq 10\%$ early AFP improvement was associated with reduced risk of death (HR 0.63, 95% CI 0.45-0.89, $p = 0.009$). **Conclusion:** Early changes in AFP within 2 months of ICI initiation predict treatment response and overall survival in HCC patients. A cutoff of $\geq 10\%$ AFP improvement may be clinically useful for early assessment of treatment benefit and in deciding whether to continue ICI therapy in high-risk patients.



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4046-A | EFFECTIVENESS AND SAFETY OF MICROWAVE ABLATION FOR CHILD B EARLY STAGE HEPATOCELLULAR CARCINOMA

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Background: Microwave ablation (MWA) is reported to be an effective locoregional ablation modality and probably comparable to radiofrequency ablation. Since most of the subjects of clinical trials which verify feasibility of MWA are hepatocellular carcinoma (HCC) patients who have preserved liver function with Child A, the influence regarding the impact of impaired hepatic reserve on treatment outcomes has not been well established. In the current study, we aimed to investigate effectiveness and safety of MWA for HCC patients with Child B and to develop the optimal treatment for patients with reduced hepatic reserve. **Methods:** This retrospective cohort study enrolled 513 microwave ablation treatments using Emprint ablation system (Covidien) during 2017 to 2022. The ablation procedures were operated under real-time ultrasound guidance. Of those, 477 treatments were operated under the tumor settings of HCC with 3 or less lesions of 30 mm in diameter or single lesions of 50 mm without major vessel involvement or extrahepatic metastasis. We compared patient background factors and treatment outcomes of 387 patients with Child A and 90 patients with Child B. Patient background factors were gender, age, body weight, platelet count, serum albumin, total bilirubin, prothrombin time, Fibrosis-4 (FIB-4) index, Aspartate Aminotransferase to Platelet Ratio Index (APRI), liver stiffness measured by elastography (Fibroscan, Echosense) and tumor settings (number and maximum diameter). Treatment outcomes were recurrence-free survival, severe complication rate, and incidence of postoperative bile duct injury (dilatation). **Results:** In the analysis of entire cohort, there was a significant increase in the number of tumors and the maximum tumor diameter in Child B cases compared with Child A cases. However, 477 subjects finally enrolled in the analysis under the limited tumor settings, the number of tumors and the maximum tumor diameter were comparable in both groups. Not only factors related to hepatic reserve, platelet count (Child A vs. Child B, 153 vs. 115×10^9/L, $p = 0.0352$) and liver stiffness (Child A vs Child B, 19.4 vs 32.5 kPa, $p < 0.0001$) showed significant difference in each group. All of the outcomes showed worse result in Child B cases in severe complication rate (Child A 3/384 0.8% vs Child B 4/86 4.4%, $p = 0.0234$), recurrence-free survival, and incidence of bile duct dilatation. Furthermore, ascites was extracted as an independent factor as a risk factor contributing to bile duct dilatation. **Conclusion:** Child B patients are at increased potential risk for portal hypertension and low platelet counts in addition to impaired hepatic reserve, which may contribute to poor treatment outcomes. Aside from considering liver transplantation, proactive preoperative measures such as expanding the TPO receptor agonist indication criteria or adequate ascites control is needed for effective and safe MWA procedure.

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4047-A | EFFECTIVITY AND TOLERABILITY OF CHEMOSATURATION OF THE LIVER WITH MELPHALAN FOR PATIENTS WITH PRIMARY OR SECONDARY LIVER TUMORS

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Background: Chemosaturation by percutaneous hepatic perfusion (CS-PHP, CHEMOSAT®, Delcath) allows temporary administration of melphalan hydrochloride directly to the liver. This approach was shown to be effective in controlling tumor growth in patients with primary or secondary liver tumors. In those studies, CS-PHP was applied in various frequencies ranging from one to six times. We have retrospectively analysed the effectiveness and tolerability of CS-PHP given on an eight-weekly basis. **Methods:** CS-PHP was applied to patients with primary or secondary liver tumors based on board decision in one German center until disease progression, intolerability or complete response. Overall survival (OS) and overall response rates (ORR) were retrospectively assessed according to Response Evaluation Criteria In Solid Tumors (mRECIST). OS was analysed by Kaplan-Meier estimation. ORR included patients achieving complete (CR) or partial response (PR) after each treatment. Toxicity associated with CS-PHP was assessed according to Common Terminology Criteria for adverse events (CTCAEv4.03). **Results:** A total of 31 patients (21 (68%) female) was treated with 90 (median 2, range 1-6) CS-PHP between 2016 and 2022. Included patients had either unresectable intrahepatic metastases of ocular melanoma (OM, $n = 17$), intrahepatic cholangio carcinoma (ICC, $n = 8$), hepatocellular carcinoma (HCC, $n = 2$), ciliary body melanoma ($n = 1$), acinar cell carcinoma ($n = 1$), hepatic spread of pancreatic (PC, $n = 1$) or tonsillar carcinoma ($n = 1$). CS-PHP was performed 6 times in 5, 5 times in 4, 4 times in one, three times in 4, two times in 7 and one time in 10 patients.

The median OS of all patients since decision for CS-PHP was 67 (range, 41.31-92.89) weeks, and for patients with OM 76 (range, 56.5-95.5) weeks and for ICC 37 (range, 32.11-41.88) weeks, respectively. ORR was 66% to all CS-PHP treatments (60/90), including 85% of OM and 31.25% of ICC patients. In 5 patients, CR was achieved after a median of 5 (range, 2-6) CS-PHP. CS-PHP was abandoned due to disease progression in three patients after first CS-PHP, due intolerability in two and due to lost in follow up in 7 patients. Presence of extrahepatic tumor manifestations before CS-PHP was not associated with response or survival. In 12 patients developing extrahepatic tumor progress, one of them with bone marrow infiltration, CS-PHP was continued if liver tumors were still controlled. Hematological AEs included leukopenia (grade 2) or thrombocytopenia (grade 2-3) were transient. Febrile neutropenia occurred in two cases and was treated with G-CSF. **Conclusion:** CS-PHP induced response in the majority of malignant primary or secondary liver tumors. The procedure was safe and had few hematological side effects. The effectivity CS-PHP as long-term treatment needs to be validated in future studies.

Disclosures: The following people have nothing to disclose: Rhea Veelken, Sebastian Ebel, Manuel Florian Struck, Christian Girbardt, Focke Ziemssen, Timm Denecke, Thomas Berg, Florian Van Bömmel

4048-A | EFFECTS AND MECHANISMS OF THE SUBTYPES OF APOLIPOPROTEIN E TO THE IMMUNE STATE AND PROGNOSIS OF HEPATOCELLULAR CARCINOMA PATIENTS

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Background: Apolipoprotein E (apoE), mainly synthesized by the liver, which consists of three main isoforms: apoE2, apoE3 and apoE4, is one of the key molecules for lipid transportation and metabolism. Recent studies in melanoma have found that different subtypes apoE possess different levels of abilities of inhibiting the survival of myeloid-derived suppressor cells (MDSCs), thereby reducing their abundance and relieving their inhibitory effects on the immune response to tumours. It is a question worth further investigation as to whether tumour progression, immune status and prognosis of HCC patients may also differ depending on the subtype and expression of apoE. **Methods:** The first cohort included samples and clinical, pathological, laboratory information, along with 10 years' follow-up data of 360 HCC patients. Immunofluorescence staining of combinations of CD11b$^+$/LOX1$^+$ and CD14$^+$/HLA-DR$^{-/low}$ was performed on the tissue microarrays of tumor samples to assess the abundance of infiltrating polymorphonuclear granulocyte-like MDSCs (PMN-MDSCs) and monocyte-like MDSCs (M-MDSCs); immunohistochemistry was used to detect the expression of apoE2, apoE3, apoE4, arginase (ARG) and inducible nitric oxide synthase (iNOS). Survival analysis was performed using univariate and multivariate COX regression and the Kaplan-Meier method. Additional 39 patients who were diagnosed with HCC or hepatic vascular smooth muscle lipoma (AML, benign) were included in the second cohort. Peripheral blood samples were collected and divided into three groups of high/normal/low levels of apoE. Flow cytometry was applied to detect immune cells abundance. ANOVA and t-test were applied to compare the differences among groups. $p < 0.05$ was considered statistically significant in this study. **Results:** COX regression analysis showed H-score of apoE2 in tumour tissues below 16.01 ($HR = 6.140$, $p = 0.00005$) and H-score of apoE4 above 4.05 ($HR = 7.001$, $p = 0.009$) were significantly associated with shorter overall survival (OS). The density of infiltrated PMN-MDSCs (> 2.87 cells/mm^2 ($HR = 3.762$, $p = 0.000009$)) and proportion of M-MDSCs of total cells ($< 89.32\%$ ($HR = 0.454$, $p = 0.006$)) in tumour tissues were independent risk factors for shorter recurrence-free survival (RFS). A higher abundance of MDSCs in the blood in low apoE group was detected compared to the normal and high blood apoE levels. The number of CD14$^+$/HLA-DR$^{-/low}$ M-MDSCs ($p = 0.0399$) were higher than in the apoE high level group. CTLA-4$^+$ T lymphocytes were detected higher in the low apoE group than in the normal group. **Conclusion:** This study suggested that in HCC patients, the elevated abundance of MDSCs in the peripheral blood was negatively correlated with the level of apoE in peripheral blood, and the abnormal level of apoE was also associated with elevated levels of PD-1$^+$ and CTLA-4$^+$ T lymphocytes. ApoE2 subtype was a potential protective factor for HCC patient's OS and apoE4 subtype suggested poor prognosis.

Disclosures: The following people have nothing to disclose: Bowen Gao

4049-A | EFFECTS OF PROTON BEAM THERAPY ON LOCAL CONTROL AND HEPATIC RESERVE IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Background: Proton beam therapy (PBT) achieves excellent long-term tumor control with minimal toxicity in patients with unresectable hepatocellular carcinoma (HCC); however, its effect on hepatic reserve have not been adequately studied. If the tumor size is large (> 3 cm) or located in an area that is difficult to ablate, combined radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) (TACE+RFA) is the standard locoregional therapy. This study compared the therapeutic effect of PBT with that of TACE +RFA on local control and hepatic reserve in patients with unresectable HCC. **Methods:** We retrospectively analyzed data of 68 patients with HCC unsuitable for surgical resection or RFA monotherapy due to tumor size, location, or comorbidities such as cardiopulmonary dysfunction, who were treated with PBT (22 patients) or TACE+RFA (46 patients) from January 2010 to March 2022. The PBT protocol was 66.0–80.5 CGE in 10–38 fractions. The therapeutic effects were assessed using local progression-free survival (PFS), 5-year overall survival (OS), and changes in hepatic reserve. **Results:** Among the patients treated with PBT/TACE+RFA, the median (range) age was 74 (54–88)/74 (57–85) years; median (range) tumor size was 2.7 (1.2–9.3)/2.7 (1.4–7.0) cm; median follow-up period was 34.9/38.8 months; 66.7/69.6% were modified Albumin-Bilirubin (mALBI) grade 1 or 2a. The 5-year local PFS was over 65% for both PBT and TACE+RFA. The OS at 5-year post-treatment was 82% and 28% in patients treated with PBT and TACE+RFA, respectively (hazard ratio, 0.29; 95% confidence interval, 0.13–0.64; $P < 0.05$). The baseline ALBI score was maintained for 12 months in patients treated with PBT, but it was worse at 1 month and remained worsen for 12 months in patients treated with TACE+RFA. ($P < 0.01$). At the 2nd and 3rd additional treatments, the baseline ALBI score was maintained in patients treated with PBT, but was worse in patients treated with TACE+RFA ($P < 0.05$). **Conclusion:** In patients with unresectable HCC, PBT effectively maintains hepatic reserve and OS is better than that with TACE+RFA. PBT maintains hepatic reserve by reducing damage to non-tumorous liver tissue. PBT may be an effective first-line treatment for unresectable HCC.

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4050-A | EFFICACY AND SAFETY OF LENVATINIB AS A FIRST-LINE THERAPY IN ELDERLY PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

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Background: Few studies have evaluated the efficacy and safety of lenvatinib (LEN) in elderly (≥ 80 y of age) patients with advanced hepatocellular carcinoma (HCC), which we investigated and compared with other age groups as controls. **Methods:** In total, 53 elderly patients and 173 controls who underwent LEN treatment between March 2018 and November 2022 were recruited. Propensity score matching was used to reduce confounding factors, with adjustment for sex, maximum tumor diameter, tumor number, tumor embolization, and metastasis. This resulted in 52 patients in each group. The primary endpoint was overall survival (OS), and factors related to OS were examined. **Results:** There were no significant differences in patient characteristics between the two groups. The median survival duration was 14.5 months in the elderly group and 14.3 months in the control group ($P = 0.254$). The 1-, 2-, and 3-year cumulative OS rates were 54.1%, 20.2%, and 10.1% in the elderly group and 64.0%, 25.7%, and 19.3% in the control group, respectively. Multivariate analysis revealed that Child–Pugh class and maximum tumor diameter were significantly related to OS ($P = 0.01$, 95% confidence interval [CI] 1.002–1.014, hazard ratio 1.008), ($P = 0.004$, 95% CI 1.279–3.657, hazard ratio 2.163). The median progression-free-survival duration was 12.5 months in the elderly group and 8.4 months in the control group; the difference was not significant. The response rate was 22.6% in the elderly group and 24.5% in the control group ($P = 0.819$). The number and rate of Grade 3 or higher adverse events were significantly lower in the elderly group (n = 17, 32.7%) than in the controls (n = 33, 63.5%) ($P = 0.029$). **Conclusion:** LEN is effective and safe to use in elderly patients ≥80 years of age.

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4051-A | EFFICACY AND SAFETY OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT IN PATIENTS WITH HEPATOCELLULAR CARCINOMA – A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Patients with hepatocellular carcinoma (HCC) and cirrhosis can present with features of severe portal hypertension, which can be worsened further with associated portal vein tumoral thrombosis (PVTT). Due to the technical difficulties and short survival of these patients, HCC was traditionally considered a relative contraindication for transjugular intrahepatic portosystemic shunt (TIPS). However, there is an increasing body of evidence supporting the use of TIPS in HCC. The present study aimed to analyze the efficacy and safety of TIPS in patients with HCC. **Methods:** A literature search of MEDLINE, Embase, and Scopus was conducted from 2000 to October 2022 for studies analyzing the outcome of TIPS in HCC. The primary outcomes were technical and clinical success, adverse events (AE), and mortality. The event rates were pooled using a random effects model. **Results:** A total of 19 studies with 1498 patients were included in the final analysis. The pooled technical and clinical success rates with TIPS in HCC were 98.8% (98.0 – 99.7) and 94.1% (91.2 – 97.0), respectively. The mean reduction in hepatic venous pressure gradient from baseline varied from 10 to 20.2 mm Hg, with a pooled mean difference of 13.65 mm Hg (95% CI: 12.05 – 15.24). After TIPS, ascites was controlled in 89.2% (85.1 – 93.3) of the cases, while rebleeding was observed in 17.2% (9.4 – 25.0) of cases on follow-up. The pooled incidence of overall AE, serious AE, and post-TIPS hepatic encephalopathy was 5.2% (2.5 – 7.9), 0.1% (0.0 – 0.4), and 25.1% (18.7 – 31.5), respectively. The reported serious AEs included: acute liver failure, tumor rupture causing intraabdominal bleeding, and post-TIPS intraabdominal bleeding. On follow-up, 11.9% (7.8 – 15.9) of the patients developed shunt dysfunction requiring reintervention. The pooled 1-year mortality rate with TIPS in HCC was 34.2% (95% CI: 18.9 – 49.5), with mortality being significantly higher in those undergoing TIPS for portal vein tumoral thrombosis (64.5%, 95% CI: 34.9 – 94.2) than those without (22.7%, 95% CI: 13.1 – 32.3) (p = 0.009). Table 1 summarizes the findings of the present analysis with subgroup analysis. **Conclusion:** The present analysis supports the feasibility, safety, and efficacy of TIPS in the management of portal hypertension in patients with HCC.

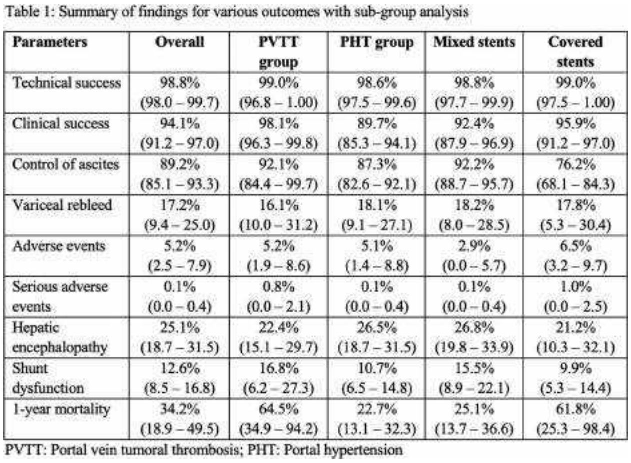

Table 1: Summary of findings for various outcomes with sub-group analysis

Parameters	Overall	PVTT group	PHT group	Mixed stents	Covered stents
Technical success	98.8% (98.0 – 99.7)	99.0% (96.8 – 1.00)	98.6% (97.5 – 99.6)	98.8% (97.7 – 99.9)	99.0% (97.5 – 1.00)
Clinical success	94.1% (91.2 – 97.0)	98.1% (96.3 – 99.8)	89.7% (85.3 – 94.1)	92.4% (87.9 – 96.9)	95.9% (91.2 – 97.0)
Control of ascites	89.2% (85.1 – 93.3)	92.1% (84.4 – 99.7)	87.3% (82.6 – 92.1)	92.2% (88.7 – 95.7)	76.2% (68.1 – 84.3)
Variceal rebleed	17.2% (9.4 – 25.0)	16.1% (10.0 – 31.2)	18.1% (9.1 – 27.1)	18.2% (8.0 – 28.5)	17.8% (5.3 – 30.4)
Adverse events	5.2% (2.5 – 7.9)	5.2% (1.9 – 8.6)	5.1% (1.4 – 8.8)	2.9% (0.0 – 5.7)	6.5% (3.2 – 9.7)
Serious adverse events	0.1% (0.0 – 0.4)	0.8% (0.0 – 2.1)	0.1% (0.0 – 0.4)	0.1% (0.0 – 0.4)	1.0% (0.0 – 2.5)
Hepatic encephalopathy	25.1% (18.7 – 31.5)	22.4% (15.1 – 29.7)	26.5% (18.7 – 31.5)	26.8% (19.8 – 33.9)	21.2% (10.3 – 32.1)
Shunt dysfunction	12.6% (8.5 – 16.8)	16.8% (6.2 – 27.3)	10.7% (6.5 – 14.8)	15.5% (8.9 – 22.1)	9.9% (5.3 – 14.4)
1-year mortality	34.2% (18.9 – 49.5)	64.5% (34.9 – 94.2)	22.7% (13.1 – 32.3)	25.1% (13.7 – 36.6)	61.8% (25.3 – 98.4)

PVTT: Portal vein tumoral thrombosis; PHT: Portal hypertension

Disclosures: The following people have nothing to disclose: Marko Kozyk, Suprabhat Giri, Ankita Singh, Akash Roy, Kateryna Strubchevska, Taraprasad Tripathi, Ranjan Kumar Patel

4052-A | EFFICACY AND TOLERABILITY OF IMMUNE CHECKPOINT INHIBITORS FOR ADVANCED HEPATOCELLULAR CARCINOMA WITH CHILD-PUGH CLASS B: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Immune checkpoint inhibitors (ICIs) are increasingly used in patients with advanced hepatocellular carcinoma (HCC). However, data on ICI therapy in patients with advanced HCC and impaired liver function is scarce. Herein, we performed a meta-analysis to provide evidence for the efficacy and safety of ICI treatment for advanced HCC with Child-Pugh class B. **Methods:** PubMed, Embase, Web of Science, and Cochrane library were searched for relevant studies through 2022/6/15. Randomized controlled trials, cohort studies, or single-arm studies that investigated the efficacy or safety of ICI therapy for advanced HCC with Child-Pugh class B were included. Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were followed to extract data. A random-effects model was adopted if the heterogeneity was significant (I^2 statistic > 50%); otherwise, the fixed-effects model was used. The objective response rates (ORR) and overall survival (OS) were considered to be the primary outcomes for the efficacy outcomes of ICI treatment for advanced HCC with Child-Pugh class B. The incidence of treatment-related adverse events (trAEs) was set as the major measure for the safety outcome. **Results:** A total of 22 studies, including 699 Child-Pugh B and 2114 Child-Pugh A advanced HCC patients, were included. Upon pooled analysis, the ORR and disease control rates (DCR) of Child-Pugh B patients treated with ICIs were 14% (95% confidence interval [CI] 11-17%) and 46% (95%CI 36-56%), with a median OS and median progression-free survival (PFS) of 5.49 (95%CI 3.57-7.42) and 2.68 (95%CI 1.85-3.52) months, respectively. The rates of any grade trAEs in Child-Pugh B patients were 40% (95%CI 34-47%), grade 3 or higher trAEs 12% (95%CI 6-23%). When compared to Child-Pugh A patients, the ORR (OR 0.59, 95%CI 0.43-0.81, $p < 0.001$) and DCR (OR 0.64, 95%CI 0.50-0.81, $p < 0.001$) of Child-Pugh B were lower. Child-Pugh class B was an independent predictor of a worse OS in advanced HCC patients treated with ICIs (hazard ratios (HR) 2.72, 95%CI 2.34-3.16 and adjusted HR 2.33, 95%CI 1.81-2.99). However, ICI did not associate with increased trAEs in patients with Child-Pugh class B. **Conclusion:** While the safety of ICI treatment was comparable between patients with versus without advanced liver disease, and this treatment resulted in a significant number of radiological responses, survival outcomes following ICI treatment are still inferior in Child-Pugh class B HCC patients questioning the effectiveness of ICI in this population.

Disclosures: Ju Dong Yang – AstraZeneca: Consultant, No, No; Eisai: Consultant, No, No; Exact Sciences: Consultant, No, No; Exelixis: Consultant, No, No; Fujifilm Medical Sciences: Consultant, No, No; Merck: Consultant, No, No;

The following people have nothing to disclose: Enrui Xie, Yee Hui Yeo, Bernhard Scheiner, Yue Zhang, Atsushi Hiraoka, Xinxing Tantai, Petros Fessas, Tiago De Castro, Antonio D'Alessio, Shuo Xu, Claudia Angela Maria Fulgenzi, Hong-Ming Tsai, Swetha Kambhampati, Wenjun Wang, Xu Gao, Zixuan Xing, Matthias Pinter, Yih-Jyh Lin, Zhanjun Guo, Arndt Vogel, Takaaki Tanaka, Hsin-Yu Kuo, Kate Kelley, Masatoshi Kudo, David James Pinato, Fanpu Ji

4053-A | EFFICACY COMPARISON OF FIRST-LINE THERAPIES OF UNRESECTABLE HEPATOCELLULAR CARCINOMA IN OLDER AGE PATIENTS

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Background: After the IMbrave150 trial, atezolizumab plus bevacizumab (AteBeva) became the first-line therapy for unresectable hepatocellular carcinoma (HCC). However, few studies compared efficacy in elderly patients older than 65 with lenvatinib or sorafenib, the other first-line therapies. This study compared the efficacy of first-line agents for unresectable HCC in patients over 65. **Methods:** Between September 2020 to December 2022, 162 patients older than 65 from eight hospitals of Catholic Medical Center receiving AteBeva, lenvatinib, and sorafenib were included. We excluded the patients who received systemic treatment before this therapy. Overall survival (OS), time to progression (TTP), and progression-free survival (PFS) were measured in each treatment group of patients. **Results:** In baseline characteristics, there were no significant differences among the three treatment groups in terms of median age, sex, etiology, Child-Pugh class, performance status of patients, and BCLC stage. At the time of analysis, 57 patients (35 %) had died. Survival rate was comparable between these treatment cohorts with AteBeva having a mean survival of 8.9 months compared to 11.0 months for those receiving lenvatinib, and 10.6 months for sorafenib (p = 0.646). Mean TTP and PFS showed differences between these groups (TTP 6.7 vs. 10.7 vs. 5.3 months, respectively, p = 0.014; PFS 5.8 vs. 7.8 vs. 4.5 months, p = 0.055). In best response analysis, AteBeva and lenvatinib show superiority to sorafenib in terms of objective response rate (ORR) and disease control rate (DCR) with statistical significance (ORR 30.9 vs. 37.1 vs. 11.1%, respectively, p = 0.032; DCR 72.7 vs. 71.4 vs. 44.4%, p = 0.013). **Conclusion:** In patients older than 65, there was no significant difference in the treatment efficacy of the three first-line therapies for unresectable HCC in terms of OS. However, in TTP, ORR, and DCR, AteBeva and lenvatinib show superiority to sorafenib, and in PFS, lenvatinib is superior to sorafenib with statistical significance. Therefore, if elderly patients cannot be received AteBeva due to any complication risks, lenvatinib are commendable alternative without concern for decreased therapeutic effect. Further studies are needed to compare the exact treatment response.

Disclosures: The following people have nothing to disclose: Ahlim Lee, Hyun Yang

4054-A | EFFICACY OF LENVATINIB VERSUS SORAFENIB IN THE PRIMARY TREATMENT OF ADVANCED HEPATOCELLULAR CARCINOMA: A META-ANALYSIS

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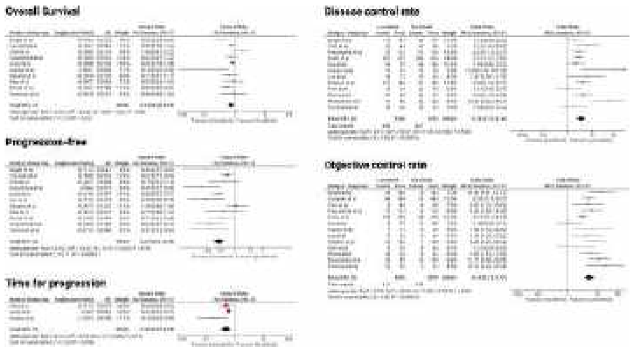
Background: Molecular-targeted agents such as Lenvatinib and Sorafenib have been approved to treat hepatocellular carcinoma (HCC). However, the choice of drug among these two agents in the primary treatment for advanced HCC is still under debate with conflicting results. We sought to evaluate the efficacy of Lenvatinib and Sorafenib among patients with hepatocellular carcinoma. **Methods:** We performed a systematic literature search using PubMed, Embase, and Scopus for relevant articles from inception until 10th February 2023. The primary outcome of this meta-analysis was overall survival (OS). The secondary outcomes were progression-free survival (PFS), time to progression, objective response rate (ORR), and disease control rate (DCR). **Results:** A total of 13 studies with 3705 patients (1635 Lenvatinib vs. 2070 Sorafenib) were included in our analysis. The mean age of the patients in both groups was comparable (66.81 vs. 65.9 y). The pooled analysis of primary outcomes showed that compared with Sorafenib, the Lenvatinib-treated group of patients was associated with significantly better OS (HR 0.82 [95%CI: 0.69-0.97], P = 0.02). The pooled analysis shows that PFS (HR 0.67 [95%CI: 0.57-0.78], P < 0.00001) and time to progression (HR 0.49 [95%CI: 0.31–0.79; P = 0.004] were significantly better in the Lenvatinib group compared to Sorafenib. The pooled analysis also showed that the Lenvatinib group of patients had significantly better ORR (OR 5.43 [95% CI: 3.71–7.97; P < 0.00001], and DCR (OR 2.35 [95% CI: 1.75–3.16]; P < 00001) than those of the Sorafenib group. **Conclusion:** Our study shows that Lenvatinib was superior to Sorafenib in overall survival and progression-free survival in advanced hepatocellular carcinoma patients.



Disclosures: The following people have nothing to disclose: Vikash Jaiswal, Maha Hameed, Sidra Naz, Helen Huang, Shiva Gupta, Poulami Roy, Novonil Deb, Amira Mohamed Taha, Abdelrahman M Attia, Supti Dev Nath, Dattatreya Mukherjee, Mostafa A Solimn

4055-A | EFFICACY OF YTTRIUM-90 (Y90) RADIOEMBOLIZATION FOR DOWNSTAGING OR BRIDGE TO TRANSPLANTATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Meghana Ghattu, Rutgers Robert Wood Johnson Medical Center, Bjorn Engstrom, Abbott Northwestern Hospital - Allina Health, Sandra Castro-Pearson, Allina Health and John R. Lake, University of Minnesota

Background: Liver transplantation (LT) remains one of the few curative treatments for hepatocellular carcinoma (HCC).[1] Due to organ scarcity and stringent selection criteria many patients with HCC are unable to qualify or are subject to long waitlists.[1] Liver directed therapy (LDT) is commonly used in this population for down-staging and as a bridge to transplant, with Y90 having a growing role.[2] However, there is relatively little information on long term outcomes in patients who received LT after Y90. **Methods:** We conducted a retrospective analysis of patients who underwent Y90 and subsequent LT at our center from Jan. 2013 – Dec. 2019. EMR was used to obtain baseline patient characteristics, explant histologic analysis, and long term follow up data. The cohort was divided into those with 100% necrosis of lesion on explant histology and 99% or less. Outcomes reported include overall survival (OS) and recurrence-free survival (RFS) at 2 and 5 years. Time-to-endpoint analyses were estimated using Kaplan–Meier curves. Univariate analyses were performed using a log-rank test. The small number of events prevented multivariate analyses. **Results:** In the study period, 28 patients underwent Y90 followed by LT. 9 patients were down-staged into Milan Criteria. 18 experienced 100% necrosis and 10 experienced 99% or less. At 2 years after LT, 3 of the 10 patients with 99% or less necrosis had recurrence followed by death in 2 (OS: 0.80, RFS: 0.70). Of the 18 patients with 100% necrosis, one patient experienced recurrence and death within 2 years from LT (OS: 0.94, RFS: 0.94). At 5 years from LT, 4 patients from the 99% or less group had recurrence and 2 died (OS: 0.80, RFS: 0.60). In those with 100% necrosis, 3 experienced recurrence and death within 5 years from LT (OS: 0.83, RFS: 0.83). None of the differences in OS or RFS were statistically significant at the 0.05 level. **Conclusion:** In this study we show that Y90 with subsequent LT has favorable long term recurrence free survival. In our cohort, most patients experienced 100% necrosis by explant histology, which was associated with a trend in improved outcomes at both 2 and 5 years from LT. The goal of Y90 LDT should be 100% necrosis. Extensive or complete necrosis after Y90 has been shown to have favorable long-term outcomes after LT in larger cohorts.[3] The small sample size limited the statistical power although these findings again support Y90 as an effective LDT for both down-staging and bridge to LT in patients with HCC.

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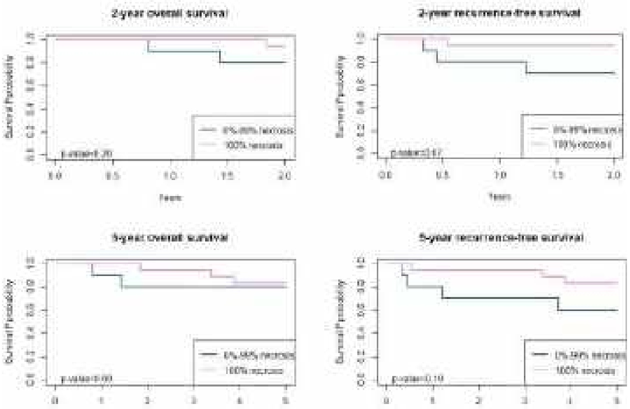

Figure 1: Kaplan-Meier curves for overall survival and recurrence-free survival*

Disclosures: The following people have nothing to disclose: Meghana Ghattu

Disclosure information not available at the time of publication: Bjorn Engstrom, Sandra Castro-Pearson, John R. Lake

4056-A | ENHANCING LAPAROSCOPIC HEPATECTOMY OUTCOMES IN LIVER CANCER WITH INDOCYANINE GREEN FLUORESCENCE IMAGING: A SYSTEMATIC REVIEW AND META-ANALYSIS★

Muhammed Elhadi Elfaituri, Ala Khaled, Hazem Faraj and Ahmed Msherghi, University of Tripoli

Background: Liver cancer is a significant global health challenge. Laparoscopic hepatectomy is increasingly recognized as a preferred surgical intervention, and Indocyanine Green (ICG) fluorescence imaging has emerged as a crucial component due to its capacity to enhance real-time intraoperative visualization of liver segments and vascular structures. However, the effects of ICG fluorescence imaging on operative outcomes following laparoscopic hepatectomy for liver cancer require comprehensive evaluation. This study aimed to determine the impact of ICG fluorescence imaging on operative outcomes, including operative time, blood loss, length of hospital stay, blood transfusion rate, and overall postoperative complications in laparoscopic hepatectomy for liver cancer. **Methods:** Electronic databases (PubMed, EMBASE, Cochrane Library, and Web of Science) were searched up to March 2023. Studies were included if they reported on patients undergoing laparoscopic hepatectomy for liver cancer and compared outcomes between groups using ICG fluorescence imaging and those not. Outcomes were presented as Mean Difference (MD) for continuous outcomes and Relative Risk (RR) for dichotomous outcomes. A random-effects meta-analysis was performed, and heterogeneity was assessed using the I^2 statistic. Statistical analyses were performed using R (version 4.0.3) with the metafor and meta packages. **Results:** The meta-analysis included eight studies with 635 patients (280 in the ICG fluorescence group and 355 in the non-fluorescence group). ICG fluorescence imaging significantly reduced operative time (MD: -24.34 minutes, 95% CI = -47.33 to -1.35, P = 0.04, $I^2 = 93\%$), blood loss (MD: -76.92 mL, 95% CI = -111.00 to -42.83, P < 0.01, $I^2 = 77\%$), and length of hospital stay (MD: -1.57 days, 95% CI = -2.04 to -1.09, P < 0.01, $I^2 = 74\%$). The rate of blood transfusions was not significantly different between the groups (RR: 0.69, 95% CI = 0.30 to 1.55, P = 0.37, $I^2 = 61\%$). However, the incidence of overall postoperative complications was significantly lower in patients who underwent ICG fluorescence imaging (RR: 0.54, 95% CI = 0.38 to 0.77, P < 0.01, $I^2 = 0\%$). **Conclusion:** This study suggests that ICG fluorescence imaging in laparoscopic hepatectomy for liver cancer may lead to significant improvements in short-term operative outcomes, including reduced operative time, less blood loss, and shorter hospital stays. Additionally, it appears to be associated with fewer overall postoperative complications. These findings underscore the potential value of ICG fluorescence imaging in improving surgical outcomes in liver cancer treatment. Further high-quality studies are needed to confirm these findings and evaluate this technology's cost-effectiveness.

Disclosures: The following people have nothing to disclose: Muhammed Elhadi Elfaituri, Ala Khaled, Hazem Faraj, Ahmed Msherghi

4057-A | ETIOLOGY OF HEPATOCELLULAR CARCINOMA IN THE 27-COUNTY ROCHESTER EPIDEMIOLOGY PROJECT CATCHMENT AREA, 2010-2021

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Background: Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths globally, and the incidence of HCC in the US is rising. Risk factors for HCC, including viral hepatitis, non-alcoholic fatty liver disease, and alcoholic liver disease have been fluctuating in prevalence over the course of the last several decades. For example, hepatitis C treatment became widely available in the mid-2010s, raising the possibility of a decline in Hep C-related HCC. The Rochester Epidemiology Project (REP) was established in 1966 as a database for patient records in Olmsted County, MN, where the original campus of the Mayo Clinic resides. Beginning January 2010, the REP expanded to cover 27-counties in SE MN and W WI. This database contains 2,816,905 medical records from 1,354,296 persons. It is a rich resource for epidemiological studies and, on average, covers 66.2% of the population per census data (with Olmsted County in particular being upwards of 100% coverage). Previous REP studies have shown that the incidence of HCC has increased between 1976 and 2008, with chronic hepatitis C virus being replaced by alcoholic liver disease as the most common comorbidity. Over 2000 to 2014, hepatitis B virus increased among HCC patients while hepatitis C trended downwards. **Methods**: HCC patient records were identified from the REP using ICD-9 and 10 codes. Charts were hand-screened to ensure accurate coding. Patient records were reviewed for inclusion criteria: new diagnosis of HCC, age 20+ years at diagnosis, resident of 27-county area 1+ year before HCC diagnosis (to exclude patients traveling to the area for care). In total,1494 charts were flagged and reviewed, of which 36.75% met inclusion criteria for a final sample of 549 patients. The 2010-2021 period was split into 2 eras for analysis. Charts were reviewed by hand and using natural language processing to collect variables of interest including comorbidities and clinical outcomes. **Results**: Over the course of 2010-2021, hepatitis B and C virus rates remained steady among HCC patients. Prevalence of NAFLD and diabetes remained similar, though rates of hypertension and non-alcoholic steatohepatitis were statistically significantly higher in the second era as compared to the first (p = 0.013 and p = 0.00094, respectively). Prevalence of smoking was also unchanged. Analysis of clinical presentation and outcomes is in progress. Conclusion: It is essential to identify etiology of HCC to improve screening and diagnosis. This study provides a comprehensive update on the state, etiology, and outcomes of HCC in the area surrounding Rochester, MN. With this and subsequent studies, we will be able to track changes in risk factors over time and work to enhance screening protocols to target the most vulnerable populations.

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Disclosure information not available at the time of publication: Lewis R. Roberts

4058-A | EVOLVING TRENDS IN HEPATOCELLULAR CARCINOMA IN INDIA - EXPERIENCE FROM A TERTIARY CARE CENTER

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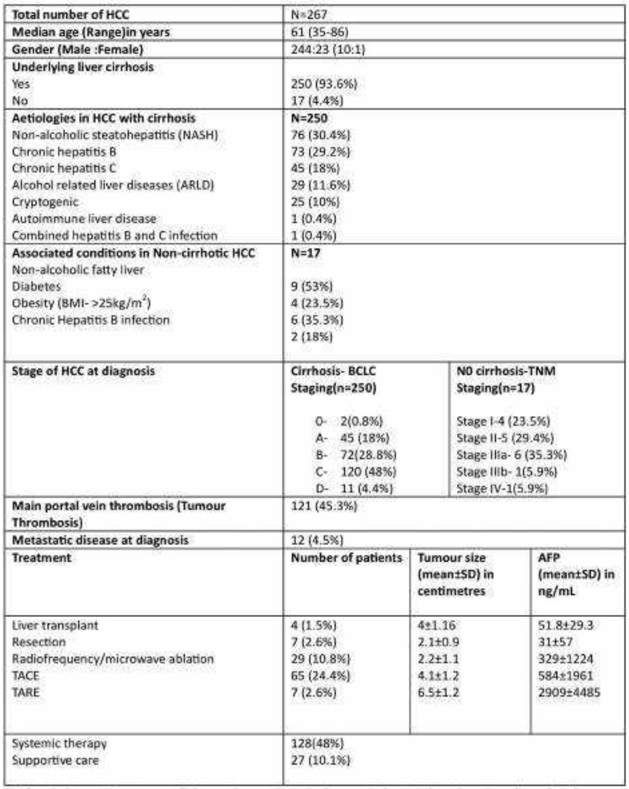
Background: Hepatocellular carcinoma (HCC) is a major complication and one of the leading causes of mortality in chronic liver diseases. The causes of HCC coincide with those of liver cirrhosis and there are epidemiological differences in different geographical areas. Hepatitis B virus (HBV) etiology is prevalent in China, India, Southeast Asia, and sub-Saharan Africa whereas chronic alcohol related liver disease is the most prevalent aetiology in central Europe and North America. Non-alcoholic steatohepatitis (NASH) related liver cirrhosis is increasing in prevalence world wide. Viral hepatitis B and C used to be leading causes of HCC in India. However, with a strong immunization program and availability of effective antiviral medications the trends in epidemiology of HCC in India are changing. In this study, we aim to identify the main etiological factors and clinical parameters of HCC patients in a tertiary care center in India. **Methods:** This is an observational study. We recorded the demographic details of all patients diagnosed with HCC at AIG hospitals, from November 2021 to April 2023 over a period of 18 months. HCC diagnosis was based on triphasic computerised tomography scan or dynamic magnetic resonance imaging of liver or biopsy as per INASL consensus. Aetiologies, prior comorbidities, stage of disease at diagnosis, presentation and treatment received were recorded. Barcelona clinic liver cancer (BCLC) system was applied for staging of HCC in patients with underlying cirrhosis whereas, TNM staging was done in non-cirrhotic HCC. **Results:** The results of the study are detailed in table 1. A total of 267 patients were diagnosed with HCC over a period of 18 months out of which 244 (91.3%) were males. Median age at presentation is 61years (Range-35-86 y). Out of 267 HCC patients, 250 (93.6%) had co-existing liver cirrhosis. Among cirrhotic HCC patients, non-alcoholic steatohepatitis (NASH) was the leading cause [n = 76 (30.4%)] followed by chronic hepatitis B and hepatitis C infections. Even among non-cirrhotic patients with HCC, underlying non-alcoholic fatty liver (NAFL) was observed in 9 (53%) patients. Most patients were diagnosed at BCLC – C stage and were offered systemic therapy [n = 120 (45%)]. Among advanced and terminal HCC patients (n = 139), who were not amenable for surgical or locoregional therapies, NASH was the leading aetiology found in 60 (43%) patients followed by hepatitis B [n = 31 (22.3%)]. **Conclusion:** NASH is the leading cause of HCC in our study. Most patients diagnosed with advanced HCC had NASH as the underlying aetiology. Even among non-cirrhotic HCCs, NAFL was a commonest association. Worldwide NASH is emerging as a leading cause of HCC. Hence, effective preventive strategies and population screening are the need of the hour.

Table 1. Demographic features, aetiology and clinical characteristics of patients with HCC



Total number of HCC	N=267		
Median age (Range)in years	61 (35-86)		
Gender (Male :Female)	244:23 (10:1)		
Underlying liver cirrhosis			
Yes	250 (93.6%)		
No	17 (4.4%)		
Aetiologies in HCC with cirrhosis	**N=250**		
Non-alcoholic steatohepatitis (NASH)	76 (30.4%)		
Chronic hepatitis B	73 (29.2%)		
Chronic hepatitis C	45 (18%)		
Alcohol related liver diseases (ARLD)	29 (11.6%)		
Cryptogenic	25 (10%)		
Autoimmune liver disease	1 (0.4%)		
Combined hepatitis B and C infection	1 (0.4%)		
Associated conditions in Non-cirrhotic HCC	**N=17**		
Non-alcoholic fatty liver			
Diabetes	9 (53%)		
Obesity (BMI- >25kg/m^2)	4 (23.5%)		
Chronic Hepatitis B infection	6 (35.3%)		
	2 (18%)		
Stage of HCC at diagnosis	**Cirrhosis- BCLC Staging(n=250)**	**N0 cirrhosis-TNM Staging(n=17)**	
	O- 2(0.8%)	Stage I-4 (23.5%)	
	A- 45 (18%)	Stage II-5 (29.4%)	
	B- 72(28.8%)	Stage IIIa- 6 (35.3%)	
	C- 120 (48%)	Stage IIIb- 1(5.9%)	
	D- 11 (4.4%)	Stage IV-1(5.9%)	
Main portal vein thrombosis (Tumour Thrombosis)	121 (45.3%)		
Metastatic disease at diagnosis	12 (4.5%)		
Treatment	**Number of patients**	**Tumour size (mean±SD) in centimetres**	**AFP (mean±SD) in ng/mL**
Liver transplant	4 (1.5%)	4±1.16	51.8±29.3
Resection	7 (2.6%)	2.1±0.9	31±57
Radiofrequency/microwave ablation	29 (10.8%)	2.2±1.1	329±1224
TACE	65 (24.4%)	4.1±1.2	584±1961
TARE	7 (2.6%)	6.5±1.2	2909±4485
Systemic therapy	128(48%)		
Supportive care	27 (10.1%)		

Abbreviations- HCC- Hepatocellular carcinoma, BMI- Body mass index, BCLC staging- Barcelona clinic liver cancer staging, TNM staging- Tumour-node-metastasis- staging, AFP- alpha-feto protein, TACE- trans arterial chemoembolization, TARE- trans arterial radioembolization.

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Disclosure information not available at the time of publication: Archana Chintam, Duvurr Nageshwar Reddy

4059-A | EXPLORATORY EFFECTIVENESS OF ATEZOLIZUMAB PLUS BEVACIZUMAB IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC) BEYOND RADIOLOGICAL PROGRESSION: A REAL-WORLD, MULTICENTER COHORT STUDY

Takaya Tabuchi[1], Nobuhito Taniki[1], Ryosuke Kasuga[1], Po-sung Chu[1], Yukie Nakadai[1], Mayuko Kondo[1], Fumie Noguchi[1], Rei Morikawa[1], Shunsuke Shiba[2], Toshiyuki Tahara[2], Hirokazu Komatsu[3], Yuriko Fujita[3], Fumihiko Kaneko[4], Hitomi Hoshi[4], Keisuke Ojiro[5], Yasuo Hosoda[6], Akihiro Yamaguchi[6], Seiichiro Fukuhara[7], Yukishige Okamura[8], Hideaki Kanamori[9], Takanori Kanai[1] and Nobuhiro Nakamoto[1], (1)Keio University School of Medicine, (2)Saiseikai Utsunomiya Hospital, (3)Yokohama Municipal Citizen's Hospital, (4)Saitama Municipal Hospital, (5)Tokyo Dental College Ichikawa

General Hospital, (6)National Hospital Organization Saitama Hospital, (7)National Hospital Organization Tokyo Medical Center, (8)Sano Kosei General Hospital, (9)Hino Municipal Hospital

Background: The patterns of tumor response by immune checkpoint inhibitors may behave like 'flare effect', such transient tumor increase could be evaluated as progressive disease (PD), which may result in discontinuation of treatment despite the therapeutic effect is achieved. Subgroup analysis of IMbrave150 shows efficacy in patients with unresectable hepatocellular carcinoma (HCC) treated with atezolizumab (Atezo) plus bevacizumab (Bev) beyond PD until loss of clinical benefit (Toh ASCO GI 2022). In the current study, we investigated the exploratory efficacy of Atezo plus Bev beyond radiological progression in real-world. **Methods:** 101 unresectable HCC patients who were treated with Atezo plus Bev were enrolled from 9 liver centers across Japan. In the presence of clinical benefit, patients with PD assessed by RECIST 1.1 could continue treatment until development of unacceptable toxicity or loss of clinical benefit judged by investigator. Loss of clinical benefit was defined as symptoms and signs indicating unequivocal progression of disease, decline in performance status that could be attributed to disease progression, and tumor progression at critical anatomical sites. Patients who received 2 or more cycles of Atezo plus Bev after first PD were classified as beyond PD group, and their outcomes were compared with patients who were treated with alternative regimens or discontinued chemotherapy after first PD. **Results:** The response rate of entire cohort was 24%, and the disease control rate was 69%. The median overall survival (OS) was 21.3 months, and the median progression-free survival (PFS) was 6.9 months. Of those, 44 patients had PD, of whom 17 patients continued Atezo plus Bev, 16 patients had alternative chemotherapy including lenvatinib, sorafenib, cabozantinib, and 11 patients discontinued chemotherapy after first PD. Of the patients who continued Atezo plus Bev, 76% were Barcelona Clinic Liver Cancer (BCLC) stage C while patients receiving other chemotherapy, 69% were BCLC stage C. Other patients background factors including hepatic reserve (35% Child-Pugh A5 vs 29% Child-Pugh A5) were also comparable in each group at first PD. The median OS from the time of first PD in beyond PD group was 17.9 months, while 4.7 months in patients who received alternative chemotherapy or discontinued chemotherapy ($p = 0.04$ log-rank test). In addition, the median OS of the 16 patients who had alternative chemotherapy showed 4.7 months, which was tend to be shorter compared with beyond PD group ($p = 0.269$ log-rank test). **Conclusion:** Our data suggest that patients who received Atezo plus Bev beyond radiological PD with maintained clinical benefit may contribute to prolong prognosis to some extent. Since there is a limitation by selection bias related to excluding patients with loss of clinical benefit, further investigation is needed to detect predictor that define treatment efficacy in such cases.

Disclosures: The following people have nothing to disclose: Takaya Tabuchi, Nobuhito Taniki, Ryosuke Kasuga, Po-sung Chu, Yukie Nakadai, Mayuko Kondo, Fumie Noguchi, Rei Morikawa, Shunsuke Shiba, Toshiyuki Tahara, Hirokazu Komatsu, Yuriko Fujita, Fumihiko Kaneko, Hitomi Hoshi, Keisuke Ojiro, Yasuo Hosoda, Akihiro Yamaguchi, Seiichiro Fukuhara, Yukishige Okamura, Hideaki Kanamori, Takanori Kanai, Nobuhiro Nakamoto

4060-A | EXPRESSION AND CLINICOPATHOLOGICAL SIGNIFICANCE OF FIBROBLAST GROWTH FACTOR RECEPTOR 2 (FGFR2) IN COMBINED HEPATOCELLULAR-CHOLANGIOCARCINOMA

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Background: Fibroblast growth factor receptor 2 (FGFR2) fusions are detected in 10-20% of intrahepatic cholangiocarcinoma (iCCA) and are promising therapeutic targets for FGFR2 inhibitors. Combined hepatocellular –cholangiocarcinoma (cHCC-CCAs) shares various features such as histological findings of iCCA components, etiologies and possible cell origin with small duct type iCCA, however, there were few studies on FGFR2 fusions in cHCC-CCA, so far. Immunohistochemical FGFR2 expression is a candidate surrogate marker for detecting FGFR2 fusions. We examined the expression FGFR2 and their clinicopathological significance in combined hepatocellular – cholangiocarcinoma (cHCC-CCA) , in comparison with small and large duct types iCCA and hepatocellular carcinoma (HCC). **Methods:** FGFR2 expression was immunohistochemically assessed in the liver sections from 75 patients with cHCC-CCA (male[M]/female[F] = 51/24; etiology, B/C/alcohol/non-alcoholic fatty liver disease [NAFLD]/unknown: 24/24/5/6/16), 39 with small duct-type iCCA (M/F = 28/11; 1/8/6/1/23), 30 with large duct-type iCCA (M/F = 16/14; 2/2/0/1/25), and 35 with HCC (M/F = 32/3; 10/14/6/3/2). FGFR2 fusions were also detected by PCR and direct sequence. The association of FGFR2 expression with clinicopathological findings including histological features, etiologies and genetic alterations such as p53, ARID1A and BAP1 was analysed. **Results:** FGFR2 expression was detected in more frequently in patients with cHCC-CCA (21.3%) and small duct-type iCCA (23.1%), compared to patients with large duct type iCCA (3.3%) and HCC (0%) ($p < 0.05$). FGFR2 was not expressed in nonneoplastic bile ducts and hepatocytes. FGFR2 expression was significantly more prevalent in cHCC-CCA with a component of cholangiolocellular carcinoma ($p < 0.01$).

FGFR2-positive cHCC-CCAs and small duct-type iCCAs were significantly smaller size, compared to FGFR2-negative ones ($p < 0.05$). Genetic alterations of ARID1A, BAP1 and multiple genes were significantly more frequent in FGFR2-positive cHCC-CCAs, compared to FGFR2-negative cHCC-CCAs ($p < 0.05$). FGFR2 fusions were confirmed by PCR and direct sequence in FGFR2-positive cHCC-CCA and small duct-type iCCAs. **Conclusion:** FGFR2 expression was detected in cHCC-CCAs as frequently as small duct-type iCCAs. This finding suggests a possible therapeutic indication of FGFR2 inhibitors for the patients with cHCC-CCAs.

Disclosures: The following people have nothing to disclose: Motoko Sasaki, Yasunori Sato, Yasuni Nakanuma

4061-A | EXTERNAL BEAM RADIATION THERAPY AND LIVER TRANSPLANTATION WITHOUT BRACHYTHERAPY IN THE CONTEXT OF PERI-HILAR CHOLANGIOCARCINOMA: A PROOF OF CONCEPT STUDY

Lydia Aurora Mercado[1], Harpreet K. Bhangu[1], Fernando Gil Lopez[1], Stephen Ko[1], Liu Yang[1], Justin H. Nguyen[2], Terri Menser[1] and Denise M. Harnois[1], (1) Mayo Clinic Florida, Ponte Vedra Beach, FL, (2)Mayo Clinic, Jacksonville, FL

Background: Perihilar cholangiocarcinoma (pCCA) is a rare malignant tumor, frequently presenting in an unresectable stage, with a poor short-term prognosis. Neoadjuvant chemoradiotherapy (Neo-CRT) followed by orthotopic liver transplantation (OLT) has achieved outstanding results in highly selected patients. The Mayo Clinic Rochester Protocol (MCRP) includes external beam radiotherapy (EBRT, 40-45 gray) along with infusional 5-fluorouracil (5-FU), followed by transcatheter brachytherapy (20-30 gray), and then oral capecitabine until OLT. The Mayo Clinic Florida (MCF) protocol does not include brachytherapy and instead includes larger doses of EBRT (45 Gy 1.5/day BID) and an external boost of up to 60 gray in hilum. **Methods:** We retrospectively examined the population both diagnosed with pCCA and meeting MCF protocol inclusion criteria (i.e., mass lesion with a radial diameter < 3 cm, tumor not extending below the cystic duct, medically candidate for OLT). Chart review was conducted in November 2022, and data was manually extracted including multiple years of follow-up. **Results:** A total of 15 patients were treated with Neo-CRT; 4 patients were removed from listing due to disease progression and 11 completed the modified MCRP and were transplanted. The mean age was 55 years, 60% were males, and the mean BMI was 22.71. PSC was the underlying disease (47%), alcoholic liver disease (7%), and the remainder had no underlying disease indicated. Bismuth-Corlette classification was present in 9%, 27%, 18%, and 45% for types 1, 2, 3, and 4, respectively. Tumor size diameter was 1-3 cm in 93% and < 1 cm in 7%. 93% of patients had endoscopic biopsy confirmation prior to OLT; 100% of patients' tumors were visible by imaging. All treated patients received DBD whole livers using the surgical piggyback technique, with a mean operating time of 321 minutes. On average, 3.8 units of blood were used during OLT. None of the patients presented hepatic artery thrombosis, biliary leakage, or biliary strictures after OLT. At explant, histopathology findings post-OLT included pCCA (45%), adenocarcinoma and intraductal papillary neoplasm (27%), and no remaining tumor (27%). Vascular grafts were used in 18% of the transplants ($n = 2/11$). The two- and five-year survival rates were 55% ($n = 6/11$) and 44% ($n = 4/9$), while the recurrence free survival rates were 64% ($n = 7/11$) and 56% ($n = 5/9$), respectively. **Conclusion:** When compared with historical data, the results of the modified MCRP using EBRT and OLT without brachytherapy showed similar survival and recurrence rates. The use of EBRT minimized the need for vascular grafts, this may represent another advantage to the use of EBRT rather than brachytherapy.

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Disclosure information not available at the time of publication: Harpreet K. Bhangu, Fernando Gil Lopez, Stephen Ko, Justin H. Nguyen, Denise M. Harnois

4062-A | FUNCTIONAL CURE OF HEPATITIS B IN CANCER PATIENTS UNDERGOING IMMUNE CHECKPOINT INHIBITORS

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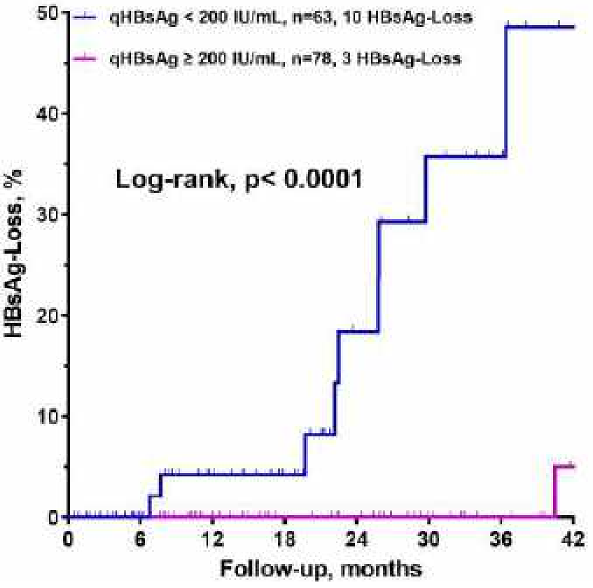
Background: Immune checkpoint inhibitors (ICIs) by blocking program death 1 (PD-1)/ programmed cell death-ligand 1 (PD-L1) axis can restore exhausted T cell immunity not only for cancer treatment but also potentially for curing chronic hepatitis B (CHB). One phase 1 study by one shot of very low-dose nivolumab in accompanied with nucleotide analogue (NUC) had substantial effect on hepatitis B surface antigen (HBsAg) decline. It is interesting to delineate the impact of regular anti-cancer dosage of ICIs on HBsAg seroclearance in cancer patients, and the factors associated HBsAg loss. **Methods:** From 2016 to 2022, consecutive HBsAg-positive cancer patients receiving ICIs in Taipei Veteran General Hospital were retrospectively recruited. Patients co-infected with HCV, HDV, or HIV were excluded. Biochemical, virological factors and duration of ICIs were carefully recorded. **Results:** There were 165 cancer patients enrolled in this analysis, including 112 (67.9%) hepatocellular carcinoma (HCC) patients, and 139 under anti-PD-1 treatment. Of them, 128 (77.6) had already on NUC before ICI treatment. The median cycles of ICIs treatment were 11 (ranged 6-20). During a median follow-up of 18.8 months, 13 (7.9%) patients achieved HBsAg seroclearance. All the 13 patients had on NUCs during ICI treatment. In univariate analysis adjusting competing risk of death, low baseline HBsAg titer (<100 IU/mL; HR = 0.059, $p < 0.001$), and low baseline HBV DNA (<200 IU/ml; HR = 0.150, $p = 0.070$) were associated with HBsAg loss. In multivariate analysis, low HBsAg level was the only factor significantly associated with HBsAg seroclearance. Interestingly, the cumulative incidences of HBsAg loss in the 50 patients whose baseline HBsAg level <100 IU/ml were 5.2% at 12 months, 21.2% at 24 months, and 35.6% at 36 months. **Conclusion:** For cancer patients with baseline HBsAg <100 IU/ml, ICIs treatment could accelerate the chance of HBsAg seroclearance in whom on NUCs. This finding may provide important information for future trial design of ICIs to achieve functional cure in CHB patients.

Figure. HBsAg-Loss ratio separated by HBsAg 200 IU/mL prior ICI treatment.



Disclosures: The following people have nothing to disclose: Hsien-Chen Mon, Pei-Chang Lee, Ya-Wen Hung, Chi-Jung Wu, Chieh-Ju Lee, Chen-Ta Chi, I-Cheng Lee, Ming-Chih Hou, Yi-Hsiang Huang

4063-A | GEOGRAPHIC DISPARITIES IN HEPATOCELLULAR CARCINOMA INCIDENCE

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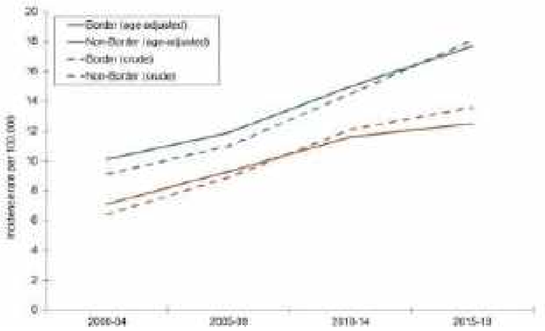
Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality in the U.S., with the highest incidence rate in Texas, although there is geographic variation within the state. To evaluate geographic disparities, we compared incidence rates and characteristics of persons with HCC along the Texas-Mexico border vs. other regions of Texas. **Methods:** We identified adults newly diagnosed with HCC and estimated age-adjusted incidence rates using population-based data from the Texas Cancer Registry between January 1, 2000 and December 31, 2019. Demographic and socioeconomic variables were obtained from the Robert Wood Johnson Foundation's County Health Rankings and the Area Health Resource File. We compared individual-, census tract-, and county-level characteristics of persons diagnosed with HCC living in the 32 Texas counties comprising the Texas-Mexico border and non-border counties. **Results:** From 2000 to 2019, age-adjusted incidence rates of HCC were 14.1 vs. 10.6 per 100,000 in border and non-border counties, respectively. There was a greater rise in HCC incidence rates in border compared to non-border counties from 2000-04 to 2015-19. Age-adjusted incidence rates were higher in border counties for men (incidence rate ratio [IRR] 1.32, 95% CI 1.27, 1.37) and women (IRR 1.48, 95% CI 1.39, 1.57), age ≥65 years (IRR 1.71, 95% CI 1.64, 1.78), and local (IRR 1.35, 95% CI 1.29, 1.41), regional (IRR 1.12, 95% CI 1.04, 1.21), and distant (IRR 1.42, 95% CI 1.30, 1.54) stage disease. Hispanic persons living in border counties were significantly older than non-border counties, as reflected by the difference in crude IRR (1.14, 95% CI 1.10, 1.18) vs. age-adjusted IRR (0.84, 95% CI 0.81, 0.87). Persons with HCC in border counties were more likely to be foreign-born (31.6% vs 9.7%), have Medicaid (24.5% vs 14.9%), and live in higher poverty neighborhoods (76.5% vs 36.2%) vs. non-border counties. Border counties have fewer primary care providers (40.3 vs 69.1 per 1,000) and gastroenterologists (0.9 vs 3.8 per 1,000), fewer persons with a college degree or higher (13.9% vs 23.9%), more uninsured (31.1% vs 25.9%) and unemployed persons (6.8% vs 4.8%), and more children living in poverty (41.9% vs 21.4%) than non-border counties. **Conclusion:** HCC incidence rates are higher and rising faster along the Texas-Mexico border compared to non-border counties, potentially related to higher prevalence of Hispanic minorities, lower educational attainment, and greater rates of poverty. Improving access to healthcare through policy changes and clinical infrastructure expansion may address these social inequities.

Figure 1. Age-adjusted and crude incidence rates of hepatocellular carcinoma in border vs. non-border counties by five-year time periods, Texas Cancer Registry, 2000 – 2019



Disclosures: Amit G. Singal – Genentech: Consultant, No, No; AstraZeneca: Consultant, No, No; Bayer: Consultant, No, No; Eisai: Consultant, No, No; Exelixis: Consultant, No, No; Boston Scientific: Consultant, No, No; Gycotest: Consultant, No, No; Exact Sciences: Consultant, No, No; Roche: Consultant, No, No; FujiFilm Medical Sciences: Consultant, No, No; GRAIL, LLC: Consultant, Yes, No; Freenome: Consultant, No, No; Histosonics: Consultant, No, No;

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4064-A | GERIATRIC NUTRITIONAL RISK INDEX FOR PREDICTING MUSCLE VOLUME LOSS IN HEPATOCELLULAR CARCINOMA PATIENTS: STRAIGHTFORWARD APPROACH FOR UTILIZATION

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Background: Muscle volume decline (MVD) is a crucial prognostic factor for chronic liver disease (CLD) patients, though clinical prediction requires findings obtained with special technologies that are often expensive and not readily available, such as software for computed tomography or bioelectrical impedance analysis. This study examined use of geriatric nutritional risk index (GNRI), calculated using only serum albumin level, height, and body weight, to predict high risk for MVD in CLD patients with hepatocellular carcinoma (HCC). **Methods:** Four hundred forty-two HCC patients in Japan examined without prior treatment from January 2017 to June 2022 were enrolled (median age 74 y, male 72.6%, HCV:HBV:HBV and HCV:alcohol:others = 188:36:2:84:132, Child-Pugh A:B:C = 357:67:18, beyond Milan criteria 41.0%). With GNRI utilized to assess nutritional status, MVD was evaluated using the skeletal muscle index cut-off value of the Japan Society Hepatology (Hepatol Res 2016). This retrospective evaluation was conducted to investigate the relationship between GNRI and MVD. **Results:** MVD was noted in 105 (23.8%) patients and a significant relationship of GNRI with albumin-bilirubin (ALBI) score was found ($r = -0.738$, 95% CI: -0.778 to -0.692, $P < 0.001$). Values for GNRI nutritional status normal:mild decline:moderate decline:severe decline were 283:53:76:30, with the cut-off GNRI score for predicting MVD was 99.7 (specificity/sensitivity = 0.709/0.800) (AUC 0.813, 95% CI: 0.766-0.859), approximately the upper limit of mild nutritional decline status. For GNRI mild decline status (score < 98), the cut-off ALBI score was -2.478 (specificity/sensitivity = 0.867/0.764) (AUC 0.892, 95% CI: 0.863-0.921). Also, after excluding patients with ascites, the cut-off GNRI score for MVD was 99.7 (specificity/sensitivity = 0.760/0.744) (AUC 0.803, 95% CI: 0.747-0.858). MVD incidence increased with worsening nutritional status (normal 9.9%, mild decline 37.7%, moderate decline 47.4%, severe decline 70.0%; $P < 0.001$). **Conclusion:** GNRI in conjunction with body weight and serum albumin level can serve as an easy, effective tool for predicting MVD in CLD patients. Maintaining a normal GNRI score is important during the CLD clinical course before HCC development, and nutritional intake assessment and nutritional intervention should be proactively considered for patients with an abnormal score.

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4065-A | GLUTAMINE METABOLISM REPROGRAMMING IN LIVER TISSUES FROM HEPATOCELLULAR CARCINOMA PATIENTS

Vincent Tambay[1], Valérie-Ann Raymond[2], Louise Rousseau[1], Simon Turcotte[1,3] and Marc Bilodeau[1,4], (1)

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

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Background: Hepatocellular carcinoma (HCC) is the most prevalent and deadly hepatic malignancy. The liver is a central organ of protein metabolism. Metabolic reprogramming is a hallmark of cancers, including HCC. This study aimed to identify changes in key pathways of glutamine, the most abundant amino acid, in HCC compared to cirrhotic and non-cirrhotic liver tissues. **Methods:** HCC ($n = 32$), adjacent paired cirrhotic liver (CL, $n = 20$), and non-cirrhotic liver (NCL, $n = 20$) samples were obtained from a single-center patient cohort at the Centre hospitalier de l'Université de Montréal. mRNA analyses were performed by qPCR whereas protein expression was measured by Western blotting. **Results:** Glutamine synthetase (GS) mRNA was higher in HCC samples compared to CL and NCL ($p < 0.05$). Kidney glutaminase (GLS1) mRNA was also higher in HCC than NCL ($p < 0.05$) but not CL. Liver glutaminase (GLS2) mRNA was lower in HCC compared to both CL and NCL (both $p < 0.0001$). Albumin (ALB) was also lower in HCC relative to CL ($p < 0.05$) and NCL ($p < 0.0001$), though CL also had decreased ALB levels compared to NCL ($p < 0.001$). As for protein expression, GS was higher in HCC than in CL and NCL ($p < 0.05$); its expression in HCC being much higher than in paired CL ($p < 0.0001$). GLS1 proteins were highly expressed in HCC but not in CL nor NCL ($p < 0.0001$), whereas GLS2 protein levels were higher in CL and NCL compared to HCC samples ($p < 0.0001$). Receiver operating characteristic (ROC) analyses between non-tumoral liver (CL and NCL) and HCC samples were performed for both mRNA and protein analyses. For mRNA, GLS2 was the best classifier of tissue sample type (AUROC = 0.947, $p < 0.0001$). Calculating the GS/GLS2 ratio increased ROC performance (AUROC = 0.955, $p < 0.0001$). Including albumin led to even improved ROC performance: GS/(ALB*GLS2) (AUROC = 0.969 (95%CI = 0.93-1.00), $p < 0.0001$). For protein expression, GS (AUROC = 0.926, $p < 0.0001$) and GLS2 (AUROC = 0.925, $p < 0.0001$) had better classifying performance than GLS1 (AUROC = 0.867, $p < 0.0001$). Similar to mRNA expression, calculating the GS/GLS2 protein ratio increased ROC performance (AUROC = 0.961 (95% CI = 0.91-1.00), $p < 0.0001$). **Conclusion:** HCC is characterized by a major reprogramming of key pathways of glutamine metabolism. Whereas GS and GLS1 are increased in HCC samples compared to both CL and NCL, GLS2 and ALB are both decreased in human HCC samples. Glutamine metabolism reprogramming has significant discriminative ability between HCC and non-tumoral liver samples.

Disclosures: The following people have nothing to disclose: Vincent Tambay, Valérie-Ann Raymond, Louise Rousseau, Simon Turcotte, Marc Bilodeau

4066-A | GLYPICAN-3 PROTEIN QUANTITATION AND CELLULAR LOCALIZATION IN PEDIATRIC LIVER TUMORS

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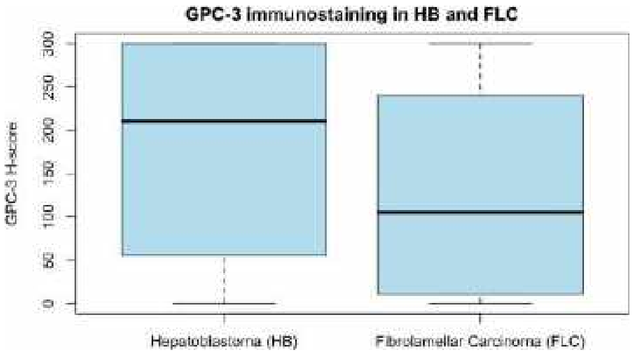
Background: Glypican 3 (GPC3), a heparan sulfate proteoglycan and cell surface oncofetal protein which actives the canonical Wnt/beta-catenin pathway is highly expressed on hepatocellular carcinoma, fibrolamellar carcinoma (FLC) and hepatoblastoma (HB). Although studies to date have shown elevated GPC3 protein in FLC and HB, quantitative patterns of GPC3 expression including cellular localization (canalicular, cytoplasmic, membranous) have not been analyzed in these tumors. A variety of immunotherapeutic approaches that target GPC3 in clinical trials include vaccines, monoclonal and bispecific antibodies, antibody-drug conjugates, cytolytic T-cells, and CAR T-cells. In using GPC3-targeted immunotherapy in pediatric patients, one concern involves possible physiologic expression of GPC3 in the non-tumor liver, particularly in the first year of life. We aim to determine patterns of GPC3 protein in primary HB and FLC tumors and adjacent non-tumor liver tissue with GPC3 immunohistochemistry. **Methods:** Tissue microarrays of 27 HB, and 10 FLC were constructed. We evaluated the Cellmark GPC3 (1G12) mouse monoclonal antibody to detect GPC3 protein, by calculating an H-score, multiplying intensity of staining (0-3) with percent cells staining (0-100). H-score < 10, was considered negative. In addition, the pattern of protein staining (canalicular, cytoplasmic, membranous) was noted. **Results:** GPC3 positive staining was present in 21 of 27 HB with H-scores: range = 0-300, median = 210, interquartile range = 55-300. GPC positive staining was present in 8 of 10 FLC with H-scores: range = 0-300, median = 105, interquartile range = 18-225. The predominant pattern of GPC3 staining in HB was (5/21 canalicular, 11/21 cytoplasmic, 5/21 membranous) and in FLC was (2/8 canalicular, 3/8 cytoplasmic, 3/8 membranous). High level of GPC3 staining with H-score > 150 was identified in 15/27 HB (56%) and in 4/8 FLC (50%). Adjacent benign liver was analyzed in 25 HB cases and in 8 FLC cases, all of which were GPC3 negative. **Conclusion:** GPC3 protein is expressed in a large percentage of HB and FLC tumors, but with variable intensity and distribution. Characterization of GPC3 tumor protein H-score and pattern of immunoreactivity are two independent parameters that may be helpful to quantitate GPC3 immunostaining of tumor and correlate with treatment response to a variety of GPC3 targeted therapeutics.



Disclosures: The following people have nothing to disclose: Sepideh Besharati, Sofia Shaikh, Victoria Remotti, Ladan Fazlollahi, Helen Remotti

4067-A | HEPATIC ADENOMA IN WOMEN UNDERGOING IN VITRO FERTILIZATION (IVF): INSIGHTS FROM A COHORT STUDY

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Background: The use of *in vitro* fertilization (IVF) now accounts for 1-3% of live births in the US and Europe. IVF involves the administration of hormones such as LH, FSH, and estrogen to induce ovulation and enhance fertility. While the association between estrogen levels and hepatic adenoma growth has been established in the context of oral contraceptive use and pregnancy, the impact of IVF on hepatic adenomas is unknown. To address this knowledge gap, our study compares three patient cohorts with hepatic adenoma who underwent: IVF alone, IVF-pregnancy, and spontaneous pregnancy. **Methods:** We conducted a retrospective cohort study at a single center, focusing on reproductive-aged females with a mean age of 34 years (range 18-49) who underwent IVF and/or experienced pregnancy, and were diagnosed with hepatic adenoma between 2010 and 2021. Of the 150 patients identified through the Stanford Research Repository (STARR) tool, 18 met our inclusion criteria. We analyzed patient charts to evaluate the radiographic growth of hepatocellular adenomas before and after IVF and pregnancy. **Results:** Among the 18 patients included in the study, 28% (n = 5) comprised the IVF-only group, 33% (n = 6) composed the IVF-pregnancy group, and the remaining 39% (n = 7) formed the spontaneous pregnancy group. Hepatic adenoma diagnosis was based on characteristic imaging findings on CT or MRI in 83% of patients (n = 15), while 17% (n = 3) had biopsy-confirmed adenomas. Of the 18 patients, 28% (n = 5) had pre-existing hepatic adenomas, while 72% (n = 13) of adenomas were incidentally discovered during imaging conducted for IVF or pregnancy. Among the 11 patients who received IVF treatment, 7 were diagnosed with hepatic adenoma after starting IVF. Two of these patients had prior imaging that did not show any adenoma, indicating potential development during the hyperestrogenic state. Complications due to adenoma from IVF were rare. None of the patients with adenoma in the IVF-only and IVF-pregnancy cohorts needed surgical intervention and all were monitored conservatively. They neither experienced intralesional hemorrhage, transformation to hepatocellular carcinoma (HCC), or significant adenoma growth upon follow up imaging. **Conclusion:** In this study, we present the largest series of cases of hepatic adenoma in patients who underwent IVF. Most adenomas were incidentally detected during IVF treatment, raising questions about the need for screening in these patients. Moreover, IVF as an hyperestrogenic state may be associated with an increased risk for adenoma development, which needs to be confirmed in larger studies. Reassuringly, no significant growth of adenomas or complications were observed during IVF treatment or subsequent pregnancy in the patients studied. These findings provide valuable evidence to counsel patients with hepatic adenoma undergoing IVF that monitoring the adenomas without intervention is likely safe and appropriate.

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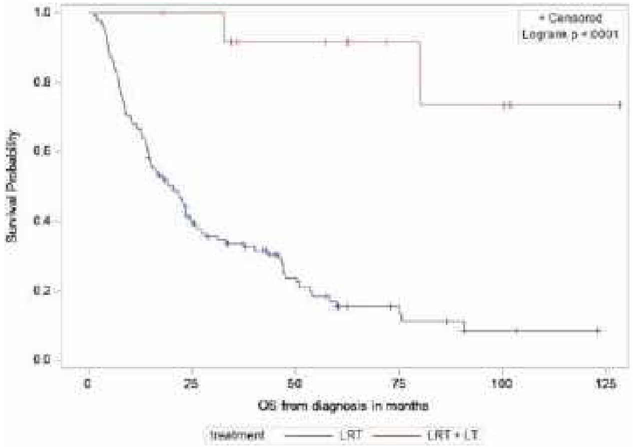
Disclosure information not available at the time of publication: Lea Lemaitre, Renumathy Dhanasekaran

4068-A | HEPATOCELLULAR CARCINOMA MANAGEMENT IN PATIENTS OVER AGE 70

Paul P. Hong[1], Karolina Krawczyk[1], John C. Hickernell[1], Kayeromi Gomez[2], Steven J. Scaglione[3], Christopher Molvar[1] and Jonah N. Rubin[1], (1)Loyola University Medical Center, Chicago, IL, (2)Loyola University Chicago, (3)Loyola University Health System

Background: Hepatocellular carcinoma (HCC) is the second most lethal cancer with an average age at diagnosis of 63 to 65 years old in North America and Europe. For those who qualify, standard of care is locoregional therapy (LRT) with or without liver transplantation (LT). Patients older than 70 years are at higher risk for poor outcomes with LT due to comorbidities and frailty. There is a lack of data regarding the optimal approach for these patients. The aim of our study is to determine whether LT has an effect on survival compared to LRT alone. **Methods:** We performed a single-center retrospective study of HCC patients from 2012-2022. Patients were included if they were diagnosed with HCC at 70 years old or above and received LRT. Etiology of liver disease, baseline MELD score, comorbidities, BCLC score, Milan criteria, UCSF criteria, and LT outcomes were collected. Favorable treatment response was defined with LI-RADS or the mRECIST criteria. Wilcoxon Rank-Sum Test was used to compare patients age between the LRT and the LRT plus LT populations. Chi-square test and Fisher Exact Test were used in the remaining bivariate analysis. A log-rank test was used to compare the overall survival between the LRT and the LRT plus LT populations. **Results:** 690 patients who were diagnosed with HCC above the age 70 were identified with 127 patients undergoing LRT and 13 patients undergoing LRT followed by LT. Median age was 74 with 86% Male and 64% NASH cirrhosis. Patients who were younger were more likely to be transplanted ($p < 0.01$). The median baseline MELD score was 11 (IQR 9-15). 75 patients (54%) received Yttrium-90 (Y90) therapy, 54 received transarterial chemoembolization (TACE), and 12 patients received microwave ablation as the initial LRT. 100 patients (71%) treated with LRT had a favorable treatment response. Of the 13 patients who underwent LT, 10 received TACE and 5 patients received Y90 with favorable responses including 3 patients downstaging into Milan criteria. Average time on the LT waitlist was 343.1 days. Post-transplant median RETREAT score was 1 (IQR 0-7) and 2 patients developed tumor recurrence resulting in 1 death. Overall survival was improved with LT (71.9 versus 60.5 months, p-value < 0.0001) with 11 still alive. **Conclusion:** LT had a favorable effect on overall survival in HCC patients over 70 years old with a low rate of tumor recurrence. Patients over 70 years old should be continued to be considered for a transplant evaluation due to improved overall survival.



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4069-A | HEPATOCELLULAR CARCINOMA RECURRENCE FOLLOWING TRANSPLANT: RISK FACTORS FOR OLIGOMETASTATIC VERSUS POLYMETASTATIC DISEASE

Nicole Paul[1], Timothy Lin[1], Diana Cheung[1], Harry Luu[1], Behnam Saberi[2], Shane Ottmann[1], Ahmet Gürakar[1], Mark Yarchoan[1], Amol Narang[1], Amy K. Kim[1] and Jeffrey Meyer[1], (1)Johns Hopkins University School of Medicine, (2)Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School

Background: Despite utilization of pre-transplant selection guidelines like Milan and/or UCSF criteria, recurrence of hepatocellular carcinoma (HCC) occurs in up to one-fifth of liver transplantations. Furthermore, there is a lack of risk factors to predict the patterns of HCC recurrence, which carries significant implications for prognosis and therapeutic decisions. We aimed to investigate pre-transplant risk factors associated with limited (oligometastatic) vs. widespread (polymetastatic) recurrence. **Methods:** A retrospective review was conducted at a single institution to identify patients with HCC who underwent liver transplantation and subsequently experienced disease recurrence. Baseline demographics and clinical characteristics (such as downstage status and pre-transplant locoregional treatments) were recorded. Explant pathology, including cellular differentiation and evidence of microvascular invasion, was reviewed. Post-transplant imaging at the time of recurrence was examined, and any site of radiographic recurrence was considered a metastatic lesion. Oligometastatic disease was defined as $< =3$ lesions at recurrence, while polymetastatic disease was defined as > 3 metastases. Overall survival (OS) was compared between groups via the Kaplan-Meier method, and regression analyses were used to identify predictors of polymetastatic disease. **Results:** Forty-three patients in our cohort experienced HCC recurrence and were eligible for the study between 2005-2022. Patients with oligometastatic disease ($n = 27$) had improved survival compared to those with polymetastatic disease ($n = 16$) with a median survival of 16.2 (95% CI 11.3, 21.1) vs. 4.0 (95% CI 1.4, 6.6) months (log-rank $P = 0.001$) and 3-year OS rates of 28.4% vs. 6.3%. Pre-transplant clinical variables are outlined in Table 1.

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

Alpha-fetoprotein (AFP) level before transplantation > 100 ng/mL (OR = 4.4, 95% CI [1.107 – 17.482]), poor cellular differentiation (OR = 5.25, 95% CI [1.231 – 22.390]) and presence of microvascular invasion (MVI) in the explanted liver (OR = 21.82, 95% CI [2.503 – 190.121]) were predictors of polymetastatic HCC. In multivariable analysis, the impact of MVI was still observed (OR = 14.64, 95% CI [1.480-144.766]). **Conclusion:** The presence of microvascular invasion on explant pathology is a strong predictor of aggressive, polymetastatic HCC in post-transplant patients who have shorter survival than those with oligometastatic HCC. Risk factors for polymetastatic disease also include poor cellular differentiation on explant pathology and AFP > 100 ng/mL.

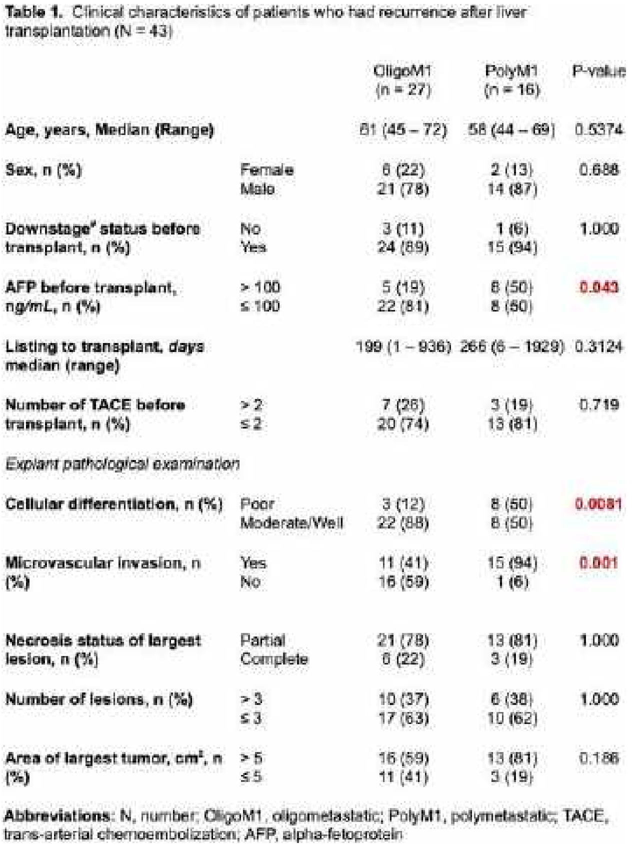

Table 1. Clinical characteristics of patients who had recurrence after liver transplantation (N = 43)

		OligoM1 (n = 27)	PolyM1 (n = 16)	P-value
Age, years, Median (Range)		61 (45 – 72)	58 (44 – 69)	0.5374
Sex, n (%)	Female Male	6 (22) 21 (78)	2 (13) 14 (87)	0.688
Downstage[a] status before transplant, n (%)	No Yes	3 (11) 24 (89)	1 (6) 15 (94)	1.000
AFP before transplant, ng/mL, n (%)	> 100 ≤ 100	5 (19) 22 (81)	8 (50) 8 (50)	0.043
Listing to transplant, days median (range)		199 (1 – 936)	266 (6 – 1929)	0.3124
Number of TACE before transplant, n (%)	> 2 ≤ 2	7 (26) 20 (74)	3 (19) 13 (81)	0.719
Explant pathological examination				
Cellular differentiation, n (%)	Poor Moderate/Well	3 (12) 22 (88)	8 (50) 8 (50)	0.0081
Microvascular invasion, n (%)	Yes No	11 (41) 16 (59)	15 (94) 1 (6)	0.001
Necrosis status of largest lesion, n (%)	Partial Complete	21 (78) 6 (22)	13 (81) 3 (19)	1.000
Number of lesions, n (%)	> 3 ≤ 3	10 (37) 17 (63)	6 (38) 10 (62)	1.000
Area of largest tumor, cm^2, n (%)	> 5 ≤ 5	16 (59) 11 (41)	13 (81) 3 (19)	0.186

Abbreviations: N, number; OligoM1, oligometastatic; PolyM1, polymetastatic; TACE, trans-arterial chemoembolization; AFP, alpha-fetoprotein

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4070-A | HEPATOCELLULAR CARCINOMA-SPECIFIC ANTIGENIC PEPTIDE-MODIFIED DENDRITIC CELL EXOSOMES COMBINED WITH ANTI-PD-L1 TO ENHANCE IMMUNE RESPONSE IN HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma is still a serious disease threatening people's health, and the number of incidences is expected to exceed one million cases in 2025. To clarify the value and potential of dendritic cell exosomes (DEX) modified with hepatocellular carcinoma-specific antigenic peptides in immunotherapy of hepatocellular carcinoma and to explore its potential immune mechanisms. Tumor cells can evade immune surveillance by overexpression of PD-L1 or activation of PD-L1/PD-1 signaling pathway, and high expression of PD-L1 in HCC tissues has been demonstrated; however, there are no clinical studies related to the treatment of HCC with PD-L1 inhibitors. **Methods:** DEX was extracted by ultracentrifugation and loaded with the hepatocellular carcinoma-specific antigens AFP and GPC3 and the N1ND peptide ($\text{DEX}_{\text{AFP-GPC3-N1ND}}$) that enhances cellular immune responses, and the role of $\text{DEX}_{\text{AFP-GPC3-N1ND}}$ in combination with anti-PD-L1 in hepatocellular carcinoma immunotherapy was investigated using liver cancer cell lines and humanized HCC-CDX mice. **Results:** In vitro: $\text{DEX}_{\text{AFP-GPC3-N1ND}}$ has hepatocellular carcinoma-specific immunogenicity and can effectively activate T cells, enhance the killing effect of T cells on hepatocellular carcinoma cell lines and elicit specific immune responses. It can effectively activate T cells and enhance T cell secretion of cytokine IFN-γ ($P = 0.037$). In vivo: $\text{DEX}_{\text{AFP-GPC3-N1ND}}$ inhibited the proliferation of hepatocellular carcinoma cells, affected the tumor microenvironment, and retarded tumor development in mice. In addition, the combination of PD-L1 monoclonal antibody could greatly enhance the anti-tumor immune function of $\text{DEX}_{\text{AFP-GPC3-}}$

$_{N1ND}$ by enhancing the immune memory against tumor rechallenge in hepatocellular carcinoma mice. **Conclusion:** The new findings demonstrate the immunomodulatory role of DEX$_{AFP-GPC3-N1ND}$ in combination with PD-L1 monoclonal antibody during HCC immunotherapy and provide a basis for the formulation of DEX vaccines targeting hepatocellular carcinoma, providing a scalable approach for personalized immunotherapy of HCC that can be extended to other tumors without the need to identify tumor antigens.

Disclosures: The following people have nothing to disclose: Weihua Li, Shumin Luo, Jing Chen, Fang Xu, Li Xiao

4071-A | HOW FIELD PRACTICE COMPLIES WITH BCLC 2022 RECOMMENDATIONS FOR HEPATOCELLULAR CARCINOMA MANAGEMENT

Eleonora Alimenti[1], Massimo Iavarone[2], Mariangela Bruccoleri[2], Angelo Sangiovanni[2], Barbara Antonelli[3], Anna Maria Ierardi[4] and Pietro Lampertico[2,5], (1) Department of Medical Sciences, University of Pavia, Pavia, Italy, (2)Division of Gastroenterology and Hepatology, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, (3)Division of General Surgery, Liver Transplant Center, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, (4) Radiology Department, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, (5)CRC "a. M. and a. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan

Background: In 2022 the BCLC staging and treatment algorithm for hepatocellular carcinoma (HCC) management has been updated, granting for higher flexibility and customized management with a multidisciplinary decision process in the choice of the therapeutic strategy for HCC patients as compared to the 2018 version. Aim: To evaluate the adherence to BCLC 2022 in daily clinical practice as compared to the BCLC 2018 and its impact on patients' survival. **Methods:** 464 patients with de novo HCC in different stages, 317 BCLC 0-A, 77 BCLC B, 65 BCLC C and 5 BCLC D were discussed in a multidisciplinary team (MTD) meeting and were treated accordingly to the decision of the team. All patients were then followed until death or end of follow-up. **Results:** Overall, adherence to BCLC 2022 recommendations were similar to BCLC 2018 (72.2% vs 70.3%, $p = 0.56$), corresponding to an adherence per stage of 79% in BCLC 0/A, 63% BCLC B, 49% BCLC C and 60% BCLC D. Overall survival was higher in patients treated according to the BCLC 2022 algorithm ad compared to other treatment strategies (72.1% vs 43.7% at 5 y, p-value < 0.001) in BCLC 0/A patients. In BCLC B an upward stage migration was associated to a higher overall survival (96% vs 66% at 2 y $p = 0.007$), meanwhile no significant differences were observed in BCLC C (43.8% vs 33.3% $p = 0.28$). **Conclusion:** In our hands, the upgraded BCLC staging and treatment system did not modify the adherence to the algorithm, while we observed that the adherence to BCLC 2022 was associated with a better survival in early stages of HCC. In the intermediate stage the access to more radical treatments could improve survival compared to the BCLC 2022 proposals, while no differences were observed in the advanced stage.

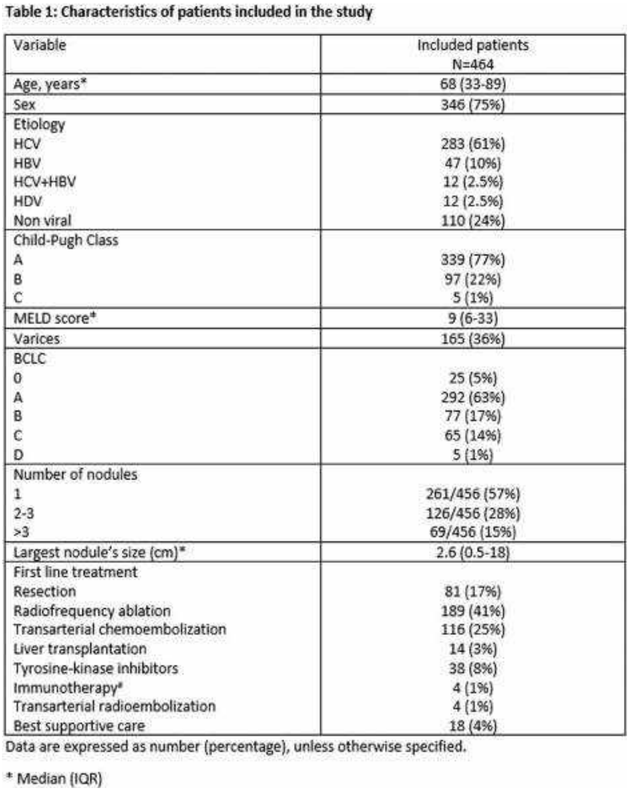

Table 1: Characteristics of patients included in the study

Variable	Included patients N=464
Age, years*	68 (33-89)
Sex	346 (75%)
Etiology	
HCV	283 (61%)
HBV	47 (10%)
HCV+HBV	12 (2.5%)
HDV	12 (2.5%)
Non viral	110 (24%)
Child-Pugh Class	
A	339 (77%)
B	97 (22%)
C	5 (1%)
MELD score*	9 (6-33)
Varices	165 (36%)
BCLC	
0	25 (5%)
A	292 (63%)
B	77 (17%)
C	65 (14%)
D	5 (1%)
Number of nodules	
1	261/456 (57%)
2-3	126/456 (28%)
>3	69/456 (15%)
Largest nodule's size (cm)*	2.6 (0.5-18)
First line treatment	
Resection	81 (17%)
Radiofrequency ablation	189 (41%)
Transarterial chemoembolization	116 (25%)
Liver transplantation	14 (3%)
Tyrosine-kinase inhibitors	38 (8%)
Immunotherapy*	4 (1%)
Transarterial radioembolization	4 (1%)
Best supportive care	18 (4%)

Data are expressed as number (percentage), unless otherwise specified.

* Median (IQR)

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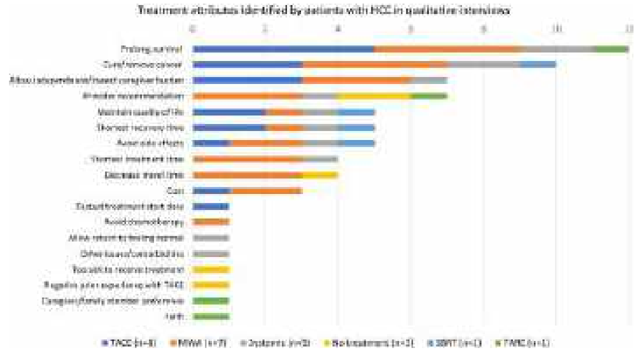
Pietro Lampertico – ALIGOS: Advisor, No, No; ANTIOS: Advisor, No, No; EIGER: Advisor, No, No; MYR: Advisor, No, No; SBRING BANK: Advisor, No, No; JANSSEN: Advisor, No, No; ALNYLAM: Advisor, No, No; ARROWHEAD: Advisor, No, No; MSD: Advisor, No, No; ABBVIE: Speaking and Teaching, No, No; GSK: Advisor, No, No; GILEAD SCIENCES: Advisor, No, No; ROCHE: Advisor, No, No; BMS: Advisor, No, No; VIR: Advisor, No, No;

The following people have nothing to disclose: Eleonora Alimenti, Mariangela Bruccoleri, Angelo Sangiovanni, Barbara Antonelli, Anna Maria Ierardi

4072-A | IDENTIFYING IMPORTANT TREATMENT ATTRIBUTES AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA: A QUALITATIVE STUDY

Andrew M. Moon[1], Randall Teal[1], Myra Waheed[1], Jessica Carda-Auten[1], Daniel Richardson[1], Hanna Sanoff[1], Robert S Sandler[1], Ethan Basch[1], Stephanie Wheeler[1], David Mauro[1], Ted K Yanagihara[1], David A. Gerber[2], Donna M. Evon[1] and Alfred Sidney Barritt IV[1], (1)University of North Carolina, (2)University of North Carolina at Chapel Hill

Background: Hepatocellular carcinoma (HCC) treatment decisions are often complex and may become increasingly so as new treatment options become available. To address this complexity, multidisciplinary tumor boards have emerged. Tumor boards improve survival in HCC but do not explicitly include input from patients. Preference-elicitation tools such as discrete choice experiments offer an opportunity to integrate patient preferences into tumor boards to improve the shared-decision making process. We performed qualitative interviews with HCC patients to identify common and important treatment attributes for inclusion in a discrete choice experiment. **Methods:** Participants with HCC identified through a multidisciplinary HCC clinic engaged in one-on-one, semi-structured interviews conducted by three qualitative interviewers prior to treatment (for patients who received treatment). Interviews were composed of open-ended questions about the disease experience, discussion of treatment options with providers, expected (or experienced) treatment risks/benefits, and patient values. Immediately following each baseline interview, interviewers performed a preliminary report identifying relevant or compelling concepts that arose across interviews. A full thematic analysis is ongoing. **Results:** The current analysis is based upon 25 of 30 patients with HCC who completed baseline interviews. Patients were 64% male, 79% white, 18% black, 4% Hispanic and 36% from rural areas. Treatments included TACE (32%), thermal ablation (29%), systemic therapy (20%), stereotactic body radiation therapy (4%), TARE (4%), and no treatment (12%). 21/25 (84%) of patients listed more than 1 attribute considered in treatment decisions and patients listed a median of 3 attributes (range 0-8) (Figure 1). The most commonly listed attributes were prolonging survival (n = 12) and/or, as described by patients, "cure/remove [the] cancer" (n = 10). Other commonly mentioned attributes included maintaining independence/reducing caregiver burden (n = 7), avoiding side effects (n = 5), and reducing treatment time (n = 4) or travel time (n = 4). **Conclusion:** In this study, most patients considered more than one attribute in HCC treatment decisions. In addition to prolonging life and maximizing treatment effectiveness, several additional treatment attributes were identified by patients with HCC. Attributes such as minimizing recovery time, treatment time, travel and costs may be used to facilitate shared-decision making for HCC treatments. Further work is needed to determine if treatment preferences would change if patients were informed of the non-curative nature of most HCC treatments. The treatment attributes discovered during this qualitative study will be synthesized with a literature review and provider interviews to be considered for inclusion in a discrete choice experiment of treatment attributes for patients with HCC.



Disclosures: Andrew M Moon – TARGET RWE: Consultant, Yes, No;

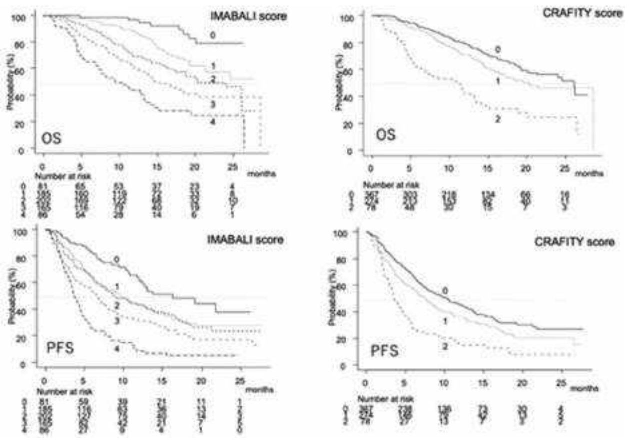
Donna M. Evon – HighTide Therapeutics: Consultant, No, Yes;

Disclosure information not available at the time of publication: Randall Teal, Myra Waheed, Jessica Carda-Auten, Daniel Richardson, Hanna Sanoff, Robert S Sandler, Ethan Basch, Stephanie Wheeler, David Mauro, Ted K Yanagihara, David A. Gerber, Alfred Sidney Barritt IV

4073-A | IMMUNOTHERAPY FOR HEPATOCELLULAR CARCINOMA – NEWLY DEVELOPED PROGNOSIS PREDICTION MODEL INCLUDING HEPATIC RESERVE FUNCTION

Yoshiko Fukunishi[1], Atsushi Hiraoka[1], Toshifumi Tada[2], Masashi Hirooka[2], Kazuya Kariyama[2], Ei Itobayashi[2], Tsuji Kunihiko[2], Toru Ishikawa[2], Hidenori Toyoda[2], Takeshi Hatanaka[2,3], Satoru Kakizaki[2], Atsushi Naganuma[2], Tomomitsu Matono[2], Hideko Ohama[1], Fujimasa Tada[1], Kazuhiro Nouso[2], Yoichi Hiasa[2] and Takashi Kumada[2], (1)Ehime Prefectural Central Hospital, (2)Relpec Study Group and HCC 48 Group, (3)Gunma Saiseikai Maebashi Hospital

Background: Atezolizumab plus bevacizumab (AB) is approved for hepatocellular carcinoma (HCC) treatment, with CRAFITY score, using c-reactive protein (CRP) and alpha-fetoprotein (AFP), a useful prognostic model for immunotherapy in HCC cases. However, hepatic reserve function is also an important prognostic factor. A new prognosis prediction model based on modified albumin-bilirubin (ALBI) grade (mALBI: ALBI grade 2 divided into 2a and 2b using score of -2.27) (Liver Cancer 2017) was examined for hepatic reserve function assessment. **Methods:** We retrospectively assessed 719 advanced/unresectable HCC patients (u-HCC) treated with AB from October 2000 to December 2022 (median age 74 y, males 577 (80.3%), initial line use 487 (67.7%), BCLC (0:A:B:C:D = 11:44:257:390:17, HCV:HBV:HBV/HCV:alcohol:others = 239:117:1:159:203). As a new predictive model, AB use-line (later), age (≥75 y), gender (female), body mass index (≥25 kg/m^2), basal liver disease (non-viral hepatitis), BCLC stage (≥C), CRP (≥1.0 mg/dL), AFP (≥100 ng/mL), and mALBI (2a or ≥2b) were used as prognostic factors, then prognostic predictive value was compared with CRAFITY. **Results:** Cox-hazard univariate analysis showed AFP (≥100 ng/mL) (HR 1.706: 95%CI 1.327-2.194), BCLC stage ≥C (HR 1.587: 95%CI 1.219-2.067), CRP (≥1.0 mg/dL) (HR 1.884: 95%CI 1.426-2.488), mALBI 2a (HR 1.726: 95%CI 1.190-2.501), and mALBI (≥2b) (HR 2.233: 95%CI 2.351-4.447) as significant factors (each P < 0.001), while AFP (≥100 ng/mL) (HR 1.531: 1.185-1.977, P = 0.001), BCLC stage ≥C (HR 1.393: 95%CI 1.061-1.828, P = 0.017), mALBI 2a (HR 1.765: 1.218-2.559, P = 0.003), and mALBI ≥2b (HR 2.967: 95%CI 2.141-4.111, P < 0.001) were that in multivariate analysis. Immunotherapy with AFP, BCLC, and mALBI (IMABALI) score, based on sum of points with 1 for AFP ≥100 ng/mL, BCLC stage ≥C, and mALBI 2a, and 2 for mALBI ≥2b according to HR, was developed. Akaike information criterion and concordance index values for OS and PFS were better (2799.0/0.688 and 5217.7/0.608, respectively) than those for CRAFITY (2846.5/0.606 and 5246.2/0.574, respectively). **Conclusion:** IMABALI score including detailed hepatic reserve function assessment might be a useful prediction model for AB against HCC in clinical practice.



Disclosures: Takeshi Hatanaka – Eisai: Speaking and Teaching, Yes, No;

The following people have nothing to disclose: Yoshiko Fukunishi, Atsushi Hiraoka, Toshifumi Tada, Masashi Hirooka, Kazuya Kariyama, Ei Itobayashi, Tsuji Kunihiko, Toru Ishikawa, Hidenori Toyoda, Satoru Kakizaki, Atsushi Naganuma, Tomomitsu Matono, Hideko Ohama, Fujimasa Tada, Kazuhiro Nouso, Yoichi Hiasa, Takashi Kumada

4074-A | IMPACT OF FIRST-LINE SYSTEMIC THERAPY WITH ATEZOLIZUMAB PLUS BEVACIZUMAB IN PATIENTS WITH HCC

Kaho Aoe[1], Toshifumi Tada[2], Takashi Kumada[3], Atsushi Hiraoka[3], Masashi Hirooka[3], Kazuya Kariyama[4], Ei Itobayashi[3], Tsuji Kunihiko[3], Toru Ishikawa[3], Hidenori Toyoda[5], Takeshi Hatanaka[6], Satoru Kakizaki[7], Hideko Ohama[8], Fujimasa Tada[9], Kazuhiro Nouso[3] and Yoichi Hiasa[10], (1)Japanese Red Cross Society Himeji Hospital, (2)Japanese Red Cross Himeji Hospital, Himeji, Japan, (3)Relpec Study Group and HCC 48 Group, (4)Okayama City Hospital, (5)Ogaki Municipal Hospital, (6)Gunma Saiseikai Maebashi Hospital, (7) National Hospital Organization Takasaki General Medical Center, Takasaki, Gunma, Japan, (8) Takarazuka City Hospital, (9)Ehime Prefectural Central Hospital, (10)Ehime, Toon-shi, Ehime, Japan

Background: The study goal was to compare the outcomes of patients with unresectable hepatocellular carcinoma (HCC) who received atezolizumab plus bevacizumab (Ateoz/Bev) as either first- or later-line systemic therapy. **Methods:** A total of 430 patients with unresectable HCC treated with Atezo/Bev were included. Patients treated with Atezo/Bev as first-line systemic therapy for HCC were defined as the first-line group (n = 268), while those treated with Atezo/Bev as second- or later-line systemic therapy were defined as the later-line group (n = 162). **Results:** The median progression-free survival times in the first- and later-line groups were 7.7 months (95% confidence interval [CI], 6.7–9.2) and 6.2 months (95% CI, 5.0–7.7), respectively (p = 0.021). The median overall survival times in the first- and later-line groups were not available [NA] months (95% CI, 18.5–NA) and 17.8 months (95% CI, 15.1–20.3), respectively (p = 0.084). Regarding treatment-related adverse events, hypertension of any grade was more common in the first-line group than in the later-line group (p = 0.025). Univariate analysis with Cox proportional hazards modeling adjusted by inverse probability weighting, including patient and HCC characteristics, showed that the later-line group (hazard ratio [HR], 1.304; 95% CI, 1.006–1.690; p = 0.045) was

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

significantly associated with progression-free survival. In a subgroup analysis of patients with Barcelona Clinic Liver Cancer (BCLC) stage B, the median progression-free survival times in the first- and later-line groups were 10.5 months (95% CI, 6.8–13.8) and 6.8 months (95% CI, 5.0–9.4), respectively ($p = 0.021$). In addition, among patients with a history of lenvatinib therapy, the median progression-free survival times in the first- and later-line groups were 7.7 months (95% CI, 6.3–9.2) and 6.2 months (95% CI, 5.0–7.7), respectively ($p = 0.022$). **Conclusion:** The use of Atezo/Bev as first-line systemic therapy in patients with HCC is expected to prolong survival.

Disclosures: Takeshi Hatanaka – Eisai: Speaking and Teaching, Yes, No;

The following people have nothing to disclose: Kaho Aoe, Toshifumi Tada, Takashi Kumada, Atsushi Hiraoka, Masashi Hirooka, Kazuya Kariyama, Ei Itobayashi, Tsuji Kunihiko, Toru Ishikawa, Hidenori Toyoda, Satoru Kakizaki, Hideko Ohama, Fujimasa Tada, Kazuhiro Nouso, Yoichi Hiasa

4075-A | IMPACT OF MULTIPLE PRIMARY CANCERS ON OVERALL SURVIVAL OF PATIENTS WITH HEPATOCELLULAR CARCINOMA

Petr Hříbek[1,2], Sona Frankova[3], Johana Klasová[1], Klara Chmelova[3], Lucie Žabová[1], Jan Sperl[3] and Petr Urbánek[1], (1)Military University Hospital Prague, (2) University of Defense, Faculty of Military Health Sciences in Hradec Králové, (3)Institute for Clinical and Experimental Medicine

Background: With the increasing incidence of malignancies, we face situations where hepatocellular carcinoma (HCC) is not the only cancer in a particular patient. The increasing occurrence of multiple primary neoplasias (MPN) is a long-term trend linked with improved life expectancy, diagnostics, and progress in treatment options. The prevalence of MPN in patients with HCC and its impact on overall survival (OS) remains unknown. This problem is important in HCC patients potentially treatable by liver transplantation (LT) as the occurrence of other cancer could present a contraindication to LT. The aim of our work was to assess the frequency of MPN and its impact on treatment options and OS in these patients. **Methods:** We retrospectively analyzed a cohort of HCC patients treated at two tertiary centers in the Czech Republic. Four hundred ninety-seven patients with HCC in the cirrhotic liver (388/497 males, median age at diagnosis 65 y) were included. Liver cirrhosis etiology was ALD in 38%, viral hepatitis in 32%, NASH in 19%, autoimmune and cholestatic diseases in 10%, and 1% of other etiology. BCLC stages were 0+A 51%, B 27%, C 17%, and D 6%. The cohort was divided into two subgroups – LT (324 patients) and non-LT (173 patients). We analyzed MPN occurrence, its impact on survival, and a Cox regression analysis of risk factors worsening outcomes (obesity, cirrhosis etiology, concurrent type 2 diabetes, gender, and smoking status). **Results:** The MPN was found in 88 patients (18% of patients in the cohort). The most common MPN were prostate (15, 17%), skin (14, 15.9%), kidney (11, 12.5%), lung (9, 10.2%), and colorectal cancer (8, 9.1%), and represented 64.8% of all MPN. The median OS of the whole cohort, LT and non-LT subgroup was 70, 116, and 17 months respectively ($p < 0.0001$). The median OS in patients with HCC only and HCC with another cancer was 77 (95% CI 67– 96) and 50 months (95% CI 37–62), respectively; the difference was not statistically significant ($p = 0.25$). The survival of patients who underwent LT was significantly better than those who were contraindicated to LT owing to concomitant MPC (116 vs 35 months, $p < 0.0009$). Autoimmune etiology, NASH, HCC as the first diagnosed malignancy, and male sex were identified as factors significantly influencing patients' prognosis (HR 0.43, 3.2326, 0.70, and 1.43 respectively). **Conclusion:** In our cohort, the MPN frequency was 18%, predominantly with malignancies more frequent in males. The impact of MPN on OS was not significant, except for individual's contraindicated to LT due to MPN. The better prognosis was associated with the autoimmune etiology of cirrhosis, and HCC diagnosed as the first malignancy. Male sex and NASH worsened the outcomes.

Disclosures: The following people have nothing to disclose: Petr Hříbek, Sona Frankova, Johana Klasová, Klara Chmelova, Lucie Žabová, Jan Sperl, Petr Urbánek

4076-A | IMPACT OF NUCLEOS(T)IDE ANALOGUES ON THE RISK OF HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS B PATIENTS: A TIME-DEPENDENT COX REGRESSION ANALYSIS

Makoto Moriyama[1], Ryosuke Tateishi[1], Mizuki Kinoshita[1], Tsuyoshi Fukumoto[1], Tomoharu Yamada[1], Taijiro Wake[1], Ryo Nakagomi[2], Takuma Nakatsuka[1], Tatsuya Minami[1], Masaya Sato[1], Mitsuhiro Fujishiro[1] and Kazuhiko Koike[1,2], (1)The University of Tokyo, (2) Kanto Central Hospital of the Mutual Aid Association of Public School Teachers, Tokyo, Japan

Background: The preventive effect of nucleos(t)ide analog (NA) use on HCC development in patients with chronic hepatitis B (CHB) is controversial due to the difficulty of conducting randomized controlled trials. **Methods:** In this single-center, retrospective study, NA-

naïve CHB patients without a history of HCC were enrolled and followed-up from the first visit on or after January 2000 to December 2020. Patients were categorized into the NA group, including those who started NA after study enrollment, and the non-NA group, including patients to whom NA was never administered during the follow-up period. After propensity score matching (PSM) to balance the confounding factors, we applied a multivariable time-dependent Cox proportional regression analysis with the initiation of NA as a time-dependent covariate. We also performed 1-year and 2-year landmark analyses in the PSM cohort to mitigate the immortal time bias, where patients were stratified according to NA use prior to the corresponding time points. We further performed a subgroup analysis according to the presence or absence of cirrhosis. **Results:** The baseline characteristics of 212 pairs of patients retrieved by PSM were comparable. During the mean follow-up of 12.9 and 6.8 years in the NA and non-NA groups, respectively, 25 and 28 patients developed HCC, respectively. Multivariable analysis with time-dependent covariates showed that NA did not affect HCC risk (HR, 0.68; 95% CI, 0.36–1.31; $p = 0.25$) after adjusting for other risk factors, including age, sex, and HBV viral load. The HRs for NA at the 1- and 2-year landmarks were 0.47 (95% CI, 0.17-1.34, $p = 0.16$) and 0.43 (95% CI, 0.16-1.11, $p = 0.08$), respectively, and NA use did not significantly reduce HCC risk. Subgroup analysis showed that NA use significantly reduced the risk of HCC in cirrhotic patients (HR, 0.26; 95% CI, 0.08–0.85; $p = 0.03$). **Conclusion:** The preventive effect of NA on hepatocarcinogenesis may be limited to cirrhotic patients.

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4077-A | IMPACT OF SELF-REPORTED ANCESTRY IN HEPATOCELLULAR CARCINOMA IN HISPANIC POPULATIONS

Spencer Goble, Hennepin Healthcare, Cindy Narvaez-Barbecho, University of Minnesota, Minneapolis, Minnesota, Manaswita Tappata, University of Minnesota, Minneapolis, Minnesota, Minneapolis, MN, Jhon Edison Prieto Ortiz, Cehyd (Centro de Enfermedades Hepáticas y Digestivas), Domingo Balderramo, Hospital Privado Universitario De Córdoba, Córdoba, Argentina., Enrique Carrera Estupiñan, Departamento De Gastroenterologia y Hepatologia, Hospital Eugenio Espejo, Quito, Ecuador, Javier Diaz Ferrer, Universidad San Martin De Porres, Lima, Peru, Marco Arrese, Departamento De Gastroenterología, Facultad De Medicina, Pontificia Universidad Católica De Chile, Andre Boonstra, Erasmus University Medical Center, Rotterdam, Netherlands and Jose D. Debes, University of Minnesota

Background: Hepatocellular carcinoma (HCC) related to non-alcoholic fatty liver disease (NAFLD) is a growing health concern worldwide and particularly in areas of high NAFLD endemicity such as Latin America. This region has a mixed population with a diverse heritage that is rarely accounted for when looking at epidemiological studies. We assessed the differences in the epidemiology and outcomes of HCC in Latin Americans based on self-reported ancestry. **Methods:** We retrospectively evaluated data from the ESCALON network, which prospectively follows patients at risk of and with HCC in six countries in South America. Self-reported ancestry data was categorized as European, Amerindian, African, Asian, Indigenous, or other. For this study we divided ancestry in two categories: European and non-European. Individual's in each category were evaluated using comparative statistics for demographics, underlying liver disease, tumor characteristics and treatment. IRB approval was obtained from all participating institutions. **Results:** A total of 429 individual's with HCC from 6 countries in Latin America were studied, Argentina (34% n = 145), Chile (15% n = 66), Ecuador (15% n = 63), Peru (15% n = 66), Colombia (14% n = 60), and Brazil (7% n = 29). The median age was 68 years and 65% were male. 131 patients (30.5%) reported a European ancestry and 298 (69.5%) non-European ancestry. In those of European ancestry median age was 66 years and 72% were male. In the non-European ancestry cohort median age was 67 years and 62% were male. The most common causes of underlying liver disease were hepatitis C virus (38%) followed by alcohol use disorder (25%) in European ancestry and NAFLD (52%) followed by alcohol use disorder in non-European ancestry (23%). Both groups, European and non-European ancestry, had similar proportion of HCC diagnosed under surveillance (40% and 41% respectively) and similar presence of extrahepatic disease (47% and 50% respectively). 26% of those with European ancestry received curative therapy compared to 33% of those with non-European ancestry. **Conclusion:** This is the first study addressing ancestry in Latin Americans with HCC. We found that HCC related to NAFLD was more common in patients of non-European descent. Future studies are warranted to better understand the impact of genetics within specific regions of the continent to understand risk of HCC.

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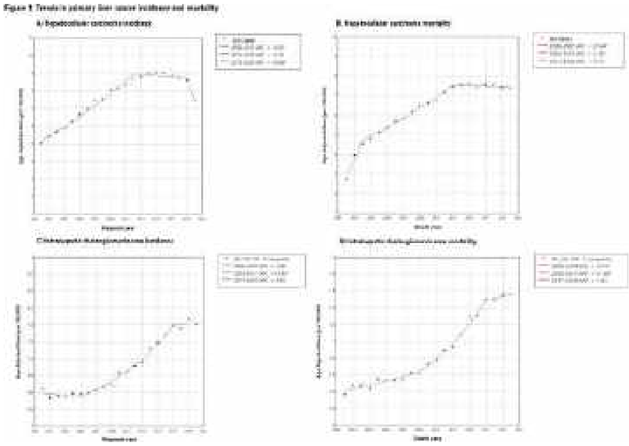
Disclosure information not available at the time of publication: Cindy Narvaez-Barbecho, Jhon Edison Prieto Ortiz, Domingo Balderramo, Javier Diaz Ferrer, Marco Arrese, Andre Boonstra

4078-A | IMPACT OF THE EARLY COVID-19 PANDEMIC ON INCIDENCE AND MORTALITY RATES OF HEPATOCELLULAR CARCINOMA AND CHOLANGIOCARCINOMA IN THE UNITED STATES

Jeff Liang[1], Yee Hui Yeo[2], Srinivas Gaddam[1], Walid S. Ayoub[1], Alexander Kuo[1], Hirsh Trivedi[1], Kamya Sankar[1], Jun Gong[1], Andrew Hendifar[1], Arsen Osipov[1], Kambiz Kosari[1], Nicholas Nissen[1], Nicole E. Rich[3], Amit G. Singal[3] and Ju Dong Yang[1], (1)Cedars-Sinai Medical Center, Los Angeles, CA, (2)Cedars-Sinai Medical Center, Culver City, CA, (3)University of Texas Southwestern Medical Center

Background: Hepatocellular carcinoma (HCC), the most common form of liver cancer, is a leading cause of cancer-related mortality in the United States; intrahepatic cholangiocarcinoma (iCCA) is the second most common form of primary liver cancer with rising incidence rates. Routine cancer surveillance in high-risk patients is recommended in HCC, but not for iCCA; however, the recent Coronavirus Disease 2019 (COVID-19) pandemic and associated quarantine policies may have limited patients' access to healthcare resources and screening tools. We aim to determine the impact of the pandemic on the incidence and mortality rate of HCC and iCCA in the U.S. **Methods:** We performed a retrospective study of the Surveillance, Epidemiology and End Results (SEER) Research Plus database, a population-representative sample obtained from 22 cancer registries covering approximately 48% of the U.S. Cases of HCC and iCCA diagnosed between 2000-2020 were identified using ICD-O-3 codes. Incidence and mortality rates per 100,000 individual's (age-adjusted to the 2000 US population) were calculated. Pearson's Chi-square test was used to compare HCC incidence stratified by sex and race. Overall incidence and mortality trends were calculated using the Joinpoint regression software. **Results:** The adjusted incidence rate of HCC in the first year of the pandemic was significantly reduced from the prior year (7.46 in 2020 vs 8.62 in 2019 per 100,000 person-years). There were no changes in sex or racial/ethnic disparities in HCC incidence in 2020 compared to the prior year ($p = 0.50$ and 0.48, respectively). In contrast, there was no significant difference in iCCA incidence rates in 2020 compared to the prior year (1.91 vs 1.81, respectively). Trend analysis of HCC incidence revealed a steep drop from 2019-2020 compared to the prior years (APC -15.1% vs -0.33%, respectively; $p < 0.001$), a pattern which was present when stratified by sex (2019-2020 APC -15.4% and -12.8% in males and females, respectively). In contrast, incidence rates of iCCA have been stable to slightly increasing since 2017 and did not change significantly in 2020. There was no significant difference in HCC or iCCA mortality in 2020 compared to prior years. **Conclusion:** There was a clinically significant reduction in HCC incidence in 2020 compared to prior years, although a significant change in mortality has not been observed. In contrast, no significant change in incidence was seen in iCCA, suggesting that the reduction in HCC diagnosis may be related to limited access to surveillance during the pandemic. Further studies examining the impact of COVID-19 on access to HCC surveillance, incidence and mortality trends are needed.



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4079-A | INCIDENCE AND CHARACTERISTICS OF NON-MALIGNANT LIVER LESIONS DETECTED THROUGH ULTRASOUND BASED HEPATOCELLULAR CARCINOMA SURVEILLANCE

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Background: Ultrasound based hepatocellular carcinoma (HCC) surveillance reduces HCC related mortality in high-risk patients but may result in increased detection of non-malignant liver lesions (NMLL). This in turn leads to an increased utility of CT, MRI, or invasive procedures and may result in surveillance related harm. In this study, we report the incidence and characteristics of NMLL in a cohort of HCC surveillance patients in Melbourne, Australia. **Methods:** We analysed all patients who received an ultrasound for HCC surveillance at a tertiary hospital network in the first six months of 2017. Patients with prior HCC were excluded. Outcomes were followed until 2021 through review of the hospital electronic record. Primary outcomes were the incidence and characteristics of NMLL and frequency of downstream investigations, stratified by cirrhosis status. The secondary outcome was the incidence of new HCC diagnoses. Subgroup analysis was performed for patients who received surveillance outside Australian and US criteria. **Results:** 553 patients were included (mean age 54.5 ± 12.3 y, males 67.5%). Cirrhosis was present in 50.3%, of whom 87.8% were Child-Pugh A. Viral hepatitis was the underlying aetiology in 80.8%. Over a median follow-up of 4.7 years (IQR 4.6-4.8 y), NMLL were detected in 90 patients (16.3%), with no difference between cirrhotic and non-cirrhotic patients (17.6% versus 14.9%, $p = 0.45$). 71.1% of patients with NMLL proceeded to further investigations, which included CT (52.2%), MRI (40%), biopsy (1.1%) and surgical resection (1.1%). When evaluated with CT or MRI, 30% of NMLL were unable to be identified, 17.2% were probable haemangiomas, 15.6% were probable cysts and 10.9% were probable dysplastic nodules. Overall, 24 cases of HCC (4.3%) were diagnosed and occurred more frequently in cirrhotic patients (7.6% versus 1.1%, $p < 0.01$). 75% of HCC cases were Barcelona Clinic Liver Cancer Stage 0 or A at diagnosis. In the subgroup who underwent surveillance outside criteria ($n = 87$), no patient was diagnosed with HCC, but 14.9% were diagnosed with NMLL. 69.2% of patients with NMLL in this subgroup then underwent further investigation with CT, MRI or surgical resection. **Conclusion:** In a real-world cohort followed up for a median of 4.7 years, HCC surveillance resulted in the detection of NMLL in 16.3% and HCC in 4.3%. The yield of surveillance was significantly lower in non-cirrhotic patients with a similar incidence of NMLL but significantly fewer HCCs identified. Patients who underwent surveillance outside clinical guidelines derived no benefit from surveillance but were exposed to potential harm. Our study highlights the limitations of HCC surveillance in certain subgroups such as non-cirrhotic patients, as well as the need to investigate and develop tailored HCC surveillance programs.

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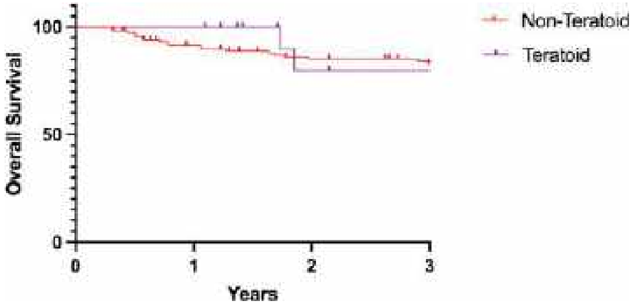
4080-A | INCREASED INCIDENCE OF METASTATIC DISEASE IN TERATOID HEPATOBLASTOMA

Andres F. Espinoza[1], Ann Wang[1], Pavel Sumazin[2], Stephen F. Sarabia[2], Martin Urbicain[2], Andras Heczey[3], Prakash Masand[1], Sarah E. Woodfield[3], Sanjeev Vasudevan[1], Dolores Lopez-Terrada[2] and Kalyani Patel[1], (1)Baylor College of Medicine, (2)Baylor College of Medicine, Texas Children's Hospital, Houston, TX, (3) Texas Children's Hospital

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



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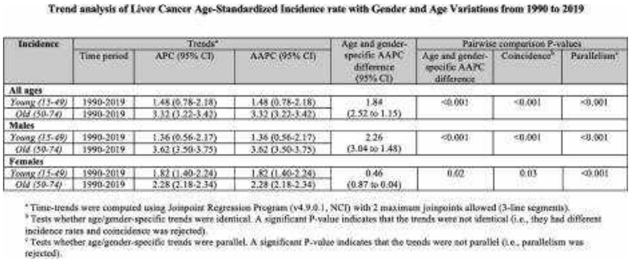
4081-A | INCREASING INCIDENCE OF LIVER CANCER IN OLD MEN: A POPULATION-BASED TIME-TREND ANALYSIS USING THE GLOBAL BURDEN OF DISEASES DATABASE, 1990-2019

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

Background: Liver cancer is a leading cause of mortality in the US. Previous data showed an increasing incidence of liver cancer with greater rates in older adults. However, there are limited data on recent age and sex-specific incidence rates. The aim of this study was to conduct a time-trend analysis of liver cancer incidence rates using the Global Burden of Diseases (GBD) 2019 study database.

Methods: Data was obtained from the GBD 2019 database, an International database that covers 100% of liver cancer diagnosed cases in the US. Liver cancer incidence rates, age-adjusted to the standard US population, were calculated using SEER*Stat software (v.8.4.0.1, National Cancer Institute "NCI") and were stratified by gender, as reported in the database. Time-trends were estimated as annual percentage change (APC) and average APC (AAPC) using Joinpoint Regression Software (v.4.9.0.1, NCI) utilizing Monte Carlo permutation analysis to generate the simplest trend. Pairwise comparison was conducted between gender-specific trends using the tests of parallelism and coincidence. Age-specific trends were also assessed in two age sub-groups: younger adults aged 15-49 years and older adults aged 50-74 years. A two-sided P-value cut-off of 0.05 was utilized for statistical significance. **Results:** 483,002 patients were diagnosed with liver cancer in the US between 1990-2019. Overall, Liver cancer incidence rates have been significantly increasing in older adults but not in younger adults ($AAPC = 3.32$ vs 1.48; AAPC $difference = 1.84$, $P < 0.001$). Age-specific trends were not identical ($P < 0.001$) nor parallel ($P < 0.001$) suggesting that liver cancer incidence rates are different and increasing at a greater rate in older adults compared to younger adults. Similar results were seen in women (150,481 patients) with an absolute AAPC difference between older and younger adults of 0.46 ($P = 0.02$). However, in men (332,521 patients), while similar results were seen, a greater AAPC difference between younger and older men of 2.26 (< 0.001) was noted suggesting that the greatest disparity between liver cancer incidence trends between age-specific groups arises from men. **Conclusion:** Our results suggest that liver cancer incidence trends have been increasing in older adults while stable in younger adults over the last three decades. The greatest difference between older and younger adults seemed to be arising from older men. While this increase can be due to increase in morbidities commonly associated with aging like alcoholic liver disease and non-alcoholic fatty liver disease, it can also represent a true increase in incidence. Future studies are warranted to investigate risk factors associated with the increasing incidence in older adults, especially older men.



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

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

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

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

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

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

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

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Background: Primary hepatic angiosarcoma (PHA) is a rare vascular malignancy of endothelial origin that accounts for only 2% of all hepatic primary tumors. It carries a poor prognosis given its highly malignant and rapidly progressive disease course. Its rarity has led to obscurity with its diverse clinical features making it an easily missed diagnosis for physicians. The diagnosis is confirmed via histopathology and a substantial percentage only by autopsy. We present a systematic review identifying patient cases of PHA to summarize and highlight new and existing literature to provide clarity of the challenges faced in the diagnosis and treatment of PHA. **Methods:** We performed a systematic literature search using predefined keywords within 3 databases (PubMed, EMBASE, and MEDLINE) to identify case reports and case series of PHA within the past ten years. A set exclusion criteria was applied. All remaining articles were assessed for selection and subsequent data extraction. We analyzed pooled individual clinical data regarding demographics, symptoms, treatments, and prognosis. **Results:** A total of 65 patients from 59 case reports/case series were included in our study. 58.5% of all patients were male and the median age of onset was 64.5 years. The most common presenting symptom was right upper quadrant pain (50.8%), followed by abdominal distention (20%), weight loss (17%), and jaundice (17%). About 10.8% of all patients initially presented with a gastrointestinal bleed. Nearly half of all patients were initially misdiagnosed with either a benign tumor or with a malignancy other than angiosarcoma. Due to the rapidly progressive nature of the malignancy, 41.5% of patients were treated with only palliative or supportive care. Chemotherapy or targeted therapy was administered to 25% of patients and 21.5% were treated surgically. The median overall survival time was 4.5 months with a 1-year survival rate of 20%. **Conclusion:** PHA is a deadly disease with a grim prognosis. Although resection, targeted immunotherapy, and chemotherapy are commonly offered as initial treatments, in many cases rapid progression of the disease allows only for palliative treatment options. The high percentage of misdiagnosis in PHA patients likely contributes to the high rate of advanced disease progression and treatment failure. A study with a larger sample would be required to draw even more definitive patterns and algorithms to help successfully diagnose PHA.

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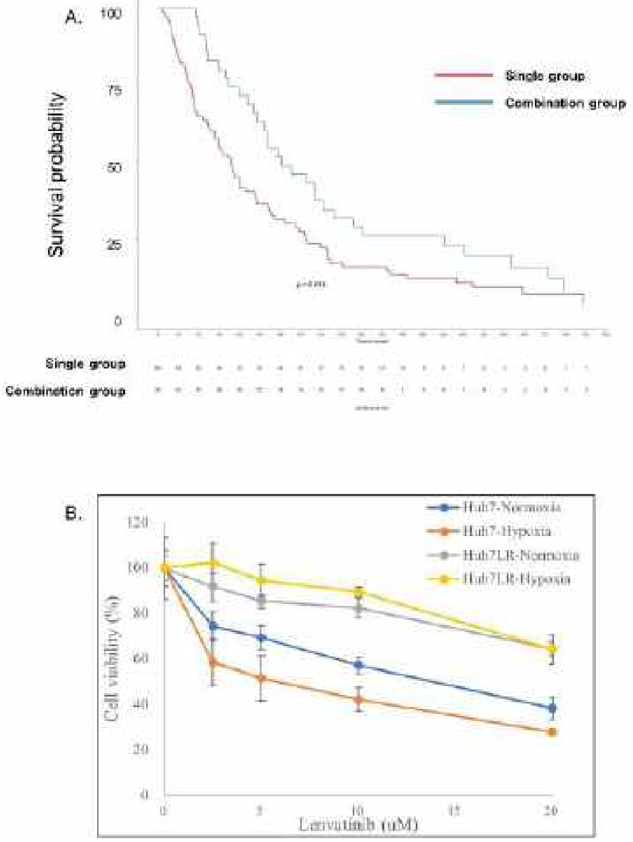
4084-A | LENVATINIB-TRANSARTERIAL CHEMOEMBOLIZATION COMBINATION TREATMENT PROLONGS SURVIVAL COMPARED TO LENVATINIB SINGLE TREATMENT IN ADVANCED HCC PATIENTS WITH INTRAHEPATIC LESIONS

Sung Won Chung, Asan Medical Center, Seoul, Korea, Republic of (South), Won-Mook Choi, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South) and Kang Mo Kim, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: To prolong survival in patients with hepatocellular carcinoma (HCC), intrahepatic tumor control is important and to achieve this goal, attempts to combine systemic treatment with transarterial chemoembolization (TACE) has been investigated ever since. This study aimed to establish clinical efficacy of lenvatinib-TACE combination treatment. **Methods:** From 2018 to 2021, patients from a single tertiary center who were diagnosed with intrahepatic HCC lesion and received Lenvatinib as first-line systemic therapy were selected. Patients were divided into those who received TACE in conjunction with lenvatinib (combination group) and those who received lenvatinib alone (single group). The primary outcome was overall survival, while progression free survival (PFS) is a secondary outcome. Propensity score matching was applied to balance two groups. To evaluate underlying mechanism, Huh-7 cell lines were treated with lenvatinib or a placebo for 48 hours under either normoxia or hypoxia. We performed immunoblots, co-immunoprecipitation, quantitative polymerase chain reaction, and cell viability assays. **Results:** After balancing with propensity score matching (all standardized mean difference < 0.1), the combination group ($n = 35$) was associated with a lower risk of death (adjusted hazard ratio [aHR] $= 0.53$, 95% confidence interval [CI] $= 0.34$–0.81, $p = 0.004$) and longer PFS (aHR $= 0.50$, 95% CI $= 0.32$–0.80, $p = 0.004$) than the single group ($n = 80$). Under hypoxic conditions, lenvatinib suppressed hypoxia inducible factor 1 alpha (HIF-1α) protein expression in Huh-7 cell lines without affecting mRNA levels. Cell viability assays confirmed a reduction in the viability of Huh-7 cells when lenvatinib was administered under hypoxic conditions. **Conclusion:** Lenvatinib and TACE combination increases overall survival and prolongs progression. Potential mechanism seems to be related to lenvatinib lowers HIF-1α expression in hypoxic HCC cells via degrading HIF-1α proteins via increasing the ubiquitination pathway. In patients with uncontrolled intrahepatic lesion, lenvatinib-TACE combination needs to be considered.



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4085-A | LIVER FUNCTION IS A PREDICTOR OF SURVIVAL IN PATIENTS WITH HEPATOCELLULAR CARCINOMA IN BEST SUPPORTIVE CARE

Claudia Campani[1], Laura Bucci[2], Valentina Adotti[3], Martina Rosi[3], Franco Trevisani[2], Fabio Marra[3] and Ita.Li.Ca., (1)University of Florence, Italy, (2)University of Bologna, (3)University of Florence

Background: The prognosis of patients with hepatocellular carcinoma (HCC) is very variable, and the relative contribution of tumor burden and liver dysfunction to survival is uncertain. Median overall survival (OS) of patients managed with best supportive care is around 3-6 months, although longer values may be observed in clinical practice. Aim of this study was to identify the factors linked to tumor or liver dysfunction associated with survival in patients with HCC treated with BSC. **Methods:** We retrospectively evaluated the clinical characteristics of 1414 patients who had an indication for BSC recorded in the Ita.Li.Ca. database between 2000 and 2020. We analyzed both patient and tumor characteristics to identify predictors of OS. **Results:** Median age was 69y and 76% of patients were male. Etiology included chronic viral infection (68.3%), alcohol use disorder (30.9%) and non-alcoholic steatohepatitis (8.3%). 67.4% of patients had a performance status 0-1 and 41.4% were in Child-Pugh B class. Median MELD was 13. 60% of patients had a multifocal HCC with a median number of 3 lesions and a median size of 33mm. 533 patients had vascular invasion. Median alpha-fetoprotein was 49.25 ng/ml. 111 patients were classified as BCLC-A, 148 as BCLC-B, 791 as BCLC-C and 325 as BCLC-D (12 unknown). No differences in terms of OS were observed considering the etiology of liver disease or the presence of cirrhosis. Obesity ($p < 0.001$), hypercholesterolemia ($p = 0.036$) and hypertriglyceridemia ($p = 0.034$) were associated with lower OS. Absence of symptoms (6 vs 10 months, $p < 0.001$), lack of vascular invasion (9.1 vs 5.03, $p < 0.001$), and absence of metastasis (8.167 vs 4.733 $p < 0.001$) were associated with a better OS. Survival in BCLC-A patients was longer than in stages B or C. Survival progressively declined according to severity of liver function using three different scores (CPS, ALBI, pALBI, $p < 001$). Women tended to survive longer 23 vs. 19 months, $p = 0.053$). Comparing patients surviving more or less than 12 months (398 vs. 1016), age, size of lesions, albumin, bilirubin, alpha-fetoprotein, and MELD were significantly different. At Cox univariate analysis presence of cirrhosis, number and size of lesions, vascular invasion, metastasis, ALBI and pALBI grades, MELD, and CPS were significantly associated with OS. Using different models to avoid colinearity ALBI, pALBI, and CPS maintained an independent prognostic role on OS. **Conclusion:** In a large series of patients with HCC in BSC, parameters of liver function are strongly associated with survival.

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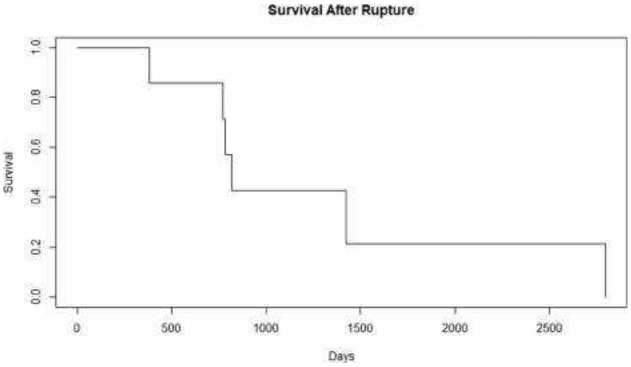
4086-A | LONG-TERM OUTCOMES OF RUPTURED HEPATOCELLULAR CARCINOMA

Kevin B. Harris, Faisal M. Nimri and Reena J. Salgia, Henry Ford Health

Background: It is estimated that spontaneous rupture of hepatocellular carcinoma (HCC) occurs in 2-5% of patients with HCC. Long-term outcomes in patients with ruptured HCC are not well described. Ruptured HCC requires a stepwise approach with control of bleeding followed by treatment for HCC. The spectrum of treatment options has expanded over the years for HCC. This study describes a single-center tertiary referral center experience with treating patients longitudinally with ruptured HCC. **Methods:** Between 2014 to 2022, our center experienced 7 cases of initial HCC presentation with a spontaneously ruptured hepatocellular carcinoma. **Results:** The average age of patients with ruptured HCC was 60 years old. Six of the patients (85.7%) were male and one patient (14.1%) was female. Six of the seven patients had underlying cirrhosis with 50% due to HCV, 33% due to alcohol and 16% due to a combination of HCV and alcohol. Three (42.9%) of the patients had Barcelona Clinic Liver Cancer (BCLC) stage B disease at presentation and four (57.1%) of the patients had BCLC stage C disease. None of the patients who presented with ruptured HCC were in an HCC screening protocol. Five (71.4%) of the patients had solitary hepatomas while two (28.6%) of the patients had multiple hepatomas at diagnosis. Both patients with multiple hepatomas had bilobar involvement. The median AFP level at presentation was 23.6 ng/mL (range 5.2 ng/mL to > 30000 ng/mL). Two (28.6%) of the patients at presentation were on aspirin and one (14.1%) was on a direct-acting oral anticoagulant (DOAC). Five of our patients were initially treated with bland embolization and two were initially treated with TACE. The patients received various subsequent treatments including bland embolization, TACE, TARE, SBRT and systemic therapies. None of our patients received surgical management or liver transplantation. The median overall survival from date of rupture was 817 days (range 381 d to 2796 d). **Conclusion:** Our series highlights the wide spectrum of outcomes for patients with ruptured HCC. With improved treatment options, patient survival has increased. In this study, all patients survived at least one year and the longest survival was over 7 years. Noting the improved consideration by UNOS to patients with distant HCC rupture being considered for liver transplantation, continued attention to this group of patients can improve their outcomes.



Disclosures: The following people have nothing to disclose: Kevin B. Harris, Reena J. Salgia
Disclosure information not available at the time of publication: Faisal M. Nimri

4087-A | MONOCYTE TO HIGH-DENSITY LIPOPROTEIN CHOLESTEROL RATIO (MHR) AND ALBI GRADE FOR THE SURVIVAL PREDICTION OF PATIENTS WITH METABOLIC ASSOCIATED FATTY LIVER DISEASE (MAFLD) RELATED HCC

Tongguo Miao[1], Xianzhe Lou[2], Shiming Dong[1], Xiaoxiao Zhang[1], Xiwei Yuan[1], Lu Li[1], Weiwei Guan[1] and Yuemin Nan[1], (1)Third Hospital of Hebei Medical University & Hebei Key Laboratory of Mechanism of Liver Fibrosis in Chronic Liver Disease, (2)North China University of Science and Technology

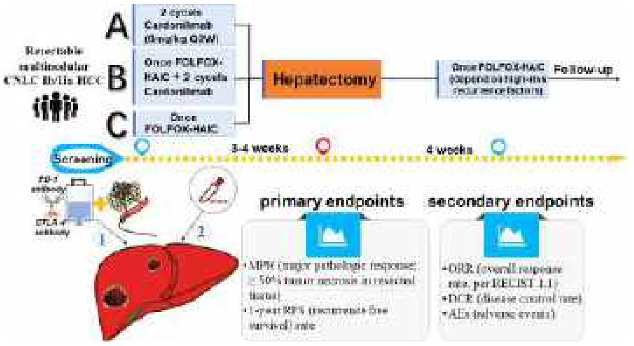
Background: Metabolic syndrome is considered as a risk factor for Hepatocellular carcinoma (HCC). Metabolic-associated fatty liver disease (MAFLD) is proposed as a new terminology to replace NAFLD. There has been a dramatic increase in the number of patients associated with metabolic syndrome or metabolic dysfunction related HCC. Monocyte to high-density lipoprotein cholesterol (HDL-C) ratio (MHR) is a new prognostic measure associated with the body inflammatory and oxidative stress status. The ALBI grade offers a simple and reliable method of assessing liver function in HCC. Our hypothesis is that incorporating MHR and ALBI grade into one survival prediction model improves the survival prediction for patients with Metabolic Associated Fatty Liver Disease related HCC(MAFLD-HCC). **Methods:** This single center retrospective cross-sectional study primary cohort included 112 patients with MAFLD-HCC, and the internal validation cohort enrolled 37 patients with MAFLD-HCC. A multivariate Cox proportional hazard regression analysis was performed to identify the independent risk factors of survive, based on which the prediction nomogram models were constructed and validated. The concordance (C)-index, receiver operating characteristic (ROC) curve, and decision curve analysis (DCA) were used to assess the prognostic discriminative ability of the nomogram, ALBI grade, MHR, and MHR + ALBI grade. The overall survival (OS) curve of risk group stratification was calculated based on the nomogram risk score. **Results:** Multivariate analyses revealed that Extrahepatic metastases [hazard ratio with 95% confidence interval (CI) = 2.014(1.077-3.766), P = 0.028], Vascular invasion [2.075(1.068–4.03), P = 0.031], Barcelona staging B[2.369(1.091-5.144), P = 0.029], C[4.449(1.957-10.114), P < 0.001], D[26.473 (7.978-87.843), P < 0.001], elevated ALBI Class 3[11.687 (1.625-84.029), P = 0.015] , C-reactive protein (CRP) [1.018(1.006-1.03), P = 0.003], lactate dehydrogenase (LDH) [0.998(0.997-1.004), P = 0.003], and MHR[1.491 (1.24-1.791), P < 0.001] were independent risk factors for prognosis of MAFLD-HCC. BCLC stage, vascular invasion, extrahepatic metastases, LDH, CRP and MHR were selected to develop the nomogram. The C-index and calibration plots of the nomogram showed good discrimination and consistency for MAFLD-HCC. Additionally, compared with the other models, MHR + ALBI grade model [AUC = 0.885, 95%CI, (0.806-0.964)] showed better survival prediction ability in MAFLD-HCC. **Conclusion:** The novel survival prediction model showed better predicational outcomes of OS in patients with MAFLD-HCC. This model provides a personalized and convenient prognostic prediction tool for clinical applications.

Disclosures: Yuemin Nan – BMS, Gilead, and GSK: Speaking and Teaching, Yes, No;
The following people have nothing to disclose: Tongguo Miao, Xianzhe Lou, Shiming Dong, Xiaoxiao Zhang, Xiwei Yuan, Lu Li, Weiwei Guan

4088-A | NEOADJUVANT CADONILIMAB (PD-1/CTLA-4 BISPECIFIC ANTIBODY) PLUS TRANSHEPATIC ARTERIAL INFUSION CHEMOTHERAPY (HAIC) WITH FOLFOX FOR RESECTABLE MULTINODULAR CNLC Ib/IIa HEPATOCELLULAR CARCINOMA

Yonguang Wei, Zhiming Zeng, Guangzhi Zhu, Zili Lv and Tao Peng, The First Affiliated Hospital of Guangxi Medical University

Background: The recurrence rate of hepatocellular carcinoma (HCC) is high after surgery. However, there are no approved standard-of-care neoadjuvant or adjuvant therapies. Multinodular HCC is a well-defined high-risk recurrence factor. Cadonilimab is a first-in-class bispecific, humanized IgG1 antibody (PD-1/CTLA-4). HAIC plus immunotherapy has synergistic antitumor effect. This trial is to evaluate the safety and efficacy of cadonilimab plus FOLFOX-HAIC as a neoadjuvant management for the resectable multinodular CNLC Ib/**a**a HCC. **Methods:** In this ongoing single-center, phase 2, open label, prospective cohort clinical trial (ChiCTR2200067161), eligible patients (pts) with resectable multinodular CNLC Ib/**a**a HCC were randomly assigned (1:1:1) to 3 arms and receive corresponding preoperative neoadjuvant therapy: (A) 2 cycles of cadonilimab (6mg/kg Q2W); (B) once FOLFOX-HAIC followed by 2 cycles of cadonilimab; (C) once FOLFOX-HAIC. All pts receive scheduled surgery on day 21-28 and postoperative adjuvant HAIC. The primary endpoints were major pathologic response (MPR rate defined as ≥50% tumor necrosis and 1-year recurrence free survival (RFS) rate. Main secondary endpoints included overall response rate (ORR, per RECIST 1.1), disease control rate (DCR), treatment-related adverse events (TRAEs). **Results:** From January 4 to May 23, 2023, 12 pts were enrolled. All pts were ECOG PS 0-1 and Child-Pugh A. Nine pts received scheming hepatectomy (4 pts in Arm A, 3 pts in Arm B, 2 pt in Arm C). Among them, all pts in Arm B achieved MPR, which all demonstrated focal heterogeneity with one lesion pathologic complete response and another partial response—0%, 10% and 70% respectively. No obvious tumor necrosis in Arm A and C, but the inflammatory infiltrating and fibrosis area in tumor accounted for 20-30% approximately. Based on RECIST 1.1 criterion, one (1/3) pts in Arm B achieved PR and other pts (9/10) met SD. DCR was 100%. The most common TEAEs in Arm B and C were ALT, AST and bilirubin increase (60.0%), which mainly resulted from HAIC. TEAEs occurred in Arm A were grade 1 bilirubin increase and triiodothyronine decrease (25%). No grade 3 or worse TEAEs occurred and no pts delayed surgery. The postoperative complications related to neoadjuvant therapy were not observed. **Conclusion:** This study preliminarily demonstrated that neoadjuvant cadonilimab plus FOLFOX-HAIC show promising antitumor activity with manageable safety for HCC. This trail is ongoing.


Resectable multinodular CNLC IIb/IIa HCC
A
2 cycles Cardonilimab (6mg/kg Q2W)
B
Once FOLFOX-HAIC + 2 cycles Cardonilimab
C
Once FOLFOX-HAIC
Hepatectomy
Once FOLFOX-HAIC (Depend on high-risk recurrence factors)
Follow-up
Screening
3-4 weeks
4 weeks
PD-1 antibody
CTLA-4 antibody
1
2
primary endpoints
secondary endpoints
•MPR (major pathologic response: ≥50% tumor necrosis in resected tissue)
•1-year RFS (recurrence-free survival) rate
•ORR (overall response rate, per RECIST 1.1)
•DCR (disease control rate)
•AEs (adverse events)

Disclosures: The following people have nothing to disclose: Yonguang Wei, Zhiming Zeng, Guangzhi Zhu, Zili Lv, Tao Peng

4089-A | NIVOLUMAB AS SECOND LINE THERAPY IMPROVES SURVIVAL IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA

Faisal M Sanai[1], Hassan Odah[1], Kanan Alshammari[2], Adnan Alzanbaqi[3], Morooj Alsubhi[1], Hani Tamim[4], Ashwaq Alolayan[2], Ahmed Alshehri[1] and Saleh A Alqahtani[5,6], (1)King Abdulaziz Medical City-Jeddah, (2) King Abdulaziz Medical City, King Abdullah International Medical Research Center, Ministry of National Guard Health Affairs, (3)King Abdallah Medical City-Makkah, (4)Alfaisal University, (5)Johns Hopkins University School of Medicine, (6)King Faisal Specialist Hospital and Research Center

Background: Limited data exists for nivolumab as a second-line treatment for hepatocellular carcinoma (HCC). We aimed to assess the efficacy and safety of nivolumab in patients with unresectable HCC who progressed during sorafenib treatment in a real-life cohort. **Methods:** In this retrospective, observational, multicenter study, adult Child-Pugh A/7B patients with HCC who tolerated sorafenib therapy but progressed were started on nivolumab (n = 38). A similar number of consecutive, unselected patients who were maintained on sorafenib therapy, regardless of tumoral response or progression, were used as historical controls (n = 42). Patients were assessed in terms of Eastern Cooperative Oncology Group (ECOG) performance status, macrovascular invasion, and extrahepatic disease to best supportive care plus oral sorafenib or intravenous nivolumab as second-line therapy. The primary endpoint was overall survival (defined as time from starting sorafenib in either group, up to death due to any cause) and analyzed by intention-to-treat. **Results:** The mean age of the overall cohort was 72.4 ± 10.1 years, of whom 87.5% were males, and 58.8% had underlying viral etiology. Patients in the two cohorts were similar except that those who received nivolumab as 2nd line therapy compared to sorafenib alone had more co-morbidities (70.0 vs 15.4%), more ECOG-2 status (21.4 vs 15.8%), and extravascular invasion (54.4 vs 21.8 %) ($P < 0.05$ for all). More patients in the nivolumab arm were Child-Pugh B (35.7 vs 21.1%), although this did not reach statistical significance ($P = 0.15$). Median survival was significantly higher in patients who received nivolumab compared to sorafenib alone (22.0 vs 11.0 mo, $P = 0.014$, Figure 1). Median survival after starting nivolumab as 2nd line therapy was 9.2 months,

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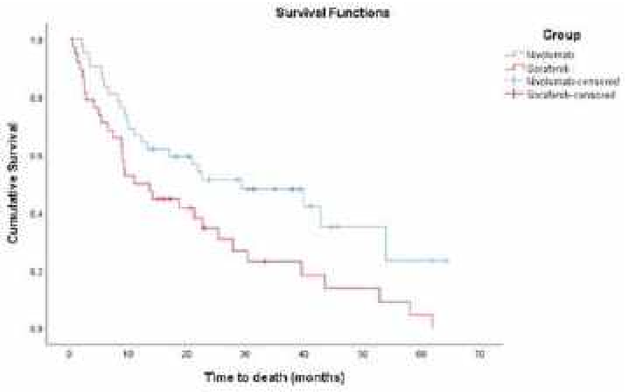
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

and time-to-tumor progression was 4.92 (IQR 3.2 – 6.3) months. **Conclusion:** Nivolumab is an effective second-line treatment option in unresectable HCC patients who progress on sorafenib, with significantly improved overall survival. These early real-life data offer encouraging results, and are similar to those shown in Phase 1/2a clinical trials, and data from larger, phase 3 clinical trials are awaited.



Disclosures: The following people have nothing to disclose: Faisal M Sanai, Hassan Odah, Kanan Alshammari, Adnan Alzanbaqi, Morooj Alsubhi, Hani Tamim, Ashwaq Alolayan, Ahmed Alshehri, Saleh A Alqahtani

4090-A | NOVEL APPROACHES FOR COMMUNITY RECRUITMENT FOR CHOLANGIOCARCINOMA GENETICS STUDY

Nellie A. Campbell[1], Karimatu Jalloh[1], Mikayla A. Schmidt[1], Matthew A. Cooley[1], Caitlin Van Lith[1], Fowsiyo Ahmed[2], Linsey E. Jackson[1], Wadid M. Sirry[1], Abdirahim A. Haji[1], Jyotroop Kaur[1], Mohamad Elgozair[1], Daniella F. Vasquez[3], Melinda Bachini[4], Lourdes Rocha-Nussbaum[4], Emma Mach[4], Stacie Lindsey[4], Younghun Han[5], Chris I. Amos[5], Manal M. Hassan[6], Katherine A. McGlynn[7] and Lewis R. Roberts[8], (1)Mayo Clinic, Rochester, Rochester, MN, (2)Mayo Clinic Rochester, Rochester, MN, (3)Mayo Clinic, Rochester, Minneapolis, MN, (4) Cholangiocarcinoma Foundation, (5)Baylor College of Medicine, (6)The University of Texas MD Anderson Cancer Center, (7)National Cancer Institute, (8)Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, MN

Background: Cholangiocarcinoma (CCA), is a highly lethal cancer that is often diagnosed at an advanced stage and consequently has a poor prognosis. The 5-year survival rate of CCA ranges from 7% to 20% and has not changed much in the past 3 decades. Although the disease is relatively uncommon, rates in the United States and internationally are rising, highlighting the need for novel, more effective treatment options. To better understand the inherited risk for CCA we aim to conduct a genome-wide association study (GWAS) on CCA patients, their family members with or without CCA, and unaffected controls. The overall goal is to verify novel loci and genetic factors that influence susceptibility to CCA by genetically delineating etiologic heterogeneity, and clinical outcomes of CCA patients by using a high-density single nucleotide polymorphism (SNP) analysis of genomic DNA from CCA patients, and controls. In addition to recruiting patients and controls from collaborating institutions within the United States and internationally, we have explored the feasibility of recruiting study participants through the website of the major advocacy group the Cholangiocarcinoma Foundation (CCF) which has 60 thousand hits per month, or alternatively at the annual cholangiocarcinoma conference organized by the CCF, which is attended by a substantial number of patients, family members, and advocates. Here we compare our experience with recruitment through the website versus recruitment in person at the annual meeting. **Methods:** Demographic information and family history are obtained for both recruitment options alongside an electronically signed consent form which gives a more detailed explanation of the study. Persons recruited through the website must locate a local laboratory or hospital to obtain the blood draw and which is willing to ship the samples back to the Mayo Clinic for centralized storage, while for the recruitment at the annual conference, we were able to obtain the blood samples at the time of enrollment and ship them in bulk back to the Mayo Clinic. **Results:** From 2021 to date, our institution has interacted with 194 patients through the CCF website and 191 patients from the 2023 Annual CCF conference. Patients were from 9 countries, with the United States making up most of the participants. **Conclusion:** A pro for the website recruitment is the ability to reach a more diverse cohort of participants regardless of the demographic location while the onsite recruitment at the conference proved to more efficient at enrolling participants. Both approaches proved effective in generating interactions with patients.

Disclosures: The following people have nothing to disclose: Nellie A. Campbell, Caitlin Van Lith, Manal M. Hassan

Disclosure information not available at the time of publication: Karimatu Jalloh, Mikayla A. Schmidt, Matthew A. Cooley, Fowsiyo Ahmed, Linsey E. Jackson, Wadid M. Sirry, Abdirahim A. Haji, Jyotroop Kaur, Mohamad Elgozair, Daniella F. Vasquez, Melinda Bachini, Lourdes Rocha-Nussbaum, Emma Mach, Stacie Lindsey, Younghun Han, Chris I. Amos, Katherine A. McGlynn, Lewis R. Roberts

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

4091-A | NOVEL SERUM BIOMARKERS OF DRUG SELECTION FOR SORAFENIB AND LENVATINIB AND THEIR APPLICATION TO PREDICTING THE EFFICACY OF ATEZOLIZUMAB PLUS BEVACIZUMAB IN HEPATOCELLULAR CARCINOMA

Satoshi Narahara, Takayuki Tokunaga, Kentaro Tanaka, Hiroki Inada, Etsuko Iio, Yoko Yoshimaru, Takehisa Watanabe, Katsuya Nagaoka, Hiroko Setoyama and Yasuhito Tanaka, Faculty of Life Sciences, Kumamoto University

Background: Atezolizumab plus bevacizumab (Atezo+Bev), lenvatinib (LEN), and sorafenib (SFN) are frequently used for systemic chemotherapy for advanced hepatocellular carcinoma (HCC). Qualified drug selection strategies are required to improve survival. The purpose of this study is to identify useful serum biomarkers for drug selection before initiation of SFN and LEN therapy and to apply them to predict Atezo+Bev efficacy. **Methods:** 326 patients (pts) who received SFN, 151 pts who received LEN, and 87 pts who received Atezo+Bev from Jun 2008 to Mar 2023 have been enrolled in this study. Treatment response was evaluated by modified RECIST 3 months after starting SFN, 1 month after starting LEN, or 6 weeks after starting Atezo+Bev, pts with progressive disease were classified into Non-Responder (NR), and the others into Responder (R). Proteome analysis was employed using 5 serum samples of SFN group and 3 serum samples of LEN group from pts in the R and NR groups before treatment, followed by confirmation using ELISA with 20 samples of LEN and SFN group as a derivation cohort. Next, serum from before and 3 weeks after Atezo+Bev treatment (R: n = 18, NR: n = 10) was then used to measure the proteins from the aforementioned study. **Results:** From the ELISA results, cutoff values for angiogenesis-related protein (AGRP) in the LEN group and cell adhesion-related protein (CARP) in the SFN group were established using ROC analysis. Evaluation based on CARP and AGRP values in 40 patients with SFN or LEN showed significantly prolonged progression-free survival in the patients used appropriately (HR = 1.193, P = 0.044). Validation in another 40 cases showed a trend toward a difference in AGRP in the LEN group (P = 0.081). In Atezo+Bev, low AGRP1 at 3 weeks after treatment initiation contributed to OS prolongation (P = 0.015), the occurrence of irAE (P = 0.045) and Grade 3 or higher AEs such as proteinuria (P = 0.031) significantly contributed to response, and high Alb (P = 0.054) and low ALBI score (P = 0.012) at 3 weeks after treatment initiation significantly prolonged PFS. **Conclusion:** We identified a novel biomarker for selecting appropriate drugs of SFN and LEN, as well as may be useful for predicting the therapeutic effect of Atezo+Bev. Further validation study in a large number of cases would be required as considering age-appropriate treatment strategies for elder HCC patients.

Disclosures: Yasuhito Tanaka – Fujirebio: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Sysmex: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual’s institution receives the research grant and manages the funds), No, No; Gilead: Speaking and Teaching, No, No; AbbVie: Speaking and Teaching, No, No;

The following people have nothing to disclose: Satoshi Narahara, Takayuki Tokunaga, Kentaro Tanaka, Hiroki Inada, Etsuko Iio, Yoko Yoshimaru, Takehisa Watanabe, Katsuya Nagaoka, Hiroko Setoyama

4092-A | NUCLEIC ACID VARIANT PROFILES IN MATCHING TUMORS, CIRRHOTIC ADJACENT TISSUE AND PLASMA FROM HCC PATIENTS USING RNASEQ AND DNASEQ ANALYSIS

Sheikh Aejaz Sayeed[1], Daniel Zezulinski[1], Timothy M. Block[1], Coppola Gianfilippo[2], Ryan Hlady[3], Chen Liu[2] and Lewis R. Roberts[4], (1)Baruch S. Blumberg Institute, (2)Yale University, New Haven, CT, (3)Mayo Clinic Rochester, Rochester, MN, (4)Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, MN

Background: Genetic mutations can change how proteins function. Some mutations trigger changes in healthy cells to develop cancer. Compared to germline mutations present throughout the genome of an individual, somatic mutations develop in a particular tissue and could be detected in both DNA and RNA of that altered tissue. Among SNP and splicing variants, the latter are known to occur more frequently in RNA of normal and tumor tissues. It is becoming increasingly clear that unique RNA profiles and mutations in RNA within individual cancers may play a major role in defining both the biology of the cancer and its response to therapy. We decided to explore genome and transcriptome wide variants in hepatocellular carcinoma (HCC). **Methods:** Five clinically diagnosed early-stage HCC subjects were investigated for RNA and DNA variants. Matching specimens from each subject included the tumor, adjacent liver cirrhotic tissue (ALCT) and plasma. Total RNA and DNA was extracted from tumor tissue and ALCT, while only total RNA was extracted from plasma. Extracted DNA and RNA samples were QCd and sequenced. The resulting FASTQ files were mapped to the hg38 human genome, using BWA for DNA and STAR for RNA to be processed using a GATK4 variant calling pipeline. The resulting variants were annotated by snpEff. Only variants found in regions shared between RNA and DNA were retained for analysis. **Results:** We report more variants in tumor tissue than in ALCT, up to 1.75 times from DNA, and up to 4.5 times from RNA. In comparing DNA with RNA, we identify up to 4 times more variants in DNA than RNA in ALCT and up to ~7 times in tumor tissue, while the DNA mean depth (per sample) is, on average, half of the RNA mean depth. In plasma RNA we identify systematically less variants than in RNA, from either tumor or ALCT. SNPs represent the predominant variant types in all samples, more so in the DNA call set than in RNA. Specifically, we find ~40 times more SNPs than INDELs in DNA and ~1.5 times in RNA. While there are ~4 times more SNPs called in DNA than in RNA, we also find ~4 times more INDEls called in RNA than in DNA. Focusing on variant impact, as annotated by snpEff, we find up to ~3 times (DNA) and up to 4.5 times (RNA) more high impact variants in tumor tissue than ALCT. Within the high impact set, we find similar proportions of variants with an effect on splicing. We find up to ~200 times more splicing related variants in RNA than in DNA from the same tissue. Interestingly, plasma RNA variants range from 20 to 75% of the tissue RNA variants. **Conclusion:** In summary, our investigations in matching specimens of HCC subjects show a higher number of variants in both DNA and RNA samples from tumors compared to ALCT samples and, importantly, shows that calling variants from RNA in tissue and plasma, may provide a potentially deeper insight in splicing perturbation events than DNA from WGS, thus revealing interesting variant profiles which could shed light on circulating biomarkers of detection of HCC in high-risk patients.

Disclosures: Sheikh Aejaz Sayeed – Exocell bio: Consultant, No, No;

The following people have nothing to disclose: Chen Liu

Disclosure information not available at the time of publication: Daniel Zezulinski, Timothy M. Block, Coppola Gianfilippo, Ryan Hlady, Lewis R. Roberts

4093-A | OSTEOPENIC OCCULT VERTEBRAL FRACTURE IS ASSOCIATED WITH POOR ONCOLOGICAL OUTCOME IN PATIENTS WITH HEPATOCELLULAR CARCINOMA AFTER HEPATIC RESECTION

Koichiro Haruki[1], Kenei Furukawa[1], Munetoshi Akaoka[1], Tomohiko Taniai[1], Masashi Tsunematsu[2], Mitsuru Yanagaki[1], Shinji Onda[2], Yoshihiro Shirai[2], Michinori Matsumoto[2] and Toru Ikegami[1], (1)The Jikei University School of Medicine, (2)The Jikei University School of Medicone

Background: Although osteopenia has been associated with poor outcomes in patients with hepatocellular carcinoma (HCC), the oncological impact of occult vertebral fracture (OVF) has not been investigated. This study aimed to evaluate the significance of OVF in patients with HCC. **Methods:** The study comprised 235 patients who had undergone primary hepatic resection for hepatocellular carcinoma between 2008 and 2019. Osteopenia was evaluated with computed tomographic measurement of pixel density in the midvertebral core of the 11th thoracic vertebra. The height of central/anterior/posterior vertebrae was measured using sagittal computed tomography reconstruction between 11th thoracic vertebra to 5th lumber vertebrae. OVF was defined if the ratios of central/ anterior or central/posterior heights of the vertebrae < 0.8. Multivariate Cox proportional hazard models were conducted to assess disease-free and overall survival adjusting for potential confounders. **Results:** OVF was identified in 93 patients (40%), while osteopenia in 65 patients (28%). Osteopenic OVF was identified in 27 patients (12%). In multivariate analysis, gender ($p = 0.001$), serum PIVKA-II level ≥ 200 mAU/ml ($p < 0.001$), multiple tumors ($p < 0.001$), type of resection ($p < 0.001$), sarcopenia ($p = 0.005$), and osteopenic OVF (HR 3.06, 95% CI 1.79-5.22, $p < 0.001$) were independent and significant predictors of cancer recurrence, while gender ($p = 0.035$), HBsAg positivity ($p = 0.041$), Child-Pugh grade B ($p = 0.008$), poor tumor differentiation ($p = 0.041$), multiple tumors ($p = 0.002$), microvascular invasion ($p = 0.026$), sarcopenia ($p < 0.001$), and osteopenic OVF (HR 2.75, 95% CI 1.62-4.66, $p < 0.001$) were independent predictors of overall survival. **Conclusion:** Occult OVF is associated with poor oncological outcome in patients with hepatocellular carcinoma after hepatic resection. Our findings provide compelling rationale for the further investigation of interplay between tumor and bone metabolism.

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Disclosure information not available at the time of publication: Masashi Tsunematsu, Shinji Onda, Yoshihiro Shirai, Michinori Matsumoto

4094-A | OSTEOSARCOPENIA IS ASSOCIATED WITH POOR ONCOLOGIC OUTCOMES IN PATIENTS WITH INTRAHEPATIC CHOLANGIOCARCINOMA AFTER HEPATIC RESECTION

Tomohiko Taniai, Koichiro Haruki, Kenei Furukawa, Mitsuru Yanagaki, Munetoshi Akaoka and Toru Ikegami, The Jikei University School of Medicine

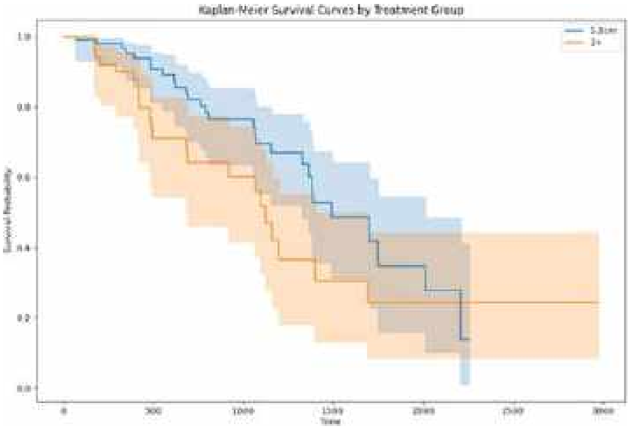
Background: The concept of osteosarcopenia, which is concomitant osteopenia and sarcopenia, has been proposed as a prognostic indicator for cancer patients. However, the prognostic significance of osteopenia, sarcopenia, and osteosarcopenia in patients with intrahepatic cholangiocarcinoma (IHCC) has not been fully investigated. The aim of this study was to evaluate the prognostic significance of osteosarcopenia in patients with IHCC. **Methods:** The subjects of this retrospective study were 41 patients who underwent hepatic resection for IHCC. Osteopenia was assessed with pixel density in the mid-vertebral core of the 11th thoracic vertebra and sarcopenia was assessed by the psoas muscle areas at the third lumbar vertebra. Osteosarcopenia was defined as the concomitant occurrence of osteopenia and sarcopenia. We analyzed the association of osteosarcopenia with disease-free and overall survival and evaluated clinicopathologic variables in relation to the osteosarcopenia. **Results:** Eighteen (44%) of the 41 patients had osteosarcopenia. The patients with osteosarcopenia revealed lower body mass index ($p = 0.03$), lower bone mineral density ($p < 0.01$), lower psoas muscle mass area ($p < 0.01$), while there was no significant difference in other clicopathological variables such as tumor marker, systemic inflammatory markers. Multivariate analysis identified osteosarcopenia (hazard ratio 3.38, 95% confidence interval: 1.49–7.68, $p < 0.01$) as an independent predictor of disease-free survival, and age ≥ 65 years ($p = 0.03$) and osteosarcopenia (hazard ratio 6.46, 95% confidence interval: 1.76–23.71, $p < 0.01$) as independent predictors of overall survival. **Conclusion:** Preoperative osteosarcopenia may be a predictor of poor prognosis in patients undergoing hepatic resection for IHCC, suggesting that preoperative management to maintain muscle and bone intensity could improve the prognosis.

Disclosures: The following people have nothing to disclose: Tomohiko Taniai, Koichiro Haruki, Kenei Furukawa, Mitsuru Yanagaki, Munetoshi Akaoka, Toru Ikegami

4095-A | OUTCOMES OF UNIFOCAL HCC: A COMPARISON OF SURVIVAL IN T1 VS T2 HCC

Suraj Pai[1], Shengchen Hao[1], Amit G. Singal[2] and Neehar Dilip Parikh[1], (1)University of Michigan, (2) University of Texas Southwestern Medical Center

Background: Although patients with T1 (< 2 cm) hepatocellular carcinoma (HCC) can be accurately diagnosed based on radiographic criteria, management of these patients remains controversial given exception points for liver transplantation (LT) are reserved for patient with T2 (³ 2 cm) tumors. Therefore, many centers choose a wait-and-ablate approach, whereby patients are observed and treated when the lesion exceeds 2 cm in maximum diameter. The clinical impact of this strategy on HCC outcomes is unknown. **Methods:** We conducted a single center retrospective study of adult patients newly diagnosed with unifocal HCC, based on LIRADS v2018, measuring between 1.0 and 3.0 cm at diagnosis between 2018 and 2023. We excluded those patients with a non-HCC liver malignancy. The primary outcome was transplant-free survival, stratified by tumor size (1-1.9 cm vs 2-3 cm). Survival analysis was completed using Kaplan-Meier, and the two groups were compared using multivariable Cox proportional hazard models. **Results:** Of 159 patients, 103 within the 1-1.9 cm category and 56 within 2-3 cm category. Patients had a median age of 65 years, 83% were Caucasian, and 70% were male. The primary etiologies of liver disease were hepatitis C virus (HCV) (28%), non-alcoholic fatty liver disease (NAFLD) (27%), and alcohol-related cirrhosis (23%). The median Child-Turcotte-Pugh (CTP) score was 6 (IQR: 5-7) and median AFP was 5 (IQR: 3-14). Nine patients (8.7%) in the 1-2 cm group and 7 (12.5%) in 2-3 cm group underwent LT, with a median time to transplant of 12.8 months. Median transplant-free survival was 49.1 (IQR: 34.8-72.7) months for the 1-1.9 cm cohort vs. 37.0 (IQR: 16.1-55.6) months for the 2-3 cm cohort ($p = 0.06$) (Figure). In multivariable analysis, decreased survival was significantly associated with age (HR 1.05 [95% CI: 1.02 – 1.09], CTP score (HR 1.91 [95% CI: 1.51 – 2.41], AFP level (HR: 1.004 95% CI: 1.002-1.006) and 2-3 cm tumor size (vs 1-1.9 cm) (HR 2.16 [95% CI: 1.20 – 3.87]. **Conclusion:** Patients with T1 HCC have superior outcomes compared to patients with T2 (2-3 cm) HCC suggesting that the widely used policy of wait-and-ablate may result in inferior patient outcomes. Current policies that give transplant priority for > 2 cm HCCs are justified, however biopsy proven T1 lesions could also be considered for transplant exception points and immediately treated, given the risks associated with larger tumor sizes.



Disclosures: Amit G. Singal – Genentech: Consultant, No, No; AstraZeneca: Consultant, No, No; Bayer: Consultant, No, No; Eisai: Consultant, No, No; Exelixis:

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

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Neehar Dilip Parikh – Eisai: Advisor, No, Yes; Exact Sciences: Consultant, No, Yes; Gilead: Advisor, No, Yes; Fujifilm Medical: Consultant, No, Yes; Freenome: Consultant, No, Yes; Exelixis: Consultant, No, No;

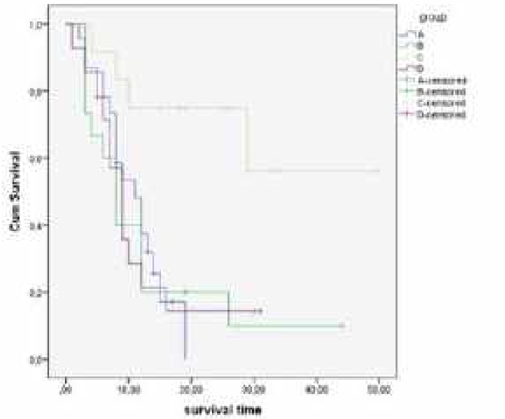
The following people have nothing to disclose: Suraj Pai, Shengchen Hao

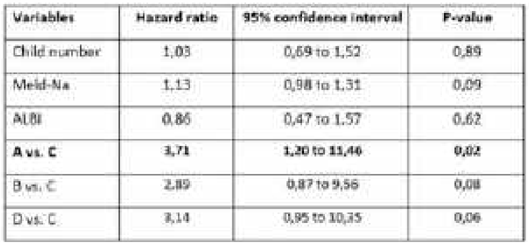
4096-A | PATTERN OF PROGRESSION TO BCLC-C STAGE SIGNIFICANTLY AFFECTS OBJECTIVE RESPONSE AND OVERALL SURVIVAL RATES IN ATEZO-BEV TREATED PATIENTS WITH ADVANCED HCC AND UNFAVORABLE OBJECTIVE TUMOR CHARACTERISTICS

Spyridon Pantzios, Antonia Syriha, Dionysia Mandilara, Orestis Sidiropoulos, Ioanna Stathopoulou, Georgia Barla, Nikolaos Ptohis, Petros Galanis and Ioannis S. Elefsiniotis, National and Kapodistrian University of Athens

Background: IMBRAVE150 study mainly included HCC patients in the BCLC-C stage with well compensated liver disease, irrespective of the type of progression to this stage. The aim of our study was to retrospectively evaluate, under real life conditions, the on-treatment survival of patients with advanced HCC (BCLC-C stage), either initially presenting in the advanced stage (iBCLC-C) or migrating from BCLC-A to BCLC-C stage (mBCLC-C) within 2 years after curative LR or RFA, treated either with atezolizumab-bevacizumab (ATZ/BEV) combination or with TKIs sequentially (sorafenib as 1st line and cabozantinib as 2nd line treatment). **Methods:** Sixty four cirrhotic patients with advanced HCC (56 males, mean age 67 years, 22 with diabetes, CPT-A = 45/B = 19, mean MELD-Na = 11, ALBI grade I = 20/grade II = 38, 28 with varices, 18 with extrahepatic disease, 24 with macrovascular invasion) who either initially presented in the BCLC-C stage and were treated with ATZ/BEV (group A, N = 23) or TKIs (group B, N = 15) or who migrated from BCLC-A to BCLC-C within 2 years after LR or RFA and were treated with ATZ/BEV (group C, N = 12) or TKIs (group D, N = 14) were evaluated. **Results:** The four groups were comparable for all the baseline parameters evaluated (age p = 0.9, gender p = 0.08, platelets p = 0.246, chronic liver disease etiology p = 0.408, coexistence of diabetes p = 0.314, presence of varices p = 0.066, CPT stage p = 0.067, ALBI grade p = 0.398) except for CPT score (p = 0.012) and MELD-Na score (p = 0.002). Objective response rates (both CR and PR) were frequently observed in group C (5/12, 41.66%) compared to group A (1/23), B (0/15) and D (1/14). Moreover, the on-treatment survival of group C patients seems to be significantly higher compared to those of group D (9m) patients (p = 0.007) as well as for group A and B. Using cox regression analysis, we observed that the ATZ/BEV on-treatment survival of group A (HR = 3.71, p = 0.02) was significantly worse than that of group C, adjusted for CPT, ALBI and MELD-Na (figure). We repeated the analysis, including only patients with MVI and/or EHD (excluding 18 patients stratified in BCLC-C due to poor PS only) and found that the survival benefit of group C patients seems to be preserved even in the most difficult-to-treat BCLC-C patients. **Conclusion:** ATZ/BEV therapy seems to benefit mainly BCLC-C patients who migrate from earlier stages after curative LR or RFA compared to patients initially presented in the advanced stage, irrespective of liver disease severity and these patients exhibit better disease response rates. These results seem to be preserved even in patients with objective tumor characteristics that reflect worst prognosis. Median survival of ATZ/BEV or TKI patients who were initially classified in BCLC-C stage was less than 12 months, irrespective of treatment schedule, as was post-recurrence survival of sequentially TKI-treated patients. Liver disease severity seems to drive the overall as well as post-recurrence survival.

Figure: Survival of group A (blue), B (green), C (yellow) and D (purple) and cox regression analysis for survival after the beginning of systemic therapy comparing group C to the other groups and adjusted for CPT, ALBI and MELD/Na scores.





Variables	Hazard ratio	95% confidence interval	P-value
Child number	1,03	0,69 to 1,52	0,89
Meld-Na	1,13	0,98 to 1,31	0,09
ALBI	0,86	0,47 to 1,57	0,62
A vs. C	**3,71**	**1,20 to 11,46**	**0,02**
B vs. C	2,89	0,87 to 9,56	0,08
D vs. C	3,14	0,95 to 10,35	0,06

Disclosures: The following people have nothing to disclose: Spyridon Pantzios, Antonia Syriha, Dionysia Mandilara, Orestis Sidiropoulos, Ioanna Stathopoulou, Georgia Barla, Nikolaos Ptohis, Petros Galanis, Ioannis S. Elefsiniotis

4097-A | PERFORMANCE OF A MULTI-CANCER EARLY DETECTION (MCED) TEST FOR DETECTION OF HEPATOCELLULAR CARCINOMA (HCC) IN PATIENTS WITH CIRRHOSIS

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Background: More than 80% of HCC cases develop in the setting of cirrhosis, informing the at-risk cohort for surveillance. Most HCCs are found beyond an early stage, highlighting a need for novel surveillance strategies. Increasing data also show heterogeneity in tumor biology and treatment response, highlighting a need for treatment response biomarkers. In this pilot study, we explored the potential of an MCED test to detect HCC in patients with cirrhosis and its association with treatment response. **Methods:** In this case-control study, biobanked plasma was processed from patients aged > 18 years with cirrhosis, without (controls) and with (cases) treatment-naive HCC. Cases and controls were matched on liver disease etiology, Child Pugh score, and Barcelona Clinic Liver Cancer (BCLC) stage. The MCED test employs a targeted methylation assay of circulating cell-free DNA with a machine learning algorithm to detect a shared cancer signal and predict cancer signal origin (CSO) across cancer types, and it was validated in the Circulating Cell-free Genome Atlas study, wherein high sensitivity for HCC was observed. Test performance for HCC detection was assessed blinded to case-control status. Test performance by treatment response was performed as an exploratory analysis. **Results:** There were no significant differences in clinical characteristics (median age, 63 years; male, 60%) between cases (n = 27) and controls (n = 17). Patients were diverse regarding race/ethnicity (36% non-Hispanic White, 36% Hispanic, 27% Black) and cirrhosis etiology (50% hepatitis C virus, 25% non-alcoholic steatohepatitis, 20% alcohol). 66% and 34% of patients had Child Pugh A and B cirrhosis, respectively. HCC cases were diverse in terms of BCLC stage (41% stage 0/A, 59% stage B), with 41% of cases being within Milan Criteria. MCED test sensitivity and specificity was 78% and 100%, respectively. CSO prediction accuracy was 100%; all cases with a cancer signal detected had a CSO prediction of liver/bile duct. All cases underwent transarterial chemoembolization (TACE) as initial HCC treatment. The MCED test detected a cancer signal in 67% of cases with an objective response to TACE and 87% of those with progressive disease (p = 0.24). **Conclusion:** Early findings in a small population indicate the MCED test's performance shows potential for early HCC detection and association with treatment response. Further research is needed to assess the full value of the test among patients at high risk for and with HCC.

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Kathryn N. Kurtzman – GRAIL, LLC: Employee, Yes, No; Illumina, Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Amit G. Singal – Genentech: Consultant, No, No; AstraZeneca: Consultant, No, No; Bayer: Consultant, No, No; Eisai: Consultant, No, No; Exelixis: Consultant, No, No; Boston Scientific: Consultant, No, No; Gycotest: Consultant, No, No; Exact Sciences: Consultant, No, No; Roche: Consultant, No, No; FujiFilm Medical Sciences: Consultant, No, No; GRAIL, LLC: Consultant, Yes, No; Freenome: Consultant, No, No; Histosonics: Consultant, No, No;

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4098-A | POORER SURVIVAL IN PATIENTS WITH DISCORDANCE BETWEEN PREOPERATIVE RADIOLOGIC AND POSTOPERATIVE PATHOLOGIC FINDINGS

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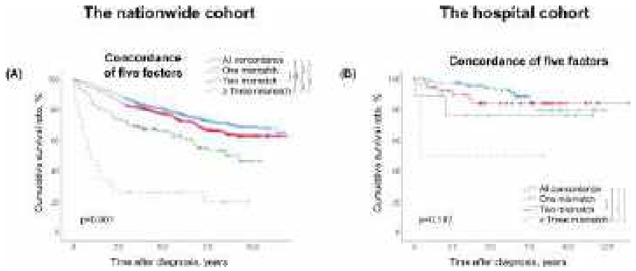
Symbols: ƒ , Poster of Distinction; ★, Foundation Award Recipient

National University Sejong Hospital, (2)Chungnam National University Hospital, (3)Department of Preventive Medicine, Chungnam National University College of Medicine, (4)Dreamcis Inc., (5)Department of Internal Medicine, Chungnam National University Hospital

Background: It has been reported that the discordance between preoperative radiologic and postoperative pathological findings adversely affects the survival rate in patients who underwent liver transplantation. However, there is no studies about impact of the discordance in patients who have undergone surgical resection. Therefore, we investigated the impact of these discrepancies on the prognosis in patients with hepatocellular carcinoma (HCC) who underwent resection. **Methods:** This study included patients who were diagnosed with HCC on magnetic resonance imaging and underwent surgical resection within 1 month of diagnosis from 2008 to 2016. A total of 1832 patients from the Korean Primary Liver Cancer Registry (KLCR) and 185 patients from Chungnam national university hospital (Daejeon, South Korea) were included in the nationwide cohorts and validation cohorts, respectively. For five factors, such as maximum tumor diameter, tumor number, vascular invasion, bile duct invasion, lymph node metastasis, the effects on the patient's survival according to the degree of discrepancies between magnetic resonance imaging and pathologic findings were analyzed using the Kaplan-Meier method. Furthermore, Cox proportion hazards regression analysis was used to evaluate the effect of the degree of discordance on survival rates independently. **Results:** When all five factors were concordant between radiologic and pathologic findings, the 1-year, 3-year, and 5-year survival rates were 96.5%, 87.0%, and 80.7%, respectively. However, in the case of three discrepancies, the 1-year, 3-year, and 5-year survival rates were 52.4%, 28.6%, and 28.6%, respectively. According to more discrepancies in five factors were, the survival rate was significantly lower ($p < 0.001$). Multivariate cox regression analysis showed that the discrepancy more than two factors between radiologic and pathologic findings (hazard ratio [HR], 4.726; 95% confidence interval [CI], 2.096-10.655), age (HR, 1.026; 95% CI, 1.013-1.040), diabetes mellitus (HR, 1.367; 95% CI, 1.065-1.755), platelet count (HR, 0.998; 95% CI, 0.997-1.000), serum albumin (HR, 0.712; 95% CI 0.559-0.905), maximum tumor diameter (HR, 1.125; 95% CI, 1.087-1.165), tumor number more than three (HR, 1.118; 95% CI, 1.405-3.773), vascular invasion (HR, 1.742; 95% CI, 1.170-2.595), lymph node metastasis (HR, 5.443; 95% CI, 2.669-11.099) were the independent significant predictors of the overall survival. **Conclusion:** Discordance between the preoperative radiologic findings and the postoperative pathological findings were significantly associated with survival rate in patients with HCC. Further studies on factors that can predict discrepancies and efforts to reduce discrepancies are needed.



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4099-A | PRECISION THERAPY IN HEPATOCELLULAR CARCINOMA: ASSOCIATION OF FGF3, FGF4, AND FGF19 AMPLIFICATION WITH RESPONSE TO SORAFENIB

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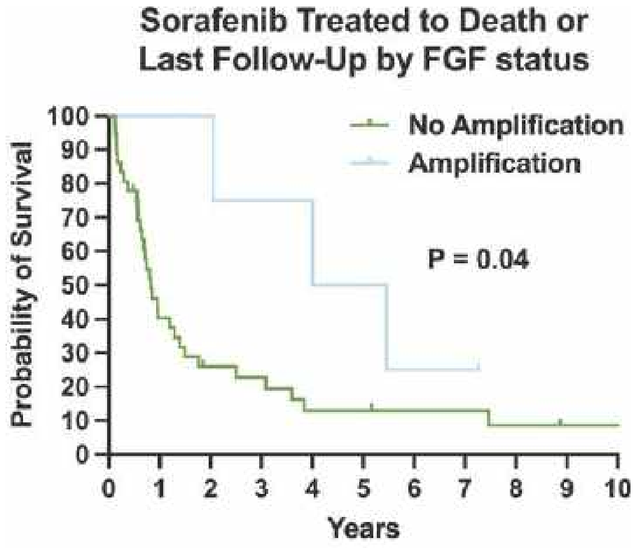
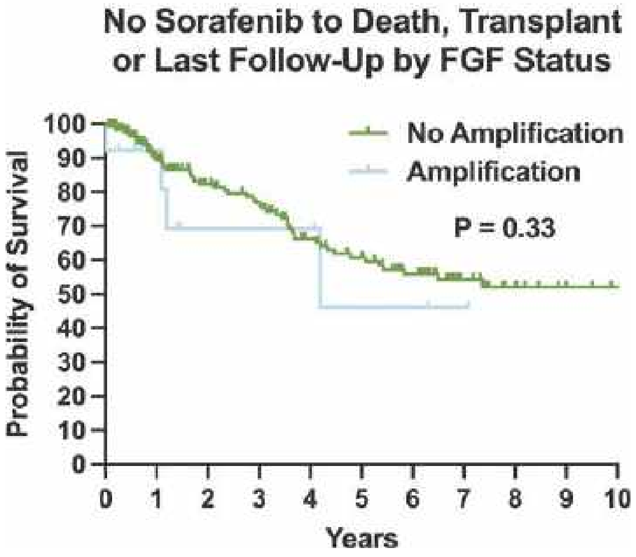
Background: Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer death globally. Many HCC patients are diagnosed at advanced stages with poor long-term survival. Sorafenib, a multi-kinase inhibitor is currently used in the second-line, providing a survival advantage over best supportive care. Most patients do not respond to sorafenib or progress on this therapy. Therefore, the validation of predictors of response that aid in the treatment selection for HCC remains of critical importance. We aimed to assess the association of FGF3, FGF4, and FGF19 amplification with response to sorafenib and survival after sorafenib initiation in patients with HCC, and also assessed the impact of FGF locus amplification on overall survival of patients not treated with sorafenib. **Methods:** 260 patients who received curative surgical treatment by resection or liver transplantation for HCC or who had liver biopsies performed for intermediate or advanced liver disease and had available formalin fixed paraffin embedded tissue were included in the analysis. All had mRNA sequencing and targeted mutational and copy number analysis performed on the Tempus platform. Statistical analysis was performed to assess the impact of FGF locus amplification on patient response and outcomes. **Results:** Of the 260 patients, 18 (6.9%) had amplification at the FGF locus, while 242 did not. Of the 18 with FGF locus amplification, 4 (22.2%) received sorafenib. All 4 initially had complete radiologic and biomarker responses to sorafenib. The median survival after initiation of sorafenib was significantly longer in the patients with FGF locus amplifications than in those without FGF amplifications (median survival 4.74 vs. 0.83 y; p = 0.04). Of the 242 patients who did not receive sorafenib, there was no difference in overall survival of patients with FGF locus amplifications vs. those without FGF amplification (median OS from the time of HCC diagnosis 4.19 vs. 10.06 y; p = 0.33). **Conclusion:** There is a significant association of FGF locus amplification with response to sorafenib, resulting in improved survival after initiation of sorafenib treatment compared to patients without FGF locus amplification. In contrast, FGF locus amplification by itself is not associated with improved survival of HCC patients in the absence of sorafenib treatment. Genomic testing at the FGF3-FGF4-FGF19 locus can be used as a predictor of response to sorafenib therapy and survival.





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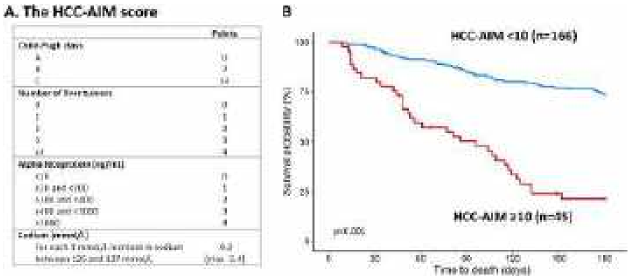
4100-A | PREDICTING EARLY HEPATIC DECOMPENSATION AND DEATH IN HEPATOCELLULAR CARCINOMA PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS: THE HCC-AIM SCORE

Michael Li[1], Kate Kelley[1], Neil Mehta[1], Francis Yao[1], Lawrence Fong[1] and Jennifer C. Lai[2], (1)University of California, San Francisco, (2)University of California-San Francisco

Background: Major immune checkpoint inhibitor (ICI) clinical trials in hepatocellular carcinoma (HCC) have been limited to Child-Pugh (CP) class A patients. Patients with more advanced liver disease and tumor burden are at increased risk of hepatic decompensation and death, though predictors of early adverse outcomes in ICI-treated patients are unknown. **Methods:** We conducted a single-center retrospective cohort study of all ICI-treated HCC patients from 2016 onwards. Hepatic decompensation was defined as development of ascites, encephalopathy, and/or variceal bleeding. The primary outcomes were early decompensation and early death (both within 90 d of ICI initiation). **Results:** In the 212 study patients, the median MELD was 10 and 62% were CP class A. Early decompensation occurred in 54 (25%) patients; ascites, encephalopathy, and variceal bleeding occurred in 59%, 44%, and 15% of these patients, respectively. Early death occurred in 47 (22%) patients. Patients with early decompensation were more likely to experience early death (59.3% vs 9.5%, RR 6.2, 95% CI 3.7-10.6, $p < 0.001$) and had shorter survival (median 80 vs 468 d, log-rank $p < 0.001$) than those without early decompensation. Furthermore, no patients with early decompensation experienced radiographic treatment response. The novel HCC-AIM (Adverse outcomes in IMmunotherapy) score was derived using LASSO regression. The four pre-treatment variables selected (CP class, # of liver tumors, AFP level, and sodium level) were assigned points based on their coefficients (Figure A). HCC-AIM had excellent discrimination (c-statistic 0.85, 95% CI 0.79-0.90) for early decompensation, with an optimism-corrected c-statistic of 0.81 on internal validation (10-fold cross-validation). HCC-AIM also performed well when predicting early death (c-statistic 0.82, 95% CI 0.76-0.88). An HCC-AIM cutoff of ≥ 10 had high specificity (91% and 86%) and high NPV (86% and 85%) for early decompensation and early death, respectively, and was associated with shorter time to death (Figure B). Only three out of 45 patients with a score ≥ 10 experienced radiographic treatment response. **Conclusion:** Early hepatic decompensation after ICI therapy for HCC is common and is strongly associated with early death. The novel HCC-AIM score predicted both early decompensation and early death and can be applied using pre-treatment data to identify high-risk patients in whom ICI treatment may be futile due to advanced liver disease and tumor burden.



Disclosures: Jennifer C. Lai – Novo Nordisk: Advisor, No, No; Genfit: Consultant, No, No; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Vir: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gore: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Flagship Pioneering: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Michael Li, Neil Mehta

Disclosure information not available at the time of publication: Kate Kelley, Francis Yao, Lawrence Fong

f 4101-A | PREDICTING RESPONSE TO ATEZOLIZUMAB PLUS BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA

Sarah Cappuyns[1,2,3], Marta Piqué-Gili[4], Roger Esteban-Fabró[4], Gino Philips[5], Roser Pinyol[4], Vincent Vandecaveye[1], Jordi Abril-Fornaguera[4], Philipp Haber[6], Chris Verslype[1], Eric Van Cutsem[1], Diether Lambrechts[5], Augusto Villanueva[2], Jeroen Dekervel[1] and Josep M Llovet[2], (1)Uz/KU Leuven, (2)Icahn School of Medicine at Mount Sinai, (3)Instituto De Investigaciones Biomédicas August Pi I Sunyer (IDIBAPS), (4)Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), (5)KU Leuven, (6) Charité Universitätsmedizin Berlin

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

Background: Single-cell transcriptomic profiling (scRNAseq) has allowed the characterization of tumor immune cell infiltration and how it relates to immunotherapy (IO) response in advanced HCC (aHCC). Here, we aimed to 1) derive gene expression signatures that recapitulate distinct single-cell derived immune cell types that can be applied to bulk RNAseq data and 2) evaluate their potential as predictive biomarkers of response to atezolizumab + bevacizumab (atezo+bev), current standard of care in aHCC. **Methods:** Using scRNAseq data from 31 aHCC biopsies, we defined gene signatures for 35 cell phenotypes using a customized bio-informatics pipeline based on differential gene expression analysis. The power of single-cell derived signatures to capture the presence of specific intra-tumoral cell types and predict IO response in bulk transcriptomic data was evaluated in 3 cohorts comprising 401 pre-treatment aHCC samples: 1) 65 atezo+bev-treated aHCCs (Training), 2) 253 patients treated with atezo+bev in the context of the IMBrave150 and GO30140 clinical trials (Validation; Zhu et al. 2022), and 3) 83 anti-PD1-treated aHCCs (Validation 2; Haber et al. 2023). We performed single-sample Gene Set Enrichment Analysis (ssGSEA) and Nearest Template Prediction (NTP) analysis. ssGSEA-derived scores and class prediction results were correlated with objective response to therapy and progression-free survival (PFS). Overall 30% responded to atezo+bev. **Results:** We successfully generated gene signatures for 21 out of 35 single-cell derived cell types in aHCC. Three signatures were consistently enriched in atezo+bev responders compared to non-responders, representing CD8 effector cells (CD8 Temra, CD8 Tex) and pro-inflammatory CXCL10+ macrophages. Tumors enriched with these immune-related signatures (immune responders; 15% of total) were significantly enriched in previously reported gene signatures of IO response, and displayed the highest transcriptomic similarity with anti-PD1 responders ($\text{FDR} < 0.01$). We identified two mechanisms associated with response: immune versus anti-angiogenic response. When evaluated by class prediction analysis (NTP), the 3 signatures defining immune HCC responders had an $> 83\%$ specificity to identify response and were associated with a significantly longer PFS when treated with atezo+bev ($p < 0.05$), but not with sorafenib. In contrast, atezo+bev responders lacking these immune-related subsets displayed a significantly higher expression of VEGFA and metabolism-related genes (anti-angiogenic responders; 15-20% of total). **Conclusion:** The combined intra-tumoural presence of CD8 effector cells and CXCL10+ macrophages prior to treatment is associated with improved survival in atezo+bev treated patients, demonstrating predictive value as biomarkers of response to atezo+bev. In a subset of patients, response to this combination may be predominantly driven by anti-angiogenic mechanisms.

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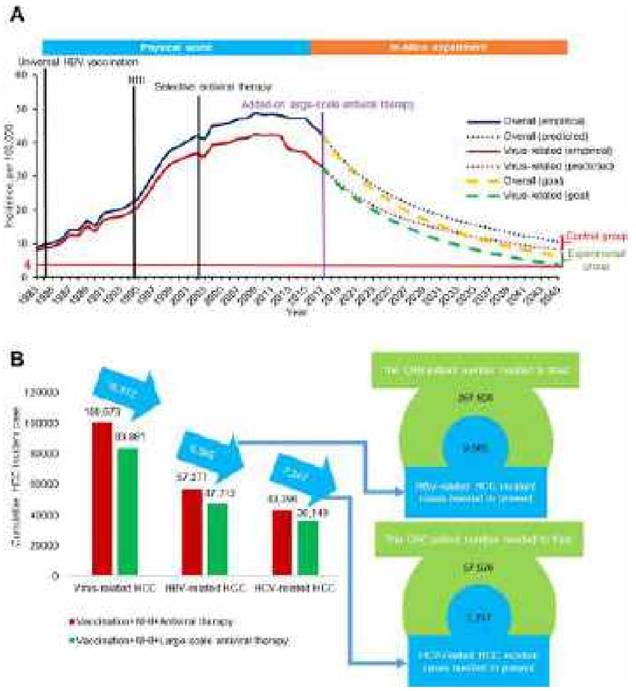
4102-A | PREDICTING THE POTENTIAL OF ELIMINATING VIRUS-RELATED HEPATOCELLULAR CARCINOMA IN TAIWAN BY DEEP MACHINE LEARNING

Sih-Han Liao[1], Kuo-Liong Chien[2], Chi-Ling Chen[3], Chen-Yang Hsu[2], Chien-Hung Chen[4], Hsiu-Hsi Chen[2] and Jia-Horng Kao[5], (1)National Taiwan University Cancer Center, (2)College of Public Health, National Taiwan University, (3)National Taiwan University College of Medicine, (4)College of Medicine, National Taiwan University, (5)National Taiwan University Hospital

Background: To reduce the incidence of hepatocellular carcinoma (HCC), three change points of interventions have been implemented in Taiwan, including hepatitis B vaccination from 1984, universal health care from 1995, and antiviral therapy from 2004. The primary aim of this study was to predict when and how the elimination of virus-related HCC could be achieved by adding large-scale antiviral therapy to the causal chains of interventions with deep machine learning method. **Methods:** The digital twin design was envisaged to produce the virtual group after learning parameters that governed the direct and indirect causal chains of three change-point interventions, including the gradual expansion of antiviral therapy when making allowance for the heterogeneity of demographic and geographic variations. Bayesian causal graphic model was adopted to estimate when and how eliminating virus-related HCC with the incidence less than 4 per 100,000 could be achieved with large-scale antiviral therapy. **Results:** Based on the incidence predicted by the virtual group after learning the long-term time trend of HCC incidence pertaining to three-change points of direct and indirect causal chains, the elimination of virus-related HCC in Taiwan would be achieved by the end of 2045 when a further 16,812 virus-related HCC incident cases could be averted after treating 267,820 and 57,976 chronic hepatitis B and C patients with large-scale antiviral therapy, respectively. **Conclusion:** We demonstrate how to use the digital twin design with Bayesian causal graphic model to achieve the elimination of virus-related HCC when adding large-scale antiviral therapy to the existing three change-point interventions for HCC.



Disclosures: The following people have nothing to disclose: Sih-Han Liao, Chi-Ling Chen, Jia-Horng Kao
Disclosure information not available at the time of publication: Kuo-Liong Chien, Chen-Yang Hsu, Chien-Hung Chen, Hsiu-Hsi Chen

4103-A | PREDICTION OF HEPATOCELLULAR CARCINOMA AND BENEFIT OF ANTIVIRAL THERAPY IN CHB PATIENTS WITH SINGLE-NUCLEOTIDE VARIANTS OF PRE-S/S REGION

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Background: There were several hepatocellular carcinoma (HCC)-associated hepatitis B virus (HBV) single-nucleotide variants (SNVs) reported in a horizontal case-control study. This study investigated the predictive value of SNVs in Pre-S/S region in HCC development and evaluated the role of antiviral therapy in these patients in a longitudinal case-control study, especially in patients of grey zone (ALT < 80 U/L or HBV DNA < 2000 IU/ml) of current treatment guidelines. **Methods:** A total of 459 chronic hepatitis B (CHB) patients were retrospectively analyzed for SNVs associated with HCC occurrence during follow up at Taipei Veterans General Hospital and National Cheng Kung University Hospital from 1994-2014. Point mutations including six SNVs in genotype B HBV as well as 21 HCC-associated SNVs in genotypes C HBV according to a previous horizontal study were detected in baseline serum samples of these CHB patients and the results of SNVs were correlated with the outcomes of HCC and the benefit of antiviral therapy in reducing HCC during follow-up period. **Results:** Among the 459 enrolled patients, 297 (64.7%) were infected by genotype B and the remaining 162 (35.3%) patients were infected by genotype C. HCC occurred in 67 patients (14.6%) in a median follow-up period of 11.6 years. The most common point-mutations included G530A (90.9%) and T724C (97.5%) in S region among genotype B while A2889G to C3097A (up to 93.4%) in Pre-S1 region among genotype C HBV-infected patients. In multivariate analysis, age (hazard ratio [HR] = 1.063, $p < 0.001$ & HR = 1.093, $p < 0.001$) and family history of HCC (HR = 5.741, $p < 0.001$ & HR = 1.398, $p = 0.046$) were associated with HCC development while antiviral therapy (HR = 0.168, $p < 0.001$ & HR = 0.027, $p < 0.001$) was protective factor in genotype B and C HBV-infected patients respectively. Importantly, T53C SNV (HR = 2.719, $p = 0.026$; HR = 2.789, $p = 0.031$) and Pre-S/S deletion (HR = 2.885, $p = 0.017$; HR = 1.165, $p = 0.043$) were statistically significant associated with HCC development both in genotype B and C HBV-infected patients. Patients with antiviral therapy had lower HCC incidence compared to those without in patients with T53C SNV and pre-S/S deletion (both log-rank $p < 0.001$). **Conclusion:** Some SNVs in Pre-S/S region are associated with HCC and antiviral therapy could decrease HCC development in these patients.

Disclosures: The following people have nothing to disclose: Wei Teng, Ting-Tsung Chang, Chien-Wei Su, Yuh-Jin Liang, Jaw-Ching Wu

4104-A | PREDICTION OF RESPONSE AND EARLY PROGRESSION IN ATEZOLIZUMAB PLUS BEVACIZUMAB THERAPY FOR HEPATOCELLULAR CARCINOMA FOCUSED ON TUMOR MARKER TRENDS

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Background: The combination therapy of atezolizumab plus bevacizumab (atezo/bev) for treating unresectable hepatocellular carcinoma (HCC) was introduced in 2020. Despite the high objective response (OR) rate in the IMbrave150 trial, some patients had progressive disease (PD) at the initial imaging evaluation (early PD). Appropriate sequential treatment is important, and this study aimed to identify early indicators of OR and early PD to atezo/bev therapy focused on tumor marker trends. **Methods:** This retrospective study included 154 patients who had received atezo/bev at our hospital and affiliated institutions by December 2022 and aimed to evaluate predictors of treatment efficacy of atezo/bev for unresectable HCC. We examined predictors of treatment response separately in the high-alpha-fetoprotein (AFP) (baseline AFP $\geq$ 20 ng/mL; n = 83) and the low-AFP (baseline AFP < 20 ng/mL; n = 71) groups. **Results:** The median patient age was 75 years, and 124 (77.4%) males were included in our study. Our cohort was characterized by mALBI grade 1/2a/2b/3: 46/38/68/2, BCLC A/B/C: 11/79/64, and a median AFP and des-gamma-carboxy prothrombin (DCP) of 31.1 ng/mL and 382.4 m AU/mL, respectively. In the high-AFP group, a decrease in AFP levels > 30% was an independent predictor of OR (odds ratio, 5.517; $p = 0.003$). In the low-AFP group, baseline DCP level < 40 mAU/mL was an independent predictor of objective response (odds ratio, 3.978; $p = 0.021$). The independent predictors of early PD were an increase in AFP level $\geq$ 30% at 3 weeks (odds ratio, 4.077; $p = 0.026$) and the presence of extrahepatic spread (odds ratio, 3.682; $p = 0.034$) in the high-AFP group and up-to-seven criteria, OUT, (odds ratio, 15.756; $p = 0.026$) in the low-AFP group.In the high-AFP group, median PFS was significantly longer with a decrease in AFP level > 30% (NE vs. 6.1 mo, $p = 0.015$).In the low-AFP group, median PFS was significantly longer in patients with baseline DCP level < 40 mAU/mL than in those with baseline DCP level $\geq$ 40 mAU/mL (not reached vs. 7.7 mo; $p = 0.001$) **Conclusion:** In atezo/bev therapy for unresectable HCC, the change in AFP levels at 3 weeks in patients with baseline AFP level $\geq$ 20 ng/mL and baseline DCP level or tumor burden in patients with AFP level < 20 ng/mL were found to predict treatment response. Thus, it appears reasonable to focus on tumor markers for early prediction of treatment response.

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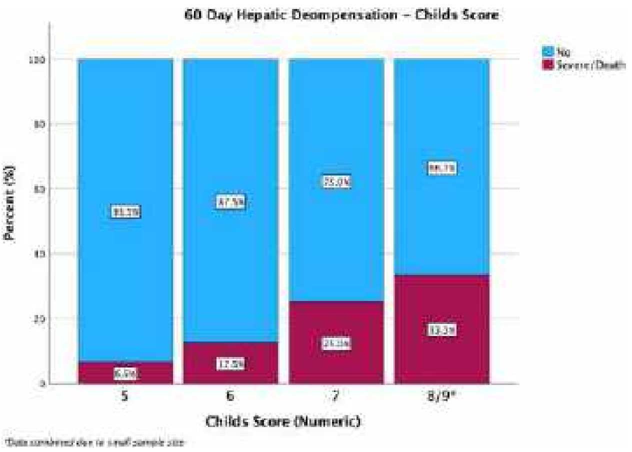
4105-A | PREDICTORS OF HEPATIC DECOMPENSATION AFTER Yttrium90 TRANSARTERIAL RADIOEMBOLIZATION

Amelia Wong, University of Hawaii, Shirley Cheng, John a. Burns School of Medicine, Anthony Herrera, The Queen's Medical Center and Linda L. Wong, Department of Surgery, University of Hawaii, Honolulu, HI, USA.

Background: Yttrium 90 transarterial radioembolization (TARE) is an effective therapy for unresectable hepatocellular carcinoma (HCC) or to bridge/downstage before transplant. Eligibility is generally limited to those with adequate renal function and bilirubin < 2-3 however, there is limited literature on optimal patient selection for TARE. This study aims to identify factors that increase readmission or liver decompensation after TARE. **Methods:** A retrospective review was conducted on patients with HCC between 2021 and 2022 who underwent Y90 TARE as their first treatment. Data collected: demographics, MELD and Childs score, tumor characteristics, treatment/readmission dates and associated complications within 60 days were extracted. Hepatic decompensation was defined as total bilirubin > 3 and any increase in MELD score resulting in readmission or death. Wilcoxon, Pearson's Chi-squared, and Fischer's tests were used to identify statistical significance. Logistic regression models were to predict the odds of decompensation in significant variables. **Results:** Of 138 patients identified, 7 (5.1%) developed hepatic decompensation requiring admission or death within 30 days and 15 (10.9%) within 60 days. Two patients (13.3%) required urgent transplant within 2 months due to decompensation. Pre-procedure albumin < 3.5 ($p = 0.0207$), INR > 1.2 ($p = 0.017$), ascites ($p = 0.036$), and elevated MELD ($p = 0.012$) and Childs ($p = 0.007$) scores are significant predictors of decompensation within 60 days while creatinine and sodium were not. Patients with Childs B score were 3-4 times more likely to have hepatic decompensation (28% vs 7.7%). For every unit increase in Child's score over 5.5, the odds of severe decompensation increased by a factor of 2.15. There were no tumor characteristics associated with increased risk of decompensation and no risk factors associated with mortality. **Conclusion:** Y90 TARE is a safe and effective treatment modality however 5% of patients have worsened liver function after treatment. As patients require reasonable renal function to receive IV contrast and ascites appears to be a significant factor in predicting decompensation, evaluating for Child's score A may be more useful in selecting candidates for TARE. Further risk stratification may be required for those with Child's score greater than 7.



*Data combined due to small sample size

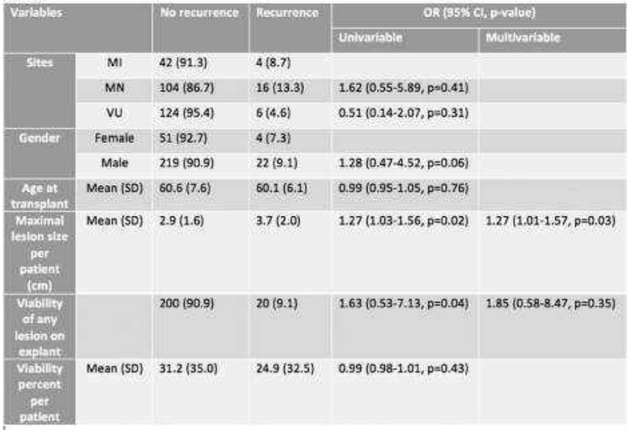
Disclosures: The following people have nothing to disclose: Amelia Wong, Shirley Cheng, Anthony Herrera, Linda L. Wong

4106-A | PREDICTORS OF POST-TRANSPLANT RECURRENCE OF HEPATOCELLULAR CARCINOMA BASED ON EXPLANT ANALYSIS: A MULTICENTER STUDY

Suraj Pai[1], Muhammad Hashim Hayat[2], Joseph Sushil Rao[3], Erin Bouquet[2], Ioannis Ziogas[2], Anthony Borgmann[2], Hassan Anbari[1], Christopher Slaughter[4], Oyedele A. Adeyi[3], Sophoclis Alexopoulos[5], Neehar Dilip Parikh[1], Varvara A. Kirchner[6] and Manhal Izzy[2], (1) University of Michigan, (2)Vanderbilt University Medical Center, (3)University of Minnesota, (4)Vanderbilt University, (5)Keck Medical Center of USC, Sacramento, CA, (6)Stanford University, Stanford, CA

Background: Liver transplantation (LT) is the curative treatment for patients with early unresectable hepatocellular carcinoma (HCC). While waitlisted for transplant, patients with HCC undergo locoregional therapy (LRT) to control tumor burden, limit drop out from waitlist, and mitigate the risk of post-LT recurrence. In this multicenter study, we aimed to identify risk factors that can predict post-LT recurrence of HCC. **Methods:** We performed a retrospective chart review of adult patients who underwent LT for HCC between 2014-2018 at three tertiary North American centers. Demographic data, clinical data, and pathology data (at the lesion level) were collected. The outcome of interest was post-LT recurrence. **Results:** We included 296 patients (270 without recurrence, 26 with recurrence) with a median age of 62 years (IQR 57-65y); 81% were male, 85% were white, 7% were African-American, and 7% were Asian. Common etiologies of liver disease were hepatitis C virus (51%), non-alcoholic steatohepatitis (35%), and hepatitis B virus (22%). Modalities of LRT included transarterial chemoembolization (178 patients), thermal ablation (30 patients), transarterial radioembolization (17 patients), and multimodal therapy (69 patients). On explant, median lesion size was 2.6cm (IQR 1.9-3.7cm) and 3.2cm (IQR 2.4-4.5cm) in the non-recurrence and recurrence groups respectively; 27% of patients had well-differentiated tumor, while 63% and 9% had moderate and poor/undifferentiated tumor, respectively. Amongst all patients, 220 (81%) had viable tumor(s) on explant, with a mean viability per subject (defined as the average of all lesions' viability on that subject) of 10%. Univariable analysis demonstrated an association between recurrence and larger lesion size (OR 1.27 [95% CI: 1.03-1.56], p = 0.02) (Table). Lesion viability on explant did not influence the risk of recurrence. Multivariable analysis confirmed that maximal tumor size independently associated with recurrence (OR 1.27 [95% CI: 1.01-1.57], p = 0.03) even after controlling for tumor differentiation. **Conclusion:** Lesion size on explant pathology is associated with higher risk of recurrence in patients who underwent LT for HCC. Neither tumor differentiation nor degree of viability predicted HCC recurrence post-LT in this study. These findings warrant validation with prospective studies.

TABLE



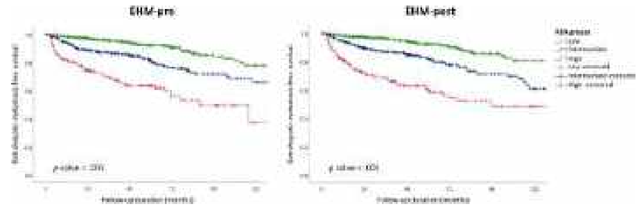
Variables		No recurrence	Recurrence	OR (95% CI, p-value)	
				Univariable	Multivariable
Sites	MI	42 (91.3)	4 (8.7)		
	MN	104 (86.7)	16 (13.3)	1.62 (0.55-5.89, p=0.41)	
	VU	124 (95.4)	6 (4.6)	0.51 (0.14-2.07, p=0.31)	
Gender	Female	51 (92.7)	4 (7.3)		
	Male	219 (90.9)	22 (9.1)	1.28 (0.47-4.52, p=0.06)	
Age at transplant	Mean (SD)	60.6 (7.6)	60.1 (6.1)	0.99 (0.95-1.05, p=0.76)	
Maximal lesion size per patient (cm)	Mean (SD)	2.9 (1.6)	3.7 (2.0)	1.27 (1.03-1.56, p=0.02)	1.27 (1.01-1.57, p=0.03)
Viability of any lesion on explant		200 (90.9)	20 (9.1)	1.63 (0.53-7.13, p=0.04)	1.85 (0.58-8.47, p=0.35)
Viability percent per patient	Mean (SD)	31.2 (35.0)	24.9 (32.5)	0.99 (0.98-1.01, p=0.43)	

Disclosures: Neehar Dilip Parikh – Freenome: Consultant, No, Yes; Gilead: Advisor, No, Yes; Exelixis: Consultant, No, No; Astra Zeneca: Consultant, No, No; Fujifilm Medical: Consultant, Yes, Yes;
The following people have nothing to disclose: Suraj Pai, Varvara A. Kirchner, Manhal Izzy
Disclosure information not available at the time of publication: Muhammad Hashim Hayat, Joseph Sushil Rao, Erin Bouquet, Ioannis Ziogas, Anthony Borgmann, Hassan Anbari, Christopher Slaughter, Oyedele A. Adeyi, Sophoclis Alexopoulos

f 4107-A | PREOPERATIVE AND POSTOPERATIVE VARIABLES FOR PREDICTING EXTRAHEPATIC METASTASIS OF HEPATOCELLULAR CARCINOMA AFTER CURATIVE SURGICAL RESECTION

Chang Hun Lee[1], Jae Hyun Yoon[2], Hoon Gil Jo[3], Eun Young Cho[3], Chung Hwan Jun[4] and In Hee Kim[1], (1)Jeonbuk National University Medical School and Research Institute of Clinical Medicine of Jeonbuk National University Hospital-Jeonbuk National University Medical School, (2)Chonnam National University Hospital, (3)Wonkwang University College of Medicine and Hospital, (4)Mokpo Hankook Hospital

Background: Factors associated with extrahepatic metastasis (EHM) after curative treatment of hepatocellular carcinoma (HCC) have rarely been investigated. This study aimed to assess EHM occurrence after curative resection in HCC patients. **Methods:** A retrospective review was conducted on treatment-naïve HCC patients who underwent curative resection between 2004 and 2019 at four tertiary hospitals. Recurrence characteristics after resection were evaluated, and predictors associated with EHM in HCC patients after curative resection were analyzed. **Results:** A total of 1,069 HCC patients treated with surgical resection were enrolled for the study. The mean age was 59.1 ± 10.2 years, with 85.8% of patients being male. The majority of patients (98.6%) had compensated liver cirrhosis, with chronic hepatitis B being the most common etiology of chronic liver disease (73.7%). During the follow-up period, there were 165 (19.6%) cases of EHM. Patients with EHM were younger and had a higher proportion of advanced modified UICC and BCLC stages, as well as a higher proportion beyond Milan criteria. Histologically, patients with EHM had larger tumor size and number, advanced Edmondson-Steiner (ES) grade, and a higher proportion of microvascular invasion, bile duct invasion, intrahepatic metastasis, and necrosis. Multivariate Cox regression analysis revealed that ln(Age), modified UICC stage, beyond Milan criteria, and ALBI grade ≥ 2 were independently significant factors associated with EHM in preoperative variables. Similarly, ln(Age), microvascular invasion, necrosis, beyond Milan criteria, and ALBI grade ≥ 2 were independently significant factors associated with EHM in postoperative variables. Kaplan-Meier plots clearly differentiated EHM-free survival among low, intermediate, and high-risk groups stratified by the EHM-preop and EHM-postop models. **Conclusion:** This study analyzed preoperative and postoperative variables to predict EHM following curative surgical resection, resulting in the development of statistical models (EHM-preop and EHM-postop). These models have the potential to aid in clinical decision-making, but further validation studies are necessary.



Disclosures: The following people have nothing to disclose: Chang Hun Lee, Jae Hyun Yoon, Hoon Gil Jo, Eun Young Cho, Chung Hwan Jun, In Hee Kim

4108-A | PREVALENCE AND IMPACT OF PORTAL VEIN THROMBOSIS IN PATIENT WITH BILIARY MALIGNANCIES

Ayobami Olafimihan[1], Chidiebele Omaliko[2], Chun-Wei Pan[3], Sania Saleem[3], Chukwunonso Ezeani[4], Ifeoluwa Stowe[4], Oghenefejiro Ogwor[5], Praise Fawehinmi[6] and Rotimi Asemota[1], (1)John H Stroger Jr. Hospital of Cook County, (2)One Brooklyn Health - Brookdale University Hospital Medical Center, (3)John H. Stroger Jr. Hospital of Cook County, (4)Baton Rouge General Medical Center, Baton Rouge, LA, (5)St Peter University Hospital, New Brunswick, NJ, (6)University of Ilorin

Background: Portal vein thrombosis (PVT) is associated with gastrointestinal malignancies such as hepatocellular, biliary, pancreatic, and colonic cancers. PVT has been shown to portend a poor prognosis in some patients; however, uncertainty exists about the impact of PVT on patients admitted with biliary malignancies (gallbladder cancer and cholangiocarcinomas). **Methods:** Retrospective cohort analyses were performed using the National Inpatient Sample (NIS) data collected between 2016 and 2020. Multivariable logistic and linear regression models were used to examine the prevalence of PVT and its impact on biliary cancer (BC) patients. **Results:** There were a total of 82,850 inpatient admissions for BC, and the overall prevalence of PVT was 14%. Black race, male gender, younger age, teaching hospital, urban hospital, and large hospital were associated with higher PVT prevalence rates. Patients admitted for BC with PVT had increased all-cause mortality of 29% compared to those without PVT (odd ratio: 1.29, 95% confidence interval (CI) 1.12-1.50, $p = 0.001$), however, multivariate analysis revealed similar inpatient mortality outcomes between both cohort (adjusted odds ratio (AOR): 1.14, 95% CI 0.97-1.34, $p = 0.112$). BC patients with PVT had shorter mean LOS (6.4 vs. 6.6 d, $p = 0.004$), and lower mean total hospital charges by over $10,000 ($73, 278 vs $85,444, $p < 0.001$) when compared to their counterparts without PVT. BC patients with PVT had reduced odds of sepsis (AOR: 0.75, 95%CI: 0.59-0.96%) and bile duct obstructions (AOR: 0.53, 95%CI: 0.46-0.61, P < 0.001), and were more likely to receive inpatient palliative team care (AOR:1.33, 1.19-1.47, P < 0.001). They were also less likely to undergo interventional procedures like common bile duct drainage (AOR: 0.3, 95% CI: 0.9-0.94, P: 0.041) and hepatobiliary duct device insertion (AOR: 0.45, 95% CI: P < 0.001) **Conclusion:** Hospitalized biliary cancer patients with PVT have similar adjusted odds of inpatient mortality, but lower LOS and healthcare utilization than biliary cancer patients without PVT.

Disclosures: The following people have nothing to disclose: Ayobami Olafimihan, Chidiebele Omaliko, Chun-Wei Pan, Sania Saleem, Chukwunonso Ezeani, Ifeoluwa Stowe, Oghenefejiro Ogwor, Praise Fawehinmi, Rotimi Asemota

4109-A | PROGNOSIS-ORIENTED DEFINITION OF BORDERLINE RESECTABLE HEPATOCELLULAR CARCINOMA

Koichiro Haruki[1], Norifumi Harimoto[2], Kenei Furukawa[1], Tomohiko Taniai[1], Munetoshi Akaoka[1], Mitsuru Yanagaki[1], Shinji Onda[3], Yoshihiro Shirai[3], Ken Shirabe[2] and Toru Ikegami[1], (1)The Jikei University School of Medicine, (2)Gunma University, (3)The Jikei University School of Medicone

Background: With the advances in multidisciplinary treatment of hepatocellular carcinoma (HCC), the definition of borderline resectable (BR) is warranted. We aimed to define BR-HCC using a prognosis-oriented approach. **Methods:** The study comprised a training cohort of 221 patients and an independent validation cohort of 181 patients who had undergone primary hepatic resection for HCC. To define the oncological borderline resectable (BR)-HCC, we investigated the risk factors for the early unresectable recurrence (beyond Milan criteria) within one year after hepatic resection using multivariate logistic regression models. We then developed BR score using identified risk factors and defined BR-HCC. The utility of the BR score was validated in the independent validation cohorts. **Results:** In the training cohort, the recurrence beyond Milan criteria within one year was observed in 28 patients (13%), and 5-year survival of those patients was 25%. Multivariate analysis identified the risk factors for the recurrence beyond Milan criteria within one year, including serum AFP level ≥ 12 ng/mL ($p = 0.02$), tumor diameter > 5 cm ($p = 0.02$), number of tumors ≥ 3 ($p = 0.001$), and macrovascular invasion ($p = 0.04$). BR-HCC was defined as tumors with more than two identified risk factors and 42 patients (19%) were recognized as BR-HCC with 5-year survival rate of 51%. In the validation cohort, BR-HCC was observed in 45 patients (25%) with 5-year survival rate of 42%. **Conclusion:** Prognosis-oriented definition of BR-HCC enable us to identify the patients who can develop early unresectable recurrence and have poor survival after hepatic resection for HCC. For BR-HCC, preoperative chemotherapy may be an option to improve the outcome after hepatic resection.

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Disclosure information not available at the time of publication: Norifumi Harimoto, Shinji Onda, Yoshihiro Shirai, Ken Shirabe

4110-A | PROGNOSTIC IMPACT OF THE PROGRESSION OF LUNG METASTASIS AFTER THE FIRST CYCLE OF ATEZOLIZUMAB PLUS BEVACIZUMAB IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Background: Atezolizumab plus bevacizumab (Atezo/Bev) has been established as a standard first-line systemic treatment for advanced hepatocellular carcinoma (HCC). We aimed to investigate overall and organ-specific responses and their impact on survival in a specific group of patients with HCC and pulmonary metastases receiving Atezo/Bev. **Methods:** This study included 73 consecutive HCC patients with at least one measurable lung metastasis and preserved liver function who received at least three 3-weekly cycles of Atezo/Bev at the Asan Medical Center, South Korea between 2018 and 2023. Responses assessment was based on RECIST v1.1: all metastatic lung lesions in present study were measurable. We defined “responders” as patients who achieved complete remission (CR) or partial remission (PR); and “progressors” as those with progressive disease (PD) at an initial evaluation after 3 cycles of treatment. The Kaplan-Meier method and Cox proportional model were used for overall survival (OS) analyses. **Results:** Of the 73 patients, 46 (63.0%) had a single lung metastasis with/without intrahepatic lesions, and 55 (70.3%) and 25 (34.2%) were accompanied by intrahepatic HCC and vascular invasion of the tumors, respectively. The OS rate at 1-, 3-, 5-years were 78.2%, 59.9%, and 49.9%, respectively in the entire cohort with a median follow-up of 10.6 months. Of entire patients, 8 (11.0%) achieved overall response (0 CR and 8 PR), with 27 (37.0%) lung-specific responders (4 CR and 12 PR). Overall and lung-specific progressors were 20 (27.4%) and 25

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

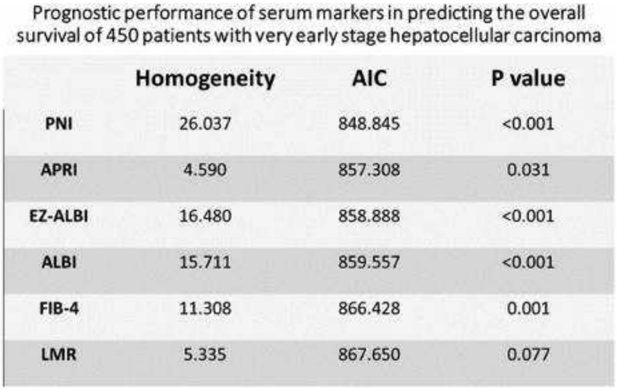
(34.2%), respectively. Overall and pulmonary progressors had significantly lower survival rates than the counterparts (59.9% vs. 83.3% and 47.0% vs. 89.9% at 1 y; $Ps < 0.05$), as was neither overall nor pulmonary responders. The lung-specific progressor and presence of macrovascular invasion were independent factors affecting survival, irrespective of other intra- and extrahepatic status of the tumors. **Conclusion:** Based on our data, pulmonary response to Atezo/Bev could help clinicians decide whether to continue the drug or switch to second-lines at an early phase of the initial therapy for HCCs with metastasis to the lung.

Disclosures: The following people have nothing to disclose: Jiwon Yang, Jonggi Choi, Won-Mook Choi, Kang Mo Kim, Han Chu Lee, Ju Hyun Shim

4111-A | PROGNOSTIC NUTRITIONAL INDEX AS A PROGNOSTIC FACTOR FOR VERY EARLY STAGE HEPATOCELLULAR CARCINOMA

Chun-Ting HO[1,2], Chien-Wei Su[1,2], Elise Chia-Hui Tan[3], Wei-Yu Kao[4], Yi-Hsiang Huang[5,6], Teh-la Huo[1,2], Ming-Chih Hou[5,7] and Jaw-Ching Wu[1], (1)National Yang Ming Chiao Tung University, (2)Taipei Veterans General Hospital, (3)China Medical University, (4)Taipei Medical University Hospital, (5)Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, (6)Faculty of Medicine, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan, (7)Department of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

Background: Field factors play more important roles in predicting the outcomes of patients compared with tumor factors in early-stage hepatocellular carcinoma (HCC). However, the prognostic ability of modern non-invasive serum marker scores for hepatic fibrosis and liver functional reserve on very early-stage HCC is still not yet determined. We aimed to investigate the performance of these serum marker scores in predicting the prognoses of patients with very early-stage HCC. **Methods:** A total of 450 patients with the Barcelona Clinic Liver Cancer (BCLC) classification stage 0 HCC diagnosed at Taipei Veterans General Hospital from 2012 to 2022 were retrospectively enrolled. Serum biomarkers and prognostic scores determining poor overall survival (OS) were analyzed by Cox proportional hazards model and logistic regression. We compared the homogeneity, and Akaike information criterion (AIC) among the prognostic nutritional index (PNI), AST to Platelet Ratio Index (APRI), albumin-bilirubin (ALBI) score, EZ (easy)-ALBI score, fibrosis (FIB)-4 score and lymphocyte-to-monocyte ratio (LMR) to determine the predictability on the OS of patients. **Results:** After a median follow-up of 35.0 months (interquartile range IQR 19.0-60.0 mo), 81 patients died, with a 5-year OS rate of 76.9%. Among the non-invasive serum marker scores, PNI had the best performance in predicting the OS of patients with the highest homogeneity and lowest AIC compared to other scores. Moreover, we stratified the patients into high-risk ($PNI < 45$) and low-risk ($PNI >= 45$) groups. It showed that the 5-year OS rates were 83.3% and 63.1% in the low-risk and high-risk PNI groups, respectively ($p < 0.001$). **Conclusion:** PNI had the best performance in predicting the OS for patients with very early-stage HCC.



Prognostic performance of serum markers in predicting the overall survival of 450 patients with very early stage hepatocellular carcinoma

	Homogeneity	AIC	P value
PNI	26.037	848.845	<0.001
APRI	4.590	857.308	0.031
EZ-ALBI	16.480	858.888	<0.001
ALBI	15.711	859.557	<0.001
FIB-4	11.308	866.428	0.001
LMR	5.335	867.650	0.077

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4112-A | PROGNOSTIC SCORING SYSTEMS FOR LOCOREGIONAL THERAPY TO PREDICT ONE YEAR SURVIVAL IN HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW

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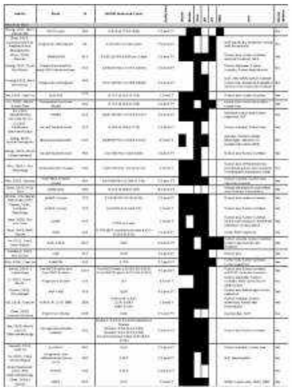
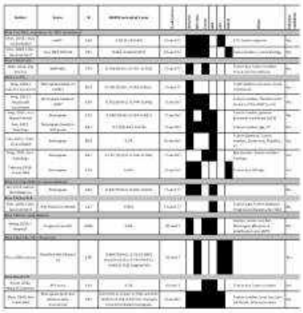
Background: Locoregional therapies (LRT) are effective in halting hepatocellular carcinoma (HCC) growth. The outcome LRT is variable. However, rigorous evaluations and comparisons of prognostic models for predicting HCC survival after LRT are lacking. We systematically reviewed the performance and methodological quality of prognostic models assessing survival at one-year LRTs in HCC treatment using parameters readily available in the clinical setting **Methods:** We searched EMBASE and PUBMED from inception to 12/9/22. Inclusion criteria focused on studies that provided data on developing or validating prognostic models using clinical variables. The primary outcome measure was the area under the receiver operating characteristics curve (AUROC) to predict one-year survival after treatment. Two investigators independently conducted data abstraction. Methodological quality was assessed using scoring systems adapted from the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement and the Steyerberg system. We defined an acceptable quality study when the methods reported adequate variable selection, validation techniques, performance, calibration, and discrimination, being acceptable quality when they had ≥ 5 for TRIPOD or ≥ 7 for Steyerberg. To further emphasize the quality of the scoring systems, external validation (EV) was also considered. **Results:** Out of 1,267, 47 studies met our inclusion and exclusion criteria (Table). These studies examined primary transarterial chemoembolization (TACE), re-TACE, transarterial radioembolization (TARE) with Yttrium (Y) 90, primary radiofrequency ablation (RFA), microwave ablation (MWA), TACE or RFA, TACE or local ablation, percutaneous alcohol/ethanol injection (PAI/PEI), or resection, and combination of the prior LRT. AUROC for 1-year survival: primary TACE (AUROC, 0.57-0.89), re-TACE (0.66-0.82), Y90 TARE (0.76), initial RFA (0.69-0.79), MWA (0.73), TACE or RFA (0.89), TACE or local ablation (0.66), TACE, PAI, PEI, or resection (0.80), mixed LRT (0.69-0.81). The top performers in each category were: ALBI/PALBI score for primary TACE (0.84). For the rest of the categories: mART for re-TACE (0.82), SNAP-HCC for Y90 TARE (0.76, not EV), nomogram based on CONUT for initial RFA (0.80), nomogram for 1st guided microwave ablation (0.64, not EV), risk prediction model for TACE or RFA (0.89, not EV), modified MELD-based JIS for TACE, PAI, PEI, or resection (0.80), and nomogram for mixed LRT (0.78). **Conclusion:** Several high-quality clinical scoring systems are available prognosticate one-year survival in patients with undergoing LRT using readily available parameters. These models can assist clinicians and patients in making informed decisions regarding choosing LRT for HCC treatment.





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4113-A | PROGNOSTIC VALUE OF EXPRESSION OF PD-1 AND CTLA-4 IN PERIPHERAL BLOOD IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Hyuk Soo Eun[1,2], Tae Hee Lee[3], Jeongdong Lee[3], Min Seok Kim[3], Woo Sun Rou[4], Hong Jae Jeon[5], Seok Hyun Kim[6], Byung Seok Lee[6], Hei-Gwon Choi[7], Ha Neul Kim[7], Tae Min Jang[8], Ji Ah Lee[8], Chae Yeon Son[8] and Jiyoon Bu[8], (1)Chungnam National University Hospital, (2)Chungnam National University, College of Medicine, (3)Daegu Health College, (4)Chungnam National University Sejong Hospital, (5)Department of Internal Medicine, Chungnam National University Sejong Hospital, (6)Department of Internal Medicine, Chungnam National University Hospital, (7)Chungnam National University, (8)Inha University

Background: Hepatocellular carcinoma (HCC) is the second most prevalent cause of cancer-related death worldwide. The poor prognosis of HCC is attributed to the lack of a biomarker that can effectively predict patients' responses to various treatments. In this study, we investigated the potential of programmed death 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) gene expressions in peripheral blood mononuclear cells (PBMCs) as prognostic biomarkers for HCC. **Methods:** This study was approved by an institutional review board of Chungnam national University Hospital, Daejeon, Korea (CNUH- 2020-10-08). The buffy coat was excepted from EL buffer for erythrocytes lysis, and was treated with 20 μl proteinase, and mixed with 200 μl lysis buffer. The samples were incubated at 57 ˚C for 15 min, then, were reacted with 200 μl of ethanol. PD-1 and CTLA-4 DNA expressions were obtained by comparing the gene expression with the reference gene, *RPP30* ($2^{-\Delta Ct}$). $\Delta Ct = Ct$ (PD-1 or CTLA-4) – Ct (RPP30). **Results:** Neither CTLA-4 nor PD-1 gene expression in PBMCs was associated with the patients' tumor size, multifocality, and modified UICC stages. Specifically, the AUROC values for determining HCC patients with tumor sizes larger than the average, multifocal tumors, and high modified UICC tumor stages (>2) were all less than 0.720 ($p > 0.05$). Nevertheless, both genes were strongly associated with patients' outcomes. A Kaplan-Meier survival analysis revealed that patients with low CTLA-4 gene expressions ($\leq$ median) exhibited a 1.51-fold ($p = 0.022$) longer mean

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

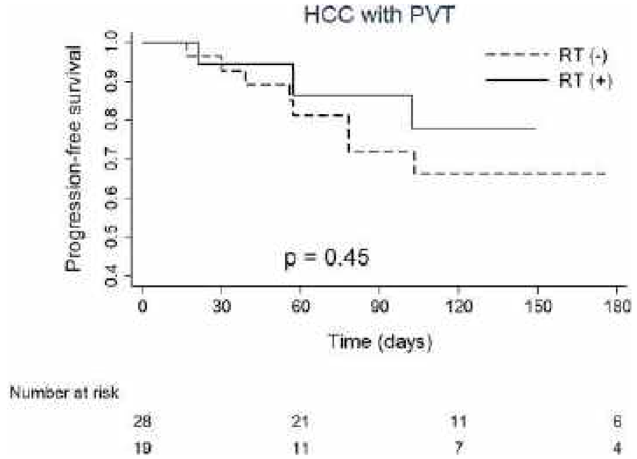
overall survival (OS) than those with high CTLA-4 gene expressions. Moreover, PD-1 gene expressions demonstrated an even higher predictive value in estimating HCC patients' survival. None of the patients with low PD-1 gene expressions (≤ median) died during this study, while patients with high PD-1 expressions showed a poor OS of 36.0 ± 9.0 months ($p < 0.001$). Interestingly, these biomarkers outperformed α-fetoprotein (AFP), which is the most frequently used biomarker in clinical trials. Patients with lower-than-the-median serum AFP scores had only a 1.17-fold longer OS than those with low serum AFP levels. Similarly, we examined the correlation between patients' progression-free survival (PFS) and the expression of each biomarker. Indeed, PD-1 gene expression was the only biomarker that showed a significant difference between patients with low and high biomarker expressions (3.06-fold longer PFS for patients with low PD-1 gene expressions; $p = 0.012$). **Conclusion:** In this study, we have demonstrated that the genes associated with immune checkpoint genes can be utilized as a prognostic biomarker for HCC. Notably, PD-1 gene expression in PBMCs has a great potential for estimating survival outcomes of patients with HCC.

Disclosures: The following people have nothing to disclose: Hyuk Soo Eun, Tae Hee Lee, Jeongdong Lee, Min Seok Kim, Woo Sun Rou, Hong Jae Jeon, Seok Hyun Kim, Byung Seok Lee, Hei-Gwon Choi, Ha Neul Kim, Tae Min Jang, Ji Ah Lee, Chae Yeon Son, Jiyoon Bu

4114-A | RADIOTHERAPY COMBINED WITH ATEZOLIZUMAB PLUS BEVACIZUMAB FOR HEPATOCELLULAR CARCINOMA WITH PORTAL VEIN TUMOR THROMBUS

Yunjeong Lee and Jin-Wook Kim, Seoul National University Bundang Hospital

Background: Based on the IMbrave150 trial, the combination of atezolizumab and bevacizumab is used as first-line standard of care for advanced hepatocellular carcinoma. However, the efficacy of the combination regimen has been unsatisfactory in HCC patients with portal vein tumor thrombosis (PVTT). The use of concomitant external beam radiation therapy may increase local tumor control rate, but it is not established whether addition of radiotherapy increases the tumor response rate in HCC patients on atezolizumab and bevacizumab combination. Here, we assessed the efficacy of the additional radiotherapy to the combination of atezolizumab/bevacizumab compared to the combination regimen alone. **Methods:** This retrospective study included 133 patients with the combination of atezolizumab and bevacizumab with or without concomitant radiotherapy from June 2003 to February 2023. The presence of portal vein thrombosis was defined as the intraluminal filling defect in portal venous system on computed tomography. The modified response evaluation criteria in solid tumors (RECIST) on CT/MRI images was used to assess treatment responses of each therapy. We carried out Kaplan-Meier and Cox regression analysis to estimate progression-free survival (PFS) and investigate the influence of concurrent radiotherapy on change in tumor burden. **Results:** A total of 56 patients received of atezolizumab and bevacizumab for HCC with portal vein invasion. Among the cohort, radiotherapy was added to 21 patients. Kaplan–Meier analysis estimated that the 6-month PFS rate of the total cohort was 70.6%. The concomitant radiation therapy was not shown to significantly improve PFS ($HR = 0.40$, 95% $CI = 0.10 – 1.65$; $p = 0.45$; Figure). **Conclusion:** Addition of external beam radiation did not significantly increase local tumor response rate in HCC patients with portal vein invasion. Further prospective studies would be warranted to validate our findings.



Disclosures: The following people have nothing to disclose: Yunjeong Lee, Jin-Wook Kim

4115-A | REAL-WORLD EXPERIENCE OF ATEZOLIZUMAB PLUS BEVACIZUMAB COMBINATION TREATMENT IN HIGH-RISK PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

Hyun Young Woo[1], Sangyoun Hwang[2], Jeong Heo[3], Hyung Jun Kim[4], Young Joo Park[1], Ki Youn Yi[1], Yu Rim Lee[5], Soo Young Park[5], Woo Jin Chung[6], Byoung-Kuk Jang[6] and Won Young Tak[7], (1)Department of Internal Medicine, College of Medicine, Pusan National University and Biomedical Research Institute, Pusan National University Hospital, (2)Dongnam Institute of Radiological & Medical Sciences, (3)Department of Internal Medicine, College of Medicine, Pusan National University, Busan, South Korea, (4)Department of

Internal Medicine, Dongnam Institute of Radiologic & Medical Sciences, (5)School of Medicine, Kyungpook National University, (6)Keimyung University School of Medicine, (7)College of Medicine, Kyungpook National University

Background: A recent phase 3 trial led to the approval of atezolizumab plus bevacizumab as first-line treatment for advanced hepatocellular carcinoma (HCC). However, real-world data regarding the response to this regimen are lacking in high-risk patients with advanced HCC. **Methods:** In this multicenter retrospective cohort study, 215 patients with advanced HCC who received atezolizumab plus bevacizumab treatment at four different tertiary hospitals were examined. High-risk patients had grade Vp4 portal vein thrombus, bile duct invasion, or more than 50% liver infiltration. **Results:** Among the 215 patients, 98 (45.6%) were in the high-risk population, 186 (86.5%) had Child-Pugh class A, 29 (13.5%) had Child-Pugh class B, and 128 (59.5%) had previously received neoadjuvant or concomitant radiation treatment. Analysis of the total population indicated that the median PFS was 8.00 months (95% CI, 6.82-9.18) and median OS was 11.25 months (95% CI, 9.50-13.10). In the high-risk population, the median progression free survival (PFS) was 6.50 months (95% CI, 3.93–9.08), and the median overall survival (OS) was 10 months (95% CI, 8.19–11.82). In the high-risk population, multivariate analysis indicated that receipt of neoadjuvant or concomitant radiation therapy was associated with better PFS and OS; median OS; 12.00 months (9.33-14.67) vs. 5.75 (3.24-8.26) and median PFS; 9.25 months (7.66-10.84) vs. 3.25 (2.27-4.23) in radiation and without radiation therapy, respectively. Ninety-two patients (42.8%) experienced adverse events of any grade; the most common adverse event was proteinuria (14.8%). **Conclusion:** Atezolizumab plus bevacizumab treatment showed consistent efficacy and tolerability in the total population and in the high-risk population. Previous radiation therapy increased PFS and OS in the high-risk group.

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4116-A | RISK FACTORS AND NATURAL HISTORY OF HEPATOCELLULAR CARCINOMA (HCC): OBSERVATIONS FOLLOWING SUCCESSFUL SOFOSBUVIR-BASED TREATMENT IN HCV PATIENTS WITH CIRRHOSIS

K Rajender Rajender Reddy[1], Therese Bittermann[1], Nour Khaddaj-Mallat[2], Ingrid Zhou[2], Janine Zhu[2], Ryan Ea[2], Catherine Frenette[3], Stacey Scherbakovsky[3], Renee-Claude Mercier[3], Xu Zhang[3], Ben L. Da[3], Anu O. Osinusi[3], Andrew Joseph Muir[4], Ira M. Jacobson[5] and Alessandra Mangia[6], (1)University of Pennsylvania, (2)University of California at San Francisco, (3)Gilead Sciences, Inc., (4)Duke University, (5)NYU Grossman School of Medicine, (6)Liver Unit, Fondazione Irccs "Casa Sollievo Della Sofferenza", San Giovanni Rotondo, Italy

Background: Hepatitis C virus (HCV) infection is a major risk factor for hepatocellular carcinoma (HCC), including even patients who have achieved sustained virologic response (SVR). There is a need to identify predictors of HCC development after SVR to improve the efficiency of HCC screening. Data were analyzed to determine risk factors of HCC and characterize the natural history of HCC development in patients who have achieved SVR with sofosbuvir-based direct-acting antiviral therapy (DAA). **Methods:** Data were collected prospectively from a Gilead-sponsored registry (#NCT02292706) which enrolled and followed those with HCV cirrhosis who had achieved SVR with a sofosbuvir-based DAA regimen for up to 5 years. The primary outcomes were HCC, death in those who developed or never developed HCC. The risk factors of these outcomes were evaluated. Baseline characteristics at time of entry into the registry included demographics, HCV genotype, prior HCV treatment experience, hemoglobin A_1C, liver chemistries, Child-Pugh-Turcotte (CPT) score, enhanced liver fibrosis (ELF) score (F0-F2 < 9.8, F3 = 9.8-11.3 and F4 > 11.3) and liver stiffness (LS) by transient elastography (TE) (F0–2: < 9.5 kPa; F3: 9.6–12.5 kPa; and F4: > 12.5 kPa). Univariate and multivariate analyses were performed to determine risk factors for development of HCC and death by Cox regression analysis. A Kaplan-Meier plot was utilized to analyze time to HCC diagnosis. **Results:** Out of 1557 individual's in the registry, 132 developed de novo HCC. Baseline characteristics of those with HCC are as follows: mean age 61 years, 74% males, 90% white, mean (SD) body mass index (BMI) 28.9 (4.83), mean (SD) platelet count 118 (59.9) x10^3/μL, median (Q1, Q3) MELD score 8 (7, 10), median (SD) ELF score 10.7 (9.9, 11.6), median (Q1, Q3) FIB4 score 3.9 (2.3,

6.0), mean (SD) AFP level 75 (774.6), median (Q1, Q3) LS 20.4 kPa (12.6, 34.3) and CPT score of 5 (67%), 6 (15%), 7 (9%), 8 (2%), 9 (1%). 52% of patients who developed de novo HCC were diagnosed greater than 2 years after the start of the registry and only 12% developed de novo HCC within the first 6 months. Baseline albumin level < 3.5 g/dL ($p = 0.002$), LS by TE F4 ($p = 0.010$), platelets $< 150\ X10^3$/uL ($p = 0.005$) and pre-treatment BMI ($p = 0.044$) were associated with de novo HCC (Table). Twenty patients (15.2%) with HCC died during the registry. Of those, patients with compensated liver disease at baseline (CPT A) had an 82% reduction in risk of death compared to those with decompensated liver disease (CPT B+C). **Conclusion:** Low albumin level, low platelet count, and F4 on LS are predictive of an increased risk of de novo HCC development in patients with cirrhosis who achieved SVR post DAA. These patients require close monitoring for several years following SVR. Mortality in those with HCC development was often in those with more advanced liver disease.

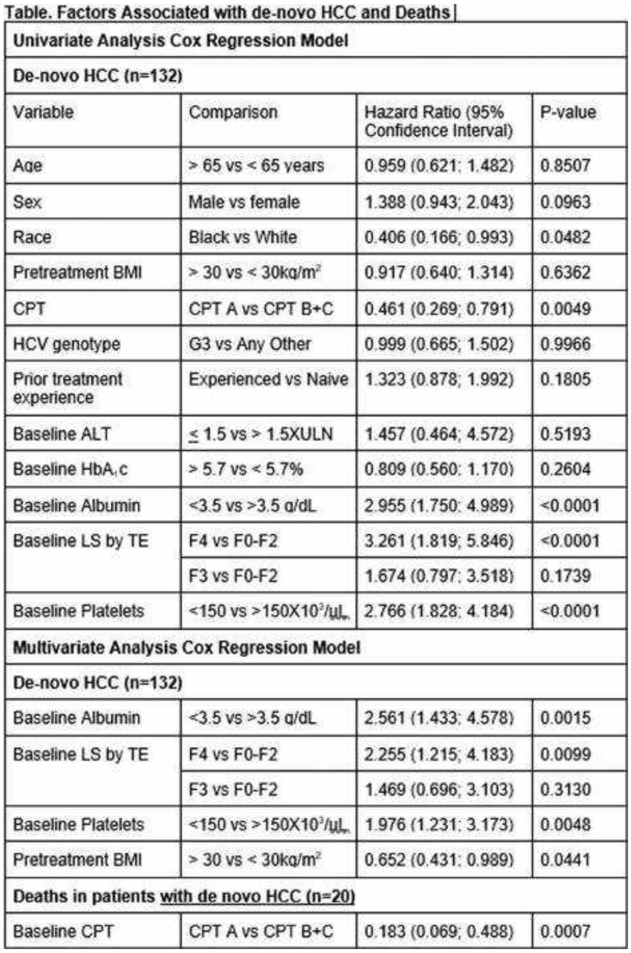

Table. Factors Associated with de-novo HCC and Deaths

Univariate Analysis Cox Regression Model			
De-novo HCC (n=132)			
Variable	Comparison	Hazard Ratio (95% Confidence Interval)	P-value
Age	> 65 vs < 65 years	0.959 (0.621; 1.482)	0.8507
Sex	Male vs female	1.388 (0.943; 2.043)	0.0963
Race	Black vs White	0.406 (0.166; 0.993)	0.0482
Pretreatment BMI	> 30 vs < 30kg/m^2	0.917 (0.640; 1.314)	0.6362
CPT	CPT A vs CPT B+C	0.461 (0.269; 0.791)	0.0049
HCV genotype	G3 vs Any Other	0.999 (0.665; 1.502)	0.9966
Prior treatment experience	Experienced vs Naive	1.323 (0.878; 1.992)	0.1805
Baseline ALT	≤ 1.5 vs > 1.5XULN	1.457 (0.464; 4.572)	0.5193
Baseline HbA$_1$c	> 5.7 vs < 5.7%	0.809 (0.560; 1.170)	0.2604
Baseline Albumin	<3.5 vs >3.5 g/dL	2.955 (1.750; 4.989)	<0.0001
Baseline LS by TE	F4 vs F0-F2	3.261 (1.819; 5.846)	<0.0001
	F3 vs F0-F2	1.674 (0.797; 3.518)	0.1739
Baseline Platelets	<150 vs >150X10^3/uL	2.766 (1.828; 4.184)	<0.0001
Multivariate Analysis Cox Regression Model			
De-novo HCC (n=132)			
Baseline Albumin	<3.5 vs >3.5 g/dL	2.561 (1.433; 4.578)	0.0015
Baseline LS by TE	F4 vs F0-F2	2.255 (1.215; 4.183)	0.0099
	F3 vs F0-F2	1.469 (0.696; 3.103)	0.3130
Baseline Platelets	<150 vs >150X10^3/uL	1.976 (1.231; 3.173)	0.0048
Pretreatment BMI	> 30 vs < 30kg/m^2	0.652 (0.431; 0.989)	0.0441
Deaths in patients with de novo HCC (n=20)			
Baseline CPT	CPT A vs CPT B+C	0.183 (0.069; 0.488)	0.0007

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Disclosure information not available at the time of publication: Nour Khaddaj-Mallat, Ingrid Zhou, Ryan Ea, Stacey Scherbakovsky, Andrew Joseph Muir

4117-A | RISK FACTORS ASSOCIATED WITH LATE HCC DETECTION IN PATIENTS WITH CHRONIC LIVER DISEASE UNDER REGULAR SURVEILLANCE

Jung Hwan Yu, Sangmi Jang, Young Joo Jin and Jin-Woo Lee, Inha University

Background: Hepatocellular carcinoma (HCC) has a very poor prognosis with a 5-year survival rate of less than 20%, and early diagnosis is very important. However, despite regular check-ups for high-risk groups of HCC, there are a few cases in which it is discovered as a late-stage of HCC. Therefore, this study intended to investigate the characteristics of patients with delayed HCC detection during regular HCC surveillance. **Methods:** Between January 2010 and December 2020, we analyzed patients with newly diagnosed HCCs who were screened for HCC by ultrasound or CT scan at least twice while following up for more than 1 year due to hepatitis B, hepatitis C, and chronic liver disease. **Results:** The mean age of a total of 223 HCC patients was 70 years, of which 152 were male, accounting for 68.1%. Among them, 196 patients (87%) were diagnosed with BCLC stage 0 or A, while 27 patients (13%) were found to be in BCLC stages B and C. When classified according to the TNM criteria, 154 patients (69%) were in stage I and 69 patients (31%) were in stage II or higher. In this study, a multivariate analysis performed to identify risk factors for patients diagnosed with late-stage HCC, CTP score was identified as a highly significant factor ($p = 0.002$, HR 1.547, 95% CI 1.177 - 2.032), while the presence of cirrhosis, BMI, and sex had no significant effect. **Conclusion:** We found that in patients with chronic liver disease who were screened regularly, patients with higher CTP scores were more likely to be diagnosed with HCC in late-stages. Therefore, although the presence of cirrhosis is also important for HCC surveillance, more careful attention is needed for patients with high CTP scores.

Disclosures: The following people have nothing to disclose: Jung Hwan Yu, Sangmi Jang, Young Joo Jin, Jin-Woo Lee

4118-A | RISK FACTORS OF HEPATOCELLULAR CARCINOMA IN US MILITARY SERVING IN VIETNAM DURING A LONG-TERM FOLLOW UP AFTER AGENT ORANGE EXPOSURE

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Background: Hepatocellular carcinoma (HCC) and its mortality are on the rise. Early detection is associated with improved overall survival. Identifying clinical risk factors is key to implementing early prevention and risk stratifying patients who might benefit from early surveillance. Agent Orange (AO) is an herbicide that has been linked to several cancers; however, its association with hepatobiliary malignancies remains unclear. We aimed to assess the association between AO exposure and HCC in a large national Veteran cohort following the Vietnam era. **Methods:** We conducted a retrospective study of Vietnam Veterans (1966-1975) with established follow-up in the Veterans' Affairs between 2000-2019. AO exposure was defined as any Veteran flagged in the disability data as having been exposed to AO based on validated clinical surveys linked to service connection. Relevant clinical risk factors were collected, including etiologies of cirrhosis and features of the metabolic syndrome. Patients were stratified based on cirrhosis status, as defined by consecutive FIB-4 scores and cirrhosis ICD-codes. Incident HCC was the primary outcome identified using the VA Central Cancer Registry or validated ICD-codes. AO and HCC association was estimated using a multivariable Cox regression analysis, with death and liver transplant as competing events. **Results:** Of the 296,505 eligible Veterans, 170,090 (57%) were exposed to AO and 35,877 (12%) had cirrhosis. Veterans not exposed to AO were more likely to smoke (86.8% vs 85.9%, p < 0.001); use alcohol (42.8% vs 42.3%, p = 0.0038) and have viral hepatitis (37.8% vs 34.7%, p < 0.001). In a multivariable competing risk model, AO exposure did not affect the risk of HCC among patients with cirrhosis. However, self-identification as Hispanic (adj.HR = 1.51, 95%CI 1.30-1.75, p < 0.0001) or Black (adj.HR = 1.18, 95%CI 1.05-1.32, p = 0.0035), viral hepatitis (adj.HR = 3.71, 95%CI 3.26-4.24, p < 0.0001), alcohol liver disease (adj.HR = 1.32, 95%CI 1.19-1.46, p < 0.0001) and NAFLD (adj.HR = 1.92, 95%CI 1.72-2.15, p < 0.0001) were associated with incident HCC. Among Veterans without cirrhosis, hypertension (adj.HR = 1.63, 95%CI 1.23-2.15, p = 0.0006) and diabetes (adj.HR = 1.52, 95%CI 1.13-2.05, p = 0.0053) were also associated with HCC. Age at deployment was inversely associated with HCC in patients with cirrhosis (adj.HR = 0.96, 95%CI 0.95-0.98, p0.0001). After stratifying age at deployment by decades, we observed that early smoking and alcohol use were driving the HCC risk. **Conclusion:** AO exposure was not significantly associated with HCC in the largest national retrospective cohort of Vietnam Veterans to-date. Smoking, alcohol, viral hepatitis and NAFLD were the most important clinical risk factors for HCC. Metabolic risk factors were significant prior to the onset of cirrhosis. Our study highlights key modifiable risk factors that should be addressed early in HCC prevention.

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4119-A | RISK OF ACUTE KIDNEY INJURY BY CHEMOTHERAPEUTIC AGENTS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA UNDERGOING TRANSARTERIAL CHEMOEMBOLIZATION

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Background: Acute kidney injury (AKI) is a crucial factor for the prognosis of liver cirrhosis and it can develop in patients with hepatocellular carcinoma (HCC). This study aimed to evaluate the effect of chemotherapeutic agents on the risk of AKI in patients with HCC undergoing transarterial chemoembolization (TACE). **Methods:** A total of 370 HCC patients with baseline serum creatinine (SCr) ≤1.5 mg/dL undergoing TACE as an initial therapy were included. We compared the differences in the development of AKI between the use of doxorubicin and cisplatin in patients undergoing TACE for HCC. Also, the risk factors for the development of AKI were investigated during TACE. The AKI was defined based on the International Club of Ascites (ICA)-AKI criteria. **Results:** The mean age was 60.8 years. The mean SCr levels at baseline, one day, two months, and four months after TACE were 0.9, 0.9, 0.9, and 1.1 mg/dL, respectively. The AKI within four months after TACE developed in 43 patients (12%). The AKI stages were non-AKI in 327 (88%), stage 1 in 13 (4%), stage 2 in 12 (3%), and stage 3 in 18 patients (5%). The proportion of the use of cisplatin and doxorubicin was 18% (n = 65) and 82% (n = 305), respectively. There was no difference in baseline sCr levels between cisplatin group and doxorubicin group (0.9 ± 0.2 mg/dL vs. 0.9 ± 0.3 mg/dL, p = 0.490). However, the risk of AKI in cisplatin group was significantly higher than in doxorubicin group (29% vs. 8%, p < 0.001). Multivariable analysis indicated that the risk factors for AKI were serum albumin ≤3.5 g/dL (hazard ratio [HR] 3.44 with 95% confidence interval [CI] 1.51-7.82, *p* = 0.003), BCLC stage C (HR 6.48 with 95% CI 2.65-15.87, *p* < 0.001), presence of ascites (HR 9.43

with 95% CI 4.21-21.10, $p < 0.001$), and use of cisplatin (HR 3.02 with 95% CI 1.24-7.32, $p = 0.015$). **Conclusion:** The risk of AKI development is high in HCC patients treated with cisplatin-based TACE. The chemotherapeutic agent in patients receiving TACE for HCC should be chosen considering its nephrotoxicity in patients with hypoalbuminemia, advanced stage, and the presence of ascites, in particular.

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f 4120-A | RISK OF HEPATITIS B VIRUS REACTIVATION IN HEPATOCELLULAR CARCINOMA PATIENTS WITH CURRENT OR PAST HEPATITIS B INFECTION RECEIVING IMMUNOTHERAPY: A TERRITORY-WIDE COHORT STUDY

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Background: Immunotherapy (IO) has emerged as a promising treatment for patients with hepatocellular carcinoma (HCC). However, patients with current or past hepatitis B virus (HBV) infection receiving IO carry a risk of HBV reactivation (HBVr). Thus, we examined their risk of HBVr and the impact of nucleos(t)ide analogue (NA) prophylaxis. **Methods:** Adult patients with current or past HBV infection receiving IO for HCC from March 2015 to March 2023 were identified using a territory-wide electronic database in Hong Kong. Current HBV infection was defined with positive hepatitis B surface antigen (HBsAg) and/or diagnosis codes. Past HBV infection was defined with negative HBsAg with positive hepatitis B core antibody. The primary outcome was HBVr defined according to the American Association for the Study of Liver Diseases (AASLD) criteria (*i.e.*, ≥1,000 IU/mL, ≥10,000 IU/mL, or ≥100-fold increase for current HBV with undetectable, unknown, and detectable baseline HBV DNA respectively; or development of detectable HBV DNA and/or HBsAg for past HBV). Secondary outcomes were HBVr based on the Asian Pacific Association for the Study of the Liver (APASL) and American Gastroenterological Association (AGA) guidelines. Patients were followed from the date of IO until the occurrence of HBVr, death, or last follow-up. **Results:** Of 414 HCC patients on IO (mean age 62 ± 11 y, 85.5% males), 89.4% and 10.6% had current and past HBV infection, of which 99.7% and 75.0% received NA prophylaxis respectively. Of the 414 patients, 23.2%, 16.7%, and 60.1% received atezolizumab-bevacizumab, nivolumab-ipilimumab, and pembrolizumab respectively; 43.7%, 26.1%, and 28.7% received HCC targeted therapy, transarterial chemoembolization (TACE), and systemic chemotherapy within 12 months before IO respectively. At a median (25th-75th percentile) follow-up of 7.0 (2.3-18.4) months, 8 (1.9%), 14 (3.4%), and 32 (7.7%) patients developed HBVr based on AASLD, APASL, and AGA criteria respectively. In multivariable analysis, NA prophylaxis (adjusted odds ratio [aOR] 0.05, 95% confidence interval [CI] 0.01-0.33, p = 0.002) and TACE within 12 months before IO (aOR 6.31, 95% CI 1.34-29.69, p = 0.020) were independently associated with a reduced and an increased risk of HBVr respectively (Table). Similar results were observed using the APASL and AGA criteria for HBVr. **Conclusion:** HBV-related HCC patients receiving IO have a risk of HBVr, especially those with prior TACE for HCC and without NA prophylaxis. Clinicians should closely monitor these patients and provide NA prophylaxis to prevent HBVr.

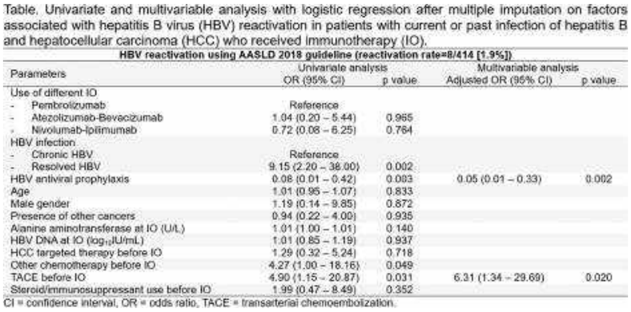

Table. Univariate and multivariable analysis with logistic regression after multiple imputation on factors associated with hepatitis B virus (HBV) reactivation in patients with current or past infection of hepatitis B and hepatocellular carcinoma (HCC) who received immunotherapy (IO).

HBV reactivation using AASLD 2018 guideline (reactivation rate=8/414 [1.9%])

Parameters	Univariate analysis OR (95% CI)	p value	Multivariable analysis Adjusted OR (95% CI)	p value
Use of different IO				
- Pembrolizumab	Reference			
- Atezolizumab-Bevacizumab	1.04 (0.20 – 5.44)	0.965		
- Nivolumab-Ipilimumab	0.72 (0.08 – 6.25)	0.764		
HBV infection				
- Chronic HBV	Reference			
- Resolved HBV	9.15 (2.20 – 38.00)	0.002		
HBV antiviral prophylaxis	0.08 (0.01 – 0.42)	0.003	0.05 (0.01 – 0.33)	0.002
Age	1.01 (0.95 – 1.07)	0.833		
Male gender	1.19 (0.14 – 9.85)	0.872		
Presence of other cancers	0.94 (0.22 – 4.00)	0.935		
Alanine aminotransferase at IO (U/L)	1.01 (1.00 – 1.01)	0.140		
HBV DNA at IO ($\log_{10}$IU/mL)	1.01 (0.85 – 1.19)	0.937		
HCC targeted therapy before IO	1.29 (0.32 – 5.24)	0.718		
Other chemotherapy before IO	4.27 (1.00 – 18.16)	0.049		
TACE before IO	4.90 (1.15 – 20.87)	0.031	6.31 (1.34 – 29.69)	0.020
Steroid/immunosuppressant use before IO	1.99 (0.47 – 8.49)	0.352		

CI = confidence interval, OR = odds ratio, TACE = transarterial chemoembolization.

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4121-A | SCOPING REVIEW OF VALUES ELICITATION TOOLS FOR TREATMENT DECISIONS IN HEPATOCELLULAR CARCINOMA

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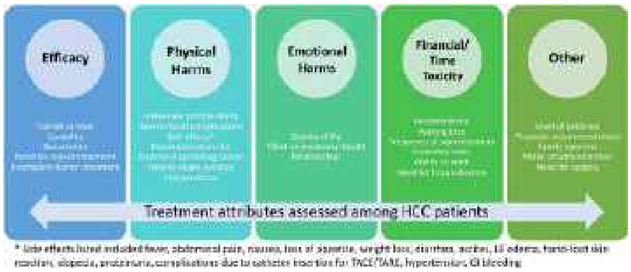
Background: Better understanding of patient and clinician preferences and tradeoffs in hepatocellular carcinoma (HCC) treatment decisions could inform multidisciplinary tumor board discussions and shared decision making in clinic. Values elicitation methods assess preferences for treatment options or attributes of treatments. We performed a scoping review to summarize the published literature on the use of values elicitation tools for HCC treatment decisions. **Methods:** We included studies that (1) assessed the role of preference elicitation tools or willingness to pay/willingness to accept methods for treatment options for HCC and (2) included a study population of patients, caregivers and/or providers. We searched PubMed, EMBASE, Scopus and Cochrane Library databases for articles published before August 18, 2022 and extracted relevant characteristics from each included study. **Results:** The initial search yielded 1,434 unique results. After exclusion of non-relevant references, 10 studies remained. These included studies examining patient-preferences in early or advanced stage HCC (n = 5), a smartphone-based HCC treatment decision system (n = 2) and tradeoffs/treatment decisions of surgeons (n = 2) and GI/hepatologists (n = 1). Three (30%) of these studies were industry funded. No studies focused on intermediate stage HCC. The 9 studies quantifying patient or physician preferences used web-based surveys to offer hypothetical choice between treatment options to patients with cirrhosis or physicians who cared for patients with HCC. The studies of physicians focused exclusively on how treatment preferences are mediated by clinical factors (e.g., liver disease etiology/severity, waiting time to transplant) and facility-level factors (e.g. academic, transplant, HCC treatment volume). Attributes of treatment utilized in studies of patients are shown in Figure 1 with most focusing on efficacy, physical harms, and financial/time toxicity. Specific physical harms assessed were dependent on the study population/treatments assessed (e.g., hand-foot-skin reaction for tyrosine kinase inhibitors). Many of the studies reviewed suggested that patients place the most value on extending their overall survival but may be willing to forgo overall survival to avoid toxicities and maintain quality of life. **Conclusion:** Ten published studies have evaluated the role of preference elicitation tools or willingness to pay/accept methods in HCC treatment studies. The studies revealed a large scope of potential attributes that may be important to patients. Some studies suggested that patient preferences may differ from physician recommendations. More work needs to be done to compare and contrast patient and physician preferences for HCC treatment, particularly in intermediate stage HCC, and to synthesize this empirical evidence into useable decision support tools for patients.



Disclosures: Donna M. Evon – HighTide Therapeutics: Consultant, No, Yes;

Andrew M Moon – TARGET RWE: Consultant, Yes, No;

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

Disclosure information not available at the time of publication: Gabrielle Ritaccio, Alfred Sidney Barritt IV, Jamie Conklin, Daniel Richardson, Hanna Sanoff, Robert S Sandler, Ethan Basch, Stephanie Wheeler

4122-A | SERIAL CHANGES IN LIVER STIFFNESS MEASUREMENT PREDICT HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS B PATIENTS WITH VIROLOGICAL RESPONSE

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Background: To determine the predictive value of changes in liver stiffness measurement (LSM) for hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients with virological response, especially the serial LSM changes. **Methods:** This retrospective study enrolled CHB patients taking antiviral treatment and achieving virological response (hepatitis B virus DNA < 1000 IU/ml for more than 12 mo) between 2016 and 2019. Patients had at least two reliable LSMs by two-dimensional shear-wave elastography (2D SWE), and the first LSM was performed after achieving virological response. Univariable and multivariable Cox regression analysis were used to determine the risk factors for HCC. **Results:** Among 302 patients including 42 cirrhotic patients, 23 developed HCC. LSM changes included the change between first and last LSM and serial LSM changes. Serial LSM changes were classified into stable low LSM (≤ 7.0 kPa), unstable LSM (≤ 7.0 kPa at least once, > 7.0 kPa at least once), and stable high LSM (> 7.0 kPa). In the Cox regression analysis, single LSM (the first and last LSM), change between the first and last LSM, and unstable LSM were not associated with HCC; age at the time of first LSM and stable high LSM turned out to be the independent risk factors for HCC. The area under receiver operating characteristic curve of serial LSM changes (0.811) was similar to that of the multivariable model (0.748, $P = 0.170$). The performance of serial LSM changes was not affected by serial changes in alanine aminotransferase. In the subgroup analysis, only stable high LSM was significantly associated with HCC in non-cirrhotic patients ($P < 0.001$); neither the change between two LSMs nor serial LSM changes were associated with HCC in cirrhotic patients. **Conclusion:** Stable high LSM (> 7.0 kPa) by 2D SWE was more important in predicting HCC than single LSM and change between two LSM in CHB patients with virological response, especially in non-cirrhotic patients.

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4123-A | SERUM LEVELS OF CIRCULATING SOLUBLE B- AND T-LYMPHOCYTE ATTENUATOR IN UNRESECTABLE HEPATOCELLULAR CARCINOMA AS A PREDICTOR OF RESPONSE TO ATEZOLIZUMAB AND BEVACIZUMAB

Naoshi Odagiri, Hoang Hai, Le Thi Thanh Thuy, Yoshimi Yukawa-Muto, Kohei Kotani, Hiroyuki Motoyama, Ritsuzo Kozuka, Etsushi Kawamura, Atsushi Hagihara, Hideki Fujii, Sawako Uchida-Kobayashi, Masaru Enomoto and Norifumi Kawada, Osaka Metropolitan University Graduate School of Medicine

Background: Atezolizumab and bevacizumab (Atezo+Bev) therapy is widely used as a first-line drug for unresectable hepatocellular carcinoma (HCC). However, biomarkers that can predict its response and survival have not yet been established. We focused on circulating soluble immune checkpoint proteins (sICPs) and assessed the predictive and prognostic utility for clinical outcome of Atezo+Bev therapy. **Methods:** 33 patients with unresectable HCC who received Atezo+Bev therapy [24 males and 9 females; median age, 74 (range, 66–80) years] were included. Serum samples were collected at baseline and 4-7 days after the start of Atezo+Bev therapy. The concentration of 17 sICPs, including soluble form of B- and T- lymphocyte attenuator (sBTLA), sCD27, sCD28, T-cell immunoglobulin mucin-3 (sTIM-3), herpes virus entry mediator (sHVEM), sCD40, glucocorticoid-induced tumor necrosis factor receptor-related protein (sGITR), GITR ligand (sGITRL), lymphocyte-activation gene 3 (sLAG-3), sTLR-2, sPD-1, sCTLA-4, sCD80, sCD86, sPD-L1, sPD-L2, and inducible T-cell co-stimulator (sICOS) were measured using multiplexed fluorescent bead-based immunoassays with the Milliplex Map Kit (EMD Millipore Corporation, Burlington, MA, USA). **Results:** Of the 33 patients evaluated for treatment efficacy, the objective response rate (ORR) and disease control rate (DCR) were 30.3% (10/33) and 75.8% (25/33), respectively, with 1, 9, 15, and 8 patients experiencing complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), respectively. Compared to the baseline, the concentrations of sBTLA, sCD27, sCD28, sCD80, sGITR, sGITRL, sICOS, sLAG-3, and sTLR-2 were significantly increased, while sCD40, sHVEM, sPD-1, and sTIM-3 were significantly decreased after the start of Atezo+Bev.

Baseline concentration of sBTLA (pg/mL) was higher in patients with objective response (138.45 vs. 106.11, p = 0.022). In the univariate Cox regression model, first line therapy (hazard ratio [HR] = 0.393 [95% CI: 0.159-0.974], p = 0.044) and baseline sBTLA ≥ 120 pg/mL (HR = 0.237 [95% CI: 0.085-0.660], p = 0.006) were significant prognostic factors relevant to progression free survivial (PFS). Multivariable Cox regression analysis revealed that baseline sBTLA ≥ 120 pg/mL was an independent prognostic factor of PFS (HR = 0.294 [95% CI: 0.102-0.848], p = 0.023). The baseline sBTLA ≥ 120 pg/mL group showed a significantly prolonged median PFS compared with the baseline sBTLA < 120 pg/mL group (9.3 vs. 4.2 mo, p = 0.003, log-rank test). **Conclusion:** We demonstrated that most sICPs undergo changes even within the early stage of 4-7 days after starting Atezo+Bev therapy. Furthermore, the baseline concentration of sBTLA has a prognostic value for objective response and is also an independent prognostic factor of PFS. Our results suggest that sBTLA has the potential to serve as a prognostic biomarker in patients with HCC receiving Atezo+Bev therapy.

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4124-A | SEX-RELATED DIFFERENCES IN EFFICACY AND SAFETY OF IMMUNOTHERAPY IN HEPATOCELLULAR CARCINOMA: SYSTEMATIC REVIEW AND META-ANALYSIS OF LANDMARK PHASE III TRIALS AND VALIDATION IN ROUTINE CLINICAL PRACTICE

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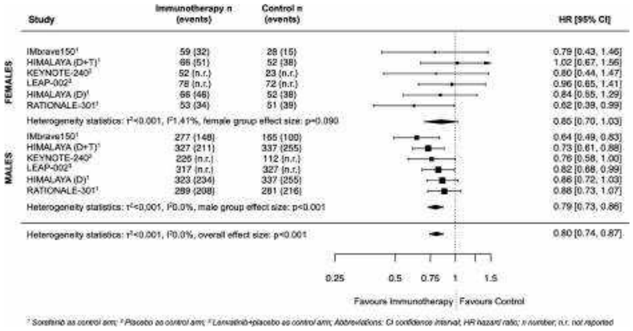
Background: Atezolizumab plus bevacizumab (A+B) represents a standard of care front-line treatment in patients with advanced hepatocellular carcinoma (HCC). We investigated potential differences in efficacy and safety of immunotherapy between female versus male HCC patients. **Methods:** A restricted maximum likelihood random effects meta-analysis of five phase III trials that evaluated immune checkpoint inhibitors (ICI) in advanced HCC and reported overall survival (OS) hazard ratios according to sex was performed to evaluate sex-related differences in OS.

In a real-world cohort of 840 HCC patients from 22 centres included between 2018 and 2023, we directly compared the efficacy and safety of A+B between females and males. Best radiological response was reported according to RECISTv1.1. Univariable and multivariable Cox regression analyses were calculated for OS, progression-free survival (PFS), and time to progression (TTP). **Results:** In the meta-analysis, immunotherapy was associated with a significant OS benefit only in male (pooled HR: 0.79 [95%CI: 0.73-0.86]) but not in female HCC patients (pooled HR: 0.85 [95%CI: 0.70-1.03], Figure). Among 840 patients, 677 patients (81%) were male (mean age 66 ± 11 y), and 163 patients (19%) were female (mean age 67 ± 12 y). Prevalence of cirrhosis, liver function and tumour stages were comparable between the two sexes. Grade ≥3 AEs occurred in 15% of female and 12% of male patients ($p = 0.312$). Type and severity of AEs were similar between the two groups. OS (median OS, 15.9 mo, 95%CI: 14.0-17.8 vs. 15.0 mo, 95%CI: 11.8-18.2; $p = 0.409$), PFS (median PFS, 6.6 mo, 95%CI: 5.7-7.5 vs. 7.3 mo, 95%CI: 4.8-9.9), and TTP (median TTP, 7.1 mo, 95%CI: 6.3-7.9 vs. 7.3 mo, 95%CI: 4.3-10.4) were comparable between male and female patients upon uni- and multivariable analyses (adjusted hazard ratio for OS, PFS, and TTP: 0.79 [95%CI: 0.59-1.04], 1.02 [95%CI: 0.80-1.30], 0.90 [95%CI: 0.68-1.18]). Objective response rate (24% vs. 22%) and disease control rate (59% vs. 59%) were also similar between males and females. **Conclusion:** Female phase III trial participants experienced worse OS following ICI therapy for advanced HCC, a finding that differs from real-world experience of patients treated with A+B. Further investigation of sex as a determinant of responsiveness to ICI should be prioritised.



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Neehar Dilip Parikh – Freenome: Consultant, No, Yes; Gilead: Advisor, No, Yes; Exelixis: Consultant, No, No; Astra Zeneca: Consultant, No, No; Fujifilm Medical: Consultant, Yes, Yes;

The following people have nothing to disclose: Lorenz Balcar, Bernhard Scheiner, Claudia Angela Maria Fulgenzi, Antonio D'Alessio, Katharina Pomej, Jae-kyung Cheon, Pei-Chang Lee, Linda Wu, Celina S-P Ang, Anja Krall, Anwaar Saeed, Bernardo Stefanini, Antonella Cammarota, Tiziana Pressiani, Yehia I Mohamed, Shadi Chamseddine, Brooke Wietharn, Alessandro Parisi, Yi-Hsiang Huang, Samuel Phen, Caterina Vivaldi, Francesca Salani, Gianluca Masi, Dominik Bettinger, Arndt Vogel, Johann von Felden, Kornelius Schulze, Marianna Silletta, Michael Trauner, Adel Samson, Henning Wege, Fabio Piscaglia, Peter R. Galle, Rudolf E. Stauber, Masatoshi Kudo, Susanna Ulahannan, Alessio Cortellini, Ahmed Kaseb, Lorenza Rimassa, Hong Jae Chon, David James Pinato, Matthias Pinter

4125-A | SINGLE-CELL RNA-SEQ-BASED SYSTEMIC IMMUNE PROFILING PREDICTS RESPONSE TO COMBINATION IMMUNOTHERAPY FOR ADVANCED HEPATOCELLULAR CARCINOMA

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Background: Immune checkpoint inhibitor has revolutionized the treatment of advanced hepatocellular carcinoma (HCC). The combination therapy of Atezolizumab with Bevacizumab (Atezo/Bev) has shown to improve the overall survival compared to sorafenib. However, little is known about how circulating immune cells would contribute to the response to Atezo/Bev therapy. Herein, we performed systemic immune profiling in advanced HCC patients using single-cell RNA sequencing (scRNAseq). **Methods:** Peripheral blood mononuclear cells (PBMCs) were collected from HCC patients who received Atezo/Bev therapy in a prospectively registered multicenter study. We conducted scRNAseq and single-cell T cell receptor (scTCR) sequencing of PBMCs from 5 responders and 5 non-responders before and 6 weeks after Atezo/Bev therapy. After UMAP clustering and cell type annotation, differentially expressed genes between responders and non-responders and the diversity of TCR repertoire were analyzed. **Results:** First, 231,383 cells of 20 PBMCs from 10 patients were broadly annotated into 16 major subtypes based on their expression of canonical gene markers. Frequencies of naive-like CD4T cells and naive B cells tended to be higher in responders at pretreatment and those of naive B cells were significantly higher in responder during therapy. Next, we focused on monocytes and T/NK cells. When 124,058 T and NK cells were re-clustered, 22 distinct clusters were identified. There was a difference in the frequency of CD4T cell subsets between responders and non-responders. The frequencies of clusters in CD8T cell didn't differ between groups, however, the GO analysis revealed that CD8T cell was more activated in responders than non-responders at pretreatment. The subset of monocytes, expressing gene X, exhibited higher frequencies in non-responders both at pretreatment and during therapy compared to those in responders. The diversity of TCR repertoire was greater in responders at pretreatment than non-responders. **Conclusion:** Our study proposes that the profile of circulating immune cells at pretreatment may be able to predict the response to Atezo/Bev therapy in HCC patients.

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4126-A | SPATIOTEMPORAL REGULATION OF CHOLANGIOCARCINOMA GROWTH AND DISSEMINATION BY PERITUMORAL MYOFIBROBLASTS IN A Vcam1-DEPENDENT MANNER

Cheng Tian, St. Jude Children's Research Hospital and Liqin Zhu

Background: Intrahepatic cholangiocarcinoma (iCCA) is a type of highly aggressive primary liver cancer characterized by its dense desmoplastic stroma. Myofibroblasts (MFs) are present both within the tumor mass (intratumoral MFs, iMFs) and at the tumor border (peritumoral MFs, pMFs). The protumorigenic role of iMFs has been widely demonstrated in iCCA. However, little is known about the role of pMFs in iCCA development. We aim to investigate the spatiotemporal impact of pMFs on iCCA tumor cells and the potential underlying molecular mechanisms that mediate the dynamic iCCA-pMF interaction. Using a spheroid-based coculture system, we show that the initial iCCA-pMF contact is growth suppressive to tumor cells. However, prolonged iCCA-pMF interaction elicits significant tumor cell invasion and dissemination. **Methods:** An orthotopic allograft of metastatic ICC was generated to track the activation of iMFs and pMFs. Multiple coculture systems were established to assess the impact of iMFs and pMFs on ICC development. RNA-seq transcriptomic profiling was performed to examine ICC-induced liver host response. **Results:** iCCA-liver interaction induces rapid pMF activation in vivo; pMFs exhibit a strong suppressive effect on iCCA growth; prolonged iCCA-pMF interaction, however, elicits significant tumor cell invasion and dissemination; and (2) when tumor invades, pMFs gradually infiltrate into the tumor and become iMFs; iMFs promote tumor growth but have a weaker impact on tumor dissemination than pMFs. Molecularly, iCCA-pMF interaction induced upregulation of vascular cell adhesion molecular 1 (Vcam1) in tumor cells. Vcam1 knockout (Vcam1KO) iCCA cells reveals a heavy involvement of Vcam1 in epithelial-to-mesenchymal transition. While Vcam1KO has only a limited impact on iCCA cell growth in their monoculture, Vcam1KO tumor spheroids cocultured with pMFs exhibit severe defects in growth but significantly increased dissemination. Consistently, pharmacological inhibition ofVcam1 in vivo slows down tumor mass growth but promote tumor cell dissemination. **Conclusion:** his study suggests that tumor-pMF interaction is beyond simple pro- or anti-tumorigenic in iCCA, involving both the attempt of pMFs to block tumor growth and that of tumor cells to grow and disseminate under the pMF suppression in a Vcam1-dependent manner.

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4127-A | SQUAMOUS CELL CARCINOMA AS A HISTOLOGICAL VARIANT OF INTRAHEPATIC CHOLANGIOCARCINOMA: FROM CASE REPORTS TO A NATIONAL CANCER DATABASE ANALYSIS OF 48 CASES

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Background: Squamous cell carcinoma (SCC) is a rare subtype of intrahepatic cholangiocarcinoma (IHC). Prognosis is reportedly poor, limiting its previous literature to case series. Squamous cells of the intrahepatic bile ducts (IHBD) can become malignant in the setting of chronic inflammation, resulting in primary SCC. Metaplasia of underlying liver cysts is another proposed mechanism for the formation of SCC in the IHBD. The primary aim was to describe demographics, tumor characteristics, and survival outcomes in a cohort of 48 cases of primary SCC of the IHBD to better characterize this tumor. The secondary aim was to compare the findings to characteristics of patients with adenocarcinoma, the common IHC histological type. **Methods:** This retrospective study utilized data from the National Cancer Database. Patients were included if they had an ICD-O-3 (International Classification of Disease for Oncology, third edition) diagnosis of SCC (histology codes: 8070-8071) and adenocarcinoma of the IHBD (histology codes: 8140-9144-8310-8310-8480-8490). Demographics (age, race, sex, comorbidity index Charlson-Deyo score), tumor characteristics (grade, tumor size, metastatic sites, therapeutic approach, margin positivity), and survival outcomes were analyzed and compared between the SCC group and the adenocarcinoma group (control). A multivariate analysis was conducted after adjusting for relevant confounders. **Results:** 5207 patients with IHC were included: adenocarcinoma N = 5,159 and SCC N = 48. 0.92% of the patients had SCC, median age was 67.5 years with predominance of white males. Both groups shared similar demographic characteristics, tumor grade, Charlson-Deyo Score and metastatic sites. However, the SCC group had a significantly larger median tumor size(76.5 vs. 66 mm; p = 0.019). Tumor pathological stage was not included due to missing data in 45/48 SCC patients. Treatment modalities did not differ significantly between the two groups. (Table 1) In the multivariate analysis for survival, larger tumor size and positive surgical margins were each shown to be associated with increased mortality, respectively hazard ratio (HR) 1.455 [1.102-1.923] (p = 0.008) and HR 1.767 [1.274-2.451] (p = < 0.001). Females had better survival (HR 0.714 [.550- 0.926], p = 0.011). While SCC group had a higher tumor size, no significant differences in survival were found between SCC and adenocarcinoma patients (HR = 1.454; 95%CI = [0.541; 3.907], p = 0,458). **Conclusion:** The SCC variant of IHC is sparsely described in the literature. SCC is similar to adenocarcinoma in terms of characteristics and survival. Tumor size is larger for patients with SCC compared to adenocarcinoma. Due to the low prevalence of the SCC variant, more research is needed to better characterize this rare histological type. We recommend an extensive workup for alternative primary sites when encountering SCC of the IHBD given the paucity of cases.

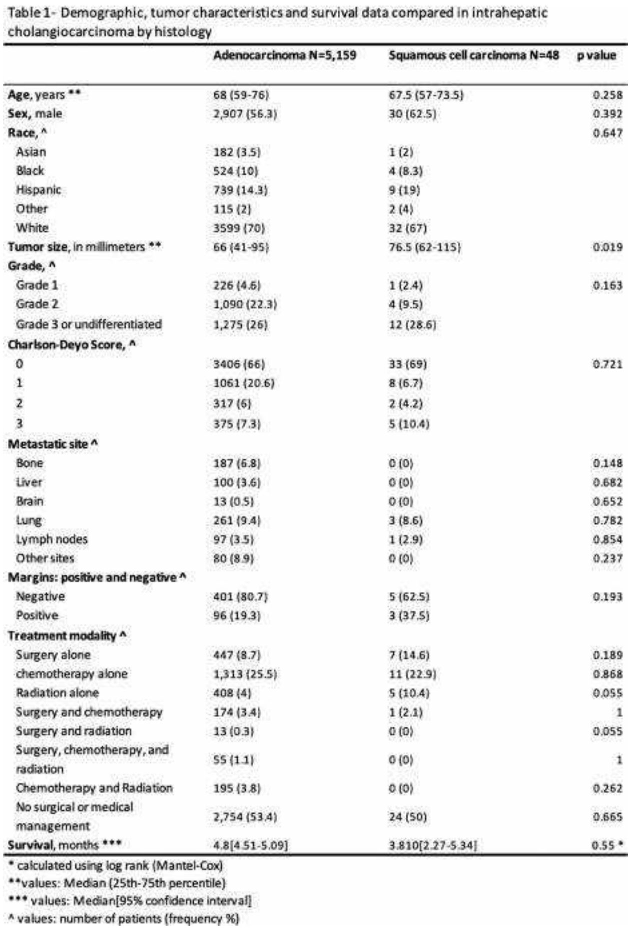

Table 1- Demographic, tumor characteristics and survival data compared in intrahepatic cholangiocarcinoma by histology

	Adenocarcinoma N=5,159	Squamous cell carcinoma N=48	p value
Age, years **	68 (59-76)	67.5 (57-73.5)	0.258
Sex, male	2,907 (56.3)	30 (62.5)	0.392
Race, ^			0.647
Asian	182 (3.5)	1 (2)	
Black	524 (10)	4 (8.3)	
Hispanic	739 (14.3)	9 (19)	
Other	115 (2)	2 (4)	
White	3599 (70)	32 (67)	
Tumor size, in millimeters **	66 (41-95)	76.5 (62-115)	0.019
Grade, ^			
Grade 1	226 (4.6)	1 (2.4)	0.163
Grade 2	1,090 (22.3)	4 (9.5)	
Grade 3 or undifferentiated	1,275 (26)	12 (28.6)	
Charlson-Deyo Score, ^			
0	3406 (66)	33 (69)	0.721
1	1061 (20.6)	8 (6.7)	
2	317 (6)	2 (4.2)	
3	375 (7.3)	5 (10.4)	
Metastatic site ^			
Bone	187 (6.8)	0 (0)	0.148
Liver	100 (3.6)	0 (0)	0.682
Brain	13 (0.5)	0 (0)	0.652
Lung	261 (9.4)	3 (8.6)	0.782
Lymph nodes	97 (3.5)	1 (2.9)	0.854
Other sites	80 (8.9)	0 (0)	0.237
Margins: positive and negative ^			
Negative	401 (80.7)	5 (62.5)	0.193
Positive	96 (19.3)	3 (37.5)	
Treatment modality ^			
Surgery alone	447 (8.7)	7 (14.6)	0.189
chemotherapy alone	1,313 (25.5)	11 (22.9)	0.868
Radiation alone	408 (4)	5 (10.4)	0.055
Surgery and chemotherapy	174 (3.4)	1 (2.1)	1
Surgery and radiation	13 (0.3)	0 (0)	0.055
Surgery, chemotherapy, and radiation	55 (1.1)	0 (0)	1
Chemotherapy and Radiation	195 (3.8)	0 (0)	0.262
No surgical or medical management	2,754 (53.4)	24 (50)	0.665
Survival, months ***	4.8[4.51-5.09]	3.810[2.27-5.34]	0.55 *

* calculated using log rank (Mantel-Cox)

**values: Median (25th-75th percentile)

*** values: Median[95% confidence interval]

^ values: number of patients (frequency %)

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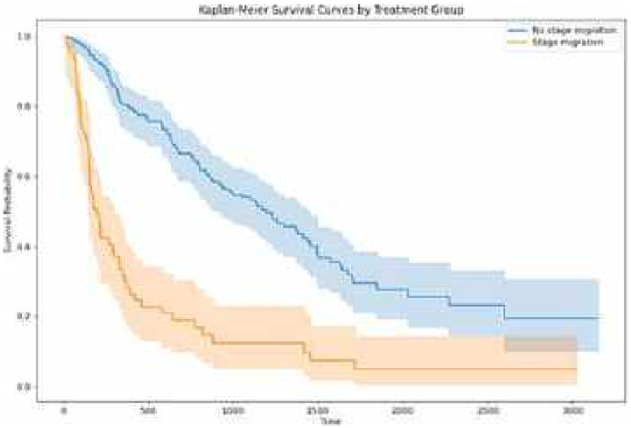
4128-A | STAGE MIGRATION AFTER RADIATION THERAPIES FOR HEPATOCELLULAR CARCINOMA IS A SURROGATE OF OVERALL SURVIVAL

Suraj Pai[1], Shengchen Hao[1], Jonathan Melendez-Torres[2], Isaiah Brown[3], Muhammad Tahir[4], Anna Mae Diehl[3], Ammar Sarwar[4], Amit G. Singal[2] and Neehar Dilip Parikh[1], (1)University of Michigan, (2)University of Texas Southwestern Medical Center, (3)University of Chicago, (4)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and a major cause of cancer-related mortality worldwide. Locoregional therapies including stereotactic body radiation therapy (SBRT) and radioembolization (TARE) are recommended for intermediate stage disease; however, lack of surrogate endpoints have limited feasibility of conducting comparative effectiveness clinical trials. We aimed to evaluate the association between stage migration and overall survival in patients with HCC undergoing treatment with SBRT or TARE. **Methods:** We conducted a retrospective study of adult patients from four tertiary care institutions in the United States. We included patients with HCC who received SBRT or TARE as initial treatment for HCC between 2008 and 2019. We excluded those with prior treatment, Barcelona Clinic Liver Cancer (BCLC) stage D disease, or those who died within 6 months of first HCC treatment. The primary outcome was transplant-free survival, with transplantation as a competing risk. The independent variable of interest was stage migration to a more advanced BCLC stage (e.g., BCLC stage B à C) within 6 months of HCC diagnosis. Survival analysis was completed using Kaplan-Meier and multivariable Cox proportional hazard models used to identify predictors of survival. **Results:** We included 266 patients with a median age of 65 years; 77% male and 66% White. The primary etiologies of liver disease were hepatitis C virus (32%), non-alcoholic fatty liver disease (21%), and alcohol-related cirrhosis and cryptogenic (14% each). Most (75%) had Child-Pugh class A and 25% Child Pugh B. Stage migration within 6 months was observed in 61 (23%) patients. Kaplan-Meier log rank analysis showed significantly shorter survival for those who experienced stage migration at 6 months (median 196 [IQR 103-421] days) vs those who did not (median 1197 [IQR 581-2274] days) (Figure). In multivariate Cox analysis, stage migration was significantly associated with worse survival (HR 3.99 [95% CI: 2.78 – 5.74]). Other predictors of worse survival included older age, Child-Pugh B cirrhosis, and higher AFP. **Conclusion:** Stage migration at 6 months is a surrogate endpoint for overall survival in patients with HCC undergoing radiation-based locoregional therapies (SBRT or TARE) and could be considered as an endpoint for future clinical trials.



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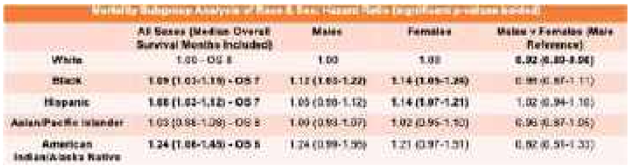
The following people have nothing to disclose: Suraj Pai, Shengchen Hao, Jonathan Melendez-Torres, Isaiah Brown, Muhammad Tahir, Ammar Sarwar

4129-A | SURVIVAL OF CHOLANGIOCARCINOMA: SIGNIFICANCE OF RACE, SEX, AND OTHER TUMOR CHARACTERISTICS

Reena Razdan, Rutgers New Jersey Medical School and Nikolaos T. Pyrsopoulos, Rutgers University, Newark, NJ

Background: Cholangiocarcinoma (CCA) is a rare cancer derived from the bile ducts that is characterized by its late diagnosis and high mortality. The aim of this epidemiology study is to compare outcomes amongst demographics and tumor characteristics of CCA in order to better understand predictive markers for survival. **Methods:** We retrospectively analyzed the Surveillance Epidemiology and End Results (SEER) database of 17 registries made available by the National Cancer Institute in the USA. Patients with a histological diagnosis of malignant CCA per ICD-O-3 codes from years 2000-2019 were included. Demographic and tumor characteristics such as age, sex, race, primary tumor site, tumor stage, histologic grade, surgical intervention, and survival months (deaths attributable to cancer) were examined. We compared overall survival for patients with CCA using Cox proportional hazard regression analysis. Gender differences were further analyzed based on race. **Results:** We identified 23,501 patients with CCA. The median age was 69 years. Patient demographics included: 51.2% men, 48.8% women, 62.8% White, 15.9% Hispanic, 12.4% Asian/Pacific Islander, 8.0% Black, and 0.9% American Indian/Alaska Native. In our survival analysis, women had a lower risk of mortality as compared to men (HR 0.95, $p < 0.005$). However, this difference was eliminated on subgroup analysis by race- with only White women maintaining longer survival as compared to their men counterparts (HR 0.92, $p < 0.005$). Blacks (HR 1.09, $p < 0.005$, median

Overall Survival 7 mos), Hispanics (HR 1.08, $p < 0.005$, mOS 7 mos), and American Indians (HR 1.24, $p < 0.01$, mOS 6 mos) had worse outcomes compared to Whites (mOS 8). Patients who had surgery performed had longer survival compared to those who did not have surgery performed (HR 0.33, $p < 0.005$, mOS 34 mos vs mOS 5 mos). Higher histological grade was associated with poorer outcomes, with undifferentiated anaplastic Grade IV having the highest mortality (HR 1.61, $p < 0.005$, mOS 8 mos). While only 3.9% of CCAs arose from the gall bladder, this tumor location had one of the worst survival outcomes (HR 1.33, $p < 0.005$, mOS 5 mos). Conversely, CCA derived from the extrahepatic bile duct accounted for 29.6% of CCAs, but had the best survival outcomes (HR 0.85, $p < 0.005$, mOS 9 mos). **Conclusion:** Mortality differences between men and women were only maintained in White patient populations. Blacks, Hispanics, and American Indians had worse survival compared to Whites. Tumor location was associated with differences in mortality outcomes, with gall bladder CCAs having one of the poorest overall survival outcomes compared to other tumor locations. Further studies are needed to elucidate determinants of poor survival amongst these groups.



Mortality Subgroup Analysis of Race & Sex, Hazard Ratio (significant p-values bolded)

	All Sexes (Median Overall Survival Months Included)	Males	Females	Males v Females (Male Reference)
White	1.00 - OS 8	1.00	1.00	0.92 (0.89-0.96)
Black	1.09 (1.03-1.15) - OS 7	1.12 (1.03-1.22)	1.14 (1.05-1.24)	0.99 (0.87-1.11)
Hispanic	1.08 (1.03-1.12) - OS 7	1.05 (0.99-1.12)	1.14 (1.07-1.21)	1.02 (0.94-1.10)
Asian/Pacific Islander	1.03 (0.98-1.08) - OS 8	1.00 (0.93-1.07)	1.02 (0.95-1.10)	0.96 (0.87-1.05)
American Indian/Alaska Native	1.24 (1.06-1.45) - OS 6	1.24 (0.99-1.55)	1.21 (0.97-1.51)	0.82 (0.51-1.33)

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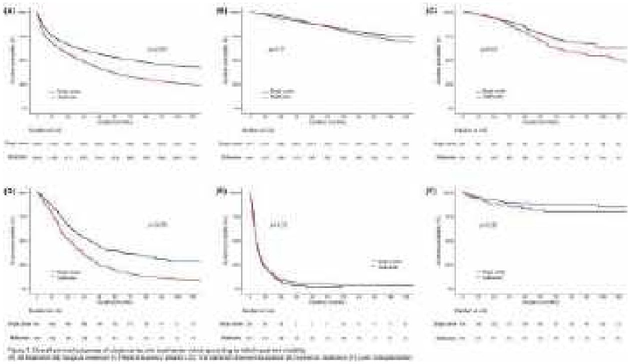
4130-A | SURVIVAL OUTCOMES OF SINGLE CENTER COHORT VERSUS MULTICENTER COHORT ACCORDING TO THERAPEUTIC METHODS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Ye Rim Kim[1], *Sung Won Chung*[1] *and Ju Hyun Shim*[2], *(1)Asan Medical Center, Seoul, Korea, Republic of (South), (2)Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*

Background: Previous randomized controlled trials have demonstrated that multicenter studies provide higher level of external validity than single center studies; however, it is uncertain whether this finding necessarily indicates that results of retrospective single center cohort studies cannot be generalized to real-world clinical practice. Applicability of single center studies is particularly of relevance for hepatocellular carcinoma (HCC), a heterogeneous disease with various treatment options based on disease stage and liver function. We therefore aimed to compare the overall survival (OS) of HCC patients between a nationwide multicenter cohort and a representative single center cohort to evaluate the external validity of single center research. **Methods:** Patients diagnosed with HCC between January 2008 and December 2018 were retrospectively analyzed using data from the Korean Primary Liver Cancer Registry (multicenter cohort, $n = 16{,}443$), and Asan Medical Center HCC registry (single center cohort, $n = 15{,}655$). Primary outcome was OS, which was estimated using log-rank test and Cox proportional hazard analysis. OS was additionally compared among subpopulation of patients who met each AASLD guideline and received the corresponding treatment (radiofrequency ablation [RFA], transarterial chemoembolization [TACE], surgical resection, liver transplantation [LT], and systemic treatment) as initial therapy. **Results:** Overall, the multicenter cohort had shorter OS than the single center cohort (adjusted hazard ratio [aHR] = 1.17, 95% confidence interval [CI] = 1.13–1.20, $p < 0.001$). In patients who received RFA (aHR = 1.45, 95% CI = 1.08–1.95 $p = 0.01$) or TACE (aHR = 1.73, 95% CI = 1.49–2.02 $p < 0.001$) in accordance with the current AASLD guideline, the multicenter cohort showed higher risk of death. However, risk of mortality in patients who received systemic therapy (aHR = 0.94, 95% CI = 0.81–

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

1.10, p = 0.46), surgical resection (aHR = 1.06, 95% CI = 0.93–1.22, p = 0.38), and LT according to Milan criteria (aHR = 1.09, 95% CI = 0.54–2.18, p = 0.82) did not differ between the two cohorts. **Conclusion:** Despite the representative volume of our single center, there was a significant difference in OS between the single center and the multicenter cohort, and the difference was only minimal in patients who received systemic therapy, surgical resection, or LT according to the current treatment guidelines. Retrospective single center cohort studies must be interpreted with caution particularly when evaluating outcomes in HCC patients with heterogeneous tumor features.



Disclosures: The following people have nothing to disclose: Ye Rim Kim, Sung Won Chung, Ju Hyun Shim

f 4131-A | TEMPORAL TRENDS IN CLINICAL PATTERNS AND OUTCOMES OF PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer death in patients with cirrhosis. Efforts to improve patient outcomes include optimization of surveillance strategies, expansion of curative treatment eligibility, and introduction of new therapy options. We aimed to characterize temporal trends of clinical outcomes in a large cohort of patients with HCC. **Methods:** We conducted a retrospective cohort study at two large health systems of patients diagnosed with HCC between January 2008 and December 2021. We created three subgroups, each spanning ~5 years, based on HCC diagnosis date: group 1 (2008–2012), group 2 (2013-2017), and group 3 (2018-2021). We used multivariable logistic regression to assess associations with early-stage HCC detection (BCLC stage 0/A), and curative treatment (liver transplant, surgical resection, or local ablation). We used multivariable Cox regression analysis to characterize associations with overall survival. **Results:** Of 2,042 patients with HCC (group 1: n = 566; group 2: n = 748; group 3: n = 728), median age was 61.4 years, and 76.1% were male. The cohort was diverse regarding race/ethnicity (36.0% White, 28.6% Hispanic, 28.1% Black) and etiology (56.8% hepatitis C, 39.9% alcohol, 15.0% NAFLD). Over time, median age increased (57.8, 60.6, and 63.9 y) and proportions of males decreased (77.7, 76.2, and 74.7%). The prevalence of hepatitis C (65.0, 60.7, and 46.4%) and alcohol (45.1, 41.7, and 34.1%) decreased, whereas NAFLD increased (7.8, 13.9%, and 21.7%). The proportion of BCLC stage 0/A increased over time (38.7, 44.7, and 56.2%; group 3 vs. 1: OR 2.27, 95% CI 1.63-3.20). Compared to group 1, patients in group 2 (OR 2.27, 95%CI 1.61-3.23) and group 3 (OR 1.88, 95%CI 1.28-2.77) had increased curative treatment. Median survival for groups 1, 2, and 3 were 9.8 (95%CI, 8.1-12), 19 (95%CI, 16-22), and 24 (95%CI 20-30) months, respectively. Group 2 (HR 0.83, 95%CI 0.72-0.95) and group 3 (HR 0.68, 95%CI 0.58-0.80) had significantly reduced mortality versus group 1. Group 3 had no significant difference in curative treatment than group 2 (OR 0.73, 95%CI 0.53-1.01) but improved survival (HR 0.81, 95%CI 0.69-0.95). **Conclusion:** There have been significant improvements in early HCC detection, curative treatment receipt, and overall survival among patients with HCC. However, over one-third of HCC are detected beyond an early stage and median survival remains below 3 years, highlighting a need for improvements in surveillance.

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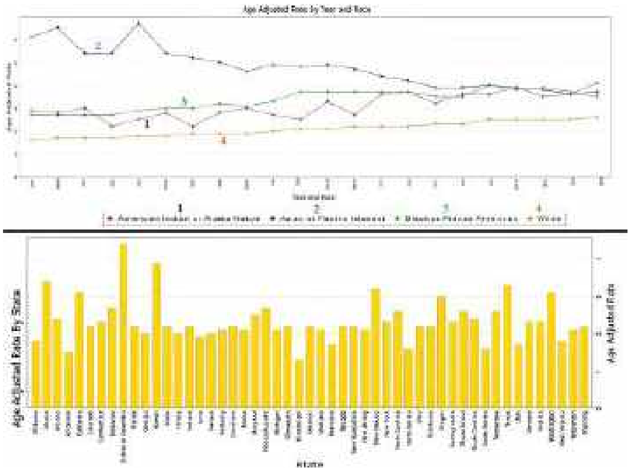
The following people have nothing to disclose: Karim Seif El Dahan, Darine Daher, Ahmad Anouti, Alva Cano, Michael Gonzalez, Sara Verschleisser, Crystal Ransom, Erik Juarez Farfan, Osiris Carranza, Lisa Quirk, Todd Morgan, Lisa B. VanWagner, Sarah Rosanna Lieber, Thomas G. Cotter, Jeremy Louissaint, Madhukar Patel, Adam C. Yopp

4132-A | TEMPORAL TRENDS OF HEPATOCELLULAR CARCINOMA IN THE UNITED STATES FROM 1999 TO 2020

Alexander Kusnik, Sarath Lal Mannumbeth Renjithlal, Keerthi Mannumbeth Renjith and Asim Mushtaq, Rochester Regional Health

Background: Hepatocellular Carcinoma (HCC) is a significant public health concern in the US, resulting in cancer-related deaths despite improvements in detection and treatment. To comprehensively understand HCC outcomes among different demographic groups (e.g., sex, race/ethnicity, location of death), it is important to observe trends and patterns to evaluate the effectiveness of past interventions. **Methods:** A cross-sectional analysis was conducted using the CDC-WONDER database to investigate the mortality patterns linked to Hepatocellular Carcinoma (HCC) using the ICD code (C22.0). The study employed death certificate data from the CDC WONDER database to identify deaths associated with HCC between 1999 and 2020. Age-adjusted mortality rates (AAMR) per 100.000 individual's and corresponding annual percentage changes (APC), along with 95% confidence intervals, were calculated using Joinpoint regression analysis. The analysis focused on assessing demographic and racial trends. **Results:** Between 1999 and 2020, there were 184,073 deaths related to Hepatocellular Carcinoma (HCC). Analysis of yearly trends showed an increase in the age-adjusted mortality rate (AAMR) from 1.9 (95% CI 1.8-1.9) in 1999 to 2.8 (95% CI 2.7-2.8) in 2020. Overall, the AAMR from 1999 to 2018 had an Annual Percentage Change (APC) increase of 1.92 (95% CI: 1.7 to 2.2). When considering gender, males had a higher AAMR of 4.1 (95% CI: 4.0-4.1), while females had a lower AAMR of 1.0 (95% CI: 1.0-1.0). Among ethnicities, Asian or Pacific Islanders had the highest AAMR of 4.5 (95% CI: 4.5-4.6), followed by Black or African Americans with an AAMR of 3.5 (95% CI 3.5-3.5), American Indian or Alaskan Natives with an AAMR of 3.3 (95% CI 3.1-3.4), and Whites with an AAMR of 2.1 (95% CI 2.1-2.2). Geographically, non-metropolitan rural areas had lower AAMR compared to urban areas. The highest AAMR was seen in the District of Columbia and Hawaii. Information on the location of death was available for all recorded deaths. Among these, 34.85% (64,157) occurred during inpatient admission or in the emergency room , 41.19% (75,825) occurred at home, 16.47% (64,930) occurred in nursing homes or long-term care facilities, 0.42% (17,620) were reported in hospices, and 3.36% (13,261) occurred at other or unspecified places. **Conclusion:** This study highlights a notable rise in the incidence of hepatocellular carcinoma (HCC), primarily affecting males. This increase can be attributed to various factors, including the persistent opioid crisis, the growing prevalence of obesity and diabetes, and the underdiagnosis of hepatitis B virus (HBV), despite advancements in hepatitis C virus (HCV) treatment. Additionally, a significant proportion of HCC-related deaths occurred at home, indicating a potential requirement for expanded home-based services to accommodate the increasing HCC incidence.



Disclosures: The following people have nothing to disclose: Alexander Kusnik, Sarath Lal Mannumbeth Renjithlal, Keerthi Mannumbeth Renjith, Asim Mushtaq

4133-A | THE CLINICAL SIGNIFICANCE AND TUMOR MICROENVIRONMENT OF VESSELS ENCAPSULATING TUMOR CLUSTERS (VETC)-POSITIVE HEPATOCELLULAR CARCINOMA

Tomohiko Taniai, Koichiro Haruki, Kenei Furukawa, Mitsuru Yanagaki, Munetoshi Akaoka and Toru Ikegami, The Jikei University School of Medicine

Background: Vessels encapsulating tumor clusters (VETC), which form cobweb-like networks and encapsulate tumor clusters, have been reported as poor prognostic indicators for patients with hepatocellular carcinoma (HCC). However, the clinical significance of VETC remains unclear. The aim of this study is to identify the clinical significance of VETC in patients with HCC and to elucidate immune cell profiling of VETC-positive HCC. **Methods:** This study comprised 229 patients with HCC underwent hepatic resection. The relationship between VETC and disease-free survival (DFS) or overall survival (OS) was retrospectively analyzed. We performed immunohistochemistry for CD34, CD8, CD163 to assess VETC, T cell, and macrophage, respectively. Immune cell count was performed in two lesions: tumor center (CT) and invasive margin (IM), and classified 3 categories: low, intermediate, and high. Thereafter, we retrospectively analyzed the clinicopathological characteristics of patients with VETC-positive HCC. **Results:** VETC was a poor prognostic indicator of DFS ($p < 0.01$) and OS ($p < 0.01$). In multivariate analyses, serum AFP $\geq$ 20 ng/ml ($p < 0.01$), multiple tumors ($p < 0.01$), and VETC-positive ($p = 0.02$) were significant poor prognostic factors for DFS, while moderate/poor differentiation ($p = 0.02$), tumor size $\geq$ 5 cm ($p = 0.02$), and VETC-positive ($p = 0.03$) were significant poor prognostic indicators for OS. Clinicopathologic characteristics in patients with VETC HCC were higher serum PIVKA-II level ($p < 0.01$), moderate/poor differentiation ($p < 0.01$), larger tumor ($p < 0.01$), multiple tumor ($p = 0.02$), high vascular invasion ($p < 0.01$), fewer CD8+CT ($p < 0.01$), and fewer CD163+CT ($p = 0.02$). **Conclusion:** VETC is a poor prognostic indicator in patients with HCC and is related to high PIVKA-II, poor differentiation, large and multiple tumors, high vascular invasion, and immune cold tumor micro environment.

Disclosures: The following people have nothing to disclose: Tomohiko Taniai, Koichiro Haruki, Kenei Furukawa, Mitsuru Yanagaki, Munetoshi Akaoka, Toru Ikegami

4134-A | THE COMPARATIVE EFFICACY OF COMBINED LOCOREGIONAL AND SYSTEMIC THERAPIES IN HEPATOCELLULAR CARCINOMA (HCC) BCLC CLASS B: A BAYESIAN NETWORK META-ANALYSIS

Zixuan Xing[1], Yee Hui Yeo[2], Gin-Yi Lee[3], Mohammad Saeid Rezaee-Zavareh[4], Wenjun Wang[1], Fanpu Ji[5] and Ju Dong Yang[6], (1)The Second Affiliated Hospital of Xi'an Jiaotong University, (2)Cedars-Sinai Medical Center, Culver City, CA, (3)Department of Hospital Medicine, Rhode Island Hospital, MA, USA, (4)Middle East Liver Disease Center, (5)The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, (6) Cedars-Sinai Medical Center, Los Angeles, CA

Background: Hepatocellular carcinoma (HCC) is the sixth leading cause of cancer death. It exhibits pronounced clinical and molecular heterogeneity. Locoregional therapy remains the primary treatment for HCC patients within the Barcelona Clinic Liver Cancer (BCLC) class B. Despite this, several subgroup analyses from large-scale trials have suggested potential benefits of systemic therapy in this patient population. Our study aimed to perform a network meta-analysis comparing locoregional and systemic therapies for patients with BCLC class B HCC. **Methods:** A comprehensive literature search was conducted on PubMed, Scopus, Web of Science, the Cochrane Controlled Register of Trials, clinicaltrials.gov, and WHO's International Clinical Trials Registry Platform, from inception to March 20, 2023. Double-blinded, randomized controlled trials investigating first-line systemic or locoregional therapies for HCC BLCL class B were obtained. Hazard ratios (HR) for overall survival (OS) were extracted. The regimens were grouped into four groups (transarterial chemoembolization [TACE] alone, TACE combined with immunotherapy, and TACE combined with tyrosine kinase inhibitor [TKI]). A Bayesian network meta-analysis was performed to compare and rank these regimens. **Results:** From a total of 17,206 records initially retrieved, 559 were included for full-text screening and nine eligible trials were included for network meta-analysis of OS. Six of the studies were performed in Asia. Regarding OS, compared to TACE alone, TACE-immunotherapy (HR: 0.60; 95% credible interval [CrI]: 0.39-0.92) was associated with a significantly higher survival probability, surpassing that of TACE-TKI (HR: 0.87; 95% CrI: 0.74-1.02) (Table 1). Data on progression-free survival, treatment response rates, and adverse events were meta-analyzed. **Conclusion:** This network meta-analysis supports the combination of TACE-immunotherapy and TACE-TKI for treating patients with HCC BCLC class B. Additional evidence on efficacy, adverse events, and subgroup analysis by tumor characteristics could further refine treatment strategies to optimize patient outcomes.

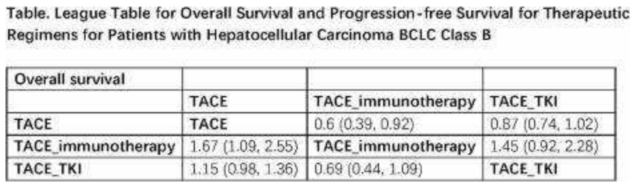


Table. League Table for Overall Survival and Progression-free Survival for Therapeutic Regimens for Patients with Hepatocellular Carcinoma BCLC Class B

Overall survival			
	TACE	TACE_immunotherapy	TACE_TKI
TACE	TACE	0.6 (0.39, 0.92)	0.87 (0.74, 1.02)
TACE_immunotherapy	1.67 (1.09, 2.55)	TACE_immunotherapy	1.45 (0.92, 2.28)
TACE_TKI	1.15 (0.98, 1.36)	0.69 (0.44, 1.09)	TACE_TKI

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Fujifilm Medical Sciences: Consultant, No, No; Merck: Consultant, No, No;

The following people have nothing to disclose: Zixuan Xing, Yee Hui Yeo, Gin-Yi Lee, Mohammad Saeid Rezaee-Zavareh, Wenjun Wang, Fanpu Ji

4135-A | THE CONDITION OF ACHIEVED SVR AT INITIATION OF 1st LINE SYSTEMIC THERAPY ON THE PATIENTS WITH HCV-RELATED UNRESECTABLE HEPATOCELLULAR CARCINOMA, PREMISING 2nd LINE THERAPY

Takayuki Tokunaga, Kentaro Tanaka, Satoshi Narahara, Hiroki Inada, Etsuko Iio, Yoko Yoshimaru, Takehisa Watanabe, Katsuya Nagaoka, Hiroko Setoyama and Yasuhito Tanaka, Faculty of Life Sciences, Kumamoto University

Background: The impact of eradication of hepatitis C virus (HCV) on the prognosis of the patients with HCV-related unresectable hepatocellular carcinoma (HCV-uHCC) remains to be clarified. We aimed to investigate the relationship between the condition of sustained virological response (SVR) and the clinical outcome of HCV-uHCC who received 1st line systemic therapy, premising 2nd line systemic therapy. **Methods:** Between October 2009 and August 2022, 124 HCV-uHCC with Child-Pugh class A liver function (CP-A) and performance status of 0-1 (PS0-1) received 1st line systemic therapy, including sorafenib, lenvatinib and atezolizumab plus bevacizumab therapy, consecutively in our hospital. Among them, 110 patients who had progression on 1st line systemic therapy were enrolled (median observation periods: 16.9 mo). The factors associated with overall survival (OS), time to progression (TTP), the eligibility for 2nd line systemic therapy (maintaining CP-A and PS0-1 at the progression of 1st line systemic therapy) and post progression survival (PPS) were analyzed, including the condition of SVR at the initiation of 1st line systemic therapy. **Results:** The analyzed 110 patients were characterized by PS0/1 (n = 94/16), Child-Pugh score 5/6 (n = 67/43) and Barcelona Clinic Liver Cancer Stage A/B/C (n = 8/43/59). Thirty-eight patients had achieved SVR before the initiation of 1st line systemic therapy. Median OS, TTP and PPS was 19.4, 3.6 and 14.5 months, respectively. The achieved SVR (HR, 0.47) and Child-Pugh score 5 liver function (HR, 0.49) at the initiation of 1st systemic therapy were favorable OS factors, compared to reference defined as non-SVR and Child-Pugh score 6 liver function, respectively. PPS was longer in those with SVR (21.2 mo) than those without (12.9 mo), while TTP was similar between those with and without SVR (3.9 vs. 3.4 mo). Between the patients with and those without SVR, there were weak correlation between OS and TTP (r = 0.42 and 0.34) and strong correlation between OS and PPS (r = 0.98 and 0.98). Sixty-five patients (59.1%) were eligible for 2nd line systemic therapy. The condition of both SVR and Child-Pugh score 5 liver function at the initiation of 1st line systemic therapy (OR, 4.9) was positively associated with the eligibility for 2nd line systemic therapy, with the condition of both non-SVR and Child-Pugh score 6 liver function defined as a reference. The patients who received subsequent therapy after progression of 1st line systemic therapy had favorable PPS (HR, 0.13) compared with those who did not. **Conclusion:** HCV-uHCC with SVR would have favorable OS and favorable PPS compared with those without SVR. HCV-uHCC with both SVR and Child-Pugh score 5 liver function especially could be eligible for 2nd line systemic therapy at the progression of 1st line systemic therapy. HCV-uHCC might have favorable PPS by achieving SVR after the progression of 1st line systemic therapy.

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4136-A | THE EFFECT OF CIRCULATING IMMUNE-RELATED BIOMARKERS ON THE RISK OF HEPATOCELLULAR CARCINOMA DEVELOPMENT IN THE USA

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Background: Dysregulation of immunological networks play a key role in the development and progression of hepatocellular carcinoma (HCC); however, the specific immunogenic processes influencing hepatic tumor development remain incomplete. There are limited reports about circulating immune factors that may serve as markers for HCC diagnosis. We aimed to assess the associations of blood-based biomarkers involved in immune responses and HCC diagnosis. **Methods:** Between 2001 and 2014, all newly diagnosed HCC patients were ascertained as part of an ongoing IRB-approved study at The University of Texas MD Anderson Cancer Center. Control participants were selected from healthy spouses of patients who were diagnosed with cancers other than liver and gastrointestinal cancers. Blood samples were collected at time of diagnosis or enrollment and sent to Myriad RBM, Inc. to test for a panel of 30 immune-related biomarkers. Using the median values of the biomarkers among the controls as a cutoff point, all participants were categorized into subjects with high and low levels of biomarkers. Odds ratio (OR) and 95% confidence interval (CI) values were estimated using multivariable conditional logistic regression analysis with adjustment for relevant confounders. **Results:** A total of 200 HCC case patients and 200 pair-matched healthy controls (age, sex, and race) were analyzed. The mean age (± SD) for cases was 59.72 ± 10.11 years, and for controls, it was 60.17 ± 9.53 years. Most of the study population was white (72.0%). Table 1 presents the estimated OR and corresponding 95% CIs for HCC risk among subjects with high levels of biomarkers (> median values of the controls) as compared to those with low levels (≤ median value of the controls) after adjusting for age, sex, race, smoking, alcohol consumption, family history of cancer, viral hepatitis, and history of type II diabetes mellitus. The table highlights the significant associations between 11 immune-related biomarkers and HCC diagnosis. For example, subjects with a high level of angiopoietin-2 had 10-fold (95% CI:2.62-4.27) increased risk for HCC compared to subjects with low levels. Restricted analysis found significant association between the biomarkers and HCC risk in the absence of viral hepatitis and may be assessed in non-alcoholic fatty liver disease patients as diagnostic markers. We also found significant variations in the biomarker distribution among HCC case patients in the presence and absence of cirrhosis (diagnosed by pathology or radiology). **Conclusion:** Eleven immune-related markers showed significant and independent association with increased risk of HCC. These observations suggest a potential value of these plasma biomarkers in predicting the risk of HCC and expanding our current understanding of the role of inflammation in HCC development. Future validation of the results in independent population will need to be assessed for independent samples of HCC cases and controls.

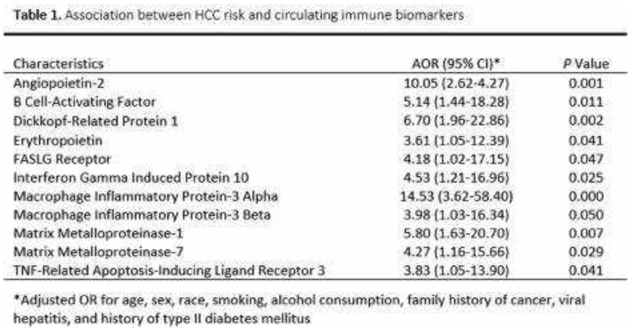

Table 1. Association between HCC risk and circulating immune biomarkers

Characteristics	AOR (95% CI)*	*P* Value
Angiopoietin-2	10.05 (2.62-4.27)	0.001
B Cell-Activating Factor	5.14 (1.44-18.28)	0.011
Dickkopf-Related Protein 1	6.70 (1.96-22.86)	0.002
Erythropoietin	3.61 (1.05-12.39)	0.041
FASLG Receptor	4.18 (1.02-17.15)	0.047
Interferon Gamma Induced Protein 10	4.53 (1.21-16.96)	0.025
Macrophage Inflammatory Protein-3 Alpha	14.53 (3.62-58.40)	0.000
Macrophage Inflammatory Protein-3 Beta	3.98 (1.03-16.34)	0.050
Matrix Metalloproteinase-1	5.80 (1.63-20.70)	0.007
Matrix Metalloproteinase-7	4.27 (1.16-15.66)	0.029
TNF-Related Apoptosis-Inducing Ligand Receptor 3	3.83 (1.05-13.90)	0.041

*Adjusted OR for age, sex, race, smoking, alcohol consumption, family history of cancer, viral hepatitis, and history of type II diabetes mellitus

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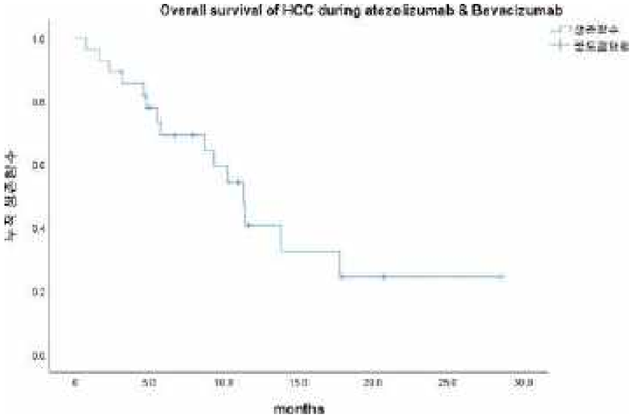
The following people have nothing to disclose: Rikita I. Hatia, Donghui Li, Ping Chang, Ahmed O. Kaseb, Manal M. Hassan

4137-A | THE EFFICACY AND SAFETY OF ATEZOLIZUMAB & BEVACIZUMAB IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA: THE REAL WORLD DATA

Sung Hwan Yoo, Hyun Woong Lee and Jung Il Lee, Gangnam Severance Hospital

Background: Treatment responses of unresectable hepatocellular carcinoma (HCC) remain unacceptably low and treatment modalities are limited. After the IMbrave 150 trial was announced, there are still few published data on the atezolimumab and bevacizumab in South Korea. We analyzed the efficacy and safety of atezolizumab & bevacizumab based on real world data. **Methods:** In retrospective cohort study, data on 28 patients with unresectable HCC, with Child-Pugh (CP) scores of 5-8, were collected from a university hospital between September 2020 and October 2022. All patients were treated with 1200mg of atezolizumab plus 15mg per kilogram of body weight of bevacizumab intravenously every 3 weeks. **Results:** From 28 patients with unresectable HCC, 92.8% were classified as Child-Pugh (CP)-A, 64.2% as Barcelona Clinic Liver Cancer (BCLC)-C. The median overall survival (OS) and time to progression (TTP) were 11.2 months, and 3.6 months in the atezolizumab & bevacizumab group. In univariate analysis, operation, European Cooperative Oncology Group, sodium level, PIVKA-II, hepatic encephalopathy, ascites, Child-Pugh score group, maximum tumor size, were significant prognostic factors of OS (p = 0.049, 0.011, 0.004, 0.013, 0.049, 0.005, 0.013). In multivariate analysis, PIVKA-II, hepatic encephalopathy, Child-Pugh score group, maximum tumor size were significant prognostic factors of OS (p = 0.007, 0.002, 0.002, 0.008). Major complications included hyperbilirubinemia (44.8%), ALT elevation (34.5%), liver failure (14.2%), infection (2.1%), cerebral haemorrhage (0.04%), and hematuria (0.04%). **Conclusion:** For managing unresectable HCC, atezolizumab & bevacizumab may be a valuable and safe treatment modality, but long-term follow-up and large scale studies are needed in the future.



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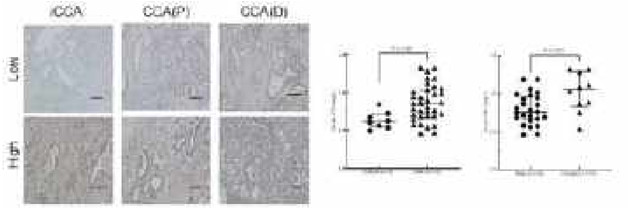
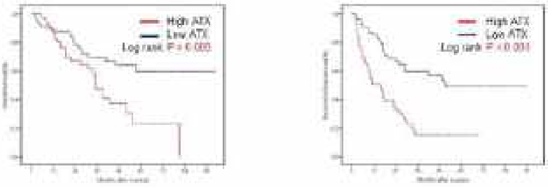
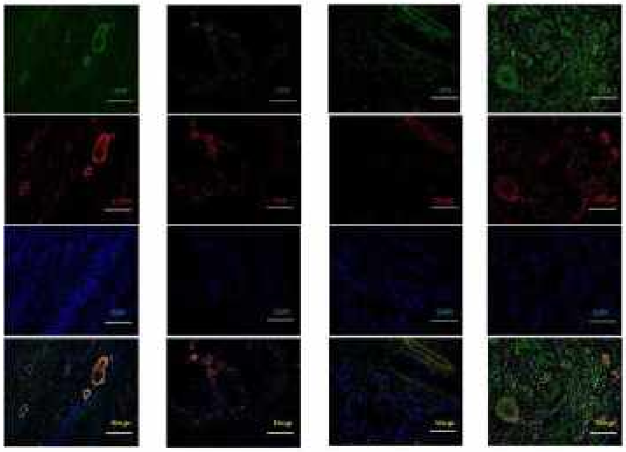
4138-A | THE EXPRESSIONS OF AUTOTAXIN–LYSOPHOSPHATIDATE SIGNALING-RELATED PROTEINS IN CHOLANGIOCARCINOMA

Xuefeng Li, Kyoto University

Background: The expression of autotaxin (ATX)-lysophospholipid (LPA) signaling-related proteins have been shown to be associated with the physiological and pathological activities of various cancers. However, little is known about the clinical implications of ATX and LPA receptors (LPAR) in cholangiocarcinoma (CCA). **Methods:** Tumor tissue samples from 110 CCA patients were evaluated. The expressions of ATX, LPAR2, and LPAR6 were detected by immunohistochemistry (IHC). Moreover, the cellular localization of ATX in the tumor microenvironment was detected by immunofluorescence (IF) staining. Furthermore, serums from 35 CCA patients (collected and frozen within 1 week before hepatectomy) and 8 healthy volunteers were determined.Serum ATX levels were measured using a fluorescent enzyme immunoassay. **Results:** In CCA tissue, correlations between ATX and LPAR2 expression (Spearman r = 0.214; p = 0.0025), LPAR2 and LPAR6 expression (Spearman r = 0.775; $p \leq 0.001$) were detected.High ATX expression was associated with poorer tumor grade (p = 0.038)and lymphatic metastasis (p = 0.024). The correlation of high ATX with shorter overall survival (OS) (p = 0.005) and recurrence-free survival (RFS) ($p < 0.001$) was detected by Kaplan-Meier curve analysis. In Cox regression analysis, high ATX expression (p = 0.001) was an independent factor associated with shorter RFS. Serum ATX levels were significantly higher in CCA patients compared with healthy controls (p = 0.007). Additionally, female CCA patients had significantly higher serum ATX levels than male CCA patients (p = 0.017). Moreover, we also determined that in the tumor microenvironment of CCA, ATX protein was expressed in tumor cells, cancer-associated fibroblasts, plasma cells, and epithelial cells. **Conclusion:** The highlight of this study is that it provides the first clinical evidence for the involvement of ATX in human CCA. Our present study demonstrated that the increased expression of ATX may promote tumorigenesis and progression of cholangiocarcinoma, affecting the long-term survival of patients.







Disclosures: The following people have nothing to disclose: Xuefeng Li

4139-A | THE IMPACT OF COVID-19 ON THE DIAGNOSIS AND TREATMENT OF HEPATOCELLULAR CARCINOMA: ANALYSIS OF A NATIONWIDE REGISTRY FOR ADVANCED LIVER DISEASES (REAL)

Kazuya Okushin[1], Ryosuke Tateishi[1], Shinya Hirakawa[2], Hisateru Tachimori[2], Koji Uchino[1], Ryo Nakagomi[1], Tomoharu Yamada[1], Takuma Nakatsuka[3], Tatsuya Minami[3], Masaya Sato[3], Mitsuhiro Fujishiro[3], Kiyoshi Hasegawa[1], Yuichiro Eguchi[4], Tatsuya Kanto[5], Hitoshi Yoshiji[6], Namiki Izumi[7], Masatoshi Kudo[8] and Kazuhiko Koike[3,9], (1)The University of Tokyo, Tokyo, Japan, (2)Keio University, Tokyo, Japan, (3)The University of Tokyo, (4)Saga University, Saga, Japan, (5)National Center for Global Health and Medicine, Chiba, Japan, (6)Nara Medical University, (7)Musashino Red Cross Hospital, Tokyo, Japan, (8)Kindai University Faculty of Medicine, Osaka-Sayama, Japan, (9)Kanto Central Hospital of the Mutual Aid Association of Public School Teachers, Tokyo, Japan

Background: The novel coronavirus disease 2019 (COVID-19) had a tremendous impact on the treatment status of several malignancies and chronic diseases. We aimed to clarify the clinical situation for hepatocellular carcinoma (HCC) in the era of COVID-19 using a novel nationwide REgistry for Advanced Liver diseases (REAL) in Japan. **Methods:** We retrieved patients' data initially diagnosed with HCC between January 2018 and December 2021 from REAL. We analyzed patients' characteristics, including age, sex, background etiology, laboratory data, and symptoms and treatment modalities for each admission. We compared the treatment situation of HCC in the era before COVID-19 (2018 and 2019) and in the era of COVID-19 (2020 and 2021). **Results:** We analyzed 13,671 patients initially diagnosed with HCC in the relevant period (8,020 patients in the era before COVID-19 and 5,651 patients in the era of COVID-19). In terms of the etiology of liver diseases, the proportion of non-B, non-C was increased (from 55.4% to 60.2%) in the era of COVID-19, whereas the proportions of HBV and HCV were decreased. The maximum size of intrahepatic tumors did not change in the era of COVID-19 compared with the era before COVID-19 (mean [standard deviation, SD] = 4.4 [3.9] cm and 4.4 [3.9] cm), whereas the number of intrahepatic tumors was decreased (single, 2-3, and > 3 in 72.0% and 74.2%, 22.7% and 20.8%, and 5.3% and 5.0%, respectively). The rates of vascular invasions and extrahepatic spread remained unchanged. Liver function as expressed by Child-Pugh class was also unchanged (Child A, B, and C in 80.5% and 80.5%, 16.7% and 16.5%, and 2.8% and 3.0%, respectively). Overall, HCC was diagnosed in similar BCLC stages (0, A, B, C, and D in 19.5% and 18.8%, 26.9% and 26.6%, 35.4% and 35.3%, 14.9% and 15.9%, and 3.2% and 3.4%, respectively). Regarding treatment modality, systemic therapy was increased in the era of COVID-19 (from 3.7% to 6.8%). Stratified with the etiology, HCC was diagnosed at similar BCLC stages before and during the era of COVID-19 in HBV and non-B, non-C, whereas at later BCLC stages in HCV. In the HCV group, the number of intrahepatic tumors decreased (single, 2-3, and > 3 in 72.1% and 75.5%, 23.1% and 20.4%, and 4.8% and 4.1%, respectively), but the proportion of portal vein invasion increased (from 9.2% to 12.0%). **Conclusion:** The treatment status of HCC remained largely unchanged during the COVID-19 pandemic in Japan, but the impact varied according to etiology. The maximum size of intrahepatic tumors remained unchanged, and more patients were diagnosed with single nodule HCC in the era of COVID-19. These results might indicate the robustness of the HCC surveillance system in Japan.

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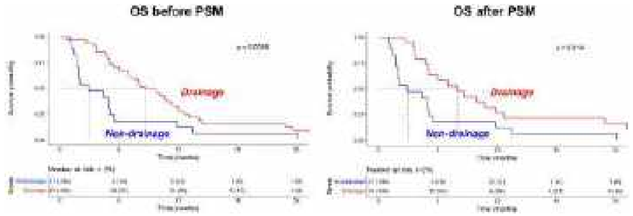
4140-A | THE PROGNOSTIC EFFICACY OF BILIARY DRAINAGE IN HCC WITH BILE DUCT INVASION: A MULTICENTER RETROSPECTIVE COHORT STUDY WITH PROPENSITY SCORE MATCHING

Keungmo Yang[1], Hyun Yang[1], Chang Wook Kim[1], Heechul Nam[1], Ji Hoon Kim[1], Ahlim Lee[1], U Im Chang[1], Jin Mo Yang[1], Hae Lim Lee[1], Jung Hyun Kwon[1], Soon Woo Nam[1], Soon Kyu Lee[1], Pil Soo Sung[2], Ji Won Han[1], Jeong Won Jang[1], Si Hyun Bae[1], Jong Choi[1], Seung Kew Yoon[1] and Hee Yeon Kim[1], (1)The Catholic University of Korea, (2)The Catholic University Liver Research Center, Department of Biomedicine & Health Sciences, College of Medicine, the Catholic University of Korea

Background: Bile duct invasion (BDI) is rarely observed in advanced hepatocellular carcinoma (HCC), which can lead to hyperbilirubinemia. Nevertheless, it remains uncertain whether pre-treatment biliary drainage is effective for HCC patients with BDI and obstructive jaundice. This research aims to investigate the impact of biliary drainage on the prognostic outcomes of these patients. **Methods:** We retrospectively enrolled a total of 200 HCC patients with BDI from multicenter cohorts. Patients without obstructive jaundice (total bilirubin level < 3 mg/dL; n = 99) or those who did not undergo HCC treatment (n = 37) were excluded from the further analysis. Finally, 64 patients with obstructive jaundice (43 with drainage and 21 without drainage) were included, and propensity score matching (PSM) was conducted. The modalities of biliary drainage were percutaneous transhepatic biliary drainage or endoscopic retrograde cholangiopancreatography. **Results:** Alpha-fetoprotein (≥ 400 ng/mL) and the duration between BDI diagnosis and HCC treatment were significantly different variables in baseline characteristics between the groups receiving biliary drainage and those without drainage in HCC patients with obstructive jaundice. The biliary drainage group showed better overall survival (Median OS, 8.9 vs. 2.9 mo; $P = 0.006$) and progression-free survival (Median PFS, 4.5 vs. 2.0 mo; $P = 0.009$) compared to the non-drainage group. Multivariate analysis demonstrated that biliary drainage was a significantly favorable prognostic factor for OS (Hazard ratio 0.44, $P = 0.013$) and PFS (Hazard ratio 0.44, $P = 0.086$). Furthermore, the biliary drainage presented the beneficial results in the first response evaluation after HCC treatment ($P = 0.001$). Remarkably, there were similar results in OS ($P = 0.014$) and PFS ($P = 0.007$) after PSM analyses. **Conclusion:** Biliary drainage is an independent favorable prognostic factor for HCC patients with BDI and obstructive jaundice. Therefore, this study suggests that biliary drainage should be contemplated in the treatment of advanced HCC patients with BDI for better survival outcomes.



Disclosures: The following people have nothing to disclose: Keungmo Yang, Hyun Yang, Chang Wook Kim, Heechul Nam, Ji Hoon Kim, Ahlim Lee, U Im Chang, Jin Mo Yang, Hae Lim Lee, Jung Hyun Kwon, Soon Woo Nam, Soon Kyu Lee, Pil Soo Sung, Ji Won Han, Jeong Won Jang, Si Hyun Bae, Jong Choi, Seung Kew Yoon, Hee Yeon Kim

4141-A | THE ROLE OF ALFA-FETOPROTEIN IN HCC SURVEILLANCE IN A NATIONAL HEALTH INSURANCE CLAIMS DATABASE

Sang Bong Ahn[1], Dae Won Jun[2], Joo Hyun Oh[3] and Eileen Yoon[2], (1)Nowon Eulji Medical Center, (2) Hanyang University College of Medicine, (3)Eulji Medical Center

Background: Early detection of HCC increases the possibility of receiving curative treatment and is a very important factor in improving survival rate. Abdominal ultrasonography and serum AFP are the most commonly used methods for HCC surveillance. However, the role of AFP in HCC surveillance has not yet been established. This study aimed to investigate the management status of high-risk patients with HCC and the effect of AFP test on survival using National Health Database. **Methods:** We used data from the National Health Claims Database established by the National Health Insurance Service (NHIS) of Korea. The HCC patients were defined as all patients with newly diagnosed HCC (C22.0) between 2008 and 2014. **Results:** From 2008 to 2018, 185,316 patients were registered with KNHIS with HCC, and 81,520 patients newly diagnosed with HCC between 2008 and 2014 were enrolled in the study analysis. In all HCC patients, the survival rate was significantly higher when the AFP test was performed 3 or more times during the 2 years before HCC diagnosis. When analyzed by causative disease, HBV patients showed a marked increase in survival rate as the number of AFP tests increased compared to alcohol and HCV patients. **Conclusion:** In HCC surveillance, AFP is helpful in improving survival rates. In particular, hepatitis B patients showed a significant increase in survival rate

Disclosures: The following people have nothing to disclose: Sang Bong Ahn, Dae Won Jun

Disclosure information not available at the time of publication: Joo Hyun Oh, Eileen Yoon

4142-A | THE USEFULNESS OF THE MUSCLE ATROPHY AND SUBCUTANEOUS ADIPOSE TISSUE RADIODENSITY IN PREDICTING THE PROGNOSIS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Masatsugu Ohara[1], Goki Suda[1], Takashi Kitagataya[2], Masato Nakai[3], Takuya Sho[1], Koji Ogawa[1] and Naoya Sakamoto[1], (1)Hokkaido University Hospital, (2)Mayo Clinic, (3)Hokkaido University Hospital, Sapporo, Japan

Background: Evaluation of skeletal muscle mass in patients with hepatocellular carcinoma (HCC) is considered as useful for predicting prognosis and identifying patients who are eligible for nutritional and exercise therapy. Although there are several methods of assessing skeletal muscle mass, we have previously reported that psoas muscle mass index (PMI) by manual tracing is more useful than BIA and PMI cutoff values. Recently, it has also been reported that subcutaneous adipose tissue (SAT) radiodensity affect the prognosis of patients with chronic liver disease including HCC. Therefore, we aimed to evaluate whether the PMI cutoff values in Japanese patients with HCC can be used to assess prognosis, and to evaluate whether the

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prognosis can be further stratified by PMI and SAT radiodensity. **Methods:** We retrospectively evaluated 201 patients with HCC who underwent CT and had muscle mass evaluated at our hospital between July 2015 and May 2021. Skeletal muscle mass was measured in the iliopsoas muscle in the L3 region using the manual tracing method, and we reported the cut off values (3.74 cm^2/m^2 for men and 2.29 cm^2/m^2 for women). SAT radiodensity were calculated using the previously reported cut off values (-83 HU for men and -74 HU for women, normal when lower than the cutoff values, and High SAT when higher than the cutoff values). **Results:** Patient characteristics was as follows: median age 71 years, 154 males, Child Pugh classification (A, B or C): 155 / 46, cirrhosis: 146, median observation period: 2.8 years. Muscle atrophy (MA) was observed in 67 patients (33.3%), and the patients with MA were significantly worse prognosis in the patients without MA (hazard ratio, HR 1.88; 95% confidence interval [CI] 1.18 - 2.99; $p < 0.004$). Prognosis stratified by SAT radiodensity was also significantly worse in the patients with high SAT radiodensity (HR 2.66; 95% CI 1.18 - 5.958; $p < 0.001$), as previously reported. Finally, stratification by MA and SAT radiodensity into 4 groups showed significantly different prognoses, and especially the patients with MA and high SAT had a poor prognosis (median OS in the patients without MA and with or without high SAT was undefined, 4.29 years in the patients with MA and without high SAT, and 1.04 years in the patients with MA and with high SAT; $p = 0.0017$). Furthermore, among the patients with Child-Pugh grade A, the patients with MA tended to be poor prognosis ($p = 0.05$), and the patients with high SAT had similar prognosis ($p = 0.12$). While, the patients with MA and high SAT had a significantly poorer prognosis (HR 3.48; 95% CI 1.03 - 11.7; $p = 0.044$). **Conclusion:** Combined evaluation of MA and SAT radiodensity can stratify the poor prognosis group in hepatocellular carcinoma and may serve as an evaluation item during nutritional intervention.

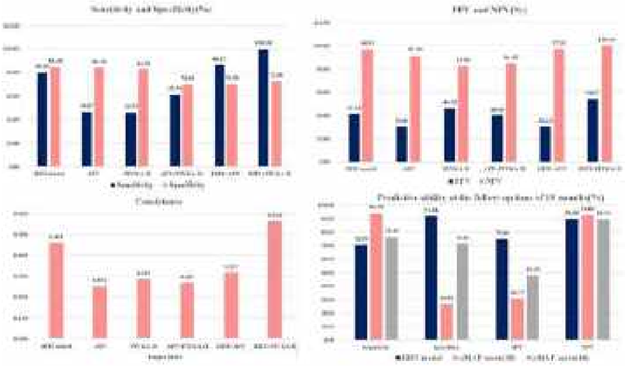
Disclosures: The following people have nothing to disclose: Masatsugu Ohara, Takashi Kitagataya, Masato Nakai

Disclosure information not available at the time of publication: Goki Suda, Takuya Sho, Koji Ogawa, Naoya Sakamoto

4143-A | THE VALUE OF HIFI MODEL BASED ON cfDNA GENOMIC FEATURES IN EARLY DIAGNOSIS AND PREDICTION OF HEPATOCELLULAR CARCINOMA

Linhan Li[1], Xiaobo Lu[2], Xiaozhong Wang[3], Xuan An[4], Quan Zhang[5], Hong Ren[1], Peng Hu[1], Dachuan Cai[1], Yinghua Lan[1], Dazhi Zhang[1] and Juan Kang[1], (1)Key Laboratory of Molecular Biology for Infectious Diseases (Ministry of Education), Institute for Viral Hepatitis, the Second Affiliated Hospital of Chongqing Medical University, (2)The First Affiliated Hospital of Xinjiang Medical University, (3)The Fourth Affiliated Hospital of Xinjiang Medical University (Xinjiang Hospital of Traditional Chinese Medicine), (4)Chongqing University Three Gorges Hospital, (5)The Affiliated Hospital of Guizhou Medical University

Background: The detection of cell-free DNA (cfDNA) is a promising early diagnosis method for hepatocellular carcinoma (HCC). We validated the cfDNA-based comprehensive diagnostic model (HIFI) and explored its value in the early diagnosis and prediction of HCC. **Methods:** cfDNA detection was performed in 126 patients with or without chronic liver disease from 5 centers, multi-dimensional gene variation indicators were analyzed, the results of HIFI was obtained and compared with imaging or HCC markers to evaluate the advantages of HIFI model compared with traditional methods. Moreover, we also conducted long-term follow-up to evaluate the predictive value of HIFI model in the occurrence of HCC. In addition, the sensitivity, specificity, PPV, and NPV of the aMAP score and HIFI models were compared at 10 months of follow-up to assess their predictive value for HCC. **Results:** Chi-square test and Kappa analysis showed that the diagnostic consistency between HIFI model and traditional methods (i.e., biopsy, hepatic arteriography, etc.) was significantly higher than that of AFP and PIVKA-II (Kappa = 0.461 vs 0.251 vs 0.287, $P \leq 0.05$). Moreover, the consistency of HIFI model combined with PIVKA-II was significantly higher than that of AFP combined with PIVKA-II and HIFI model combined with AFP (Kappa = 0.564 vs 0.267 vs 0.317, $P \leq 0.05$). During follow-up, a total of 103 patients were invovled with a median time of 11.5 months, the consistency of the HIFI model with traditional diagnostic methods was kappa = 0.530 at the 3 months($P = 0.000$). In addition, we used the HIFI model as a predictive model and compared it with the aMAP score at 10 months, the sensitivity, specificity, PPV and NPV of HIFI model in predicting HCC was 70.59%, 91.84%, 75.00% and 90.00%. When 50/60 is seted as the cut-off value of aMAP score, the sensitivity, specificity, PPV and NPV was 94.12/76.47%, 26.53/ 71.43%, 30.77/ 48.15% and 92.86 /89.74%. **Conclusion:** The study demonstrated the superiority of the cfDNA-based HIFI model as a method of early warning and diagnosis of HCC compared with the traditional serum markers AFP and PIVKA-II. Moreover, the predictive efficacy of the HIFI model remained high at 10 months, in terms of specificity and PPV, the HIFI model was even better than the aMAP score. Especially for non-HCC patients with negative HIFI result, the probability of progression to HCC in 10 months was very low. HIFI combined with PIVKA-II may be a reliable means for early warning and diagnosis of HCC.



Disclosures: The following people have nothing to disclose: Linhan Li, Xiaobo Lu, Xiaozhong Wang, Xuan An, Quan Zhang, Hong Ren, Peng Hu, Dachuan Cai, Yinghua Lan, Dazhi Zhang, Juan Kang

4144-A | THERAPEUTIC EFFECTS OF GNMT INDUCERS FOR NON-ALCOHOLIC FATTY LIVER DISEASE AND HEPATOCELLULAR CARCINOMA

Yi-Ming Arthur Arthur Chen, Fu Jen Catholic University; National Health Research Institutes

Background: Glycine-N-methyl transferase (GNMT) downregulation results in nonalcoholic fatty liver disease (NAFLD) and spontaneous hepatocellular carcinoma (HCC) both. Overexpression of GNMT inhibits the accumulation of lipid in hepatocytes, the proliferation of liver cancer cell lines and prevents carcinogen-induced HCC, suggesting that GNMT induction is potential approaches for anti-NAFLD and anti-HCC therapy. **Methods:** Herein, we used Huh7 GNMT promoter-driven screening to identify two GNMT inducers from natural plant extracts library and small molecule library. First, 1,2,3,4,6-pentagalloyl glucose (PGG) was identified from the extract of Paeonia lactiflora Pall (PL). Second, compound K78 was identified and validated for its induction of GNMT and inhibition of Huh7 cell growth. Subsequently, we employed structure−activity relationship analysis and found a potent GNMT inducer, K117. The GNMT expression was further confirmed by reverse transcription-quantitative PCR (RT-qPCR) and Western blotting (WB) analysis using both in vitro and in vivo systems. **Results:** PGG and metformin were shown to upregulate liver mitochondrial GNMT protein expression. The high-fat diet (HFD)-induced NAFLD mice were treated with PGG and metformin. The combination of PGG and metformin nearly completely reversed weight gain, elevation of serum aminotransferases, and hepatic steatosis and steatohepatitis. In addition, the downregulated GNMT expression in liver tissues of HFD-induced NAFLD mice was restored. On the other hand, K117 inhibited Huh7 cell growth in vitro and xenograft in vivo. Oral administration can inhibit Huh7 xenograft in a manner equivalent to the effect of sorafenib. A mechanistic study revealed that both PGG and K117 are MYC inhibitors. Ectopic expression of MYC using CMV promoter blocked PGG- and K117-mediated MYC inhibition and GNMT induction. **Conclusion:** Our findings show that GNMT expression plays an important role in the pathogenesis of NAFLD and HCC, PGG and K117 are potential compounds for NAFLD-, HCC- and MYC-dependent cancers.

Disclosures: Yi-Ming Arthur Arthur Chen – The One Biopharmaceutical Co., Ltd.: Executive role , Yes, No;

4145-A | THERAPEUTIC EXPERIENCE WITH HEPATECTOMY FOR INTRAHEPATIC RECURRENCE AFTER RADIOTHERAPY IN LIVER TUMORS: IMPLICATION OF THERAPEUTIC EFFECT BY PD-L1 ELEVATION VIA RADIATION

Keisuke Oyama, Yoshifumi Iwagami, Shogo Kobayashi, Kazuki Sasaki, Daisaku Yamada, Yoshito Tomimaru, Takehiro Noda, Hidenori Takahashi, Yuichiro Doki and Hidetoshi Eguchi, Osaka University

Background: Radiation therapy for liver tumors has become widespread with the development of stereotactic body radiotherapy (SBRT) and reported to have a high local therapeutic effect. Radiation therapy could affect tumor immunity not only locally but also outside the irradiation site. Based on the experience of hepatectomy for local recurrence after radiotherapy, we investigated the effects of radiotherapy for liver tumors on operative course and tumor immunity. **Methods:** From 2010 to 2022, we retrospectively analyzed patients who underwent hepatectomy for recurrence of the irradiated site after radiotherapy for liver tumors. Excluding radiotherapy for cholangiocarcinoma, 48 patients underwent radiotherapy for liver tumors. Of the 6 patients who underwent surgery, 1 patient with recurrence of liver tumor outside the irradiation site was excluded. Surgical course and pathological findings were investigated in 3 recurrence cases of hepatocellular carcinoma and 2 cases of metastatic colorectal cancer. **Results:** SBRT (50-55Gy/5 or 10fr) was performed for recurrent or refractory tumor after prior hepatectomy or transcatheter arterial chemoembolization (TACE). Tumor could be controlled temporarily after SBRT, however, recurrence occurred after 2.4 (0.9-5.5) years at the irradiation site. All 5 patients underwent hepatectomy for local lesions at the irradiation site. Only mild hepatic-diaphragmatic adhesions and hepatic atrophy were observed in surgical

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

findings. No postoperative complications were observed in any of the patients. There were no patients with decreased liver function or nutritional indicators (cholinesterase and albumin) 3 months after surgery. In the resected specimen, necrosis associated with radiotherapy was observed in the tumor area. Inflammation and fibrosis in the surrounding non-cancerous area did not show any clear changes compared to the previous operation. Expression of CD68 and PD-L1 was observed around the tumor on immunohistochemistry. While SBRT had a strong therapeutic effect on the tumor, a decrease in tumor immunity might be indicated around the irradiated tumor site. No recurrence was observed 3.2 (0.9-5.1) years after surgery. In all cases, no intrahepatic recurrence and metastases was observed outside the irradiation site after radiotherapy. **Conclusion:** Hepatectomy for recurrence of the irradiated site after SBRT was performed successfully without complications. Although tumor immunosuppression might be induced after radiotherapy in the irradiated site for liver tumors, tumor recurrence outside the irradiated site were not observed.

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Disclosure information not available at the time of publication: Yoshifumi Iwagami

4146-A | TISLELIZUMAB IN COMBINATION WITH ANLOTINIB AS FIRST-LINE TREATMENT FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA: A SINGLE-CENTER, SINGLE-ARM, EXPLORATORY PHASE II CLINICAL STUDY

Shixue Laoguo, Huasheng Huang, Jie Zeng, Yangfeng Jiang, Cuizhen Liu, Ning Mo, Guangzhi Zhu, Fuchao Ma, Tao Peng, Lihua Yang, Zhiming Zeng and Jie Ma, The First Affiliated Hospital of Guangxi Medical University

Background: Patients with advanced hepatocellular carcinoma (HCC) have limited therapeutic options and poor overall prognosis. Programmed cell death protein-1(PD-1) inhibitors combined with tyrosine kinase inhibitors (TKIs) has demonstrated excellent clinical efficacy in the treatment of multiple malignancies. Therefore, based on the clinical results of tislelizumab (anti-PD-1 antibody) and anlotinib (a multi-target tyrosine kinase inhibitor) in HCC, we evaluated the efficacy and safety of tislelizumab in combination with anlotinib in patients with postoperative recurrence or advanced HCC. **Methods:** This was a single-center, single-arm, phase II clinical trial. Key inclusion criteria: aged 18-75 years, with unresectable HCC, ECOG PS 0-3, BCLC stage A-C and Child-Pugh score A-C were enrolled. Patients who met the inclusion criteria received tislelizumab (intravenous drip, 200 mg/d1, Q3W) and anlotinib (oral, 8-12 mg/d1-14, Q3W). The primary endpoint was objective response rate (ORR) per mRECIST. The secondary endpoints included disease control rate (DCR), overall survival (OS), progression-free survival (PFS), adverse events (AEs), and serious adverse events (SAEs). **Results:** In this study, a total of 30 HCC patients were enrolled from September-2020 to December-2021. They were followed up and their clinical data were tracked. The median age of the pts was 52.5 years (ranged 31-72 y), 17 pts (53.1%) ECOG PS 1, 19 pts (63.3%) BCLC stage C, 20 pts (66.7%) Hepatitis B virus infection and 14 pts (46.7%) had received prior local regional therapy. The ORR per mRECIST was 30% (95% CI, 12.6%-47.4%), with 6.7% (2/30) complete response (CR), 23.3% (7/30) partial response (PR), and 46.7% (14/30) stable disease (SD). The DCR was 76.7%(95%CI,60.6%-92.7%) With a median follow-up of 18.2 months, the estimated median PFS was 11.8 months, and the median OS was not reached. The most common AEs during follow-up were AST increased (53.3%), γ-GT increased (46.7%), and hypoalbuminemia (43.3%). No SAEs were observed. **Conclusion:** Tislelizumab combined with anlotinib in the treatment of unresectable HCC has showed high antitumor activity and good tolerance, which may be an effective and safe treatment option.

Disclosures: The following people have nothing to disclose: Shixue Laoguo, Huasheng Huang, Jie Zeng, Yangfeng Jiang, Cuizhen Liu, Ning Mo, Guangzhi Zhu, Fuchao Ma, Tao Peng, Lihua Yang, Zhiming Zeng, Jie Ma

4147-A | TRANS ARTERIAL CHEMOEMBOLIZATION COMBINED WITH RADIOFREQUENCY ABLATION PROVIDES A BETTER OUTCOME IN HEPATOCELLULAR CARCINOMA IN TUMORS WITHIN MILAN CRITERIA

Mithun Sharma[1], Jagdeesh Singh[2], Padaki Nagaraja Rao[1], Sowmya T R[1], Manasa Alla[1], Anand V. Kulkarni[1] and Nageshwar D. Reddy[1], (1)Aig Hospitals, Hyderabad, India, (2)Asian Institute of Gastroenterology, Hyderabad, Telangana, India

Background: Transarterial chemoembolization (TACE) combined with radiofrequency ablation (RFA) is hypothesized to offer a better complete response when compared with TACE alone for tumors within the Milan criteria. However, the data is scarce. Therefore, this study aimed to evaluate and compare the efficacy of sequential use of TACE plus RFA (TACE + RFA) versus RFA alone in HCC. **Methods:** This was a retrospective analysis of patients undergoing TACE +RFA and was compared with TACE alone. Since this was a retrospective review, the selection of patients in either arm was based on the preference of the interventional radiologist. The primary outcome was to compare response at 3 months, overall survival (OS) at 1 year, and disease-free survival (DFS). **Results:** Out of a total of 51 patients with a tumor size of 6.2. ± 2.3 cms, 26 patients underwent TACE + RFA. Majority (80%) of patients were in CHILD PUGH A/B and were not ready for a surgical intervention or liver transplantation. Complete response(CR) and partial response (PR) at 3 months as per the mRECIST criteria were noted in 18/26(69.2%) vs 16/25 (64%) and 4/26(15.2%) vs 10/25 (40%)patients respectively with TACE + RFA vs TACE alone. 3(11.56%) vs 3 (12%) in both arms had stable disease. The OS at 1 yr was better in the TACE+RFA arm [23(88.46%) when compared to TACE alone arm [20(80%)] . The rate of complications and duration of hospital stay was not different between the two arms. **Conclusion:** TACE + RFA vs TACE alone had similar short-term outcome though there was trend towards a better overall survival at the end of 1 year with similar rates of adverse event

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Disclosure information not available at the time of publication: Anand V. Kulkarni

4148-A | TREATMENT WITH GEMCITABINE/CISPLATIN AND DURVALUMAB FOR BILIARY TRACT CANCER – FIRST REAL-WORLD DATA FROM A GERMAN PATIENT COHORT

Florian Gerhardt[1], Christian Müller[2], Jack Chater[3], Aaron Schindler[1], Sebastian Ebel[4], Marino Venerito[5], Thomas Berg[4] and Florian Van Bömmel[1], (1)University Hospital Leipzig, (2)University Hospital Magdeburg, (3) Klinikum Chemnitz, (4)University Hospital of Leipzig, (5) Otto-Von-Guericke Universität Magdeburg

Background: Biliary tract cancers (BTC) is a rare and heterogenous disease with poor prognosis. Based on the results of the TOPAZ-1 trial, the combination therapy of gemcitabine and cisplatin with the immune checkpoint inhibitor durvalumab (GC+D) has recently been approved in Europe and in the US for the treatment of BTC. However, the role of this treatment outside of clinical studies has not yet been studied. We have studied tolerability and efficacy of GC +D in real-world patients. **Methods:** We retrospectively included patients treated with GC+D in German tertiary medical centers. Before approval of durvalumab, patients were treated based on cost approval by the their health insurance. Response was defined by RECIST1.1 criteria based on tomography after 12 weeks of treatment. Adverse events were categorized by CTCAE. **Results:** A total of 36 patients were treated with GC+D in 3 participating centers between August 2022 and May 2023 hereby receiving a mean of 4 (range, 1-11) cycles over a mean duration of 18 ± 13 (range, 4-60) weeks. Twenty-six, 7, 2 and 1 patient were in the age groups <70, 70-75, 76-80 and >80 years, respectively, 21 (58%) were female and 2 had liver cirrhosis. ECOG performance status grades were 0, 1 and 2 in 14, 21 an 1 patient. Nineteen patients had intrahepatic, 12 extra hepatic cholangio carcinoma and 5 gall bladder carcinoma. Staging after 12 weeks was performed in 20 patients, hereby showing stable disease in 8 (40%), partial response in 3 (15%) and progressive disease in 9 patients (45%). At the last reported staging, complete response was found in 1 (15%), stable disease in 8 (40%) and progressive disease in 9 (45%) patients. Grade 3/4 adverse events occurred in 5 patients and included anemia, thrombocytopenia and neutropenia. 3 patients had to stop treatment due to side effects. Immune-mediated side effects did not occur. Second line treatment was given to 6 patients, including FOLFOX (n = 3) and ivosidenib (n = 3). Fife patients died 1, 3, 3 and 6 months after GC+D treatment initiation due to thrombosis (n = 1) or cholangitis (n = 4), all of which were ECOG 1 or 2 at treatment initiation. **Conclusion:** The addition of durvalumab to gemcitabine and cisplatin did not lead to immune mediated side effects in this real-world cohort. Longer follow up and larger patient populations are needed to define the role of GC+D treatment for BTC outside of clinical trials.

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Disclosure information not available at the time of publication: Christian Müller, Jack Chater, Aaron Schindler, Marino Venerito, Florian Van Bömmel

4149-A | TUMOUR SEEDING WITH BIOPSY OF HEPATOCELLULAR CARCINOMA—A SYSTEMATIC REVIEW

Chunpeng Nie[1], Marcus Vaska[2], Jason Wong[1], Oliver F. Bathe[1], Stefan Przybojewski[1], Kelly Warren Burak[1], Patricia A. Tang[1] and Stephen E. Congly[1], (1)University of Calgary, (2)Alberta Health Services

Background: Biopsy of hepatocellular carcinoma (HCC) is not frequently done as contrast-enhanced imaging is generally able to provide a diagnosis non-invasively, and the potential risk of seeding remains a concern. However, biopsies of malignant liver masses may be valuable to confirm a diagnosis of HCC to allow for selection of appropriate chemotherapy when imaging is inconclusive. A systematic review of the literature was conducted to understand the overall risk of tumour seeding with biopsy of HCC. **Methods:** EMBASE, MEDLINE (Ovid), CINAHL and Web of Science were reviewed from inception until August 31, 2022, with the search strategy design assisted by a medical librarian. Inclusion criteria were prospective or retrospective human cohort studies including randomized control trials (RCTs) and case series of any percutaneous liver biopsy of a lesion found to be a HCC, with the outcome of tumour seeding being reported. Studies reporting on non-liver cancers or seeding after intervention were excluded. Two individual's independently screened abstracts and extracted data; discrepancies were resolved by consensus. **Results:** A total of 2339 unique abstracts were identified. 94 underwent full text review and 37 studies were included in the analysis. All studies were retrospective in nature. 43% of the studies were from Asia, 38% from Europe and 16% from North America. The overall rate of tumour seeding was 0.62% (range 0-7.77%) in 13,959 biopsies performed. The average of the reported median lengths of follow-up was 35.8 months (range 10.5-60 mo). The mean duration between biopsy and diagnosis of cancer was 17.2 months. Risk factors for seeding reported included large tumour sizes and increased number of passes. **Conclusion:** Overall, the risk of tumour seeding with biopsy of HCC is low, and if clinically indicated the seeding risk should not preclude biopsy.

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Disclosure information not available at the time of publication: Marcus Vaska, Jason Wong, Oliver F. Bathe, Stefan Przybojewski, Kelly Warren Burak, Patricia A. Tang

4150-A | UNCOVERING THE BURDEN OF BILIARY TRACT CANCER IN ASIA: GLOBAL BURDEN OF DISEASE STUDY PERSPECTIVES

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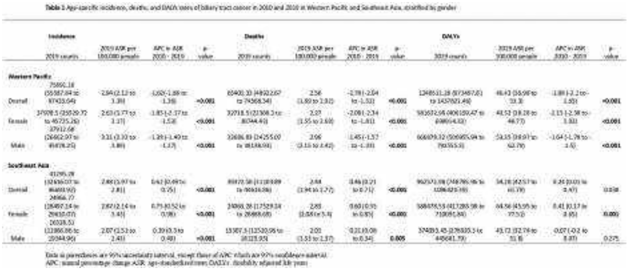
Background: Biliary tract cancer (BTC) is the second most common type of hepatobiliary cancer worldwide and is known for its high mortality rate due to its advanced stage at diagnosis. The incidence of BTC varies globally, with certain regions in Asia exhibiting exceptionally high rates. However, research focusing on the disease burden in Asia is relatively scarce compared to the Western regions. To address the existing healthcare disparities, our study evaluated the burdens of BTC in Asia among all age groups, specifically in Southeast Asia (SEA) and the Western Pacific (WP). **Methods:** We retrieved the data from the Global Burden of Disease study to conduct a comprehensive analysis of the BTC burdens, including the incidence, mortality, and disability-adjusted life years (DALYs) of BTC across SEA and WP regions, from 2010 to 2019. The study also examined the trends and disparities in the burden of BTC across different nations and genders. **Results:** In 2019, the WP region had a higher incidence of BTC when compared to SEA (75,891 vs. 41,295). Over the study period, there was an increase in the BTC incidence rate in SEA (APC +0.62). In contrast, WP exhibited a decline (APC-1.62). Furthermore, the mortality trend decreased in WP (APC–1.78) but increased in SEA (APC+0.46). Nevertheless, the overall mortality in 2019 was higher in WP (65,405) than in SEA (39,373). In the SEA region, females carried greater burdens of BTC than males, with higher incidence (24,966 vs. 16,328), mortality

(24,065 vs. 15,307), and DALYs (588,478 vs. 374,093). These burdens exhibited increasing trends among SEA's females, with rising incidence (APC+0.75), mortality (APC+0.60), and DALYs (+0.41). **Conclusion:** All burdens of BTC in WP remained high in 2019 despite decreasing trends over the past decade. In contrast, SEA experienced a significant increase in the overall incidence and mortality rates, posing potential healthcare burdens in the near future. Additionally, females in SEA experienced significantly increasing rates in the incidence, mortality, and DALYs associated with BTC, while males showed opposite trends regarding DALYs. These findings emphasize the urgent need for studying BTC within specific Asian regions. Further research is required to elucidate the underlying cause of this high-burden disease with gender disparities.



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4151-A | UNMET SYSTEMIC THERAPY NEED FOR CHILD-PUGH CLASS B PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA – COMPARISON OF ATEZOLIZUMAB PLUS BEVACIZUMAB AND LENVATINIB

Hideko Ohama[1,2,3], Atsushi Hiraoka[1,2], Toshifumi Tada[2], Masashi Hirooka[2], Kazuya Kariyama[2], Ei Itobayashi[2], Tsuji Kunihiko[2], Toru Ishikawa[2], Hidenori Toyoda[2], Takeshi Hatanaka[2], Satoru Kakizaki[2], Atsushi Naganuma[2], Tomomitsu Matono[2], Fujimasa Tada[1,2], Kazuhiro Nouso[2], Yoichi Hiasa[2] and Takashi Kumada[2], (1)Ehime Prefectural Central Hospital, (2)Relpec Study Group and HCC 48 Group, (3)Takarazuka City Hospital

Background: Systemic treatment is generally recommended for unresectable hepatocellular carcinoma (uHCC) patients with Child-Pugh (CP)-A status. However, not all who undergo systemic treatment have good hepatic function, as some are known to develop poor hepatic function as a clinical manifestation. Given the urgent need for effective therapeutic strategies to treat u-HCC patients with CP-B, this study was conducted to compare the efficacy of lenvatinib (LEN) with that of atezolizumab plus bevacizumab (Atez/Bev). **Methods:** A total of 145 uHCC patients with ECOG performance status 0 or 1 and CP-B liver function who received Atez/Bev (n = 53) or LEN (n = 92) as initial systemic treatment from April 2018 to December 2022 were enrolled. Therapeutic response, evaluated using RECIST version 1.1, as well as clinical features and prognosis were retrospectively evaluated. **Results:** Median age for all patients was 71 years (interquartile range 61-77) and 113 (77.9%) were male. CP score was 7 for 105, 8 for 31, and 9 for 9 patients, while median ALBI score was -1.71. The Atez/Bev and LEN groups did not differ significantly for best response (complete response:partial response:stable disease: progressive disease = 0:12:20:12 vs. 5:22:24:19, p = 0.265). Also, there was no significant difference for progression-free survival (PFS) between them [median 5.7 (95% CI 3.6-7.9) vs. 4.4 (95% CI 3.5-5.9) months, p = 0.581]. Post-progression treatment was performed in 27.8% (5/18) of treatment failure cases in the Atez/Bev group and in 38.3% (23/60) of those in the LEN group (p = 0.58). Adverse events (AEs) (any grade/ ≥ grade 3) were observed in 83.0%/36.4% (n = 44/16) of the Atez/Bev group and 78.3%/36.1% (n = 72/26) of the LEN group (p = 0.53 and p = 1.0, respectively). **Conclusion:** PFS, post-progression treatment rate, and incidence of AEs were not significantly different between the Atez/Bev and LEN groups. Although both treatments showed equivalent effects, neither demonstrated sufficient therapeutic efficacy in the present cases. Development of an effective systemic therapy for uHCC patients with CP-B is needed in the near future.

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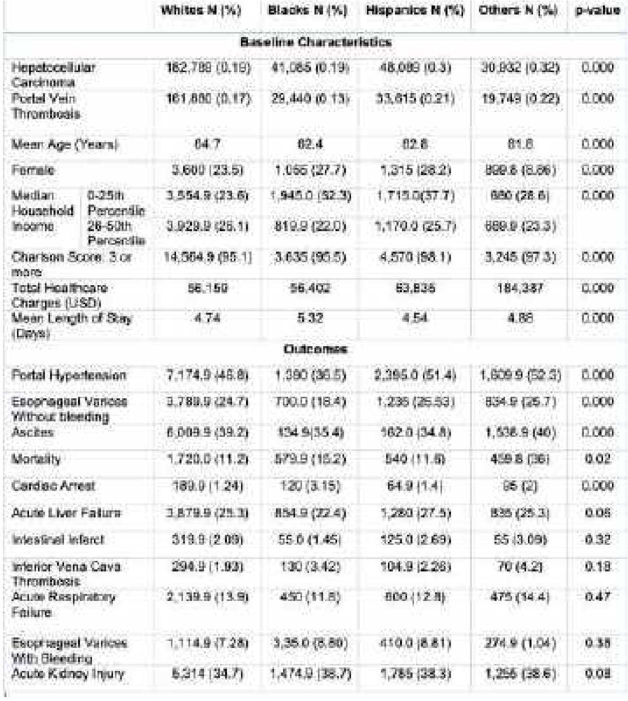
4152-A | UNVEILING RACIAL DISCREPANCIES IN THE OUTCOMES OF PORTAL VEIN THROMBOSIS ASSOCIATED WITH HEPATOCELLULAR CARCINOMA - A 5-YEAR NATIONWIDE ANALYSIS

Fnu Vikash[1], Sindhu Vikash[1], Yassine Kilani[2], Vikash Kumar[3], Noor Syed[4], Sobaan Taj[5], Abu Abbasi[6], Syeda

Ashna Fatima Kamal[7], Dushyant Dahiya[8] and Sunny Patel[1], (1)Jacobi Medical Center/Albert Einstein College of Medicine, (2)Lincoln Medical Center, (3)The Brooklyn Hospital Center, (4)Santa Clara Valley Medical Center, (5)Hackensack Meridian Jersey Shore University Medical Center, (6)Loyola University Medical Center, Chicago, IL, (7)Southern Illinois University (SIU)), (8)The University of Kansas School of Medicine

Background: Portal vein thrombosis (PVT) is considered a negative prognostic factor in hepatocellular carcinoma (HCC) patients. Our study is the first to compare the baseline characteristics, hospital utilization, and outcomes associated with PVT in HCC patients across different racial groups within the United States (US). **Methods:** This is a retrospective longitudinal study of patients with a primary diagnosis of HCC. We retrieved data from the Nationwide Inpatient Sample (NIS) databases from the years 2016 to 2020 using ICD-10 CM codes. Multivariate regression analysis was applied to compare the outcomes in races, adjusted for patient and hospital confounders. A T-Test and Chi-Square test were performed to compare baseline characteristics (table 1). We used STATA® Version 17.0 Software for analysis. The p-value was set at $p < 0.05$ for statistical significance. **Results:** Among a total of 310,774 adults with HCC, 81% (N = 252,455) had PVT. Hispanic patients had the highest rate of PVT among all races. Black and Hispanic patients were found to have a lower income ($p = 0.00$) (table 1). Hispanic patients had a significant increase in total healthcare costs (coefficient: 39,753 US Dollars, $p = 0.006$, CI 95%: 11,260 - 68,2461) and higher (3+) Charlson Comorbidity Index ($p = 0.00$) as compared to Whites. Black patients had a higher mean length of stay (5.32 d, $p = 0.00$). In terms of the outcomes, Black patients had lower rates of portal hypertension (36.5%, $p = 0.00$) and esophageal varices without bleeding (18.4%, $p = 0.00$) as compared to White patients. Hispanic patients had lower rates of ascites (34.8%, $p = 0.00$). Black patients had the highest rate of in-patient mortality (15.2%, $p = 0.02$) and cardiac arrest (3.15%, $p = 0.00$). However, there was no significant difference found in terms of acute liver failure, intestinal infarction, inferior vena cava thrombosis, acute respiratory failure, or renal impairment among all race cohorts. **Conclusion:** Although Black patients had lower rates of complications related to PVT in HCC compared to other races, our study found that they had higher rates of cardiac arrest and mortality. This suggests that while Black patients may experience fewer PVT-related complications, they face significant risks of severe outcomes including higher mortality. Large-scale studies are necessary to determine factors associated with these findings.



		Whites N (%)	Blacks N (%)	Hispanics N (%)	Others N (%)	p-value
Baseline Characteristics						
Hepatocellular Carcinoma		182,789 (0.18)	41,085 (0.19)	48,089 (0.3)	30,932 (0.32)	0.000
Portal Vein Thrombosis		161,880 (0.17)	29,440 (0.13)	33,615 (0.21)	19,749 (0.22)	0.000
Mean Age (Years)		64.7	62.4	62.8	61.6	0.000
Female		3,600 (23.5)	1,055 (27.7)	1,315 (28.2)	899.8 (6.86)	0.000
Median Household Income	0-25th Percentile	3,554.9 (23.6)	1,945.0 (52.3)	1,715.0(37.7)	880 (28.6)	0.000
	26-50th Percentile	3,929.9 (25.1)	819.9 (22.0)	1,170.0 (25.7)	689.9 (23.3)	
Charlson Score: 3 or more		14,584.9 (95.1)	3,635 (95.5)	4,570 (98.1)	3,245 (97.3)	0.000
Total Healthcare Charges (USD)		56,159	56,402	63,835	184,387	0.000
Mean Length of Stay (Days)		4.74	5.32	4.54	4.86	0.000
Outcomes						
Portal Hypertension		7,174.9 (46.8)	1,390 (36.5)	2,395.0 (51.4)	1,609.9 (52.3)	0.000
Esophageal Varices Without bleeding		3,789.9 (24.7)	700.0 (18.4)	1,236 (26.53)	834.9 (26.7)	0.000
Ascites		6,009.9 (39.2)	134.9(35.4)	162.0 (34.8)	1,536.9 (40)	0.000
Mortality		1,720.0 (11.2)	579.9 (15.2)	540 (11.6)	459.8 (36)	0.02
Cardiac Arrest		189.0 (1.24)	120 (3.15)	64.9 (1.4)	95 (2)	0.000
Acute Liver Failure		3,879.9 (25.3)	854.9 (22.4)	1,280 (27.5)	835 (25.3)	0.06
Intestinal infarct		319.9 (2.09)	55.0 (1.45)	125.0 (2.69)	55 (3.09)	0.32
Inferior Vena Cava Thrombosis		294.9 (1.93)	130 (3.42)	104.9 (2.26)	70 (4.2)	0.18
Acute Respiratory Failure		2,139.9 (13.9)	450 (11.8)	600 (12.8)	475 (14.4)	0.47
Esophageal Varices With Bleeding		1,114.9 (7.28)	3,35.0 (8.80)	410.0 (8.81)	274.9 (1.04)	0.38
Acute Kidney Injury		5,314 (34.7)	1,474.9 (38.7)	1,785 (38.3)	1,256 (38.6)	0.08

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4153-A | UNVEILING THE IMPACT OF HYPONATREMIA ON MORBIDITY, MORTALITY, AND RESOURCE UTILIZATION IN HEPATOCELLULAR CARCINOMA: FIVE YEAR NATIONWIDE ANALYSIS 2016-2020

Vikash Kumar[1], Fnu Vikash[2], Yassine Kilani[3], Uchit Thapa[4], Sindhu Vikash[2], Vijay Gayam[1] and Naresh Kumar[1], (1)The Brooklyn Hospital Center, (2)Jacobi Medical Center/Albert Einstein College of Medicine, (3) Lincoln Medical Center, (4)Bassett Medical Center

Background: Hyponatremia has long been recognized as a crucial prognostic marker in cirrhosis. In addition, a number of studies reported that the baseline serum sodium level and survival in liver cirrhosis patients awaiting liver transplantation are well correlated as part of a model for end-stage liver disease (MELD- Na). Hyponatremia is a common electrolyte disturbance in cancer patients and has been linked to unfavorable outcomes in a variety of malignancies. Risk factors for hyponatremia in cancer patients include pain, narcotic drugs, chemotherapy, treatment-induced nausea and vomiting, hydration, physical and emotional stress. However, to the best of our knowledge, its prognostic role in the field of Hepatocellular carcinoma has been less investigated. Therefore, we evaluated mortality, morbidity, and resource utilization in Hepatocellular carcinoma patients secondary to hyponatremia. **Methods:** A retrospective analysis was performed by utilizing the National Inpatient Sample database 2016 -2020 and the ICD- 10 codes were used to identify the patients $>$ 18 years old with the principal diagnosis of Hepatocellular carcinoma. Effect of hyponatremia was studied on mortality, morbidity, and resource utilization. Continuous variables were compared using the t- test, and Categorical variables were compared using the chi-square test. Multivariable regression analyses were performed adjusting for demographics, hospital-level characteristics, and relevant comorbidities. Confounding variables were adjusted using multivariate logistic and linear regression analyses. These included: gender, race, Charlson Comorbidity Index, chronic kidney disease, congestive heart failure, cirrhosis, nephrotic syndrome, hypothyroidism, adrenal insufficiency, alcohol use disorder, and admission for hypovolemia or psychogenic polydipsia and various patient and hospital characteristics.

Results: We identified a total of 237,905 patients with primary diagnosis of Hepatocellular carcinoma in 2016 to 2020, Of whom 23.3% (55,514) had hyponatremia on presentation. Mean age was 64 years and 77.3% were male. Patients with hyponatremia had 12.8 % in-hospital mortality, while 8.5% for patients without hyponatremia. After adjusting for confounders, hyponatremia imparted higher odds of mortality (Adjusted odds ratio (aOR) for mortality 1.47, 95% confidence interval (CI): 1.35–1.61, $P<0.01$). Hepatocellular cancer patients with hyponatremia have higher odds of Sepsis (Odd ratio = 1.72), Acute kidney injury (Odd ratio = 2.37), and Acute liver failure (Odd ratio = 1.59). Hyponatremia also resulted in higher resource utilization marked by the length of stay, and hospital charges.

Conclusion: Our research suggests that having hyponatremia with hepatocellular carcinoma increases the risk of morality, lengthens hospital stays, and raises healthcare costs.

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4154-A | VALIDATION OF A MACHINE LEARNING ALGORITHM, EVENDO, FOR PREDICTING HIGH-RISK ESOPHAGEAL VARICES IN HEPATOCELLULAR CARCINOMA

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Background: For advanced unresectable hepatocellular carcinoma (HCC), treatment with atezolizumab and bevacizumab has become the standard of care since the IMBrave 150 trial in 2020. However, treatment with antiangiogenic agents carries increased gastrointestinal bleeding risk. Therefore, patients are often required to undergo esophagogastroduodenoscopy (EGD) prior to initiating therapy, which can delay care. In 2019, the EVendo score was developed and validated as a non-invasive model to predict presence of esophageal varices (EV) in non-HCC cirrhotic patients. We sought to validate whether the EVendo score could be used to accurately predict the presence of EV and varices needing treatment (VNT) in patients with HCC. **Methods:** From 9/2004 to 12/2021, within two hospital systems, we identified 263 patients with HCC. We excluded 168 patients who did not receive an EGD after HCC diagnosis or did not lab information available. Of the remaining 95 patients, we collected clinical variables for 100 total EGDs. We included demographic data, prognostic scores (CTP, MELD-Na), and clinical parameters needed to calculate an EVendo score at the time of EGD (INR, AST, BUN, hemoglobin, platelet count, and presence of ascites). We compared the EVendo model prediction to the gold standard endoscopic report in predicting presence of EV. VNT was defined as medium or large varices, or small varices with high risk stigmata. Varices not needing treatment (VNNT) were defined as small varices without high risk stigmata or no EV. **Results:** Of the 95 patients analyzed, 50.5% were non-white, 83.15% were male, and the average age was 66.9 years. 64.2% of patients had CTP A, and 18.9% had CTP B. The average MELD-Na score was 12.35 (range 6-36). Of the 100 EGDs performed the EVEndo score had a sensitivity of 100%, specificity of 42.8% for VNT, positive predictive value of 34.9%, and a negative predictive value of 100%. A total of thirty six EGDs in this cohort could have been deferred if the EVendo score was applied **Conclusion:** The EVendo score was 100% sensitive and had a 100% negative predictive value in predicting VNT in a cohort of patients with HCC. These results are comparable to the Baveno VII criteria that have previously only been validated in non-HCC cirrhotic patients. Although additional validation cohorts are needed, this suggests that EVendo could potentially be applied in patients with HCC to avoid unnecessary EGDs, healthcare costs, and delays in initiating HCC treatment.

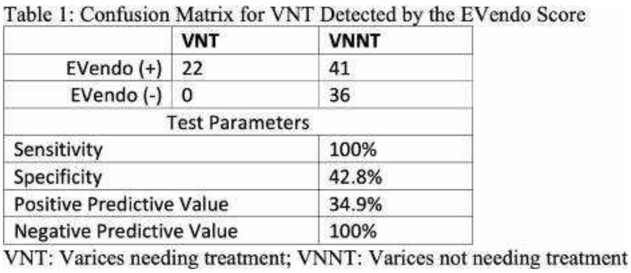

Table 1: Confusion Matrix for VNT Detected by the EVendo Score

	VNT	VNNT
EVendo (+)	22	41
EVendo (-)	0	36
Test Parameters		
Sensitivity		100%
Specificity		42.8%
Positive Predictive Value		34.9%
Negative Predictive Value		100%

VNT: Varices needing treatment; VNNT: Varices not needing treatment

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Disclosure information not available at the time of publication: Punya Chittajallu

4155-A | VALIDATION OF THE "AMAP" SCORE FOR PREDICTING HEPATOCELLULAR CARCINOMA DEVELOPMENT IN CHRONIC HEPATITIS B PATIENTS IN THAILAND

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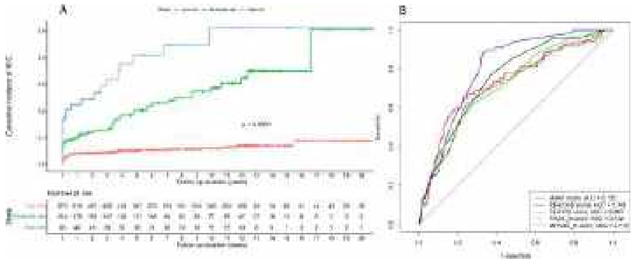
Background: Hepatocellular carcinoma (HCC) is a prevalent cancer worldwide, including in Thailand. Identifying high-risk patients for HCC surveillance is crucial. The aMAP score, introduced in 2020, has demonstrated accurate HCC risk prediction across various etiologies and populations. However, its external validation in Thai chronic hepatitis B patients has not been assessed. This study aimed to evaluate the aMAP score's efficacy and compare it with other risk scores for predicting HCC development in Thai chronic hepatitis B (CHB) patients. **Methods:** We retrospectively analyzed CHB patients from January 1, 2011, to December 31, 2019. Data on demographics, clinical parameters, cirrhotic status, HCC imaging, and AFP were collected to calculate the aMAP score (0-100) based on age, gender, albumin-bilirubin, and platelets. The aMAP score's predictive accuracy was assessed using time-dependent area under the receiver operating characteristic (AUROC) curve. **Results:** The study included 1060 eligible CHB patients with a mean follow-up time of 8.6 years, and 124 patients (11.7%) developed HCC. The cumulative HCC incidences in the aMAP low-, moderate-, and high-risk groups at 1, 3, 5, and 10 years were significantly different (log-rank P < 0.0001) (Figure 1A). The aMAP score's AUROCs for HCC prediction at 1, 3, 5, and 10 years were 0.696, 0.714, 0.732, and 0.740, respectively. Among the risk scores, CU-HCC had the highest AUROCs (0.800), followed by REACH-B (0.748), aMAP (0.732), PAGE-B (0.722), and mPAGE-B (0.719) (Figure 1B). **Conclusion:** The aMAP score is a valuable tool for predicting HCC risk in Thai CHB patients and can enhance surveillance strategies. Nonetheless, its performance was inferior to CU-HCC, suggesting the need for new predictive tools for HCC surveillance.



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4156-A | Y-90 MICROSPHERE TREATMENT OF HEPATOCELLULAR CARCINOMA (HCC) PATIENT-DERIVED TUMOROIDS AND CELL LINES REVEALS HETEROGENEITY OF RESPONSE

Christopher Malone[1], Alexander Zheleznyak[2], Naomi Sonnek[2], Robert Sullentrup[2], Valerie Blanc[2], Benjamin S Strnad[2], Darren Nix[2], Xiuli Liu[2], Paul Cliften[2], Jason Weber[2], Ryan Fields[2], Matthew Ciorba[2] and Nicholas Davidson[3], (1)Washington University in St. Louis, St. Louis, MO, (2)Washington University in St. Louis, (3) Washington University Medical School, Departments of Medicine and Molecular Biology and Pharmacology, Saint Louis, MO

Background: Despite the reported positive relationship between tumor absorbed dose and response in patients with hepatocellular carcinoma (HCC) undergoing Y-90 radioembolization (Y-90-RE), significant heterogeneity in outcomes remain. This supports the role underlying HCC biological heterogeneity plays in treatment response. Here, we assess the response of human HCC cell lines spanning the transcriptomic spectrum and patient-derived tumoroids to glass Y-90 microspheres *in vitro*. **Methods**: A panel of Human HCC cell lines (HepG2 and PLC/PRF/5 characterized by high expression of hepatocyte and liver progenitor genes, and SNU-449 and SNU-423, characterized by high expression of stem cell and epithelial-mesenchymal transition genes) and a selected tumoroid were treated at escalating activities (0-20 MBq/ml) of glass Y-90 microspheres (Therasphere, Boston Scientific) for 10 days *in vitro*. Cell viability was determined with MTT assay to generate area-under-curve (AUC) values. Patient-derived HCC tumoroids were generated from extra tumor tissue obtained from eligible patients presenting for standard of care biopsy or ablation of suspected HCC through an ongoing adaptive approach. **Results**: The tumoroid derived of a patient with Hepatitis C liver disease with a solitary 7 cm, moderately differentiated HCC who underwent Y-90-RE with local recurrence 7 months after treatment was selected for *in vitro* Y-90 microsphere treatment given its potential for clinical and *in vitro* correlation. Tumoroid whole exome sequencing demonstrated mutations in known HCC driver genes *AXIN1*, *TERT*, and *KEAP1* and histological cellular morphology representative of the original tumor. This tumoroid demonstrated relative resistance to Y-90 microsphere treatment *in vitro*, with an AUC similar to the SNU-423 cells (Fig 1A). In contrast, PLC/PRF/5 cells demonstrated greater sensitivity to Y-90 treatment (Fig 1A). Similarly, SNU-449 cells demonstrated resistance to *in vitro* treatment compared to HepG2 cells that was most pronounced when utilizing Y-90 microspheres of low specific activity (51 Bq/sphere) (Fig 1B). **Conclusion**: HCC cell lines and tumoroids demonstrate heterogenous sensitivity to Y-90 microsphere treatment *in vitro*, potentially reflected by underlying transcriptomic profiles. Establishing patient derived HCC tumoroids for *in vitro* Y-90 microsphere treatment screens is feasible and serves as a powerful platform to assess biological underpinnings of Y-90-RE response with the advantage of being linked to clinical metadata.

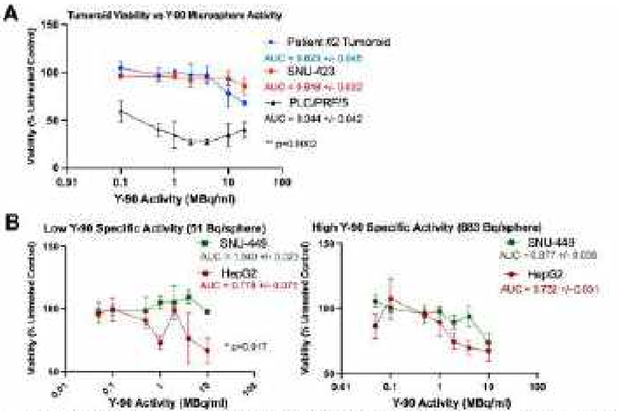

Fig 1. Data represented as mean +/- standard dev from triplicate conditions. Differences assessed by 2-tailed unpaired t-test

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4157-A | A cfDNA SEQUENCING-BASED ASSAY EXHIBITED HIGH PERFORMANCE IN HCC SCREENING

Bo Li[1], Binbin Chen[1], Xinyan Li[2], Wenyu Wang[1], Yan Zhou[2], Xiaoping Chen[3], Zhiwei Xie[1], Ying Tan[1], *Chunlan Zhang[1], Luping Lin[1], Huimin Fan[1], Aiqi Lu[1], Zhuxiang Zhao[2], Yujuan Guan[1] and Jianping Li[1], (1) Guangzhou Eighth People's Hospital, Guangzhou Medical University, (2)Guangzhou First People's Hospital, (3)Guangdong Provincial People's Hospital*

Background: Hepatocellular carcinoma (HCC) is one malignancy with the fourth highest morbidity and the second highest mortality among all cancers in China. Most patients were found at middle- or late-stage with poor therapeutic response and high recurrence rate. It is of great significance to apply a highly sensitive and specific assay to HCC screening to reduce the HCC incidence and increase the early detection rate. In this study, a liquid biopsy-based circulating cell-free DNA (cfDNA) sequencing assay was used for HCC screening in HCC high-risk population. We hope that the present study may provide a new strategy for HCC prevention in the population. **Methods:** Patients were recruited based on the definition of HCC high-risk and very high-risk population in the Chinese guideline for liver cancer screening (2022, Beijing). Ten milliliters of peripheral blood were collected and the plasma was isolated for cfDNA detection. The assay detects a panel of methylation, mutation and protein markers developed for HCC screening, and a diagnostic model was established by combining the assay results with family history and demographic information. The interpretation of the assay was dichotomized into positive and negative groups. The dynamic changes of conventional serological markers and ultrasound/CT/MRI/pathological examinations were followed up. Statistics were performed to calculate the positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity. **Results:** A total of 95 HCC high-risk and very high-risk patients were recruited from 3 medical centers, with an average age of 50. 63 ± 11.49 years (mean ± SD), in which 72. 6% (69/95) of patients were male. The assay was positive in 26 cases and negative in 69 cases. Mutations of one or more related genes (TP53, CTNNB1, TERT) were found in 13.7% (13/95) of patients, with a mutation abundance between 0.5 0 and 3%. Among them, 5 patients with confirmed HCC exhibited a mutation abundance between 0.90 and 3%, while 8 patients without HCC exhibited a mutation abundance between 0.50 and 20 . A total of 92 patients were followed up for 6-12 months, and eight of them were diagnosed HCC by dynamic contrast-enhanced CT/MRI or pathology. The PPV was 29.2% (7/24), and the NPV was 98.5% (67/68), and the sensitivity was 87.5% (7/8) at a specificity of 79.8% (67/84). In contrast, the sensitivity was only 50.0% (4/8) for AFP. The assay detected HCC 1-6 months prior to the diagnosis by CT/MRI in 4 of 7 patients with confirmed HCC diagnosis, and detected the rest 3 HCC patients in parallel with CT/MRI. **Conclusion:** The performance of the HCC screening assay was superior to the existing serological markers in the high-risk and very high-risk population of HCC. It detected HCC earlier than imaging examinations and may help clinicians diagnose and treat early-stage HCC.

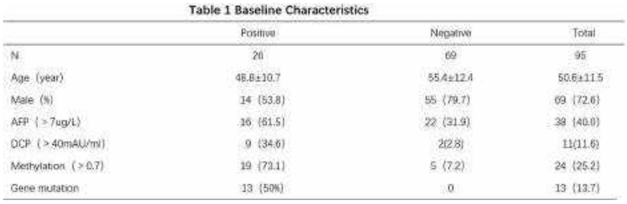

Table 1 Baseline Characteristics

	Positive	Negative	Total
N	26	69	95
Age (year)	48.8±10.7	55.4±12.4	50.6±11.5
Male (%)	14 (53.8)	55 (79.7)	69 (72.6)
AFP (＞7ug/L)	16 (61.5)	22 (31.9)	38 (40.0)
DCP (＞40mAU/ml)	9 (34.6)	2(2.8)	11(11.6)
Methylation (＞0.7)	19 (73.1)	5 (7.2)	24 (25.2)
Gene mutation	13 (50%)	0	13 (13.7)

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f 4158-A | A DEDICATED AUTOMATIC RECALL HEPATOCELLULAR CANCER SURVEILLANCE PROGRAM IMPROVES RETENTION RATES: A POPULATION BASED COHORT STUDY

Mayur Brahmania[1], Stephen E. Congly[1], Kelly Warren Burak[1], Yashasavi Sachar[2], Brendan Cord Lethebe[1], Jessie Hart Szostakiwskyj[1], David Lautner[1], Alexandra Medellin[1], Deepak Bhayana[1], Jason Wong[1], Matthew Sadler[3], Meredith A. Borman[1], Alexander Aspinall[1], Carla S. Coffin[1], Mark Gordon Swain[1] and Abdel Aziz Shaheen[1], (1)University of Calgary, (2)Western University, (3)Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

Background: Hepatocellular carcinoma (HCC) surveillance programs are affected by adherence, which may be due to patient, clinician and system barriers. The impact of a dedicated automatic recall HCC surveillance program on retention rates in patients eligible for screening is unknown. We aimed to describe and evaluate the largest HCC surveillance program in the Canadian public health care system. **Methods:** Data was collected from January 1, 2013 to December 31, 2022 from a retrospective cohort of subjects enrolled in a semi-annually surveillance program as per AASLD HCC guidance. The program is a publicly funded automated recall system servicing eligible patients in the Calgary Health Zone (~1.6 million), Canada. Patients were excluded if there was incomplete data or did not meet indications for screening. Multivariable logistic regression was used to identify predictors of non-retention to surveillance. All statistical analyses were done in R (version 4.1.1). **Results:** A total of 7,432 patients were included in the

study. The median was age 55.5 years (IQR: 45.5-63.8), 60% were male, 46% of Asian descent, and 53% with HBV infection as the reason for HCC surveillance, while 46% had cirrhosis (36% alcohol). Median follow-up was 4.9 years (IQR: 1.5-7.2). Overall, 54% of patients were retained in the surveillance program, while 21% left for potential medical reasons at some point of time in the study (7% death; 62.3% with a high risk ($>$1cm) or an inconclusive lesion identified or did not scan well), and 25% were not retained. Median time in the program for those not retained was 0.78 (IQR: 0.0-2.0) years (vs 6.4 years retained; IQR: 5.0-8.3; $p = < 0.001$). Subjects not retained (vs retained) were more commonly male (61% vs 58%; $p = < 0.001$), Caucasian (42% Caucasian vs 38% Asian vs 12% African; $p = 0.001$), and had either HBV (46%) or HCV (22%) as their primary diagnosis for screening (vs 17% alcohol; 5% autoimmune; 7% NASH; $p = 0.001$). In multivariable logistic regression analysis, older age at enrollment (OR = 0.99; CI = 0.98-0.99), Asian descent (OR = 0.64; CI = 0.54-0.76) and having a non-HCV etiology (Alcohol OR = 0.75; CI: 0.58-0.98; HBV: OR = 0.54; CI = 0.38-0.69; NASH: OR = 0.55, CI = 0.42-0.74) were factors associated with enhanced retention in the screening program. **Conclusion:** A dedicated automated recall HCC surveillance program has a high retention rate in a large multi-ethnic cohort of patients. Significant factors associated with with non-retention included a diagnosis of HCV and younger age, highlighting potential populations to target for intervention.

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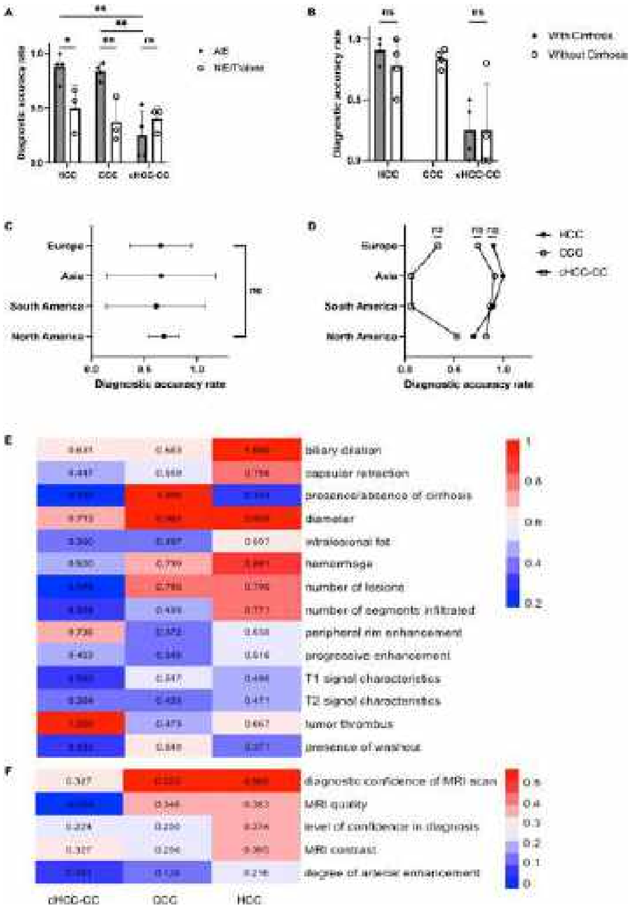
4159-A | A REASSESSMENT OF NON-INVASIVE APPROACH FOR THE DIAGNOSIS OF HEPATOCELLULAR CARCINOMA

Yuquan Qian[1], Qiaoyuan Lu[2], Isaac Rodriguez[1], Xiangde Min[3], Matthias Froelich[1], Muzaffer Reha Ümütlü[4], German A. Castrillon[5], Carlos Romero Alaffita[6], Juan Alberto Garay Mora[7], Zhiqiang Guo[8], Christel Weiss[1], Stefan Schönberg[1], Matthias Ebert[1], Yingshi Sun[2] and Andreas Teufel[1], (1)Medical Faculty Mannheim, Heidelberg University, (2)Peking University Cancer Hospital and Institute, (3)Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, (4)University Hospital, Lmu Munich, (5) University of Antioquia, (6)Universidad Autónoma De San Luis Potosí, (7)Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán, (8)Shanxi Province Fenyang Hospital

Background: Under current guidelines, hepatocellular carcinoma (HCC) diagnosis primarily relies on CT or MRI, with biopsy strictly regulated. However, combined hepatocellular-cholangiocarcinoma (cHCC-CC), a type of liver cancer exhibiting histological elements of both HCC and cholangiocellular carcinoma (CCC), typically presents a combination of HCC and CCC radiological features on imaging. Moreover, platinum drugs offer the most promising initial treatment for patients with unresectable or advanced cHCC-CC, deviating significantly from the approach for HCC. Therefore, our study aims to investigate the ability of imaging techniques to differentiate between HCC, CCC, and cHCC-CC, thereby emphasizing its clinical significance. **Methods:** A database search was conducted to identify patients diagnosed with HCC, CCC, and cHCC-CC between June 2010 to September 2020. Following quality control measures, the study included 68 MRI scans from patients, comprising 30 with HCC, 23 with CCC, and 15 with cHCC-CC. The diagnoses of all patients were confirmed through histological evidence obtained within a maximum of four weeks prior to or following the MRI scans. Subsequently, seven radiologists from Asia, Europe, North America, and South America, including abdominal imaging experts (AIEs) and non-abdominal imaging experts (NIEs) or trainees, independently and blindly assessed the MRI scans. They evaluated various MRI features and established a differential diagnosis encompassing HCC, CCC, and cHCC-CC.

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



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4160-A | CLINICAL PHENOTYPES OF BENIGN HEPATIC LESIONS

Michael Bradley Andrews[1]*, Manaswitha Thota*[1]*, Jonathan Paul Van Name*[1]*, Tamas Gal*[1] *and Richard K. Sterling*[2]*, (1)Virginia Commonwealth University, (2) Virginia Commonwealth University Health System*

Background: Most benign hepatic lesions occur in isolation. The clinical and demographic phenotype in patients (pts) with more than one lesion can overlap making treatment decisions challenging. To address this gap in knowledge, our aim was to describe the clinical and demographic characteristics in a cohort of pts with benign hepatic lesions to predict the lesion based on clinical data and oral contraceptive (OCP) use. We particularly wanted to know how common the two more clinically relevant lesions, hepatic adenoma (HA) and focal nodular hyperplasia (FNH) occurred and could a "clinical phenotype" identify these patients. **Methods:** This was a single institution retrospective case series using bioinformatics and natural language processing to identify eligible pts with HA, FNH, hemangioma (HM), and cysts (C) undergoing imaging (MRI, CT, or US). Demographics and laboratory values such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, hemoglobin (Hgb), platelets, prothrombin time (PT), and OCP use were collected. Descriptive analysis was performed. Differences between groups were assessed by ANOVA or Wilcoxon tests for continuous variables and chi-square for categorical variables with alpha 0.05. Variables identified on univariate analysis with $p < 0.2$ were included in multivariate analysis to identify independent factors associated with the different lesion groups. **Results:** The statistically significant differences across all groups (n = 216) on univariate ANOVA were age, sex, AST, ALP, albumin, Hgb, platelets, PT, and OCP use (Table). After adjusting for ALT in the multivariate model, statistically significant differences across all groups were age, sex, ALP, and Hgb. The statistically significant differences between HA and FNH on univariate ANOVA were sex, AST, ALT, ALP, albumin, and Hgb. After adjusting for platelets, PT and OCP use, there remained significant differences in ALP and Hgb between those with HA and those with FNH. Combination lesions were observed in 28 (12%): C + HM (2), C + FNH (8), C + HA (4), HM + FNH (7), HA + HM (2), FHN + HM (1), and HA + FNH (4). **Conclusion:** Predicting the etiology of benign hepatic lesions based on patient demographics, common laboratory values, and a brief history including OCP use alone is difficult. However, we identified the most important demographic (age, sex) and laboratory values (ALP, Hgb) to assist in building a differential.

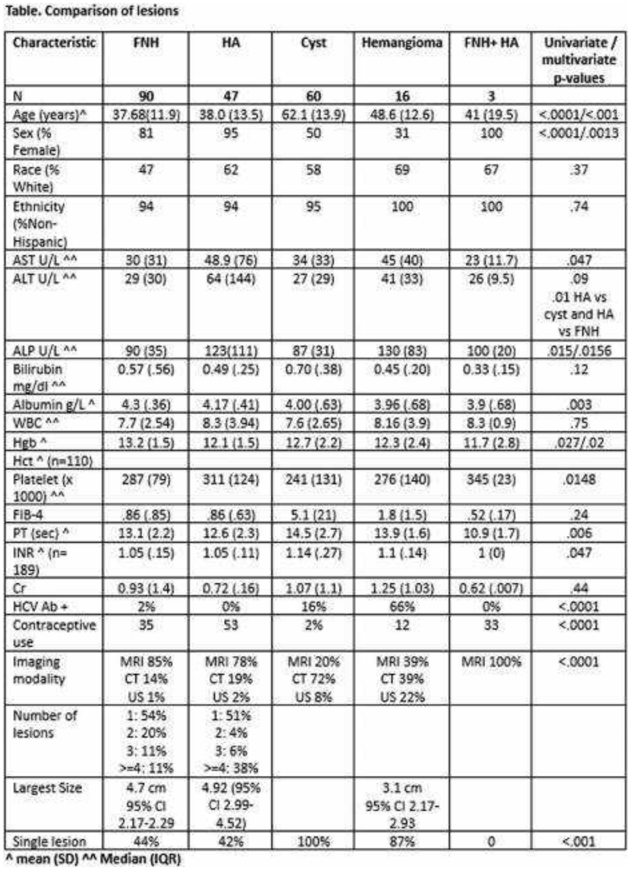

Table. Comparison of lesions

Characteristic	FNH	HA	Cyst	Hemangioma	FNH+ HA	Univariate / multivariate p-values
N	90	47	60	16	3	
Age (years)^	37.68(11.9)	38.0 (13.5)	62.1 (13.9)	48.6 (12.6)	41 (19.5)	<.0001/<.001
Sex (% Female)	81	95	50	31	100	<.0001/.0013
Race (% White)	47	62	58	69	67	.37
Ethnicity (%Non-Hispanic)	94	94	95	100	100	.74
AST U/L ^^	30 (31)	48.9 (76)	34 (33)	45 (40)	23 (11.7)	.047
ALT U/L ^^	29 (30)	64 (144)	27 (29)	41 (33)	26 (9.5)	.09 .01 HA vs cyst and HA vs FNH
ALP U/L ^^	90 (35)	123(111)	87 (31)	130 (83)	100 (20)	.015/.0156
Bilirubin mg/dl ^^	0.57 (.56)	0.49 (.25)	0.70 (.38)	0.45 (.20)	0.33 (.15)	.12
Albumin g/L ^	4.3 (.36)	4.17 (.41)	4.00 (.63)	3.96 (.68)	3.9 (.68)	.003
WBC ^^	7.7 (2.54)	8.3 (3.94)	7.6 (2.65)	8.16 (3.9)	8.3 (0.9)	.75
Hgb ^	13.2 (1.5)	12.1 (1.5)	12.7 (2.2)	12.3 (2.4)	11.7 (2.8)	.027/.02
Hct ^ (n=110)						
Platelet (x 1000) ^^	287 (79)	311 (124)	241 (131)	276 (140)	345 (23)	.0148
FIB-4	.86 (.85)	.86 (.63)	5.1 (21)	1.8 (1.5)	.52 (.17)	.24
PT (sec) ^	13.1 (2.2)	12.6 (2.3)	14.5 (2.7)	13.9 (1.6)	10.9 (1.7)	.006
INR ^ (n= 189)	1.05 (.15)	1.05 (.11)	1.14 (.27)	1.1 (.14)	1 (0)	.047
Cr	0.93 (1.4)	0.72 (.16)	1.07 (1.1)	1.25 (1.03)	0.62 (.007)	.44
HCV Ab +	2%	0%	16%	66%	0%	<.0001
Contraceptive use	35	53	2%	12	33	<.0001
Imaging modality	MRI 85% CT 14% US 1%	MRI 78% CT 19% US 2%	MRI 20% CT 72% US 8%	MRI 39% CT 39% US 22%	MRI 100%	<.0001
Number of lesions	1: 54% 2: 20% 3: 11% >=4: 11%	1: 51% 2: 4% 3: 6% >=4: 38%				
Largest Size	4.7 cm 95% CI 2.17-2.29	4.92 (95% CI 2.99-4.52)		3.1 cm 95% CI 2.17-2.93		
Single lesion	44%	42%	100%	87%	0	<.001

^ mean (SD) ^^ Median (IQR)

Disclosures: The following people have nothing to disclose: Michael Bradley Andrews, Manaswitha Thota, Jonathan Paul Van Name, Tamas Gal, Richard K. Sterling

4161-A | CLINICOPATHOLOGICAL CHARACTERISTICS AND MOLECULAR ANALYSIS OF LYMPHOCYTE-RICH HCC

Kana Tsutsui[1], Masamichi Nakayama[1], Sachiko Ogasawara[1], Jun Akiba[2] and Hirohisa Yano[1], (1) Kurume University School of Medicine, (2)Kurume University Hospital

Background: In the WHO Classification of Digestive System Tumours, 5th Edition (2019), a new subtype of hepatocellular carcinoma (HCC), designated lymphocyte-rich HCC (LR-HCC), has been proposed. In LR-HCC, lymphocytes outnumber tumor cells in most fields on H&E staining. HCC is one of the malignant tumors with poor prognosis, whereas this new subtype is considered to have a relatively good prognosis. As it is a newly proposed subtype with rare frequency (< 1% of all HCCs), there have been few coherent reports on its clinical and pathological features. In this study, we examined the clinicopathological and molecular features of LR-HCC. **Methods:** 1) In the present study, 451 surgically-resected HCC cases without previous treatment history from 2012 to 2021 at our hospital were analyzed. Clinicopathological characteristics of LR-HCC and the other HCC (non-LR-HCC) subtypes were compared. To evaluate intratumoral infiltrating lymphocytes, immunostaining for CD3, CD20, and CD8 was performed in LR-HCC. 2) Neoplastic and nonneoplastic hepatocytes from LR-HCC (n = 4) were collected with a laser microdissection system, and RNA was extracted, followed by microarray analysis to examine molecules involved in lymphocytic infiltration. 3) The immunohistochemical expression of identified molecules was examined in LR-HCC (28 cases) and non-LR-HCC (30 cases). **Results:** 1) There were 28 cases (6%) of LR-HCC. No statistically significant differences were found in the clinicopathological features, including prognosis, between LR-HCC and non-LR-HCC cases. The 5-year survival rate for LR-HCC was over 90%. There were significantly more CD3+ cells than CD20+ cells ($p < 0.0001$) in tumor infiltrating lymphocytes, and most of them were CD8+ T cells. 2) Microarray analysis revealed that CCL20 which induces lymphocyte migration, was highly expressed in LR-HCC cases. 3) Immunohistochemical study revealed that CCL20 expression was significantly higher in LR-HCC ($p < 0.01$) tumor cells compared with non-LR-HCC. Expression of CCR6, the only known receptor for CCL20, was confirmed in infiltrating lymphocytes in LR-HCC. **Conclusion:** This study suggests that LR-HCC is not a very rare subtype with no significant differences in clinicopathological features compared with non-LR-HCC subtypes although the 5-year survival rate was favorable and over 90%. CCL20 expression appears to contribute to rich CD8+ lymphocyte infiltration in LR-HCC.

Disclosures: The following people have nothing to disclose: Kana Tsutsui, Masamichi Nakayama, Sachiko Ogasawara, Jun Akiba, Hirohisa Yano

4162-A | CONTRAST-ENHANCED ULTRASOUND (CEUS) FOR THE DIAGNOSIS OF HEPATOCELLULAR CARCINOMA (HCC) IN ADULTS WITH CHRONIC LIVER DISEASE. A COCHRANE SYSTEMATIC REVIEW AND METANALYSIS

Mirella Fraquelli[1], Tin Nadarevic[2], Agostino Colli[1], Cristina Manzotti[3], Vanja Giljaca[4], Damir Miletic[5], Davor Stimac[5] and Giovanni Casazza[3], (1)Fondazione Irccs Ospedale Maggiore, Policlinico Milano, (2)University of Rijeka, (3)University of Milan, (4)Heart of England NHS Foundation Trust, Birmingham, UK, (5)Clinical Hospital Centre Rijeka

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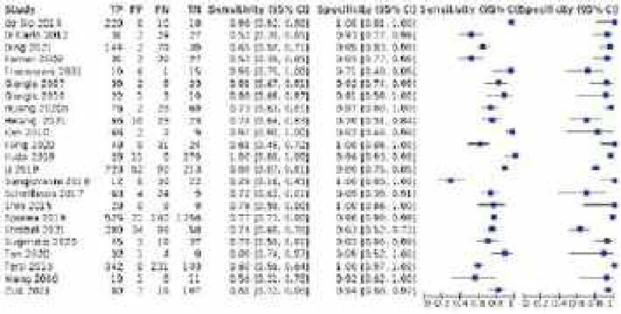
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Background: HCC mostly occurs in people with chronic liver disease (CLD) and ranks fourth in terms of cancer-related deaths. CEUS is used as an add-on test to confirm focal liver lesions suspected as HCC after prior diagnostic tests (abdominal ultrasound and/or alpha-foetoprotein measurement). According to guidelines either computed tomography (CT) or magnetic resonance imaging (MRI), showing typical hallmarks are sufficient to diagnose HCC in cirrhotics. However, a significant number of tumors showing atypical imaging features are missed. The use of CEUS in the diagnostic HCC algorithm remains controversial, with relevant guidelines disagreement. This systematic review assesses CEUS the diagnostic accuracy of CEUS for the diagnosis of HCC of any size and at any stage and of resectable HCC in adults with CLD, in a surveillance program or in a clinical setting. **Methods:** Cross-sectional designs, using one of the acceptable reference standards (pathology of the explanted liver and histology of resected or biopsied focal liver lesion with at least a six-month follow-up) were included. Standard Cochrane methods were used to screen studies, extract data, and assess the risk of bias and applicability concerns, using the QUADAS-2 checklist. The bivariate model was used for the estimation of summary sensitivity and specificity. Certainty of the evidence was graded using GRADE. **Results:** We included 23 studies (6546 participants), all judged at high-risk of bias in at least one domain; 13/23 studies were at high concern for applicability. For HCC of any size and any stage: sensitivity was 77.8% (95%CI 69.4% to 84.4%) and specificity 93.8% (95%CI 89.1% to 96.6%); for resectable HCC: sensitivity 77.5% (95%CI 62.9% to 87.6%) and specificity 92.7% (95%CI 86.8% to 96.1%). The observed heterogeneity in the results remains unexplained. **Conclusion:** Using CEUS, as an add-on test following abdominal ultrasound, to diagnose HCC of any size and stage, 22% of people with the tumor would be missed, and 6% of people without it would unnecessarily undergo further testing or inappropriate treatment. As to resectable HCC we found that 23% of people with resectable tumor would incorrectly be unresected, while 8% of people without it would undergo further inappropriate testing or treatment. Our ability to draw confident conclusions is limited by the high risk of bias of included studies, heterogeneity, imprecision of the results and concerns on their applicability.

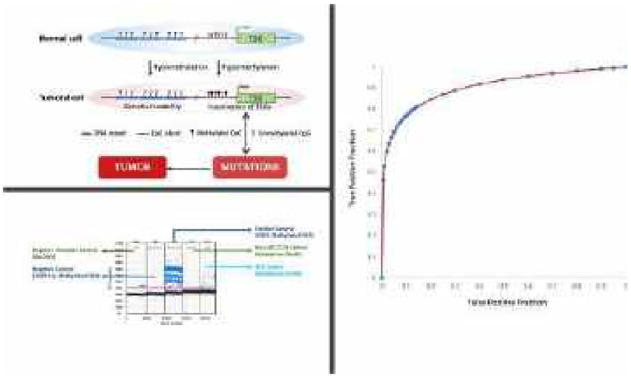


Disclosures: The following people have nothing to disclose: Mirella Fraquelli, Tin Nadarevic, Agostino Colli, Cristina Manzotti, Vanja Giljaca, Damir Miletic, Davor Stimac, Giovanni Casazza

4163-A | DETECTION OF HYPERMETHYLATED CpG ISLANDS IN CELL-FREE DNA: A BETTER CLINICAL TOOL IN THE DIAGNOSIS AND MANAGEMENT OF HEPATOCELLULAR CARCINOMA.

Dinesh Jothimani[1], Srikar Raman[2], Mullaiezhili Manoharan[3], Evangeline Simon[3], K Sree Durgalakshmi[4], Hemalatha Ramachandran[3], Ashwin Rammohan[3], Mukul Vij[3], Vasanthakumar Gunasekaran[3], Mohamed Rela[3] and Mohammed Farouk[3], (1)Rela Institute and Medical Centre, (2) Tvaster, (3)Dr Rela Institute and Medical Centre, (4) Tvaster Genkalp, Chennai

Background: Advances in the field of genetics has enabled novel modalities to diagnose hepatocellular carcinoma (HCC) since it is well known that the current diagnosis through biomarkers such as alpha fetoprotein has low sensitivity and specificity. Genetic-based diagnosis is challenging since HCC occurs through extremely complex genetic alteration process, and occurs from multiple genetic aberrations. To use mutational markers for detecting HCC can be achieved only by using expensive and time-consuming modalities such as Next Generation Sequencing (NGS). Alternatively, developments in the field of epigenetics is aiding in exploration of epigenetics for diagnostic applications for various cancers. Epigenetic modifications usually occur through DNA methylation regulating tumorigenesis and cancer progression. Herein, we report affordable and accessible methylation profiling using droplet digital PCR (ddPCR) in combination with Sequencing Independent Quantitative Methylation Profiling (qSIMP) platform based screening tool (qSIMP-HCC) for detection, recurrence monitoring and surveillance of HCC. **Methods:** Using a novel multiplex panel of 4 genes, we determined hypermethylation levels in CpG islands of multiple genes namely Vimentin, RGS10, RUNX2 and ST8SIA6. Methylation levels of cfDNA extracted from blood was analyzed using ddPCR and multiparameter approach was deployed to assess the risk status of patients based on methylation levels. We analyzed a cohort of plasma samples from HCC patients (n = 39) and control individual's including cirrhotic patients not diagnosed with HCC (n = 89). The results for combined sample set ($n_{total} = 128$) was determined and qSIMP-HCC results was compared with AFP. **Results:** The training set results indicated a marked difference in methylation levels between the control and HCC subjects wherein a two tailed p value of 0.0022 ($p < 0.01$) at 95% confidence interval suggests the difference between the groups is very statistically significant. A receiver operating characteristic curve (ROC) of our model to detect HCC patients revealed AUC of 0.91 (95% CI = 0.88–0.94) with sensitivity, specificity and accuracy of 82.05%, 83.15% and 82.81% respectively. The data was significantly better than AFP marker (n = 122) that showed a sensitivity of 40% at cut off value at 10ng/ml. **Conclusion:** Based on the data, the epigenetic qSIMP-HCC tool has a great potential to serve as a robust platform for surveillance, detection and management of HCC.



Disclosures: The following people have nothing to disclose: Dinesh Jothimani, Srikar Raman, Mohamed Rela

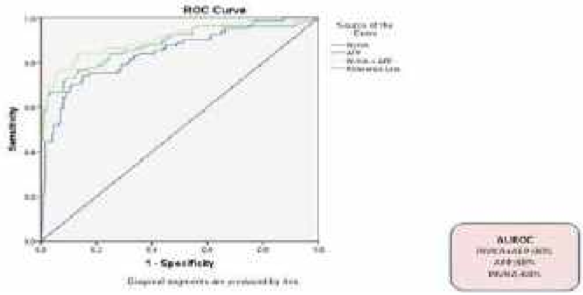
Disclosure information not available at the time of publication: Mullaiezhili Manoharan, Evangeline Simon, K Sree Durgalakshmi, Hemalatha Ramachandran, Ashwin Rammohan, Mukul Vij, Vasanthakumar Gunasekaran, Mohammed Farouk

4164-A | DIAGNOSTIC ACCURACY OF PROTEIN INDUCED BY VITAMIN K ABSENCE (PIVKA-II) FOR HEPATOCELLULAR CARCINOMA (HCC) AMONG CAUCASIAN CIRRHOTIC PATIENTS WITH DIAGNOSTIC OR NON-DIAGNOSTIC SERUM A-FETOPROTEIN (AFP) LEVELS

Antonia Syriha, Dionysia Mandilara, Spyridon Pantzios, Petros Galanis, Ioanna Stathopoulou, Georgia Barla and Ioannis S. Elefsiniotis, National and Kapodistrian University of Athens

Background: To evaluate the accuracy of serum biomarkers (AFP, PIVKA-II) for HCC diagnosis among patients with liver cirrhosis. **Methods:** 218 consecutive patients with liver cirrhosis with (n = 90, HCC group) or without (n = 128, control group) concomitant histologically confirmed HCC were evaluated for serum levels of the two biomarkers, during a programmed outpatient visit. Patients with HCC (n = 90) were categorized in stage 0/A (n = 12, 13.3%), stage B (n = 21, 23.3%), stage C (n = 48, 53.3%) and stage D (n = 9, 10%), according to BCLC staging system. **Results:** The two groups were comparable according to all baseline parameters evaluated (gender, CPT score, MELD score, ALBI grade, presence of varices, cirrhosis etiology), except for age, platelet count and presence of diabetes. Mean/median levels of AFP (14310/239.1 vs 11.3/4.0, $p < 0.001$) and PIVKA-II (11676/4082 vs 882/45.8, $p < 0.001$) were significantly higher in HCC group compared to control group. The AUROC curve and the best proposed cut-off value for HCC diagnosis were 88%/ 12.35 ng/ml and 84.4%/ 677.13 mAU/ml for AFP and PIVKA-II, respectively, whereas the diagnostic accuracy was slightly better (AUROC 90.2%) combining the two biomarkers. The diagnostic accuracy of each biomarker separately was low for BCLC 0/A (AUROC 65.8% for AFP and 65% for PIVKA-II) and BCLC B HCC patients (AUROC 86.4% for AFP and 79.5% for PIVKA-II) and was acceptable only among BCLC-C stage HCC patients (AFP: AUROC = 94.3%, best proposed cut-off value = 12.35 ng/ml and PIVKA-II: AUROC = 91.3%, best proposed cut-off value = 253.51 mAU/ml). The combination of the two biomarkers presented acceptable diagnostic curves in BCLC-B (AUROC = 92.4%) as well as BCLC-C (AUROC = 95.7%) stage HCC patients. Excluding HCC patients with AFP levels above 400 ng/ml, the diagnostic accuracy of each biomarker separately as well as the combination of them was low (less than 90%) in the whole group and in all BCLC groups, except for the combination of biomarkers in the BCLC-C group (AUROC = 90.5%). **Conclusion:** Each biomarker separately showed moderate accuracy in detecting HCC in patients with liver cirrhosis, except for those staged in BCLC-C stage. The combination of the two biomarkers presented acceptable results in the HCC diagnosis of BCLC-B as well as BCLC-C patients. The diagnostic accuracy of PIVKA-II in patients with relatively low AFP levels (<400 ng/ml) remained at low level except for those of BCLC-C stage.

Figure 1. ROC curves for AFP, PIVKA-II and their combination for the diagnosis of HCC in the whole study population.



Disclosures: The following people have nothing to disclose: Antonia Syriha, Dionysia Mandilara, Spyridon Pantzios, Petros Galanis, Ioanna Stathopoulou, Georgia Barla, Ioannis S. Elefsiniotis

4165-A | ELEVATIONS IN LIVER TESTS PREDICT THE PRESENCE OF LIVER METASTASES IN PATIENTS WITH COLORECTAL CANCER

Alexandra V. Kimchy[1], Harjit Singh[1], Esha Parikh[1], Jessica Rosenberg[1], Kavya Sanghavi[2] and James H. Lewis[1], (1)Georgetown University Hospital, (2)Medstar Research Institute

Background: The predictive value of biochemical liver tests in patients (pts) w/ liver metastases (mets) has not been fully characterized. We analyzed liver tests in pts w/ liver mets from primary colorectal cancer (CRC) at the time of diagnosis of mets. **Methods:** Inpatient encounters were retrospectively reviewed for pts w/ CRC from 2016-2020. ICD9/ICD10 was used to identify pts w/ CRC liver mets who were compared to age, gender matched controls who had CRC w/o liver mets. Pt characteristics, treatment and diagnostics were acquired from chart extraction. Liver test results were obtained from the time detection of liver mets w/ imaging. Pts w/ a history of liver disease or w/o imaging and/or biopsy confirming liver mets were excluded. Differences in medians were determined using Kruskal Wallis or Wilcoxon rank-sum tests and categorical variables using chi-square analyses. Sensitivity (SE) and specificity (SP) were calculated for abnormal values of liver tests in relation to liver mets using 2x2 contingency tables. **Results:** Of the 499 pts w/ CRC, 68 pts (14%) had a diagnosis of liver mets confirmed with imaging. Bone mets were present in few pts w/ CRC and rates did not significantly differ in those w/ and w/o liver mets. Median liver enzyme levels were significantly higher in pts w/ liver mets than w/o liver mets (AST 36 vs 21; $p < 0.001$) (ALT 26 vs 24; $p = 0.018$) (ALP 135 vs 94; $p < 0.001$) but not for total bilirubin (0.5 vs 0.4; $p > 0.05$). Most pts w/ liver mets presented w/ elevated AST (52%) or ALP (56%) while fewer pts had elevations in ALT (29%) or total bilirubin (15%). Pts w/ liver mets presented w/ AST, ALT, or ALP $\geq$3xULN in 37%, 25% and 29% of pts. None of the pts w/o liver mets had elevations to this degree (Table 1). SE and SP of elevated liver tests for the presence of liver mets were AST (51%, 78%), ALT (29%, 94%), and ALP (56%, 76%). The optimal cutoff for diagnosis of liver mets according to SE and SP was $\geq$2xULN for AST (60%, 90%), $\geq$1.25xULN ALT (85%, 33%), and $\geq$1.5xULN for ALP (79%, 85%). Elevations in AST and ALP, or AST and ALT increased the SP of the tests for liver mets to 93% and 94%. **Conclusion:** Liver enzymes were significantly higher in pts w/ liver mets than those w/o liver mets. AST, ALT or ALP $\geq$3xULN were indicative of the presence of liver mets as those w/o liver mets did not have elevations to these levels. Elevated AST and ALP or AST and ALT demonstrated high SP for the presence of liver mets. Our results suggest that using the thresholds of $\geq$2xULN for AST, $\geq$1.25xULN for ALT, and $\geq$1.5xULN for ALP may improve the diagnostic accuracy of these tests for liver mets and indicate which pts should undergo further evaluation with diagnostic imaging. Longitudinal studies of liver tests following the diagnosis of CRC are needed to confirm elevations are predictive of mets prior to detection w/ imaging.

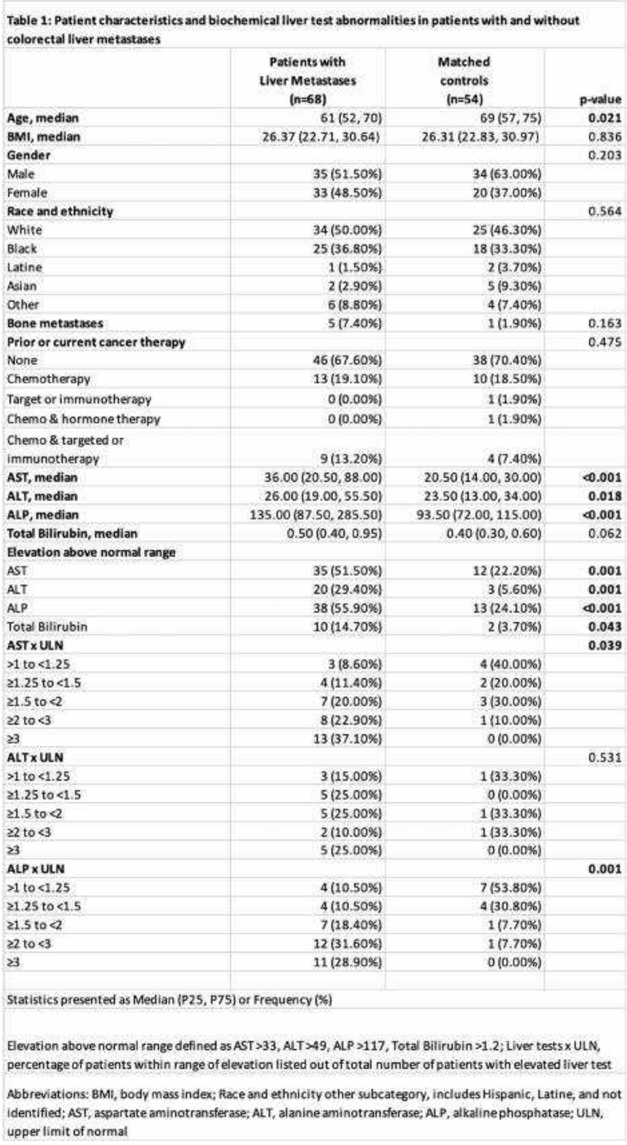


Table 1: Patient characteristics and biochemical liver test abnormalities in patients with and without colorectal liver metastases

	Patients with Liver Metastases (n=68)	Matched controls (n=54)	p-value
Age, median	61 (52, 70)	69 (57, 75)	**0.021**
BMI, median	26.37 (22.71, 30.64)	26.31 (22.83, 30.97)	0.836
Gender			0.203
Male	35 (51.50%)	34 (63.00%)	
Female	33 (48.50%)	20 (37.00%)	
Race and ethnicity			0.564
White	34 (50.00%)	25 (46.30%)	
Black	25 (36.80%)	18 (33.30%)	
Latine	1 (1.50%)	2 (3.70%)	
Asian	2 (2.90%)	5 (9.30%)	
Other	6 (8.80%)	4 (7.40%)	
Bone metastases	5 (7.40%)	1 (1.90%)	0.163
Prior or current cancer therapy			0.475
None	46 (67.60%)	38 (70.40%)	
Chemotherapy	13 (19.10%)	10 (18.50%)	
Target or immunotherapy	0 (0.00%)	1 (1.90%)	
Chemo & hormone therapy	0 (0.00%)	1 (1.90%)	
Chemo & targeted or immunotherapy	9 (13.20%)	4 (7.40%)	
AST, median	36.00 (20.50, 88.00)	20.50 (14.00, 30.00)	**<0.001**
ALT, median	26.00 (19.00, 55.50)	23.50 (13.00, 34.00)	**0.018**
ALP, median	135.00 (87.50, 285.50)	93.50 (72.00, 115.00)	**<0.001**
Total Bilirubin, median	0.50 (0.40, 0.95)	0.40 (0.30, 0.60)	0.062
Elevation above normal range			
AST	35 (51.50%)	12 (22.20%)	**0.001**
ALT	20 (29.40%)	3 (5.60%)	**0.001**
ALP	38 (55.90%)	13 (24.10%)	**<0.001**
Total Bilirubin	10 (14.70%)	2 (3.70%)	**0.043**
AST x ULN			**0.039**
>1 to <1.25	3 (8.60%)	4 (40.00%)	
≥1.25 to <1.5	4 (11.40%)	2 (20.00%)	
≥1.5 to <2	7 (20.00%)	3 (30.00%)	
≥2 to <3	8 (22.90%)	1 (10.00%)	
≥3	13 (37.10%)	0 (0.00%)	
ALT x ULN			0.531
>1 to <1.25	3 (15.00%)	1 (33.30%)	
≥1.25 to <1.5	5 (25.00%)	0 (0.00%)	
≥1.5 to <2	5 (25.00%)	1 (33.30%)	
≥2 to <3	2 (10.00%)	1 (33.30%)	
≥3	5 (25.00%)	0 (0.00%)	
ALP x ULN			**0.001**
>1 to <1.25	4 (10.50%)	7 (53.80%)	
≥1.25 to <1.5	4 (10.50%)	4 (30.80%)	
≥1.5 to <2	7 (18.40%)	1 (7.70%)	
≥2 to <3	12 (31.60%)	1 (7.70%)	
≥3	11 (28.90%)	0 (0.00%)	

Statistics presented as Median (P25, P75) or Frequency (%)

Elevation above normal range defined as AST >33, ALT >49, ALP >117, Total Bilirubin >1.2; Liver tests x ULN, percentage of patients within range of elevation listed out of total number of patients with elevated liver test

Abbreviations: BMI, body mass index; Race and ethnicity other subcategory, includes Hispanic, Latine, and not identified; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ULN, upper limit of normal

Disclosures: The following people have nothing to disclose: Alexandra V. Kimchy, Harjit Singh, Esha Parikh, Jessica Rosenberg, Kavya Sanghavi, James H. Lewis

4166-A | EXHALED VOLATILE ORGANIC COMPOUNDS AS POTENTIAL DIAGNOSTIC BIOMARKER FOR EARLY HEPATOCELLULAR CARCINOMA IN AT-RISK POPULATION

Roongruedee Chaiteerakij, Thanikarn Sukaram, Chonlada Phathong, Rungsun Rerknimitr and Rossarin Tansawat, Chulalongkorn University

Background: Volatile organic compounds (VOCs) were shown as promising biomarkers for diagnosis of several cancers including hepatocellular carcinoma (HCC). We previously found that HCC patients had different VOCs profile from non-HCC individual's. We aimed to investigate the performance of VOCs for diagnosing early-stage HCC in patients who are at-risk for HCC. **Methods:** We prospectively collected exhaled breath samples from 87 early-stage HCC patients, 90 cirrhotic patients, and 72 chronic HBV-infected patients. VOCs were identified using thermal desorption-gas chromatography/field-asymmetric ion mobility spectrometry. An association between VOCs and HCC was determined using logistic regression analysis. ROC curves were generated to assess the discrimination power between early HCC and non-HCC patients. Diagnostic performance of VOCs was compared to serum alpha-fetoprotein (AFP) using c-statistics. **Results:** Of the 87 HCC patients, 35 (40%) and 52 (60%) were in BCLC stage 0 and A, respectively. Mean age as well as proportion of males, patients with chronic HBV and HCV infection, NAFLD, and diabetes were not statistically different between the three groups. HCC and cirrhosis groups had similar proportions of patients with Child-Pugh class A (91% vs. 91%) and class B (9% vs. 9%). The median (range) AFP levels were 4.8 (1-643) vs. 3.0 (1-18) vs. 1.9 (1-6) in the HCC, cirrhosis, and HBV groups respectively, $p < 0.001$. Of the 9 investigated VOCs, the levels of 5 VOCs including acetone dimer, 1,4-pentadiene, acetone monomer, isopropyl alcohol, and dimethyl sulfide were significantly different between the three groups. By multivariate analysis adjusted for liver function tests and AFP level, acetone dimer was the VOC most significantly associated with early HCC, with an adjusted OR of 31.30 (5.35-183.14), $p < 0.001$. Likewise, among cirrhotic patients, acetone dimer was independently associated with HCC, with an adjusted OR of 15.61 (2.76-88.28), $p = 0.002$. Acetone dimer at an optimal cutoff of 4.668 AU outperformed AFP at an optimal cutoff of 3.02 ng/mL in differentiating between HCC vs. non-HCC patients, with 88.5% vs. 67.1% sensitivity, 82.7% vs. 65.4% specificity, 84.7% vs. 66.0% accuracy, and AUROC of 0.914 vs. 0.724; $p = 0.017$, 0.0001, < 0.001, and 0.001, respectively. These findings remained true for differentiating between HCC vs. cirrhotic patients, i.e., 86.2% vs. 61.2% sensitivity, 87.6% vs. 66.2% specificity, 86.9% vs. 63.5% accuracy, with AUROC of 0.908 vs. 0.665; $p = 0.007$, < 0.001, < 0.001, and 0.002, respectively. **Conclusion:** Exhaled VOC has potential for non-invasive biomarker for early HCC diagnosis in high-risk patients. Utility of VOCs as a HCC surveillance tool is needed to be further explored.

Disclosures: The following people have nothing to disclose: Roongruedee Chaiteerakij

Disclosure information not available at the time of publication: Thanikarn Sukaram, Chonlada Phathong, Rungsun Rerknimitr, Rossarin Tansawat

4167-A | HEPATOCELLULAR CARCINOMA SURVEILLANCE WITH PERSONALIZED SCREENING INTERVALS INCORPORATING RISK STRATIFICATION USING MRI IN CIRRHOSIS: INTERIM ANALYSIS OF PROSPECTIVE COHORT STUDY

Byeong Geun Song, Myung Ji Goh, Seungchul Han, Wonseok Kang, Tae Wook Kang, Geum-Youn Gwak, Yong-Han Paik, Moon Seok Choi, Joon Hyeok Lee, Dong Hyun Sinn and Woo Kyoung Jeong, Samsung Medical Center

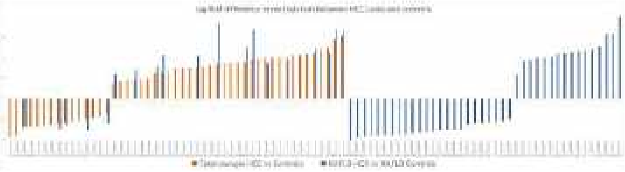
Background: The current recommend method for hepatocellular carcinoma (HCC) surveillance using US has limited sensitivity in detecting early-stage tumor, which can result in surveillance failure (HCC diagnosed at an advanced stage). This prospective cohort study was designed to evaluate effectiveness of HCC surveillance using gadoxetic acid-enhanced MRI at a personalized screening intervals in patients with cirrhosis. **Methods:** We prospectively included a total of 86 patients with cirrhosis between May 2021 and October 2022. Included patients received HCC surveillance using gadoxetic acid-enhanced MRI according to pre-defined personalized screening intervals for a period of three years. Patients were categorized into low risk (no radiologic feature or hallmark of cirrhosis), intermediate risk (radiological cirrhosis), and high risk (high risk nodules considered LR-3 or LR-4 on LI-RADS) according to MRI at enrollment. Then, HCC surveillance was performed using MRI according to pre-defined personalized screening intervals (3 to 36 months according to current and/or previous MR findings). The primary outcome was screening failure, defined as the diagnosis of HCC at an advanced stage (above Milan criteria). The secondary outcomes were tumor diagnosed at very early stage (single tumor < 2cm in diameter) and missing rate (interval HCC, defined by tumor detected outside MRI screening). The cohort size was set at 86, taking into account a significance level of 0.10, a power of 0.80, a one-sided expected difference of 6% of surveillance failure rate, and an estimated drop-out rate of 2%. **Results:** This is an interim analysis based on pre-defined protocol, as 10 cases of HCC was diagnosed in this cohort. The median follow-up duration was 17.7 months (range: 10.4-26.3 mo), and 143 MRI was performed (min – max, 1-5 times per person). There was no case of screening failure. There was one case of missed cancer, which diagnosis was triggered by increased serum alpha-fetoprotein level. Among nine HCC patients detected during MRI surveillance, seven patients were diagnosed at a very early stage, and two patients were diagnosed at early stage (tumor size was less than 3cm). **Conclusion:** This interim analysis showed that HCC surveillance with personalized screening intervals that take into account the risk stratification of HCC using gadoxetic acid-enhanced MRI may be promising surveillance strategy in patients with liver cirrhosis. The study expected to end in April 2025.

Disclosures: The following people have nothing to disclose: Byeong Geun Song, Myung Ji Goh, Seung-chul Han, Wonseok Kang, Tae Wook Kang, Geum-Youn Gwak, Yong-Han Paik, Moon Seok Choi, Joon Hyeok Lee, Dong Hyun Sinn, Woo Kyoung Jeong

ƒ 4168-A | METHYLATION MARKERS OF HEPATOCELLULAR CARCINOMA ARE DETECTABLE IN CELL-FREE SALIVARY DNA

Catherine Mezzacappa[1], Zhanwei Wang[2], Lingeng Lu[1], Harvey Risch[1], Tamar H. Taddei[1] and Herbert Yu[1,3], (1) Yale University, New Haven, CT, (2)University of Hawaii, (3)Department of Epidemiology, the University of Hawaii Cancer Center, Honolulu, HI, USA

Background: Alterations to DNA methylation have been identified in both hepatocellular carcinoma (HCC) tumor tissue and peripheral blood cell-free DNA (cfDNA) from affected individual's. DNA methylation patterns in non-viral HCC differ from those in virally mediated HCC. These markers have potential applications in HCC screening, prognostication, and treatment. Non-invasive markers of HCC risk are needed as metabolic dysfunction associated liver disease becomes increasingly prevalent. **Methods:** This is an observational feasibility study performed on a subset of cases and controls identified from a previously conducted case control study of genetic and environmental risk factors for HCC. Cases included adults aged 47 – 85 years with a first diagnosis of HCC and without a history of viral hepatitis diagnosed between January 2011 and February 2016 residing in three northeastern states. Controls were matched on age, sex, and state and contacted using random-digit dialing. Cell-free DNA was extracted from frozen saliva samples from 12 cases and 12 controls, half of whom (6 cases and 6 controls) had metabolic dysfunction associated steatotic liver disease (MASLD). The log fold change in cfDNA methylation was measured at 1359 CpG sites representing 25 candidate genes previously identified to have aberrant methylation in HCC in the total sample and in the MASLD subset. **Results:** Of the 25 candidate genes, 16 had at least one CpG site with significantly different methylation across HCC cases and controls in the total sample. In the MASLD subset, 59 CpG sites representing 19 of the 25 candidate genes were differentially methylated across HCC status. Fifteen genes were shared by both groups. Sites differentially methylated in HCC cases included genes encoding tumor suppressors (APC, p15, p16, PRDM2, RASSF1A, RASSF5), regulators of cell cycle progression and death (DAPK1, SFRP1, WIF1), DNA repair (MGMT, MLH1), and transcription factors for related proteins (NKX6-2, RUNX3, TBX15, TP73). **Conclusion:** Cell-free DNA extracted from saliva may be a feasible alternative to blood in the era of non-invasive cancer screening and risk stratification.



Disclosures: The following people have nothing to disclose: Catherine Mezzacappa, Herbert Yu
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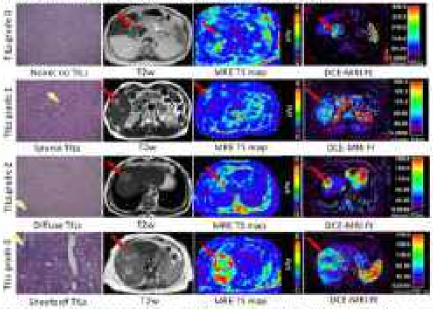
4169-A | MULTIPARAMETRIC MRI PREDICTS HCC IMMUNOPHENOTYPE

Octavia Bane[1], Enamul Bhuiyan[1], Paul Kennedy[1], Muhammed Shareef[1], Pauline Hamon[1], Mark Buckup[1], Sacha Gnjatic[1], Stefanie Hectors[1], Hung Kam Cheung[2], Elizabeth Miller[2], Maria Isabel Fiel[3], Stephen C. Ward[1], Myron E. Schwartz[1], Thomas Marron[1], Miriam Merad[1] and Bachir Taouli[4], (1)Icahn School of Medicine at Mount Sinai, (2)Regeneron Pharmaceuticals, (3)Icahn School of Medicine at Mount Sinai (ISMMS), (4)Mount Sinai Hospital, New York, NY

Background: Immunotherapy is now considered first line therapy for unresectable hepatocellular carcinoma (HCC), with overall response rates as high as 36% at 18 months (when combining atezolizumab with bevacizumab). There is however little knowledge about predictive factors of immunotherapy response in HCC, with data suggesting that background tumor immunophenotype plays a role. The purpose of our study is to assess the value of multiparametric magnetic resonance imaging [(mp)MRI] for prediction of HCC immunophenotype. **Methods:** This is a single-center prospective study in which 30 patients (M/F 22/8, mean age 61.8 y) with resectable HCC underwent mpMRI, of which a subset of 17 patients underwent neoadjuvant immunotherapy (with cemiplimab) followed by post-treatment mpMRI prior to resection. An mpMRI protocol containing sequences without and with hepatoboliary contrast agent was performed 3 months prior to resection. The following whole tumor functional characteristics were measured: stiffness (using MR elastography), T1 relaxation time (using T1 mapping), apparent diffusion coefficient (using diffusion-weighted imaging) and flow/perfusion (using dynamic contrast-enhanced MRI). Background immunophenotype was characterized based on grade of tumor infiltrating lymphocytes (TILs) (none: grade 0, sparse: grade 1, diffuse: grade 2, sheets of TILs: grade 3) assessed on resected tumor samples. Differences between independent groups were tested for significance using Mann Whitney U tests. ROC analysis was performed to evaluate the diagnostic performance of the MRI parameters for prediction of abundant TILs (grade 3). **Results:** Out of 30 tumors (mean size 4.89 ± 3.79 cm, range: 1.5-16.2 cm) assessed, 10 tumors demonstrated abundant TILs (grade 3) at histopathology, the rest demonstrating grade 0-2. Tumors with TILs grade 3 were larger, stiffer and had lower flow than tumors with TILs grades 0-2 (Figure 1). Tumor size at MRI, tumor stiffness measured with MRE, and perfusion/flow parameters mean transit time, arterial flow, total flow, time-to-peak, upslope had very good diagnostic performance (Figure 1, AUC = 0.74-0.81, p = 0.008-0.035) for identification of tumors with TILs grade 3 vs grade 0-2. Native/HBP T1 and ADC were not significantly associated with TILs. A binary logistic regression model combining tumor stiffness and time-to-peak showed very good diagnostic performance for identifying tumors with abundant TILs with AUC (CI) = 0.86 (0.71-0.99), p = 0.002, sensitivity 0.89 and specificity 0.67. **Conclusion:** Our results demonstrate the potential utility of mpMRI parameters in predicting background HCC immunophenotype. These findings require validation in an independent cohort.

Figure 1: Top: Examples of patients with HCC tumors of different MRI findings and immunophenotypes. 73-year-old male (HCC with TILs grade 0), 45-year-old male (HCC with TILSs grade 1), 68-year-old male (HCC with TILSs grade 2; and 77-year-old female (HCC with TILSs grade 3) are illustrated (red arrows indicate the lesions in the images). Slides in the first column illustrate histopathological characteristic tumor infiltration lymphocytes grades (0, 1, 2, 3, yellow arrow). The second column illustrates anatomical T2w images, the third column illustrates stiffness maps of MRE and the fourth column illustrates perfusion maps (total flow Ft) of DCE-MRI. Tumors with abundant TILs are larger and stiffer, with reduced flow.



Bottom: Comparison of MRI parameters and AFP measured in tumors and the corresponding AUC for pathological characteristics, tumor infiltration lymphocytes (TILs) at resection.

Parameter	TILs grade 0–2 (n=20)	TILs grade 3 (n=10)	p*	AUC	p**	95% CI
Tumor size at MRI (cm)	**4.31±3.33**	**6.43±4.16**	**0.035**	**0.74**	**0.035**	**0.56–0.92**
T1-mapping						
¹Native T1 (ms)	684.88±92.53	713.69±70.12	0.288	0.63	0.251	0.42–0.84
²T1-hepatobiliary phase (ms)	567.75±127.43	606.47±93.06	0.408	0.60	0.440	0.36–0.82
Magnetic Resonance Elastography						
³Tumor stiffness* (kPa)**	**4.34±1.73**	**5.98±1.09**	**0.017**	**0.75**	**0.018**	**0.61–0.90**
Dynamic contrast-enhanced MRI (DCE-MRI)						
Ve (%)	44.43±13.49	40.80±22.16	0.907	0.52	0.891	0.37–0.67
MTT (min)	**16.20±10.80**	**38.84±23.08**	**0.034**	**0.76**	**0.025**	**0.57–0.94**
fi (%)	1.58±1.87	3.54±3.09	0.360	0.61	0.333	0.37–0.85
ki (min⁻¹)	2.75±2.92	2.31±2.39	0.367	0.60	0.376	0.37–0.83
Fa (ml/100ml/min)	**218.27±171.38**	**88.02±62.04**	**0.007**	**0.80**	**0.008**	**0.64–0.96**
Fp (ml/100ml/min)	76.97±221.69	15.4±26.35	0.520	0.58	0.406	0.37–0.79
Ft (ml/100ml/min)	**295.34±333.16**	**95.43±76.70**	**0.005**	**0.81**	**0.006**	**0.66–0.97**
AFT (%)	86.53±10.80	81.13±27.80	0.083	0.51	0.968	0.26–0.76
TTP (s)	**41.91±21.79**	**65.40±48.10**	**0.011**	**0.79**	**0.013**	**0.59–0.98**
Upslope (μM/s)	**7.86±6.58**	**3.21±3.28**	**0.015**	**0.78**	**0.016**	**0.59–0.98**
Diffusion-weighted imaging (DWI)						
ADC (x10⁻³ mm²/s)	1.63±0.47	1.49±0.27	0.422	0.58	0.403	0.37–0.79
Serum Biomarker						
Alpha fetoprotein (AFP)	213.82±806.52	8524.21±17465.40	0.074	0.70	0.071	0.49–0.92

*: Mann-Whitney test, **: p-value for AUC, ¹Native T1 measured in 29; ²T1-hepatobiliary phase measured in 26 and ³Tumor stiffness measured in 27 tumors.

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Bachir Taouli – Regeneron Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;
The following people have nothing to disclose: Octavia Bane, Enamul Bhuiyan, Muhammed Shareef, Pauline Hamon, Mark Buckup, Sacha Gnjatic, Maria Isabel Fiel, Stephen C. Ward, Myron E. Schwartz, Thomas Marron, Miriam Merad

4170-A | NOVEL GLYPICAN-3 TARGETED PEPTIDE BINDER FOR THE DEVELOPMENT OF RADIOPHARMACEUTICAL THERAPY TO TREAT HEPATOCELLULAR CARCINOMA

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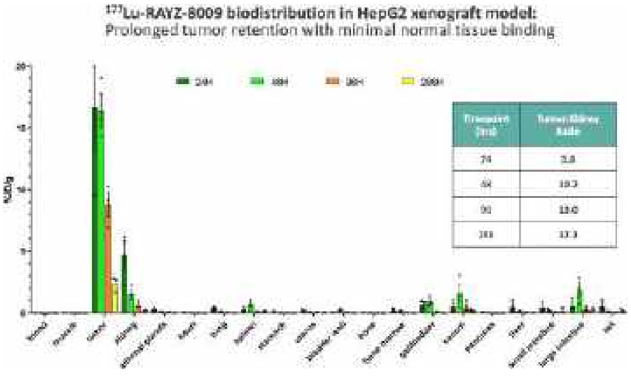
Chen[1], Abhijit Bhat[1], Guangzhou Han[1] and Gary Li[1], (1) Rayzebio, (2)Peptidream

Background: Glypican-3 (GPC3) is a membrane-associated heparan sulfate proteoglycan primarily involved in embryonic development, and is minimally expressed in normal adult tissues. Significant upregulation of GPC3 protein has been observed in hepatocellular carcinomas (HCC), and is associated with poor prognosis. The differential expression of GPC3 between tumor and normal tissues provides an opportunity for targeted radiopharmaceutical therapy (RPT) to treat HCC, a leading cause of cancer-related deaths worldwide. **Methods:** RAYZ-8009 is comprised of a proprietary macrocyclic peptide binder to GPC3, which is connected to chelator DOTA that can be complexed with different radioisotopes. The binding affinity was determined by surface plasma resonance (SPR), and radioligand binding assay in human HCC cell line HepG2. The cross-species binding was assessed by radioligand binding with recombinant mouse, cynomolgus monkey, and human GPC3. Internalization was measured in HepG2 cells at various time points. In vivo biodistribution and anti-tumor efficacy studies were performed in nude mice bearing subcutaneous or orthotopic xenografts. The non-human primate (NHP) PET imaging was performed with ^{64}Cu-labeled binder. **Results:** RAYZ-8009 showed high binding affinity to human GPC3 with a K_D of 0.7 nM. The binding potency was maintained across mouse, cynomolgus monkey and human GPC3. Potent cellular binding was confirmed in HepG2 cells, and was independent of the choice of isotope. ^{177}Lu-RAYZ-8009 achieved efficient internalization upon binding to HepG2 cells. Biodistribution of ^{177}Lu-RAYZ-8009 showed sustained tumor uptake and fast renal clearance. Minimal or no uptake was observed in other normal tissues. Tumor-specific uptake was also demonstrated in orthotopic tumors with no uptake in surrounding liver tissue. In the NHP PET study, rapid clearance in the kidneys and minimal uptake in other organs were observed. Furthermore, significant tumor growth inhibition and survival benefit were achieved with ^{177}Lu- and ^{225}Ac-labeled RAYZ-8009 in GPC3-expressing HCC xenografts. **Conclusion:** Preclinical in vitro and in vivo data in multiple species demonstrate the potential of RAYZ-8009 as a theranostic agent for the treatment of patients with GPC3-positive HCC.



Disclosures: Fanching Lin – RayzeBio: Employee, Yes, No;
Renee Clift – RayzeBio: Employee, Yes, No;
Takeru Ehara – PeptiDream: Employee, Yes, No;
Hayato Yanagida – PeptiDream: Employee, Yes, No;
Alain Noncovich – RayzeBio: Employee, Yes, No;
Steven Horton – RayzeBio: Employee, Yes, No;
Katrina Salvador – RayzeBio: Employee, Yes, No;
Samantha Richardson – RayzeBio: Employee, Yes, No;
Matt Guest – RayzeBio: Employee, Yes, No;
Greg Chen – RayzeBio: Employee, Yes, No;
Abhijit Bhat – RayzeBio: Employee, Yes, No;
Guangzhou Han – RayzeBio: Employee, Yes, No;
Gary Li – RayzeBio: Employee, Yes, No;

4171-A | PREDICTION OF HEPATOCELLULAR CARCINOMA THROUGH ACCURATE CHARACTERIZATION OF INDETERMINANT LIVER NODULES USING AI ANALYSIS OF MULTIPARAMETRIC MR SCANS

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Background: Accurate assessment of precancerous nodules in the liver assists in timely detection of malignancies and the overall management of Hepatocellular carcinoma (HCC). However, current radiological characterization of indeterminate nodules is challenging as these lesions have vague and unclear characteristics and some of them eventually turn into HCC. In this preliminary study, we aim to develop a model that performs an automated analysis of indeterminate liver nodules in multiparametric MR scans and classifies them into low and high-risk (nodules developing into HCC during follow up) nodules. **Methods:** An extensive radiomic analysis of liver nodules in cirrhotic patients was performed using a set of 41 multiparametric MR scans including 11 healthy (i.e., having benign LIRAD-2 or 3 nodules) and 30 pre-HCC (i.e., having nodules that later turned into HCC-LIRAD-4). Hundreds of radiomic features consisting of size, shape, signal intensity and textural properties of liver nodules were extracted and considered for statistical analysis. In a thorough comparative examination, several textural features were identified that were unique and significantly different between the two groups. Subsequently, an artificial intelligence (AI) classifier was trained to perform automated binary classification of these MR scans based on the newly identified predictors using the same 41 scans. A three-fold cross-validation was performed to evaluate the performance of the proposed model. **Results:** The radiomic analysis identified 25 statistically significant radiomic features of liver nodules that help distinguishing benign nodules and those turning into HCC, including inverse clusters, heterogeneity, entropy, and joint energy (Figure 1). The average classification accuracy, sensitivity, and specificity achieved in each validation fold was 76%, 0.76 and 0.75 respectively (95% CI:0.5-0.92). **Conclusion:** This study is a proof of concept that AI analysis can identify unique radiomic features of indeterminant liver nodules using multiparametric MR scans and adequately assist in the categorization of benign and high risk lesions. Such features are usually uninterpretable by current radiological parameters or unappreciated by the naked eye. By performing automated analysis of indeterminate nodules, the proposed model identifies those that are likely to turn into HCC, assisting in early detection of the HCC.

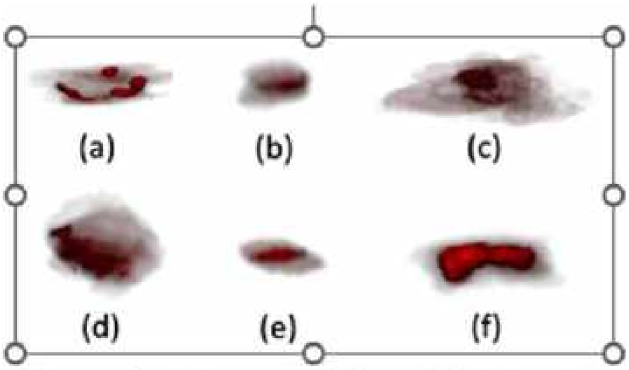

Figure 1: Joint heat map of statistically significant features. (a-c) benign nodules, (d-f) nodules turned into HCC later.

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Walid S. Ayoub – Intercept: Speaking and Teaching, No, No; GIlead: Speaking and Teaching, No, No; Mirum: Independent contractor (including contracted research), No, No; Madrigal: Independent contractor (including contracted research), No, No; GSK: Independent contractor (including contracted research), No, No; Ipsen: Independent contractor (including contracted research), No, No; Genfit: Independent contractor (including contracted research), No, No; Zydus: Independent contractor (including contracted research), No, No; Cymabay: Independent contractor (including contracted research), No, No; Genkyotex: Independent contractor (including contracted research), No, No; perspectum: Speaking and Teaching, No, No; Intercept: Independent contractor (including contracted research), No, No; Gilead: Independent contractor (including contracted research), No, No;

Disclosure information not available at the time of publication: Toussef Qureshi, Linda Azab, Lixia Wang, Yibin Xie, Debiao Li, Shenaz Hussain

4172-A | SENSITIVITY AND SPECIFICITY OF CT/MRI LIVER IMAGING REPORTING AND DATA SYSTEM CATEGORY 5 VS COMBINED 4 AND 5 FOR THE DIAGNOSIS OF HCC: A SYSTEMATIC REVIEW AND META-ANALYSIS

Sunyoung Lee, Severance Hospital, Yonsei University College of Medicine, Claude B. Sirlin, University of California, San Diego and Victoria Chernyak, Memorial Sloan-Kettering Cancer Center

Background: To estimate pooled meta-analytic sensitivities and specificities of CT/MRI Liver Imaging Reporting and Data System (LI-RADS, LR)-5 vs combined LR-4 and LR-5 (LR-4/5) categories for the diagnosis of hepatocellular carcinoma (HCC). **Methods:** Comprehensive searches of MEDLINE and EMBASE databases was conducted from inception to January 03, 2023, reporting the diagnostic performance of LR-5 and combined LR-4/5 for HCC with use of CT/MRI LI-RADS version 2014, 2017, or 2018. A bivariate random-effects model was used to calculate the pooled per-observation sensitivity and specificity. Subgroup analysis was performed based on imaging modalities and type of MRI contrast material. **Results:** Sixty-nine studies qualified for the meta-analysis, comprising 15,108 observations including 9,928 HCCs. The combined LR-4/5 showed significantly higher pooled sensitivity (83.0% [95% CI, 80.3–85.8%] vs 65.7% [95% CI, 62.4–69.1%]; $P < 0.001$), but lower pooled specificity (75.0% [95% CI, 70.5–79.6%] vs 91.7% [95% CI, 90.2–93.1%], $P < 0.001$) than LR-5. Subgroup analyses showed that the sensitivities of combined LR-4/5 were higher than those of LR-5 (67.4% vs 50.5%, $P = 0.018$ for CT; 86.5% vs 73.2%, $P < 0.001$ for extracellular agent [ECA]-MRI; and 84.8% vs 63.9%, $P < 0.001$ for gadoxetate disodium [Gx]-MRI), and the pooled specificities of combined LR-4/5 were lower than those of LR-5 (82.0% vs 93.8%, $P < 0.001$ for CT; 76.3% vs 92.6%, $P = 0.035$ for ECA-MRI; and 73.4% vs 92.1%, $P < 0.001$ for Gx-MRI). **Conclusion:** Our meta-analysis estimated the magnitude of changes in the sensitivity and specificity of imaging criteria when LR-4 and LR-5 categories are combined. These findings may inform management guideline across the globe.
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4173-A | SERUM ALPHA-FETOPROTEIN VALUES DIFFER BY ETIOLOGY OF LIVER DISEASE IN PATIENTS WITH CIRRHOSIS

Nicole J. Kim[1], *Philip Vutien*[1], *Martha C Michel*[2] *and George Ioannou*[1,2], *(1)University of Washington, (2) Veterans Affairs Puget Sound Healthcare System*

Background: Hepatocellular carcinoma (HCC) screening with imaging and serum alpha-fetoprotein (AFP) testing is recommended every 6 months in patients with cirrhosis. A serum AFP value > 20 is considered positive. We aimed to assess whether serum AFP values differ by etiology of liver disease in patients with cirrhosis. **Methods:** Using data from the national U.S. Veteran Affairs Corporate Data Warehouse, we identified all patients with a new diagnosis of cirrhosis documented between 1/1/2001 and 1/1/2019, who were still alive and without a diagnosis of hepatocellular carcinoma (HCC) as of 1/1/2019 and who had a serum AFP level measured in calendar year 2019 (n = 56,869) – the last year before COVID-19 disrupted HCC screening. We assessed serum AFP levels performed in 2019 (median and by category 0-5, > 5-10, > 10-20, > 20-100, and > 100 ng/mL) overall and by etiology of liver disease (categorized as cured hepatitis C [HCV], active HCV, alcohol-associated liver disease [ALD], non-alcoholic fatty liver disease [NAFLD], and other [chronic hepatitis B virus, hemochromatosis, primary biliary cholangitis, autoimmune hepatitis, primary sclerosing cholangitis, and cryptogenic liver disease]). **Results:** This cohort of 56,869 cirrhosis patients with serum AFP measurements in 2019 included 36.0% with cured HCV (n = 20,482), 25.2% with ALD (n = 14,324), 15.4% with NAFLD (n = 8,755), 13.7% with active HCV (n = 7,772), and 9.7% with other etiologies (n = 5,536) of cirrhosis. Among all patients with cirrhosis, the median AFP level was 3.46 ng/mL and 4.5% (n = 2,539) had an AFP > 20 ng/mL. When evaluating by etiology of cirrhosis, median AFP values were 4.32 ng/mL in active HCV, 3.70 ng/mL in cured HCV, 3.33 ng/mL in ALD, 3.00 ng/mL in NAFLD, and 2.90 ng/mL in other cirrhosis ($p < 0.0001$). The proportion of patients with an AFP > 20 was 12.2% (n = 949) in active HCV, 4.4% (n = 906) in cured HCV, 2.4% (n = 346) in ALD, 2.1% (n = 188) in NAFLD, and 2.7% (n = 150) in other cirrhosis ($p < 0.0001$). **Conclusion:** Among U.S. Veterans with cirrhosis, the proportion with AFP > 20 varies by almost 5-fold according to etiology of liver disease. Patients with active HCV had the highest AFP levels, followed by cured HCV, ALD, and NAFLD cirrhosis. Additional studies are needed to evaluate how the performance of AFP as a screening test for HCC varies by etiology of liver disease and whether the threshold value that determines a positive screening test needs to vary by etiology of liver disease.

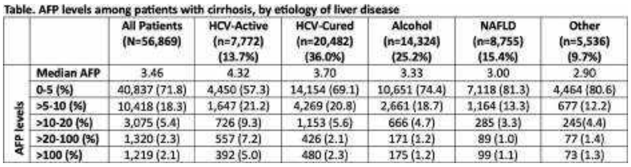

Table. AFP levels among patients with cirrhosis, by etiology of liver disease

		All Patients (N=56,869)	HCV-Active (n=7,772) (13.7%)	HCV-Cured (n=20,482) (36.0%)	Alcohol (n=14,324) (25.2%)	NAFLD (n=8,755) (15.4%)	Other (n=5,536) (9.7%)
AFP levels	Median AFP	3.46	4.32	3.70	3.33	3.00	2.90
	0-5 (%)	40,837 (71.8)	4,450 (57.3)	14,154 (69.1)	10,651 (74.4)	7,118 (81.3)	4,464 (80.6)
	>5-10 (%)	10,418 (18.3)	1,647 (21.2)	4,269 (20.8)	2,661 (18.7)	1,164 (13.3)	677 (12.2)
	>10-20 (%)	3,075 (5.4)	726 (9.3)	1,153 (5.6)	666 (4.7)	285 (3.3)	245(4.4)
	>20-100 (%)	1,320 (2.3)	557 (7.2)	426 (2.1)	171 (1.2)	89 (1.0)	77 (1.4)
	>100 (%)	1,219 (2.1)	392 (5.0)	480 (2.3)	175 (1.2)	99 (1.1)	73 (1.3)

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Disclosure information not available at the time of publication: Philip Vutien, Martha C Michel

f 4174-A | SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS AND REDUCED RISK OF LIVER CANCER IN PEOPLE WITH TYPE 2 DIABETES: A POPULATION-BASED COHORT STUDY

Pin-Chia Huang[1] *and Kevin Sheng-Kai Ma*[1,2,3], *(1) Harvard T.H. Chan School of Public Health, (2) University of Pennsylvania, (3)Massachusetts General Hospital*

Background: Patients with type 2 diabetes mellitus (T2DM) are at a great risk of liver cancers including hepatocellular carcinoma (HCC). However, it remains unclear whether new antidiabetic treatments have the potential to prevent HCC or potentially increase its incidence. Therefore, the objective of this study was to assess the effect of sodium glucose co-transporter 2 inhibitors (SGLT2i) on the risk of developing liver cancer in patients with type 2 diabetes mellitus (T2DM) compared to other oral antidiabetic drugs. **Methods:** Patients with T2DM treated with SGLT2i, dipeptidyl peptidase-4 inhibitors (DPP4i) or glucagon-like peptide-1 receptor agonists (GLP-1 RA) between 2014 and 2023 were retrieved from a population-based cohort study across the United States. Patients with T2DM on SGLT2i were propensity score matched on demographic characteristics, comorbidities, medical history, and lab data with patients with T2DM on DPP4i and on GLP-1 RA, respectively. The primary outcome of interest was the occurrence of new-onset liver cancer, including hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Logistic regression was employed to estimate the odds ratio (OR) and its corresponding 95% confidence intervals (CIs), while Cox proportional hazards regression was used to estimate the hazard ratio (HR) and its 95% CIs for the development of liver cancer. **Results:** A total of 1,877,388 patients diagnosed with T2DM were included in the study before propensity score matching. After propensity score matching, among the SGLT2i group, out of the 706,381 individual's, 1,042 individual's developed incident liver cancer during the follow-up period. In comparison, within the DPP4i group consisting of 706,379 individual's, 1,766 individual's developed incident liver cancer during the follow-up period. Patients on SGLT2i were associated with a significantly reduced risk of new-onset liver cancer as compared to those on DPP4i (HR = 0.87, 95% CI: 0.81, 0.95; OR = 0.59, 95% CI: 0.55, 0.64). Likewise, patients on SGLT2i presented with a significantly lower risk of new-onset liver cancer, as compared with those on GLP-1 RA (OR = 0.86, 95% CI: 0.77, 0.95). **Conclusion:** Findings of the present study demonstrated a significantly reduced risk of liver cancer following the use of SGLT2i in patients with T2DM. Clinical trials are warranted to validate the findings.

Disclosures: The following people have nothing to disclose: Pin-Chia Huang, Kevin Sheng-Kai Ma

4175-A | SONIC HEDGEHOG EXPRESSION IN STEATOHEPATITIC HEPATOCELLULAR CARCINOMAS AND ITS CLINICOPATHOLOGIC SIGNIFICANCE

Hironori Kusano[1,2], Sachiko Ogasawara[2], Minori Omuraya[2], Masayuki Okudaira[3], Shinji Mizuochi[2], Yutaro Mihara[2], Yoshinao Kinjyo[2], Yuta Yano[2], Masamichi Nakayama[2], Reiichiro Kondo[2], Yoshiki Naito[4], Jun Akiba[4], Osamu Nakashima[5] and Hirohisa Yano[2], (1)National Hospital Organization Kokura Medical Center, (2)Kurume University School of Medicine, (3)National Hospital Organization Nagasaki Medical Center, (4)Kurume University Hospital, (5)St Mary's Hospital

Background: The dysregulation of the Hedgehog signaling pathway has been reported to be implicated in the pathogenesis of non-alcoholic steatohepatitis, and the expression of the sonic hedgehog (SHh) protein, a pivotal molecule in the Hedgehog pathway, is found in ballooned hepatocytes. This study aims to investigate the clinicopathologic significance of SHh expression in steatohepatitic hepatocellular carcinoma (SH-HCC). **Methods:** Real-time PCR and immunohistochemistry were employed to examine the gene and protein expression of SHh in SH-HCC. Additionally, a series of conventional HCC (C-HCC) was analyzed as a control group. Clinicopathologic analysis was also carried out. **Results:** The prevalence of SH-HCC was 3%, and it was significantly associated with a high prevalence of diabetes mellitus. SHh mRNA was detected in all cases of SH-HCC, while 23% of C-HCC cases did not show SHh mRNA expression. Statistically, there was no significant difference in SHh mRNA expression level between SH-HCC and C-HCC. At the protein level, the high expression group of SHh was more frequent in SH-HCC. Although there was no significant prognostic difference between SH-HCC and C-HCC, high SHh protein expression was an independent poor prognostic factor in HCCs. **Conclusion:** SHh expression was significantly higher in SH-HCC compared to C-HCC at the protein level. High SHh protein expression was identified as an independent poor prognostic factor in HCCs. Our findings suggest that SHh could potentially serve as a therapeutic target for patients with HCC.

Disclosures: The following people have nothing to disclose: Hironori Kusano, Sachiko Ogasawara, Yutaro Mihara, Masamichi Nakayama, Jun Akiba, Hirohisa Yano

Disclosure information not available at the time of publication: Minori Omuraya, Masayuki Okudaira, Shinji Mizuochi, Yoshinao Kinjyo, Yuta Yano, Reiichiro Kondo, Yoshiki Naito, Osamu Nakashima

4176-A | TUMOR STIFFNESS MEASUREMENT USING MAGNETIC RESONANCE ELASTOGRAPHY CAN PREDICT RECURRENCE AND SURVIVAL AFTER CURATIVE RESECTION OF HEPATOCELLULAR CARCINOMA

Hayato Abe, Yukiyasu Okamura, Tatsuo Kanda and Masahiro Okada, Nihon University School of Medicine

Background: Tumor stiffness measurement using magnetic resonance elastography (MRE) can assess tumor mechanical properties and predict hepatocellular carcinoma (HCC) recurrence. This study aimed to investigate preoperative tumor stiffness on MRE as a predictor of overall survival (OS) and recurrence-free survival (RFS) in patients with solitary nodular HCC who underwent curative resection. **Methods:** Seventy-eight patients with solitary nodular HCC who underwent preoperative MRE and curative resection were retrospectively analyzed. Potential associations of tumor stiffness and other clinicopathological variables with OS and RFS were analyzed in both univariate and multivariate Cox proportional hazards analyses. The optimal tumor stiffness cutoff value was determined using the minimal *P*-value approach. **Results:** In multivariate analysis, tumor stiffness (hazard ratio [HR] 1.29; 95% confidence interval [CI], 1.06–1.56; $P = 0.013$) and vascular invasion (HR 2.56; 95% CI, 1.24–5.17; $P = 0.012$) were independent predictors of RFS. For OS, tumor stiffness (HR, 1.33; 95% CI, 1.02–1.76; $P = 0.037$) was the only independent predictor. The optimal tumor stiffness cutoff value was 5.81 kPa for both OS and RFS. Patients with tumor stiffness ≥ 5.81 kPa had a significantly greater risk of death (HR 6.10; 95% CI, 2.11–21.90; $P < 0.001$) than those with

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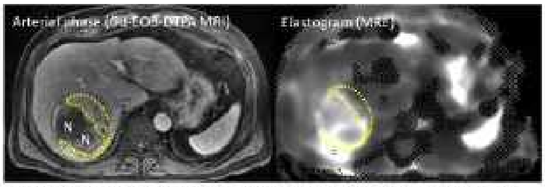
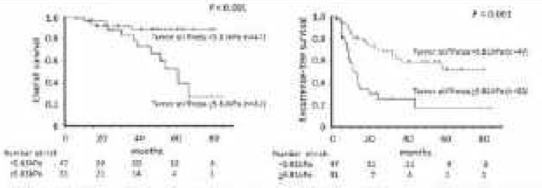
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

tumor stiffness < 5.81 kPa. **Conclusion:** Preoperative tumor stiffness as measured by MRE was a predictor of OS and RFS in HCC patients who underwent curative resection. Higher tumor stiffness was associated with higher risk of recurrence and death.



Case1: On the elastogram map, the mean tumor stiffness (dotted line), referring to the arterial phase and excluding a necrotic area (N), was 6.75 kPa.



Kaplan–Meier curves for overall and recurrence-free survival with patients stratified according to tumor stiffness.

Disclosures: The following people have nothing to disclose: Hayato Abe, Yukiyasu Okamura, Tatsuo Kanda, Masahiro Okada

4177-A | ULTRASOUND LIVER IMAGING REPORTING AND DATA SYSTEM VERSION 2017: A SYSTEMATIC REVIEW AND META-ANALYSIS

Sunyoung Lee, Severance Hospital, Yonsei University College of Medicine, Claude B. Sirlin, University of California, San Diego and Victoria Chernyak, Memorial Sloan-Kettering Cancer Center

Background: We performed a systematic review and meta-analysis to determine the pooled proportions for each ultrasound (US) category and visualization score, the pooled percentages of probably or definitely hepatocellular carcinoma (HCC) and malignancy for US-3 category, and risk factor for US visualization score C on US Liver Imaging Reporting and Data System (LI-RADS) version 2017. **Methods:** We systematically searched databases to identify research articles that performed screening or surveillance US in patients at high risk for HCC according to US LI-RADS version 2017, published from January 1, 2017 to January 3, 2023. A random-effects model was used to calculate the meta-analytic pooled proportions and odds ratios (ORs). **Results:** Fifteen articles were finally included in the analysis, which consisted of 27,681 US examinations. The pooled proportions of each US LI-RADS category were 89.7% (95% CI [confidence interval], 86.7–92.6%) for US-1, 3.8% (95% CI, 1.8–5.9%) for US-2, and 6.3% (95% CI, 4.6–8.0%) for US-3. The pooled percentages of probably or definitely HCC and malignancy were 19.0% (95% CI, 12.3–25.6%) and 20.0% (95% CI, 14.5–25.5%), respectively. The pooled proportions of each US LI-RADS visualization score were 54.7% (95% CI, 44.2–65.2%) for A, 33.9% (95% CI, 27.5–40.2%) for B, and 6.7% (95% CI, 5.2–8.3%) for C. Obesity (OR, 2.37; 95% CI, 1.57–3.59; $P < 0.001$), nonalcoholic fatty liver disease (OR, 2.24; 95% CI, 1.64–3.06; $P < 0.001$), and Child-Pugh classification B or C (OR, 2.41; 95% CI, 1.43–4.06; $P = 0.001$) were significantly associated with US visualization score C. **Conclusion:** Approximately 90% of US screening or surveillance examinations were negative, 4% subthreshold, and 6% positive. Approximately one in five US-3 observations represents probably or definitely HCC. Approximately 7% of US examinations had severe limitations for visualization. Alternative surveillance strategies might be considered in patients with risk factors for severe visualization limitations.

Disclosures: The following people have nothing to disclose: Sunyoung Lee

Disclosure information not available at the time of publication: Claude B. Sirlin, Victoria Chernyak

f 4178-A | A NEAR-INFRARED-MODULATED SYSTEM ENABLING EFFICIENT DELIVERY OF GLUCOSE DERIVATIVE AS A NEW THERAPEUTIC STRATEGY FOR LIVER CANCER

Kyo Sasaki[1], Satoshi Arai[2], Keisuke Hino[3] and Sohji Nishina[1], (1)Kawasaki Medical School, (2)Kanazawa University, (3)Shunan Memorial Hospital, Ube, Japan

Background: 2-Deoxy-D-glucose (2DG), a glucose derivative, has been reported to have cytotoxic effects against several cancers. However, the clinical application of 2DG was not recognized because of adverse events due to high dose administration. We developed cancer-specific drug delivery system (DDS) using 2DG encapsulated poly [lactic-co-glycolic acid (PLGA) nanoparticles (2DG-PLGA-NPs) (Cell Mol Gastroenterol Hepatol 2021). This system showed strong antitumor effect by cytotoxicity and antitumor immunity without any adverse events in mouse HCC models. The aim of this study was to assess antitumor effect of a novel DDS which delivers and releases 2DG more efficiently into cancer cells, using thermodynamic cell engineering. **Methods**: We engineered the liposomal nanoparticles (LNPs) where 2DG was encapsulated and a photothermal agent (a near-infrared absorbing dye) was embedded in the lipid membrane. The surface of LPNs was modified with cancer cell-targeting cyclic peptide (iRGD) which specifically binds to $\alpha v\beta 3/\alpha v\beta 5$ integrin highly expressed on the surface of tumor vessels and

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

tumor cells and then exposes CRGDK peptide after degradation by protease. LNPs are specifically transported into tumor cells by binding to neurophilin-1 through CRGDK peptide. Consequently, this engineered LNPs (termed as iRGD-2DG-nanoheater [iRGD-2DG-NanoHT]) was more specifically delivered to tumor cells and enabled more vigorous release of 2DG through the phase transitions after near-infrared irradiation. **Results:** We found that iRGD-2DG-NanoHT was much more accumulated in liver tumors than 2DG-NanoHT without iRGD in DEN-treated mice. Compared with 2DG-PLGA-NPs, iRGD-2DG-NanoHT exhibited more vigorous antitumor effect, which promoted necroptosis evidenced by phosphorylation of RIPK3 and MLKL and increased the release of high mobility group box-1 (HMGB-1) that functions as damage-associated molecular pattern (DAMP). Interestingly, iRGD-2DG-NanoHT also enhanced antitumor immunity demonstrated by increased $CD8^+$ T cell infiltration and suppressed Treg infiltration. **Conclusion:** iRGD-2DG-NanoHT which exhibits more cytotoxicity and antitumor immunity may be a promising DDS as a new therapeutic strategy for HCC.

Disclosures: The following people have nothing to disclose: Kyo Sasaki, Satoshi Arai, Keisuke Hino, Sohji Nishina

4179-A | A NOVEL TUMOR SUPPRESSIVE ROLE OF NUCLEAR RECEPTOR NR2E3 IN HEPATOCARCINOGENESIS

Kyounghyun Kim[1], Yuet-Kin Leung[1], Soeun Park[1], Sung-Gwon Lee[2] and Chungoo Park[2], (1)University of Arkansas, (2)Chonnam National University

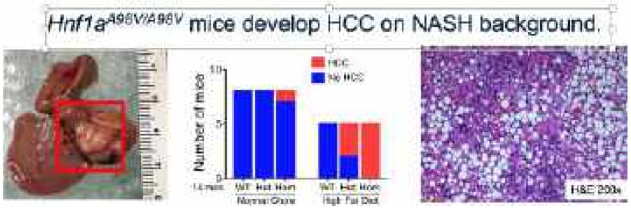
Background: We previously reported that an orphan nuclear receptor NR2E3 is essential for activating p53 in toxicant-induced liver injuries. Without NR2E3 expression, p53 was inactive in toxicant-induced liver injuries due to reduced chromatin accessibility of DINO (Damage Induced Noncoding RNA) induced by NR2E3 loss. DINO is a long noncoding RNA that interacts and stabilizes p53 protein to activate the p53 signaling cascade. Since p53 is a well-established tumor-suppressor gene in liver cancer, we aim to determine further the role of NR2E3 in toxicant-induced liver injury and carcinogenesis. **Methods:** We used DEN (diethylnitrosamine) as a hepatotoxicant to induce liver injury and carcinogenesis in wild-type and NR2E3 knockout (KO) mice. To determine the effects of NR2E3 loss on gene expression and chromatin accessibility changes, we performed RNA-seq and FAIRE (Formaldehyde-Assisted Isolation of Regulatory Elements)-seq analyses using wild-type and NR2E3 KO liver tumor lysate. **Results:** There were increased levels of DEN-induced liver injury and p53 inactivation observed in NR2E3 KO mice. Consistently, we observed significantly enhanced liver tumor progression and formation in NR2E3 KO mice, supporting a tumor suppressive and preventive role of NR2E3. Furthermore, gene set enrichment analysis (GSEA) results indicated that NR2E3 loss dysregulated multiple signaling pathways, such as c-Myc and mTOR, which can contribute to liver tumor development.Moreover, FAIRE-seq analysis revealed that the NR2E3 loss altered global chromatin accessibility corresponding to the pro-oncogenic signaling pathways. Lastly, to confirm whether c-myc and mTOR pathways are dysregulated in liver cancer patients expressing low levels of NR2E3, we divided liver cancer patients in TCGA data into two groups: NR2E3 high vs. Low expressing patient groups and then performed GSEA analysis. In the patient group expressing low NR2E3, we consistently observed the dysregulated or activated c-myc and mTOR signaling pathways. **Conclusion:** The loss of NR2E3 leads to altered chromatin accessibility at the epigenetic level, resulting in dysregulation or activation of crucial signaling pathways linked to liver injuries and tumor formation. Our data support that NR2E3 is a novel preventive and tumor suppressor gene in liver injuries and cancer by regulating epigenetic homeostasis.

Disclosures: The following people have nothing to disclose: Kyounghyun Kim, Yuet-Kin Leung, Soeun Park, Sung-Gwon Lee, Chungoo Park

4180-A | A SINGLE NUCLEOTIDE POLYMORPHISM IN HNF1A INDUCES NAFLD AND HEPATOCELLULAR CARCINOMA

Juanita L. Merchant, Heyu Song and Matthew Vance, University of Arizona, AZ

Background: We recently reported that a single nucleotide polymorphism (Rs1800574) in the DNA binding domain of transcription factor Hepatic Nuclear Factor 1 alpha (HNF1A) occurs with increased frequency in subjects with early onset colorectal cancer. The missense mutation changes an alanine to a valine residue at 98 and is sufficient to create reduced protein function ($HNF1A^{A98V}$), which we recently demonstrated using gel shift assays. Mutations in this locus are also associated with diabetes, dyslipidemia and hepatic adenomas. Therefore, we tested the hypothesis that this loss of function mutation also perturbs liver function. **Methods**: A point mutation was introduced into the mouse genome by CRISPR/Cas9. Mice were bred onto a C57BL/6 genetic background and mice heterozygous ($HNF1A^{A98V/+}$) and homozygous ($HNF1A^{A98V/A98V}$) for the variant were placed on a high fat diet (HFD, 60% fat) for up to 12 -14 months. Bulk RNA-Seq, qPCR, immunohistochemistry and western blots were used to quantify changes. To dissect how elevated fat might affect levels with reduced HNF1A function, we performed bulk RNA-Seq and identified differentially expressed genes between the six groups. Plasma was analyzed for changes in liver enzymes and evidence of metabolic changes. **Results**: Within 6 months, only mice carrying the missense mutation developed fatty liver, elevated serum triglyceride and ALT levels. Similarly, insulin levels were elevated consistent with the presence of the metabolic syndrome. Using the picrosirius red stain revealed the presence of higher fibrosis in the mutant mice on the HFD. There were no significant changes in these parameters in mice on a normal chow or WT mice on the HFD demonstrating that the loss of function mutation was sufficient to induce changes but only in the presence of a fatty meal. Genes related to increased inflammation such as STAT3 and SOCS3 were differentially expressed and was highest in the homozygous group on the HFD. By 12 months, 2/8 *HNF1A*$^{A98V/A98V}$ mice developed liver tumors within a background of fatty liver on normal chow, while none of the WT or heterozygous mice developed tumors. By contrast, on the HFD, 3/5 heterozygous and 5/5 homozygous mice for the HNF1A^{A98V} variant developed tumors. None of the WT mice on the HFD developed liver tumors. The histology was consistent with hepatocellular carcinoma and stained for oncogenes such as cMET. **Conclusion**: A loss of function mutation in the DNA binding domain predisposes mice and possibly human subjects to NAFLD and HCC.



Disclosures: Juanita L. Merchant – Boston Scientific: Consultant, No, No;

The following people have nothing to disclose: Heyu Song, Matthew Vance

4181-A | ADMINISTRATION OF INTERLEUKINS 2 AND 18 WITH ANTI-PD-L1 ANTIBODY SUPPRESSES LIVER TUMOR GROWTH BY INCREASING EARLY MEMORY CD8 T CELL NUMBERS

Kiminori Kimura[1], Masamichi Kimura[1], Michinori Kohara[2], Haruki Okamura[3] and Yoshimasa Tanaka[4], (1) Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, (2)Tokyo Metropolitan Institute of Medical Science, (3)Hyogo College of Medicine, (4)Nagasaki University

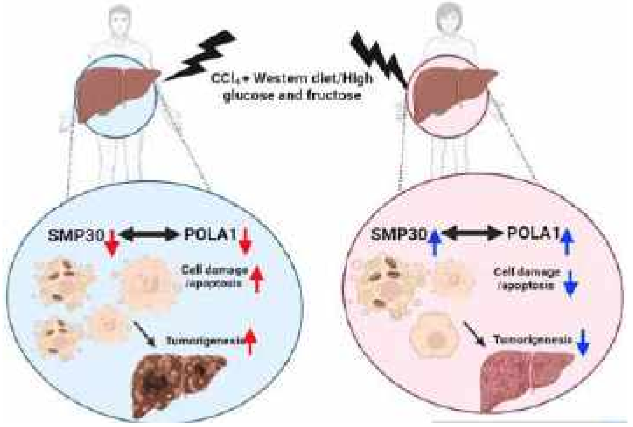
Background: Hepatocellular carcinoma (HCC) is an intractable cancer with poor prognosis. Although various therapeutic drugs, including immune checkpoint inhibitors and tyrosine kinase inhibitors, have been evaluated for HCC treatment, their efficacies have, to date, been insufficient; the development of new drugs is therefore desired. **Methods:** A combination treatment with recombinant interleukin (IL)-2+recombinant IL-18 +anti-programmed death-ligand 1 (aPD-L1) antibody (Ab) was developed to activate an antitumor immune response. We found that it exerted antitumor effects against liver tumors in aged *Mdr2*-knockout mice, a hepato-carcinogenesis model with persistent liver inflammation similar to human hepatocellular carcinoma. The antitumor effects were evaluated based on tumor size assessed using computed tomography scans and serum alpha fetoprotein levels.To evaluate which inflammatory cell populations were infiltrated and activated, intrahepatic lymphocytes (IHLs) were isolated from the liver, and immunological analysis was performed. To investigate which T cells are essential for the antitumor effect of rIL-2+rIL-18+aPD-L1Ab administration, the changes in tumor size were examined using aCD8 neutralizing Ab, aasisloGM1 Ab, and aCD4 neutralizing Ab. Finally, to evaluate whether IL-18 and IL-18BP are involved in human liver diseases, serum IL-18BP levels from patients with HCC were compared with those in healthy volunteers (n = 24) and patients with HCV-derived chronic hepatitis (CH; n = 30), liver cirrhosis (LC) (n = 15), and HCC (n = 69). **Results:** The antitumor effects in terms of tumor progression were observed after rIL-2+rIL-18+aPD-L1Ab treatment but not after rIL-2+aPD-L1Ab or rIL-18+aPD-L1Ab treatment. Intrahepatic lymphocyte analysis showed marked infiltration by CD8 T cells, especially $CD44^{-}CD62L^{+}$, $CD44^{+}CD62L^{+}$, and $Ly108^{+}CD69^{+}$ cells, following administration of the three drugs. In addition, serum interferon gamma, tumor necrosis factor alpha, and CXCL10 levels increased and IL-18 binding protein (BP) levels decreased. The antitumor effect was abolished with co-administration of aCD8-neutralizing Ab but not with aCD4-neutralizing Ab and aasialoGM1, indicating that CD8 T cells are required for this effect. Patients with HCC showed significantly higher levels of serum IL-18BP than patients with LC or CH. **Conclusion:** This triple combination treatment induced and maintained early memory CD8 T cells in the liver and may thus be a promising new immunotherapy for HCC.

Disclosures: The following people have nothing to disclose: Kiminori Kimura, Masamichi Kimura, Michinori Kohara, Haruki Okamura, Yoshimasa Tanaka

4182-A | ATTENUATED LIVER TUMORIGENESIS IN FEMALE MICE IS ATTRIBUTED TO CONSERVED POLA1 EXPRESSION BY SMP30

Su-Min Baek and Jin-Kyu Park, Kyungpook National University

Background: POLA1 is located on X chromosome as well as SMP30. Traditionally, POLA1 is known to have a central role in DNA replication. However, in more recent studies, POLA1 is suggested to be involved in DNA repair process. Most of the studies were performed on the cancer cell lines only, so in the present study, we observed the role of POLA1 in hepatocellular tumorigenesis in mouse gender difference models associated with SMP30 expression levels. **Methods:** liver tumorigenesis was induced by combination of CCl_4 and Western diet administration for 28 weeks. Gross examination and histopathological analysis, serum ALT, AST, and ALB levels, immunofluorescence and immunohistochemistry were additionally analyzed to assess liver injury and tumorigenesis. Microarray analysis and qRT-PCR were performed to reveal the related genes. AML12, HepG2 and Hepa1c1c7 cells were also used to replicate *in vivo* condition. **Results:** Liver tumorigenesis was induced in all the mice regardless of gender. However, the number and maximum tumor nodule sizes were remarkably higher in male mice than in female mice ($p < 0.01$). Serum ALT, AST, and ALB levels and MPO positive neutrophils also showed higher liver injuries in male mice. Consistent with liver injury, glutamine synthetase, a liver tumorigenesis marker, showed higher positive cells in male mice both in nodule and parenchymal lesions. In both microarray analysis and qRT-PCR, POLA1 expression was upregulated in female tumor group while the gene was decreased in male tumor group. In addition, POLA1 expression was also increased in female tumor group than in female control group while no significant changes were observed between male tumor group and male control group. SMP30 showed a similar pattern. Consistent with *in vivo*, POLA1 expression was the highest in AML12, a normal hepatocyte cell line, but decreased in HepG2 and Hepa1c1c7, hepatocellular carcinoma cell lines. Moreover, in AML12 cells, POLA1 decreased with cell injuries following the increase in dose of palmitic acid and CCl_4. Moreover, SMP30 siRNA showed gradual decrease in POLA1 expression levels dose-dependently while POLA1 expression levels did not affect SMP30 expression levels in HepG2 cells. **Conclusion:** The study suggests the novel role of POLA1 and its association with SMP30 in liver tumorigenesis. The different expression levels of POLA1 and SMP30 expression levels in male and female ultimately resulted in gender disparity in the liver tumorigenesis.

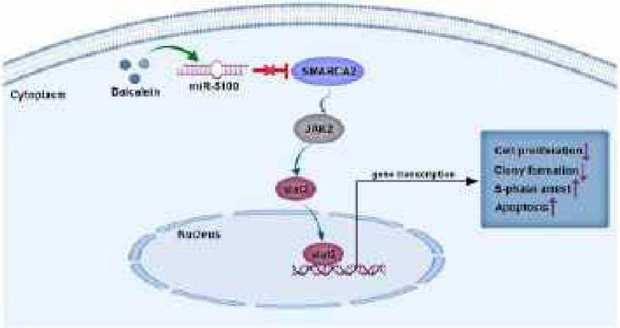


Disclosures: The following people have nothing to disclose: Su-Min Baek, Jin-Kyu Park

4183-A | BAICALEIN INHIBITS THE PROLIFERATION OF HUMAN HEPATOCELLULAR CARCINOMA CELLS VIA MIR-5100-MEDIATED REGULATION OF SMARCA2-JAK2-STAT3 SIGNALING

Ying Guo[1,2,3], Jun Li[1,2], Jin Sun[1,2], Beibei Bie[1,2], Hongwei Tian[1,2], Mengjiao Shi[1,2], Mengchen Zhu[1,2], Jiazhen Zhu[1,2], Pengfei Liu[1,2] and Zongfang Li[1,2,3], (1) National & Local Joint Engineering Research Center of Biodiagnositics and Biotherapy, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China., (2) Shaanxi Provincial Clinical Research Center for Liver and Spleen Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China., (3)Shaanxi International Cooperation Base for Inflammation and Immunity, Xi'an, China

Background: Baicalein is a bioactive flavonoid that has been shown to have anticancer activity. However, it is unclear whether baicalein's antiproliferative effects are related to its regulation of miRNA expression such as miR-5100 in hepatocellular carcinoma. **Methods:** We used qRT-PCR experiments to verify whether the changes in miR-5100 expression after baicalein intervention were consistent with the previous miRNA chip results. The expression of miR-5100 in 36 pairs of human hepatocellular carcinoma and paracancerous samples was also detected by qRT-PCR. CCK-8, plate clone formation assay and flow cytometry were used to detect the effects of overexpression of miR-5100 on proliferation, clone formation, cell cycle distribution and apoptosis of two hepatoma cell lines. Further luciferase reporter and western blotting were used to identify target genes, while exploring possible downstream molecular mechanisms. **Results:** We demonstrated that baicalein can inhibit cell proliferation in human hepatoma cells, and the expression of miR-5100 in cells is significantly upregulated after baicalein intervention. The expression of miR-5100 in clinical HCC samples was decreased ($n=36$, $P=0.0007$), and it was negatively correlated with SMARCA2 expression ($n=36$, $P=0.0013$). Overexpression of miR-5100 can inhibit proliferation and clone formation of hepatoma cells, block cell cycle in S phase, and induce apoptosis (the total apoptosis rate increased from $19.58 \pm 2.0\%$ to $34.30 \pm 3.0\%$, $13.85 \pm 1.3\%$ to $40.97 \pm 3.2\%$, respectively). After baicalein or miR-5100 treatment, the expression of target gene SMARCA2 protein was down-regulated. Luciferase report experiment confirmed that miR-5100 could bind to the 3 'UTR of SMARCA2. Mechanistic analysis showed that baicalein directly targeted SMARCA2 by upregulating miR-5100, thereby inhibiting the transduction of the JAK2-STAT3 signaling pathway. **Conclusion:** The study confirmed for the first time that baicalein regulates the activity of JAK2-STAT3 signaling pathway by upregulating the expression of miR-5100 in hepatoma cells, thereby inhibiting the proliferation and clonal formation, blocking the S-phase cell cycle, and inducing apoptosis of hepatoma cells.



Disclosures: The following people have nothing to disclose: Jun Li, Mengchen Zhu, Pengfei Liu, Zongfang Li

Disclosure information not available at the time of publication: Ying Guo, Jin Sun, Beibei Bie, Hongwei Tian, Mengjiao Shi, Jiazhen Zhu

4184-A | BETA-CATENIN INFLUENCES B CELL RECRUITMENT TO THE TUMOR MICROENVIRONMENT IN BETA-CATENIN-MUTATED HEPATOCELLULAR CARCINOMA CONTRIBUTING TO PATIENT SURVIVAL

Brandon M. Lehrich[1], Junyan Tao[1], Evan Delgado[1], Aatur Singhi[2], Silvia Liu[1] and Satdarshan (Paul) Monga[1,2], (1)University of Pittsburgh, (2)University of Pittsburgh Medical Center

Background: Immune checkpoint inhibitors (ICIs) for hepatocellular carcinoma (HCC) focus on T cell and tumor cell engagement. ICIs demonstrate improved overall survival (OS) for subsets of HCC patients, yet nearly all β-catenin-mutated HCC patients exhibit no benefit. The mechanisms underlying lack of response to ICIs in this subset remain poorly understood. Recently, B cells aggregated in tertiary lymphoid structures (TLS) have been implicated in ICI response in other solid tumors. Here, we investigate the role of B cells in β-catenin-mutated HCC. **Methods:** We queried TCGA and Cancer Digital Slide Archive for HCC patients with CTNNB1 mutation (encoding β-catenin), for B cell gene signatures and presence of TLS on hematoxylin and eosin (H&E) slides. We surveyed our clinically relevant HCC mouse models of T41A-CTNNB1-G31A-NFE2L2, S45Y-CTNNB1-hMET, cMYC-hMET, and FGF19-hMET for B cell markers by immunohistochemistry (IHC). Also, β-catenin-mutated models were treated with b-catenin inhibitor to address influence of β-catenin on immune cell infiltration. Lastly, we compared bulk RNA-sequencing data of β-catenin knockout (β-KO) and β-catenin-mutated livers and performed promoter enrichment analysis (PEA) on the differentially expressed genes (DEGs). **Results:** We observed the cohort of 97 β-catenin-mutated HCC cases to have low expression of 101/200 genes from a previously reported B cell gene signature. Importantly, in TCGA increased expression of multiple B cell surface markers (CD20, CD37, CD38, and CD79A) and presence of TLS were prognostic for improved disease-free survival specifically in β-catenin-mutated HCC patients. We independently confirmed lack of B cell infiltration in glutamine synthetase (a marker for β-catenin activity) positive patients at UPMC. In our HCC mouse models, we noted decreased $CD20^{+}$ and $CD79A^{+}$ immune infiltration via IHC in both β-catenin-mutated models compared to cMYC-hMET and FGF19-hMET non-b-catenin mutated models. Also, utilizing b-catenin inhibitor to the CTNNB1-mutated tumors not only reduced tumor burden, but also transformed the tumor microenvironment (TME). Analysis of DEGs using the Molecular Signatures Database demonstrated increased expression of pathways in B cell activation, proliferation, and lineage commitment. To address mechanism of β-catenin driving a B cell excluded TME, we performed PEA on the DEGs comparing β-KO and β-catenin-mutated livers and found low expression of POU2F1, a known regulator of CXCL13 (a chemokine promoting B cell recruitment and TLS formation) in β-catenin-mutated livers. **Conclusion:** β-catenin influences B cells in the TME of β-catenin-mutated HCCs and correlates to the patient survival. Future studies aim to explore the POU2F1/CXCL13 axis in driving ICI response.

Disclosures: The following people have nothing to disclose: Brandon M. Lehrich, Evan Delgado, Aatur Singhi, Satdarshan (Paul) Monga

Disclosure information not available at the time of publication: Junyan Tao, Silvia Liu

4185-A | CHARACTERIZATION OF CEACAM6 MOLECULAR FUNCTION AND MECHANISM IN GALLBLADDER CANCER AGGRESSIVENESS

Raisatun Nisa Sugiyanto[1], Felicia Truckenmueller[1], Kira Guer[1], Thorben Huth[1], Aslihan Inal[1], Ivonne Heinze[2], Joanna Kirkpatrick[2], Angelika Fraas[1], Benjamin Goeppert[1], Stefan Pusch[3,4], Arianeb Mehrabi[5], Peter Schirmacher[1], Alessandro Ori[2] and Stephanie Roessler[1], (1)Pathology Institute, University Hospital Heidelberg, (2)Leibniz Institute on Aging, Fritz Lipmann Institute, (3)Clinical Cooperation Unit Neuropathology, German Cancer Research Center (DKFZ), (4) Department of Neuropathology, Institute of Pathology, University Hospital Heidelberg, (5)Department of General Visceral and Transplantation Surgery, University Hospital Heidelberg

Background: Gallbladder cancer (GBC) represents the most common biliary tract cancer. The molecular drivers for GBC aggressiveness are poorly identified. Carcinoembryonic Antigen-related Cell Adhesion Molecule 6 (CEACAM6) has been reported to be oncogenic in various tumor entities, yet CEACAM6 function in GBC is poorly understood. This study combines proteomic analysis of GBC patient samples, in vitro and in vivo characterizations of CEACAM6 function, and molecular mechanism investigation of CEACAM6 function in supporting GBC aggressiveness **Methods:** Mass-spectrometric analysis of 5 GBC and 5 healthy gallbladder FFPE tissues was performed. Differentially expressed proteins were analyzed to elucidate oncogenic protein in GBC. Transient siRNA knockdown and stable inducible cells were established to understand the CEACAM6 molecular function in vitro. RNASeq was conducted to reveal significant pathways perturbed by CEACAM6 expression. The molecular functions investigation in vivo was done by injecting cells to ATYM-Foxn1nu/nu nude mice via lateral tail-vein injection and to observe tumor cell growth in mice lungs for 4 weeks. BirA-BioID followed by mass-spectrometry was conducted to identify CEACAM6 interaction partners. Co-immunoprecipitation (CoIP), proximity ligation assay (PLA), and siRNA knockdown experiment were performed to validate the interacting partner candidates' physical interaction and molecular function. **Results:** Carcinoembryonic Antigen-related Cell Adhesion Molecule 6 (CEACAM6) presented as one of the strongest upregulated proteins in GBC proteomics (fold-change $= 5.54$, adjusted pval ≤ 0.01). CEACAM6 overexpression promoted migration and invasion of GBC cells, but reduced cell adhesion and colony formation. Less cell adhesion and tumor growth of cells with higher CEACAM6 expression were also observed in the in vivo lateral tail-vein injection experiment. Conversely, the knockdown of CEACAM6 reduced cell proliferation, colony formation, and migration, but increased cell adhesion. BirA-BioID followed by CoIP and PLA revealed that CEACAM6 signaling to promote migration was independent of Integrin Alpha-2 (ITGA2), but dependent on Integrin Beta-1 (ITGB1) and Protein Kinase C Delta (PRKCD). Correspondingly, integrin, AKT, and ERK signaling pathways were among the most significantly enriched pathways after CEACAM6 overexpression and knockdown in RNASeq analysis. Inhibition of AKT and ERK with inhibitors abrogated their downstream signaling and counter-attacked the CEACAM6-induced migration. **Conclusion:** CEACAM6 supports GBC aggressiveness by promoting cell migration and invasion, but reducing cell adhesion. CEACAM6 directly interacts with ITGA2, ITGB1 and PRKCD, and the migratory promotion of CEACAM6 depends on ITGB1 and PRKCD. Inhibition of CEACAM6 and/or administration of AKT and ERK inhibitors might be potential strategies to abrogate GBC aggressiveness.

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4186-A | CHOLESTASIS-ACTIVATED PORTAL FIBROBLASTS REGULATE HEPATOCYTE SENESCENCE AND HEPATOCARCINOGENESIS IN AGED Mdr2 KO MICE

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Background: Portal fibroblasts are activated (aPFs) in response to cholestatic liver injury. They proliferate, upregulate Collagen Type I and critically contribute to liver fibrosis. aPFs express Mesothelin (Msln) and mucin16 (Muc16), both of which activate TGFβ1 signaling and Thy-1 which prevents TGFβ1 signaling. We investigated the role of $Msln^+$, $Muc16^+$, and Thy-1^+ aPFs in the pathogenesis of cholestatic fibrosis and cancer in aged (16-18 mo) multidrug resistance protein 2 knockout mice (Mdr2-/- mice), which develop sclerosing cholangitis and biliary fibrosis due to a defect in phosphatidylcholine secretion into bile. **Methods:** Mdr2-/- mice were crossed with Msln-/-, Muc16-/-, or Thy-1-/- mice. Development of liver fibrosis and cancer was compared in male and female mice ($n > 12$/group) using immunohistochemistry, qRT-PCR, and Western blotting. **Results:** All mice in the Mdr2-knockout background developed adenomas and hepatocellular carcinoma ($GPC3^+Sox9^+$ HCC) but not cholangiocarcinoma. HCC size and numbers were reduced in Mdr2-/-Msln-/- and Mdr2-/-Muc16-/- mice, which were associated with downregulation of tumor-associated markers AFP, Nox2, p67phox, phospho-Stat3. The numbers of F4/80+ myeloid cells, Desmin+, αSMA+ HSCs, and CD34 + aPFs were reduced in the non-tumor tissues of these mice (vs Mdr2-/- mice). Expression of inflammatory (CD68, Ly6G, IL1β, IL6, IL8) and fibrogenic genes (Col1a1, αSMA, TIMP1, TGFβ1) was also reduced in Mdr2-/-Msln-/- mice and Mdr2-/-Muc16-/- mice. In contrast, Mdr2-/-Thy-1-/- and Mdr2-/- mice showed no differences in tumor size/numbers, although expression of HCC-associated genes AFP and GPC3, inflammation, and liver fibrosis were exacerbated in aged Mdr2-/-Thy1-/- mice (due to increased aPF activation). Since recent studies linked HCC in aged mice to the increased accumulation of senescent hepatocytes, we assessed hepatocyte senescence. Indeed, expression of senescent markers β-gal, p21, p16, Bcl-2, Bcl-w and Bim was markedly reduced in Mdr2-/-Thy-1-/- and Mdr2-/- mice, while proliferation markers Ki67, Cyclin D, phospho-Akt were upregulated (vs Mdr2-/- or Mdr2-/-Thy-1-/- mice), suggesting that genetic deletion of Muc16 (which serves as a signal transduction receptor of Msln) and Msln prevents hepatocyte senescence in Mdr2-/- mice. **Conclusion:** Here we report a novel function of portal fibroblasts as drivers of cholestatic fibrosis, ductular reaction, inflammation, hepatocyte senescence, and HCC in aged mice, demonstrating the key role of the tumor microenvironment.

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4187-A | CLAUDIN-1 MEDIATES CHOLANGIOCELLULAR CARCINOMA INVASION AND METASTASIS BY REPROGRAMMING THE TUMOR MICROENVIRONMENT

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Background: Cholangiocarcinoma (CCA) is a highly aggressive adenocarcinoma with unsatisfactory treatment options. Claudin-1 (CLDN1) is a transmembrane protein expressed in tight junctions and at non-junctional localization mediating cell plasticity and signaling. We have previously developed highly specific monoclonal antibodies (mAbs) targeting exposed CLDN1 with an excellent safety profile (Roehlen et al. Science Transl Med 2022). Here, we aimed to investigate the role of non-junctional CLDN1 as a driver and therapeutic target for invasive and metastatic CCA. **Methods:** Comprehensive expression analyses were used to evaluate CLDN1 as a target for CCA treatment. Proof-of-concept studies were performed using humanized H3L3 CLDN1 mAbs in cell line-derived (CDX) and patient-derived xenograft (PDX) mouse models. CT imaging was used to investigate CLDN1 mAbs efficacy on CCA metastasis *in vivo*. Perturbation studies combined with single-cell and bulk RNA-Seq as well as proteomics were applied to study tumor cell fate and signaling. **Results:** Analyses of CLDN1 protein and RNA expression in CCA patient tissues revealed a robust CLDN1 upregulation. Single-cell RNA-Seq unraveled a high CLDN1 expression in tumor cells and cancer-associated fibroblasts (CAFs) showing an EMT phenotype with an upregulated vimentin and TNFα signaling. Targeting non-junctional CLDN1 using highly specific mAb H3L3 demonstrated a significant anti-tumoral effect in intra- and extra-hepatic CCA CDX and PDX models. CLDN1 mAbs strongly inhibited migration and invasion in cell-based models and lung metastasis formation *in vivo*, suggesting a key role of CLDN1 in tumor metastasis. Mechanistically, CLDN1 mAb suppressed key signaling pathways implicated in CCA pathogenesis and their downstream target genes, including Notch1, SRC-Akt, and Hippo-YAP. CLDN1 mAbs suppressed pathways associated with stemness, EMT and extracellular matrix remodeling in single-cell RNA-Seq of CCA PDX model. Finally, patient-derived CLDN1-expressing CAFs markedly enhanced CCA tumor growth *in vivo* and modulated CCA EMT in co-culture studies. **Conclusion:** Collectively, our results uncover CLDN1 as a driver for CCA invasion and metastasis by modulating tumor cell signaling, EMT and the tumor microenvironment. Proof-of-concept studies using CLDN1-specific mAbs as a single agent reveal CLDN1 as an innovative therapeutic target for advanced CCA.

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4188-A | CROSS TALK BETWEEN SIRT6 AND TGF-BETA SIGNALING MODULATE HUMAN NASH-HCC

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Background: NASH driven HCC is rising alarmingly in the US. Yet, signaling mechanisms that control transformation to cancer are incompletely understood. SIRT6, a protein deacetylase, limits lipogenic activity and protects against TGF-β induced liver fibrosis. We identified a key regulatory loop in NASH/HCC development, where TGF-β signaling-βII-spectrin (SPTBN1) and SMAD3, induces SIRT6 expression *(FASEB J 2022;36.6)*. Liver-specific βII-spectrin knockout (LSKO) blocks NASH and HCC *(Sci Transl Med 2021;13:624)*. In addition, a highly expressed human HCC βII-spectrin-D1089Y somatic mutation disrupts SMAD3 activity (*Gastro 2018; 154:195-210*). Human HCC TCGA data reveal decreased SIRT6 correlating with altered TGF-β signaling. Here we explored the extent of βII-spectrin-D1089Y regulation of SIRT6 expression through SMAD3, and the combined roles of SIRT6 and SPTBN1 in human HCC. **Methods:** SIRT6 levels were examined in SPTBN1^{D1089Y} mutant and LSKO liver tissues. TGF-β/Smad3 pathway activity was analyzed in SPTBN1^{D1089Y} mutant cells with/without TGF- β treatment. SIRT6 expression was examined in mouse and human NAFLD/NASH (CITE-seq dataset (GSE156059 and NASH/HCC (GSE48452). snRNA-seq analysis of liver tissue from LSKO mice fed on NC, WD, and WD plus DEN was conducted. Differential microbiome phenotypes were explored in HCC patients with altered SIRT6 and SPTBN1. **Results:** SIRT6 RNA/protein levels are decreased in liver tissue from SPTBN1^{D1089Y} mutant and SIRT6 is decreased to a greater extent in LSKO mice ($p < 0.05$). TGF-β pathway activity is significantly impaired in SPTBN1^{D1089Y} mutants with decreased phospho-Smad3 levels and 3-TP promoter luciferase activity ($p < 0.05$). SIRT6 RNA expression in mice with NAFLD/NASH is significantly decreased in macrophages. Analyses of human NASH-HCC ($n = 15$), snRNA-seq data identify a subset of hepatocytes with an increase in SPTBN1 and SIRT6, but not SMAD3. Microbiome analysis show that the microbiome species such as Metallospheara, Fodinicurvata, and Sclerodarnavirus are significantly higher ($p < 0.05$) in HCC patients with altered SIRT6 and SPTBN1. **Conclusion**: Our studies indicated that 1. SIRT6 is regulated by βII-spectrin-D1089Y. Yet only part of SIRT6 regulation by βII-spectrin is through Smad3. 2. The data support a SMAD dependent as well as a SMAD3 independent role of SPTBN1 in regulating SIRT6. 3. βII-spectrin-D1089Y together with SIRT6 deficiency increased susceptibility to NASH/HCC in mice via regulating the microbiome.

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4189-A | DEVELOPMENT OF NOVEL HUMAN HEPATOCELLULAR CARCINOMA MODELS USING GENETICALLY MODIFIED HUMAN HEPATOCYTES IN FSRG HUMANIZED LIVER MICE

Marisa Carbonaro and Zhe Li, Regeneron Pharmaceuticals

Background: The incidence of liver cancer is growing worldwide, and it is estimated that by 2025, over 1 million individual’s will be affected by liver cancer every year.

Hepatocellular carcinoma (HCC) accounts for about 90% of primary liver cancer cases and is one of the leading causes of death from cancer worldwide. Establishing animal models that faithfully replicate the human disease is critical to improve our understanding of HCC pathogenesis and to test new therapeutic strategies. Here, we describe a novel human HCC model using genetically modified human hepatocytes in a humanized liver mouse. **Methods:** Primary human hepatocytes (PHH) were modified *ex vivo* through lentivirus or Lipid Nanoparticle (LNP)-mediated delivery of CRISPR/Cas9 components, resulting in over-expression of oncogenes or inactivation of tumor suppressor genes. These genetically engineered PHH were engrafted into the livers of FSRG ($Fah^{-/-}$, $Sirpa^{hu/hu}$, $Rag2^{-/-}$, $Il2rg^{-/-}$) mice, developed by Regeneron VelociGene technology, in which mouse liver parenchyma can be replaced with human hepatocytes. **Results:** Tumor formation was validated in livers engrafted with human hepatocytes after different combinations of genetic modification, including over-expression of cMYC plus $HRAS^{v12}$, and cMYC over-expression together with p53 KO. Tumor progression could be monitored by measuring human Alpha Fetoprotein (AFP) in serum of engrafted mice. Liver tumors were positive for fumarylacetoacetate hydrolase (FAH) and human Asialoglycoprotein Receptor 1 (ASGR1), confirming their human origin, as well as the proliferation marker, Ki67, and Glypican-3 (GPC3), which is frequently over-expressed in HCC and a potential therapeutic target. **Conclusion:** In these studies, mice were engrafted with a mix of lentivirus-transduced and non-transduced hepatocytes, resulting in humanized livers with both normal and transformed human hepatocytes, providing an ideal system to recapitulate neoplastic transformation and clonal expansion of human hepatocytes carrying oncogenic mutations as well as to test the specificity of novel therapies. By combining genetic manipulation of human hepatocytes with the FSRG humanized liver mouse platform, we have established a flexible system to model clinically relevant combinations of HCC mutations for both new target discovery and therapeutic testing.

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Zhe Li – Regeneron Pharmaceuticals, Inc.,: Employee, No, No;

4190-A | EFFICACY OF RNAi-MEDIATED BETA-CATENIN INHIBITION IN MULTIPLE IMMUNOCOMPETENT MOUSE MODELS OF HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality globally. Approximately 25-35% of HCC patient tumors have mutations in β-catenin (CTNNB1). Several studies have indicated that this HCC subclass is almost entirely resistant to immunotherapy regimens, which are the current standard of care. Preclinical studies have elucidated addiction to β-catenin signaling in β-catenin-mutated HCC, making this target prime for precision medicine therapeutics. **Methods:** We inhibited β-catenin mRNA levels in the G31A-NFE2L2-T41A-β-catenin and hMet-S45Y-β-catenin mouse models of HCC which each represent around 9-12% of all human HCC. Starting at two different timepoints following hydrodynamic tail vein injection (HDTVi), animals were administered siRNAs formulated in lipid nanoparticles (LNP) targeting either CTNNB1 (LNP-CTNNB1) or scrambled control (LNP-CTRL). **Results:** LNP-CTNNB1 administered once weekly for six weeks starting at 5 weeks post HDTVi, when microscopic tumor foci were present, demonstrated complete tumor responses (CR) compared to LNP-CTRL in both models. Three days following the last dose in each model, the LNP-CTNNB1 group had normal liver weight/body weight ratio (4-4.5%) and histologically normal liver parenchyma compared to significant tumors in the LNP-CTRL group ($p < 0.001$). Additionally, the LNP-CTNNB1 group had durable responses up to 3 weeks following treatment cessation. Notably, a delayed treatment with LNP-CTNNB1 starting at 8 weeks post HDTVi, when macroscopic tumor nodules were present, delayed disease progression. To investigate the underlying mechanisms, livers were harvested 3 days after a single LNP dose. LNP-CTNNB1 treatment decreased activation of several β-catenin target genes (Glul, Axin2, Lect2), along with decreasing tumor cell proliferation markers (Ki67, Ccnd1), inhibition of mTOR pathway signaling components, and increased tumor cell death observed via TUNEL immunohistochemistry. Strikingly, the LNP-CTNNB1 group revealed dynamic shifts in the tumor microenvironment, including alterations in gene signatures related to type I interferon response, lymphoid progenitor cell differentiation, antigen presentation, and T cell cytokine production. **Conclusion:** Our studies demonstrated the efficacy of RNAi-mediated inhibition of CTNNB1 for β-catenin-mutated HCC and provide strong preclinical evidence to support clinical translation as monotherapy as well as in combination with other treatments.

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4191-A | EPIGENETIC CONTROL OF SLC7A11 UPREGULATION BY TET1 INHIBITS FERROPTOSIS IN CHOLANGIOCARCINOMA

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Background: Ferroptosis is a form of iron-dependent cell death and has emerged as a potential cancer target. It is commonly observed that iron overload occurs in patients with chronic liver diseases, which are risk factors for cholangiocarcinoma (CCA) incidence. However, ferroptosis is not active in CCA patients, suggesting that some mechanisms may block the activation of ferroptosis pathways in CCA. This study aimed to determine the epigenetic control of ferroptosis in CCA. **Methods:** The expression of ferroptosis-associated genes and DNA methylation enzymes were analyzed using RNA sequencing data retrieved from the TCGA and GEO resources. The Kaplan-Meier analysis was used to investigate the correlation between these gene levels and CCA survival. In vitro cell culture and in vivo preclinical CCA models were adopted to evaluate the causative impacts of the identified genes on ferroptosis and CCA progression. **Results:** We found that the ferroptosis suppressing gene-SLC7A11 is associated with poor prognosis in human CCA patients. Besides, high TET1 is correlated with CCA prognosis, suggesting the potential link between TET1 and SLC7A11. Knockdown of TET1 suppresses CCA cell survival due to increased cell ferroptosis since the ferroptosis inhibitor robustly reversed the impact of TET1 downregulation on CCA cells. Consistently, inhibiting TET1 reduced SLC7A11 expression, resulting in ferroptosis. Overexpression of SLC7A11 rescued the effects of TET1 knockdown on CCA cells. Mechanistically, inhibiting TET1 enzymatic functions downregulated SLC7A11 expression resulting in ferroptosis in CCA cells. In contrast, activating TET1 induced SLC7A11 levels leading to reduced ferroptosis. The treatment of DNA methylation inhibitor 5-azacytidine reversed the suppressive effects of TET1 downregulation on SLC7A11, thereby suggesting that TET1 regulates ferroptosis in CCA tumors through epigenetic control of SLC7A11. Further, we found that the ferroptosis inducers (Erastin and RSL3) suppressed CCA viability robustly but to a less extent in TET1 knockdown CCA cells. Similarly, UC-514321 significantly inhibited CCA malignant progression by suppressing the TET1-mediated SLC7A11 mechanism. More importantly, all these treatments substantially suppressed CCA malignant progression in the orthoptic CCA xenograft model. **Conclusion:** Our data demonstrated that ferroptosis is inhibited in CCA by the TET1-mediated SLC7A11 upregulation. Targeting the TET1/SLC7A11 axis may be potential therapeutic approach for CCA patients.

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4192-A | EXTRACELLULAR MATRIX REMODELING IN THE PROGRESSION OF PRIMARY SCLEROSING CHOLANGITIS TO CHOLANGIOCARCINOMA: INSIGHTS FROM AN ANIMAL MODEL

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Background: Primary Sclerosing Cholangitis (PSC) is a chronic biliary disease characterized by peribiliary fibrosis evolving to cholangiocarcinoma (CCA). As PSC, CCA is characterized by prominent extracellular matrix (ECM) accumulation. Despite this association, the mechanisms by which fibrosis is accompanied by dysplasia and malignant transformation remain uncharted, reflecting the lack of an appropriate experimental model to capture the sequence from PSC to CCA (CCA/PSC). In this study, we aimed at developing an animal model of CCA/PSC to assess changes in ECM proteins typically up-regulated in CCA (Osteopontin (OPN), Tenascin C (TnC) and Periostin (POSTN)), as potential biomarkers enabling early detection of tumoral lesions in PSC. **Methods:** Mrd2$^{-/-}$ mice, a well-established PSC model, were treated with thioacetamide (TAA), a profibrogenic toxicant, to induce CCA, and sacrificed at different time points (12 and 28 weeks, both n = 4) and compared with controls (Mdr2$^{-/-}$

without TTA and WT+TAA mice, both n = 4). ECM phenotyping was performed in liver sections from mice and human archival samples of CCA/PSC (n = 5) by immunohistochemistry (IHC) for OPN, TnC and POSTN. *In vitro*, human CCA cells (HUCCT-1, EGI-1) and primary human PSC cells were treated for 24h with OPN (10nM), TnC (100nM), and POSTN (100nM) to evaluate cell viability (MTS), migration (wound healing), and cancer stem cell (CSC)-like phenotypic switch (CD133 and CD44, real-time PCR). **Results:** Upon TTA treatment, $Mdr2^{-/-}$ mice but not controls developed biliary dysplasia (2/4 at 12, 1/4 at 28 weeks) and intrahepatic CCA (1/4 at 12, 3/4 at 28 weeks). IHC showed a progressive increase from classic ductal to dysplastic and neoplastic lesions for TnC, POSTN, and more prominently for OPN, similarly to what seen in human samples. *In vitro,* 24h treatment with ECM proteins enhanced migratory properties in CCA, but not in PSC cells. POSTN, and less efficiently TnC and OPN, induced a significant upregulation of CD133 and CD44 in both CCA and PSC cells, signature of CSC-like phenotype. **Conclusion:** The $Mdr2^{-/-}$+TAA mouse recapitulates the pathogenetic sequence biliary fibrosis-biliary dysplasia-CCA. In both murine and human samples OPN, TnC and POSTN are overexpressed in malignant lesions. *In vitro*, ECM proteins, particularly POSTN, induce a CSC-like switch in CCA and PSC cells, in support of their tumor-initiating role. ECM proteins may serve as putative tissue biomarkers for CCA surveillance in PSC patients.

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4193-A | FUNCTIONAL DICHOTOMY OF BILIARY PRIMARY CILIA IN LIVER INJURY AND CHOLANGIOCARCINOMA DEVELOPMENT

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Background: We have previously published that Primary cilia (Pc) mediate canonical Hedgehog (Hh) signalling in the ductular reaction (DR) in experimental and human cirrhosis. However, our recent publication indicated that Pc loss in biliary epithelial cells (BEC) induced the proliferation of BECs and biliary cystic formation in experimental fibrosis models. We now aim to examine the effect of Pc loss on the development of cholangiocarcinoma in BEC-specific PTEN knockout (KO) mice. **Methods:** C57BL/6J-congenic Pten-flox and kif3a-flox mice crossed with CK19CreERT knockin mice to produce BEC-specific KO of PTEN, kif3a (Pc loss) or both (DKO) following tamoxifen (TAM) administration in adult mice. Thioacetamide (TAA) was used to induce liver injury and fibrosis for up to 20 weeks. Mice were culled at weeks 14 and 18 post-TAM administration. Tissue samples were examined with histopathological assays and RNA-seq. The SLHD Animal Welfare Committee approved animal breeding and experimental protocols. **Results:** In BEC-specific PTEN KO mice (PTEN-BKO), intraductal papillary neoplasm of the bile duct was evidenced in the large intrahepatic bile ducts. TAA administration induced cholangiocarcinoma (CCA) formation. Pc were lost in these CCA cells. To test whether Pc loss actually played a role in the development of CCA, PTEN-BKO mice were crossed with BEC-specific kif3a KO mice to produce double KO (DKO) mice. When these DKO mice consumed TAA, the number and size of CCAs were significantly increased compared with PTEN-BKO mice. Histological analysis indicated increased expression of PCNA, Sox9, phospho-ERK, infiltration of neutrophils and macrophages, and the presence of significant stroma formation similar to that seen in human CCA. RNA-seq analysis revealed that expression levels of 288 genes were significantly increased in PTEN-BKO and DKO liver tissues compared with wild-type (WT) liver tissues. For example, CCA tumour marker genes, such as msln, S100A6, and DMBT1, were dramatically increased in PTEN-BKO and DKO livers compared with WT livers. More importantly, a set of genes over-expressed in human CCA with poor prognosis were enriched in PTEN-BKO and DKO liver tissues. Multiple MAPK genes or signalling pathways and some stem cell markers, such as CD44 and DCLK1, were upregulated in PTEN KO or DKO livers. Interestingly, more than 8% of up-expressed genes in PTEN-BKO and DKO livers are targets of the JNK pathway, which was well-documented to promote CCA growth. Further analysis is ongoing. **Conclusion:** Loss of Pc in BEC could have been secondary to the oncogenic transformation, but the increase of CCA in DKO mice indicates a role for Pc in the progression of CCA. Cholangiocarcinoma in such mice shared significant features of human CCA, including many overlapping upregulated genes, thus providing a pre-clinical model for testing new therapeutic approaches.

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Disclosure information not available at the time of publication: Fan Zhang, Ken Liu, Sofia Ferreira-

Gonzalez, Jennifer R Gamble, Emad Ei-Omar, James G Kench

4194-A | GDF11 ACTS AS A CHEMO-SENSITIZER WITH CISPLATIN AND SORAFENIB TREATMENTS IN HCC-DERIVED CELLS

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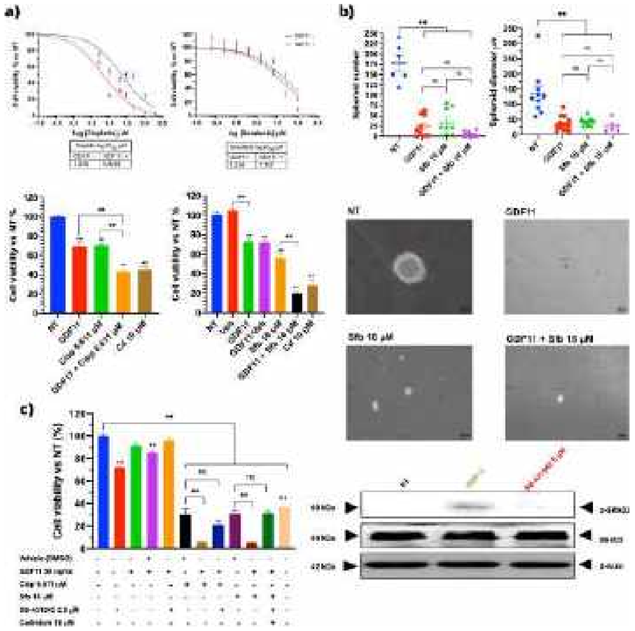
Background: Hepatocellular carcinoma (HCC) accounts for 90% of liver tumors, representing the third leading cause of cancer-related deaths worldwide. Actual drugs have poor therapeutic outcomes in HCC and novel effective therapies are required for the treatment of this disease. The Growth and Differentiation Factor 11 (GDF11) is a TGF-β superfamily member with several biological roles including cancer. Our group has demonstrated the anti-tumoral activity of GDF11 on HCC-derived cell lines reducing cell proliferation, metabolism, migration, and invasive capacity. In the present work, we also report the chemo-sensitizing effects of GDF11 in the HCC-derived Huh7 cell line in combination with sorafenib (Sfb) and cisplatin (Cisp) treatments. **Methods:** The Huh7 cell line was pre-treated with 50 ng/ml of GDF11 for 72 h with changes of medium every 24 h. After pre-treatment of GDF11, we added Cisp or Sfb at different concentrations and incubated the cells for 48 h. For ALK5 receptor inhibition experiments, we added 5 μM of SB-431542 in the GDF11 pre-treatments. Subsequently, we performed cell viability, spheroid formation assays and western blot analysis. We report the data as the mean ± S.E.M. of at least three independent experiments. We performed an analysis of variance (ANOVA) followed by the Tukey multiple comparison test. Significance was set at $p \leq 0.05$. **Results:** The GDF11 pre-treatment reduced the IC_{50} of Cisp in the Huh7 cell line from 22.11 μM to 6.611 μM and the Sfb concentration from 17.12 μM to 12.8 μM. GDF11 decreased the cell viability in the Huh7 cell line in combination with 6.611 μM Cisp or Sfb 16 μM compared to treatment alone. Also, GDF11 alone significantly lessened the spheroid diameter, NT: 114.4 μm, GDF11: 35.58 μm, Sfb: 43.43 μm and GDF1 + Sfb: 28.26 μm; and the spheroid number, NT: 177.5 ± 46.28, GDF11: 25.00 ± 25.13, Sfb: 34.22 ± 32.05 and GDF1 + Sfb: 5.667 ± 6.59. Also, we characterized that the GDF11 chemo-sensitizing effects are mediated through the ALK5 receptor. The ALK5 inhibitor SB-431542 abrogated the phosphorylation of SMAD-2 and counteracted the chemo-sensibilization effects induced by GDF11 pre-treatment. **Conclusion:** The GDF11 could be a promising new adjuvant therapy in the HCC treatment, allowing the use of lower chemotherapeutic doses and reducing the adverse side effects of these therapies. Grant: Antonio Ariza Cañadilla, FUNDEHPA.



Disclosures: The following people have nothing to disclose: Natanael German Ramirez, Arturo Simoni Nieves, Maria Guadalupe Isabel Domínguez Gómez, Monserrat Gerardo Ramirez, Benjamín Peréz Aguilar, Leticia Bucio Ortiz, Verónica Souza Arroyo, Roxana Uri Miranda Labra, Concepcion Gutierrez Ruiz, Luis Enrique Gómez Quiroz

4195-A | GP130 INCREASES SORAFENIB-RESISTANCE IN HEPATOCELLULAR CARCINOMA THROUGH PREVENTION OF BECN1-MEDIATED MITOPHAGIC CELL DEATH

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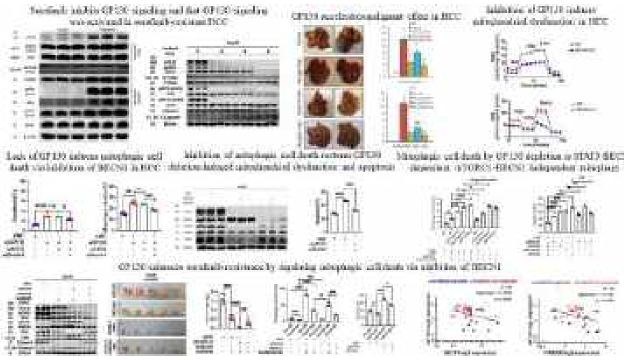
University College of Pharmacy, (2)University of California, San Diego, La Jolla, CA, (3)Cedars-Sinai Medical Center, Torrance, CA

Background: Sorafenib-resistance is often seen in the patients with late-stage hepatocellular carcinoma (HCC) and it is a serious concern for the treatment of these patients. Of note, Sorafenib induces mitochondrial dysfunction and mitophagic cell death. Sorafenib resistance is associated with the activation of GP130 signaling, inhibiting mitochondrial quality. However, how mitophagic cell death regulates sorafenib resistance through GP130 and mitochondrial dysfunction in HCC is not fully understood. **Methods:** Hepatocyte-specific TAK1 deleted (TAK1ΔHep) and TAK1/ GP130ΔHep were used for in vivo study. Histology, immunoblots, qPCR, microscopy, FACS, and seahorse bioanalyzer were used for analyzing liver and tumor tissues and Hep3B cells. **Results:** We identified that sorafenib suppressed GP130 signaling and that GP130 signaling was activated in sorafenib-resistant HCC. The number and maximum size of spontaneous HCC in 9-month-old TAK1ΔHep mice were decreased when hepatocyte GP130 was additionally deleted. Expression of pro-carcinogenic H-19, c-SRC, and MDM2 was increased in 1-month-old TAK1/GP130ΔHep mice compared to TAK1ΔHep mice. An additional GP130 deletion induced decreases in mitochondrial respiration and glycolysis, suggesting that GP130 protects against mitochondrial dysfunction in HCC. Interestingly, GP130 deletion increases PRKN and BECN1 interaction and translocation to normal mitochondria and subsequent degradation, hereafter referred to as mitophagic cell death. Furthermore, inhibition of BECN1 restores GP130 deletion-induced mitophagic cell death in HCC, suggesting that GP130-mediated mitophagic cell death is dependent on BECN1. Mechanistically, GP130 inhibited BECN1-mitophagic cell death through STAT3 (T705) phosphorylation independently of mTORC1 activation. Notably, enhanced BECN1 through a combination of sorafenib and inhibition of GP130 increased mitophagic cell death, reducing sorafenib resistance and tumor growth. In addition, enhanced mitophagic cell death through inhibition of GP130 effectively killed sorafenib-resistant HCC cells by silencing sorafenib resistance. We further defined the relationship between GP130, BECN1, and PRKN expression and sorafenib resistance in terms of HCC patients, RNA sequencing datasets. **Conclusion:** These results provide the importance of GP130 in the development of sorafenib resistance and could be an innovative treatment strategy for sorafenib-resistant patients by regulating the GP130-STAT3-BECN1-regulated mitophagic cell death.



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4196-A | INTERFERON-RELATED GENE EXPRESSION CHANGES MEDIATED BY ALPHA-FETOPROTEIN IN PATIENTS WHO DEVELOPED HEPATOCELLULAR CARCINOMA AFTER HEPATITIS C VIRUS ERADICATION

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Background: Alpha fetoprotein (AFP) is a serum protein found in fetuses during early pregnancy and has been used as a tumor marker for hepatocellular carcinoma (HCC). Serum AFP levels are often elevated in chronic hepatitis C, even in the absence of HCC. In fact, we have reported that even slightly elevated AFP levels in the range of less than 20 ng/mL are a risk factor for liver carcinogenesis in chronic liver disease (J Gastroenterol. 2011; 46: 92.). Thus, AFP expression increases with hepatitis and tumor growth, but conversely, it is not well understood whether AFP expression affects the cellular environment in hepatocarcinogenesis. **Methods:** To elucidate the function of AFP in

liver/ hepatocellular carcinoma cells, *in vitro* experiments were conducted using human cell lines (hepatocarcinoma-derived cells HepG2 and normal hepatocyte-like cells HuSE) with an AFP overexpressing expression system. The human AFP gene was cloned, and the AFP protein was expressed using pcDNA3-Flag vector. RNA was extracted from the cells, and RNA-seq was performed using a next-generation sequencer to comprehensively analyze changes in gene expression. In addition, from patients who developed hepatocellular carcinoma after Sustained Virological Response (SVR) of chronic liver disease type C, RNA was extracted from the cancerous and non-cancerous parts of liver resection specimens and changes in gene expression were analyzed. **Results:** Comprehensive analysis of gene expression changes in AFP-expressing cell lines and bioinformatics analysis by Gene Set Enrichment Analysis (GSEA) revealed that differentially expressed genes in the AFP-expressing cells were significantly associated with interferon-α/γ, and genes involved in fatty acid metabolism than in the control. Analysis of cancerous and non-cancerous area of liver resected tissue showed a significant positive correlation between AFP gene expression and interferon-α related gene expression, both cancerous and non-cancerous area. In addition, the expression of AFP gene expression and VEGFA gene expression were strongly correlated in cancer regions. **Conclusion:** These results showed a correlation between the elevated AFP gene expression in hepatocellular carcinoma tissue with elevated interferon-α-related gene expression and altered VEGFA gene expression in patients with chronic liver disease with slightly elevated serum AFP levels in the range of less than 20 ng/ml. These results suggest that even a slight increase in AFP expression may have a certain impact on the hepatocellular carcinoma microenvironment.

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Disclosure information not available at the time of publication: Masakuni Tateyama, Sotaro Kurano, Hideaki Naoe

f 4197-A | IRF2 EXPRESSION IN Β-CATENIN-MUTATED HEPATOCELLULAR CARCINOMAS PROMOTES INFLAMMATION AND REDUCED TUMOR BURDEN

Evan Delgado[1], *Panari Patel*[2], *Junyan Tao*[1], *Yekaterina Krutsenko*[2], *Brandon M. Lehrich*[1], *Anya Singh Varma*[1], *Ravi Rai*[1], *Minakshi Poddar*[1], *Sucha Singh*[1], *Aaron W. Bell*[3], *Reben Raeman*[1] *and Satdarshan (Paul) Monga*[1], *(1)University of Pittsburgh, (2)University of Pittsburgh School of Medicine, (3)University of Pittsburgh, Sewickley, PA*

Background: The current standard of care for unresectable HCC is combination immune checkpoint inhibitors (ICIs), whose foundation was laid by the IMbrave150 trial. Because of imperfect response rates to ICIs, specific molecular aberrations have been implicated in diverse responses to ICI therapy. 30% of patients that harbor mutations in *CTNNB1*, the gene that encodes β-catenin, seem to respond poorly to ICI intervention. However, understanding if *CTNNB1* mutations directly contribute to immune escape in clinical HCC is still in need of investigation. Here, we investigate whether promoting an inflammatory response is sufficient to prevent HCC progression. **Methods:** Bioinformatic analysis was performed on b-catenin loss or gain of function livers to identify mechanisms of immune cell regulation. Next, HCCs generated in mice by co-delivering mutant-β-catenin-(S45Y) and the MET tyrosine kinase (B+M model) that represent 11% subset of HCCs with a 69% genetic accuracy to patients was used to validating *in silco* findings. The interferon response transcription factor, IRF2, was delivered alongside oncogenes in the B+M model. HCC burden was assessed in controls and +IRF2 condition. IRF2 activity was also measured by immunoblot and immunostaining. Intrahepatic and peripheral immune populations were characterized by FACS and by immunostaining to identify shifts in the immune microenvironment and exhaustion. **Results:** Overexpression of IRF2 was detectable in HCC nodules by 4 weeks post-HCC induction, which led to a significant reduction in overall tumor burden 7.5 weeks after HCC induction. We also found a significant accumulation of intratumoral CD45^{+} cells after IRF2 expression in the B+M model. FACS identified significant shifts towards a less exhausted immune microenvironment, and a decreased accumulation of immunosuppressive FoxP3+ T-regulatory cells. We also asked if endogenous IRF2 stimulation is sufficient to drive a functional inflammatory response. B+M animals treated daily with 1×10^4 IU IFNy for 4 weeks led to a modest 10% reduction in overall disease burden. **Conclusion:** Activating the interferon response in *CTNNB1*-mutated HCC is sufficient to reduce overall tumor burden and disease. This is driven by an inflammatory response characterized by less exhausted cytotoxic T-cells and immunosuppressive T-regs. Our data indicates inducing cytotoxic inflammation in β-catenin-mutated HCCs may be an effective method to produce an anti-tumor response.

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Disclosure information not available at the time of publication: Panari Patel, Junyan Tao, Yekaterina Krutsenko, Anya Singh Varma, Aaron W. Bell

4198-A | KIDNEY GLUTAMINASE IN HEPATOCELLULAR CARCINOMA: A NOVEL DRUGGABLE TARGET ADDRESSING CANCER CELL METABOLIC REPROGRAMMING

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Background: Hepatocellular carcinoma (HCC) is a major contributor to the global cancer burden, in part due to very limited therapies. Reprogramming of glutamine metabolism is a putative determinant of HCC pathogenesis. Glutaminase (GLS) is a major pathway used by cancer cells to metabolize glutamine. **Methods:** Tumorigenic murine HCC Dt81Hepa1-6 (Dt81) cells and isolated primary murine hepatocytes (HP) were cultured with CB-839, a kidney GLS (GLS1) inhibitor. The influence of CB-839 on cellular activity was assessed on viability (MTT), proliferation, ammonia production, and glutamine and glutamate content (LC/MS). The expressions of various genes or proteins linked to glutamine metabolism were measured by qPCR and Western blotting, respectfully. Glutamine consumption was measured by ^{3}H-glutamine uptake assay. **Results:** GLS1 mRNA expression was higher in Dt81 than in HP ($p < 0.01$), whereas that of liver GLS (GLS2) was inversely higher in HP than in Dt81 ($p < 0.01$). In Dt81 cells, CB-839 [1 μM] significantly decreased ammonia production from 0.75 ± 0.06 to 0.19 ± 0.09 μmol/mg protein ($p < 0.01$), but not in HP. The Dt81 glutamine/glutamate ratio increased from 2.54 ± 0.14 to 9.20 ± 0.34 upon CB-839 [1 μM] treatment ($p < 0.0001$), suggestive of decreased glutaminolysis. CB-839 decreased ^{3}H-glutamine uptake in HP ($p < 0.05$) but to a lesser extent than in Dt81 ($p < 0.0001$). GLS1 mRNA increased ($p < 0.01$) in a dose-dependent manner with CB-839 in Dt81 but not in HP, whereas GLS2 remained unchanged in both cell types. Lactate dehydrogenase tended to decrease whereas glutamine and asparagine synthetases tended to increase with CB-839 exposure. CB-839 decreased HP and Dt81 viability ($p < 0.0001$), Dt81 being more sensitive to CB-839 (23.2 ± 1.36% decrease at 1μM) than HP (11.9 ± 3.0% decrease at 1μM). CB-839 treatment also slowed Dt81 cell doubling time from 36.04 ± 2.02h to 129.4 ± 52.8h [10 μM] ($p < 0.05$). Interestingly, replenishing α-ketoglutarate, a metabolite downstream GLS, restored cell viability in Dt81 treated with CB-839 ($p < 0.0001$). **Conclusion:** In murine HCC cells, GLS reprogramming is targetable through the non-competitive inhibitor CB-839. Indeed, targeting GLS in HCC impairs cancer cell metabolism, which in turn leads to cell death and decreased proliferative capacity. These findings highlight the fundamental importance for glutamine metabolism in murine HCC cells compared to normal hepatocytes.

Disclosures: The following people have nothing to disclose: Vincent Tambay, Valérie-Ann Raymond, Marc Bilodeau

f 4200-A | LOSS OF GLUTAMINE SYNTHETASE EXACERBATES MYELOID CELL INDUCED IMMUNOSUPPRESSION IN β-CATENIN-MUTATED HEPATOCELLULAR CARCINOMAS

Evan Delgado[1], Panari Patel[2], Junyan Tao[1], Silvia Liu[3], Brandon M. Lehrich[1], Minakshi Poddar[1], Sucha Singh[1], Aaron W. Bell[4] and Satdarshan (Paul) Monga[1], (1) University of Pittsburgh, (2)University of Pittsburgh School of Medicine, (3)Pittsburgh Liver Research Center, (4)University of Pittsburgh, Sewickley, PA

Background: Around 30% of HCC cases harbor mutations in *CTNNB1*, the gene that encodes β-catenin. These tumors can be identified with high sensitivity and specificity on histology by tumor-wide positivity for Glutamine Synthetase (GS), encoded by *Glul,* a well-known b-catenin target gene. Previously, the b-catenin-GS-glutamine-mTORC1 axis has been examined in b-catenin-mutated HCCs which demonstrate high susceptibility to mTOR inhibitors in preclinical models. Here, we investigate this axis further by targeting GS in b-catenin-mutated HCCs with a major focus on tumor immune environment. **Methods:** HCCs were induced in *Glul*-floxed mice by co-delivering mutant-β-catenin-(T41A) and mutant nuclear factor erythroid 2–related

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

factor 2 (Nrf2-G31A) (B+N model). *Glul* elimination following tumorigenesis was achieved by delivering AAV8 carrying Cre-recombinase. HCC burden was assessed in *Glul*-KO and controls. We preformed 10x Genomics Spatial Gene Expression profiling to measure mRNA with fluorescent immunostaining in tandem, as well as single-cell RNA-sequencing (scRNA-Seq) to identify changes in the immune microenvironment in *CTNNB1*-mutated HCCs ± GS. **Results:** *Glul* was sufficiently deleted by two weeks from HCCs in the B+N model using AAV8-Cre. This was associated by decreased intratumoral glutamine levels. Interestingly, 4.5-weeks post *Glul* elimination, a significant increase in LW/BW ratio indicating a greater tumor burden was observed which also persisted at 7-weeks. Spatial expression analysis showed decreases in *Mrc1*, *Adgre1*, *Cd68*, *Vsig4*, and *Cxcr4,* markers of myeloid cells, which was also validated by immunohistochemistry. sc-RNA-Seq data identified a specific increase in the numbers of myeloid cells expressing immunosuppressive patterns in GS-knockdown HCCs. Finally, disease burden is unchanged following macrophage depletion in B+N control animals. **Conclusion:** Our data indicate that GS-loss increases the immunosuppressive function of myeloid cells thus contributing to the increase in disease burden in *Glul*-KO animals. Since myeloid cells are still detected in these tissues, our data suggests intrinsic *Glul* expression and in turn tumoral glutamine levels in β-catenin-mutated HCCs alter resident macrophage function and physiology. It is unclear if tumor associated macrophages in HCCs are dysfunctional Kupffer cells or originate from other myeloid populations. More information may provide insight into HCC disease pathogenesis and information regarding ICI efficacy.

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Disclosure information not available at the time of publication: Panari Patel, Junyan Tao, Silvia Liu, Aaron W. Bell

4201-A | LOSS OF hepaticTsc1 PROMOTES LIVER CYSTOGENESIS AND TUMORIGENESIS VIA A NON-CANONICAL mTORC1-TFEB-DEPENDENT MECHANISM

Chen Zhang[1], *Sha Neisha Williams*[1], *Hong-Min Ni*[2] *and Wen-Xing Ding*[3], *(1)The University of Kansas Mediacal Center, (2)The University of Kansas Medical Center, (3) University of Kansas Medical Center, Kansas City, KS*

Background: The integration of various environmental cues by mTORC1 is crucial in regulating cell growth and metabolism. Activation of mTORC1 occurs when growth factors or amino acids stimulate Rag GTPase heterodimeric complexes, such as Rag A/C, at the lysosomal surface. In mice, the loss of Tsc1 leads to activation of mTORC, increased ductular reaction (DR), cystogenesis, and spontaneous liver tumorigenesis. While mTORC1-mediated phosphorylation inactivates Transcription factor EB (TFEB), a master transcription factor of autophagy and lysosomal biogenesis, emerging evidence highlights that TFEB is dephosphorylated and hyper-activated in TSC-associated kidney cystogenesis and cancer. The purpose of this study was to investigate whether and how loss of hepatic Tsc1 activates TFEB and promotes liver cystogenesis and tumorigenesis. **Methods:** *Tsc1* Flox/Flox and *Tfeb* Flox/Flox mice were crossed with albumin Cre mice to generate liver-specific *Tsc1* knockout (L-*Tsc1* KO) and L-*Tsc1/Tfeb* double KO (DKO) mice. Additionally, a liver-specific *Tfeb* knockin (L-*Tfeb*-KI) mouse was created. These mice were housed for various time points up to 12 months, and biochemical and histological analysis was conducted on blood and liver tissues. **Results:** In L-*Tsc1* KO mice, levels of phosphorylated S6 and 4EBP1 increased, indicating the activation of mTORC1. Surprisingly, L-*Tsc1* KO mice also had increased levels of dephosphorylated TFEB with increased TFEB nuclear translocation resulting in increased lysosomal biogenesis, indicating TFEB activation in a noncanonical-mTORC1 dependent mechanism. Mice with L-*Tsc1* KO developed liver cysts, hepatocellular carcinoma, and cholangiocarcinoma when they were aged at 8-12-months old. This was significantly inhibited by further deletion of TFEB in L-*Tsc1* KO mice (DKO mice). We also observed increased YAP1 activation, decreased HFN4α, and increased Rag A/C proteins in L-*Tsc1* KO mice, which were all blunted by deletion of TFEB, indicating a feed-forward loop of TFEB-mTORC1. Moreover, L-*Tfeb*-KI mice had increased DR, hepatocyte degeneration, fibrosis at 2-months-old, and developed polycystic liver diseases and cholangiocarcinoma-like phenotypes at 8-months-old, reminiscent but worsened phenotypes of L-*Tsc1* KO mice. **Conclusion:** Our findings reveal a non-canonical mTORC1 pathway that promotes TFEB activation leading to hepatocyte degeneration, increased DR, cystogenesis, and liver tumorigenesis. Selective targeting of this non-canonical mTORC1 pathway may be a promising approach for polycystic liver disease and cholangiocarcinoma mediated by TSC1 mutations.

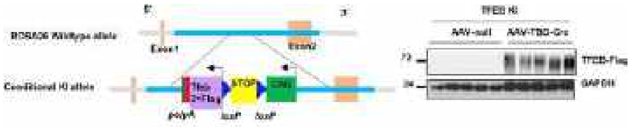

Figure. Generation of conditional TFEB KI mice. (A) TFEB-flag$^{fl/+}$ mice were injected with AAV8-null or AAV8-TBG-cre (2X10e 11 GC/mouse) to generate liver-specific TFEB-KI mice. (B) After AAV injection for 14 days, total liver lysates were subjected to western blot analysis.

Disclosures: Wen-Xing Ding: WEN-XING DING, Sha Neisha Williams, Hong-Min Ni

4202-A | LOWER LEVELS OF BILE ACIDS FROM FGF15 OVEREXPRESSION IS ASSOCIATED WITH REDUCED HEPATOCELLULAR CARCINOGENESIS IN A NOVEL HCC MOUSE MODEL WITH COMBINED FXR DEFICIENCY AND CO-EXPRESSION OF C-MET/Β-CATENIN

Bo Kong[1], Katherine D Otersen[2], Vik Meadows[3], Zhenning Yang[1], Rulaiha E Taylor[4], Zakiyah Henry[2], Veronia Basaly[2] and Grace L. Guo[3], (1)Rutgers, the State University of New Jersey, (2)Rutgers University, (3)Rutgers University, Piscataway, NJ, (4) Environmental and Occupational Health Sciences Institute, Rutgers, the State University of New Jersey, Piscataway, NJ

Background: Nuclear receptor farnesoid X receptor (FXR) induces fibroblast growth factor 19 (FGF19) in humans, and FGF15 in mice, to suppress bile acid (BA) synthesis in the liver through the activation of FGF receptor 4 (FGFR4) on hepatocytes. The BA-FXR-FGF15-FGFR4 signaling axis has been implicated in promoting hepatocyte cell proliferation and liver regeneration in mice. While FGF19 is implicated in human HCC formation, FXR deficiency leads to increased hepatocellular carcinoma (HCC) development. Our previous study found that FGF15 overexpression prevented HCC development in FXR knockout (KO) mice. Since FXR can prevent HCC development in both BA-dependent and -independent pathways, and FGF15 is also involved in regulating a variety of liver functions, the underlying mechanisms by which FGF15 prevents HCC development induced by FXR deficiency were investigated. **Methods:** Six to eight weeks old male FXR KO mice with and without enterohepatic *Fgf15* overexpression (FXR KO/*Fgf15* Tg) were injected with 20 mg plasmids of pT3-EF1a-H-c-Met and pT3-EF1a-H-N90-β-catenin, along with the Sleeping Beauty transposase (pCMV-SB10), using hydrodynamic tail vein injection. HCC prevalence and tumorigenesis gene expression, at both mRNA and protein levels, were determined in all mice six weeks post injection. **Results:** Co-expression of human c-Met and β-catenin mutation (ΔN90-β-catenin) led to enhanced liver tumor prevalence in both FXR KO and FXR KO/*Fgf15* Tg mice. Compared to FXR KO/*Fgf15* Tg mice, FXR KO mice had increased tumor burden, revealed by higher liver weight and liver/body weight ratio after hydrodynamic transduction. Western blotting of cell proliferation markers, CyclinD1 and PCNA, and Ki-67 immunohistochemistry with semi-quantification, further confirmed higher cell proliferation in livers of FXR KO compared to FXR KO/*Fgf15* Tg livers. **Conclusion:** BAs act as promoting agents and are implicated in c-Met/b-Catenin-driven HCC development. These findings suggest that the reduced bile acid levels due to FGF15 overexpression may contribute to the amelioration of tumorigenesis in FXR KO mice.

Disclosures: The following people have nothing to disclose: Bo Kong, Zakiyah Henry, Veronia Basaly, Grace L. Guo

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f 4203-A | MET AND FIBROBLAST GROWTH FACTOR 19 CO-ACTIVATION IN HEPATOCELLULAR CARCINOMA: BIOLOGICAL IMPLICATIONS AND CLINICAL RELEVANCE

Brandon M. Lehrich[1], Junyan Tao[1], Silvia Liu[1] and Satdarshan (Paul) Monga[1,2], (1)University of Pittsburgh, (2)University of Pittsburgh Medical Center

Background: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-associated mortality globally with limited treatment options. Developing clinically relevant models may improve our understanding of the heterogenous biology of HCC and provide a platform to screen potential therapeutic targets. Met is frequently overexpressed in HCC, yet selective Met inhibitors have not yielded improved patient outcomes, necessitating the need to explore how other driver oncogenes cooperate in the pathogenesis of Met-activated HCC. Here, we investigate cooperation between Met and fibroblast growth factor 19 (FGF19) signaling in HCC. **Methods:** We queried The Cancer Genome Atlas (TCGA) for co-activation of Met and FGF19 in HCC to derive a Met/FGF19 gene signature. We also followed HCC development in mice through co-overexpression of Met/FGF19 via hydrodynamic tail vein injection delivery with sleeping beauty transposon/transposase (HDTVi-SBTT) system. Lastly, we compared similarity of gene expression signatures between the Met/FGF19 mouse model to human HCC. **Results:** Overall, 43 (11%) of 377 HCC patients in TCGA exhibited co-activation of Met/FGF19. Co-expression of Met & FGF19 in mice via HDTVi-SBTT yielded well differentiated HCC development and mortality by 13-15 weeks. These HCC were positive for the FGF19 receptor, FGFR4, along with mammalian target of rapamycin (mTOR) pathway targets, including p-mTOR-S2448, p-S6-235/236, p-S6-240/244, and p-4EBP1-T37/46. Bulk RNA-sequencing and Ingenuity pathway analysis (IPA) on differentially expressed genes (DEGs) comparing Met/FGF19 mouse tumors to normal mouse liver revealed activation of metabolism

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pathways (oxidative phosphorylation, fatty acid beta-oxidation, and cholesterol biosynthesis). Interestingly, analysis of the DEGs from the mouse model using the Molecular Signatures Database showed activation of T and B cell activation, proliferation, and lineage commitment pathways. Also, immunohistochemistry demonstrated increased intratumoral infiltration of CD4$^+$, CD8$^+$, and CD20$^+$ immune cells. We also observed a high concordance (74.9% transcriptome similarity and 48 common IPA pathways) of the preclinical model to human HCC with Met/FGF19 co-activation. **Conclusion:** Co-activation of Met & FGF19 occurs in a significant subset of HCC patients with co-expression leading to HCC development in mice. This Met/FGF19 preclinical model provides an improved platform to test various targeted and immunotherapies.

Disclosures: The following people have nothing to disclose: Brandon M. Lehrich, Satdarshan (Paul) Monga

Disclosure information not available at the time of publication: Junyan Tao, Silvia Liu

4204-A | METHYLTRANSFERASE-LIKE PROTEIN 3 (METTL3) PROMOTES CHOLANGIOCARCINOMA DEVELOPMENT AND PROGRESSION: EVIDENCE FOR INVOLVEMENT OF HIPPO-TAZ SIGNALING AND REGULATION BY NOTCH PATHWAY

Wenbo Ma, Tulane University, New Orleans, LA

Background: N6-methyladenosine (m6A) modification of RNA has recently emerged as a new regulatory mechanism in carcinogenic processes. In this study, we aimed to investigate the effect and the mechanism of the m6A methyltransferase METTL3 in cholangiocarcinoma (CCA) development and progression. **Methods:** The development of CCA was induced by SB transposase-mediated integration of oncogenes (NICD/Akt) to the FVB/NJ mice via hydrodynamic tail vein (HDTV) injection. CCA xenograft was developed by inoculation of human CCA cells with or without METTL3 depletion by shRNA into the livers of SCID mice. m6A RNA immunoprecipitation followed by high-throughput sequencing (MeRIP-seq) was used to map transcriptome-wide m6A in METTL3 depleted cells. **Results:** Our data show that METTL3 is upregulated in human CCA and promotes the growth and invasiveness of CCA cells. Depletion of METTL3 by shRNA or by the next generation GapmeR antisense oligonucleotides (ASOs) significantly inhibited human CCA cell growth *in vitro* and in SCID mice. We also observed increased METTL3 expression in mouse CCA induced by hydrodynamic tail vein injection of NICD and myr-Akt. Knockdown of METTL3 by shRNA reduced the development of NICD/Akt-induced CCA in mice. Our findings suggest that METTL3 inhibition may represent a potential therapeutic strategy for the treatment of CCA. Mechanistically, our data show that METTL3 mediated m6A modification enhanced the expression of the Hippo pathway effector TAZ protein in an YTHDF1 dependent manner. Depletion of METTL3 by shRNAs or GapmeR ASOs reduced the level of TAZ protein. Furthermore, our data showed that Notch signaling is involved in the upregulation of METTL3 in CCA cells. Accordingly, inhibition of Notch signaling decreased the protein levels of MELLT3 and its downstream effector TAZ. **Conclusion:** This study describes a novel Notch-METTL3-TAZ signaling axis which is importantly implicated in cholangiocarcinoma development and progression. Our findings provide encouraging preclinical evidence for targeting METTL3-mediated RNA m6A modification in cholangiocarcinoma treatment.

Disclosures: The following people have nothing to disclose: Wenbo Ma

4205-A | MICRORNA-1297 IS INVOLVED IN THE RESISTANCE OF LENVATINIB IN HEPATOCELLULAR CARCINOMA

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Background: Lenvatinib for treating hepatocellular carcinoma (HCC) has a superior response rate, although its overall survival is non-inferior to sorafenib, suggesting tumor cells acquire resistance during therapy. Hypoxia in the tumor microenvironment has been reported to play a critical role in the acquisition of drug resistance. Tyrosine kinase inhibitors with inhibitory effects on VEGF prevent tumor angiogenesis, resulting in significant hypoxia in the tumor. We aimed to elucidate the mechanism of lenvatinib resistance acquisition and the involvement of microRNAs under hypoxia in HCC. **Methods:** HCC cell lines, PLC/PRF/5, HepG2, Hep3B, and Huh7 were cultured in 95% air and 5% CO_2 (normoxia) or in 94% N_2 with 1% O_2 and 5% CO_2 (hypoxia). Anchorage-dependent proliferation was assessed with a metabolic assay, and induction of apoptosis was evaluated by morphologically and caspase-3/7 assay. A genome-wide profiling using 3D-Gene® Human miRNA/mRNA Oligo chips (Toray Industries) was performed to identify microRNAs altered in acquiring resistance to lenvatinib. HCC cells were electroporated with synthetic precursors of microRNAs to force the expression. **Results:** Lenvatinib inhibited cell growth in a concentration-dependent manner. IC_{50} of lenvatinib (72 hr) by MTS assay significantly increased under hypoxia in all cell lines tested, suggesting the acquisition of lenvatinib resistance.

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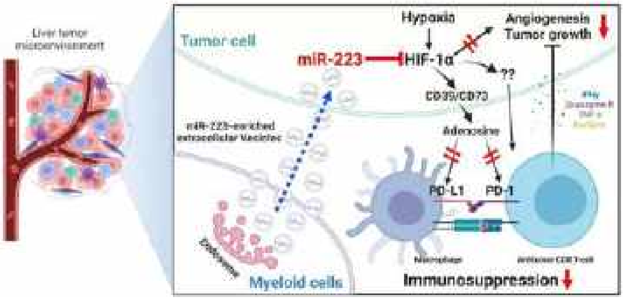
Under hypoxia, the number of morphologically determined apoptotic cells induced by lenvatinib was 22.4% and 19.6% decreased, and caspase-3/7 activity was 26.4% and 18.7% decreased compared to normoxia in PLC/PRF/5 and HepG2, respectively. A genome-wide profiling showed 42 microRNAs with increased expression in PLC/PRF/5 treated with lenvatinib under normoxia, and 28 of these showed decreased expression under hypoxia. Among these, we focused on microRNA-1297 (miR-1297) for further investigation. Prior forced expression of miR-1297 by electroporation of synthetic precursor partially restored the impaired cytotoxicity of lenvatinib against HCC cells under hypoxia. To investigate the genes regulated by miR-1297, we performed genome-wide profiling of mRNA in PLC/PRF/5 under forced expression of miR-1297. By the forced expression of miR-1297, 27 genes decreased more than 2-fold. Network analysis of these genes suggested that miR-1297 regulates a group of genes with TGF-b receptor1 as a hub. **Conclusion:** miR-1297 may play a role in lenvatinib resistance induced by hypoxia by regulating TGF-b receptor1 signaling. These observations demonstrate that microRNAs could be an attractive target for overcoming lenvatinib resistance in HCC.

Disclosures: The following people have nothing to disclose: Takayuki Kogure, Mari Satoh, Takehito Ito, Kennichi Satoh

4206-A | MICRORNA-223 ATTENUATES HEPATOCARCINOGENESIS BY BLOCKING HYPOXIA-DRIVEN ANGIOGENESIS AND IMMUNOSUPPRESSION

Yaojie Fu, National Institutes of Health (NIH)

Background: The current treatment for hepatocellular carcinoma (HCC) to block angiogenesis and immunosuppression provides some benefits only for a subset of patients with HCC, thus optimized therapeutic regimens are unmet needs, which require a thorough understanding of the underlying mechanisms by which tumor cells orchestrate an inflamed tumor microenvironment with significant myeloid cell infiltration. MicroRNA-223 (miR-223) is highly expressed in myeloid cells but its role in regulating tumor microenvironment remains unknown. **Methods:** Wild-type and miR-223 knockout mice were subjected to two mouse models of inflammation-associated HCC induced by injection of diethylnitrosamine (DEN) or orthotopic HCC cell implantation in chronic carbon tetrachloride (CCl4)-treated mice. **Results:** Genetic deletion of miR-223 markedly exacerbated tumorigenesis in inflammation-associated HCC. Compared with wild-type mice, miR-223 knockout mice had more infiltrated programmed cell death 1 (PD-1+) T cells and programmed cell death ligand 1 (PD-L1+) macrophages after DEN+CCl4 administration. Bioinformatic analyses of RNA sequencing data revealed a strong correlation between miR-223 levels and tumor hypoxia, a condition that is well-documented to regulate PD-1/PD-L1. In vivo and in vitro mechanistic studies demonstrated that miR-223 did not directly target PD-1 and PD-L1 in immune cells rather than indirectly downregulated them by modulating tumor microenvironment via the suppression of hypoxia-inducible factor 1α-driven CD39/CD73-adenosine pathway in HCC. Moreover, gene delivery of miR-223 via adenovirus inhibited angiogenesis and hypoxia-mediated PD-1/PD-L1 activation in both HCC models, thereby hindering HCC progression. **Conclusion:** MicroRNA-223 plays a critical role in modulating hypoxia-induced tumor immunosuppression and angiogenesis, which may serve as a novel therapeutic target for HCC.



Disclosures: The following people have nothing to disclose: Yaojie Fu

f 4207-A | MIRABEGRON LIMITS HCC PROGRESS UNDER HIGH-FATTY TUMOR MICROENVIRONMENT VIA ACTIVATION OF ADIPOSE BROWNING

Juan Gao, Karolinska Institutet; The Third Affiliated Hospital of Sun Yat-Sen University

Background: Obesity, a metabolic syndrome (MS) with increasing incidence worldwide, is also a high-risk factor for various tumors. Metabolic associate fatty liver disease was considered as the liver manifestations of MS. Systematic free fatty acids (FFAs) accumulation leads to tumor progress by inducing the tumor's metabolic reprogramming. Our previous studies suggested cold exposure suppresses tumor growth by brown fat activation alters global metabolism (Seki et al., 2022, Nature 608). Brown fat activation is a promising therapeutic approach to reverse systematic metabolic disorders and reshape the metabolism of tumor microenvironment. Mirabegron, a β3-adrenoreceptor agonist approved for treating overactive bladder syndrome in patients, was indicated as an

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activator the brown adipose and triggers of white adipose beigeing (Sui W, et al. PNAS. 2019 May). We are interested in how the host metabolism reshapes the hepatocellular carcinoma (HCC) microenvironment. We also gain insight into the potential mechanisms of the combination of metabolic stimulators and existing drug therapies. **Methods:** To establish metabolic abnormalities in animal models, adult male C57BL/6N mice were fed with high-fat diet (HFD, 60% fat calories) for more than 3 months to reach obesity and liver steatosis. Hepa1-6 hepatocarcinoma cells were implanted in the mice's liver under inhaling anaesthetization as the orthotopic HCC models. Approximately 1 week after tumor implantation, mice were randomly grouped. 1mg/kg mirabegron or equivalent vehicle (PEG) were orally administrated to mice for 8 weeks. Then mice were sacrificed, blood, liver with tumor and adipose tissue were collected for histological and biochemistry analysis. **Results:** Compared to the vehicle group, the body weight and BMI of obese mice showed a reduce in the mirabegron group in the second week, with noticeable differences between the two groups ($p < 0.05$) after 8 weeks of treatment. Histological analysis of brown adipose tissue supported an activated phenotype in the mirabegron group, which comprised the smaller diameter of lipid droplets in adipocytes. The tumor volumes of HCC were limited in the mirabegron group than in the vehicle group ($p < 0.05$). Furthermore, histopathology showed that the liver steatosis was relieved in the mirabegron group ($p < 0.01$). And cell proliferation and fatty acid uptake of the tumor were decreased in the mirabegron group, showed by IHC staining of KI67 ($p < 0.01$) and CD36 ($p < 0.05$). Besides, qPCR indicated that several metabolic-related genes were downregulated in the tumors of the mirabegron-treated group, such as *cd36* ($p < 0.001$), *fabp4* ($p < 0.001$), *plin2* ($p < 0.05$) and *glut1* ($p < 0.001$). **Conclusion:** Mirabegron limits HCC progress under high-fatty tumor microenvironment via activation of adipose browning. The combination of adipose activators and other therapies may contribute to better outcomes in HCC patients with metabolic disorders.

Disclosures: The following people have nothing to disclose: Juan Gao

4208-A | MITOCHONDRIAL BIOENERGETIC CAPACITY DICTATES THE PROLIFERATIVE POTENTIAL OF HUMAN HEPATOCELLULAR CARCINOMA CELLS

Elizabeth R M Zunica, Christopher L Axelrod and John P Kirwan, Pennington Biomedical Research Center

Background: Hepatocellular carcinoma (HCC) is the most frequent primary hepatic malignancy, with limited therapeutic options for most patients, and thus, a leading cause of global cancer-related death. Mitochondrial efficiency is essential to cancer survival and progression by supplying the energy and macromolecules requisite to initiate and sustain growth and is implicated as a key mediator of plasticity and drug resistance. Here, we evaluated the extent by which mitochondrial efficiency contributes to HCC cell growth by using a pharmacological uncoupler of oxidative phosphorylation (OXPHOS) to restrict bioenergetic efficiency. **Methods:** Bioenergetic efficiency was evaluated by high-resolution respirometry and extracellular acidification monitoring in non-malignant hepatocytes (AML12) and a malignant HCC (HEPG2) line. Dose-response relationships between BAM15, a mitochondrially-targeted uncoupler, and proliferation/apoptosis were determined by light microscopy and Caspase 3-7 activity assay with Sorafenib as a validation agent. Cell viability was then simultaneously measured in 17 human immortalized HCC cell lines using a DNA-barcode multiplexed profiling after exposure to BAM15. **Results:** HCC cells displayed a classical Warburg-like energetic phenotype with downregulated OXPHOS and upregulated glycolysis. Loss of OXPHOS capacity in HCC was predominantly associated with impaired succinate oxidation, which serves as the primary coupling control pathway in hepatocytes. We observed that in HEPG2 cells, BAM15 decreased cell proliferation in the low, micromolar range, with an $IC_{50} = 3.7$ μM. Furthermore, we observed that in HEPG2 cells, BAM15 more effectively and sensitively induced cellular apoptosis than Sorafenib. From lineage-based screening, we observed that the anti-proliferative effects of BAM15 were not cell-line specific, with a median $IC_{50} = 2.9$ μM and ~85% with $IC_{50} < 4$ μM across HCC's, consistent with HEPG2 cells. **Conclusion:** HCC is associated with loss of OXPHOS capacity via impairments in succinate-linked coupling of ATP synthesis. Congruently, restricting bioenergetic efficiency broadly impairs proliferative potential and induces apoptosis in HCC. Taken together, these data support bioenergetic efficiency as a potentially druggable metabolic process to treat HCC.

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4209-A | ORAL SMALL-MOLECULE LIVER-TROPIC PD-L1 INHIBITOR PHARMACOKINETICS FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA

Arpita Mondal, Emily P. Thi, Ingrid Graves, Gavin Heffernan, Fran Xu, Seyma Ozturk, Amanda Pohl, Kristi Y. Fan, Andrew Cole, Troy Harasym, Angela M. Lam

and Michael J. Sofia, Arbutus Biopharma, Warminster, PA

Background: Hepatocellular carcinoma (HCC) is a global challenge due to its high morbidity and mortality rate. The standard of care for advanced HCC in front line and second line therapy consists of two distinct systemic approaches: tyrosine-kinase and immune checkpoint inhibitors; however, relapses and dose-limiting tolerability associated with systemic adverse events following treatment with either therapy have been observed. Development of oral, tissue-tropic immune checkpoint small-molecule inhibitors that could facilitate ease of administration, exhibit better tissue penetration, and reduce systemic exposure may potentially result in improved efficacy for advanced HCC with reduced systemic toxicity. As a preclinical proof-of-concept, small-molecule PD-L1 inhibitors with differential liver and plasma pharmacokinetic profiles were evaluated in a novel orthotopic syngeneic immunocompetent HCC model to evaluate the correlation between pharmacokinetics and anti-tumor efficacy. **Methods:** A H22 mouse hepatoma cell line expressing human PD-L1 and luciferase was generated and cells were intrahepatically transplanted into BALB/c-hPD-1/hPD-L1 double knock-in mice to develop a humanized orthotopic syngeneic HCC model. Animals were orally administered small-molecule human PD-L1 inhibitors once-daily for 26 days, and tumor growth was monitored by *in vivo* bioluminescence imaging. Target occupancy in tumors was determined by flow cytometry. Additionally, the combination of a small-molecule PD-L1 inhibitor with VEGFR2-TIE2 inhibitor regorafenib was also assessed. **Results:** 88% of tumor-bearing mice demonstrated 80% or higher tumor growth inhibition (TGI) after 26 days of oral treatment with a small-molecule PD-L1 inhibitor either alone or in combination with regorafenib. For the small-molecule PD-L1 inhibitors tested, higher liver concentrations and high liver-to-plasma ratio was associated with increased efficacy in this orthotopic HCC mouse model. Efficacy was associated with $\geq$ 60% PD-L1 target occupancy in animals treated with small-molecule PD-L1 inhibitors. **Conclusion:** Treatment with oral small-molecule PD-L1 inhibitors possessing liver-tropic pharmacokinetic profiles was associated with increased efficacy and tumor clearance in a novel humanized orthotopic HCC mouse model. These data suggest that development of small-molecule PD-L1 inhibitors with biodistribution to the liver may provide benefit in the treatment of HCC.

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Disclosure information not available at the time of publication: Ingrid Graves, Gavin Heffernan, Fran Xu, Seyma Ozturk, Amanda Pohl, Kristi Y. Fan, Andrew Cole, Troy Harasym, Angela M. Lam, Michael J. Sofia

4210-A | PGAM5 KNOCKOUT IN HEPATOCELLULAR CARCINOMA CELLS REDUCES FABP1 EXPRESSION AND LONG-CHAIN FATTY ACID UPTAKE

Andrea N. Johnston, Chin-Chi Liu and Ganesan Muthusamy, Louisiana State University

Background: Overexpression of tumoral phosphoglycerate mutase 5 (PGAM5), the Ser/His/Thr phosphatase, is correlated with reduced survival in hepatocellular carcinoma, colon cancer, and melanoma. In hepatocellular carcinoma, interference with PGAM5 expression reduces tumor growth. This phenotype has been attributed to decreased mitophagy and promotion of apoptosis, but whether PGAM5 influences lipid metabolism in hepatocellular carcinoma, as it does in colon cancer, is unexplored. **Methods:** ATP production, cell growth, and long-chain fatty acid uptake were measured in wild type and PGAM5 knockout HepG2 and Huh7 cells. Expression of hepatocellular fatty acid transporters, CD36, SLC27A2, SLC27A5, and FABP1, was measured by real-time qPCR and Western blot. **Results:** Deletion of PGAM5 attenuates hepatocellular carcinoma cell growth and ATP production. PGAM5 knockout reduced palmitate induced steatosis and expression of FABP1 in HepG2 and Huh7 cell lines. **Conclusion:** PGAM5 regulates fatty acid metabolism in hepatocellular carcinoma. Downregulation of the fatty acid transporter FABP1 caused by PGAM5 knockout, may be responsible for reduced long-chain fatty acid uptake and a dysregulated intracellular lipidome.

Disclosures: The following people have nothing to disclose: Andrea N. Johnston

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4211-A | PHARMACOLOGICAL INHIBITION OF INDOLEAMINE 2, 3-DIOXYGENASE (IDO1) FOR IMMUNO-PREVENTION OF NAFLD-RELATED HCC

Sumit Kumar Mishra[1], Subhojit Paul[1], Hiroyuki Suzuki[2], Arun Kumar Jajoriya[1], Naoto Kubota[3], Asim Hassan[1], Courtney Katz[1], Cesia A. Marquez[1], Indu Raman[1], Prithvi Raj[1], Nicole E. Rich[4], Hao Zhu[1], Amit G. Singal[4],

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Adam C. Yopp[4], Emilie Crouchet[5], Thomas F. Baumert[5], Naoto Fujiwara[1] and Yujin Hoshida[1], (1)UT Southwestern Medical Center, Dallas, USA, (2)Kurume University School of Medicine, Japan, (3)Keio University School of Medicine, Tokyo, Japan, (4) University of Texas Southwestern Medical Center, (5) University of Strasbourg, Inserm, Institut De Recherche Sur Les Maladies Virales Et Hépatiques Umr-S1110, 67000 Strasbourg, France

Background: Prevention of NAFLD-related HCC is an urgent unmet need. Our previous study in NAFLD cirrhosis patient cohorts identified a transcriptomic signature of HCC risk (Prognostic Liver Signature [PLS]-NAFLD) and IDO1+ dendritic cells in the fibrotic portal tracts as a candidate target that may be treated with a small molecule inhibitor, epacadostat, under clinical development in various solid cancers. **Methods:** Epacadostat was orally given (50 mg/kg, 5 d/week) to CDA/HFD rats ($n = 10$ per arm for each sex) for 8 weeks after establishing cirrhosis and before developing HCC. Tumor number, histology including NAS components, and immunostaining of relevant immune cell markers were assessed. Bulk and single-nuclei RNA-seq of liver tissues and metagenomic 16S rRNA-seq of stool, liver, and blood samples were conducted. Organotypic ex vivo culture of precision-cut liver slice (PCLS) from NAFLD patients was also performed. **Results:** Fewer tumor nodules were observed in the epacadostat-treated rats compared to the vehicle controls irrespective of tumor size ($p = 0.03$). The chemopreventive effect was more prominent in male ($p = 0.02$) compared to female ($p = 0.45$) rats. Of note, amelioration of hepatocyte injury (measured by AST/ALT) was minimal. Reduction of liver fibrosis was measurable only by Sirius red-based collagen proportionate area but not fibrosis staging. There was a trend of reduction of in the number of IDO1$^+$ cells in fibrotic tissues near the portal tracts. RNA-seq of liver tissues revealed modulation of immune-suppressive tissue microenvironment that involves certain subsets of macrophages, Tregs, T cells, and NK cells. Sex difference in modulation of gut dysbiosis was observed. In the ex vivo clinical PCLS culture, epacadostat modulated high-risk pattern of PLS-NAFLD signature in a subset of patients, supporting its clinical relevance. **Conclusion:** Our pre-clinical study suggests that epacadostat is a candidate HCC immuno-preventive agent to be considered for early clinical testing in NAFLD patients at risk of developing HCC.

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Thomas F. Baumert – Alentis Therapeutics: Advisor, No, No;

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4212-A | PREDICTING THE EFFICACY OF COMBINATION CHEMOTHERAPY FOR ADVANCED HEPATOCELLULAR CARCINOMA BY TUMOR IMMUNE MICROENVIRONMENTAL ANALYSIS

Shuhei Yamamoto[1], Takahiro Kodama[1], Kazuki Maesaka[1], Akifumi Kuwano[2], Kenta Motomura[2], Akira Doi[1], Yuki Tahata[1], Akira Nishio[1], Hayato Hikita[1], Tomohide Tatsumi[1] and Tetsuo Takehara[1], (1)Osaka University Graduate School of Medicine, (2)Iizuka Hospital

Background: Atezolizumab/bevacizumab (Atezo/Bev) combination immunotherapy became the first line therapy of advanced hepatocellular carcinoma (HCC). However, about 20% of patients are non-responders. We explored predictors of therapeutic efficacy of Atezo/Bev by analyzing tumor immune microenvironment. **Methods:** Total 23 advanced HCC patients who underwent liver tumor biopsy prior to Atezo/Bev therapy were enrolled in this study. RNA-seq of tumor biopsy specimens was performed and the relationship between transcriptome data and treatment response was investigated. We utilized transposon-based intrahepatic delivery of a pooled 10-oncogene cDNA library via hydrodynamic tail vein injection (HTVi), resulting in multiple genetically-heterogenous HCC formation in wild-type mice. We treated these mice with either vehicle or combination immunotherapy using anti-PD-L1 and anti-VEGF antibodies, and sought for secreted factors elevated in the immunotherapy-sensitive or resistant tumors. **Results:** The response rate of 23 HCC patients was 43.5% by mRECIST and the median progression-free survival (PFS) was 167 days. RNA-seq results showed that the gene expression related to T cell migration, activation, and exhaustion were significantly higher in responders compared to non-responders. Gene signature analysis showed that effector T cells were abundant in responder. The Interferon and antigen-presentation (IFNAP) signature, Atezolizumab Bevacizumab response signature (ABRS), Immune signature, T cell exhaustion signature were higher in responder than non-responders. PFS was significantly prolonged in patients with high ABRS scores compared to those with low ABRS scores. Single set gene set enrichment analysis showed activation of antigen processing and presentation mechanisms, Jak/Stat signaling pathway, B cell and T cell signaling pathways, and chemokine signaling pathway in responders, but no correlation with WNT signaling pathway. In HCC mouse models, combination immunotherapy suppressed angiogenesis, increased CD8T cells, CD4T cells, and dendritic cell markers within the tumor, and prolonged survival. Treatment-resistant tumors showed poor lymphocytic infiltration (TIL) within the tumor and significant downregulation of various MHC class I and II molecules. **Conclusion:** In advanced hepatocellular carcinoma, the presence of TILs may be important for response to ATZ/BEV therapy.

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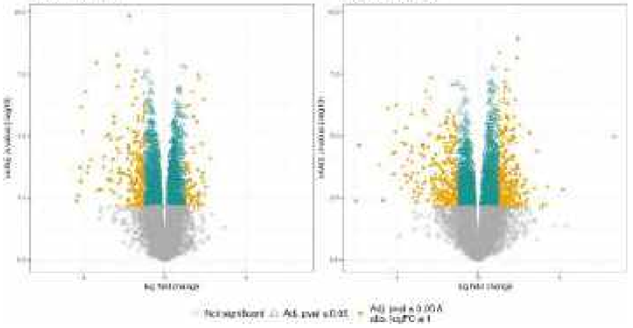
The following people have nothing to disclose: Shuhei Yamamoto, Takahiro Kodama, Akira Doi, Yuki Tahata, Akira Nishio, Hayato Hikita, Tomohide Tatsumi, Tetsuo Takehara

Disclosure information not available at the time of publication: Akifumi Kuwano, Kenta Motomura

4213-A | RACE-RELATED DIFFERENTIAL ALTERNATIVE RNA SPLICING OF POLYBROMO 1 (PBRM1) IN HEPATOCELLULAR CARCINOMA

Kara Wegermann[1], Bonnie LaCroix[2], Kathleen Cuprak[3], Tyler Allen[2], Nicholas O'Grady[2], Rachel A Myers[2], Cynthia Moylan[2], Anna Mae Diehl[2], So Young Kim[2], Muthana Al Abo[2], Steven Patierno[2] and Jennifer Freedman[2], (1)Duke University, Hillsborough, NC, (2) Duke University, (3)Q2 Solutions

Background: Racial disparities in outcomes of hepatocellular carcinoma (HCC) are multifactorial. We previously reported differential alternative RNA splicing between HCC from Black and White patients in The Cancer Genome Atlas (TCGA). One of these events was exon 28-29 skipping in polybromo 1 (*PBRM1*), which participates in chromatin remodeling. The aim of this study was to assess whether expression of race-related *PBRM1* splice variants affected HCC cell biology and/or transcriptome. **Methods:** CRISPR-Cas9 genome editing of Huh7 and Hep3B HCC cells was performed to generate pools expressing *PBRM1* skipping exons 28-29. Single cell clones were isolated using single cell plating and limiting dilution. Incucyte proliferation and migration (WoundMaker) assays and RNAseq using total RNA were used to compare phenotypes of parental and edited cells. **Results:** CRISPR-Cas9 edited single cell clones did not express *PBRM1* exons 28-29. No overall differences in proliferation or migration between parental and edited cells were observed. For Huh7 and Hep3B, as shown in Figure 1, 280 genes (71 upregulated, 209 downregulated) and 530 genes (278 upregulated, 252 downregulated), respectively, were differentially expressed between parental and edited cells (adjusted p-value $<$ 0.05, log FC of at least +/- 1). 32 genes were differentially expressed in both Hep3B and Huh7 between parental and edited cells. Among the most significant were amphiregulin (*AREG)*, a member of the *EGF* family, apolipoprotein B mRNA editing enzyme catalytic subunit 3C (*APOBEC3C*), an RNA editing enzyme, and 3-hydroxy-3-methylglutaryl-CoA synthase 1 (*HMGCS1*), an enzyme in the mevalonate pathway that is inhibited by metformin. Each was previously linked to survival in HCC. Genes with large fold change included plasminogen activator inhibitor-1 (*SERPINE1*), which inhibits fibrinolysis and has roles in cell adhesion and migration, and solute carrier family 51 subunit beta (*SLC51B*), a bile acid transporter. Gene set enrichment analysis using clusterProfiler with all genes over each cell line and splicing event revealed significant enrichment in 106 (Huh7) and 10 (Hep3B) KEGG pathways. **Conclusion:** CRISPR-Cas9 genome editing to generate Huh7 and Hep3B cells expressing a differential alternative RNA splicing event between HCC from Black and White patients in TCGA *(PBRM1* skipping exons 28-29) resulted in significant changes in aggregate gene expression, without altering cell proliferation or migration. Race-related differential alternative RNA splicing of *PBRM1* may have implications for HCC biology and disparities. Acknowledgements: The authors gratefully acknowledge the contributions of Taylor Ackley and Malarie Schexnider.



Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

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Disclosure information not available at the time of publication: Bonnie LaCroix, Kathleen Cuprak, Tyler Allen, Nicholas O'Grady, Rachel A Myers, So Young Kim, Muthana Al Abo, Steven Patierno, Jennifer Freedman

4214-A | ROLE OF ACYL-CoA MEDIUM-CHAIN SYNTHETASE 5 IN HEPATOCELLULAR CARCINOMA

Lei Yang, Kien Pham, Yibo Xi and Chen Liu, Yale University, New Haven, CT

Background: Liver cancer is a significant public health concern as it is the second leading cause of cancer-related deaths worldwide. Hepatocellular carcinoma (HCC) is the most common type of liver cancer, and despite advances in treatment, it remains a malignancy with a poor prognosis. Understanding the molecular mechanisms underlying HCC is essential for developing effective treatments. Acyl-CoA medium-chain synthetase 5 (ACSM5), an enzyme involved in fatty acid metabolism, is downregulated in HCC, but its oncogenic roles in this cancer are not well understood. **Methods:** In the study, we analyzed the expression levels of ACSM5 in HCC patient samples and cell lines. The *in vitro* and *in vivo* effects and regulatory mechanisms of ACSM5 were investigated with a newly established ACSM5-overexpressing stable HCC cell line, Huh7-ACSM5. **Results:** Our results showed that ACSM5 was downregulated in HCC patient samples, as well as in Huh7 and HepG2 cells. Overexpression of ACSM5 in Huh7 cells led to decreased proliferation and migration in vitro, reduced cell colony formation capacity, and inhibited tumor growth in mouse xenografts. Furthermore, we found that overexpression of ACSM5 reduced the phosphorylation of STAT3, which, in turn, regulated TGF-β expression. **Conclusion:** Our findings suggest that ACSM5 downregulation may contribute to the development of HCC, providing new insights into the oncogenic role of ACSM5 in HCC and highlighting its relevance as a potential biomarker and therapeutic target for this deadly cancer.

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4215-A | SELECTIVE PAD4 INHIBITION DELAYS METASTATIC TUMOR GROWTH IN THE LIVER BY MODULATING THE HEPATIC TUMOR MICROENVIRONMENT

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Background: Liver metastasis is the most important determinant for patients with pancreatic ductal adenocarcinoma (PDAC) and colorectal cancer (CRC). Liver microenvironment affected by underlying liver disease, such as alcoholic liver disease, can impact the progression of liver metastasis. However, the molecular mechanism of liver metastasis affected by underlying liver disease is not fully understood. Infiltration of neutrophils is a typical feature of alcoholic liver disease, and neutrophils can change hepatic microenvironment. Peptidylarginine deiminase 4 (PAD4) is an enzyme primarily expressed in neutrophils, and is involved in protein citrullination that contributes to neutrophil extracellular traps (NETs) formation and modulate extracellular matrix, such as collagen. In this study, we investigated the role of PAD4 in liver metastasis using a novel PAD4 inhibitor in development by Jubilant Therapeutics Inc. **Methods:** C57BL/6 wild-type or neutrophil-specific PAD4-deleted mice were intrasplenically injected with either mouse PDAC Pan02 or CRC MC38 cells to develop liver metastasis. Neutrophil-specific PAD4-deleted mice were generated by crossing Pad4 flox mice with MRP8-Cre mice. A novel PAD4 selective inhibitor, JBI-1044, was administered twice daily via oral gavage. Alcoholic liver injury was induced by feeding mice either an isocaloric or 5% (v/v) ethanol Lieber-DeCarli diet for 6 weeks. **Results:** Chronic ethanol feeding exacerbated liver metastasis along with increased PAD4 expression, neutrophil infiltration and collagen deposition, as well as decreased survival rate of tumor-bearing mice. In contrast, PAD4 deletion in neutrophils suppressed metastatic tumor growth in the liver by suppressing neutrophil infiltration and collagen deposition. Selective inhibition of PAD4 with JBI-1044 significantly improved the survival of mice bearing PDAC or CRC tumors in the liver by reducing their metastatic burden. Pad4 inhibition resulted in decreased neutrophil infiltration and collagen accumulation. The levels of citrullinated type 1 collagen were also reduced by PAD4 inhibition. **Conclusion:** PAD4 expression is associated with the progression of PDAC and CRC liver metastasis. PAD4 plays pivotal roles in reshaping liver tumor microenvironment through the modulation of neutrophil functions and collagen deposition. PAD4 inhibition by JBI-1044 suppressed liver metastasis, providing new insight of potential therapies targeting PAD4 in PDAC and CRC liver metastasis.

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Disclosure information not available at the time of publication: Dhanalakshmi Sivanandhan, Luca Rastelli

4216-A | SELECTIVE TARGETING OF INTEGRIN avβ8 EFFECTIVELY SUPPRESSES TUMOR GROWTH IN THE NEW PSC-ASSOCIATED CHOLANGIOCARCINOMA MODEL (SB CCA.Mdr2-/- MOUSE)

Pinzhu Huang[1], Wen Gao[1], Heansika Matta[1], Disha Skelton-Badlani[1], Natalia Blanco[2], Min Lu[2], Blaise Lippa[2], Bruce N Rogers[2] and Yury V. Popov[1], (1)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (2)Morphic Therapeutics

Background: We have established a new model of cholangiocarcinoma (CCA) in Mdr2-/- with primary sclerosis cholangitis (PSC)-like disease (termed SB CCA.*Mdr2-/-*) which recapitulates predisposition to CCA in human PSC. Systemic TGF-β blockade has been reported to enhance anti-tumor efficacy of immune checkpoint inhibitors, but its development has been hindered by systemic toxicity. Here we report therapeutic efficacy of selective antibody targeting of TGFb-activating integrins avβ6 and avβ8 in comparison to pan-TGFb inhibition in our SB CCA. *Mdr2-/-* model. **Methods:** Ten-week old Mdr2-/- mice with advanced congenital PSC-like progressive biliary disease were subjected to hydrodynamic tail vein injection of sleeping beauty transposon-transposase system with activated forms of AKT (myr-AKT) and Yap (YapS127A). Neutralizing antibodies for pan-TGF-β (1D11), integrin avβ8 (C6D4), or integrin avb6 (3G9) alone and with anti-PD-1 mAb were administered into tumor-bearing mice 1-4 weeks post transduction, in comparison to IgG control or anti-PD1(n = 10-16/group). Expression of TGF-β1, integrin β6, PD-1, PD-L1, and CK7 were analyzed by immunohistochemistry (IHC), integrin β8 was determined by in situ hybridization. Tumor burden was analyzed by CK7+ tumor numbers and mRNA levels of AKT and YAP1. Desmoplastic stroma of the tumors was analyzed via Sirius Red morphometry. **Results:** In our SB CCA.*Mdr2-/-* model, TGF-β1 expression was prevalent in all CCA tumors and 88.2% of CCA tumors expressed various levels of integrin b6 and were positive for integrin β8 mRNA. PD-L1+ tumor cells, PD-1+ and CD8+ infiltrating lymphocytes were enriched in desmoplastic CCA tumors. However, anti-PD-1 alone was not efficacious. Monotherapy with 1D11 or 3G9 led to a trend of decreased tumor burden, but only C6D4 significantly reduced tumor growth (CK7+ tumor numbers) compared to the IgG group (30.00 ± 4.68 vs. 59.87 ± 5.67, $p = 0.0109$). Combination of 1D11/anti-PD-1 showed only a trend to enhance the efficacy of pan-TGFb mAb alone.

Interestingly, C6D4/anti-PD-1and 3G9 /anti-PD-1 combinations did not show synergistic anti-tumor activity. Tumor burden assessed by mRNA levels of transgene oncogenes YAP1/AKT or morphometric analysis of CK7+ tumors showed that monotherapy with the C6D4 alone was superior to combination therapy with anti-PD-1 as a CCA treatment. Collagen morphometric analysis showed that the 1D11 potently attenuated desmoplastic reaction in all CCA tumors. Integrin avβ8- or avβ6-targeting resulted in diminished desmoplastic reaction in only a subset (about 50%) of tumors, which suggested that anti-tumor efficacy was not primarily driven by suppression of desmoplastic tumor stroma. **Conclusion:** We show that integrin avβ8 is required for desmoplastic CCA growth and represents a novel therapeutic target for CCA. These data support clinical development of avβ8 integrin-selective inhibitors for CCA.

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Disclosure information not available at the time of publication: Natalia Blanco, Min Lu, Blaise Lippa, Bruce N Rogers

4217-A | SORT1 PROMOTE THE METASTASIS AND INVASION OF HEPATOCELLULAR CARCINOMA VIA P38/Β-CATENIN/ZEB1 SIGNALING PATHWAY

Hongjie Chen[1], Shaohang Cai[1], Jie Peng[1], Chen Shuwei[2], Wei Liao[2] and Lili Liu[2], (1)Nanfang Hospital, Southern Medical University, (2)Sun Yat-Sen University Cancer Center

Background: Metastasis stands as the primary determinant of the dismal prognosis observed in hepatocellular carcinoma (HCC) patients. Hence, unraveling the intricate molecular mechanisms governing hepatocellular carcinoma (HCC) metastasis is of paramount importance in the field. **Methods:** We conducted an analysis of SORT1 expression in a tissue microarray (TMA) consisting of 781 HCC samples. The impact of SORT1 on HCC onset and progression was investigated both in vivo and in vitro. **Results:** Elevated SORT1 expression was positively correlated with increased tumor number, advanced TNM stage and vascular invasion. Mechanistically, SORT1 binds to p38 and enhances its stability. Furthermore, p38 phosphorylate GSK-3β at Ser9, which promotes nuclear accumulation of β-catenin, leading to the transcription of ZEB1 and secretion of exosomes. Knockdown of SORT1 and ZEB1 inhibited HCC metastasis, whereas upregulation of ZEB1 restored SORT1 knockdown-induced suppression of HCC metastasis. SORT1 is regulated by SREBP2 through protein-protein interaction, as confirmed by IP-MS, CO-IP, immunofluorescence, and CHX experiments. **Conclusion:** In light of these results, SORT1 as a potential prognostic biomarker in HCC and targeting p38/β-catenin signaling pathway, could be an effective therapeutic strategy against HCC metastasis.

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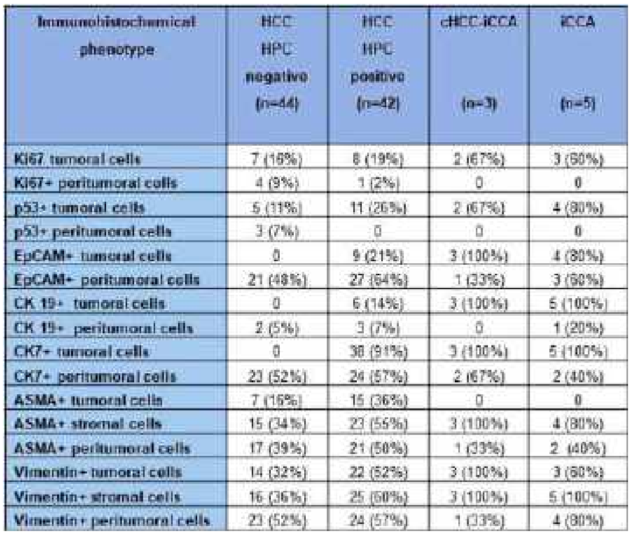
4218-A | STEMNESS AND EPITHELIAL-MESENCHYMAL TRANSITION CONTINUITY IN PRIMARY LIVER CARCINOMAS SPECTRUM

Joana Espírito Santo[1,2], Ana Ladeirinha[2], Ana Alarcão[2], Eugeniu Strelet[3], Marco Reis[3], Rui Santos[1] and Lina Carvalho[1,2], (1)Coimbra Hospital and University Centre, (2)Faculty of Medicine, University of Coimbra, (3) Department of Chemical Engineering, University of Coimbra

Background: Tumor cell plasticity promotes primary liver carcinomas (PLC) cellular heterogeneity and is likely to contribute to therapy resistance. Hepatocellular carcinomas (HCCs), combined hepatocellular-cholangiocarcinomas (cHCC-CCAs) and intrahepatic cholangiocarcinomas (iCCAs) are composed of different degrees of hepatocytic and/or cholangiocytic differentiation, often displaying stemness and epithelial-mesenchymal transition (EMT) features. We aimed to analyze the expression of hepatic progenitor cells (HPC) and mesenchymal markers across the PLC spectrum. **Methods:** A series of 44 HCCs without HPC features, 42 HCCs with at least one HPC immunomarker expressed, 3 cHCC-iCCAs and 5 small-duct type iCCAs was studied. World Health Organization 2019 histopathological criteria were applied; proliferation (ki67;p53) HPC/cholangiocytic (EpCAM/BerEp4; CK19; CK7) and mesenchymal (ASMA; vimentin) markers immunoexpression was searched in tumor and peritumoral parenchyma. **Results:** Thirty-six HCCsHPC-, 38 HCCsHPC+, 2 cHCC-iCCAs and 3 iCCAs developed in a cirrhotic background; alcoholic liver disease was the dominant etiology and metabolic associated fatty liver disease was relevant in HCCHPC- and iCCA cases. Moderately differentiated tumors (G2) prevailed across the spectrum. Distinct immunoexpressions ($p < 0.05$) were reported (Table 1):

- Ki67 positive tumor cells were less frequent in HCCsHPC- (n = 7) when compared with HCCsHPC + (n = 8), cHCC-iCCAs (n = 2) and iCCAs (n = 3);
- p53 tumoral expression was predominant in iCCAs (n = 4) in comparison with HCCsHPC+ (n = 11) and HCCsHPC- (n = 5);
- EpCAM expression predominated in cHCC-iCCAs (n = 3) and in iCCAs (n = 4), but no difference was observed in between the 2 groups of carcinomas;
- CK19 and CK7 expression prevailed in cHCC-iCCAs and iCCAs, with CK7 expression being more frequent than CK9 expression in HCCsHPC+ (n = 6 vs n = 38);
- ASMA positive tumoral cells were mostly seen in HCCsHPC+ (n = 15), however ASMA expression in stromal cells was more prevalent in cHCC-iCCAS (n = 3) and in iCCAs (n = 4);
- HCCsHPC- (n = 14) expressed vimentin in tumor cells less frequently than cHCC-iCCAs (n = 3), while vimentin stromal cells expression was progressively more frequent in HCCsHPC+ (n = 25) and in cHCC-iCCAs (n = 3) and iCCAs (n = 5).

Conclusion: Stemness and EMT continuity in PLC seems to be reflected by a gain of tumoral HPC and vimentin expression and ASMA and vimentin stromal expression from HCCsHPC+ to iCCAs, where combined tumors are likely to be closer to iCCAs rather than to HCCs. This study emphasizes the translational relevance of understanding tumor cell plasticity in relation to stemness and EMT during PLC carcinogenesis.



Immunohistochemical phenotype	HCC HPC negative (n=44)	HCC HPC positive (n=42)	cHCC-iCCA (n=3)	iCCA (n=5)
Ki67 tumoral cells	7 (16%)	8 (19%)	2 (67%)	3 (60%)
Ki67+ peritumoral cells	4 (9%)	1 (2%)	0	0
p53+ tumoral cells	5 (11%)	11 (26%)	2 (67%)	4 (80%)
p53+ peritumoral cells	3 (7%)	0	0	0
EpCAM+ tumoral cells	0	9 (21%)	3 (100%)	4 (80%)
EpCAM+ peritumoral cells	21 (48%)	27 (64%)	1 (33%)	3 (60%)
CK 19+ tumoral cells	0	6 (14%)	3 (100%)	5 (100%)
CK 19+ peritumoral cells	2 (5%)	3 (7%)	0	1 (20%)
CK7+ tumoral cells	0	38 (91%)	3 (100%)	5 (100%)
CK7+ peritumoral cells	23 (52%)	24 (57%)	2 (67%)	2 (40%)
ASMA+ tumoral cells	7 (16%)	15 (36%)	0	0
ASMA+ stromal cells	15 (34%)	23 (55%)	3 (100%)	4 (80%)
ASMA+ peritumoral cells	17 (39%)	21 (50%)	1 (33%)	2 (40%)
Vimentin+ tumoral cells	14 (32%)	22 (52%)	3 (100%)	3 (60%)
Vimentin+ stromal cells	16 (36%)	25 (60%)	3 (100%)	5 (100%)
Vimentin+ peritumoral cells	23 (52%)	24 (57%)	1 (33%)	4 (80%)

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4219-A | TARGETING CDK5/PAK1 ATTENUATES LIPID OVERLOAD-INDUCED HEPATOCELLULAR CARCINOMA VIA SUPPRESSING LYSOSOMAL STRESS-DEPENDENT M2 MACROPHAGE TRANSITION.

Tongguo Miao[1], Ying Zhang[1], Xianzhe Lou[2], Weiwei Guan[1], Lu Li[1], Xiwei Yuan[1] and Yuemin Nan[1], (1)Third Hospital of Hebei Medical University & Hebei Key Laboratory of Mechanism of Liver Fibrosis in Chronic Liver Disease, (2) North China University of Science and Technology

Background: Immunotherapy has revolutionized cancer treatment. Unfortunately, most tumor types do not respond to immunotherapy due to a lack of enhancing inflammation in tumor microenvironment (TME), a contributing factor is lysosomal stress (LS). How LS impacts the TME remains understudy. **Methods:** We investigated the role of the CDK5/PAK1 pathway in the regulation of lysosomal stress in hepatocellular carcinoma (HCC) development by conducting metabolomic analysis, gene expression profiling and immunohistochemistry analyses in RAW264.7 cells, oncogene-induced HCC mouse models and human HCC samples. **Results:** We investigated the role of the CDK5/PAK1 pathway in the regulation of lysosomal stress in hepatocellular carcinoma (HCC) development by conducting metabolomic analysis, gene expression profiling and immunohistochemistry analyses in RAW264.7 cells, oncogene-induced HCC mouse models and human HCC samples. **Conclusion:** This study suggests that CDK5/PAK1 pathway inhibition is a potential approach to broaden immunity therapies by suppressing lipid overload-mediated, LS-dependent M2 transition and supports the translation of this novel approach to further improve response rates for proliferation and metastatic hepatocellular carcinoma.
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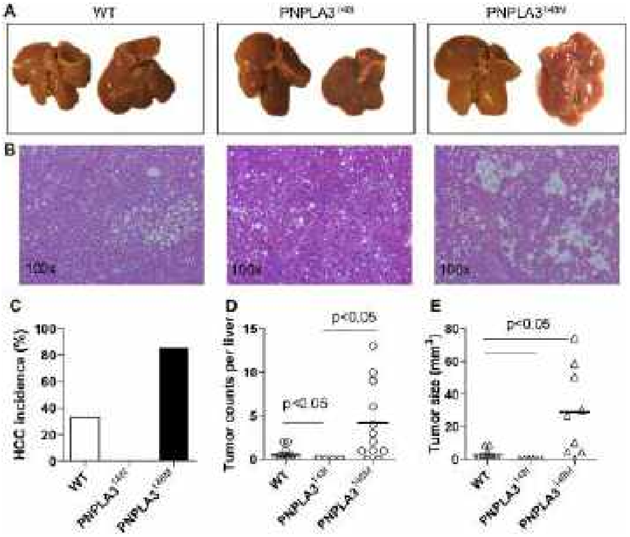
The following people have nothing to disclose: Tongguo Miao, Ying Zhang, Xianzhe Lou, Weiwei Guan, Lu Li, Xiwei Yuan

4220-A | THE PNPLA3 rs738409 VARIANT EXACERBATES ALCOHOL-ASSOCIATED LIVER CANCER DEVELOPMENT

Jung-Hyo Cho[1], Hyeong-Geug Kim[2], Chang-Hyun Gil[2], Alex Lu[3], Sheng Liu[2], Menghao Huang[4], Wenjun Zhang[5], Burcin Ekser[2], Wanqing Liu[6], Jun Wan[2] and X Charlie Dong[2], (1)Daejeon University, (2)Indiana University School of Medicine, (3)Park Tudor School, (4) Indiana University School of Medicine, Indianapolis, IN, (5) *Division of Transplant Surgery, Department of Surgery, University School of Medicine, (6)Wayne State University*

Background: The human PNPLA3 rs738409 variant encoding methionine at residue 148, commonly known as 148M variant, has been implicated in a broad spectrum of liver diseases including alcoholic and nonalcoholic fatty liver diseases; however, its role in alcohol-associated liver cancer pathogenesis remains elusive. **Methods:** To investigate the impact of the PNPLA3-148M variant on alcohol-associated liver cancer, we treated control and PNPLA3-148M transgenic mice with 5% ethanol diet for 12 weeks plus once a week carbon tetrachloride injection for 10 weeks. Liver histology was analyzed after animal euthanasia. Cancer-related genes and pathways were analyzed by RNA-seq and confirmed by immunoblotting. Tumor microenvironment was analyzed by spatial transcriptomics. **Results:** After the 12-week ethanol diet feeding, PNPLA3-148M transgenic mice developed multi-nodule hepatocellular carcinoma (HCC). The incidence of HCC in the PNPLA3 transgenic mice was 2.5 fold higher than that in the wild-type control mice. Biochemical analysis revealed that the PNPLA3-148M mouse livers had much higher levels of oxidative stress and DNA damage. RNA-seq analysis uncovered changes in multiple pathways including upregulation of steroid hormone biosynthesis and chemical carcinogenesis and downregulation of cell adhesion, cell differentiation, and immune processes. Spatial transcriptomics further identified multiple differential cell clusters, including a cluster downregulated in the PNPLA3-148M liver, which had enriched genes in defense response and cell death regulation. Immunoblotting and immunostaining confirmed a number of those genes. **Conclusion:** Our data have demonstrated a critical role of the 148M variant of PNPLA3 in the alcohol-associated liver cancer development. PNPLA3-148M has a remarkable effect on multiple cell processes in the liver that contribute to the elevated risk of liver cancer.



Disclosures: The following people have nothing to disclose: Jung-Hyo Cho, Hyeong-Geug Kim, Chang-Hyun Gil, Alex Lu, Sheng Liu, Menghao Huang, Wenjun Zhang, Burcin Ekser, Wanqing Liu, Jun Wan, X Charlie Dong

4221-A ǀ THE POSITIVE CORRELATION BETWEEN SPLENOMEGALY AND HEPATOCELLULAR CARCINOMA PROGRESSION BY ESTABLISHING A MOUSE MODEL VIA HYDRODYNAMIC TAIL VEIN INJECTION OF ONCOGENE PLASMID

Yanhua Mu[1,2], Ke Du[1,2], Yameng Wei[1,2], Ni Guo[1,2], Junqiao Feng[1,2], Qian Wang[1,2], Gaixia He[1,2], Jin Sun[1,2] and Zongfang Li[1,2,3], (1)National & Local Joint Engineering Research Center of Biodiagnositics and Biotherapy, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China., (2)Shaanxi Provincial Clinical Research Center for Liver and Spleen Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China., (3)Department of General Surgery, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.

Background: Splenomegaly is common in patients with hepatocellular carcinoma (HCC) during clinical treatment, but the reason remains unclear. We establish mouse model of HCC by hydrodynamic tail vein injection (HTVI) to explore the relationship between spleen and liver cancer progression. **Methods:** 6-8 weeks male balb/c mice were injected with 10% volume of body weight solution containing oncogene plasmids within 8 seconds. Mice in the control group were given an equal volume of PBS by HTVI. 12 weeks later, mice were sacrificed and tumor formation was observed. **Results:** Hepatocellular carcinoma (HCC) is the main type of primary liver cancer. A mouse model of hepatocellular carcinoma was established by HTVI of Sleeping Beauty (SB) plasmid and oncogenic plasmid. Compared with control group, the body weight of the mice in liver cancer group decreased, and the liver weight ratio increased significantly. The liver surface of mice in normal group was smooth and elastic with normal morphology. The liver volume of the mice in liver cancer group was significantly increased, the texture was harder, and a large number of granular and nodular changes appeared on the liver surface, with obvious tumor formation. In addition, we found that the spleen weight of the liver cancer group was larger than normal group, and spleen weight was positively correlated with liver tumor formation. Finally, we infer that splenomegaly is closely related to the progression of HCC.

Conclusion: Our data suggest that the spleen may play a role in the occurrence and development of HCC, which provides new ideas for the clinical treatment of liver cancer.

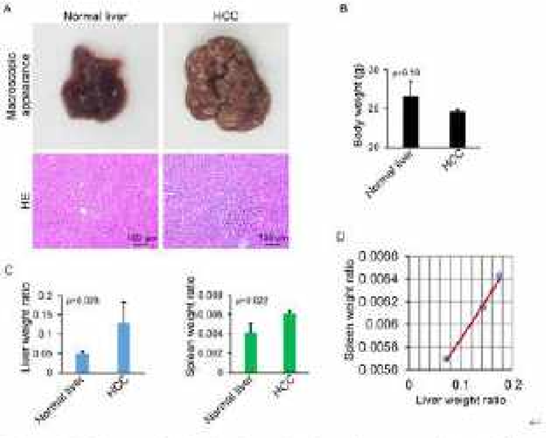


Figure1. Splenomegaly is closely related to the progression of liver cancer. A. Macroscopic and histological features of mouse model. B. Body weight data for each group of mice. C. Liver index and spleen index of mice in each group (liver index means liver to body weight ratio, spleen index means spleen to body weight ratio). D. Correlation between liver index and spleen index in HCC group mice.

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Disclosure information not available at the time of publication: Ke Du, Yameng Wei, Ni Guo, Junqiao Feng, Qian Wang, Gaixia He, Jin Sun

4222-A | THE PRESENCE OF TGF-β1/SMAD3-ENHANCED GLI2 ISOFORMS CONTRIBUTES TO MALIGNANT BEHAVIORS OF HEPATOCELLULAR CARCINOMA

Jia Ding[1], Yue Ma[2], Yongyu Yang[2], Li Zhang[2], Huiyan Li[2], Pingguo Liu[3] and Jian Wu[2,4,5], (1)Department of Gastroenterology, Shanghai Jing'an District Central Hospital, Shanghai 200040, China, (2)Dept. of Medical Microbiology, Fudan University School of Basic Medical Sciences, Shanghai 200032, China, (3)Dept. of Hepatobiliary Surgery, Zhongshan Hospital Affiliated to Xiamen University, Xiamen 361004, China, (4)Shanghai Institute of Liver Diseases, Fudan University Shanghai Medical College, Shanghai 200032, China, (5)Fudan University, Department of Gastroenterology and Hepatology, Zhongshan Hospital, Shanghai, China

Background: Major focus has been paid to pivotal roles of hedgehog signaling (Hh) in hepatocellular carcinoma (HCC) and considered Hh as a potential target. However, inconsistent expression between Sonic ligands (SHh) and GLI2 was demonstrated in our preliminary analysis of HCC specimens, which accompanied with increased TGF-β1 and SMAD3 protein. This study aims to evaluate the correlation between SHh-independent GLI2 expression with clinicopathologic characteristics, and investigate the promoting effect of TGF-β1/SMAD3 on GLI2 and its isoforms in HCC. **Methods:** Critical components of Hh and TGF-β1 pathways were examined in 21 pairs of HCC specimens, and SHh-independent GLI2 expression was verified in a separate cohort of 56 HCC patients by immunochemistry (IHC) staining. Different gene profiles of four GLI2 isoforms and mutual target genes co-regulated by GLI2 and p-SMAD3 were investigated by chromatin immunoprecipitation (ChIP) assay. The effect of the TGF-β receptor inhibitor on lung metastasis was evaluated in an *in situ* xenograft mouse model. **Results:** SHh and GLI2 protein were increased in 52.38% and 47.62% of HCC specimens. However, SHh protein was not increased in 80% GLI2-positive specimens compared to their pericancerous counterparts. Among them, TGF-β1/SMAD3 were present in 75% GLI2-positive specimens with SHh-low expression. Positive GLI2 staining was found in 72.2% of sections with low SHh staining of 56 HCC patients; whereas SMAD3 protein displayed an increase in 61.54% of SHh-low and GLI2-positive sections. Mean overall survival (OS) of patients with high and low GLI2 protein was 18.3 months and 17.6 months ($p = 0.68$); and patients with high GLI2 protein had a shorter disease-free survival (DFS) than those with low GLI2 expression (12.40 *vs* 16.31 months, $p = 0.0429$). Neither OS nor DFS displayed statistically significant difference in patients with high and low SHh immunopositivity. In addition to five known isoforms, two new GLI2 isoforms 6&7 were identified with transactivating activity in HCC specimens. CoIP and ChIP assay demonstrated that p-SMAD3 interacted with active GLI2 isoforms to transactivate mutual target genes (NOTCH2, VIM, ABCC1 and MMP2) in modulation of stemness, epithelial-mesenchymal transition, chemoresistance and metastasis in poorly-differentiated hepatoma cells. A dual TGF-β receptor inhibitor, LY2109761 sensitized poorly-differentiated hepatoma cells to Sorafenib, and reduced pulmonary metastasis in mice with *in situ* liver xenograft tumors. **Conclusion:** High GLI2 expression was correlated with recurrence in HCC. SMAD3 interacted with active GLI2 isoforms to enhance transcription of genes involved in stemness, epithelial-mesenchymal transition, chemo-resistance and metastasis. The elucidation of the non-canonical hedgehog signaling mechanisms via TGF-β1/SMAD3/GLI2 axis may facilitate to optimize therapeutic strategies for advanced HCC.

Disclosures: The following people have nothing to disclose: Jia Ding, Yue Ma, Yongyu Yang, Li Zhang, Huiyan Li, Pingguo Liu, Jian Wu

4223-A | THE RNA METHYLTRANSFERASE METTL16 ENHANCES CHOLANGIOCARCINOMA GROWTH THROUGH PRDM15-MEDIATED FGFR4 EXPRESSION

Nianli Liu[1], Jinqiang Zhang[1], Weina Chen[1], Wenbo Ma[1] and Tong Wu[1,2], (1)Tulane University, New Orleans, LA, (2)Tulane Medical Center

Background: RNA N6-Methyladenosine (m6A) modification is implicated in the progression of human cancers including cholangiocarcinoma (CCA). METTL16 is recently identified as a new RNA methyltransferase responsible for m6A modification, although the role of METTL16 in CCA has not yet been examined. The current study aims to investigate the effect and mechanism of the RNA methyltransferase METTL16 in CCA. **Methods:** We analyzed the mRNA expression of METTL16 in several human CCA cohorts and evaluated its protein expression by immunochemical staining of human CCA tissues. CRISPR/Cas9 and siRNA approaches were used to knockdown METTL16 in CCA cells, and the cells were analyzed for their malignant characteristics in vitro and in SCID mice. To identify METTL16 targets, we performed m6A-seq and RNA-seq, followed by m6A-qPCR, qPCR, RIP, and ribosome immunoprecipitation assays. We performed ChIP-qPCR and co-immunoprecipitation assays to determine the regulatory mechanisms of METTL16 expression in CCA cells. **Results:** We observed that the mRNA and protein levels of METTL16 were noticeably increased in human CCA tissues when compared to normal bile ducts. We found that depletion of METTL16 by CRISPR/Cas9 or siRNA significantly inhibited human CCA cell proliferation in vitro and decreased CCA progression in SCID mice. We identified PRDM15 as a key target of METTL16 in CCA cells by analyzing m6A-seq data. Accordingly, depletion of METTL16 reduced PRDM15 expression in CCA cells. Mechanistically, our data showed that METTL16 regulated PRDM15 protein expression via YTHDF1-dependent translation. We observed that restoration of PRDM15 expression partially rescued the deficiency of CCA cell proliferation/colony formation induced by METTL16 depletion. Our subsequent analyses revealed that METTL16-PRDM15 signaling regulated the expression of FGFR4 in CCA cells. Specifically, we observed that PRDM15 protein was associated with the FGFR4 promoter to regulate its expression. Regulation of FGFR4 by METTL16 signaling was further corroborated by the positive correlation between METTL16 and FGFR4 expression in human CCA tissues under immunohistochemical stains. Furthermore, we showed that the histone acetyltransferase p300 cooperated with the transcription factor YY1 to regulate METTL16 gene expression via histone H3 lysine 27 (H3K27) acetylation in CCA cells. **Conclusion:** This study describes a novel METTL16-PRDM15-FGFR4 signaling axis which is crucial for CCA growth and may have important therapeutic implications.

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4224-A | TRANSPOSON-BASED ONCOGENES INTEGRATION IN Abcb4(Mdr2)-/- MICE RECAPITULATES HIGH SUSCEPTIBILITY TO CHOLANGIOCARCINOMA IN PRIMARY SCLEROSING CHOLANGITIS

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Background: Cholangiocarcinoma (CCA) is a dreaded complication of primary sclerosing cholangitis (PSC), difficult to diagnose and associated with high mortality. Lack of animal models of CCA recapitulating the hepatic microenvironment of progressive sclerosing cholangitis hinders development of novel treatments. Here we sought to develop and characterize such PSC-associated CCA model in mice. **Methods:** Ten-week-old *Mdr2*-/- mice with congenital PSC-like progressive biliary disease, and healthy wild-type littermates (WT) were subjected to either modified retrograde biliary instillation or hydrodynamic tail vein injection of sleeping beauty transposon-transposase plasmid system with activated forms of AKT (myr-AKT) and Yap (YapS127A) protooncogenes (SB AKT/YAP1). ALK5 inhibitor (SB-525334, 300 mg/kg in diet) or placebo diet was administered into tumor-bearing mice to interrogate the functional role of TGFβ signaling in our model. Tumor phenotype, burden and desmoplastic reaction were analyzed based on histological staining. **Results:** While SB AKT/YAP1 plasmids via retrograde biliary injection caused tumors in *Mdr2*-/- but not in healthy wildtype mice, only 26.67% (4/15) of these tumors were CCA. Alternatively, hydrodynamic tail vein injection of SB AKT/YAP1 resulted in robust tumorigenesis in all fibrotic *Mdr2*-/- mice with high CCA burden relative to healthy mice. Tumors expressed CK19, and exhibited a profound desmoplastic reaction. Pharmacological pan-TGFβ inhibition via ALK5 inhibitor reduced both tumor burden and desmoplastic tumor stroma compared to placebo. **Conclusion:** We established a new high-fidelity cholangiocarcinoma model in mice, termed SB CCA.*Mdr2-/-*, which recapitulates the increased susceptibility to CCA in the setting of progressive biliary injury and fibrosis observed in PSC. Furthermore, pharmacological targeting of ALK5 in our model suggests that TGFβ signaling functionally drives CCA tumorigenesis and promotes desmoplastic reaction.

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Disclosure information not available at the time of publication: Yi Lin, Xin Chen, Alicia Lugovskoy

4225-A | ULTRASOUND NONINVASIVELY STIMULATING THE SPLEEN TO ENHANCE HEPATOCELLULAR CARCINOMA IMMUNOTHERAPY

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Background: The spleen is the largest secondary lymphoid organ and distributed with an extensive meshwork of nerve fibers in all splenic compartments. Ultrasound triggering the splenic neural-immune reflex showed a significant mitigation effect on chronic inflammatory diseases, but the potential roles and underlying mechanisms in cancer management have not been defined and reported. This study was designed to explore whether ultrasound stimulating spleen was effective in alleviating hepatocellular carcinoma (HCC) proliferation, and the mechanism of enhanced antitumor immunity. **Methods:** We first verified the therapeutic efficacy in various HCC tumors by spleen modulation with ultrasound under specific parameters screened before. Furthermore, we investigated whether ultrasound stimulating spleen could improve antitumor immunity by increasing the proportions of CD4 T cells, CD8 T cells, NK cells, B cells, Mφ, DCs to resist the immunonegative Treg cells and MDSCs, or regulating inflammatory and anti-inflammatory cytokines. Subsequently, scRNA, nerve blockade and immune cell clearance were utilized to reveal immune cell activation, metastasis and its communication with cancer cells. **Results:** Ultrasound stimulating spleen could effectively suppress proliferation of xenograft HCC (Figure 1A-B) and HCC in situ (Figure 1C-D). Flow cytometry proved that specific cancer-suppressing immune cells, CD8 T cells, NK cells, Mφ and DCs, increased significantly in spleen and tumor after ultrasonic irradiation (Figure 1E-F). And the number of immunonegative cells (i.e. MDSC, Treg) was significantly reduced. These results sufficiently proved the application prospect of ultrasound stimulating spleen to increase the number of cancer-fighting immune cells for HCC immunotherapy. **Conclusion:** Ultrasound could non-invasively, targeted and safely stimulate the spleen to activate immune cells suppressing tumor proliferation, which will open a new era of clinical treatment of cancer.

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4226-A | ZONATION-SPECIFIC HEPATOCARCINOGENESES UNDER NASH AND ASH IN DIABETIC MICE

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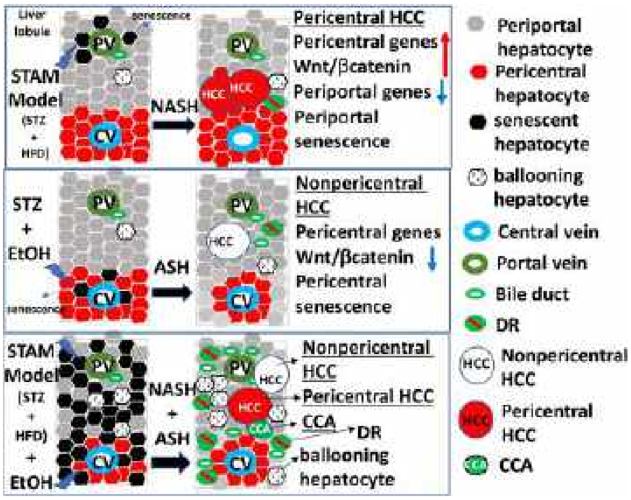
Background: Nonalcoholic steatohepatitis (NASH) and alcoholic steatohepatitis (ASH) are high risk factors for hepatocellular carcinoma (HCC). Both NASH and ASH are two histologically similar liver pathologies but their hepatocarcinogeneses in relation to liver zonation remain elusive. It is difficult to study these pathological processes in human due to their asymptomatic phenotype at early stage. This study aims to compare NASH or ASH progression to HCC in diabetic murine livers. **Methods:** NASH-associated HCC (NASH-HCC) was induced by neonatal subcutaneous administration of streptozotocin (STZ) and high fat diet (HFD) feeding in the STAM model. Another two models of alcohol-induced HCC were generated in STZ-treated livers with or without HFD feeding. RNA seq analysis in these tumors and adjacent tissues were compared. Digital spatial profiling (DSP) was also performed to discern extent of immune cell infiltration, cell proliferation, and cell death using barcoded antibodies. **Results:** Pericentralized/deperiportalized tumors expressing gene signatures like Hoshida subclass S3 in human HCC that contained ß-catenin mutations were found in the STAM model. These tumors resulted from periportal senescence and upregulated Wnt/ß-catenin targets including glutamine synthetase (Gs), and downregulation of genes in urea cycle, amino acid catabolism, and growth hormone/Ras signaling. Superimposed alcohol exposure in the STAM model exacerbated steatosis, hepatocyte damage, and ductular reaction (DR). Although alcohol decreased occurrence rates of the Gs^{+} HCC, it provoked nonpericentral Gs^{-} tumors and promoted cytokeratin 19^{+} cholangiocarcinoma (CCA). In the third model, alcohol alone after STZ administration caused pericentral senescence and triggered HCC that was opposite to the Gs^{+} NASH-HCC in the STAM model. We observed downregulation of Wnt/ß-catenin targets including stemness regulators Lgr5, Tbx3, axin2, and Lef1. This type of ASH-HCC resembled Hoshida subclass S1 of human HCC with predominant activation of transforming growth factor (TGF)ß and Myc pathways. Furthermore, the ASH-HCC were Gs^{-} depericentral tumors and mimicked metabolic reprogramming in human livers with alcoholic hepatitis (AH). DSP revealed differential immune cell infiltrations and cell death activation in cell fractions of Gs^{+} HCC, Gs-HCC, and CCA compared to intratumoral myofibroblasts, and their adjacent tissues. **Conclusion:** HFD induces Gs^{+} pericentral HCC due to periportal senescence in the STAM model, whereas alcohol inhibits the Gs^{-} depericentral HCC. Superimposed alcohol exposure causes synergistic effects of NASH and ASH that exacerbates steatosis, hepatocyte damage, and DR leading to tumor heterogeneity with extensive DR and mixed HCC/CCA. These models mimic liver pathologies in human HCC/CCA and provide new platforms to dissect molecular mechanisms of distinct hepatocarcinogenesis among NASH, ASH, or both.


Liver lobule
senescence
STAM Model (STZ + HFD)
PV
CV
NASH
HCC
HCC
Pericentral HCC
Pericentral genes
Wnt/βcatenin
Periportal genes
Periportal senescence
STZ + EtOH
senescence
ASH
HCC
Nonpericentral HCC
Pericentral genes
Wnt/βcatenin
Pericentral senescence
STAM Model (STZ + HFD) + EtOH
NASH + ASH
HCC
CCA
Nonpericentral HCC
Pericentral HCC
CCA
DR
ballooning hepatocyte
Periportal hepatocyte
Pericentral hepatocyte
senescent hepatocyte
ballooning hepatocyte
Central vein
Portal vein
Bile duct
DR
Nonpericentral HCC
Pericentral HCC
CCA

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4300-A | 25HC3S ALLEVIATES INJURED LIVER FUNCTION AND DECREASES MORTALITY BY PROMOTER 5mCpG DEMETHYLATION SIGNALING PATHWAYS

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Background: Acute liver failure (ALF) is a dramatic and devastating disease. ALF often results in severe hepatocyte injury and apoptosis, leading to massive necrosis in the liver and the sudden death. Severe lipopolysaccharide (LPS)- and acetaminophen (ATMP)-induced hepatotoxicity are the most frequent causes of ALF. Currently, treatment options for ALF are extremely limited. 25-Hydroxycholesterol 3-sulfate (25HC3S, DUR928, or larsucosterol) has been demonstrated to alleviate injured liver function and decrease mortality in the acute liver failure in mouse models. The present study was designed to explore molecular mechanism(s) by which 25HC3S can be used to treat ALF. **Methods:** ALF mouse models were established by intravenous injection with LPS or ATMP. The injured liver function was treated with intraperitoneal administration of 25HC3S. Serum enzymatic activities were determined in our clinic laboratory. Western blot and mRNA sequencings were used to determine levels of gene expression; Whole genome bisulfite sequencing (WGBS) analysis was used to determine demethylation of ^{5m}CpG in promoter regions; DSS software (DSS 2.34.0) was used to identify differentially methylated regions (DMRs); and KOBAS software (KOBAS 2.0) was to test the statistical enrichment of DMR related genes in KEGG pathways. **Results:** Administration of 25HC3S decreased serum liver-impaired markers and alleviated liver, lung, and kidney injury. Subsequently, 25HC3S increased the survival rates in the LPS- or ATMP-induced mouse model, only 10% of the animals survived 96 hours without 25HC3S versus 90% survival with the 25HC3S. These effects resulted from the inhibition of the expression of genes involved in the pro-inflammatory response and apoptosis as well as the simultaneous induction of the expression of genes involved in cell survival. WGBS analysis showed that 25HC3S increased demethylation of ^{5m}CpG in key promoter regions and thereby increased expression of genes involved in the MAPK-ERK and PI3K-Akt signaling pathways. 25HC3S exhibited significantly stronger effects in these activities, indicating that 25HC3S, a potent epigenetic regulator, plays an important role in the inflammatory response, cell apoptosis, and cell survival by demethylation of promoter ^{5m}CpG and upregulation of MAPK and PI3K signaling pathways in vivo. **Conclusion:** 25HC3S is a potent epigenetic regulator and has the potential to serve as a novel biomedicine in the therapy of ALF and acute multiple organ failure.

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f 4301-A | A SIMPLE DYNAMIC SCORE ILBS-ALF-DYNAMIC SCORE (ILADS) RELIABLY PREDICTS MORTALITY IN ACUTE LIVER FAILURE PATIENTS WITH CEREBRAL EDEMA

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Background: The outcomes of acute liver failure (ALF) have improved with increasing use of therapeutic plasma-exchange (TPE) and continuous renal replacement therapy (CRRT). Currently, there are no dynamic scores which incorporate assessment of cerebral edema, and impact of these therapeutic modalities for determining outcome in these patients. **Methods:** Prospective cohort of 170 adult patients with ALF requiring mechanical ventilation for cerebral edema (confirmed by CT-scan) with no option of liver transplant were enrolled. One point each for the class value was assigned for the significant parameters from the Cox-regression model for the calculation of the score for prediction of 21-day mortality. The score was calculated for day 2 and day 3 and compared to the other prognostic scores. **Results:** Patients with ALF (aged 31.0 ± 11.0 yrs, 47.6% males, 33% meeting KCH criteria 79% viral-related, 50% with sepsis) were enrolled of which 47.6% died. Sixty-one patients (36%) underwent TPE and/or CRRT. Five dynamic variables serum bilirubin (mg/dl) [(< 12 vs 12-18 vs. ≥ 18) [HR 1:2.11(1.10,4.04):3.59(1.99,6.46)], arterial lactate;(umol/L)[< 2.6 vs.2.6-5.0 vs. ≥ 5) [HR1:(3.84,1.72-8.57):(6.66,2.95-15.04)], ammonia ≥ 211mg/dl, (HR 1.90 (1.19-3.02) international normalized ratio (INR) ≥ 4.16 (HR 2.78,1.79-4.30) and optic nerve sheath diameter (ONSD) (< 4.5 vs.4.5-5.12 vs. ≥ 5.12 mm) [HR 1: (2.82,1.34-5.93): (5.32,2.58-10.96) and 2 fixed variables jaundice-to-encephalopathy time (days) (HR1.05 ,1.01-1.09) and age (≥ 32 y) (HR 2.13, (1.38-3.30) predicted 21-day mortality. With each unit increase in the (ILADS) ILbs-ALF-Dynamic Score, the hazard of death increased by 49% [HR1.4, 1.3-1.6)]. Patients who underwent TPE/CRRT had significantly lower mortality (26.4% vs 57.3%; p < 0.001, HR 0.43, 0.24-0.78). The ILADS ≥ 12 at day 1 (sensitivity 95.5%, specificity 72.0%; AUROC 0.89 (0.79-0.94)] and ILADS ≥ 11 at day 2 or 3 for patients who underwent TPE/CRRT (sensitivity 92.3%, specificity 53.8%; AUROC 0.80 (0.67-0.92)] accurately predicted mortality. At day 2, a progressive or persistent increase in serum bilirubin (≥ 16mg/dl); (HR 2.381.53,3.70), lactate (≥ 3.9 umol/L) (HR 2.85,1.76,4.59), ammonia (≥ 410 mg/dl) (HR 1.65, 0.82-3.30), INR (≥ 6.7) (HR 3.22,1.88,5.51) and ONSD (≥ 4.0mm)(HR 2.49,1.59,3.89) independently predicted worse outcomes. The ILADS score performed better than other scores; Harrell's C-index; ILADS (0.78), SOFA (0.61), APACHE (0.60), ALFED (0.62) and KCH (0.61). **Conclusion:** The ILADS score comprising of 5 simple dynamic and 2 fixed prognostic variables can reliably stratify patients of ALF with cerebral edema at high risk of 21-day mortality. Therapeutic interventions targeting the components of ILADS could be assessed dynamically with the score to stratify patients for super-urgent liver transplant.

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f 4302-A | ACTIVATION OF HEPATOCYTE p53 TRIGGERS ACUTE LIVER FAILURE WITH MULTIPLE ORGAN DYSFUNCTION.

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Background: Acute liver failure (ALF) is characterized by massive hepatocyte cell death in a short term for which no effective treatment exists except liver transplantation. We previously reported that constitutive activation of p53 in hepatocytes caused continuous hepatocyte cell death leading to liver fibrosis and carcinogenesis. Meanwhile, its impact on acute liver diseases remains unknown. This work aims to study the role of p53 on ALF and investigate its potential as a therapeutic target. **Methods:** Gene Expression Omnibus (GEO) dataset was used for the analysis of RNA-seq in human ALF liver (GDS4387). Acetaminophen (APAP) or concanavalin A (ConA) were used to induce ALF in mice. Mdm2, a negative regulator of p53, was knocked out inducibly and specifically in hepatocytes (AlbCreER $mdm2^{fl/fl}$+tamoxifen) (Mdm2Δhep mice) to analyze the impact of acute activation of hepatocyte p53. p53 was further deleted in Mdm2Δhep mice (AlbCreER $mdm2^{fl/fl}$ $p53^{fl/fl}$+tamoxifen). CL-2, HepG2 (hepatocyte cell), LX-2 (hepatic stellate cell), and HK2 (renal proximal tubule epithelial cell) were used for culture. **Results:** In GEO datasets, hepatic cdkn1a, a representative target of p53, was up-regulated in ALF patients compared with the normal liver samples. C57B6J mice administered with APAP or ConA showed upregulation of p21 mRNA and p53 protein in the liver, indicating the activation of p53 pathway. Compared with Cre- littermates, Mdm2Δhep mice showed activation of p53 signaling in hepatocytes 72 hours after tamoxifen injection. Mdm2Δhep mice demonstrated extensive cell death and senescence in hepatocyte, together with the elevation of serum ALT and bilirubin. Apart from the liver, multiple organ injury was noted as the increase of TUNEL-positive cells and infiltration of inflammatory cells in the kidney, heart, colon, and lung, and elevation of serum cystatin C. All of Mdm2Δhep mice died within 168 hours after tamoxifen injection. Of note, further deletion of hepatocyte p53 negated all of these findings in Mdm2Δhep mice. Single-cell RNA-seq and multiplex cytokine assay showed the elevation of multiple inflammatory cytokines in hepatocytes, hepatic non-parenchymal cells and serum in Mdm2Δhep mice. Among these cytokines, we focused leukemia inhibitory factor (LIF), which was the most elevated inflammatory cytokine in RNA-seq of Mdm2Δhep mice liver. LIF increased by nutlin-3, an inhibitor of Mdm2, in CL2 and HepG2, indicating that LIF is a direct target of p53 in hepatocytes. Recombinant LIF up-regulated inflammatory cytokines including LIF itself in LX-2 and HK2. LIF was elevated in multiple injured organs in Mdm2Δhep mice, suggesting the possibility of LIF-mediated systemic inflammatory reaction. **Conclusion:** Hepatic p53 was activated in the liver of ALF. Acute activation of hepatocyte p53 triggers inflammatory reaction and ALF with multiple organ injury. Activated p53 may represent a novel therapeutic target against ALF.

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Disclosure information not available at the time of publication: Yuki Makino, Yoichi Sasaki

4303-A | ACUTE LIVER FAILURE IN CORANAVIRUS DISEASE-19: A NATIONWIDE STUDY

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Background: COVID-19 is a global pandemic caused by the SARS-CoV-2 virus that can cause multiorgan damage including liver. Hepatic dysfunction has been observed in 14-53% of patients with COVID-19, and studies have shown that COVID-19 is associated with severe acute liver injury and acute liver failure. The liver may be susceptible to the virus due to ACE2 receptors in biliary and liver epithelial cells, and a hyperinflammatory response leading to a cytokine storm can also contribute to liver damage. little is known about risk factors and clinical course for patients with significant liver injury attributed to COVID-19. The aim of this article is to describe the prevalence and risk factors for development of acute liver failure in COVID-19 patients and investigate the impact its impact on patient outcomes. **Methods:** All adult patients (age > 18 y) old with COVID-19 and acute liver failure admitted in 2020 were identified from the Nationwide Inpatient Sample (NIS). Data on demographic information, baseline clinical characteristics, and outcome variables such as mortality, hospital length of stay, and total hospital charges were collected and analyzed. Statistical analysis was performed by using the survey procedures function in the STATA v.17. Statistical significance was defined by the two-sided t-test with a p value < 0.05. **Results:** A total of 1,050,045 patients were admitted to the hospital with COVID-19 pneumonia, out of which 6,665 cases (0.9%) developed acute liver failure during hospitalization. The incidence of acute liver failure in COVID-19 patients was found to be high among the black population (20.4% vs 17.8%, $p = 0.002$) and Hispanics (25.5% vs 19.8%, $p < 0.01$). The prevalence of heart failure (12% vs 8%, $p < 0.01$), chronic kidney disease (17% vs 13%, $p = 0.002$) and chronic liver disease(5% vs 1%, $p < 0.01$) were higher in patients who developed ALF. Patients with ALF had higher incidence rates of septic shock (53.79% vs 3.78%, $p < 0.001$), acute kidney failure (39.46% vs 3.11%, $p < 0.01$), and mechanical ventilation requirements (78.1% vs 8.9%, $p < 0.01$). It was associated with higher mortality (72.39% vs 10.78%, $p < 0.01$), longer duration of hospital stay (mean duration: 18 d vs 7 d, $p < 0.01$), and higher total hospital charges ($355,512 vs $76,822, $p < 0.01$) than those without acute liver failure. Advanced age, development of septic shock, and requirement of mechanical ventilation were found to be predictors of mortality in a multivariate regression model. **Conclusion:** The occurrence of acute liver failure in COVID-19 patients is associated with significant adverse outcomes, including higher mortality rates, longer hospital stays, and increased treatment costs. This emphasizes the need for effective management of acute liver failure in COVID-19 patients to improve their prognosis, reduce the burden on the healthcare system, and optimize resource allocation

Disclosures: The following people have nothing to disclose: Sajana Poudel, Ayusha Poudel, Kalpana Ghimire, Sumina Rai, Prakriti Subedi, Karun Shrestha, Manoj Ghimire

4304-A | ASSESSMENT AND PROPER DIAGNOSIS OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN THE SETTING ACUTE LIVER FAILURE

Ahmad Anouti[1], Hamza Dahshi[2], Jody A. Rule[1], Christian Wysocki[2], William M. Lee[1] and Shannan R. Tujios[2], (1)University of Texas Southwestern Medical Center, (2)University of Texas Southwestern

Background: Hemophagocytic Lymphohistiocytosis (HLH) is a severe and life-threatening disease that is challenging to diagnose and can present as acute liver failure (ALF) with coagulopathy, altered mental status and elevated liver tests. We reviewed all cases considered as possible HLH in the ALF Study Group (ALFSG) registry over the 22 years of the study, and assessed the diagnostic criteria HLH score, H score, and measured interleukin-18 (IL-18) and soluble interleukin-2 receptor (sIL-2r), recognized biomarkers of HLH, in putative cases as well as other etiologies of ALF as comparison groups. **Methods:** We analyzed data on patient demographics, biochemical features, IL-18 and sIL-2r as well as outcomes for 434 subjects enrolled in ALFSG between January 1, 2000, through December 31, 2016, who either met criteria for HLH or who had other diagnoses but striking biochemical values including elevated ferritin that might mimic HLH. Biomarkers were collected one to two days after patients were admitted to the study hospital. Differences in categorical variables between patients with and without HLH were analyzed using Chi-Square and Fishers tests. Whereas differences in continuous variables between patients with vs without HLH were analyzed using One-Way ANOVA and Kruskal Wallis tests. **Results:** 18 cases of HLH were reported within the ALFSG by the site investigator of which, upon thorough review: 7 (47%) were considered HLH definite cases, 6 (40%) were possible HLH cases, and 5 (33%) were unlikely HLH cases (Table 1). HLH definite cases had significantly greater ferritin levels ($p = 0.047$), H scores ($p < 0.001$), IL-18 ($p = 0.003$), s-IL2r ($p = 0.005$), HLH scores ($p < 0.001$), and temperature ($p = 0.002$) as well as significantly more frequent organomegaly (hepatomegaly and/or splenomegaly, $p = 0.003$) and Epstein Barr virus presence ($p = 0.001$). By comparison, APAP, DILI, and viral etiologies, as expected, had lower HLH and H scores as well as IL-18 and sIL2r levels but overlapped with many ferritin levels (Figure 1). Moreover, ROC curves for HLH definite cases showed an area under the curve of 0.69 for Ferritin, 0.93 for Total IL-18, 0.83 for sIL-2r, 0.96 for HLH score, and 0.88 for H score. Missing values for calculating H and HLH scores may have impacted the categorization of HLH cases. **Conclusion:** The proper assessment and diagnosis of HLH remains challenging. Accurate collection of requisite lab values can improve diagnosis of HLH in the setting of ALF. Ferritin levels are highest in HLH and APAP cases. Even within ALF cases, HLH diagnostic markers varied, but sIL-2r and IL-18 were significantly different compared to other etiologies and could aid in the proper diagnosis of HLH. Despite limitations, HLH and H score are highly discriminant identifying HLH in patients with ALF. EBV viremia is a common precipitant in HLH cases presenting with ALF.

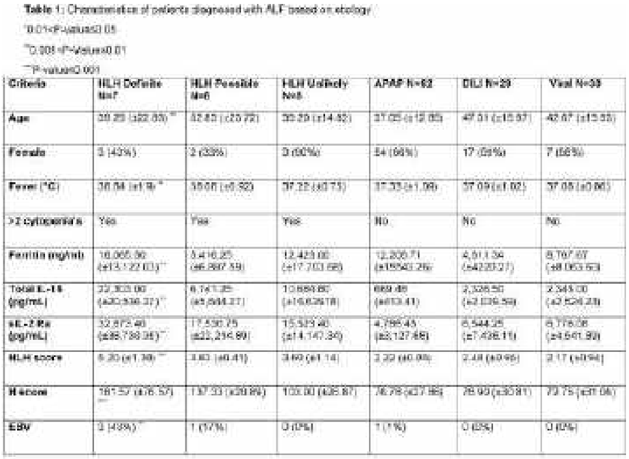

Table 1: Characteristics of patients diagnosed with ALF based on etiology

*0.01<P-value≤0.05

**0.001<P-Value≤0.01

***P-value≤0.001

Criteria	HLH Definite N=7	HLH Possible N=6	HLH Unlikely N=5	APAP N=62	DILI N=29	Viral N=33
Age	30.29 (±22.65)***	32.83 (±23.72)	33.20 (±14.62)	37.05 (±12.65)	47.31 (±15.57)	42.67 (±15.55)
Female	3 (43%)	2 (33%)	3 (60%)	54 (86%)	17 (59%)	7 (58%)
Fever (°C)	38.84 (±1.19)*	38.08 (±0.92)	37.22 (±0.73)	37.33 (±1.09)	37.09 (±1.02)	37.05 (±0.86)
>2 cytopenia's	Yes	Yes	Yes	No	No	No
Ferritin (ng/ml)	16,065.50 (±13,122.03)**	5,416.25 (±6,597.59)	12,423.00 (±17,703.66)	12,206.71 (±15540.26)	4,511.34 (±4220.27)	8,797.67 (±8,063.63)
Total IL-18 (pg/mL)	22,303.00 (±20,936.37)**	6,741.25 (±5,944.27)	10,669.60 (±16,626.18)	669.48 (±613.41)	2,326.50 (±2,036.59)	2,345.00 (±2,526.23)
sIL-2 Ra (pg/mL)	32,873.40 (±36,738.36)**	17,530.75 (±22,214.89)	15,323.40 (±14,147.34)	4,795.45 (±3,127.66)	6,544.25 (±7,436.11)	6,776.06 (±4,541.30)
HLH score	5.20 (±1.30)***	3.83 (±0.41)	3.60 (±1.14)	2.22 (±0.99)	2.48 (±0.95)	2.17 (±0.94)
H score	181.57 (±76.57)***	137.33 (±28.89)	103.00 (±26.87)	76.78 (±27.56)	76.90 (±30.81)	73.75 (±31.06)
EBV	3 (43%)**	1 (17%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)

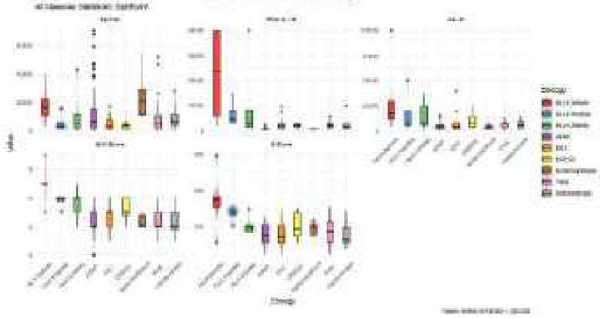

Figure 1: Box and whisker plot and violin plot comparing all quantitative variables (Ferritin, Total IL-18, sIL-2r, HLH score, H score) between HLH Definite, HLH Possible, HLH Unlikely, APAP, DILI and Viral etiologies

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

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Disclosure information not available at the time of publication: Jody A. Rule, Christian Wysocki, William M. Lee, Shannan R. Tujios

4305-A | BACTERAEMIA IN PATIENTS WITH ACUTE LIVER FAILURE IS DEPENDENT ON THE AETIOLOGY AND HYPERAMMONAEMIA

Anna Cavazza, Gjulio Ciroi T M, Tasneem Pirani, William Bernal and Mark John William McPhail, King's College Hospital

Background: Acute liver failure (ALF) is a life threatening condition associated with immunological disarray and risk of infection. The role of prophylactic antimicrobials is debated and there is increased multi-drug resistant (MDR) pathogens affecting similar populations. We aim to define the burden of resistant organisms and determine which factors predict development of bacteraemia in the modern era. **Methods:** A retrospective observational study of 571 ALF patients admitted between 2010 and 2022 to the Liver Intensive Care (LICU) at King's College Hospital, London. Demographic, laboratory and microbiological data were obtained. Statistical analysis including multivariate logistic regression was performed. Multidrug resistant organisms were defined as resistant to more than one antimicrobial. **Results:** Five hundred and seventy one ALF patients were included, 63% female (358/571), median age 40 (range 15-87) years. The aetiology was due to acetaminophen (APAP) in 48% (274/571). 25% were transplanted (141/571), 28% died (158/571), 47% spontaneously survived (272/571). The median length of stay in LICU was 21 (0-315) days.35% (122/345) and 44% (88/200) had positive cultures pre liver transplant (OLT) in the early (2010-2016) and late (2017-2022) era, 51% (43/84) and 61% (25/41) post-OLT respectively. Resistant organisms were present in cultures in 21% (76/365) in the early and 26% (52/203) late era. 11% (34/322) and 9% (17/185) developed bacteraemia in the early and late era respectively. The median time from admission to bacteraemia was 9 (0-103) days. MDR bacteraemia was observed in 41% (14/34) in the early and 35% (6/17) in the late era. Fungaemia was observed in 1.3% (4/299) and 4% (4/100) with positive β-d-glucan (BDG) in 21% (14/66) and 26% (43/163) respectively in the early and late era. Multivariate analysis showed aetiology and ammonia as significant predictors of bacteraemia (respectively Odds Ratio 3.4 (95% CI 1.1-9.8, p = 0.022); OR 1.009, (95% CI 1.0-1.0, p = 0.010). Further age/gender controlled model with aetiology and ammonia as independent predictors demonstrated aetiology significant predictor (OR 2.3, 95% CI 1.1-4.6, p = 0.016). **Conclusion:** Bacteraemia complicates 10% of ALF cases, with resistant organisms found in 23% of positive cultures. ALF aetiology and ammonia level were significant predictors of bacteraemia which remains a late complication. The role and length of antimicrobial prophylaxis requires re-evaluation in the modern era.

Disclosures: William Bernal – Flagship Pioneering: Consultant, No, No; Versantis: Consultant, No, No;

The following people have nothing to disclose: Anna Cavazza, Gjulio Ciroi T M, Tasneem Pirani, Mark John William McPhail

4306-A | CHARACTERIZATION AND THERAPY SIMULATION OF BIOENGINEERED LIVER GRAFTS FOR EXTRACORPOREAL LIVER ASSISTANCE IN ACUTE LIVER FAILURE

Aron R. Stumbras[1], Shawn A. Riesgraf[1], R. Noelle Palumbo[1], Victoria L. Nelson[1], Marie S. Balboa[1], Zachary A. Hannah[1], Ernesto R. Resnik[1], Christopher J. Fecteau[1], John R. Lake[1,2] and John J. Barry[1], (1) Miromatrix Medical Inc., (2)University of Minnesota

Background: Extracorporeal bioengineered liver (BEL) grafts offer a novel therapy for patients with Acute Liver Failure as a bridge to transplant or recovery by metabolizing ammonia and performing other hepatic functions. Miromatrix has previously reported functional BELs seeded with human and porcine hepatocytes. Here we demonstrate liver specific functions and an extracorporeal therapy simulation using BELs manufactured from entirely human-derived cells. **Methods:** Porcine livers were decellularized using previously published methods to create a porcine liver extracellular matrix (PL-ECM). The PL-ECM was seeded with human umbilical vein endothelial cells (HUVECs) and allowed to culture in a bioreactor for 8-19 days before seeding with primary human hepatocytes. Spent media was analyzed for urea, fibrinogen, alpha-1-antitrypsin (A1AT), and other BEL metabolites. Culture media was dosed with ammonium chloride, unconjugated bilirubin, or acetaminophen and sampled at relevant intervals to analyze ammonia clearance, bilirubin conjugation, and xenobiotic metabolism, respectively. To evaluate longevity of function, BELs underwent a simulated cold storage and transport study three days after hepatocyte seeding in which they were subjected to cold storage for 12 hours in Belzer UW solution and then returned to culture and functionally characterized for 72hrs. To evaluate compatibility as a bedside therapy, BELs were installed as part of an extracorporeal blood circuit (EBC) consisting of a Baxter Prismax® perfusion system, a customized

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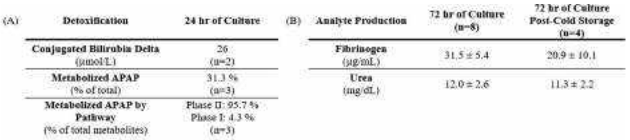
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Baxter Prismaflex® tubing set, and components from an OrganOx metra® Liver Perfusion Pack and evaluated using media perfusion. **Results:** BELs seeded with primary human hepatocytes demonstrated ureagenesis, ammonia clearance, protein production, bilirubin conjugation, and xenobiotic metabolism during 72 hours of in vitro culture. Following a cold storage and transport simulation, BELs demonstrated stable ureagenesis, ammonia clearance, and protein production for up to 96 hours. BELs also demonstrated stable ureagenesis, protein production, and other metabolic activity for the 72-hour therapy window evaluated in the EBC. **Conclusion:** The described isolation, seeding, and culturing strategy generates functional BELs capable of a variety of liver specific functions. This study demonstrates that seeding BELs with primary human hepatocytes results in retention of function after cold storage and compatibility with perfusion systems and components commonly used for EBC therapies.



(A) Detoxification	24 hr of Culture
Conjugated Bilirubin Delta (μmol/L)	26 (n=2)
Metabolized APAP (% of total)	31.3 % (n=3)
Metabolized APAP by Pathway (% of total metabolites)	Phase II: 95.7 % Phase I: 4.3 % (n=3)

(B) Analyte Production	72 hr of Culture (n=8)	72 hr of Culture Post-Cold Storage (n=4)
Fibrinogen (μg/mL)	31.5 ± 5.4	20.9 ± 10.1
Urea (mg/dL)	12.0 ± 2.6	11.3 ± 2.2

Figure 1. MIRO-001 functional characterization summary. (A) The average delta in conjugated bilirubin and percent acetaminophen (APAP) metabolized between 24 and 48 hr of culture beginning 24 hr post-hepatocyte seeding. APAP is shown as a percent of the dose metabolized and percent processed through each pathway. (B) The production of urea and fibrinogen (average ± standard deviation) between 48 and 72 hr of culture and culture post-cold storage.

Disclosures: Aron R. Stumbras – Miromatrix Medical-Inc.: Employee, Yes, No;
Shawn A. Riesgraf – Miromatrix Medical Inc.: Employee, Yes, No;
Christopher J. Fecteau – Miromatrix Medical Inc.: Employee, Yes, No;
John J. Barry – Miromatrix Medical Inc.: Executive role , Yes, No;
Disclosure information not available at the time of publication: R. Noelle Palumbo, Victoria L. Nelson, Marie S. Balboa, Zachary A. Hannah, Ernesto R. Resnik, John R. Lake

4307-A | COMPARISON OF MOLECULAR ADSORBENT RECIRCULATING SYSTEM TO STANDARD OF CARE IN ACUTE LIVER FAILURE

Kinnari Modi[1], Dylan Lopez[1], Blake Thompson[1], Wenjing Cai[1], Parvez S. Mantry[2], Mingyang Cui[1] and Hellen Oduor[1], (1)Methodist Dallas Medical Center, (2) The Liver Institute at Methodist Dallas

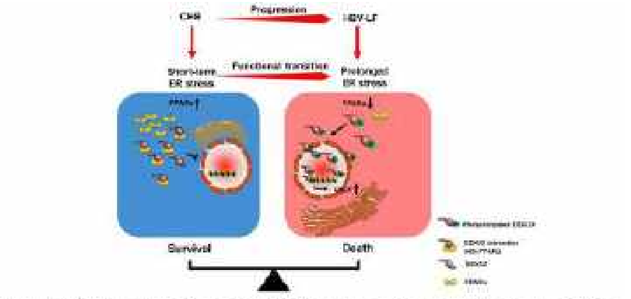
Background: Molecular Adsorbent Recirculating System (MARS) has been utilized in patients with severe liver failure with AKI and PSE at our center for the last 3 years. The aim of this study was to compare change in bilirubin, ammonia, PSE stage, and 28-day transplant free survival in those undergoing MARS to standard of care (SoC) in patients with acute liver failure (ALF) and acute-on-chronic liver failure (ACLF). **Methods:** This is a single center retrospective propensity-matched study performed at Methodist Dallas Medical Center. Data included patients with alcoholic hepatitis (AH), ACLF or ALF who underwent MARS or SoC from January 2019 to March 2022. MARS was performed 12 hrs/day for 5 days – MARS was interrupted in the case of hemodynamic instability, clinical deterioration, or in cases of substantial clinical improvement. Measured outcomes included change in bilirubin, ammonia, MELD-Na scores and PSE stage pre- and post-MARS. We assessed their overall mortality after receiving MARS or SoC therapy. Wilcoxon signed-rank test was used to compare continuous variables. Chi-squared test was used for categorical variables. **Results:** We used propensity score methods to assess efficacy of MARS vs SoC therapy in patients with ALF and ACLF. Before matching, 42 patients underwent MARS and 109 patients received SoC. After matching based on MELD-Na, age and gender, 68 patients (42 MARS and 26 SoC) were included in the final analysis. In the MARS group, mean sessions of MARS was 4. There was a statistically significant difference in bilirubin (median 20.35 vs 17) and ammonia levels (median 67 vs 31) pre- and post-MARS. The proportion of patients with stage 3 or 4 PSE significantly decreased after MARS therapy (28/42 vs 15/42). Comparing groups, the MARS groups had a significantly greater decrease in bilirubin ($p = 0.05$) and proportion of patients with PSE ($p = 0.05$). There was no significant difference in ammonia or survival. In MARS group, 28-day transplant free survival was 38.4% (15/39) – 3 patients had liver transplant. In the SoC group, 28-day transplant free survival was 42.3% (11/26) – none had liver transplant. **Conclusion:** In this propensity-matched analysis, there was a significantly greater decrease in bilirubin and proportion of patients with PSE stage 3-4 in the MARS group compared to SoC. There was not a significant difference in 28-day transplant free survival. We plan to increase the number of historical controls for future analysis.

Disclosures: The following people have nothing to disclose: Kinnari Modi, Parvez S. Mantry
Disclosure information not available at the time of publication: Dylan Lopez, Blake Thompson, Wenjing Cai, Mingyang Cui, Hellen Oduor

4308-A | DDX3X REGULATES THE FUNCTIONAL TRANSITION OF ENDOPLASMIC RETICULUM STRESS IN THE PROGRESSION OF LIVER FAILURE

Feng Ren, Xiangying Zhang, Ling Xu and Zhongping Duan, Beijing Youan Hospital Capital Medical University, Beijing, China

Background: Endoplasmic reticulum (ER) stress plays a critical role in the progression of liver failure (LF), but the underlying molecular mechanisms remainunclear. Here, we explored DDX3X to regulate cell fate under ER stress in theprogression of LF. **Methods:** Primary hepatocytes isolated from C57BL/6 mice were induced ER stress with tunicamycin (TM). DDX3X$^{fl/fl}$ and DDX3X$^{\Delta Hep}$ mice were induced ER stress with TM and liver injury with ConA, respectively. The expression of DDX3X were also analyzed in healthy, chronic hepatitis B (CHB) patients and HBV-associated LF patients. **Results:** DDX3X increased and translocated into nucleus with prolonged ER stress, and phosphorylation modification of DDX3X is the mechanism to regulate its subcellular localization. Under short-term ER stress, DDX3X was mainly expressed in cytoplasm and interacted with PPARα, which reduced the phosphorylation of DDX3X to promote the adaptive cell response. Under prolonged ER stress, phosphorylated DDX3X increased nuclear translocation to promote cell apoptosis by CHOP activation. In addition, DDX3X plays dual roles during Con A-induced liver injury, which exerts a protective effect in early phase (6 h) and a pro-injury effect in later phase (24 h). Moreover, compared with CHB, the level of DDX3X in serum and liver tissue was increased in patients with HBV-associated LF, and serum DDX3X consistent decline was correlated with a good prognosis. **Conclusion:** Our novel findings document the key regulatory function of DDX3X signalling in the pathophysiology of liver failure, and provide a rationale to target DDX3X as a refined therapeutic strategy to ameliorate liver injury.



In patients with CHB, hepatocytes suffer from mild ER stress. DDX3X is mainly expressed in the cytoplasm and interacts with PPARα, and the formation of the DDX3X/PPARα complex reduced phosphorylation of DDX3X to promote the adaptive cell response. As the disease progresses to LF, irreversible ER stress in hepatocytes leads to depression of PPARα, which promotes phosphorylation of DDX3X and increased nuclear translocation, the critical factor for initiating cell apoptosis via transcriptional activation of CHOP.

Disclosures: The following people have nothing to disclose: Feng Ren, Xiangying Zhang, Ling Xu, Zhongping Duan

f 4309-A | EARLY INITIATION OF THERAPEUTIC PLASMA EXCHANGE (TPE) IMPROVED OUTCOMES IN PATIENTS WITH IMPENDING ACUTE LIVER FAILURE (ALF)

Manasa Alla[1], Anand V. Kulkarni[1], Mithun Sharma[2], Anand Gupta[1], Shantan Venishetty[1], Sowmya T R[1] and Nagaraja Rao Padaki[1], (1)Aig Hospitals, Hyderabad, India, (2)Asian Institute of Gastroenterology, Hyderabad, Telangana, India

Background: Acute liver failure (ALF) with progressive cerebral edema is associated with high mortality for which liver transplantation is the only definitive treatment. Therapeutic plasma exchange (TPE) is an excellent bridging therapy for patients with ALF. TPE may prevent (contain) the cytokine storm and also has been reported to resolve hepatic encephalopathy (HE). We evaluated the efficacy and outcomes of early introduction of TPE in patients with impending ALF (Bil ≥ 5mg/dl, INR ≥ 1.5 with grade I/II encephalopathy) in comparison to ALF patients. **Methods:** We conducted a retrospective study from Jan 2022- March 2023 of all patients admitted with impending ALF at a tertiary care center. Among 38 patients admitted with a diagnosis of ALF, 16 patients with grade I/II HE (as per West Haven's criteria) & were categorised as impending liver failure (Group I) and 22 patients as ALF group with clinical features of (grade III/IV) HE at admission (Group II). 8 patients had spontaneous improvement in INR on follow up & were excluded for the study. Single volume TPE was offered in both the groups. Clinical & biochemical parameters & outcome measures were analysed. **Results:** Total 30(10 in group I & 20 in group II) patients were analysed. Most common aetiologies were viral hepatitis(16/30;60%) followed by drug induced liver injury (9/30; 30 %). Mean age of ALF patients was 21.2 ± 5.3 years and M:F ratio was 23:7. Mean MELD scores were comparable in group I vs group II (30.1 ± 7.4 vs 32 ± 8.1,p = 0.53). All patients received standard medical care, including N-acetyl cysteine and nutritional support. Mean bilirubin and INR was comparable in both the groups {23 ± 5.9 mg/dl vs 25 ± 7.1 mg/dl, p = 0.44; 3.91 ± 1.5 vs 4.1 ± 1.72, P = 0.76}. Higher arterial ammonia was noted in the group II {90 ± 34.7 mmol/L vs 110 ± 23.9 mmol/L, P = 0.07}. TPE was initiated in all patients with mean days post admission {1.6 ± 0.8; 2.1 ± 0.7, P = 0.59} & received higher mean no of TPE sessions in group II {2 ± 1.6 vs 4 ± 1.9, P < 0.05}. Mean days of hospitalization were higher in ALF group {9 ± 3.2 vs 12 ± 3.9 days,P = 0.04}. Incidence of AKI {20% (2/10) vs 25% (5/20) P = 0.30} & sepsis was comparable in both the groups {20% (2/10) vs 30 % (6/20), P = 0.58}. Early introduction of TPE reduced the progression to ALF in 90% (9/10) patients in the impending ALF group. 30-day transplant free survival was higher in group I {90% (9/10) vs 25% (5/20), P = 0.001}. High serum procalcitonin (≥ 2ng/mL) with AUC of 0.83 (sensitivity of 91%, specificity of 92%) and low fibrinogen (< 100mg/dl) with AUC = 0.84 (sensitivity of 88%, specificity of 90%) were found to be significantly associated with high mortality. **Conclusion:** ALF is characterised by rapid deterioration especially when cerebral edema sets in due to the hyperinflammatory state & early initiation of therapeutic plasma exchange in patients with impending ALF shows promising outcomes.

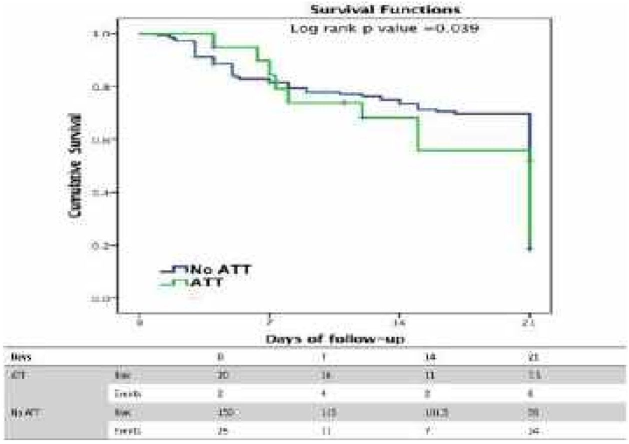
Disclosures: The following people have nothing to disclose: Manasa Alla, Anand V. Kulkarni, Mithun Sharma, Anand Gupta, Shantan Venishetty, Sowmya T R

Disclosure information not available at the time of publication: Nagaraja Rao Padaki

4310-A | EARLY LIVER TRANSPLANT MAY IMPROVE OUTCOMES IN PATIENTS WITH ANTITUBERCULAR THERAPY RELATED ACUTE LIVER FAILURE - (ATT- ALF) A PROSPECTIVE COHORT STUDY

Rakhi Maiwall[1], Ashinikumar Kumar Hidam[2], Harsh Vardhan Tevethia[1], Prashant Aggarwal[2], Rajan Vijayaraghavan[2], Shivali Panwar[2], Neha Chauhan[2] and Shiv Kumar Sarin[3], (1)Institute of Liver and Biliary Sciences, New Delhi, (2)Institute of Liver and Biliary Sciences, (3)Ilbs

Background: Patients with antitubercular related acute liver failure (ATT-ALF) have worse outcomes. Therapeutic plasma-exchange (TPE) improves survival in patients with ALF. We aimed to investigate the profile, prognostic factors, and the impact of TPE in improving outcomes of ATT-ALF compared to other etiologies. **Methods:** Prospective observational cohort study of ALF patients admitted to the intensive care unit. Cox-regression survival analysis was performed **Results:** Of the 170 ALF patients, 20(11.76 %) comprised ATT-ALF, majority had viral-related ALF in 94(79%). The most common indication of ATT was pulmonary in 40% followed by disseminated disease in 5 (25%).The most common ATT regime was rifampicin, isoniazid and ethambutol in 15 (75%). Patients with ATT-ALF were older [(39.4 ± 12.3) vs. (29.9 ± 10.34) years; $p < 0.001$], with lower aspartate and alanine aminotransferase (IU/L) [(815.08 ± 791) vs. (1769.24 ± 1449.94); $p = 0.019$], [(612.0 ± 781.0) vs. (1028.23 ± 1187.62); $p = 0.004$] respectively, and, higher proportion of patients meeting king's college criteria (KCC) [8 (61.5%) vs. 34 (36.6%); $p = 0.08$], but comparable MELD [(30.5 ±10.2) vs. (29.2±9.7); $p = 0.71$] and SOFA scores [(11.3± 2.8) vs. (11.5 ± 2.9); $p = 0.51$] compared to other etiologies. The mean jaundice to encephalopathy time was significantly longer in patients with ATT-ALF [(8.25 ± 5.73) vs. (6.04 ± 4.50) days; $p = 0.02$]. Patients with ATT-ALF had significantly worse 21-day transplant-free survival [HR 1.96, 1.01-3.89]. On multivariable analysis, higher age ($p = 0.003$, HR 1.03, 1.01-1.04), optic nerve sheath diameter (ONSD) ($P < 0.001$, HR 1.61, 1.29-1.99), presence of sepsis ($p = 0.002$, HR 2.13, 1.31-3.47) and ATT-ALF ($p = 0.049$, HR 1.76, 1.00-3.15) were independent predictors of worse survival, while use of TPE conferred better survival ($p = 0.005$, HR 0.44, 0.24-0.77). In the subset of patients with ATT-ALF, TPE could not improve survival [$p = 0.53$, (HR 0.61, 0.13-2.89)]. In these patients, higher ONSD [(7.5 ± 0.9) vs. (6.1 ± 1.0) mm; $p = 0.008$], serum bilirubin [(20.2 ± 6.1) vs. (12.3 ± 4.2)mg/dl; $p = 0.01$), serum ammonia [(313.3 ± 173.2) vs. (204.7 ± 48.7)mg/dl; $p = 0.04$),and shorter time from the initiation of ATT to the development of jaundice [(25.8 ± 14.3) vs. (87.5 ± 43.9)days; $p = 0.017$) significantly predicted higher mortality. **Conclusion:** Patients with ATT-ALF have worse outcomes and high mortality in the absence of liver transplant. TPE improves survival in patients with ALF, however, it does not confer survival benefit in ATT-ALF. Higher bilirubin and ammonia, shorter time to the development of jaundice from ATT initiation and severe cerebral edema govern worse outcomes in ATT-ALF indicating need of early liver transplantation. Trials exploring the benefits of TPE in ATT-ALF patients are needed.



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Disclosure information not available at the time of publication: Ashinikumar Kumar Hidam, Prashant Aggarwal, Shivali Panwar, Neha Chauhan

4311-A | EFFECTIVE ALBUMIN CONCENTRATION IN CHRONIC LIVER FAILURE IS DETERMINED MAINLY BY REVERSIBLE FACTORS: POSSIBLE THERAPEUTIC CONSEQUENCES

Margret Paar[1], Vera Heike Fengler[2], Gilbert Reibnegger[1], Kerstin Schnurr[3], Katja Waterstradt[3], Sebastian Patrick Schwaminger[1], Rudolf Ernst Stauber[1] and Karl Oettl[1], (1)Medical University of Graz, (2)University of Graz, (3)Medinnovation Gmbh

Background: Serum albumin from patients with chronic liver failure is reduced in its concentration, structurally modified and impaired in its functionality what led to the concept of the effective albumin concentration. Albumin exhibits binding/transport function for endo- and exogenous molecules and is used as therapeutic agent (e.g., infusion, dialysis devices); its functionality is thus of clinical and pharmacological interest. The effective albumin concentration could be affected by post-translational modifications (PTM) and bound ligands most probably influencing its conformation. We evaluated binding properties of albumin from patients with acute decompensation of cirrhosis with or without acute-on-chronic liver failure, therapeutic infusion solutions, and in vitro modified albumin to determine the impact of ligands and most frequent PTM in liver disease on albumin functionality. **Methods:** We applied EPR spectroscopy with 16-doxyl stearic acid as ligand and fluorescence titration with dansylsarcosine to characterize binding properties of albumin. The latter were investigated in i) purified albumin from plasma of liver patients and healthy controls, ii) in vitro oxidized or glycated albumin, iii) therapeutic albumin before and after stabilizer removal. Binding data were related to albumin redox states in terms of cysteine-34 (Cys-34) as well as bilirubin and fatty acid contents. **Results:** Albumin from patients with chronic liver failure and therapeutic albumin showed in part severely restricted binding properties (e.g., Binding efficiency (BE) is reduced to 34%, $P = 0.004$ in patients, and 38%, $P = 0.0005$ in therapeutic albumin). Removal of bilirubin from patients' albumin and stabilizers from therapeutic albumin led to substantial improvement of binding properties. Reversibly oxidized albumin with disulfide at Cys-34 had somewhat decreased binding properties (e.g., BE is reduced to 62%, $P < 0.0001$) while irreversible oxidation of Cys-34 or glycation had only minor impact. **Conclusion:** Impaired binding properties of albumin in patients with chronic liver failure or therapeutic albumin are determined primarily by reversible factors like binding/removal of (patho)physiological ligands or stabilizers and reversible oxidation of Cys-34. Other PTM like irreversible oxidation or glycation are less representative for albumin's effectiveness. Whether the quality of albumin is impaired primarily due to molecule modifications or by the pathological environment in terms of high ligand concentrations remains open.

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Disclosure information not available at the time of publication: Vera Heike Fengler, Gilbert Reibnegger, Kerstin Schnurr, Katja Waterstradt, Sebastian Patrick Schwaminger, Rudolf Ernst Stauber, Karl Oettl

4312-A | FOXA2 IS ESSENTIAL FOR CPS1 TRANSCRIPTION TO MAINTAIN THE UREA CYCLE AND PREVENT HYPERAMMONEMIA IN ACUTE LIVER FAILURE

Rui Liu[1], Rilu Feng[1], Chenhao Tong[1], Tao Lin[1], Xiaofeng Li[2], Carsten Sticht[3], Stefan Munker[4], Yujia Li[1], Sai Wang[1], Matthias Ebert[1], Huiguo Ding[5], Hua Wang[2], Honglei Weng[1] and Steven Dooley[1], (1)Department of Medicine II, Section Molecular Hepatology, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany, (2)The First Affiliated Hospital of Anhui Medical University, Hefei, China, (3)NGS Core Facility, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany, (4)Department of Medicine II, University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany, (5)Department of Gastroenterology and Hepatology, Beijing You'an Hospital, Capital Medical University, Beijing, China

Background: Disruption of the urea cycle results in hyperammonemia and thus causes hepatic encephalopathy (HE), a lethal complication of acute liver failure (ALF). A complete urea cycle requires six enzymes, including the rate-limiting enzyme carbamoyl phosphate synthetase I (CPS1). To date, the detailed regulation of CPS1 transcription in order to maintain urea cycle in ALF remains largely unknown. **Methods:** Expression of CPS1 and transcription factors such as FOXA2 and C/EBPα was examined by immunohistochemistry in liver tissues collected from 78 ALF patients including 27 with HE. The regulatory mechanisms of these factors on CPS1 transcription were investigated in different cell lines and primary cells. The effect of FOXA2 in ALF was further investigated in acetaminophen-treated mice with or without adeno-associated virus serotype 8 (AAV8)-Foxa2 injection. **Results:** Physiologically, CPS1 transcription requires FOXA2 to maintain chromatin accessibility on their enhancers, which provides open binding sites for C/EBPα. In ALF, hepatic C/EBPα expression is inhibited by inflammation. In this setting, retinoic acid receptor synergizes with FOXA2 to maintain CPS1 transcription. Once ALF patients suffer from massive hepatic necrosis, liver progenitor cells perform the urea cycle to prevent hyperammonemia by initiating a transcription network comprising FOXA2 and C/EBPα. In ALF, HE occurs in patients lacking expression of these transcription factors. In mice with acetaminophen-induced ALF, injection of Foxa2-AAV8 maintains urea cycle and prevents hyperammonemia. **Conclusion:** FOXA2 is essential for maintaining the urea cycle to prevent hyperammonemia. Pharmaceutical induction of hepatic FOXA2 expression might represent a novel approach to treat HE in ALF.

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Disclosure information not available at the time of publication: Rui Liu, Rilu Feng, Chenhao Tong, Tao Lin, Xiaofeng Li, Carsten Sticht, Hua Wang

4313-A | HEPATIC BIOPRINTED TISSUE THERAPEUTICS (BTTS) DEMONSTRATE COMPARABLE FUNCTION WHEN IMPLANTED INTO INTRAPERITONEAL OR SUBCUTANEOUS SITES

Christopher Dickman, Zainab A. Bazzi, Oksana Nemirovsky, Farin Vaez Livary, Fiona Li, Stephanie A. Campbell, Haley Tong, Rishima Agarwal, Matthew R. Zeglinski, Jaedyn D. Foley, Lyndsey Hayes, Paola Romero, Mahinur Efe, Simon Beyer, Tamer Mohamed, Reza Jalili, Samuel Wadsworth, Spiro Getsios and Rafal P. Witek, Aspect Biosystems

Background: Standard of care treatment for many liver diseases including acute liver failure (ALF) and urea cycle disorders (UCDs) consist of liver transplantation. This is effective but invasive and requires chronic immune suppression and can result in bleeding. Recent research has demonstrated promising results for encapsulated hepatocytes implanted into the intraperitoneal (IP) space as a treatment for pediatric ALF. It is unclear if this procedure can be completed at less invasive surgical sites. The subcutaneous (SubQ) space has the benefit of being comparatively non-invasive as well as being larger and in some liver diseases the IP space may be fouled with ascites. This abstract describes the implantation of hepatic BTTs containing primary human hepatocytes (PHHs) and mesenchymal stromal cells (MSCs) into both the IP and SubQ spaces of NSG mice. **Methods:** PHH and MSC cells were formed into spheroids prior to mixing with an alginate-based biomaterial. Using Aspect Biosystems' proprietary microfluidic 3D bioprinting technology, the spheroids were 3D printed into BTTs. BTTs were then implanted into both IP and SubQ spaces of NSG mice. Plasma was collected at regular intervals over a period of 4 weeks. Human albumin was measured via ELISA. **Results:** In mice that received BTTs into the IP space, (n = 4) mean human albumin levels were 1137 ng/mL after 1 day and rising to 2186 ng/mL after 2 weeks. Mice that received BTTs in the SubQ space (n = 5) had day 1 mean human albumin levels of 793 ng/mL with levels rising to 1970 ng/mL after 2 weeks. Mice receiving BTTs to the SubQ space had faster wound healing when compared to mice receiving IP surgery. **Conclusion:** Hepatic BTTs maintain high function when implanted into either the SubQ or IP space of NSG mice. SubQ surgeries were comparatively non-invasive. These observations suggest that a minimally invasive surgery for implantation of liver cell therapies may have several benefits. The larger space available for SubQ implantation could allow for the implantation of larger BTTs, as well as for more frequent monitoring and replacement. Decreased invasiveness may also make the procedure an option of non-life-threatening liver diseases, or in patients who may not tolerate surgery. In the future, we aim to test the implantation of larger BTTs into the SubQ space of rats and additionally examine the longer-term function of SubQ BTTs in an in vivo efficacy model of metabolic liver diseases including PKU and A1AT deficiency.

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4314-A | HEPATIC BIOPRINTED TISSUE THERAPEUTICS (BTTS) RESCUE MICE FROM CCI4-INDUCED ACUTE LIVER FAILURE

Christopher Dickman, Zainab A. Bazzi, Oksana Nemirovsky, Farin Vaez Livary, Fiona Li, Stephanie A. Campbell, Haley Tong, Rishima Agarwal, Matthew R. Zeglinski, Jaedyn D. Foley, Lyndsey Hayes, Paola Romero, Mahinur Efe, Simon Beyer, Tamer Mohamed, Reza Jalili, Samuel Wadsworth, Spiro Getsios and Rafal P Witek, Aspect Biosystems

Background: Acute liver failure (ALF) and Acute-on-chronic liver failure (ACLF) are treated with liver transplantation. The limited supply of donor organs results in a large number of patients dying while awaiting surgery. Researchers have begun to examine the transplantation of isolated primary human hepatocytes (PHHs) with promising results in pediatric ALF patients. Implementation of this process remains a challenge due to the absence of a standardized treatment. This abstract describes experiments using Bioprinted Tissue Therapeutics (BTTs) containing PHHs and mesenchymal stromal cells (MSCs) to treat immune competent mice with CCl_4-induced ALF. **Methods:** To create hepatic BTTs, PHHs and MSCs were co-aggregated into spheroids and then suspended in an alginate-based biomaterial. Aspect Biosystems' proprietary microfluidic 3D bioprinting technology was used to generate BTTs. ALF was induced in C57BL/6 mice via SubQ injection of CCl_4. Mice were implanted with hepatic BTTs or cell-free controls into either the intraperitoneal (IP) or subcutaneous (SubQ) space. Survival was measured for 7 days after implantation and livers were embedded upon loss of the mouse or at day

7. Plasma was collected at days -7, 1 and 7 post-surgery. **Results:** BTT treatment was capable of rescuing mice with ALF. When BTTs were implanted into the IP space (n = 15), B6 mice had a survival rate of 78% when compared to 46% for mice receiving cell-free controls (n = 15). When implanted into the SubQ space, BTTs were also capable of improving survival. With a day 7 survival rate of 85% vs 50% for treated (n = 7) vs control (n = 8) mice. To confirm these results this experiment was repeated with cells from an alternate PHH donor. With the alternate donor the survival rate for mice receiving SubQ BTTs was 50% (n = 8) vs 13% for control mice (n = 8). Collectively the combined survival rate for BTT-treated mice was 68% vs 35% for untreated animals with a p-value of 0.003. **Conclusion:** Hepatic BTTs are capable of rescuing mice from ALF induced via injection of CCl_4. Implantation of BTTs into either SubQ or IP sites resulted in comparable efficacy. This data suggests that BTTs could be used as a bridge to transplantation or recovery in individual's with ALF or ACLF. Given the high function of these BTTs, it is also possible that they may have efficacy in the treatment of chronic metabolic liver diseases. In the future we aim to scale these BTTs towards the treatment of a rat model of ALF.

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4315-A | HEPATOCYTE GROWTH FACTOR RECEPTOR (C-MET) IS REQUIRED FOR LIMITING HEPATOTOXICITY, PROMOTING LIVER REGENERATION AND RECOVERY FOLLOWING ACETAMINOPHEN-INDUCED ACUTE LIVER FAILURE IN MICE

Siddhi Jain[1], Ranjan Mukherjee[2], Matthew Avery Copeland[2], John Stoops[2], Wendy M. Mars[2] and Bharat Bhushan[2], (1)University of Pittsburgh, Pittsburgh, PA, (2)University of Pittsburgh

Background: c-MET receptor, also referred as hepatocyte growth factor (HGF) receptor, plays a crucial role in promoting hepatocyte proliferation following partial hepatectomy (PH). However, elimination of HGF/c-MET signaling can be compensated by other proliferative pathways in the PH model. The involvement of c-MET in acetaminophen (APAP)-induced liver injury (AILI), the clinically-relevant model of acute liver failure, remains underexplored. The role of c-MET in AILI cannot be assumed identical to its role in PH of a healthy liver, as the regenerative response in AILI is intricately governed by the presence of substantial liver injury and inflammation, distinguishing it from PH. In our earlier study, we identified a clear dose-dependent activation pattern of c-MET in response to APAP overdose in mice. **Methods:** To investigate the causal role of c-MET in AILI and associated regeneration, we utilized an albumin-CRE system to specifically delete c-MET in the liver. Both wild-type (WT) and liver-specific c-MET KO mice were given 300 mg/kg of APAP to examine liver injury, regeneration parameters, and associated signaling cascade at multiple time points. **Results:** While, the initial liver injury appeared comparable in both WT and c-MET KO mice, severe inhibition of liver regeneration was observed in c-MET KO mice leading to uncontrolled progression of liver injury and significant mortality. Hepatocyte proliferation was almost completely blocked in c-MET KO mice. WT mice showed robust regeneration response and complete recovery. In c-MET KO mice, the mechanisms that initiate APAP-induced liver injury, such as metabolic activation of APAP, formation of APAP-protein adducts, and activation of JNK, remained unaltered. ERK signaling was inhibited in c-MET KO mice causing failed activation of core cell cycle machinery (i.e., phosphorylation of retinoblastoma protein and induction of cyclin D1), resulting in impaired liver regeneration. Analysis of RNA-seq data demonstrated failed activation of several important regulators of hepatocyte proliferation in c-MET KO mice. **Conclusion:** The liver-specific c-MET deletion inhibited hepatocyte proliferative signaling and blocked liver regeneration, resulting in uncontrolled liver injury progression and failed recovery following APAP overdose. The absence of c-MET signaling was not compensated by other proliferative pathways signifying its important role in recovery following APAP-induced acute liver failure.

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Disclosure information not available at the time of publication: Ranjan Mukherjee, Matthew Avery Copeland, John Stoops, Wendy M. Mars, Bharat Bhushan

4316-A | INHIBITION OF INTERLEUKIN-6 REDUCES HEPATIC ENCEPHALOPATHY AND MEDIATORS OF IMMUNE SUPPRESSION IN MICE WITH CLINICALLY RELEVANT ACETAMINOPHEN-INDUCED ACUTE LIVER FAILURE

Bryan L. Copple, Jenna Strickland, Katherine Roth and Cheryl Rockwell, Michigan State University

Background: In severe cases of acetaminophen (APAP) overdose, acute liver injury rapidly progresses to acute liver failure (ALF), producing life-threatening extrahepatic complications including hepatic encephalopathy, multi-organ dysfunction syndrome, and severe immune suppression. The mechanisms linking liver injury to the pathogenesis of systemic complications remain poorly defined. **Methods:** To gain insight into these mechanisms, we utilized an experimental setting of APAP overdose in which mice were treated with a hepatotoxic dose of APAP (300 mg/kg) that fails to progress to ALF (referred to AALI) or a dose of APAP (500 mg/kg) that produces clinically relevant ALF (referred to AALF). **Results:** Compared to mice with AALI, AALF mice developed features of hepatic encephalopathy, including cerebral edema, reduced cerebral blood flow, and neurological deficits in reflexes and locomotor activity. Further, levels of IL-10 and PD-L1, associated with immune suppression in ALF patients, were markedly higher in AALF mice. Remarkably, despite striking differences in measures of hepatic encephalopathy and immune suppression, peak liver injury and blood ammonia concentrations, a putative causative factor in hepatic encephalopathy, were not different between mice with AALI and mice with AALF. Clinical studies have demonstrated an association between high blood levels of IL-6 and severity of hepatic encephalopathy in ALF patients. Consistent with these findings, plasma concentrations of IL-6 were greater in AALF mice. To examine whether IL-6 is causally involved in the pathogenesis of hepatic encephalopathy and immune suppression, AALF mice were treated with either IL-6 neutralizing antibody or isotype control antibody. Neutralization of IL-6 did not impact liver injury, blood ammonia concentrations, or hepatocyte proliferation, however, it restored cerebral blood flow, reduced brain edema, and improved neurological deficits. Further, neutralization of IL-6 reduced hepatic levels of IL-10 and PD-L1. **Conclusion:** These studies demonstrate that elevated blood concentrations of ammonia alone are insufficient to produce hepatic encephalopathy in mice with AALI. Moreover, these studies indicate that IL-6 is causally involved in the development of hepatic encephalopathy and in the immune suppression that occurs in APAP-induced ALF.

Disclosures: The following people have nothing to disclose: Bryan L. Copple, Jenna Strickland, Katherine Roth, Cheryl Rockwell

4317-A | LIVER STIFFNESS MEASUREMENT HELPS THE CLINICAL DECISION MAKING IN ACUTE LIVER FAILURE

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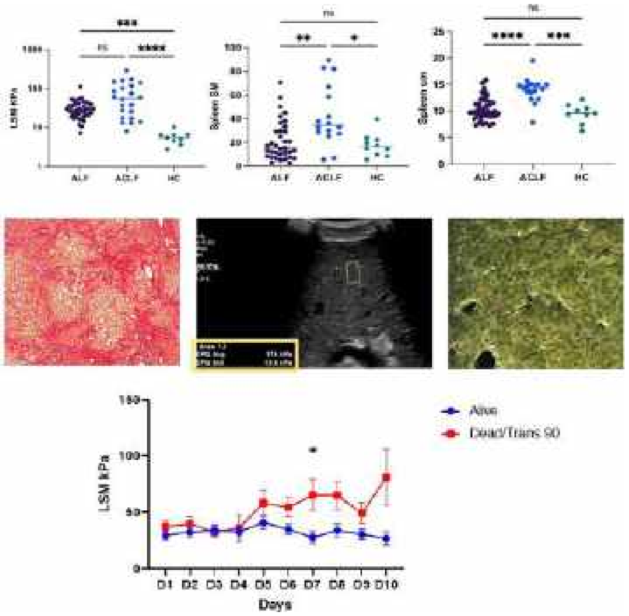
Background: Acute liver failure (ALF) is a rare life-threatening disease requiring intensive care admission and often liver transplant, where the accurate selection of patients is crucial. Liver elastography is a non-invasive tool that can measure hepatic stiffness but previous results have been inconclusive in ALF. **Methods:** Patients admitted between October 2021 to March 2023 to the Liver Intensive therapy unit at King's College Hospital with ALF and acute-on-chronic liver failure (ACLF) were recruited, with healthy individual's (HC) used as controls. Imaging was performed using a Philips Affiniti 70. Average shear wave velocity was recorded with ElastPQ on the right and left liver lobes and the spleen. Portal vein flow, hepatic artery resistive index (HARI) and peak systolic velocity were also recorded. Physiological and histological data, when available, were used as comparison. **Results:** Forty patients with ALF, 22 patients with ACLF, and 9 HC were included in the study. 30% of ALF patients died and 30% were transplanted within 90 days from admission. Liver stiffness measurement of the right lobe (LSM) accurately identified HC (5.6 ± 2 kPa), ALF (31.7 ± 17kPa) and ACLF (76.3 ± 71 kPa) patients (ALF vs ACLF, $p = 0.0301$). Spleen size and stiffness discriminated between ALF (10.4 ± 2 cm and 21.4 ± 16.6kPa) and ACLF (14 ± 2.3 cm and 42.6 ± 26 kPa). At admission LSM was not different between ALF patients that spontaneously survived vs patients who died or were transplanted in the following 90 days. However, the trend over the first 10 days of admission was different with a peak of LSM between day 6 and 8 in spontaneous survivors followed by reduction during the recovery phase. Conversely, ALF patients with poor prognosis showed a persistently increased LSM. No correlation was found with the amount of noradrenaline used, the mean arterial pressure (MAP), the central venous pressure (CVP). In ACLF, LSM correlated directly with right lobe diameter and the highest values were found in alcoholic hepatitis and Wilson's disease ($LSM > 100kPa$). 10 ALF explants and 6 ACLF explant/biopsy were analysed. Confluent hepatocellular necrosis characterised ALF, while intralobular inflammation was a feature present in both diseases. Cholestasis, particularly in the cytoplasmatic compartment was present mainly in ACLF and correlated with high values of LSM (Spearman $r = 0.54$, $p = 0.034$). **Conclusion:** LSM identifies acute from acute-on-chronic liver failure together with spleen volume and stiffness. In ALF stiffness peaks at day 7 of admission with subsequent reduction in patients spontaneously surviving. Histology suggests that cytoplasmatic cholestasis might be related to higher stiffness. Further studies, in a larger cohort, are needed to better understand the diagnostic role of liver stiffness in acute liver failure and whether addition of these values to existing prognostic criteria could improve sensitivity and specificity.

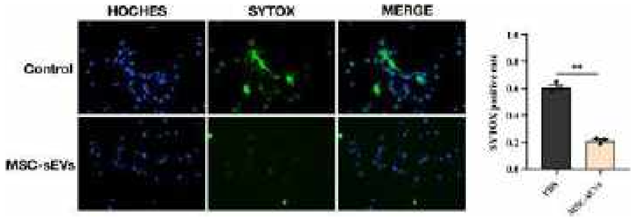


Disclosures: The following people have nothing to disclose: Francesca Maria Trovato, Florent Artru, Rosa Miquel, Tasneem Pirani, Mark John William McPhail

4318-A | MESENCHYMAL STEM CELL'S SMALL EXTRACELLULAR VESICLES PROMOTE HEPATOCYTE REGENERATION VIA ATTENUATING MACROPHAGE EXTRACELLULAR TRAPS

Zhihui Li[1], Jing Zhang[2], Shibo Meng[1], Weizhen Weng[1], Junyi Wang[1] and Bingliang Lin[1], (1)The Third Affiliated Hospital, Sun Yat-Sen University, (2)Department of Infectious Diseases, Third Affiliated Hospital of Sun Yat-Sen University

Background: Acute liver failure (ALF) is a a severe clinical syndrome characterized by dysregulated immune response and extensive hepatocytes death without effective therapies. Hepatocyte regeneration is the key to rescuing ALF. Previous studies have confirmed that macrophage extracellular traps (METs) has been associated with immune-mediated diseases and small extracellular vesicles (sEVs) act as mediators in the inhibition of inflammation by mesenchymal stem cells (MSCs). The aim of this study was to explore the role of MSC-derived sEVs (MSC-sEVs) and METs in treating mice with ALF. **Methods:** To establish the ALF cell model of THLE-2 cell line induced by H2O2 and ALF mouse model induced by LPS/D-GalN, collect and identify MSC-sEVs, and added to METs-induced macrophages THP-1 cell, then co-culture with ALF hepatocytes. To detect the proliferation and apoptosis of ALF hepatocytes by fluorescent labeling technique, meanwhile, detect the METs' quantity by immunofluorescence technique and Western Blotting. MSC-sEVs were injected into ALF mouse through the tail vein to assess the effect in ALF mouse. To test the survival, changes in serology, liver pathology, the molecules and genes of proliferation and apoptosis, and the yield of METs in different phases by Western Blotting, qPCR and immunohistochemistry technique. **Results:** The MSC-sEVs were merged with ALF cell model, and the proliferation and activity of ALF hepatocytes was increased in vitro. Likewise, the treatment of MSC-sEVs led to higher 24 h mouse survival rates and significant reductions in METs' formation and liver injury compared to treatment with sEV-free concentrated medium, and the inflammatory infiltration and hyperemia of the liver tissue were decreased. METs decreased when macrophages were subjected to MSC-sEVs(Fig), and when METs were co-cultured with hepatocytes, apoptosis increased and proliferation decreased, which were reversed by the inhibition of METs. **Conclusion:** Mesenchymal stem cell's small extracellular vesicles can improve the prognosis of acute liver failure by reducing apoptosis and promoting hepatocyte proliferation in vitro and in vivo. The function of ameliorating liver injury may be achieved by attenuating macrophage extracellular traps.



Disclosures: The following people have nothing to disclose: Zhihui Li, Jing Zhang, Shibo Meng, Weizhen Weng, Junyi Wang, Bingliang Lin

4319-A | MESENCHYMAL STEM CELLS PRETREATED WITH INTERLEUKIN-33 ATTENUATE ACUTE LIVER FAILURE BY IMPROVING MIGRATION AND POLARIZING M2 MACROPHAGES

Hui Yuan, Jiali Song, Linya Peng and Chuanlong Zhu, The First Affiliated Hospital of Nanjing Medical University

Background: Mesenchymal stem cells (MSCs) are highly effective in the treatment of acute liver failure (ALF). The efficacy of MSCs is closely related to the inflammatory environment. Therefore, we investigated

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

the functional changes of MSCs in response to interleukin-33 (IL-33) stimulation. **Methods:** The BMSCs were pretreated with 10ng/ml IL-33 for 24 h. The differentially expressed cytokines between BMSCs and IL-33 pretreated BMSCs (BMSCs-33) were screened by PCR Array and verified by western blot. Transwell and in vivo imaging were used to detect the migration ability of BMSCs and BMSCs-33. Bone marrow macrophages (BMDM) were co-cultured with BMSCs and BMSCs-33, and the ratio of M1/M2 polarization was detected by western blot and immunofluorescence, and the changes of NF-κB pathway proteins in BMDM were explored. The rat liver cell line BRL 3A was treated with 2mg/ml D-GalN and 1ug/ml LPS, and then co-cultured with BMDM. The apoptosis pathway proteins and apoptosis ratio of BRL 3A cells were detected by western blot and flow cytometry. Rats with acute liver failure were injected with 1x10^7 cells /kg BMSCs and BMSCs-33 via the tail veins, respectively. The changes in transaminase levels, HE pathology, and 7-day survival rate were compared. **Results:** PCR Array results showed that CCR2 expression was increased in BMSCs-33. CCL2 cytokine expression was the highest in the liver of ALF rats. Under the induction of CCL2, the migration number of BMSCs-33 group was higher than that of BMSCs group (123.40 ± 9.13 *vs* 81.00 ± 4.30, $p < 0.05$). In vivo imaging results showed that the number of BMSCs-33 migrating to the injured liver was significantly increased, and this effect was attenuated after knocking down CCR2. Upon LPS stimulation, the NF-κB pathway of BMDM was activated and its phenotype was polarized toward M1. BMSCs-33 inhibited the expression of p-IκBα and p-p65 protein in BMDM, and the polarization ratio of M2 macrophages was also higher than that in BMSCs group (73.30% ± 3.96% *vs* 50.99% ± 4.20%, $p < 0.05$). M2 macrophages could further inhibit the expression of inflammatory factors IL-1β and IL-6 in hepatocytes, reduced the levels of C-Caspase3 and Bax protein in hepatocytes. Finally, animal experiments showed that ALT and AST levels of rats in BMSCs-33 group were 602.20 ± 246.01 U/L and 2,354.48 ± 755.30 U/L, respectively, which were significantly lower than those in D-GalN/LPS group (11,669.75 ± 976.93 U/L, 11,966.48 ± 2381.60 U/L, $p < 0.05$).) and BMSCs group (3,270.82 ± 96.01 U/L, 7,622.17 ± 216.51 U/L, $p < 0.05$). The 7-day survival rate of BMSCs-33 group was also higher than that of BMSCs group (62.50% *vs* 37.50%). **Conclusion:** BMSCs-33 increases its homing ability to damaged liver through CCR2/CCL2 axis and inhibits the NF-κB pathway of BMDM to induce M2 macrophage polarization. IL-33 can improve the efficacy of BMSCs in the treatment of ALF, which provides a new strategy for clinical treatment.

Disclosures: The following people have nothing to disclose: Hui Yuan, Jiali Song, Linya Peng, Chuanlong Zhu

4320-A | SYSTEMATIC LITERATURE REVIEW OF BIOLOGICAL AND NONBIOLOGICAL ARTIFICIAL LIVER SUPPORT TRIALS

Robert S. Brown Jr[1], Robert A. Fisher[2], Ryan J. Imhoff[2] and William H. Thatcher[2], (1)Weill Cornell Medicine, NY, (2)Cti Clinical Trial and Consulting Services

Background: Liver failure is a leading cause of morbidity and mortality. Due to organ scarcity, research on liver support systems such as bioartificial livers (BAL), nonbiological artificial livers (NBAL), and xenogeneic whole-organ extracorporeal liver perfusion (X-ECLP) has become vital. **Methods:** A systematic approach based on PRISMA guidelines was used to search the Medline database (via PubMed) for English-language studies evaluating ex-vivo liver perfusion in humans through December 2, 2022. All studies were screened for clinical trials. Amidst the recent discussions and recommendations of porcine donors as the most feasible modality of xenoperfusion, relevant porcine X-ECLP case reports and series were also included. This was due to the absence of published trials in any whole-organ or X-ECLP approaches. **Results:** Two reviewers screened 694 records and found 58 eligible studies: 16 on BAL, 32 on NBAL, and 10 on X-ECLP using porcine livers (1 found in bibliographic review). Table 1 provides a summary of the included studies. The majority were small-scale trials, including Phase I (10), Phase I/II (1), Phase II/III (1), proof of concept (2), pilot (2), investigational device exemption (1), and investigator-initiated randomized trials (20). There were 5 porcine X-ECLP case reports and 5 case series. The average sample size was 43 (range: 1-234) among BAL/NBAL and 7 (1-45) for X-ECLP. Primary endpoints focused on safety/adverse events and survival. Some common AEs included hypotension, administration site reactions, bleeding events, and infections. Porcine X-ECLP similarly studies focused on safety and survival, while also reporting on porcine endogenous retrovirus cross-infection and donor organ survival. **Conclusion:** Ex-vivo liver support systems have had significant research interest, but trials of BALs and NBALs have not consistently demonstrated substantial improvement in patient outcomes. The lack of success may be attributed to ill-defined patient populations, small sample size, variability in patient management protocols, and the critical timing of device use. Larger randomized controlled trials and optimization of patient selection to achieve a homogeneous study group, device management, and treatment protocols are crucial. Lessons learned from past studies can guide much-needed future research in improving outcomes for patients with liver failure.

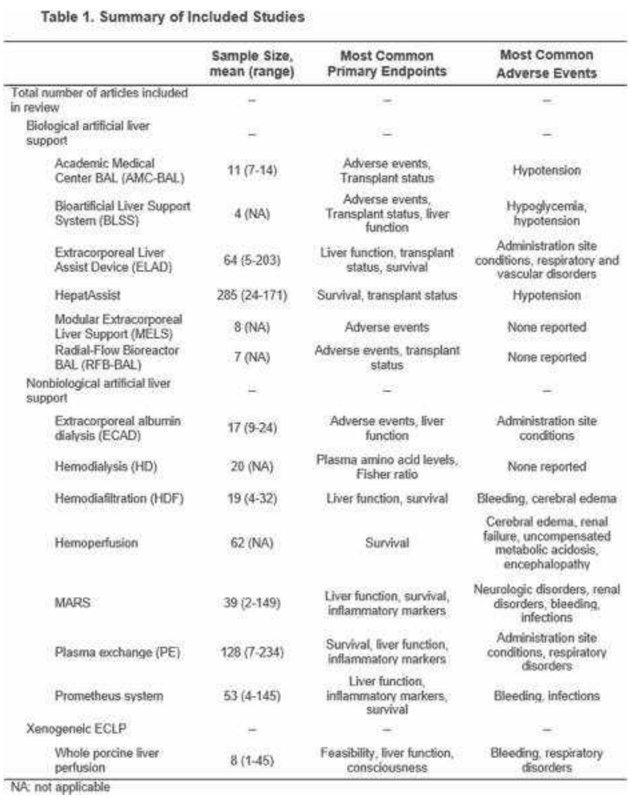


Table 1. Summary of Included Studies

	Sample Size, mean (range)	Most Common Primary Endpoints	Most Common Adverse Events
Total number of articles included in review	–	–	–
Biological artificial liver support	–	–	–
Academic Medical Center BAL (AMC-BAL)	11 (7-14)	Adverse events, Transplant status	Hypotension
Bioartificial Liver Support System (BLSS)	4 (NA)	Adverse events, Transplant status, liver function	Hypoglycemia, hypotension
Extracorporeal Liver Assist Device (ELAD)	64 (5-203)	Liver function, transplant status, survival	Administration site conditions, respiratory and vascular disorders
HepatAssist	285 (24-171)	Survival, transplant status	Hypotension
Modular Extracorporeal Liver Support (MELS)	8 (NA)	Adverse events	None reported
Radial-Flow Bioreactor BAL (RFB-BAL)	7 (NA)	Adverse events, transplant status	None reported
Nonbiological artificial liver support	–	–	–
Extracorporeal albumin dialysis (ECAD)	17 (9-24)	Adverse events, liver function	Administration site conditions
Hemodialysis (HD)	20 (NA)	Plasma amino acid levels, Fisher ratio	None reported
Hemodiafiltration (HDF)	19 (4-32)	Liver function, survival	Bleeding, cerebral edema
Hemoperfusion	62 (NA)	Survival	Cerebral edema, renal failure, uncompensated metabolic acidosis, encephalopathy
MARS	39 (2-149)	Liver function, survival, inflammatory markers	Neurologic disorders, renal disorders, bleeding, infections
Plasma exchange (PE)	128 (7-234)	Survival, liver function, inflammatory markers	Administration site conditions, respiratory disorders
Prometheus system	53 (4-145)	Liver function, inflammatory markers, survival	Bleeding, infections
Xenogeneic ECLP	–	–	–
Whole porcine liver perfusion	8 (1-45)	Feasibility, liver function, consciousness	Bleeding, respiratory disorders

NA: not applicable

Disclosures: Robert S. Brown – eGenesis: Consultant, Yes, No; Gilead: Consultant, No, No; Abbvie: Consultant, No, No; Intercept: Consultant, No, No; Mallinckrodt: Consultant, No, No; Ocelot Bio: Consultant, No, No;

Disclosure information not available at the time of publication: Robert A. Fisher, Ryan J. Imhoff, William H. Thatcher

4321-A | THE THERAPEUTIC CAPACITIES OF THREE-DIMENSIONAL HUMAN UMBILICAL MESENCHYMAL STEM CELLS IN ACUTE LIVER FAILURE MICE

Liang Peng, Third Affiliated Hospital of Sun Yat-Sen University, Shu Zhu, The Third Affiliated Hospital of Sun Yat-Sen University and Zhiyong Zhang, The Third Affiliated Hospital of Guangzhou Medical University

Background: The mortality rate of acute liver failure (ALF) is extremely high. Mesenchymal stem cells (MSCs) could alleviate liver damage as a regenerative medicine treatment. In recent years, more and more studies have shown that three-dimensional (3D) culture can increase the therapeutic potential of MSCs in other disease models. This study aims to compare the therapeutic capacities of mesenchymal stem cells cultured in 3D and 2D conditions in mice with ALF. **Methods:** We employed 3D dynamic system with microcarriers and traditional 2D culture flasks to amplify human umbilical cord MSCs. Severe liver damage formed in 8-week old male C57BL/6J mice as animal model by intraperitoneal injection of 250mg/kg thioacetamide. 1×10^6 2D or 3D MSCs dissolved in 100ul PBS or 100ul PBS alone were administered via tail vein 12 hours later after modeling. Cost, survival rate, serum transaminase, and liver necrosis area fraction of each group were measured and compared. **Results:** 1. Both 2D and 3D cultivation maintain the morphology, multidirectional differentiation ability and surface molecular marker expression of MSCs. 2.To harvest 1×10^{10} MSCs, 3D cultivation reduces labor cost, energy consumption and space occupation by 83.3%, 97%, 80% compared to 2D cultivation, respectively. 3. Compared to the PBS group, The overall survival improved significantly in both 2D and 3D MSCs groups (PBS vs. 2D, $p = 0.0124$. PBS vs. 3D, $p = 0.0009$). The level of serum aspartate aminotransferase (AST) decreased in MSCs groups. (36h: PBS vs. 2D, 8767.14 ± 2457.29U/L vs. 5673.00 ± 2541.11U/L, $p = 0.01$, PBS vs. 3D, 8767.14 ± 2457.29 U/L vs. 6289.5 ± 1935.99U/L, $p = 0.012$. 60h: PBS vs. 2D, 4325.00 ± 1025.30U/L vs. 966.67 ± 409.18U/L, $p = 0.001$, PBS vs. 3D, 4325.00 ± 1025.30U/L vs. 1400.00 ± 1020.94U/L, $p = 0.002$.) The liver necrosis area fraction decreased significantly in MSCs groups. (60h: PBS vs. 2D, 0.71 ± 0.08 vs. 0.43 ± 0.07, $p = 0.02$, PBS vs. 3D, 0.71 ± 0.08 vs. 0.34 ± 0.10, $p < 0.000$. 84h: PBS vs. 2D, 0.44 ± 0.07 vs. 0.17 ± 0.04, $p = 0.001$, PBS vs. 3D, 0.44 ± 0.07 vs. 0.13 ± 0.12, $p = 0.007$.) There was no significant difference in overall survival rate, serum level of AST, and liver necrosis area fraction between 2D and 3D MSCs in ALF mice. **Conclusion:** 1. Both 2D and 3D MSCs have achieved good therapeutic capacities in acute liver failure. The effect of 3D MSCs on acute liver failure mice was not inferior to that of 2D MSCs.

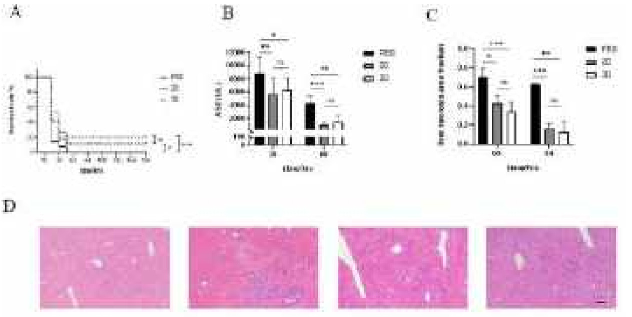


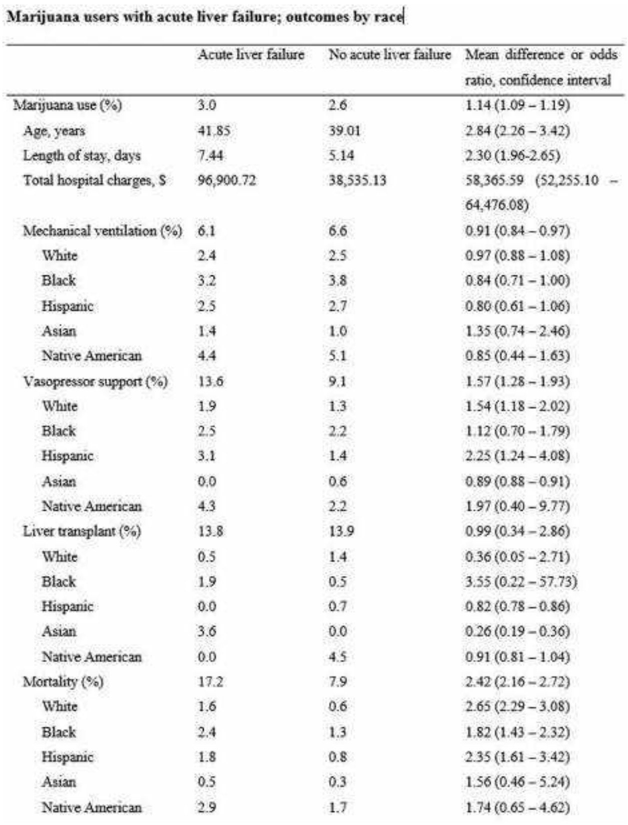
Figure. A. Survival analysis of each group. B. The serum level of AST in each group at 36h and 60h after TAA injection. C. Quantification of necrotic area fraction of each group at 36h and 60h after TAA injection. D. Representative H&E staining images of liver sample from Normal Control, PBS, 2D, 3D groups collected at 84h after TAA injection. scale bar: 100um.

Disclosures: The following people have nothing to disclose: Liang Peng, Shu Zhu, Zhiyong Zhang

4322-A | TRENDS OF ACUTE LIVER FAILURE IN MARIJUANA USERS

Raissa Nana Sede Mbakop Forlemu[1], Hamsika Moparty[2], Elizabeth Soladoye[1], Arnold Nongmoh Nongmoh Forlemu[2], Kikelomo Olaosebikan[1], Praneeth Bandaru[2], Vikash Kumar[2], Vijay Gayam[2] and Madhavi Reddy[2], (1)Piedmont Athens Regional, Athens, GA, (2) The Brooklyn Hospital Center

Background: Marijuana is among the most used recreational drugs in the United States and has been associated with a variety health hazards, including acute liver injury (ALF). A few case reports have described marijuana as rarely being associated with acute and fulminant liver failure. However, with more US states legalizing marijuana and with the growing use of this product, it is likely the prevalence and incidence of negative effects of marijuana will rise. Using a nationwide inpatient database, this study evaluated the prevalence of ALF in patients using marijuana and described the trends and hospital outcomes of ALF in marijuana users based on demographics and race. **Methods:** We conducted a nationwide review from 2016 to 2017 using the National Inpatient Sample (NIS) data. NIS is the largest publicly available all-payer inpatient database in the United States with more than seven million hospital stays each year, as a part of the Healthcare Cost and Utilization Project (HCUP). Patients $\geq$ 18 years old with ALF were identified using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. Student t-tests and chi square tests were used to analysis continuous and categorical variables respectively. Odds ratios (OR) and confidence intervals (CI) at 99% are reported. **Results:** The number of patients with ALF were 75,910. Among patients with ALF, the number of marijuana users was 2,263, with a prevalence of 3.0% of ALF patients who are marijuana users. Marijuana users with ALF were older with a female predominance compared to those users without ALF. ALF rates were higher in Native American (5.4%) and Black (3.7%) marijuana users compared to other races. Majority of marijuana users with ALF were on Medicaid or self-pay with the lowest median household income. Regarding outcomes, Asian marijuana users with ALF were more likely to be on mechanical ventilation compared to other races (1.35 (0.74 – 2.46). On the other hand, Hispanics and Whites were more likely to be on vasopressor support (OR 1.54, CI: 1.18 – 2.02; OR 2.25, CI: 1.24 – 4.08). As expected, length of stay, total hospital charges, and mortality were higher for marijuana users with ALF compared to those without ALF. **Conclusion:** We found marijuana users with ALF to be slightly older with female predominance compared to non-marijuana users with ALF. Native American and Black marijuana users were more likely to have ALF compared to other races. On the other hand, Hispanic and White marijuana users with ALF where more likely to require vasopressor support. Socioeconomic factors likely play a role in the trends observed in this study.



Marijuana users with acute liver failure; outcomes by race

	Acute liver failure	No acute liver failure	Mean difference or odds ratio, confidence interval
Marijuana use (%)	3.0	2.6	1.14 (1.09 – 1.19)
Age, years	41.85	39.01	2.84 (2.26 – 3.42)
Length of stay, days	7.44	5.14	2.30 (1.96-2.65)
Total hospital charges, $	96,900.72	38,535.13	58,365.59 (52,255.10 – 64,476.08)
Mechanical ventilation (%)	6.1	6.6	0.91 (0.84 – 0.97)
White	2.4	2.5	0.97 (0.88 – 1.08)
Black	3.2	3.8	0.84 (0.71 – 1.00)
Hispanic	2.5	2.7	0.80 (0.61 – 1.06)
Asian	1.4	1.0	1.35 (0.74 – 2.46)
Native American	4.4	5.1	0.85 (0.44 – 1.63)
Vasopressor support (%)	13.6	9.1	1.57 (1.28 – 1.93)
White	1.9	1.3	1.54 (1.18 – 2.02)
Black	2.5	2.2	1.12 (0.70 – 1.79)
Hispanic	3.1	1.4	2.25 (1.24 – 4.08)
Asian	0.0	0.6	0.89 (0.88 – 0.91)
Native American	4.3	2.2	1.97 (0.40 – 9.77)
Liver transplant (%)	13.8	13.9	0.99 (0.34 – 2.86)
White	0.5	1.4	0.36 (0.05 – 2.71)
Black	1.9	0.5	3.55 (0.22 – 57.73)
Hispanic	0.0	0.7	0.82 (0.78 – 0.86)
Asian	3.6	0.0	0.26 (0.19 – 0.36)
Native American	0.0	4.5	0.91 (0.81 – 1.04)
Mortality (%)	17.2	7.9	2.42 (2.16 – 2.72)
White	1.6	0.6	2.65 (2.29 – 3.08)
Black	2.4	1.3	1.82 (1.43 – 2.32)
Hispanic	1.8	0.8	2.35 (1.61 – 3.42)
Asian	0.5	0.3	1.56 (0.46 – 5.24)
Native American	2.9	1.7	1.74 (0.65 – 4.62)

Disclosures: The following people have nothing to disclose: Raissa Nana Sede Mbakop Forlemu, Hamsika Moparty, Elizabeth Soladoye, Arnold Nongmoh Nongmoh Forlemu, Kikelomo Olaosebikan, Praneeth Bandaru, Vikash Kumar, Vijay Gayam, Madhavi Reddy

4323-A | VIRAL KINETICS, HUMORAL IMMUNITY AND SERUM CYTOKINE PROFILES DIFFERENTIATE TYPICAL ACUTE HEPATITIS B (AVHB) FROM HBV-ASSOCIATED ACUTE LIVER FAILURE (HBVALF) AND ACUTE-ON-CHRONIC LIVER FAILURE (CHBALF)

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Infectious Diseases, National Institutes of Health, (2) University of Texas Southwestern Medical Center, (3) Department of Transfusion Medicine, Clinical Center, National Institutes of Health, Bethesda, MD

Background: The mechanisms determining the outcome in acute HBV infection: self-limited hepatitis (AVHB), acute liver failure (HBVALF), and acute-on-chronic liver failure (CHBALF), are poorly understood. We used sera from the US Acute Liver Failure Study Group and Hepatitis B Research Network to study the virus-host interplay, comparing the 3 phenotypes. **Methods:** 216 serial serum samples from 46 patients with well-characterized HBV phenotypes—13 AVHB, 25 HBVALF and 8 CHBALF—were analyzed for HBV genotype, IgM anti-HBc and anti-HBs titers, as well as quantification of HBsAg, HBV core-related antigen (HBcrAg), HBV DNA, HBV RNA and HDV RNA. Additionally, 19 cytokines were tested serially in the 3 groups. We also separated the HBVALF group into early (< 10d onset to encephalopathy, HE; N = 7), HBVALF late (> 10d, N = 11) and acute liver injury (INR 2.0, no HE; ALI, N = 7). Among HBVALF, 41% died or required transplantation: all AVHB and ALI patients survived. Titers are given in logs. **Results:** The most significant serological differences were: (a) IgM anti-HBc titers were higher in HBVALF (median, 6.6 log) than CHBALF (1.3) or AVHB (4.7); (b) HBsAg was lower in HBVALF (3.7) than in AVHB (4.7), but similar to CHBALF (3.4); (c) HBcrAg was higher in CHBALF (7.0) than HBVALF (5.9) but similar to AVHB (6.6); (d) HBV RNA was undetectable in AVHB, but present in 75% of CHBALF (4.0) and at low levels in 20% of HBVALF. All were positive for HBV DNA without significant differences between groups. Distinct cytokine profiles were observed. AVHB demonstrated significant induction of the IFN-inducible chemokine IP10 and MIP-1b, whereas HBVALF had significant elevation of the pro-inflammatory cytokines IL-4, IL-6, MCP-1, sCD137 and TNF-a. CHBALF showed the highest levels of IL-8, HBcrAg and HBV RNA along with the lowest titers of IgM anti-HBc. These patterns persisted after admission. Within the HBVALF group, distinct signatures were observed comparing HBVALF early with ALF late and ALI. The outcomes for the HBVALF late presenters were very poor (9/11 died/OLT) and significantly different from early presenters (3/7). Spontaneous survival correlated with significantly higher values of TNF and IP10 at admission. **Conclusion:** There are distinct serologic, virologic and cytokine profiles differentiating classic AVHB from HBVALF and CHBALF. Moreover, it provides the first evidence that early and late ALF differ in their profiles and outcomes suggesting different mechanisms of pathogenesis.

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4324-A | WAITLIST AND POST-TRANSPLANT OUTCOMES OF PREGNANCY VERSUS NON-PREGNANCY RELATED ALF IN THE US (1992-2021)

Sajid Jalil, The Ohio State University Wexner Medical Center, Mohamed A. Elfeki, University of South Dakota Sanford School of Medicine, Muhammad Arsalan Arshad, Avera Mckenna University Hospital and Transplant Institute, Deepan Panneerselvam, University of South Dakota, Sioux Falls, SD, Yong-Fang Kuo, University of Texas Medical Branch, Juan Pablo Arab, University of Western Ontario, London, ON, Canada, Robert J. Wong, VA Palo Alto Healthcare System, Zobair M. Younossi, Inova Health System and Ashwani K. Singal, University of South Dakota

Background: Pregnancy-related acute liver failure (P-ALF) outcomes have not been well-documented in the literature. This study aims to compare waitlist and post-transplant outcomes of P-ALF versus non-pregnancy-related ALF (NP-ALF) using the United Network of Organ Sharing (UNOS) database. **Methods:** Using the UNOS data (1992-2021), we analyzed outcomes of P-ALF and NP-ALF. Baseline characteristics were compared between groups at listing. Outcomes studied were cumulative 90-day waitlist mortality (WLM) competing for receipt of liver transplant and 5-yr post-transplant patient survival. **Results:** Of 3,542 females aged 16-43 listed for ALF, 84 (2%) listed for P-ALF were more likely to be black (21% vs11%, $p = 0.033$), have ventilatory failure (56% vs. 41%, $p < 0.005$), be on pressors (58% vs. 43%, $p < 0.005$), require dialysis (23% vs.10%, $p < 0.001$), and have higher INR (4.53 vs. 2.74, $p < 0.001$). The cumulative 90-day WLM was lower in P-ALF vs. NP-ALF (7.4 vs. 16.6%, $p < 0.001$), Fig. 1A. The post-transplant survival rates at 5-yr were similar (82% vs 79%, $p = 0.89$). Subgroup analysis after excluding listings for viral hepatitis (N = 1834, with 40 P-ALF) showed similar results on 90-day WLM (7.6% vs. 17.2%, $p < 0.001$). The 90-day WLM remained lower in P-ALF in a propensity matched cohort (1:10) of 710 ALF patients, 7.9% vs. 17.8% $p < 0.001$, (Fig. 1B). In a Fine and Gray regression model controlled for listing year and MELD score, 90-day WLM was lower in P-ALF with sub-hazard ratio of 0.42 (95%CI, 1.06-5.39, $p = 0.035$). **Conclusion:** In this UNOS database analysis of ALF among women of childbearing age, the waitlist outcome is better in pregnant compared to non-pregnant women. Further studies are needed to examine mechanisms of these findings and explore etiology-based outcomes in women with ALF during pregnancy.

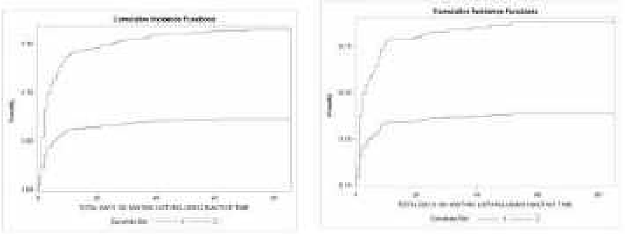

Figure 1 Cumulative incidence on 90-d WLM comparing P-ALF (red line) vs. NP-ALF (blue line) in the unmatched cohort (A) and in the matched cohort (B)

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4325-A | WAITLIST AND POST-TRANSPLANT OUTCOMES OF PREGNANCY-RELATED ACUTE LIVER FAILURE IN THE US (1987-2021)

Sajid Jalil, The Ohio State University Wexner Medical Center, Mohamed A. Elfeki, University of South Dakota Sanford School of Medicine, Muhammad Arsalan Arshad, Avera Mckenna University Hospital and Transplant Institute, Deepan Panneerselvam, University of South Dakota, Sioux Falls, SD, Yong-Fang Kuo, University of Texas Medical Branch, Juan Pablo Arab, University of Western Ontario, London, ON, Canada, Robert J. Wong, VA Palo Alto Healthcare System, Zobair M. Younossi, Inova Health System and Ashwani K. Singal, University of South Dakota

Background: The outcomes of acute liver failure (ALF) during pregnancy are shown to be better compared to ALF in women of childbearing age who are not pregnant. However, data on etiology-based outcomes of ALF in women during pregnancy are limited. We compared waitlist and post-transplant outcomes of ALF in pregnant women comparing pre-eclampsia (PE) vs. acute fatty liver of pregnancy (AFLP) using the UNOS database (1987-2021). **Methods:** Baseline characteristics among pregnant women with ALF were compared between PE vs AFLP at listing. Cumulative incidence of 90-day waitlist mortality (WLM) (competing for receiving liver transplant) and post-transplant survival estimates were analyzed. **Results:** Of 84 pregnant women listed for liver transplantation due to ALF, 45 were listed for PE and 39 for AFLP. At the time of listing, compared to AFLP, those listed for PE were more likely to have ventilatory failure (67 vs. 44%, $p=0.033$) and require pressors (69 vs. 46% $p=0.035$). A total of 9 women died within 90-day of listing, 8 with PE vs. 1 with AFLP, $p=0.067$. The cumulative incidence function of 90-day WLM was higher in women listed for PE compared to those listed for AFLP (19.3% vs 5.7% $p<0.005$), Figure 1. The 5-yr post-transplant patient survival rates were similar (80.1% vs 84.2%, $p=0.668$). On a Fine and Gray regression model controlled for listing year, the 90-day WLM was about 10-fold higher in PE vs. AFLP with sub-hazard ratio (95% confidence interval) of 9.97 (1.64-60.55), $p=0.013$. **Conclusion:** In this analysis of UNOS database on pregnant women listed for liver transplantation due to ALF, the 90-day WLM is worse if the ALF is induced by PE rather than AFLP. Studies are needed to improve management and prevention of PE during pregnancy and prevent development of ALF.

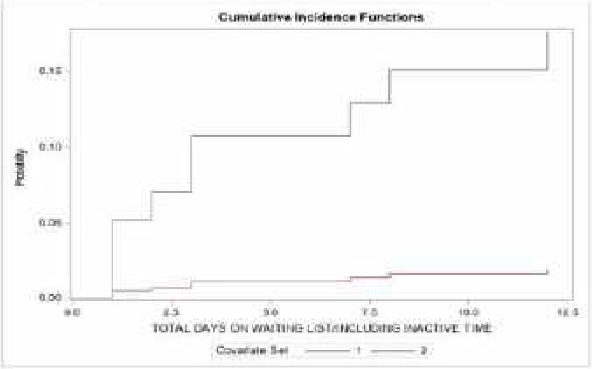

Figure 1 The cumulative incidence function of 90-day waitlist mortality comparing PE (blue line) and AFLP (red line)

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f 4400-A | ADAPTIVE RESPONSE TO AMMONIA MEDIATED IMPAIRED PROTEOSTASIS OCCURS BY INCREASED LEU UPTAKE VIA SLC7A5

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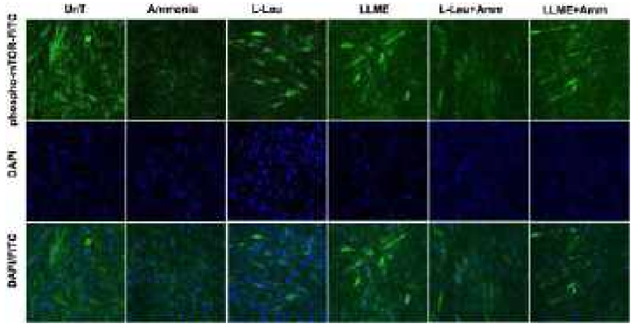
Background: Sarcopenia or loss of skeletal muscle mass and physical frailty in liver disease is mediated by an ammonia-dependent mechanism. The hyperammonemic stress response (HASR) in skeletal muscle shares some features of the amino acid starvation and the unfolded protein responses (UPR). During HASR, phosphorylation of eukaryotic initiation factor 2 alpha (eIF2a) is increased, mTORC1 signaling and protein synthesis are less, and autophagy flux is increased. L-leucine, transported intracellularly by SLC7A5, supports skeletal muscle protein homeostasis during HASR. Since expression for SLC7A5 is increased during HASR, we sought to determine if the increased expression of SLC7A5 is a cytoprotective adaptive response to HASR. **Methods:** Studies were done in differentiated murine C2C12 myotubes. HASR was induced by 10mM ammonium acetate treatment for 24h in WT and SLC7A5 knock down myotubes. The protein synthesis was analyzed by 3H phenylalanine incorporation. Sodium-dependent and independent leucine uptake and signaling responses were quantified in control (shSCR) and shRNA against SLC7A5 (shSLC7A5) myotubes infected with the corresponding lentivirus. Responses to 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid (BCH), a chemical inhibitor of SLC7A5 were evaluated to determine if SLC7A5-dependent or -independent leucine uptake occurs during hyperammonemia. Responses to 0.25mM L-leucine or 0.25mM LLME (L-Leucyl methyl ester that is transported via transporter independent cellular entry for leucine) were quantified. Also eIF2a phosphorylation, mTORC1 signaling, and autophagy markers were quantified by immunoblots. mTORC1 subcellular localization and activation was also determined by immunofluorescence. All experiments were performed in at least 3 biological replicates. **Results:** Hyperammonemia resulted in a time and concentration dependent inhibition of protein synthesis in myotubes. Leucine uptake was increased during hyperammonemia and occurred in an SLC7A5 dependent mechanism as noted by chemical and genetic depletion of SLC7A5. Additionally, transporter independent uptake of LLME but not L-leucine reverses some but not all components of HASR doing SLC7A5 depletion. LLME but not L-leucine reversed hyperammonemia induced impaired mTORC1 signaling and increased autophagy markers. LLME but not L-leucine reversed ammonia induced subcellular localization of phosphorylated mTOR in myotubes. **Conclusion:** We show by chemical and genetic modulation that the amino acid exchanger, SLC7A5 mediates an adaptive response during hyperammonemia. Targeting SLC7A5 and developing transporter independent analogs of leucine can be a potential therapeutic approach to reverse sarcopenia in liver disease. The mechanisms of transport independent rescue of the hyperammonemia-mediated decrease in mTOR signaling and increased autophagy need to be determined in future studies.



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f 4401-A | CCL19-PRODUCING FIBROBLASTS PROMOTE TERTIARY LYMPHOID STRUCTURES FORMATION AND LOCAL ANTI-TUMOR IgG RESPONSE IN COLORECTAL CANCER LIVER METASTASIS

Yifan Zhang[1], Xinyue Zhang[1], Kai Lei[1], Lixia Xu[1], Sui Peng[1], Changjun Yin[1], Zhihang Chen[1], Ming Kuang[2] and FAH-SYSU Authors' Group, (1)The First Affiliated Hospital, Sun Yat-Sen University, (2)The First Affiliated Hospital of Sun Yat-Sen University

Background: Liver metastasis is a leading cause of colorectal cancer-related deaths. Tertiary lymphoid structures (TLSs) have been believed to play a crucial role in colorectal cancer liver metastasis (CRLM), however, their formation and function in CRLM remains unclear. In current study, we aimed to investigate the clinical implication, function and neogenesis of TLSs in CRLM. **Methods:** We retrospectively included 178 patients with CRCLM treated by surgical resection. The distribution and prognostic significance of peri- and intra-tumoral TLSs were determined by pathological review. Single-cell RNA sequencing (scRNA-seq), spatial enhanced resolution omics-sequencing (stereo-Seq), and multiplexed immunofluorescence were applied to characterize the tumor immune micro-environment with or without TLSs. **Results:** Peri- and intra-tumoral TLSs were observed in 80.9% and 11.2% of patients respectively, both of which were associated with beneficial clinic outcomes. We proposed a novel classification criterion by combining the present of peri- and intra-tumoral TLSs, we showed that this new classification criterion predicts cancer prognosis independent of clinicopathological factors. Mechanistically, we revealed that TLS+ tumors are enriched with IgG+ plasma cells (PCs), while, TLS- tumors are characterized with IgA+ PCs. By analyzing BCR sequences of tumor infiltrated B cells and PCs and generating monoclonal antibodies in vitro, our data showed that IgG+ PCs produced tumor-targeting IgG antibodies locally, which in turn, promote tumor cell apoptosis. Interestingly, we identified a subset of CCL19$^+$ fibroblasts enriched around TLSs, facilitating lymphocyte trafficking in CRLM. Tumor CCL19 levels were positively correlated with benefit prognosis in CRLM patients. Furthermore, we demonstrated that CCL19 treatment promoted TLSs neogenesis in a mouse model. **Conclusion:** We characterized the spatial distribution and prognostic value of TLSs in CRLM at the single cell resolution. Moreover, we demonstrated that CCL19-producing fibroblasts regulate TLSs formation and local IgG-mediated immunity. Our data suggested novel therapeutic opportunities to control CRLM.

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f 4402-A | CELLULAR BIOENERGETIC CAPACITY TRANSITIONS FROM OXIDATIVE PHOSPHORYLATION TO GLYCOLYSIS IN TELOMERASE INHIBITION-INDUCED SENESCENT HEPATOCYTES IN MOUSE

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Background: Cellular senescence is a state in which cells become resistant to growth-promoting stimuli and apoptosis, resulting in permanent cessation of cellular proliferation. This leads to a prolonged ‘zombie-like’ state, which can have detrimental effects on tissues relying on their regenerative capacity for homeostasis, such as the liver. Cells undergo a drastic metabolic shift as they adapt to senescent phenotype, potentially affecting the function of the liver. There are diverse factors triggering senescence and this heterogeneity makes it difficult to distinguish and target senescent cells therapeutically. Therefore, in the present study, we aim to characterize, specifically, the link between telomerase inhibition-induced senescence and metabolic capacity in primary hepatocytes and hepatocyte-derived liver organoids. **Methods:** Primary hepatocytes, isolated by collagenase-perfused mice liver (C57BL6/J; 18-23 weeks), were cultured overnight in buffered William’s E-medium supplemented with 2% FBS, L-glutamine, and hepatocyte growth supplements. Hepatocyte-derived organoids were developed by culturing cells in a 3D matrix for two weeks. Cells or organoids were treated with 20 µM of BIBR-1532 (telomerase inhibitor) for 12, 24, 48, or 72 hours. Senescence was assessed by senescence-associated (SA)-β-galactosidase activity, immunofluorescence, immunoblotting (p53, p21, and γH2Ax), and senescence-associated secretory phenotype (SASP) candidates. Cellular bioenergetics was measured by XFe Seahorse analyzer with 10 mM glucose, 2 mM pyruvate, and 1 mM glutamine as substrates. **Results:** Dosages and time of treatment were optimized on the primary hepatocytes (five dosages and four-time points, from 12-72 hours). The results showed that BIBR-1532 increased phosphorylation of histone (γH2Ax), a DNA damage marker, by 10-fold ($p < 0.001$), and SA β-

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

galactosidase activity by 11-fold ($p < 0.001$) (Figure 1A). Arrested proliferation is an important feature of senescence cells and the primary hepatocytes have limited proliferation in 2D culture. To overcome this limitation, we validated the results in hepatocyte-derived organoids and observed similar findings (Figure 1A). Coincided with DNA damage, BIBR1532 stabilized p53, increased p21 levels, and SASP (CCL2, CXCL2, IL6, IL10, TNFα, and MMP13). In contrast to the studies in immortalized cell lines, telomerase inhibition initially (up to 24 hours of treatment) increased oxidative phosphorylation capacity, however, in the later senescence phase, the cellular bioenergetics became predominantly glycolytic (Figure 1B). **Conclusion:** BIBR-1532 (telomerase inhibitor) induces senescence phenotype in mouse primary hepatocytes. Cellular bioenergetic capacity transitions from oxidative phosphorylation to glycolysis in BIBR-1532 treated hepatocytes, which may affect the hepatocytes' response to toxins and inflammation.

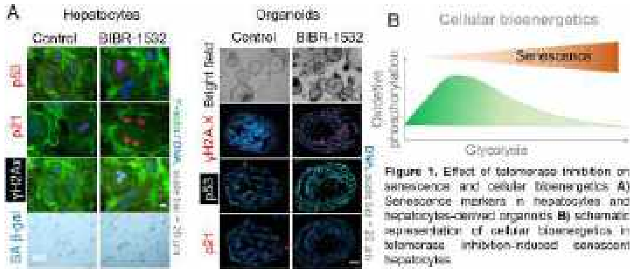

Figure 1. Effect of telomerase inhibition on senescence and cellular bioenergetics A) Senescence markers in hepatocytes and hepatocytes-derived organoids B) schematic representation of cellular bioenergetics in telomerase inhibition-induced senescent hepatocytes

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4403-A | CHARACTERIZING THE TUMOR SUPPRESSOR ACTIVITY OF RAB17 IN HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC) is the key histologic type of liver cancer, responsible for the bulk of liver cancer diagnoses and deaths. A crucial cancer event is cell polarity loss during the epithelial to mesenchymal transition which is characterized by repressed polarity protein expression, including the loss of rab17. Rab17 was first identified as an epithelial cell-specific small GTPase and we have shown it regulates transcytotic vesicle fusion at the apical membrane via interactions with syntaxin-2 (target SNARE). Others have shown that reduced rab17 levels are associated with increased HCC aggressiveness. Because rab17 expression is reduced by ERK activation during early stages of oncogenesis, and because ERK and other molecular players in the MAP kinase pathway are druggable therapeutic targets, we examined how rab17 re-expression reverses the oncogenic phenotype. **Methods:** For these studies, we have exogenously re-expressed rab17 in Clone9 cells. Notably, these hepatoma-derived cells lack endogenous rab17 expression. To uncover mechanistic details of how rab17 is anti-oncogenic, we also reintroduced rab17 in its constitutively GTP- or GDP-bound states or rab17 that is sumoylation-deficient. **Results:** Expression of wild-type rab17 led to the formation of actin-based, cholesterol-dependent (not microtubule dependent) protrusions. Marker analyses confirmed the protrusions are filopodial-like, not lamellipodia-like, and contain focal adhesion proteins. Rab17 mutant analysis revealed that protrusion formation was GTP-dependent and partially sumoylation-dependent, and expression of wildtype and GTP-bound rab17 resulted in reduced cell migration. In contrast, GDP-bound rab17 expression did not promote protrusion formation or alter cell migration. Wildtype and GTP-bound rab17 were detected in the distal tips of protrusions and colocalized with syntaxin-2. **Conclusion:** We propose that in non-polarized Clone9 cells, rab17 expression redirects vesicle fusion to syntaxin-2 at the apical surface leading to protrusion formation. We propose that rab17 expression induces more adhesive filopodia formation at the expense of Arp2/3-rich lamellipodia thereby decreasing cell migration. Because both the actin-based protrusions and invadopodia are cholesterol-dependent, we further propose that raft-associated proteins are redirected from sites of invadopodia formation to the lateral edges, thereby producing filopodia and promoting the anti-oncogenic phenotype.

Disclosures: The following people have nothing to disclose: Lauren R. Bassaro

Disclosure information not available at the time of publication: Pamela L. Tuma

f 4404-A | DUAL LOSS OF Β- AND Γ-CATENINS FROM CHOLANGIOCYTES LEADS TO ACUTE CHOLESTASIS AND MORTALITY DUE TO HEPATOBILIARY INJURY AND MALADAPTATION AS REVEALED BY SINGLE-NUCLEUS RNA SEQUENCING★

Yekaterina Krutsenko[1], Silvia Liu[2], Qin Li[1], Junjie Zhu[3], Minakshi Poddar[1] and Satdarshan (Paul) Monga[1], (1) University of Pittsburgh, (2)Pittsburgh Liver Research Center, (3)University of Pittsburgh School of Pharmacy

Background: β-catenin has been shown to be indispensable for normal liver development,

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

homeostasis, and regeneration. However, functions of β-catenin in cholangiocytes remains poorly understood. β-catenin is part of adherens junctions (AJs) where its loss is known to be compensated by γ-catenin, a highly homologous desmosomal protein. In the present study we inducibly and specifically delete both β- and γ-catenins from biliary epithelium to determine role of AJs in bile ducts. **Methods:** We utilized *Opn-iCreERT2+/-; Ctnnb1-fl/fl; Jup-fl/fl* mice (DKO), in which both β-catenin (*Ctnnb1*) and γ-catenin (*Jup*) are acutely deleted from biliary epithelium by Tamoxifen-inducible, cholangiocyte-specific osteopontin-driven expression of Cre-recombinase. 4 doses of Tamoxifen (100mg/kg) were administered to adult animals intraperitoneally and tissues were harvested at various time points after the injections. Tamoxifen-treated *Opn-iCreERT2-/-* sex-matched littermates were used as controls. **Results:** DKO mice showed acute mortality as compared to the controls with survival dropping to 50% within 3 weeks and 100% by 4.5 weeks. DKO mice exhibit decreased body weight, jaundice and lethargy and showed significantly elevated serum ALT, AST, ALP, BR, cholesterol and reduced glucose. A 10-fold decrease in bile flow rate was evident in DKOs following duct cannulation. Total bile acid (BA) levels increased 10^3- fold in the serum and 10-fold in the liver tissue of DKO mice and distinct BA profiles with majority being primary hydrophilic conjugated species. Histology revealed multiple biliary infarcts, inflammation, stellate cell activation and severe portal fibrosis in DKO livers. These findings along with alterations in BA metabolism were corroborated by bulk-RNA sequencing ingenuity pathway analysis (IPA) as well. qRT-PCR showed alterations in number of BA transporters and synthesis genes. CK19-positive bile ducts were malformed, irregular, and sometimes with absent lumen. India ink injections in the common bile duct, showed abundant blebbing throughout the biliary tree. Single-nucleus RNA sequencing (Nuc-Seq) revealed novel hepatocyte clusters as well as distinct population of cholangiocytes in DKO livers. The DKO-associated genetic signature included 381 DEGs that depict aberration in the epithelial cell junctions and upregulation of necroptosis. **Conclusion:** Dual loss of b-catenin and g-catenin from cholangiocytes causes serious intrahepatic cholestatic injury which is associated with notable morbidity and mortality. This model may provide novel insights in the role of cell-cell junctions in bile duct structure and function.

Disclosures: The following people have nothing to disclose: Yekaterina Krutsenko, Minakshi Poddar, Satdarshan (Paul) Monga

Disclosure information not available at the time of publication: Silvia Liu, Qin Li, Junjie Zhu

f 4405-A | DYNAMIC REGULATION OF HEPATIC STEATOSIS BY TORSINA AND ITS ACTIVATORS

Ji-Yeon Shin[1], Antonio Hernandez-Ono[1], Yi-Peng Susan Zhao[1], Cecilia Ostlund[1], Michael Lee[1], William T. Dauer[2], Henry N. Ginsberg[1] and Howard J. Worman[1], (1)Columbia University, New York, NY, (2)University of Texas Southwestern Medical

Background: Abnormal hepatic lipid metabolism leads to nonalcoholic fatty liver disease, which can progress to nonalcoholic steatohepatitis (NASH). TorsinA is an ATPase in which lacks intrinsic enzyme activity without its activators lamina-associated polypeptide 1 (LAP1) or luminal domain-like LAP1 (LULL1). We previously demonstrated that while depletion of torsinA leads to striking triglyceride (TG) accumulation in hepatocytes, depletion of LAP1 showed moderate hepatic steatosis. We therefore tested if LULL1, another activator of torsinA, is involved in the process. We next tested if depletion of both activators *in vivo* leads to similar hepatic steatosis phenotypes seen in liver-specific torsinA deletion (A-CKO) mice. We further tested if the marked TG accumulation phenotype of A-CKO mice is reversible upon the acute restoration of torsinA *in vivo*. **Methods:** We generated hepatocyte-specific LULL1 conditional knockout mice (LUL-CKO) and injected these mice with a viral vector carrying a shRNA against LAP1 to deplete hepatocytes of both LULL1 and LAP1. We also used viral vectors to express flag-tagged wild type torsinA onto A-CKO mice. We then measured the hepatic TG content, TG secretion rate and performed fluorescence confocal microscopy to analyze lipid droplets in isolated hepatocytes. **Results:** LUL-CKO mice with depletion of LULL1 from hepatocytes had a minimal reduction in hepatic TG secretion and no steatosis. However, depletion of LAP1 from hepatocytes of LUL-CKO mice (depletion of both LAP1 and LULL1) led to marked hepatic steatosis (Figure 1) and reduction in TG secretion. Confocal microscopic analysis showed a marked accumulation of cytosolic lipid droplets in hepatocytes with combined depletion of both LAP1 and LULL1. Restoration of torsinA expression rescued hepatic steatosis phenotype of A-CKO mice within five days post injection of adenovirus expressing wild type torsinA (Figure 1). **Conclusion:** Combined LAP1 and LULL1 depletion from mouse hepatocytes delineate a functional relationship of these activators of torsinA in liver TG secretion and steatosis. LAP1 appears to be a more important activator of torsinA in hepatocytes than LULL1. However, LULL1 still activates torsinA to some degree in hepatocytes, as depletion of both LAP1 and LULL1 results in marked steatosis similar to those that occur with torsinA depletion. Acute restoration of torsinA *in vivo*normalizes marked hepatic steatosis phenotypes of A-CKO mice. These collective data demonstrate that torsinA and its activators dynamically regulate hepatic steatosis *in vivo*.

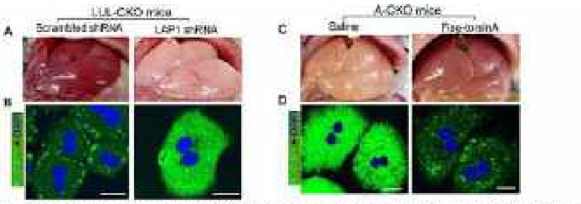

Figure 1. Marked hepatic steatosis in LUL-CKO mice injected with adenovirus expressing LAP1 shRNA and rescue of hepatic steatosis in A-CKO mice by acute restoration of torsinA expression. (A) Photos of livers from LUL-CKO mice injected with adenovirus expressing scrambled shRNA (left panel) or LAP1 shRNA (right panel) (B) Fluorescence confocal microscopy of BODIPY and DAPI stained hepatocytes isolated from the above mice. Scale bars: 20 µm. (c) Photos of livers from A-CKO mice injected with saline (left panel) or adenovirus expressing flag-torsinA (right panel) (D) Fluorescence confocal microscopy of BODIPY and DAPI stained hepatocytes isolated from the above mice. Scale bars: 20 µm.

Disclosures: The following people have nothing to disclose: Ji-Yeon Shin

Disclosure information not available at the time of publication: Antonio Hernandez-Ono, Yi-Peng Susan Zhao, Cecilia Ostlund, Michael Lee, William T. Dauer, Henry N. Ginsberg, Howard J. Worman

4406-A | HEPATOCYTE-INTRINSIC HUMORAL FACTORS DETERMINE THE ENVIRONMENTAL NICHE FOR HEPATOCYTE FATE DECISION AND MAINTENANCE

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Background: The tissue-specific microenvironment determines cell identity; therefore, in vitro fate maintenance of primary cells, such as human hepatocytes (HH), has been regarded implausible. The implementation of 3D culture, microscale-bioprinting approach, or the supplementation of 5 chemicals (5C), have been shown to reduce the extent of fate decline. Furthermore, our recent work refining 2D-HH culture approach revealed that HH undergo processes of recovery from injury imposed by the procurement procedure and reinstating proper characteristics, all of which point to a role of hepatocyte-intrinsic factors in defining the fate of HH. **Methods:** HH, either primary or humanized liver chimeric mice (HLCM)-derived, were cultured with medium containing hepatocyte-specific supplements for 7 days, allowing HH to restore their genuine characteristics. The medium of fate recovered-HH was pooled as the conditioned medium (CM), and its impact on HH fate and function was contrasted with that of fresh medium (FM), FM supplemented with 5C, or Matrigel. Freshly isolated HH were cultured for 7 days with CM, FM, FM-5C, or FM-Matrigel, followed by the assessment of transcriptome, bile excretion function, CYP activity, and hepatitis B virus (HBV) infectivity. In addition, CM- or FM-treated HH were implanted to the host mouse of HLCM to validate its role on fate maintenance. **Results:** The transcriptome of CM-treated (CM-HH) exhibited a significant degree of similarity to that of freshly isolated HH. In contrast, HH treated with FM, FM-5C, or FM-Matrigel revealed significant upregulation of TGFβ-YAP/TAZ pathway and dedifferentiation or cholangiocyte transdifferentiation marker genes. Consequently, the activity of bile excretion and CYP enzymes, and HBV infectivity were all superior in CM-HH compared to other conditions. Moreover, the engraftment of CM-HH in the liver of HLCM host mouse demonstrated a level of efficiency comparable to that of freshly isolated HH, providing additional evidence on the significance of CM. Furthermore, the proteome analysis of CM and follow up studies with loss of function approach suggested that the formation of macromolecular complex comprised of ECM-related molecules and coagulation factors serves as the critical determinant of HH fate maintenance. **Conclusion:** Our work revealed that hepatocyte-intrinsic humoral factors produced from terminally differentiated HH create the environmental niche required for hepatocyte fate decision and maintenance.

Disclosures: Yasuhito Tanaka – Fujirebio: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Sysmex: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AbbVie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Speaking and Teaching, No, No; AbbVie: Speaking and Teaching, No, No;

The following people have nothing to disclose: Yuji Ishida, Go Sugahara, Chihiro Yamasaki, Sho Morioka, Mikaru Yamao, Jae-Jin Lee, Meng Li, Hyungjin Eoh, Chise Tateno, Takeshi Saito

4407-A | IDENTIFICATION OF THE ELUSIVE LIPOPHAGY RECEPTOR FOR LIPID TURNOVER IN LIVER

Debajyoti Das[1], Mridul Sharma[1], Deepanshi Gahlot[2,3], Jennifer T. Aguilan[4], Simone Sidoli[4], Mathieu Bourdenx[5,6], Lipi Thakural[2,3], Nuria Martinez-Lopez[1,7] and Rajat Singh[1,4,7], (1)University of California, Los Angeles, (2)Csir-Institute of Genomics and Integrative Biology, (3)Academy of Scientific and Innovative Research, (4)Albert Einstein College of Medicine, (5) UCL Queen Square Institute of Neurology, (6)UK Dementia Research Institute, (7)Liver Basic Research Center at University of California Los Angeles

Background: Lipophagy is a cellular mechanism for degradation of lipid droplets (LD) via autophagy. It is well-established that defects in lipophagy/autophagy lead to hepatic lipotoxicity across the broad pathophysiological spectrum of fatty liver disease. Indeed, dampened autophagy and steatosis during obesity underscore the importance of this pathway in liver pathobiology. Despite extensive research, little is known about the mechanisms of selective recognition and sequestration of LD by autophagosomes, which will lead to ultra-precise targeting to selectively activate lipophagy without affecting other forms of autophagy. **Methods:** Animal models: Studies were performed in 2-10-month-old male and female mice. Liver-specific *Atg7*^{KO} mice were generated by administration of AAV8-TBG-iCre and control and *Atg7*^{KO} livers were harvested after 8 weeks. DNA or siRNA transfection: Transfections in NIH3T3 cells and AML12 hepatocytes were performed using Lipofectamine3000. In vivo DNA and siRNA delivery was performed using in vivo-jetPEI® and Invivofectamine™ 3.0, respectively. Phosphoproteomics: Fed and 20-hour fasted liver homogenates, and control and 6-hour serum-starved AML12 hepatocytes were homogenized in 2% SDS + 5 mM DTT buffer, and proteins were digested in S-trap columns, and peptides analyzed by nLC-MS/MS. Confocal imaging: Hepatocytes in serum-free medium in presence or absence of oleic acid were subjected to multiplex colocalization using spinning disc super-resolution microscopy (Nikon CSU-W1). Statistical analyses were performed via unpaired Student's t-test or one/two-way ANOVAs and appropriate post-hoc testing. **Results:** We report fasting-induced enrichment of selective phosphosites in liver that regulate hepatic lipid metabolism. From amongst these phosphoproteins, we identified a novel receptor for lipophagy that governs LD degradation in liver during fasting and lipotoxic stress. We show that Casein kinase 2 (CSNK2)(EC 2.7.11.1)-mediated phosphorylation regulates the function of this novel protein towards LD sequestration. We have identified lipid binding and LC3 (light chain 3) interacting regions on this phosphoprotein, which allow binding to LD and autophagosomes, respectively, and inactivating these regions cause lipid accumulation. These findings have informed the generation of a highly sensitive and specific lipophagy reporter that will provide an efficient readout for lipophagy flux in cellulo and in vivo. **Conclusion:** We have identified a previously unknown selective receptor that targets LDs for lysosomal degradation. Selective phosphorylation of this target is of crucial importance for recognition and degradation of LDs in lysosomes. This discovery and the novel reporter will help develop novel compounds to selectively activate lipophagy to prevent human NAFLD and NASH.

Disclosures: The following people have nothing to disclose: Debajyoti Das, Mridul Sharma, Deepanshi Gahlot, Jennifer T. Aguilan, Simone Sidoli, Mathieu Bourdenx, Lipi Thakural, Nuria Martinez-Lopez, Rajat Singh

f 4408-A | IMPAIRED EXERCISE RESPONSES IN LIVER DISEASE IS MEDIATED BY MOLECULAR AND METABOLIC PERTURBATIONS DURING HYPERAMMONEMIA

Annette Bellar[1], Avinash Kumar[2], Nicole M. Welch[1], Saurabh Mishra[1] and Srinivasan Dasarathy[1], (1) Cleveland Clinic, (2)All India Institutes of Medical Sciences

Background: The benefits of endurance exercise (EE) in healthy subjects have been well studied and include reduction in fat mass, improved cardiorespiratory responses, and mitochondrial function. In sedentary adults, EE can also increase lean body mass to a limited extent. EE has been used as a treatment for cardiac and metabolic disorders and may be beneficial in cirrhosis, however there are limited data on response to EE in patients with liver disease. EE also increases ammonia generation, which may increase comorbidities of cirrhosis including hepatic encephalopathy and sarcopenia. In this study, we evaluated the effect of voluntary wheel running (VWR) in a mouse model of hyperammonemia. **Methods:** Hyperammonemia was induced in 8-week aged, wild type, C57BL6 mice by surgical placement of osmotic pumps to deliver 2.5mmol/kg/day Ammonia Acetate (AmAc) or vehicle (PBS) for 6weeks. After 2 weeks of pump placement, the PBS or AmAc treated mice were randomly assigned to 4w of VWR or usual activity (UA). Body weight and grip strength were measured weekly. All animals were

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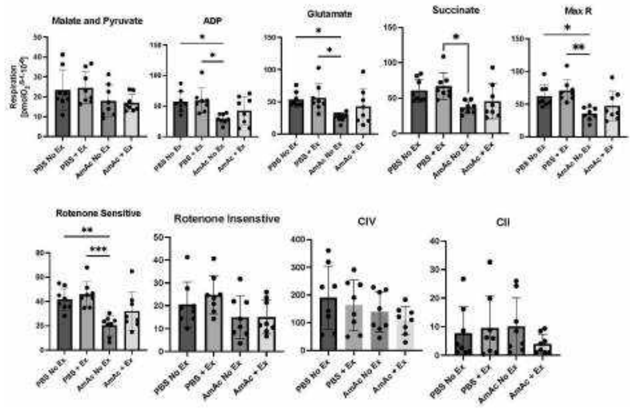
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

sacrificed after 4 weeks of UA or VWR and organs including skeletal muscle were harvested and weighed. A portion of fresh muscle tissue was used for mitochondrial oxygen consumption studies by high sensitivity respirofluorometry using substrate, uncoupler, inhibitor, titration protocols. **Results:** We found no change in total bodyweight, lean body mass, or fat mass between the 4 groups (PBS-UA, PBS-VWR, AmAc-UA, AmAc-VWR) pre- and post-exercise (Fig1). Gastrocnemius muscle mass was not different in response to exercise in the PBS group (PBS-UA vs. PBS-VWR, $p > 0.05$). AmAc-UA mice has lower gastrocnemius muscle mass compared to PBS-VWR ($p = 0.004$) or PBS-UA ($p = 0.003$). Gastrocnemius muscle mass in AmAc-VWR was greater than that in the AmAc-UA group ($p = 0.047$). Interestingly, muscle mass in the AmAC-VWR was similar to that in the PBS-UA group, but less than that in the PBS+VWR mice ($p = 0.04$). Grip strengths did not change in any of the groups over time. Mitochondrial oxidative responses were similar in the gastrocnemius muscle in the PBS-UA, PBS+VWR, and AmAc-VWR mice. Complex I linked (ADP/Glutamate), rotenone sensitive, Complex II (Succinate), and maximum respiration was less in the AmAc-UA ($p \leq 0.05$) vs. PBS+UA/VWR or AmAc+VWR. EE for 4 weeks in a validated mouse model of hyperammonemia did not alter body composition. However, gastrocnemius muscle mass was lower during hyperammonemia and was partially restored by 4-weeks of VWR that recapitulates EE in preclinical models. Mitochondrial oxidative responses were impaired by hyperammonemia that were also partially reversed by VWR (EE). Lack of improvement in grip strength is consistent with previous data on EE. **Conclusion:** Responses to EE were impaired by hyperammonemia. Ammonia lowering measures and potentially adding resistance exercise may be more beneficial in reversing sarcopenia of liver disease.

Figure 1 Mitochondrial Data



Disclosures: The following people have nothing to disclose: Annette Bellar, Avinash Kumar, Nicole M. Welch, Saurabh Mishra, Srinivasan Dasarathy

4409-A | JCAD DEFICIENCY ACCELERATES NASH-HCC DEVELOPMENT THROUGH LEAKAGE OF BILE ACIDS DUE TO IMPAIRED INTRAHEPATIC BILIARY DUCT INTEGRITY

Li Zhang[1], Yongyu Yang[1], Yuan Zhou[1], Zhonghua Wang[1], Jia Ding[2] and Jian Wu[1,3,4], (1)Dept. of Medical Microbiology, Fudan University School of Basic Medical Sciences, Shanghai 200032, China, (2)Shanghai Jing'an District Central Hospital, (3)Shanghai Institute of Liver Diseases, Fudan University Shanghai Medical College, Shanghai 200032, China, (4)Fudan University, Department of Gastroenterology and Hepatology, Zhongshan Hospital, Shanghai, China

Background: JCAD was originally recognized as an E-cadherin-based cell conjunction, and is attributed to development of cardiovascular disorders. Our previous study demonstrated that JCAD acts as an upstream regulator of Hippo signaling pathway *in vitro*. The present study aims to investigate the influence of JCAD on hepatocellular canaliculus and biliary epithelial cell (BEC) integrity during NASH-HCC development. **Methods:** Wild-type (WT) and JCAD knockout (KO) mice were fed high-fat and calorie diet plus high fructose and glucose in drinking water (HFCD-HF/G) for 14 mon or choline-deficient high fat diet (CD-HFD) for 12 mon respectively for induction of NASH-HCC ($n = 10$). NASH phenotypes and tumor incidence were investigated. **Results:** JCAD knockout increased liver tumor incidence and malignancy in both HFCD-HF/G (10/10 vs. 5/10; $p < 0.05$) and CD-HFD (4/10 vs. 2/10) models. Lipid metabolism and insulin resistance did not differ between WT and KO mice, however liver hydroxyproline content was significantly increased in JCAD-KO mice (0.8 vs. 0.3 μg/mg, $p < 0.001$ in HFCD-HF/G model; 0.4 vs. 0.25 μg/mg, $p < 0.05$ in CD-HFD model). Notably, cholestatic manifestations including significantly elevated bile acid levels (71 vs. 9 μmol/L, $p < 0.001$ in HFCD-HF/G model; 86 vs. 9 μmol/L, $p < 0.05$ in CD-HFD model), dilated bile canaliculi and increased expression of CK19, diminished tight junction protein of occludin and zonula occludens protein 2 as well as altered gene expression of bile acid production, absorption and transportation in KO mice indicate that JCAD knockout contributed to cholestasis which facilitated the NASH-HCC progression. Mass spectrometric analysis revealed that strikingly elevated serum tauroconjugates of β-muricholic acid and cholic acid mainly accounted for the difference in bile acid. Incubation of primary hepatocytes with mixed bile acids and 1% CA feeding as well as BDL model in mice recapitulated the cholestasis-elicited expression of genes involved in pluripotency and stemness of hepatocytes. Moreover, JCAD deficiency led to impaired barrier function *in vitro* as indicated by reduced transepithelial electrical resistance (TER) by 42%

($p < 0.001$) and increased FITC-dextran leakage (siJCAD vs. siCNTL: 1278 vs. 1027 AU/h, $p < 0.05$); whilst, intra-hepatocyte paracellular permeability was increased in JCAD-KO mice (KO vs. WT: 754 vs. 572 AU/5min, $p < 0.01$). **Conclusion:** Loss of JCAD disrupted structural and functional integrity of tight junction in both hepatocytes and BECs, which led to BA leakage. JCAD-KO mice fed NASH diet for a long term accelerated malignant transformation through BA toxicity. Delineation of bile acid impacts on hepatic malignant transformation enables to develop new strategies in NASH-HCC prevention and treatment.

Disclosures: The following people have nothing to disclose: Li Zhang, Yongyu Yang, Yuan Zhou, Jia Ding, Jian Wu

Disclosure information not available at the time of publication: Zhonghua Wang

f 4410-A | LIPID-DRIVEN mTORC1 SIGNALING IN LIVER

Henrietta Bains[1], Debajyoti Das[2], Nuria Martinez-Lopez[2], Jennifer T Aguilan[1], Simone Sidoli[1], Mathieu Bourdenx[3,4], Laura Beth J McIntire[5] and Rajat Singh[1,2,6], (1)Albert Einstein College of Medicine, (2) University of California, Los Angeles, (3)UCL Queen Square Institute of Neurology, (4)UK Dementia Research Institute, (5)Weill Cornell Medicine, NY, (6) Liver Basic Research Center at University of California Los Angeles

Background: mTOR complex 1 (mTORC1) signaling is critical for growth and proliferation. Dysregulation of mTORC1 signaling in obesity alters lipid metabolism in liver through its effects on lipogenesis and autophagy. In the physiological state, mTORC1 signaling is activated by diverse nutrients. However, whether lipids activate mTORC1 in liver *in vivo* remains unknown. **Methods:** *Animal models*: Studies were performed in 4-8-month-old C57BL/6 male mice fed a regular chow or a high-fat diet (HFD; 60% kcal from fat). As model of dietary lipid availability, mice were fasted for 3 hours (to shut down mTORC1 activity) and subjected to an oral gavage of corn oil for 30 minutes. *Nucleic acids transfections*: Hepatocyte cell lines were transfected with DNAs or siRNAs using Lipofectamine3000 or RNAiMAX Reagent, respectively. Liver-specific delivery of siRNAs was performed using Invivofectamine™ 3.0 Reagent. *Lipidomics*: Lipids from liver homogenates were extracted and analyzed by LC-MS/MS. *Proteomics*: co-IP eluents from cell lysates were resuspended in 2% SDS/5 mM DTT buffer, digested in S-trap columns, and peptides were analyzed by nLC-MS/MS. *Confocal imaging*: Serum-starved cells exposed to phosphatidic acid or amino acids were tracked via laser scanning microscopy to monitor mTOR subcellular localization. *Statistics*: Unpaired Student's T-test, one-way or two-way ANOVA followed by appropriate multiple-comparisons tests. **Results:** Our studies show that mTORC1 in liver is activated by a dietary corn-oil gavage. Follow up studies in hepatocytes indicate that distinct lipid species, including phosphatidic acids (PA), activate mTORC1 in culture. Elevated levels of PA during obesity lead to mTORC1 hyperactivation in hepatocytes, likely contributing to fatty liver disease. Using proteomics, we have also found that availability of PA is sensed by unique mTOR binding partners, not known to regulate sensing of amino acids or cholesterol. These unique mTOR-binding proteins drive PA-driven mTORC1 activation at late and recycling endosomes. In fact, deletion of these newly identified protein factors blocked mTORC1 activity in response to PA. **Conclusion:** Our ongoing studies reveal that selective targeting of novel mTOR-binding proteins could be a new therapeutic approach in protecting against fatty liver by curtailing age- and obesity-associated mTORC1 hyperactivity.

Disclosures: The following people have nothing to disclose: Henrietta Bains, Debajyoti Das, Nuria Martinez-Lopez, Jennifer T Aguilan, Simone Sidoli, Mathieu Bourdenx, Laura Beth J McIntire, Rajat Singh

f 4411-A | MITOCHONDRIA-LOCALIZING FLUOROPHORES ARE MARKERS TO VISUALIZE LOBULAR ZONATION IN MOUSE LIVER

Kenji Takemoto, Matthew Savoca, Zhi Zhong and John J. Lemasters, Medical University of South Carolina

Background: The liver has a complex architecture to manage its various physiological roles. Liver lobular zonation is a well-known feature of liver parenchymal organization. Understanding of lobular involvement in liver disease provides important insights into pathophysiology. In general, visualization of liver zonation requires specific immunostaining procedures. Here, we developed a novel method to visualize mouse liver zonation using mitochondria-localizing fluorophores. **Methods:** Male C57BL/6J mice were injected by tail vein with 0.05 or 0.5 µmol of Mitotracker Red (MTR), which covalently labels polarized mitochondria, 1 h prior to liver fixation or intravital multiphoton microscopy. After paraformaldehyde fixation, liver tissues were mounted in 5% agarose, and 100-µm sections were prepared with a vibratome. Sections were incubated anti-CYP2E1 (pericentral) and/or anti-E-cadherin (periportal) antibodies for 72 h. Fixed sections were imaged with a Zeiss LSM 880 confocal microscope in super resolution Airyscan mode. Intravital imaging was performed with an Olympus FV1200 multiphoton microscope. Some mice were injected with

0.05 μmol rhodamine 123 (Rh123), a fluorophore that non-covalently labels polarized mitochondria, at 1 h after MTR injection followed by intravital imaging. **Results:** On intravital imaging, MTR and Rh 123 fluorescence co-localized into mitochondria. Intensities of MTR and Rh123 fluorescence positively correlated ($r = 0.678$, $p < 0.0001$), which indicated similar distribution. Intensity of MTR and Rh 123 fluorescence in pericentral regions averaged 64 and 74% less than in periportal regions. In fixed liver sections, strong CYP2E1 labeling was confined to pericentral regions, whereas strong E-cadherin labeling was confined to periportal regions with relatively sharp demarcations between the two areas. However, gradation of MTR fluorescence across the liver lobule was continuous without a sharp demarcation between zones at both 0.05 and 0.5 μmol MTR. The maximum ratio of periportal to pericentral MTR fluorescence in sections was ~2. **Conclusion:** After tail vein injection, mitochondria-localizing fluorophores label periportal hepatocytes more strongly than pericentral hepatocytes, providing a new approach to identify zones of the liver lobule. This novel method may allow cell sorting of living periportal and pericentral hepatocytes without using immunologic tags.

Disclosures: The following people have nothing to disclose: Kenji Takemoto, John J. Lemasters

Disclosure information not available at the time of publication: Matthew Savoca, Zhi Zhong

f 4412-A | MITOCHONDRIA-LYSOSOME RELATED ORGANELLES MEDIATE MITOCHONDRIAL CLEARANCE TO PROMOTE HEPATOCYTE DEDIFFERENTIATION

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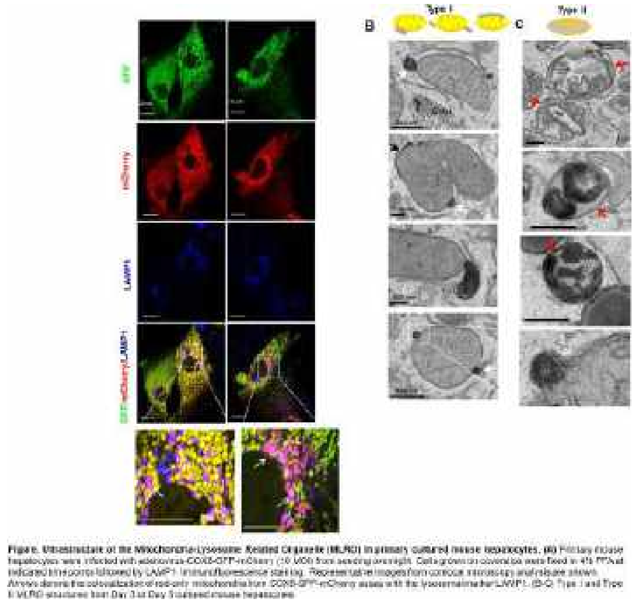
Background: Hepatocyte dedifferentiation is a common feature for chronic liver diseases such as alcohol-associated hepatitis (AH) and non-alcoholic steatohepatitis (NASH). Mitochondria play critical roles in regulating cellular redox homeostasis, lipid metabolism, energy production, and cell death. Mitochondrial dysfunction is associated with various chronic diseases including AH and NASH. To maintain hepatic mitochondrial homeostasis, Dysfunctional and surplus mitochondria can be removed via multiple pathways such as mitophagy, a selective autophagy process. However, whether and how mitochondria homeostasis would affect hepatocyte dedifferentiation are unknown. **Methods:** Primary cultured mouse hepatocytes from wildtype or genetic knockout of PARKIN, ATG5 and DRP1 as well as GFP-mCherry-COX8 mitophagy reporter assay and super-resolution and ultrastructural electron microscopy analysis were used in this study. **Results:** We identify a previously undescribed intracellular hybrid mitochondria-lysosome organelle (termed the mitochondria-lysosome related organelle, MLRO) in prolonged cultured hepatocytes. MLRO is an electron-dense organelle that has either a single or double membrane with both mitochondria and lysosome markers. Mechanistically, MLRO is likely formed from the fusion of mitochondria-derived vesicles (MDVs) with a lysosome through a PARKIN, ATG5, and DRP1-independent process, which is negatively regulated by transcription factor EB (TFEB) and associated with mitochondrial protein degradation and hepatocyte dedifferentiation. MLRO, which is galectin 3 positive, is reminiscent of damaged lysosome and could be cleared by overexpression of TFEB resulting in attenuation of hepatocyte dedifferentiation. **Conclusion:** Results from this study indicate that MLRO may act as a novel alternative mechanism for mitochondrial quality control independent of canonical autophagy/mitophagy involved in hepatocyte dedifferentiation. Manipulation of TFEB may be beneficial for improving the pathogenesis of AH and NASH by inhibiting hepatocyte dedifferentiation.



Disclosures: The following people have nothing to disclose: Chen Zhang, Xiaowen Ma, Hong-Min Ni, Wen-Xing Ding

f 4413-A | REGULATION OF MITOCHONDRIAL FISSION IN THE FASTED LIVER

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Background: Fasted livers take up free fatty acids from circulation to support mitochondrial respiration. We do not completely understand the mechanisms driving these mitochondrial adaptations when nutrients are scarce. **Methods:** *Animals*: Studies were performed in 2-10-month-old male and female mice. Liver-specific *Rictor* knock-out (*Rictor*^{KO}) mice were generated by injecting *Rictor*$^{flox/flox}$ mice with AAV8-TBG-iCre for 8 weeks. *DNA/siRNA transfections*: In vitro transfections were performed using Lipofectamine3000. Delivery of DNA to liver was performed via In vivo-jetPEI®, and siRNA was delivered using Invivofectamine™ 3.0. *Subcellular fractionation* was performed as described by Wieckowski MR et al. *Nat Protoc* (2009). Phosphoproteomics: Liver homogenates and mitochondrial-associated membranes (MAM) or co-IP eluents were resuspended in 2% SDS/5 mM DTT buffer, digested in S-trap columns, and peptides were analyzed by nLC-MS/MS. *Confocal imaging*: Serum-starved cells exposed to MitoTracker™ Green FM (to stain for mitochondria) were tracked via laser scanning microscopy. *Statistics*: Unpaired Student's T-test, one-way or two-way ANOVA followed by appropriate multiple-comparisons tests. **Results:** We have found that extended periods of fasting paradoxically stimulate the nutrient-sensitive mTORC2 pathway in liver. mTORC2 reactivation in liver supports fasting-induced increases in mitochondrial fission and respiration. Accordingly, inactivation of mTORC2 in liver by knocking-out its regulatory protein, RICTOR (*Rictor*^{KO}), impairs fasting-induced increases in fission and mitochondrial respiration. Consequently, fasted *Rictor*^{KO} livers exhibit marked accumulation of triglycerides due to failure to mobilize these lipids. Using quantitative phosphoproteomics, we identified a new role for mTORC2 and its downstream phosphotargets in driving mitochondrial fission in liver by regulating the recruitment of novel regulatory proteins to MAMs, which are contact sites for ER-mediated mitochondrial fission. **Conclusion:** Nutrients activate mTOR signaling for anabolic functions; however, fasting-induced reactivation of mTORC2 plays an unexpected role in mitochondrial division and respiration. Stimulating mTORC2 could help prevent NAFLD by stimulating mitochondrial function and lipid disposal.

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4414-A | SDR CHARACTERIZATION IN HEPATIC METABOLISM

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Background: The liver is a critical hub for numerous physiological processes, including macronutrient metabolism, endocrine control of growth signalling pathways, lipid and glucose homeostasis, bile acid production, and amino acid metabolism. Over the years, several proteins and signalling nodes have been identified as playing key roles in regulating the response of the liver to fasting. Despite these advances, new discoveries are constantly emerging and our understanding of the molecular mechanisms controlling this important biological process keeps evolving. Therefore, the main objective of this project is to identify and characterize new proteins regulating liver metabolism in response to fasting. **Methods:** We used hepatocytes isolated by serial dilutions and obtained more than 30 new clonal lines. Hepatic glucose production was assessed in these clonal lines since it is a process that occurs during fasting. Some of these lines produced low glucose amounts (Low Lines) whereas others produced high amounts (High Lines). To identify the factors involved in this variability between these lines, we performed transcriptomic assays between High and Low lines, and obtained 25 new targets that were never linked to the hepatic response to fasting before. **Results:** Our first interesting candidate is a *short dehydrogenase reductase* (*Sdr*) gene whose expression is higher in High Lines versus Low Lines. This *Sdr* gene encodes for a protein of unknown function. Using immunofluorescence studies, we identified SDR as a mitochondrial protein. Our studies also indicate that *Sdr* is induced by fasting and PPARα, and repressed by insulin. Knockdown of *Sdr* in vitro decreases oxygen consumption and fatty acid oxidation, suggesting a role in mitochondrial metabolism. Furthermore, the FXR signalling pathway is downregulated in hepatocytes knockdown for *Sdr*. *In vivo*, mice with *Sdr* knockout exposed to a high fat diet have an impaired hepatic glucose production. **Conclusion:** With our work, we hope to elucidate SDR function in systemic metabolism.

Disclosures: The following people have nothing to disclose: Nolwenn Samson, Cristina R. Bosoi, Mathilde

Mouchiroud, Laura Tribouillard, Yves Gélinas, André Marette, Mathieu Laplante

4415-A | THE INTERACTION BETWEEN CD36 AND oxLDL CONTRIBUTES TO LYMPHATIC DYSFUNCTION IN CHRONIC LIVER DISEASE

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Background: Chronic liver disease disrupts the trafficking of high molecular weight proteins and cells out of the liver via the lymphatics. This lymphatic dysfunction can be attributed to an oxidized low-density lipoprotein (oxLDL) mediated increase in the expression of the key junctional protein, VE-Cadherin. However, the precise molecular mechanism by which oxLDL impacts lymphatic permeability in the liver is unknown. In these studies, we aimed to define the cell surface receptors and signaling pathways that are activated by oxLDL to reduce lymphatic function in the liver. **Methods:** To define this signaling pathway, we utilized both siRNA mediated knock-down and blocking antibody treatments to prevent oxLDL binding to cell surface receptors in primary human lymphatic endothelial cells (hDLEC) and primary Liver Sinusoidal Endothelial Cells (hLSECs). Using western blot, flow cytometry, and immunofluorescence, we measured VE-cadherin surface levels after oxLDL treatment with or without receptor blockade in LECs. Furthermore, we defined the signaling pathway activated by oxLDL using both phospho-kinase arrays and western blot. Finally, we utilized transwell assays to define the cell surface receptors that regulate LEC permeability *in vitro.* **Results:** Here we found that oxLDL stimulation results in a rapid (1-2h) upregulation of cell surface VE-cadherin in LECs but not LSECs. This increase is contingent on CD36 receptor signaling. Additionally, this effect is not the result of preventing oxLDL uptake entirely, as CD36 blockade did not impact the amount of oxLDL that entered the cells. Furthermore, this CD36-dependent upregulation of VE-Cadherin is unique to oxLDL, as treatment with the CD36 ligand, Palmitic Acid, does not result in increased VE-Cadherin expression in LECs. Finally, oxLDL treatment of LECs results in the CD36 dependent activation of a signaling cascade that involves both SRC-family kinase activation and GSK-3a inhibition to stabilize VE-Cadherin on the cell surface. **Conclusion:** The above studies demonstrate that the specific interaction between oxLDL and the CD36 receptor induces VE-Cadherin increase to change permeability in LECs. It also identifies likely downstream signaling intermediates mediating this response. This lays the groundwork for understanding lymphatic dysfunction in chronic liver disease and potential therapeutic targets for restoring lymphatic function and liver homeostasis during disease.

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Matthew A. Burchill: Matthew A. Burchill
Disclosure information not available at the time of publication: Alyssa Goldberg, Megan E. Ferguson, Jamie Shirley, Beth A. Jiron Tamburini

4416-A | TWO HEPATIC PEROXISOME POPULATIONS DIFFERENTIALLY RESPOND TO ALCOHOL-INDUCED OXIDATIVE STRESS VS LIPID OVERLOAD

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Background: Peroxisomes have a wide array of functions, and are constantly responding to cellular metabolic states including ROS and lipid overload. Oxidative stress and hepatic steatosis are well known hallmarks of alcohol associated liver diseases. Here we propose that two peroxisome populations differentially respond to alcohol-induced ROS vs. lipid overload. **Methods:** Peroxisome numbers, distributions, morphology, dynamics, and peroxisome-organelle contacts were examined morphologically (using confocal microscopy) or biochemically (by immunoblotting) in polarized hepatic WIF-B cells treated in the absence or presence of EtOH and/or oleic acid (to mimic Western diet) or in livers from EtOH -fed rats (5 weeks; Lieber Decarli). **Results:** Our studies revealed that at steady state, there is considerable peroxisomal heterogeneity. Few peroxisomes are labeled with catalase whereas there are greater numbers of peroxisomes positive for ABCD3, a long chain fatty acid transporter. When treated with EtOH, peroxisome numbers increased for both populations, but the increase was greater for catalase+ peroxisomes suggesting their enhanced response to EtOH-induced ROS. Studies with the CYP2E1 inhibitor, diallyl sulfide, and the anti-oxidant, n-acetylcysteine confirmed these results. We also determined that peroxisome distributions were microtubule dependent and that in EtOH-treated cells, the ABCD3+ peroxisomes (but not catalase+ ones) colocalized with acetylated microtubules emanating from canalicular surface preventing interactions with that surface. We further observed that the ABCD3+ peroxisomes (but not catalase+ ones) in cells treated with both EtOH and oleic acid form several contacts with the large lipid droplets and that these contacts were dependent on acetylated microtubules. Catalase+ peroxisomes made many fewer droplet contacts. These results suggest that the two peroxisome populations differentially respond to EtOH-induced ROS (catalase+) vs. lipid overload (ABCD3+).

Conclusion: Considering there are no treatments available to alleviate or reverse the disease state in the progression of ALD, explicitly understanding the specific molecular mechanisms that contribute to observed clinical pathologies is essential in identifying novel therapeutic targets. Since peroxisomes are involved in a wide array of cellular functions including, but not restricted to, regulating oxidative stress and lipid homeostasis, investigating their response to alcohol is of paramount importance.

Disclosures: The following people have nothing to disclose: Ramyajit Mitra, Oluwaseyi Okesooto

Disclosure information not available at the time of publication: Pamela L. Tuma

4417-A | CHOLESTENOIC ACID AS ENDOGENOUS EPIGENETIC REGULATOR DECREASES LIPID ACCUMULATION IN HUMAN HEPATOCYTES

Yaping Wang, William Pandak and Shunlin Ren, Virginia Commonwealth University

Background: Cholestenoic acid (CA), along with 27HC and 25HC, is a natural ligand for LXRs and is synthesized in mitochondria. Previous studies have demonstrated the involvement of 27HC and 25HC in lipid metabolism, inflammatory responses, and cell apoptosis. However, the physiological and pathological roles of CA remain unclear. This study aimed to investigate the molecular mechanism underlying the potential role of CA in hepatic lipid homeostasis. **Methods:** Enzyme kinetic analysis was utilized to examine the impact of CA on the activities of three DNA methyltransferases (DNMTs). Human hepatocytes cultured in high glucose medium were utilized as a non-alcoholic fatty liver disease model. Human whole-genome bisulfite sequencing (WGBS) and messenger RNA sequencing were used to investigate the relationship between DNA methylation and gene expression. Additionally, untargeted lipidomics analysis was performed to assess the impact of CA on lipid levels. **Results:** Enzyme kinetic studies revealed that CA specifically inhibits the activity of DNMTs.WGBS analysis showed an increased number of differential methylation regions (DMRs) over time between the control and CA-treated groups. Hypomethylated DMRs in the promoter region after CA treatment were significantly enriched in lipid metabolism-related processes and metabolic signaling pathways. mRNA sequencing analysis indicated significant modulation of numerous gene clusters by CA, with the number of differentially expressed genes increasing over time. Down-regulated genes were significantly enriched in lipid biosynthesis processes and KEGG pathways related to steroid biosynthesis, terpenoid backbone biosynthesis, metabolic pathways, and cholesterol metabolism. RT-qPCR and western blot analyses validated the results of RNA sequencing and WGBS, confirming the time- and dose-dependent decrease in gene expression and protein levels of key genes involved in lipid synthesis, along with the increase in regulatory genes associated with calcium and ERK signaling pathways. Untargeted lipidomics analysis further demonstrated that CA significantly decreased lipid levels. **Conclusion:** This study highlights CA as a distinct endogenous epigenetic regulator that decreases lipid accumulation in human hepatocytes by demethylating DNA ^{5m}CpG of essential genes involved in hepatic lipid metabolism. This study emphasize the significance of CA as a potential therapeutic target for metabolic disorders, specifically hyperlipidemias.

Disclosures: Shunlin Ren – License related payment from DURECT Co.: Royalties or patent beneficiary, No, No;

The following people have nothing to disclose: Yaping Wang, William Pandak

4418-A | DISCOVERY OF A NOVEL REGULATORY MOLECULE: 3β-HYDROXY-5-CHOLESTENOIC ACID 3-SULFATE, SECRETED BY HEPATOCYTES AND SUPPRESSES INFLAMMATORY RESPONSES IN MACROPHAGES

Yaping Wang, William Pandak and Shunlin Ren, Virginia Commonwealth University

Background: Cholestenoic acid (CA) is a natural ligand for LXRs and is synthesized in mitochondria, along with 27HC and 25HC. Our previous study uncovered CA as an endogenous epigenetic regulator that reduces lipid accumulation in human hepatocytes by demethylating key genes related to lipid metabolism. Nevertheless, the metabolic pathway of CA remains elusive. This study aims to investigate the metabolic pathway of CA in human hepatocytes and explore the biological functions of its metabolites. **Methods:** LC-MS/MS was used to monitor the metabolic pathway of CA in human hepatocytes. Human hepatocytes cultured in high glucose medium were used as a non-alcoholic fatty liver disease (NAFLD) model to examine the effect of CA3S on lipid metabolism. Human macrophage cells induced by 2 ug/ml Lipopolysaccharide (LPS) were used as an inflammation response model to investigate the effect of CA3S on inflammation response. RT-qPCR was used to analyze the effect of CA3S on gene expression related to lipid metabolism and inflammation response. **Results:** HepG-2 cells were treated with 20 uM CA for various durations (0, 1.5, 3, 6, 12, and

24 hours). The cultured media samples were collected, extracted, and analyzed using LC-MS/MS. The results showed a decrease in CA (m/z 415) levels in the cultured media as culturing time increased. A new molecular ion (m/z) 495 appeared at 1.5 hours and reached a maximum (90%) at 24 hours. Further investigation using tandem MS fragmentation revealed three major fragments: m/z 80, m/z 97, and m/z 415. Comparison with a synthesized compound confirmed the new m/z 495 compound as 3β-hydroxy-5-cholestenoic acid 3-sulfate (CA3S). The analysis revealed the presence of CA3S in the intercellular space of HepG-2 cells with CA treatment, indicating its sulfation and release from hepatocytes. To explore its biological function, CA3S was synthesized and purified in the lab. Treatment of HepG-2 cells with purified CA3S downregulated lipid biosynthesis genes (hmgr, fas, and pcsk9) according to RT-qPCR results. Additionally, treating macrophage cells with CA3S significantly reduced the expression of inflammatory cytokine genes (il-1a, il-6, and cox2) induced by LPS, as demonstrated by RT-qPCR. **Conclusion:** Our findings indicate that CA can be sulfated to CA3S in human hepatocytes and subsequently released. CA3S exhibits an anti-inflammatory effect on human macrophage cells, suggesting its potential as a therapeutic agent for inflammation-related conditions.

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The following people have nothing to disclose: Yaping Wang, William Pandak

4419-A | EFFICACY OF VEGFR2-TARGETED THERAPY AFTER ATEZOLIZUMAB AND BEVACIZUMAB COMBINATION THERAPY IN HEPATOCELLULAR CARCINOMA

Kouki Nio[1], Gen Sugiyama[1], Hikari Okada[1] and Taro Yamashita[2], (1)Kanazawa University Graduate School of Medicine, (2)Kanazawa University

Background: Atezolizumab, an anti-PD-L1 antibody, plus bevacizumab, an anti-VEGFA antibody, combination (ABC) therapy for advanced hepatocellular carcinoma (HCC) has widely been used in clinical practice as a first-line treatment. Ramucirumab, an anti-VEGFR2 antibody, has been shown to be effective for advanced HCC with high AFP levels, but its efficacy after ABC therapy is unclear. In this study, we aimed to analyze the effect of the anti-VEGFR2 antibody after combination therapy with anti-PD-L1 and anti-VEGFA antibodies in vivo. **Methods:** A patient-derived xenograft (PDX) model was used to confirm the efficacy of anti-mouse VEGFR2 antibody (DC101), provided by Eli Lilly and Company, on human HCC xenograft. A syngeneic mouse model of AFP/EpCAM-positive HCC, which shows poor prognosis with stem cell features, was used to assess the efficacy of DC101 after combination therapy with anti-PD-L1 and anti-VEGFA antibodies. The dose of 40 mg/kg/mouse of DC101 was administered intraperitoneally to mice twice a week. In a syngeneic model, DC101 was administered for 5 weeks sequentially after 2 weeks of combination therapy. Gene expression in tumor tissues was examined by microarray expression analysis. Protein expression in tumor tissues was determined by immunohistochemical staining, immunofluorescent staining, and multiplexed spatial proteomics. The identity of single cells in tumor tissue was defined by protein expression profiles from multiplex spatial proteomics **Results:** In a PDX model, DC101 significantly suppressed tumor growth with the inhibition of the proximity of AFP-positive human HCC cells and VEGFR2-positive mouse vascular endothelial cells. In addition, in a syngeneic mouse model, sequential DC101 treatment after combination therapy showed a significant anti-tumor effect. Analysis of gene and protein expression in tumor tissues revealed that DC101 significantly suppressed a stem cell marker EpCAM expression as well as the vascular endothelial marker. Interestingly, DC101 treatment reduced the number of CD8-T cells positive for PD-L1 and TIGIT in tumor tissues, which are immune checkpoint molecules associated with T-cell exhaustion. **Conclusion:** The anti-VEGFR2 antibody not only inhibits angiogenesis but also suppresses cancer stem cells and activates tumor immunity, and it might be effective in AFP-positive advanced HCC after ABC therapy.

Disclosures: The following people have nothing to disclose: Kouki Nio, Taro Yamashita

Disclosure information not available at the time of publication: Gen Sugiyama, Hikari Okada

4420-A | EFFICIENT ENGRAFTMENT, VIRAL TRANSDUCTION AND CORRECTION OF LIPID ACCUMULATION IN HUMAN HEPATOCYTES IN AN FRG RAT LIVER HUMANIZATION MODEL

Marisa Carbonaro and Zhe Li, Regeneron Pharmaceuticals

Background: Humanized liver models, in which the host liver parenchyma is replaced by human hepatocytes, have been increasingly used in drug development and disease research. In the leading humanized liver mouse model, Fumarylacetoacetate Hydrolase (Fah), Recombination Activating Gene (Rag)-2 and Interleukin-2 Receptor Gamma (Il2rg) genes are inactivated simultaneously. Rag2/Il2rg KO results in immuno-suppression, while Fah KO leads to hepatoxicity, allowing for repopulation with FAH^{+} human hepatocytes (HH). However, generation of similar recipient rats by inactivating multiple genes simultaneously in this species has been challenging. **Methods:** Using VelociGene and 1-cell-embryo-targeting technologies we generated an $Fah^{-/-}$, $Rag1/2^{-/-}$, $Il2rg^{-/-}$ (FRG) rat. FRG rats were maintained on NTBC to prevent Fah KO-induced toxicity. Liver damage in FRG rats upon NTBC withdrawal was validated by survival and hepatotoxicity studies and $Fah^{+/+}$ rat, mouse or human hepatocytes were used to rescue the lethal phenotype. Engraftment of HH in FRG rats was confirmed by serum ELISA of human proteins and liver IHC/ISH with human-specific hepatocyte markers. HH-specific gene delivery was achieved by viral transduction *in vivo* using AAV-NP59, or *in vitro* by lentiviral infection of primary human hepatocytes prior to engraftment. Moreover, to correct hepatosteatosis in the humanized liver rat model, we restored IL6 signaling through ectopic expression of rat IL6R via *ex vivo* lentiviral infection of HH, or *in vivo* AAV9-hIL6 dosing. **Results:** FRG rats could be highly engrafted with HH. Humanized liver rats expressed human proteins in the serum (hALB, etc.), had normal liver zonation and could be infected with the HH-specific AAV-NP59. We also developed methods to transduce primary human hepatocytes with lentivirus *ex vivo,* followed by efficient repopulation in the FRG rat. We found that rat IL6R expression restored IL6 signaling and resulted in a significant reduction in lipid accumulation. Finally, we showed that supplementing human IL6 reversed hepatosteatosis in the humanized rat liver. **Conclusion:** We have developed an FRG rat model in which rat livers can be repopulated with HH. Further, excessive lipid accumulation in engrafted HH, a major defect of the model, can be corrected by restoring IL6 signaling. Importantly, we developed approaches for gene delivery through viral transduction of HH, providing a novel platform to study liver disease and hepatocyte-targeted therapies.

Disclosures: Marisa Carbonaro – Regeneron Pharmaceuticals: Employee, No, No;

Zhe Li – Regeneron Pharmaceuticals, Inc.,: Employee, No, No;

4421-A | ESTABLISHMENT OF PRIMARY HEPATOCYTE METHODS TO EVALUATE THE BINDING AND ENDOCYTOSIS EFFICIENCY OF GALNAC CONJUGATES

Mengjie Wang, Xiaoting Du, Rui Li, Yunbo Wang, Zhengxian Gu and Qiong Zhou, Wuxi Apptec

Background: The development of oligo therapeutics is impaired by lack of efficient and specific delivery strategies. Significant progresses have been made by conjugating oligo to triantennary GalNAc (T-GalNAc) targeting ASGPR, which is contributed to the specific and abundant expression of ASGPR on hepatocytes. To expedite the development of oligo drugs, it is essential to assess the binding and endocytosis efficiency of GalNAc conjugates in cell-based assays. Towards this end, we established ex vivo assays of primary hepatocytes to assess and predict the hepatic delivery efficiency of GalNAc-oligo conjugates. **Methods:** Primary hepatocytes of human (PHH), mouse (PMH) and C. monkey (PCMH), as well as HepG2 cells were used for assessing the delivery efficiency of GalNAc-oligos. ASGPR protein and mRNA in PHH were assessed by immunofluorescence and RT-qPCR, respectively. Binding and uptake efficiency of GalNAc in hepatocytes were evaluated by direct (fluorescent labeled GalNAc) and competitive (unlabeled GalNAc) flow cytometry (FCM) methods. In the competitive FCM, Cy5 labeled GalNAc (EE-Cy5) was used as a competitor. GalNAc3 conjugated and free siRNAs were used to determine the GalNAc dependence of the endocytosis. To test the robustness of the assays, EE-Cy5 was tested at different concentrations in PHH, and T-GalNAc ligand L96 was tested in various cells. Furthermore, T-GalNAc, mono GalNAc and GalNAc3 conjugated molecules were tested to further validate the system. **Results:** ASGPR mRNA and protein were successfully detected in PHH by RT-qPCR and immunofluorescence, respectively. In the binding assay, EE-Cy5 had Vmax values of 14313 in PHH and 19879 in PMH, but only 1983 in HepG2 cells. The direct FCM analysis exhibited that EE-Cy5 was efficiently taken up by both PHH and HepG2 cells. GalNAc3-siRNA conjugates, but not free siRNAs, competitively inhibited the EE-Cy5 uptake, indicating the GalNAc dependence of the endocytosis. Furthermore, the competitive FCM assay with different concentrations of EE-Cy5 in PHH and L96in PHH, PCMH and HepG2 cells showed high performance with Z factor values of >0.55. In addition, MonoGalNAc, T-GalNAc3 and GalNAc3 siRNA conjugates had inhibition of EE-Cy5 uptake and the assay showed high reproducibility. **Conclusion:** We have established a set of ex vivo assays to assess the binding and uptake efficiency of GalNAc conjugates in primary hepatocytes from various species, as well as HepG2 cells. We propose to apply the methods to assessment of delivery efficiency of GalNAc conjugates at the early stage to expedite the development of oligo drugs.

Disclosures: The following people have nothing to disclose: Xiaoting Du, Qiong Zhou

Disclosure information not available at the time of publication: Mengjie Wang, Rui Li, Yunbo Wang, Zhengxian Gu

4422-A | HEPATOCELLULAR CARCINOMA PROGRESSION DUE TO INCREASED EMT THROUGH NOX2-MEDIATED SREBP2 STIMULATION IN HEPATOCYTES

Hei-Gwon Choi[1], Ha Neul Kim[1], Eun Hyuk Soo[2] and Soon Ok Kim[1], (1)Chungnam National University, (2) Chungnam National University Hospital

Background: Progression of hepatocellular carcinoma (HCC) is a disease caused by the transformation of hepatocytes into malignant cells, that is, the transformation of normal cells into cancer cells was involved various causes. To date, the effects of several NOX families on the development and occurrence of HCC have been studied. But Studies on the effects of NOX2 on HCC development are lacking. Therefore, we investigated the effects of NOX2 on hepatocarcinogenesis and development. **Methods:** Mouse HCC model Mouse HCC model genetically induced HCC using the Sleeping Beauty transposon system. To genetically induce HCC, HRASG12V was overexpressed and NOX2 and p53 were silenced in the liver. MOUSE treated with the Sleeping Beauty transposon system were sacrificed after 5 weeks. Patient sample Patient tissues were obtained from HCC patients who underwent surgery at Chungnam National University Hospital. **Results:** To investigate the effect of NOX2 activity on HepG2, NOX2 activity was induced by treatment with palmitate. As a result, NOX2 activity by palmitate treatment in HepG2 inhibited AMPK activity and induced SREBP2 activity. In addition, it was confirmed that this NOX2 activity mainly occurs in the membrane, not in the cytoplasm. Interestingly, NOX2 silencing reduced HCC trans-migration, whereas NOX2 overexpression increased HCC trans-migration. In this process, slug and N-cadherin, which are EMT signaling, are involved. In particular, it was confirmed that NOX2 has an association with slug. In addition, it was confirmed that SREBP2 is involved between NOX2 and EMT signaling, and that SREBP2 silencing leads to a decrease in slug as well as HCC trans-migration. Through this, we thought that the NOX2-EMT-SREBP2 pathway would induce the development of HCC, and to prove this, We decided to test the effect of NOX2 silencing on hepatocarcinogenesis in the MOUSE HCC model. As a result, NOX2 silencing significantly reduced the number and size of HCC in mouse HCC model. Moreover, in mice, intrahepatic NOX2 silencing resulted in decreased SREBP2 activity and EMT signailing in HCC tissue. It was confirmed that intrahepatic NOX2 silencing led to decreased generation and development of HCC. NOX2 expression in the patient's HCC did not correlate with the size of HCC, but showed a tendency toward reduced survival. And It was demonstrated that NOX2 expression in HCC was proportional to N-cadherin and slug expression through western blot and proportional to SREBP2 expression through qPCR. **Conclusion:** NOX2 regulates HCC migration by regulating EMT signaling through SREBP2. This suggests that NOX2 can be used as a new indicator for the severity of HCC as well as a new treatment target.

Disclosures: The following people have nothing to disclose: Hei-Gwon Choi, Ha Neul Kim, Eun Hyuk Soo Disclosure information not available at the time of publication: Soon Ok Kim

4423-A | IDENTIFICATION OF microRNAs INVOLVED IN RESISTANCE OF LENVATINIB UNDER HYPOXIA IN HEPATOCELLULAR CARCINOMA

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Background: Among the multi-kinase inhibitors for the treatment of hepatocellular carcinoma (HCC), lenvatinib has shown a superior response rate. However, its overall survival is non-inferior to sorafenib, suggesting the acquisition of resistance during the treatment. Lenvatinib induces severe hypoxia in the tumor by inhibiting VEGF receptors, which could be the critical factor in resistance to multi-kinase inhibitors. We aimed to elucidate the mechanism of lenvatinib resistance under hypoxia in HCC. **Methods:** Human HCC cell lines were cultured in 95% air and 5% CO_2 (normoxia) or 94% N_2 with 1% O_2 and 5% CO_2 (hypoxia). Anchorage-dependent proliferation was assessed with an MTS assay. The genome-wide profiling of microRNAs and mRNAs was performed using 3D-Gene® Human miRNA Oligo chips or 3D-Gene® Human mRNA Oligo chips (Toray Industries) in HCC cells. HCC cells were electroporated with synthetic precursors of microRNAs to force the expression. **Results:** HCC cells, PLC/PRF/5, and Huh7 showed a marked increase of HIF1a protein with no significant change in the growth curve through 96 hours of culture in hypoxia. Lenvatinib inhibited cell growth in a concentration-dependent manner, and this effect was reduced under hypoxia with an IC_{50} (normoxia/hypoxia, μM) of 13.1/21.6 in PLC/PRF/5 and 22.7/25.0 in HepG2. 48 microRNAs were differentially expressed in PLC/PRF/5 treated with lenvatinib in the normoxic condition (42 increased and 6 decreased). Of the 42 microRNAs increased, 28 showed decreased expression in PLC/PRF/5 treated with lenvatinib under hypoxia. Among these, we focused on microRNA-491-5p (miR-491), which showed

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

the most significant change in expression. Using the MTS assay, we examined whether forced expression of miR-491 restores the decreased cytotoxicity of lenvatinib on HCC cells under hypoxia. The viability of cells treated with lenvatinib (12.5 and 25 μM) under hypoxia was 79.8% and 58.2% with miR-491 forced expression, significantly lower than 90.2% and 75.9% with negative control, respectively. Similar results were observed in Huh7, Hep3B, and HepG2. The genome-wide profiling of mRNAs in HCC cells with miR-491 forced expression was performed to identify its targets. The 168 genes were commonly altered in PLC/PRF/5, Huh7, and HepG2, associated with RNA splicing, cell cycle, and cell adhesion. **Conclusion:** miR-491 is involved in hypoxia-induced lenvatinib resistance, and modulating its expression restores lenvatinib cytotoxicity partly. These observations identify microRNAs as a promising target to overcome lenvatinib resistance in HCC.

Disclosures: The following people have nothing to disclose: Mari Satoh, Takayuki Kogure, Takehito Ito, Kennichi Satoh

Disclosure information not available at the time of publication: Masanori Takahashi, Kensuke Usui, Kouji Okada

4424-A | INVITROGEN" VIVOFECTAMINE" LNP FORMULATIONS FOR SAFE AND EFFECTIVE LIVER-SPECIFIC IN VIVO GENE DELIVERY

Koshi Kunimoto, Neha Parayath, Virginia Sanabria Aragon, Ty Jaouni, Peter Lam, Arezki Boudif, Joel A Jessee, Genia Verovskaya and Jason Potter, Thermo Fisher Scientific

Background: The rapidly expanding use of gene products such as mRNA, siRNA, and gRNA as therapeutic tools has created a need for innovative and optimized delivery methods. Leveraging over 30 years of lipid-based delivery expertise and the Design of Experiments (DOE) approach, we developed lipid nanoparticles (LNPs) capable of efficiently delivering gene products specifically to the liver, lung, and spleen. Here, we report on our Vivofectamine™ LNP formulations that allow for organ-specific delivery to the liver as safe nanocarriers for gene products. Our LNPs are suitable for enzyme replacement, gene knockdown and genome editing applications (for research use only). **Methods and Results:** Lipid solutions were formulated with firefly luciferase mRNA and luciferase activity was visualized in mice 4 hours after intravenous injection. Our leading candidate liver LNP was 15000x more potent than its first-generation predecessor and has shown dose-dependent bioluminescence from luciferase activity. To understand cellular targeting in the liver, we utilized Ai14 Tomato reporter mouse model. After delivery of Cre mRNA-LNP complexation, targeted cells were visualized by cryosectioning and staining tissues with markers for cholangiocytes, sinusoidal cells, and Kupffer cells. Our results demonstrated that virtually all hepatocytes became tdTomato+ after delivery of 0.1 mg/kg mRNA-LNP dose. We further performed in vivo knockdown using Factor VII (FVII) siRNA. The siRNA knockdown efficiency reached over 95% at a 0.2mg/kg siRNA dose. Finally, we analyzed the efficiency of In vivo gene editing by delivering Cas9 mRNA and gRNA complexed with our lipids, and observed over 40% knockout of transthyretin (TTR) gene after a single injection. To understand the safety of our lipids, we analyzed changes in body weight, liver enzymes, serum cytokines, organ histology and hematological parameters. Our results confirmed that our LNP had low toxicity over a range of doses. **Conclusion:** Liver-specific Vivofectamine™ LNPs can efficiently achieve in vivo gene expression, knockdown, and knockout with good safety. Our Vivofectamine™ LNP Library aims to help our customers solve their nucleic acid delivery challenges by speeding up the translation from the bench to the clinic. Research Use Only.

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Disclosure information not available at the time of publication: Neha Parayath, Virginia Sanabria Aragon, Ty Jaouni, Peter Lam, Arezki Boudif, Joel A Jessee, Genia Verovskaya, Jason Potter

4425-A | LIVERCELLPATH: A RESOURCE TO HELP EVALUATE HUMAN LIVER CELL LINES AS MODELS FOR HUMAN LIVER BIOLOGY

Brian D Halligan[1], Yue Chen[2], Antonino Oliveri[3], Maurice Tohme[1] and Elizabeth K. Speliotes[4], (1) University of Michigan School of Medicine, (2)University of Michigan, (3)University of Michigan, Ann Arbor, MI, (4)University of Michigan Medical School

Background: Primary hepatocytes are difficult to obtain and dedifferentiate quickly in cell culture making them challenging to use to model chronic liver disease. Human hepatocellular carcinoma (HCC) lines can be easily propagated but are often aneuploid and important genes or biological pathways of interest may not be expressed. We used RNAseq to measure gene expression and to determine exome genotypes from five different HCC lines and compared these to normal human primary heptocytes. We also determined exonic variation in these cell lines. We created a new software

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application, CorrPaths, that reports gene expression and exonic variation across these cell lines to facilitate identifying cell lines suitable for modeling particular aspects of liver biology and diseases. **Methods:** RNAseq was performed on HepG2, HepG2-C3A, HuH-7, SNU-475 and THLE-1 cell lines and compared with RNAseq from six primary hepatocyte datasets from GEO. Gene expression levels for HCC lines were determined using TopHat and DESeq2 and compared to primary hepatocytes with CorrPaths. Exome sequences from HCC lines were mapped to reference human genome sequences using GATK. Some results were confirmed with Western blotting. **Results:** Examination of the Reactome XENOBIOTICS pathway (R-HSA-211981) shows that many of the P450 cytochromes expressed by primary hepatocytes (CYP2E1, CYP2C8, CYP2C9, CYP3A4, CYP2A6) are nearly completely absent in all cell lines. Analysis of the GLYCOGEN_SYNTHESIS pathway (R-HSA-3322077) shows that unlike primary hepatocytes and liver tissue, all cell lines express the muscle form of glycogen synthase (GYS1) rather than the liver form of glycogen synthase (GYS2). This result was confirmed by Western blotting of GYS1 and GYS2 in HuH-7 cells compared with liver tissue extracts. Genotyping HuH-7 and HepG2 shows that both HuH-7 and HepG2 cell lines are homozygous for the PNPLA3 SNP (rs738409; I148M) known to increase NAFLD making them good models for this disease. The liver specific output from CorrPaths, LiverCellPath, can be used online or offline. Its produces an Excel file that can be easily shared with other users, exported to HTML, and can be encrypted for use with sensitive data. **Conclusion:** Choosing the correct model biological system is critical for functional experimentation. Using LiverCellPath as an experimental design tool can guide users to chose a cell line suitable for their biology based on gene expression and exonic variation.

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4426-A | LONG NON-CODING RNA DDX11-AS1 CONTRIBUTES TO HEPATOCELLULAR CARCINOMA PROGRESSION VIA ACTIVATING CARBONIC ANHYDRASE IX EXPRESSION AND THE MEK/ERK PATHWAY

Jin Sun[1,2], Yingnan Li[1,2], Mengjiao Shi[1,2], Hongwei Tian[1,2], Yanhua Mu[1,2], Jiazhen Zhu[1,2], Jun Li[1,2] and Zongfang Li[1,2], (1)National & Local Joint Engineering Research Center of Biodiagnositics and Biotherapy, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China., (2) Shaanxi Provincial Clinical Research Center for Liver and Spleen Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.

Background: The molecular mechanisms driving hepatocellular carcinoma (HCC) remain largely obscure. Long non-coding RNAs (lncRNAs) as critical factors play key roles in HCC progression. The aim of this study was to investigate the expression, roles, and mechanisms of action of the lncRNA DDX11-AS1 in HCC. **Methods:** The expression of DDX11-AS1 was determined by qRT-PCR. Subcellular distribution of DDX11-AS1 was detected by RNA-FISH. The roles of DDX11-AS1 in HCC was evaluated by performing in vitro and in vivo loss-of-function assays. The potential DDX11-AS1-controlled genes was identified by RNA-seq. The biological role of DDX11-AS1 in promoting HCC progression through its downstream gene CA9 was validated by rescue experiments. **Results:** DDX11-AS1 was elevated in several HCC cell lines as well as tissues. DDX11-AS1 was distributed both in the nucleus and the cytoplasm of HCC cells. Knockdown of DDX11-AS1 could significantly suppress cell proliferation, migration as well as invasion, and induce a cell cycle arrest and apoptosis in vitro. Tumor growth in subcutaneous mouse model was also inhibited by DDX11-AS1 knockdown. RNA-seq revealed that a total of 365 differentially expressed genes (DEGs) were screened out, including 211 up-regulated and 154 down-regulated genes, respectively. KEGG enrichment analysis and western blot validation demonstrated DDX11-AS1 could positively modulate the MEK/ERK pathway. In addition, rescue experiments showed that DDX11-AS1 could accelerate HCC progression via upregulating its downstream gene carbonic anhydrase IX (CA9). **Conclusion:** Long non-coding RNA DDX11-AS1 contributes to hepatocellular carcinoma progression via activating CA9 expression and the MEK/ERK pathway.

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4427-A | MITOCHONDRIAL AND NUCLEAR GENOME-MATCHING HYPOTHESIS WITH RESPECT TO ATP SYNTHESIS DURING RAPID LIVER REGENERATION

Akira Tanaka, Kyoto, Japan

Background: 13 genes of ATP synthesis remain in mitochondria (MT), although ca 350 genes had moved to nucleus (NU). Complex I, III and IV of electron (e) transfer system coupled with proton (p) pumps yield membrane potential (MP) across MT inner membrane , while ATP synthetase convert ADP and Pi to ATP by p-translocation through p-channel using the gradient. MT assembly is performed in the phospholipid bilayer both by MT-gene-coded subunits which are transcripted in MT ribosome and by NU-gene-coded subunits which are trafficking and targeting from cytosol through the membrane to MT. During rapid hepatocyte regeneration, NU genome is duplicated by cell division cycle, while the number of MT is reduced by half due to cytosol heredity and then divide and proliferate independent of cell cycle. Therefore, MT and NU genome-matching is likely to affect MT ATP synthesis during rapid hepatocyte regeneration. We have reported the following results in isolated rabbit liver MT at 24 hours after 70% hepatectomy, kinetic study of MT oxidative phosphorylation, Mt content of cytochromes, phospholipid composition of MT membrane, inhibitor titration analysis, MP and voltage span between NADH and O2. **Methods:** To study conformational changes in e-transfer and p-translocation due to the MT and NU genome matching hypothesis, regarding e-transfer, e-current (I), V and e-resistance, regarding p-translocation, p-flow (JH+), MP and p-conductance (CMH+) were evaluated from previous studies. I and JH+ were calculated based on stoichiometry of O/e and ATP/p. E-resistance indicates biophysical characteristics of spatial position changes of e-transfer centers as Fe and Cu in the complexes independent of driving force.To elucidate the location of the conformational changes, location site of specific inhibitors and the inhibitory mechanisms of reduction of activating energy at each catalytic site were studied. **Results:** The decreased R of e-transfer by 31.4% and the increased CMH+ of p-translocation by 9.0% were found to accelerate ATP synthesis by 76.1% with changes in Km during regeneration. Biophysical changes in Complex I, III, IV and ATP synthetase were suggested by different patterns of inhibitor titration. **Conclusion:** These studies suggest that MT and NU genome-matching based on different genomic background facilitates ATP synthesis during liver regeneration and the conformational changes are likely to take place at the junction of these two type subunits.

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4428-A | PFOA EXPOSURE RESULTS IN SEX-DEPENDENT EFFECTS ON HEPATIC AND WHOLE-BODY LIPID HOMEOSTASIS THAT DIFFER BY PPARA STATUS

Frederick Ekuban[1], *Greylin Nielsen*[2], *Dibson Dibe Gondim*[1], *Wendy Heiger-Bernays*[2], *Thomas Webster*[2], *Matthew Cave*[1,3] *and Jennifer Schlezinger*[2], *(1) University of Louisville, Louisville, KY, (2)Boston University, (3)Robley Rex VAMC*

Background: Per- and polyfluoroalkyl substances (PFAS) are a large group of persistent chemicals that have been released pervasively in the environment leading to widespread exposure for human populations. Studies on animals and humans indicate that the liver is a sensitive target organ for PFAS toxicity. Here, we test the hypothesis that the effects of perfluorooctanoic acid (PFOA) exposure in mice expressing mouse PPARα are characterized largely through PPARα-dependent mechanisms while the effects of non-PPARα dependent mechanisms will be more apparent in mice expressing hPPARα and to a greater extent in PPARα null mice. **Methods:** Female and male mPPARα, hPPARα, and PPARα null mice aged 6-7 weeks were placed on a American diet and exposed to PFOA at 0 or 3.4 μM via drinking water for 14 weeks. Exposure assessments, metabolic phenotyping, liver mRNA and histological analysis were conducted. **Results:** The mean serum PFOA concentration at the end of the study was 39 + 18 μg/mL. PFOA treatment led to reduced weight gain in male mPPAR-α and female hPPARα mice, while it did not affect male hPPARα and PPARα null mice nor female mPPARα and PPARα null mice. Furthermore, PFOA increased liver-to-body weight ratio, in all genotypes and both sexes, indicating that liver enlargement occurs at least partially through non-PPARα dependent mechanisms. Although hepatic triglycerides remained unchanged across all groups, serum and hepatic cholesterol concentrations were increased by PFOA treatment in a PPARα-dependent manner in female mice. In contrast, PFOA increased serum triglycerides in male hPPARα mice. In response to PFOA exposure, mPPARα mice showed a significantly reduced total steatosis in both sexes. PFOA did not change the extent of steatosis in hPPARα or PPARα null mice. Interestingly, female hPPARα mice exhibited a substantially lower levels of both basal and PFOA-induced steatosis compared to their male counterparts. PFOA increased mRNA expression of PPARα-target genes, *Pdk4* and *Acox*, in mPPARα mice; PFOA increased CAR and PXR target gene expression only in hPPARα mice. Additionally, *Cyp7a1*mRNA expression was downregulated in a PPARα-dependent manner. **Conclusion:** These findings indicate sex-specific effects of PFOA exposure on liver and whole-body lipid homeostasis, mediated in part via PPARα dependent mechanisms with important differences between mouse and human PPARα, and identifies hPPARa mice as a valuable in vivo model for toxicological research.

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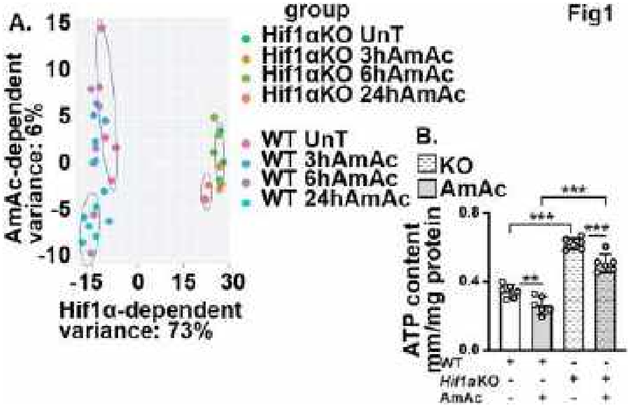
and manages the funds), No, No; Neurovigor: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Durect: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Cymabay: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Durect: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Abbvie: Speaking and Teaching, No, No;

The following people have nothing to disclose: Frederick Ekuban, Greylin Nielsen, Dibson Dibe Gondim, Wendy Heiger-Bernays, Thomas Webster, Jennifer Schlezinger

4429-A | PHYSOXIC STRESS OF HYPERAMMONEMIA IN LIVER DISEASE CAUSES SKELETAL MUSCLE MITOCHONDRIAL OXIDATIVE DYSFUNCTION AND SARCOPENIA

Nicole M. Welch[1], Saurabh Mishra[1], Annette Bellar[1], Mathew Luknis[1], Vandana Agrawal[1] and Srinivasan Dasarathy[2], (1)Cleveland Clinic, (2)Cleveland Clinic, Cleveland, OH, United States

Background: Sarcopenia (skeletal muscle loss) and physical frailty in liver disease are due to hyperammonemia-induced mitochondrial dysfunction. Skeletal muscle is a metabolic partner to hepatocytes in cirrhosis with increased uptake and metabolism of excess ammonia. Physoxic (physiological oxygenation without hypoxia) stabilizes hypoxia-inducible factor (Hif1α) during hyperammonemia. Integrated multiomics analyses with experimental validation in myotubes and muscle tissue with loss and gain of function show Hif1α- and ammonia-dependent and independent changes during physoxia. We identified Hif1α as a mediator of muscle mitochondrial dysfunction and sarcopenia in cirrhosis. **Methods:** Mice with/without *Hif1α* muscle specific deletion(*Hif1α*^{msd}) and wild-type(WT) or *Hif1α* knockout(*Hif1α*KO) murine myotubes were treated with/without ammonium acetate(AmAc, 10mM in myotubes, 2.5mmol/kg/d in mice delivered via implanted osmotic pump). Studies were done in differentiated murine C2C12 myotubes. CRISPR/Cas9 gene deletion was used to generate pools of *Hif1a*KO and WT cells. Colonies with *Hif1a*KO were selected by flow cytometry single cell sorting and expression validated by immunoblotting. Expression of HIF1a in *Hif1α*KO myoblasts were performed to replenish HIF1α. Mice with *Hif1α*^{msd} were generated by crossing *Hif1α*^{flox} mice with human skeletal actin mice with tamoxifen-inducible C*re* (JAX.org). Multiomics analyses included bulk RNAseq (with deconvolution for single nuclear analyses) and proteomics in myotubes($n=3$) and mouse skeletal muscle ($n=4$-6). Readouts included protein expression by immunoblotting, free radical detection via flow cytometry quantification of %MitoSOX fluorescence (mitochondrial free radicals), ATP generation using fluorescence assay (Promega), and tricarboxylic acid (TCA) cycle intermediates by gas chromatography/mass spectrometry. **Results:** Most differences in mRNA expression in myotubes are explained by *Hif1α* presence/absence. Ammonia results in more differentially expressed genes in WT than in *Hif1α*KO cells (Fig1A). Cellular processes enriched in genes with increased expression in *Hif1α*KO+AmAc include complex I of the electron transport chain, cellular respiration, muscle contraction, muscle tissue development. Free radicals were lower and ATP content higher in AmAc-treated myotubes with *Hif1α*KO (vs.WT). Ammonia-induced lower ATP content did not occur with *Hif1α*KO (Fig1B). Lower TCA cycle intermediates (citrate, a-ketoglutarate) with AmAc did not occur with *Hif1α*KO. Protein synthesis is increased with deletion of *Hif1α* in cellular and tissue models and AmAc-induced decrease in skeletal muscle weight is reversed with *Hif1α*^{msd}. **Conclusion:** Hyperammonemia induced mitochondrial oxidative and intermediary metabolite abnormalities with impaired protein synthesis are mediated via HIF1α, a novel target for potential therapeutics to treat sarcopenia in cirrhosis.



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4430-A | PI3K/AKT SIGNALING ON IMMUNE ESCAPE AND IMMUNE INFILTRATION IN HCC RECURRENCE

Chong Wa To[1], Soumita Ghosh[1], Xun Zhao[1], Elisa Pasini[2], Sandra Elisabeth Fischer[3], Elmar Jäckel[2], Anand Ghanekar[4], Gonzalo Sapisochin[1] and Mamatha Bhat[1], (1)University Health Network, (2)Ajmera Transplant Center, University of Toronto, Toronto, ON, Canada, (3)University of Toronto, (4)The Hospital for Sick Children

Background: Hepatocellular carcinoma (HCC) is a highly heterogeneous disease with complex mechanistic pathogenesis, which contributes to aggressive HCC recurrence. Additionally, the use of immunosuppressive medication is also considered a risk factor of HCC recurrence post-transplant. In this study, we aim to investigate the genetic evolution of HCC recurrence and the impact of immunosuppressive medication on recurrent HCC after transplantation. **Methods:** We analyzed the transcriptomic profiles of tumor samples from 12 pairs of patients with recurrent HCC. Of these patients, 7 underwent liver transplantation while 5 underwent liver resection. Only the transplant cohort received immunosuppressive medication. Functional enrichment and protein-protein interaction network analyses were performed. Top 10 hub genes were then screened and the pattern of immune infiltration in recurrent HCC tumors was also estimated. **Results:** PI3K/Akt signaling and cytokine-mediated signaling were found to play a significant role in HCC recurrence. The recurrent tumors exhibited not only upregulation of immune-escape genes, such as *CD274* and *CTLA4*, but also cytokine genes, such as *IL6* and *TNF*. Our results also showed significantly higher infiltration of activated mast cells in recurrent HCC tumors. In the transplant cohort, higher monocytes and lower M1 macrophages were infiltrated in the tumors. Furthermore, we suggested different potential drugs, such as Doxorubicin and LIN001-260, to target multiple hub genes. **Conclusion:** PI3K/Akt signaling potentially enhanced the expression of immune-escape genes and triggered cytokine secretion, leading to alterations in the immune cell infiltration pattern in HCC recurrence.

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f 4431-A | QUANTITATIVE PROTEOMICS REVEAL THE CLINICAL POTENTIAL OF AMINOACYL-tRNA SYNTHETASES IN AGGRESSIVE HEPATOCELLULAR CARCINOMA

Natalia Herman-Sanchez[1,2,3,4], Juan Luis López-Cánovas[1,2,3,4], Victor Amado[1,5,6], Javier M. Zamora-Olaya[1,5,6], Manuel Rodríguez-Perálvarez[1,5,6], Raúl M. Luque[1,2,3,4] and Manuel D. Gahete[1,2,3,4], (1) Maimónides Institute of Biomedical Research of Córdoba (IMIBIC), 14004-Córdoba, Spain., (2) Department of Cell Biology, Physiology and Immunology, University of Córdoba, 14004-Córdoba, Spain., (3)Reina Sofía University Hospital (HURS), 14004-Córdoba, Spain., (4)Ciber Pathophysiology of Obesity and Nutrition (CIBERobn), Córdoba, Spain, (5) Department of Hepatology and Liver Transplantation, Reina Sofía University Hospital, 14004- Córdoba, Spain., (6)Ciber Hepatic and Digestive Diseases (CIBERehd), Córdoba, Spain

Background: Hepatocellular carcinoma (HCC) genetic and transcriptomic signatures have been widely described. However, its proteomic characterization, which might reveal functionally relevant and potentially targetable alterations, is scarce. Therefore, we performed non-targeted quantitative proteomics of HCC samples from different aetiologies. **Methods:** Cytosolic and nuclear proteome of tissues from HCC patients (n = 42; HCC vs. adjacent tissue) and healthy controls (n = 5) were determined by SWATH-MS-based proteomics. The alterations were confirmed in 7 *in silico* HCC cohorts. *In vitro* assays (proliferation, migration, colonies/tumorspheres) were performed in liver cancer cell lines (HepG2, Hep3B, SNU-387) after silencing and overexpressing *VARS1*. Untargeted proteomics were performed on VARS1-overexpressing Hep3B and SNU-387 cells. **Results:** Non-targeted proteomics revealed a profound dysregulation of the cytosolic (n = 507 proteins) and nuclear (n = 925 proteins) tumoral proteomes. This proteomic profile identified two patients subgroups, one of them with higher aggressiveness and with a profound dysregulation of the aminoacyl-tRNA synthetases (ARSs), which catalyse tRNA aminoacylation. Their dysregulation was corroborated in *in silico* HCC cohorts and associated with aggressive and metabolic features (i.e., survival, recurrence, obesity). GSEA confirmed that patients with upregulation of the ARSs machinery have genomic (i.e. *TP53* mutations) and transcriptomic characteristics of the proliferative HCC subclass. The valine tRNA-aminoacyl synthetase, VARS1, was consistently overexpressed in HCC cohorts and associated with NASH-aetiology. VARS1 modulation had a slight impact on proliferation/migration although it significantly altered cells dedifferentiation capacity and the expression of mesenchymal and stemness-related markers. Untargeted quantitative proteomics and *in vitro* validations on Hep3B and SNU-387 cells overexpressing *VARS1* demonstrated a decreased expression of the scaffold protein *MAGI-1*, a known tumour suppressor in HCC. Thus, VARS1 might be exerting its role through the modulation of MAGI-1-mediated cell junctions. **Conclusion:** Our study demonstrates the dysregulation of the tRNA-aminoacylation machinery in aggressive HCC and the potential of these proteins, specially VARS1, as therapeutic targets in HCC. Fundings: ISCIII (ERDF/ESF, “Investing in your future”; PI20/01301), MINECO (FPU20/03957), JdA (PEMP-0036-2020, BIO-0139), FSEEN and CIBERobn/ehd.

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4432-A | RONA-APOC3, AN INVESTIGATIONAL RNAi-MEDIATED APOLIPOPROTEIN C3 GENE SILENCING, DEMONSTRATES SIGNIFICANT EFFICACY AND GOOD SAFETY IN PRECLINICAL MODELS

Xujie LIU, Guoqing Cai, Guofeng Meng, Hongli Guo, Xiaoyan Yang, Xinxin Xu, Cong Huang, Junkai Liu, Hao Zou, Jinyu Huang, Jianwu Fang and Stella Shi, Rona Therapeutics

Background: Human genetic analysis has identified that individual’s with loss-of-function mutations in apolipoprotein C3 (APOC3) have lower levels of serum triglycerides (TGs) and decreased risks of cardiovascular disease (CVD). APOC3 regulates circulating levels of TG and lipoprotein metabolism via lipoprotein lipase (LPL) -dependent and -independent pathways. Severe hypertriglyceridemia (SHTG) significantly increases risk of acute pancreatitis. Thus, reduction and maintenance of TGs levels can reduce the risks of acute pancreatitis and CVD in patients with SHTG. **Methods:** A highly potent and specific siRNA conjugate, RONA-APOC3, was designed with RAZOR^{TM} platform to target human and non-human primate (NHP) APOC3 transcripts. Primary human hepatocytes (PHH) and Hep3B cells were employed to demonstrate knockdown efficiencies *in vitro*. Human APOC3 transgenic mouse models were used to evaluate pharmacodynamic effects on reductions of serum APOC3, TG and LDL-C levels *in vivo*. Toxicities and off-target risks were evaluated in PHHs and rats. **Results:** A series of *in vitro* and *in vivo* studies were performed to confirm the candidate sequences. The half-maximal inhibitory (IC_{50}) values of RONA-APOC3 were 0.0033nM and 0.0027nM in PHH and Hep3B, respectively. In hAPOC3 transgenic mice, RONA-APOC3 significantly reduced serum APOC3 protein by up to 95.2% and lowered TG by 94.1% in parallel following a single subcutaneous injection at 3 mg/kg. At Day 70 postdosing, APOC3 level was still 49.1% lower than the baseline and TG level was 38.6% lower in parallel. Bioinformatic analysis indicated that the off-target risk of RONA-APOC3 was relatively low. Non-clinical toxicity studies showed that RONA-APOC3 has a good safety profile in rodents. **Conclusion:** RONA-APOC3 is a hepatocyte-targeted RNA interference therapeutic designed to specifically silence hepatic APOC3 mRNA expression. A series of non-clinical studies demonstrated that RONA-APOC3 reduced serum APOC3 protein and TG level with good safety and tolerability. RONA-APOC3 is a potential therapeutic option for patients with SHTG.

Disclosures: The following people have nothing to disclose: Xujie LIU, Guoqing Cai, Guofeng Meng, Hongli Guo, Xiaoyan Yang, Xinxin Xu, Cong Huang, Junkai Liu, Hao Zou, Jinyu Huang, Jianwu Fang, Stella Shi

4433-A | STABILIZATION OF O-GLCNACYLATION INCREASES EZH2 DIRECT TARGETS IN HEPATOCELLULAR CARCINOMA

Margot Thirion[1], Coline Kerbaj[1], Marie-Laure Plissonnier[1], Massimiliano Cocca[1], Vincenzo Alfano[1], Francesca Guerrieri[1], Claude Caron De Fromentel[1], Massimo Levrero[1,2] and Mirjam B. Zeisel[1], (1)Cancer Research Center of Lyon (CRCL), Umr Inserm 1052 Cnrs 5286 Mixte Clb, Université Lyon 1 (UCBL1), (2) Department of Hepatology, Croix Rousse Hospital, Hospices Civils De Lyon, France

Background: Enhancer of Zeste Homolog 2 (Ezh2) is frequently upregulated in hepatocellular carcinoma (HCC) tissues and increased Ezh2 expression correlates with HCC aggressiveness and/or poor prognosis. Ezh2 knockdown in HCC cells has been shown to reverse tumorigenicity in a nude mouse model, suggesting a potential therapeutic value of Ezh2 inhibition in HCC. The histone methyltransferase Ezh2 inhibitor tazemetostat has been FDA-approved for locally advanced or metastatic epithelioid sarcoma. However, this inhibitor demonstrated low efficacy in solid tumors suggesting that histone methyltransferase independent functions of EZH2 play an important role in cancer. As the catalytic subunit of PRC2, Ezh2 is responsible for H3K27 di- and trimethylation associated with gene repression. In additional to this canonical activity, Ezh2 can also activate gene transcription. Ezh2 activity is regulated by post-translational modifications, including glycosylation by O-GlcNAc transferase (OGT). We have previously shown that OGT expression is increased in tumor tissues from HCC patients. Interestingly, it has been reported that OGT and Ezh2 co-repress a defined tumor suppressor genes in breast and colon cancer cells. The aim of our project is to assess whether OGT and EzH2 can regulate cancer-associated pathways in HCC and to determine the underlying molecular mechanisms. **Methods:** Ezh2 and OGT expression was analyzed in paired liver tumor and peri-tumor tissue samples derived from HCC patients. Ezh2 and OGT target genes were identified in human hepatoma cells following Ezh2 or OGT silencing using RNA-sequencing (RNA-seq) and chromatin immunoprecipitation followed by sequencing (ChIP-seq). The role of O-GlcNAcylation in Ezh2 chromatin recruitment was assessed using mutant Ezh2 and ChIP-qPCR. **Results:** We show that OGT and Ezh2 are upregulated in tumor tissues as compared to peri-tumor tissues in HCC patients from two different cohorts. RNA-seq and ChIP-seq analysis of human hepatoma cells indicate that OGT and Ezh2 co-modulate the expression of a significant number of genes, including genes involved in cell cycle and cancer pathways. While a set of co-regulated genes appears to be co-repressed by Ezh2 and OGT, our data suggest that Ezh2/OGT mostly promote gene expression in liver cancer. Interestingly, stabilization of O-GlcNAcylation increased the number of Ezh2 and Ezh2/OGT target genes and EZH2 O-GlcNAcylation plays a role in EZH2 recruitment to the promoter of defined HCC-relevant direct target genes. **Conclusion:** OGT and Ezh2 are two druggable targets that co-regulate cancer-related gene expression in transformed liver cells. Our data suggest that O-GlcNAcylation of Ezh2 and/or other co-factor(s) contributes to define the repertoire of Ezh2 targets in liver cancer and provide important insights for epigenetic strategies as potential future anti-HCC therapies.

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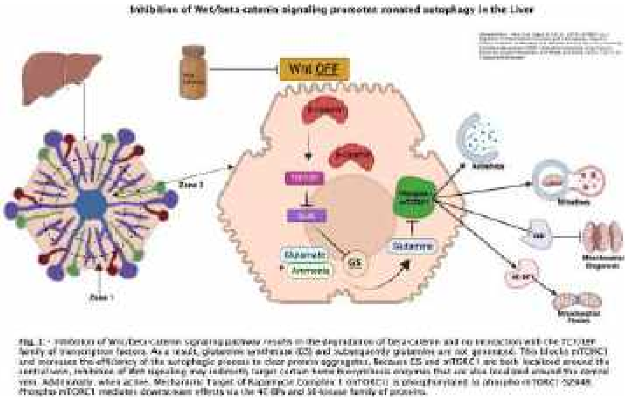
Disclosure information not available at the time of publication: Margot Thirion, Coline Kerbaj, Massimiliano Cocca, Vincenzo Alfano, Francesca Guerrieri, Claude Caron De Fromentel

4434-A | THE ROLE OF BETA-CATENIN IN REGULATING AUTOPHAGY DURING PORPHYRIA

Anu Balogun and Kari Nejak-Bowen, University of Pittsburgh

Background: The porphyrias are a group of metabolic disorders caused by inherited or acquired deficiency of any of the eight enzymes involved in heme biosynthesis, resulting in abnormal accumulation of heme precursors and their intermediates in organs such as the liver. Porphyrias are incurable, so novel therapies that have pleiotropic effects on disease progression would significantly improve patient quality of life. Because the liver is either a source or sink for accumulation of heme precursors, or porphyrins, we investigated the role of Wnt/beta-catenin signaling, a pathway that contributes to unique hepatic attributes such as zonation, autophagy, and metabolic regulation. Our earlier reports indicate that loss of hepatocyte beta-catenin protects mice from experimental porphyrin-induced liver injury. This was due to downregulation of key heme enzymes, fewer porphyrin-protein aggregates, and increased autophagy. In this study, we investigated the hypothesis that increased clearance was due to loss of glutamine synthetase (GS), a target of beta-catenin that regulates mTORC1 activation and thus autophagy. **Methods**: 3,5-Diethoxycarbonyl-1,4-dihydrocollidine (DDC), a xenobiotic compound that causes accumulation of porphyrin plugs in bile ducts, was fed to *Glul*$^{fl/fl}$ mice subjected to global Wnt inhibition using a PORCN inhibitor that blocks secretion of Wnt ligands, AAV8-Cre-mediated recombination to delete hepatic GS, or both. Half of these mice were also subjected to treatment with leupeptin to measure autophagic flux. Porphyrin accumulation, protein aggregation, autophagic vacuoles, mitochondria morphology, single cell spatial transcriptomics, mRNA expression, and mass-to-charge ratios of heme enzymes were assessed. **Results**: Our findings indicate that Cre-mediated deletion of GLUL (GS KO) or global Wnt inhibition results in defective GS activity in the liver. Phospho-mTOR-Serine2448, an indicator of active mTORC1 and autophagy in zone-3 hepatocytes, was decreased in both groups. A surplus amount of autophagic vacuoles engulfing defective mitochondria and porphyrin accumulates were observed via Transmission Electron Microscopy in GS KO as well as a decrease in heme biosynthesis and autophagy proteins. **Conclusion**: Inhibiting hepatic Wnt signaling results in lower levels of glutamine and mTOR activity, prompting an increase in autophagy that clears the accumulated porphyrin-protein complexes and helps alleviate porphyria (Figure 1). These observations collectively offer a novel opportunity to treat porphyria by targeting the Wnt/beta-catenin signaling pathway.


Inhibition of Wnt/beta-catenin signaling promotes zonated autophagy in the Liver
Wnt OFF
Zone 3
Zone 1
Glutamate
Ammonia
GS
Glutamine

Disclosures: The following people have nothing to disclose: Anu Balogun
Disclosure information not available at the time of publication: Kari Nejak-Bowen

4435-A | THE USE OF GALNAC CONJUGATED siRNA IN HEPATOPAC MICROPATTERNED HEPATOCYTE CO-CULTURES TO ASSESS GENE KNOCKDOWN IN A LONG-TERM CULTURE MODEL

Karissa Cottier, Devika Bhalerao, Jeannemarie Gaffney and Scott Heyward, Bioivt

Background: Oligonucleotide therapeutics are an increasingly popular modality due to their high selectivity and relative safety compared to small molecules. For liver diseases, N-Acetylgalactosamine (GalNAc)- conjugation of siRNA is used to direct liver delivery by its strong affinity for the hepatocyte-specific asialyglycoprotein receptor (ASGPR). The continued successful development of GalNAc-siRNA therapeutics relies on the use of validated preclinical models for screening and optimization. Here we characterized the HEPATOPAC ® model, a micropatterned co-culture for long-term (at least 28 d) primary human hepatocyte culture for ASGPR expression, GalNAc siRNA uptake, and target knockdown over a period of 14 days. **Methods:** HEPATOPAC cultures using primary human hepatocytes (PHH) from four donors. 50nM of Cy-3 GalNAc-siRNA targeting GAPDH was added to the culture medium 24-hours prior to plate fixation or RNA collection on day 0 (day 1 for Cy3-GalNac siRNA), 4, 7, 10, and 14 of culture.. ASGPR1 expression, by immunostaining, and Cy3-GalNAc siRNA uptake were visualized and quantified using high content imaging (HCI). GAPDH mRNA expression was measured using RT-PCR from Cy3-GalNAc GAPDH siRNA or GalNAc scramble siRNA treatments . The mean knockdown, Cy3-GalNAc siRNA uptake, and surface ASGPR expression were paired by PHH lot and day of culture and a linear correlation was performed. **Results:** In all lots, maximal ASGPR expression and GalNAc siRNA uptake were observed at 4 hours post plating (Day 0). In two of the PHH lots, ASGPR expression and siRNA uptake were maintained from days 2-14 (~12% change from D2-D14), while in two other lots, levels steadily declined (~37% change from D2-D14). There was a significant linear correlation of ASGPR expression vs. Cy3-GalNAc siRNA uptake ($R^2 = 0.582$, $P < 0.0001$). Knockdown of GAPDH showed less variation between lots and over time compared to ASGPR expression and siRNA uptake(2-14% difference between day 2 and 14). Percent knockdown showed a significant correlation to both ASGPR expression ($R^2 = 0.206$, $P = 0.044$) and Cy-GalNAc siRNA uptake ($R^2 = 0.398$, $P = 0.003$). **Conclusion:** The HEPATOPAC model is a long-term culture system which maintains high levels of drug metabolizing enzymes, transporters, and urea and albumin formation. In this study, HEPATOPAC cultures maintain functional ASGPR1 expression and GalNAc siRNA uptake for at least 14 days of culture. In these studies, we found a strong correlation between ASGPR expression, GalNAc-siRNA uptake, and percent knockdown of target mRNA. Together, these data support the utility of the HEPATOPAC system to examine inter-individual variation and screen GalNAc siRNA uptake and resulting knockdown in longer-term studies.

Disclosures: The following people have nothing to disclose: Karissa Cottier
Disclosure information not available at the time of publication: Devika Bhalerao, Jeannemarie Gaffney, Scott Heyward

4436-A | TRANSCRIPTIONAL REPRESSION OF POLARITY PROTEIN EXPRESSION IN HEPATOCELLULAR CARCINOMA

Saniya Davis, The Catholic University of America and Joeffrey Chahine, Medstar Georgetown

Background: Over 80% of human cancers originate from polarized epithelial cells. As the invasive phenotype is acquired, cells undergo an epithelial-mesenchymal transition (EMT) where apical-basolateral polarity is lost. The focus of our lab is to understand the mechanisms that regulate the establishment and maintenance of hepatic polarity. However, our interest has shifted to the mechanisms regulating polarity loss in hepatocellular carcinoma (HCC). Early stages of HCC are associated with chromosome 8q24 amplification and the overexpression of the potent oncogene, *c-Myc*. Myc not only activates other genes that promote oncogenesis, but also represses transcription factors responsible for polarity protein expression, including Miz1. EMT regulation by Zeb1 also promotes the loss of polarity protein expression while reinforcing c-Myc expression. Is this transcriptional regulation occurring in HCC? **Methods:** To establish this clinically, 150 resected human HCC samples were examined by immunohistochemistry. As proof of principle experiments to test for the polarity protein transcriptional regulatory loop, c-Myc, Miz1, Zeb1 and polarity protein levels are being examined in polarized hepatic WIF-B cells, and HCC-derived Hep3B cells in the presence or absence of agents that alter c-Myc, Miz1 or Zeb1 transcriptional activities. **Results:** No c-Myc or Zeb1 reactivity was observed in benign human tissue whereas nuclear staining was observed for both in malignant tissue whereas the opposite was observed

Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

for Miz1 and polarity proteins. When quantitated across grades, Miz1 and polarity protein labeling decreased for all grades whereas c-Myc and Zeb1 peaked in stages 3 and 4. In polarized WIF-B cells, both c-Myc and Zeb1 were low whereas polarity protein and Miz1 levels were high. The opposite was seen in Hep3B cells. Myc activation led to Miz1 nuclear labeling in foci consistent with its repression. When c-Myc expression was decreased, Miz1 nuclear labeling was more diffuse, consistent with its activation. When Zeb1 expression was inhibited, cells regained a more polarized phenotype. **Conclusion:** We propose that during early-stage HCC, chromosome 8q24 is amplified leading to c-Myc overexpression. As HCC progresses, Myc expression is further enhanced leading to Miz1 transcriptional repression and decreased polarity protein expression. Concomitantly, Zeb1 expression increases to drive EMT also repressing polarity gene expression.

Disclosures: The following people have nothing to disclose: Saniya Davis, Joeffrey Chahine

f 4437-A | ACTIVATION OF RECEPTOR-MEDIATED G12 SIGNALING HAS PRONOUNCED EFFECTS ON HEPATIC GLUCOSE FLUXES★

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Background: G protein coupled receptors (GPCRs) play a key role in regulating whole body glucose homeostasis. In the presence of agonist ligands, GPCRs can activate four distinct classes of heterotrimeric G proteins: Gs, Gi/o, Gq, and G12. At present, little is known about the metabolic consequences of GPCR-mediated activation of G proteins of the G12 family. **Methods:** The hepatocytes of the liver play a central role in maintaining euglycemia. To elucidate the vivo metabolic roles of hepatocyte G12 signaling, we generated a new mouse line that expresses a CNO-sensitive, G12-coupled designer GPCR (G12 DREADD; DREADD = designer receptor exclusively activated by a designer drug) selectively in hepatocytes (Hep-G12D mice). CNO is a synthetic small molecule that can selectively activate the G12 DREADD but is otherwise pharmacologically inert. In addition, we generated a mouse model that lacks functional Ga12 selectively in hepatocytes (Hep-G12 KO mice). These mutant mice were subjected to a series of metabolic tests to examine how activation of hepatic G12 signaling or hepatocyte G12 deficiency affect glucose tolerance, insulin sensitivity, in vivo glucose uptake, and various other metabolic parameters. **Results:** We found that selective activation of hepatocyte G12 signaling led to greatly enhanced blood glucose levels under both fed and fasting conditions. In vivo studies of hepatic glucose fluxes showed that these effects were due to an increased rate of glycogenolysis and gluconeogenesis. The G12D-mediated hyperglycemic effects were absent in mice lacking functional G12 in hepatocytes, indicating that the G12D designer receptor selectively activates G12. Studies with isolated hepatocytes prepared from Hep-G12D mice demonstrated that G12D-mediated glucose production required signaling via RhoA and ROCK1. We also showed that activation of endogenous sphingosine-1-phosphate receptors (subtype 1) stimulates hepatic glucose production via a similar pathway. **Conclusion:** In conclusion, our results show, for the first time, that hepatic G12 signaling plays a key role in regulating whole body glucose homeostasis.

Disclosures: The following people have nothing to disclose: Srinivas Pittala, Dhanush Haspula, Yinghong Cui, Owen P McGuinness, Asuka Inoue, Jurgen Wess

f 4438-A | DELETION OF OGT IN HEPATOCYTES: A SPONTANEOUS MODEL OF ADVANCED LIVER FIBROSIS ASSOCIATED WITH REDUCTION OF FXR ACTIVITY

Lucia Parlati[1], Fadila Benhamed[1], Marion Regnier[1], Anne Muhr-Tailleux[2], Tarik Issad[1] and Catherine Postic[1], (1)Université Paris Cité, Institut Cochin, Cnrs, Inserm, Paris, France, (2)University De Lille, Inserm, CHU Lille, Institut Pasteur De Lille, Lille, France

Background: O-GlcNAcylation (O-GlcNAc) is a post-translational modification, controlled by two enzymes, OGT (O-GlcNAc transferase), which adds a molecule of N-AcetylGlucosamine to serine or threonine residues, and OGA (O-GlcNAcase), which eliminates it. Our data report that mice with a constitutive or inducible hepatocyte *Ogt* deletion have massive necroptosis, inflammation, and fibrosis (1). Farnesoid X receptor (FXR) is a transcription factor regulated by O-GlcNAcylation and its activation has hepatic anti-inflammatory and antifibrotic effects in patients with NASH (2). We explored whether the hepatic phenotype of mice with hepatocyte *Ogt* deletion was associated with the dysregulation of FXR activity. **Methods:** We analyzed liver histologies, cytolysis and cholestasis markers, the expression of genes involved in inflammation, oxidative and ER stress and FXR target genes in control mice (OGT^{LWT}) and mice with a constitutive (OGT^{LKO}) or inducible and selective deletion of hepatocyte *Ogt* (OGT^{INDLKO}) 8 weeks after birth or after hepatocyte *Ogt* deletion, respectively. We also studied serum bile acids (BA) in 8-week-old OGT^{LKO} mice. We used male and female mice. **Results:** We confirmed that, if compared to OGT^{LWT} mice, 8-week-old OGT^{LKO} mice and OGT^{INDLKO} mice 8 weeks after hepatocyte *Ogt* deletion have increased

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markers of inflammation (*Tnfa*, *Mcp1, F4/80*) (Fig.1D, 1L), oxidative stress (*Nqo1, Nrf2, Gsta1, Gstm3*) (Fig. 1E, 1M), ER stress (CHOP) (Fig.1B,1J) and a severe hepatic phenotype with exacerbated proliferation and activation of hepatic stem cells, advanced liver fibrosis with regenerative nodules (Fig.1F, 1N) and increased transaminases and alkaline phosphatase (Fig. 1C,1K). Interestingly, $\mathrm{OGT}^{\mathrm{LKO}}$ and $\mathrm{OGT}^{\mathrm{INDLKO}}$ mice have a decreased expression of *Fxr* and its target genes (Fig. 1G, 1O) This was associated, in $\mathrm{OGT}^{\mathrm{LKO}}$ mice, with a modification in serum BA profile: the vast majority of unconjugated BA were decreased in $\mathrm{OGT}^{\mathrm{LKO}}$ mice, including TUDCA, which suppresses ER stress activation. Consistent with transcriptional analysis, the FXR antagonist named Tauro-conjugated β-muricholic acid was significantly increased in $\mathrm{OGT}^{\mathrm{LKO}}$ mice, thus confirming the reduction in FXR activity in absence of hepatocyte *Ogt* (Fig.1H). **Conclusion:** Loss of hepatocyte *Ogt* results in a severe hepatic phenotype with inflammation and fibrosis that could be associated with a dysregulation of FXR activity. Modulation of FXR O-GlcNAcylation may be a therapeutic target in the treatment of chronic liver diseases. References:

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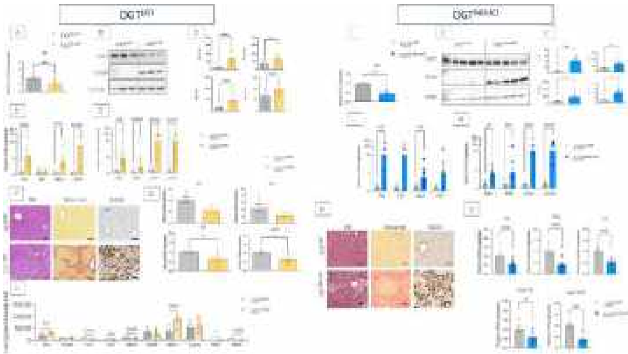

Disclosures: The following people have nothing to disclose: Lucia Parlati, Fadila Benhamed, Marion Regnier, Anne Muhr-Tailleux, Tarik Issad, Catherine Postic

f 4439-A | IL-17/ACT1 SIGNALING REGULATES TNF/TNFRI RESPONSES IN HEPATOCYTES IN MICE WITH ALCOHOL ASSOCIATED LIVER DISEASE (AALD)

Raquel Weber[1], Vivian Zhang[1], Gen Yamamoto[2], Ju Youn Kim[3], Ji Young Kim[3], Na Li[4], Leon Lin[3], Michael Karin[3], David A. Brenner[5] and Tatiana Kisseleva[5], (1) University of California San Diego, (2)University of Kyoto, (3)UCSD, (4)The Ohio State University, Wexner Medical Center, (5)University of California, San Diego School of Medicine

Background: IL-17 signaling plays a key role in the development of steatosis, fibrosis, and HCC. The hepatocyte deletion of IL-17RA in AALD mice ($\text{IL-17RA}^{\Delta\text{Hep}}$) strongly decreased expression of TNF Receptor 1 (TNFR1), suppressed ER stress, *de novo* lipogenesis, fibrosis and HCC. Re-expression of TNFR1 in hepatocytes of AALD $\text{IL-17RA}^{\Delta\text{Hep}}$ mice failed to restore steatosis and fibrosis, indicating that IL-17 may regulate TNFR1 signaling in alcohol-injured hepatocytes. Recent studies show that nuclear factor-kappa-B activator 1 (Act1) mediates IL-17 signaling by binding IL-17RA, and activating NFkB via TNF receptor Associated Factor 6 (TRAF6) ubiquitination. Act1 also phosphorylates IKK to stabilize mRNAs of IL-17 target genes. We hypothesize that IL-17RA/Act1 axis regulates key responses in alcohol-injured hepatocytes and we aim to identify the mechanism by which IL-17RA/Act1 coordinates TNF signaling and ER stress in hepatocytes in AALD. **Methods:** DEN-challenged $\text{IL-17RA}^{\Delta\text{Hep}}$ mice were infected with hepatocyte-specific AAV8-TBG-GFP-control or AAV8-TBG-TNFR1 and fed with HFD+EtOH for 18 weeks. Hepatic levels of Act1, TRAF6 and IKK were quantified. To translate our findings, primary human hepatocytes were transfected with dsi-IL-17RA, dsi-Act1 or dsi-control RNA; the hepatocytes were stimulated with IL-17A ± TNF, and the expression of IL-17A and TNF target genes/proteins were evaluated. **Results:** The expression of Act1 was decreased in livers of HFD+EtOH-fed $\text{IL-17RA}^{\Delta\text{Hep}}$ mice. As a result of Act1 downregulation, expression of Act1 targets, pIKK and TRAF6, were also reduced. Hepatic re-expression of TNFR1 did not restore TNF/TNFR1-mediated responses or the loss of Act1 phenotype in AALD $\text{IL-17RA}^{\Delta\text{Hep}}$ mice, indicating that IL-17RA/Act1 signaling is upstream of TNF signaling. Remarkably, all three transmembrane ER stress sensors (PERK, ATF6 and IRE1α) were suppressed in $\text{IL-17RA}^{\Delta\text{Hep}}$ hepatocytes, indicating that IL-17RA/Act1 is a key mediator of ER stress in AALD. In human primary hepatocytes transfected with dsi-IL-17RA stimulated with IL-17A ± TNF, the nuclear translocation of Act1 was also impaired, as shown by confocal microscopy. In support, knockdown of Act1 in human primary hepatocytes resulted in downregulation of IL-6, Cxcl1 and TNF mRNA and suppression of ER stress and lipogenesis. **Conclusion:** IL-17RA/Act1 signaling mediates TNF responses and ER stress in AALD. Targeted inhibition of IL-17RA/Act1 axis in steatotic hepatocytes may provide a new strategy to treat AALD and HCC.

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Disclosure information not available at the time of publication: Vivian Zhang, Gen Yamamoto, Ju Youn Kim, Ji Young Kim, Na Li, Leon Lin, Michael Karin, David A. Brenner, Tatiana Kisseleva

4440-A | INHIBITION OF PREGNANE-X RECEPTOR SIGNALING IMPROVES OBESITY BY SUPPRESSING ADIPOGENESIS AND INDUCING ADIPOSE TISSUE BROWNING GENES IN FEMALE MICE

Lidya H. Gebreyesus[1], Sora Choi[2], Malvin Ofosu-Boateng[1], Elizabeth Twum[1], Daniel Okuwdili Nnamani[1], Frank J. Gonzalez[3] and Maxwell Gyamfi[1], (1)The University of Tennessee Health Science Center, (2) North Carolina Central University, (3)National Cancer Institute

Background: Obesity is more prevalent in women and increases after menopause and thus poses a significant health risk. However, the underlying mechanisms of sexual dimorphic obesity remain poorly understood. Adipose tissue plays a crucial role in energy homeostasis and metabolic regulation, with the browning of white adipose tissue (WAT) emerging as a potential therapeutic target for combating obesity. Pregnane X receptor (PXR) is a nuclear receptor that detoxifies drugs and xenobiotics in the liver and intestine. Recent reports indicate that PXR regulates lipid and glucose metabolism and contributes to diet and drug-induced obesity. Interestingly, the interplay between the liver and white adipose tissue has been implicated in the pathogenesis of obesity. We hypothesized that PXR promotes severe obesity and inflammation in menopausal females by modulating adipogenesis and thermogenesis genes in white and brown adipose tissues (BAT). **Methods:** Eight-week-old female C57BL/6J wild-type and *Pxr*-null mice were subjected to either control (12% fat) or HFD (45%) for 52 weeks. A comprehensive study involved weekly assessments of body weight, food intake, glucose tolerance tests, serum analysis, gene and protein expression, and RNA sequencing. **Results:** After 52 weeks, the body weight (70.2 ± 3.7g vs 47.6 ± 3.1g, $P < 0.0001$), perigonadal WAT (9.12 ± 0.15 vs 3.76 ± 0.15, $P < 0.0001$), and BAT (0.87 ± 0.28 vs. 0.35 ± 0.32, $P < 0.01$) of the HFD-fed wild-type mice were significantly higher than the HFD-fed *Pxr*-null mice. Serum leptin (2-fold) and insulin (5-fold) levels were also increased in HFD-fed wild-type female mice. WAT adipogenesis genes such as aldo-keto reductase family 1 member B8 (*Akr1b8*) (3-fold), uncoupling protein 2 (*Ucp2*) (2-fold), and inflammatory genes, interleukin-1 receptor-associated kinase 4 (*Irak4*) (1.5-fold) were increased in HFD-fed female wild-type mice. In contrast, female *Pxr*-null mice were resistant to these changes. Similarly, RNA-seq showed that inflammatory and obesity-associated genes were only differentially upregulated in HFD-fed wild-type mice. Parallel to this, the basal levels of BAT genes, Cbp/p300-interacting transactivator 1 (*Cited1*), uncoupling protein 1 (*Ucp1*), and zinc finger protein ZIC 1 (*Zic1*) were increased in *Pxr*-null mice but not in wild-type mice. **Conclusion:** PXR deletion suppressed obesity and inflammatory genes in WAT and induced browning genes in female mice. These findings highlight the intricate interplay between PXR and metabolic processes, offering insights into the potential for PXR as a therapeutic target for obesity and inflammation-related disorders in females.
Disclosures: The following people have nothing to disclose: Lidya H. Gebreyesus, Sora Choi, Malvin Ofosu-Boateng, Elizabeth Twum, Daniel Okuwdili Nnamani, Frank J. Gonzalez, Maxwell Gyamfi

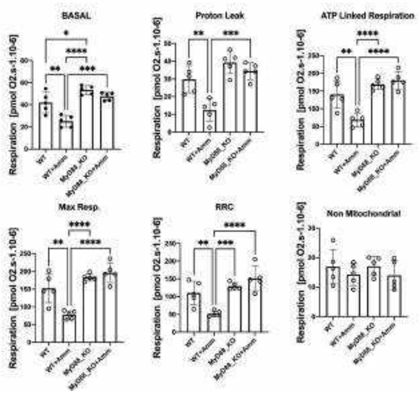
4441-A | MyD88-DEPENDENT, RHBG-INDEPENDENT SIGNALING RESPONSE RESULTS IN MITOCHONDRIAL DYSFUNCTION AND SENESCENCE IN SKELETAL MUSCLE DURING HYPERAMMONEMIA

Saurabh Mishra[1], Nicole M. Welch[1], Annette Bellar[1], Shashi S. Singh[2], Avinash Kumar[3] and Srinivasan Dasarathy[4], (1)Cleveland Clinic, (2)Case Western Reserve University, (3)All India Institutes of Medical Sciences, (4)Cleveland Clinic, Cleveland, OH, United States

Background: We have noted that Rh family B glycoprotein(RhBG), an ammonia transporter protein, interacts with Myeloid differentiation primary response 88 (MyD88), an innate immune signal transduction adaptor to initiate downstream signaling responses to activate the p65FkB-myostatin axis and cause sarcopenia in liver disease.. We dissected the molecular mechanism(s) of hyperammonemia induced mitochondrial oxidative dysfunction and post mitotic senescence. **Methods:** Differentiated murine C2C12 myotubes with knockout (KO) of RhBG or MyD88 were generated using CRISPR/Cas9. Physiological relevance was established in 8 week old, male and female C57Bl6 mice with floxed or muscle specific deletion (msd) of RhBG or MyD88. Myotubes were either untreated (UnT) or treated with 10mM ammonium acetate(AmAc) for

24h. Hyperammonemia was induced in mice by an osmotic pump that delivered either 2.5mmol/kg/d of AmAc or vehicle alone (PBS) for 4 weeks. Mitochondrial oxidative function was analyzed using high resolution respirometry. ATP content, free radicals (FR), and lipid peroxidation (thiobarbituric acid reactive substances-TBARS) were analyzed fluorometrically. Expression of proteins in the electron transport chain (ETC), carbonylated proteins, and senescence markers (p16, p21, p53, senescence associated β-galactosidase-SABG) was measured by immunoblotting. All data are expressed as mean ± SD from at least 3 biological replicates for cells and at least 6 mice in each group. **Results:** Hyperammonemia impairs mitochondrial oxidation (complexes I,III, and IV responses to substrates and inhibitors) including fatty acid oxidation (FAO) in wild type (WT) myotubes and muscle tissue from mice with RhBG$^{flox/flox}$ or MYD88$^{flox/flox}$ that are reversed by MYD88KO but not RhBGKO in both myotubes and muscle tissue. Expression of NDUFB8 expression is less with ammonia that is reversed by MYD88 not RhBG deletion. Mitochondrial FR generation, lipid peroxidation, and protein carbonylation are significantly less with MyD88KO (vs. WT) in myotuhbes and skeletal muscle from MYD88^{msd} (vs. MYD88$^{flox/flox}$) mice but not with RhBGKO. Hyperammonemia induced perturbations in response to mitochondrial oxidative dysfunction are reversed by MYD88 KO but not RhBGKO. Expression of senescence markers are significantly less with MyD88KO and deletion of MYD88 (but not RhBGKO) reversed ammonia-induced skeletal muscle post-mitotic senescence. **Conclusion:** MyD88 deletion but not RhBG, the ammonia-transceptor *in-vivo* and *in vitro* increases mitochondrial respiration and fatty acid oxidation and reverses hyperammonemia induced mitochondrial oxidative dysfunction. Consistently, deletion of MYD88 but not RhBG, reversed oxidative stress and post-mitotic senescence in skeletal muscle. Ammonia induced perturbations in mitochondrial oxidative function and senescence are mediated via an RhBG independent, MYD88 dependent mechanism.

Intact Cell Respiration in MyD88_KO C2C12 myotubes in response to Ammonia



Disclosures: The following people have nothing to disclose: Saurabh Mishra, Nicole M. Welch, Annette Bellar, Shashi S. Singh, Avinash Kumar, Srinivasan Dasarathy

f 4442-A | NUCLEAR LOCALIZATION OF ACYL-CoA THIOESTERASE 12 PROTECTS AGAINST HEPATIC STEATOSIS BY REDUCING PPARG ACETYLATION

Mariana Acuna[1], Xu Xu[2], Haiyue He[3], Lay-Hong Ang[2], Akiko Sugiyama[1], Susan J. Hagen[2] and David E Cohen[1], (1)Brigham and Women's Hospital, Harvard Medical School, (2)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (3) Xiangya Hospital of Central South University

Background: Acetyl-CoA is a substrate for both lipid synthesis and protein acetylation. Acyl-CoA thioesterase 12 (Acot12), the enzyme that hydrolyzes acetyl-CoA into acetate in liver cytosol, comprises two tandem thioesterase (THIO) domains and a C-terminal lipid-binding START domain. We have reported that Acot12 protects against hepatic steatosis by selectively downregulating the transcription of glycerolipid biosynthetic genes, which are targets of PPARg. Because PPARg is activated by acetylation, the aim of this study was to determine whether Acot12 translocates to the nucleus where it could hydrolyze acetyl-CoA and thereby reduce acetylation of nuclear proteins that control gene transcription. **Methods:** Acot12 expression in cytosolic and nuclear fractions of alpha mouse liver 12 (AML12) cells and of livers from C57BL/6J mice was determined by immunoblot analysis and by immunofluorescence. Localization of Acot12 was also assessed in Hepa1-6 cells transfected with constructs comprising eGFP-tagged full length Acot12, the THIO (Acot12ΔSTART) or the START (Acot12ΔTHIO) domain. Transfected cells were treated with leptomycin B (LMB) to inhibit nuclear efflux. Chow fed *Acot12*$^{-/-}$ and wild type mice were subjected to 6 h fasting. PPARg expression was determined by qPCR and immunoblot analysis. Protein acetylation was determined by immunoblot analysis using an acetyl-lysine antibody. Acetylation of PPARg was determined following immunoprecipitation. **Results:** Acot12 was mainly expressed in the cytosolic fraction but was also clearly identified in the nuclei of both cells and liver tissues. Nuclear localization was observed following transfection with Acot12ΔTHIO, but not full length or Acot12ΔSTART, and was more pronounced with LMB treatment. This was in keeping with the presence of a nuclear localization sequence within the START domain identified by amino acid sequence analysis. Whereas no differences in protein acetylation were observed in whole liver lysates from

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Acot12$^{-/-}$ mice, acetylation of multiple proteins were observed in nuclear fractions, including PPARg. **Conclusion:** Acot12 in liver exhibits nuclear localization that is mediated by the lipid-binding START domain. We speculate that Acot12 within the nucleus selectively reduces protein acetylation by limiting the local availability of acetyl-CoA. Acot12-mediated decreases in PPARg acetylation protect against hepatic steatosis by limiting the expression of glycerolipid biosynthetic genes.

Disclosures: David E Cohen – Esperion: Advisor, No, No; Amryt: Advisor, No, No; Pfizer: Advisor, No, No; Saliogen: Consultant, No, No; Editas: Consultant, No, Yes; PTC Therapeutics: Advisor, No, No;

The following people have nothing to disclose: Mariana Acuna, Akiko Sugiyama

Disclosure information not available at the time of publication: Xu Xu, Haiyue He, Lay-Hong Ang, Susan J. Hagen

4443-A | THE RNA BINDING PROTEIN Zfp36l1 MAINTAINS LIVER HOMEOSTASIS AND PROTECTS MICE FROM LIVER INJURY BY MODULATING Jag1/NOTCH PATHWAY

Rajesh Kumar Dutta[1], Seh-Hoon Oh[1], Kuo Du[2], Matthew B. Friedersdorf[1], Jack D. Keene[1], Perry J. Blackshear[3] and Anna Mae Diehl[1], (1)Duke University, (2)Duke University, Durham, NC, (3)National Institute of Environmental Health Sciences

Background: Liver injury triggers both de-differentiation of hepatocytes into ductal cells and differentiation of ductal cells into hepatocytes. Restoring liver homeostasis is crucial for preventing liver disease progression. ZFP36L1, a member of the ZFP36 family of RNA-binding proteins interacts with AU-rich elements found in the 3' untranslated region (UTR) of mRNA molecules, thereby modulating the expression of target genes. Hepatocyte Zfp36l1 has been implicated in the regulation of bile acid metabolism, a critical function of mature hepatocytes. We investigated the impact of L1 deficiency on liver homeostasis and its role in the development of liver diseases. **Methods:** Zfp36l1 fl/fl (L1 fl/fl) and liver-specific (albumin-Cre) zfp36l1 knockout (L1 KO) mice were subjected to models of alcoholic and nonalcoholic liver injury. We used standard biochemical and histological methods to compare liver injury and inflammation in L1 fl/fl and KO mice, and RNA seq analysis to compare gene expression in L1 KO and L1 fl/fl hepatocytes. Findings in mice were compared to liver RNA seq data from humans with fatty liver diseases. **Results:** L1 expression was significantly reduced in human nonalcoholic steatohepatitis (NASH) and severe alcohol-associated hepatitis (SAH). Hepatic expression of L1 was also decreased in mice with fatty liver injury. Depleting zfp36l1 in hepatocytes promoted ductal cell accumulation and significantly exacerbated inflammation and fibrosis in mouse models of alcoholic and non-alcoholic liver disease. Gene Ontogeny analysis of RNAseq data showed that the most significantly upregulated pathways in zfp36l1-KO hepatocytes control development and differentiation. L1 KO hepatocytes and AML12 cells with siRNA-mediated knockdown of L1 exhibited Notch pathway activation, while L1 overexpression downregulated Notch signaling, suggesting that the phenotype of L1 KO mice might be due to upregulation of some gene that is directly targeted by L1. We found that L1 directly interacts with the 3'UTR of the Notch ligand Jag1 and attenuates its expression, explaining how L1KO activates Notch L1 signaling. **Conclusion:** Hepatocytes require Zfp36l1 to limit Jag1 expression and constrain Notch signaling in order to maintain their mature phenotype.

Disclosures: Anna Mae Diehl – Inventiva: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Tune Therapeutics: Advisor, No, No; NGM: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Hanmi: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; TARGET-NASH: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boehringer-Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Hepta Bio: Advisor, No, No;

The following people have nothing to disclose: Rajesh Kumar Dutta, Seh-Hoon Oh, Kuo Du, Matthew B. Friedersdorf, Jack D. Keene, Perry J. Blackshear

4444-A | UNRAVELING THE ROLE OF HEPATOCYTE PPAR GAMMA IN PRE-CLINICAL MODELS OF NASH WITH OBESITY AND INSULIN RESISTANCE.

Marta Sierra Cruz, Samuel Man Lee, Jose Muratalla, Izabela M Hawro and Jose Cordoba-Chacon, University of Illinois at Chicago

Background: Non-alcoholic steatohepatitis (NASH) is positively associated with obesity, insulin resistance, and the expression of hepatic peroxisome proliferator-activated receptor γ (PPARγ) in mice and humans. The induction of human-like NASH with obesity and insulin resistance in mice with diets is yet challenging. Furthermore, the pathogenic role of PPARγ in hepatocytes in models of NASH remains controversial. **Methods:** To refine our model of NASH and to assess the role of hepatocyte PPARγ in NASH, control and hepatocyte-specific PPARγ knockout (Pparg$^{\Delta Hep}$) were generated in mice with pre-established diet-induced obesity (DIO, 16 weeks of high fat diet, 60% Kcal from fat diet). These mice were then fed for 8 weeks with: (1) HFCF diet: 45% Kcal from fat (trans-fat), 2% cholesterol and 22% fructose; or (2) HFC+Fr diet: 60% Kcal from fat and 2% cholesterol, plus 10% fructose in drinking water. Another cohort of adult male and female control and Pparg$^{\Delta Hep}$ mice was fed a HFC+Fr diet for 24 weeks. **Results:** In DIO mice, HFCF, but not HFC+Fr diet, reduced adiposity and insulin levels. However, both diets increased liver weight and promoted NASH. These results suggested that HFC+Fr diet may evoke a more robust model of human-like NASH with obesity and insulin resistance. Interestingly, Pparg$^{\Delta Hep}$ reduced steatosis in DIO mice, and the progression of NASH and fibrosis in HFC+Fr-fed mice. In a separate cohort of mice, HFC+Fr diet promoted severe obesity: 54.88 ± 3.75g (males) and 45.49 ± 7.42g (females), and insulin resistance. However, NASH was developed only in HFC+Fr-fed male mice. A RNAseq analysis revealed that HFC+Fr diet increased the expression of genes involved in fibrosis and inflammation in the liver of male mice. Interestingly, Pparg$^{\Delta Hep}$ reduced liver weight, plasma ALT, hepatic triglyceride accumulation, and liver fibrosis in HFC+Fr-fed male mice, without reducing adiposity or insulin resistance. Also, Pparg$^{\Delta Hep}$ reduced the expression of genes associated with fibrosis and inflammation. In addition, the expression of genes involved in amino acid and steroids metabolism were increased in Pparg$^{\Delta Hep}$ mice which may prevent NASH development and improve liver health. **Conclusion:** The composition of NASH-inducing diets is essential to reproduce human-like NASH with obesity and insulin resistance in mice. Furthermore, hepatocyte PPARγ activity is associated with the downregulation of genes involved in amino acid and steroid metabolism that might impact the development of fibrosis and inflammation.

Disclosures: The following people have nothing to disclose: Marta Sierra Cruz, Samuel Man Lee, Jose Muratalla, Izabela M Hawro, Jose Cordoba-Chacon

4445-A | ZINC FINGER PROTEIN 791 IS A NOVEL TARGET FOR INTERFERON-MEDIATED SUPPRESSION OF LIVER CANCER INITIATION

Jin Lee, University of California San Diego and Gen-Sheng Feng, University of California, San Diego

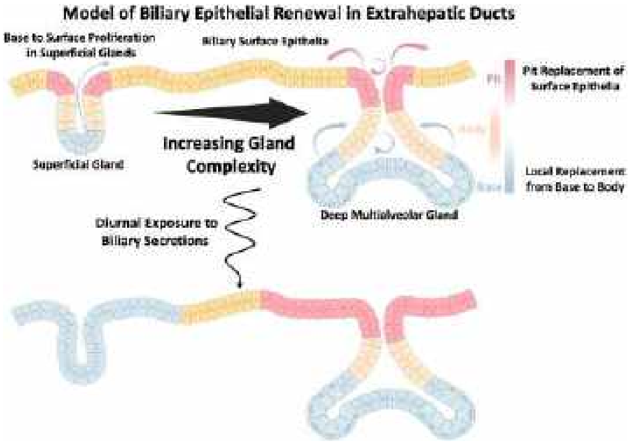
Background: The poor survival of most hepatocellular carcinoma (HCC) patients is due to: a) lack of effective diagnostic biomarkers for early stages of HCC; and b) no intervention strategy available for HCC at early stages, although it is considered as a promising option to cure HCC. While dissecting roles of cytoplasmic signaling molecules in hepatocarcinogenesis using the Mx1-cre inducible mouse gene targeting system, we identified a potent liver tumor-inhibitory effect of poly-inosinic-polycytidylic acid (polyIC), a synthetic dsRNA used to induce the *Mx1-cre* system. Injection of polyIC at the pre-cancer stage robustly suppressed HCC by eliciting multiple innate immune functions in the liver. We performed RNA-seq analysis in several mouse models following injection of polyIC to search for molecules that are possibly involved in the anti-HCC activity of the synthetic dsRNA. Interestingly, bioinformatic data analysis showed only one gene whose expression was severely suppressed by polyIC in all liver samples, i.e. a zinc finger protein (Zfp)791. Zfp791 was preferentially expressed in zone 3 hepatocytes and its expression was aberrantly increased in tumors driven by oncogenic β-catenin. Zfp791 in hepatocytes was severely suppressed in β-catenin-deficient liver but was re-appeared following exogenous expression of oncogenic β-catenin. We hypothesized that Zfp791 might operate by interacting with β-catenin in cancer cells and will be a target molecule in polyIC-mediated prevention of HCC initiation at the early HCC stage. **Methods**: This study utilized hydrodynamic tail vein injection of oncogenes (β-catenin/MET) and Zfp791-specific CRISPR/Cas9 into mice to investigate a pro-oncogenic role of Zfp791. To interrogate the mechanism of Zfp791 regulation by β-catenin, Chip-seq was conducted in cancer cell lines bearing either wild-type or oncogenic mutant β-catenin. Immunofluorescence, Western blot and qRT-PCR were used to elucidate the role of Zfp791 in Wnt/β-catenin signaling. To elucidate the underlying molecular and cellular mechanisms, we used co-culture system and chemical-induced interferon (IFN)-1 receptor knockout mice. **Results**: We identified Zfp791 as a critical player in β-catenin signaling in pericentral hepatocytes. Loss of Zfp791 suppressed β-catenin-driven hepato-oncogenesis in mice, and elevated Zfp791 expression was detected in human HCCs with *CTNNB1* mutations in association with poor prognosis. polyIC-mediated inhibition of the Zfp791/β-catenin axis was alleviated in IFN-1 receptor knockout mice and IFNs suppressed Zfp791 and β-catenin expression. Clinical data analysis revealed downregulation of Zfp791 and β-catenin signature genes in livers of IFN-treated patients with hepatitis B or C viruses. **Conclusion**: Taken together, Zfp791 could be utilized as a biomarker for HCC at the early stage and may also a new therapeutic target of IFN therapy for a subset of HCC patients with β-catenin mutations.

Disclosures: The following people have nothing to disclose: Jin Lee, Gen-Sheng Feng

4446-A | HETEROGENOUS PERIBILIARY GLANDS ORCHESTRATE COMPARTMENTALIZED EPITHELIAL RENEWAL

Serrena Singh[1], Tifanny Budiman[1], Makoto Taketo[2], Benjamin Simons[3] and Vikas Gupta[1], (1)Yale School of Medicine, New Haven, CT, (2)Kyoto University, (3) Gurdon Institute

Background: The largest branches of the biliary tree have complex glandular elements connecting to a surface epithelium. It is unknown whether a stem cell compartment is responsible for biliary epithelial renewal. We aimed to determine how epithelial renewal was organized in the large extrahepatic bile duct in a mouse model. **Methods:** Non-biased clonal lineage tracing was combined with 3-dimensional imaging to trace the fates of epithelial clones over 1.5 years. Single cell sequencing was used to transcriptomically define epithelial subpopulations, which were spatially delineated. Biased lineage tracing targeting the pit and base of the peribiliary glands was employed and quantitatively analyzed. Genetic β-catenin gain of function was used to modulate cellular identity. **Results:** We show that cholangiocytes within the pits of the peribiliary glands have higher rates of proliferation than the rest of the gland. Marker free clonal lineage tracing displayed that peribiliary pits renewed the biliary surface epithelium whereas basally localized cells contributed to maintenance of the base and body of the gland in large complex glands. This contrasted that of the minority of superficial glands, which showed base derived clones contributing to surface epithelial renewal. Lineage tracing directed at peribiliary pits displayed accelerated labeling kinetics of the surface epithelium whereas basally directed lineage tracing confirmed that cells remained within the gland of large complex glands. Single-cell sequencing with trajectory analysis identified transcriptomic gradients across the gland with Olfm4, Aqp5, and Muc6 enriched within the base of the gland. However, all cholangiocytes within the large ducts displayed marked plasticity, changing cellular identity upon fasting and refeeding. β-catenin gain of function caused expansion of the Muc6+ population and gain of gastric chief cell makers Troy and Pgc. **Conclusion:** Together, these results define how the interplay between renewal and plasticity support the maintenance and remodeling of the bile duct in response to demand and has implications for understanding the development of biliary carcinogenesis.


Model of Biliary Epithelial Renewal in Extrahepatic Ducts
Base to Surface Proliferation in Superficial Glands
Biliary Surface Epithelia
Pit Replacement of Surface Epithelia
Pit
Increasing Gland Complexity
Superficial Gland
Local Replacement from Base to Body
Base
Deep Multialveolar Gland
Diurnal Exposure to Biliary Secretions

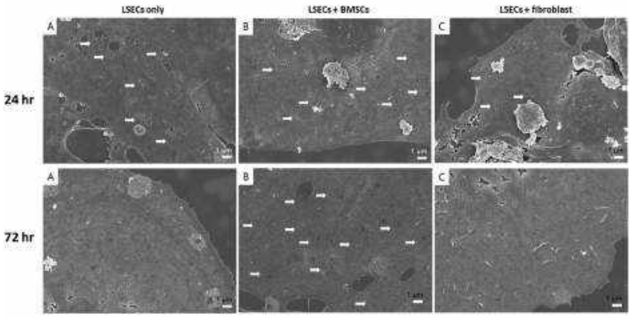
Disclosures: The following people have nothing to disclose: Serrena Singh, Tifanny Budiman, Makoto Taketo, Benjamin Simons, Vikas Gupta

4447-A | INTERACTION BETWEEN MESENCHYMAL STEM CELLS AND LIVER SINUSOIDAL ENDOTHELIAL CELLS ACTIVATES HEPATIC PROGENITOR CELLS

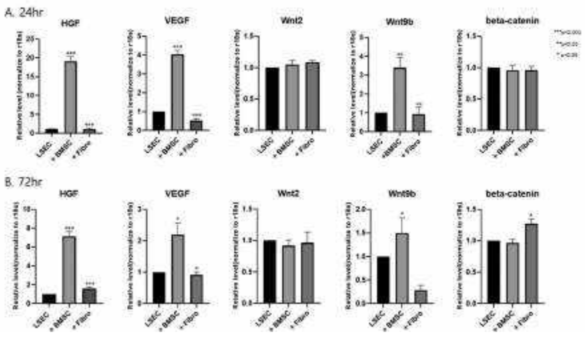
Han Seul Ki, Soon Koo Baik and Moon Young Kim, Yonsei University Wonju College of Medicine

Background: The hepatic progenitor cell (HPC) is an innate stem cell in the liver and the main cell in liver regeneration. Induce that the proliferation and regenerative activity of HPC is the main issue in the liver regeneration field. Liver sinusoidal cells (LSECs) inactivation and stabilization are essential in accelerating the regression of fibrosis and inhibiting the progression of cirrhosis. LSEC also has been known to activate HPC through the Wnt-β-catenin signaling. However, the method to stabilize LSECs is not yet established. Therefore, we investigated the functional recovery of LSECs through mesenchymal stem cells (MSCs) and whether it can induce HPCs activation. **Methods:** To evaluate the stabilization of LSEC by MSC, the recovery of fenestrae of LSECs was confirmed by Scanning Electron Microscope (SEM) after co-culture. Changes in various factors affecting the stabilization of LSEC were also confirmed by real-time polymerase chain reaction and Western blot. The specific cell markers of the isolated mouse LSECs and MSCs were confirmed by FACS. In addition, HPCs were cultured using the culture soup obtained by co-culture of LSECs and MSCs, and the activities of HPCs were analyzed. **Results:** In human-derived MSC and LSCE co-culture, LSEC showed recovery of fenestrae with increased expression of VEGF, eNOS, HGF, Wnt2, and Wnt9b in LSEC compared with control. Also, when LSECs and MSCs isolated from mice were co-cultured, the expression of VEGF and HGF, which play an important role in maintaining the morphology of LSEC, increased. The expression of Wnt9b, which acts as an angiocrine factor in liver regeneration, was also increased. In the culture of HPC, when the soup obtained from LSEC during LSEC and MSC co-culture was added, an increase in HPC activity was observed compared to the control group. The proliferation of stem progenitor cells was doubled in both 24 and 48 hours compared to the control group. Also, the expression of VEGF and Wnt2 increased in HPC at 24 hours, and the expressions of HGF, VEGF, and Wnt9b increased at 48 hours. **Conclusion:** MSC showed the property that can induce stabilization (undifferentiated) LSEC. Stabilized and functionally recovered LSEC by MSC also induced the proliferation and increased the activity of HPCs and which suggests a possibility that MSC-based recovery of LSEC in hepatic fibrosis can be helpful in the promotion of liver regeneration through HPC activation.

SEM images showing the fenestrae of mouse LSECs in co-culture with BMSCs



Change of related genes expression in mLSECs co-cultured with mBMSCs



Disclosures: The following people have nothing to disclose: Han Seul Ki, Soon Koo Baik, Moon Young Kim

f 4448-A | MODELING HEPATO-HEMATOPOIETIC DEVELOPMENT IN FETAL LIVER ORGANOIDS FROM HUMAN PLURIPOTENT STEM CELLS★

Milad Rezvani[1,2,3], *Kyle Lewis*[3], *Susanna Quach*[1], *Kentaro Iwasawa*[3], *Julian Weihs*[1], *Hasan Al Rezva*[3] *and Takanori Takebe*[3,4,5,6,7], *(1)Charité Universitätsmedizin Berlin, (2)Berlin Institute of Health (Center for Regenerative Therapies, Clinician-Scientist Program), Beijing, China, (3)Cincinnati Children's Hospital Medical Center, Cincinnati, OH, (4)Center for Stem Cell & Organoid Medicine (CuSTOM), Cincinnati Children's Hospital Medical Center, (5)Division of Developmental Biology, Cincinnati Children's Hospital Medical Center, (6)Institute of Research, Tokyo Medical and Dental University, (7)Osaka University*

Background: The fetal liver is a hematopoietic organ during development, harboring a highly heterogenous lympho-hematopoietic population. To better understand the blood-liver niche during inaccessible stages of human development, a model is required to recapitulate, probe and manipulate this dynamic microenvironment. Human liver organoids from pluripotent stem cells (PSC) recapitulate early embryogenesis yet lack the interplay between hepatic and hematopoietic ontogeny. **Methods:** We developed human fetal liver-like organoids (FLOs) endowed with a Notch-permissive niche, allowing for the concomitant emergence of endoderm-derived hepatoblasts, mesoderm-derived hemogenic endothelial cells and hematopoietic progenitors with broad myeloid, erythroid, lymphoid differentiation potential. We inferred differentiation trajectories and functional crosstalk through a comprehensive workflow involving longitudinal single-cell RNA-Sequencing, integration into the human fetal liver atlas, spatial analysis of highly multiplexed immunofluorescence and mechanistic validation via FACS-based lineage depletion. To model the divergence into heterogenous immune lineages, including neutrophil granulocytes and macrophages, we generated highly hematopoietic FLOs (hFLOs) by adding a small molecule-cytokine cocktail (UM171/IL3/IL34/GM-CSF). We assessed immunoreactive functions and hepatobiliary injury in response to bacterial, lipotoxic and cholangiotoxic milieus. **Results:** Trajectory analysis from FLOs to hFLOs revealed the emergence of 21 hematopoietic populations from 24 found in the human fetal liver atlas while maintaining hepatoblasts and fetal liver mesenchyme. Crosstalk between hepatoblasts and endothelium dominated the cellular niche interactions, mainly via Notch signaling. We found that EPCAM+ hepatoblastsand

KDR+ endothelium, but not NCAM+ mesenchyme were essential in maintaining hematopoietic output. We confirmed hepatobiliary and hematopoietic capacity via differentiation into AFP+ALB+ fetal hepatocytes with cytochrome activity, CK19+ luminal-forming cholangiocytes, erythro-myeloid colony formation and lymphoid differentiation into fetal B1-cells. Upon infection of hFLOs with bacteria or exposure to palmitic acid, we observed effective phagocytosis by macrophages and neutrophil granulocytes and a neutrophil-predominant steatohepatitis-like reaction, respectively—while exposure to biliatresone dysregulated morphogenesis to multiple lumina in a ductular-like reaction. **Conclusion:** Our data support the concept of intrinsic liver organoid capacity for hematopoietic development. FLOs serve as a tractable tool to model the blood-liver niche in human ontogeny and the multicellular response to various injury triggers.

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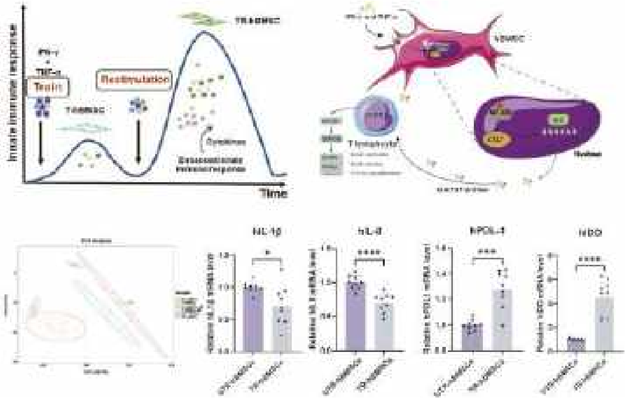
Disclosure information not available at the time of publication: Kyle Lewis, Susanna Quach, Kentaro Iwasawa, Julian Weihs, Hasan Al Rezva, Takanori Takebe

4449-A | TRAINED IMMUNITY CONTRIBUTES TO IMMUNOREGULATION IN HUMAN BONE MARROW MESENCHYMAL STEM CELLS

Bingqi Li[1], Xi Liang[2], Jing Jiang[1], Jiaojiao Xin[1], Dongyan Shi[1], Lulu He[1], Jinjin Luo[1], Shiwen Ma[1], Hui Yang[1], Xingping Zhou[1], Jiaxian Chen[1] and Jun Li[1], (1) The First Affiliated Hospital, Zhejiang University School of Medicine, (2)Taizhou Central Hospital (Taizhou University Hospital)

Background: The immunoregulation function of human bone marrow mesenchymal stem cells (hBMSCs) plays an important role in the treatment of cytokine storm in severe liver diseases. However, the complex immune microenvironment in vivo challenges the survival and function of hBMSCs. Trained immunity has been proved to improve the adaptability of immune cells and therapeutic effect. This study aims to enhance the immunoregulation function of hBMSCs by trained immunity to optimize stem cell therapy strategies. **Methods:** Trained immunity of hBMSCs (T-hBMSCs) were performed with pro-inflammatory cytokines IFN-γ and TNF-α as "trainers" to induce hBMSCs for 24 hours, the untrained-hBMSCs (UT-hBMSCs) were performed with medium as control. Then same dosage "trainers" or patient serum derived from acute-on-chronic liver failure (ACLF) were used to assess the function of hBMSCs after 48 hours cleaning. Culture supernatant and cell samples were collected to perform flowcytometry, qRT-PCR and transcriptome analysis. **Results:** The surface markers of T-hBMSCs detected by flowcytometry were positive for CD73, CD166 and CD90, but negative for CD45, CD34 and CD79a, which was consist with UT-hBMSCs. Trilineages differentiation of hBMSCs after training was also maintained. The results showed that the pro-inflammatory genes (IL-1β, IL-6 and IL-8, all $p < 0.0001$) and immunosuppressive genes (PDL-1 and IDO, both $p < 0.0001$) expressed in T-hBMSCs were all higher than UT-hBMSCs. After 48 hours cleaning, the expression of immunomodulatory genes especially IDO still significantly higher with the expression levels of inflammatory genes especially IL-1β in T-hBMSCs gradually returned to the baseline state. The results showed that the expression of IDO was significantly elevated in T-hBMSCs compared to UT-hBMSCs upon the same dosage "trainers" or ACLF patient-derived serum restimulation (5-fold vs. 4606-fold, both $p < 0.0001$). Gene set enrichment analysis revealed that trained immunity activated the NF-kB signaling pathway related to innate immune and further induced JAK-STAT pathway in T-hBMSCs causing an increase in IDO expression. The higher expression level of IDO inhibited the proliferation and activation of T lymphocytes, resulting from the enhanced immunoregulation function of T-hBMSCs. **Conclusion:** Trained immunity enhances the immunoregulation function of hBMSCs and contributes to optimize the stem cell therapy strategies, indicating the potential of T-hBMSCs for future clinical applications.



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4500-C | AUTOIMMUNE HEPATITIS PRESENTS AT A YOUNGER AGE IN LATINX PATIENTS

Gerardo Rubio Monroy[1], Javier Castro[1], Isaac Avila-Vargas[1], Melawit Tekeste[1], Maira Phelps[2], Briton Lee[1], *Swathi Kari[1], Arielle Klepper[3], Catherine Magee[1], Miranda E. Surjadi[1], Jennifer Y. Chen[1], Jacquelyn J. Maher[3], Mandana Khalili[1], Miles Conrad[1], Michael Ohliger[1], James Grenert[1], Bruce M. Wang[4], D. Montgomery Bissell[5], Sandy Feng[1], Marcial Sebode[6], Jennifer C. Price[1], Emily J. Rothbaum Perito[3], Michele M. Tana[1] and Jameson Wu[7], (1)University of California, San Francisco, (2)Chan Zuckerberg Biohub, (3) University of California, San Francisco, San Francisco, CA, (4)University of California San Francisco Medical Center, (5)University of California, San Francisco, Berkeley, CA, (6)University Medical Center Hamburg-Eppendorf, Hamburg, Germany, (7)University of Pittsburgh*

Background: AIH disproportionately affects women and Black, Indigenous, and People of Color (BIPOC). Latinx patients with AIH more frequently have cirrhosis at presentation. Prior studies have linked age of presentation with progression to cirrhosis and decompensation events. *Aims*: To assess the clinical presentation, treatment response, and clinical outcomes in prospectively followed AIH patients. **Methods:** Clinical data from AIH patients within Prospective Observational Study to Understand Liver Diseases (POSULD) were analyzed with a focus on age, disease activity (transaminases, IgG), fibrosis stage at presentation; treatment response after > =6 months of therapy; and fibrosis progression (biopsy or elastography). **Results:** Of 54 patients with AIH enrolled 2018-2023, 78% were female, 53% were Latinx, 47% non-Latinx white, 7% Black, and 9% Asian American. Among Latinx patients, 54% were born in Mexico, and 42% in Central America. Median age at presentation of AIH in Latinx patients was 53y (range 17-79) vs. 64y (range 45-79) in non-Latinx patients ($p = 0.0001$). Thirty-seven (69%) patients were Type 1. A drug/toxin was suspected as a trigger in 4%. On index biopsy ($n = 54$), 13% also had PBC, and 11% NAFLD. Six (20%) of the Latinx pts had cirrhosis at presentation, compared to 1 (3.4%) in non-Latinx patients ($p = 0.39$). AST, ALT, and IgG value at enrollment and after 6-12 months of therapy were not significantly different in the Latinx vs. non-Latinx AIH patients. Fatigue at enrollment was similar in both groups (3.00 vs. 2.95, scale 0-4, $p = 0.81$). Of 16 Latinx and 7 non-Latinx AIH pts with serial fibrosis assessments, 3 Latinx had fibrosis progression, compared to 0 non-Latinx patients ($p = 0.67$). 6% of patients died or decompensated during follow-up (5 Latinx, 3 non-Latinx). **Conclusion:** Latinx patients with AIH are, on average, significantly younger at diagnosis. Longer follow-up will determine if these patients are more likely to develop cirrhosis and experience decompensation.

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Jacquelyn J. Maher – Myovant: Consultant, No, No; Gordian Biotechnology: Consultant, No, No; BioMarin: Consultant, No, No;

Mandana Khalili – Gilead sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead sciences: Consultant, No, Yes; Intercept pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

Bruce M. Wang – Alnylam Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Mitsubishi Tanabe Pharma: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; BridgeBio: Consultant, Yes, No; Alnylam Pharmaceuticals: Speaking and Teaching, Yes, No; Disc Medicine: Advisor, Yes, No; Recordati Rare Diseases: Advisor, Yes, No; Mitsubishi Tanabe Pharma: Advisor, Yes, No; American Porphyrias Expert Collaborative: Advisor, Yes, No;

Jennifer C. Price – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Abbvie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Genentech: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Zydus: Grant/Research Support (research funding from ineligible companies should be disclosed

by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; VIR: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
Michele M. Tana – Merck: Consultant, No, Yes;
The following people have nothing to disclose: Gerardo Rubio Monroy, Arielle Klepper, Miranda E. Surjadi
Disclosure information not available at the time of publication: Javier Castro, Isaac Avila-Vargas, Melawit Tekeste, Maira Phelps, Briton Lee, Swathi Kari, Catherine Magee, Miles Conrad, Michael Ohliger, James Grenert, D. Montgomery Bissell, Sandy Feng, Marcial Sebode, Emily J. Rothbaum Perito, Jameson Wu

4501-C | AZATHIOPRINE ON RISK OF EXTRAHEPATIC MALIGNANCY IN PATIENTS WITH AUTOIMMUNE HEPATITIS: A NATIONWIDE CLAIMS STUDY IN SOUTH KOREA

Sung Hwan Yoo, Jung Il Lee and Hyun Woong Lee, Gangnam Severance Hospital

Background: Long-term immunosuppressive therapy in patients with autoimmune hepatitis (AIH) increases the risk of extrahepatic malignancy in addition to hepatocellular carcinoma. However, the risk of extrahepatic malignancy is unknown in Korean AIH patients. We aimed to evaluate the impact of azathioprine (AZT) treatment on extrahepatic malignancy risks. **Methods:** We identified all persons diagnosed with AIH between 2008 and 2020. We included 8,280 patients with AIH, using the national claims data of the Health Insurance Review and Assessment Service (HIRA). The numbers of patients treated with and without AZT were 3,059 and 5,221, respectively. We estimated the cumulative risks of extrahepatic malignancy and hazard ratios (HRs) between patients treated with and without AZT. **Results:** Among 8,280 patients, the mean age was 56.7 ± 13.5 years, 84.3% were women, and the follow-up period was 49.8 ± 43.1 months. The mean age and sex are not different between patients treated with and without AZT. However, the number of patients with diabetes was higher in patients treated with AZT (31.3% vs. 28.0%). The number of patients with liver cirrhosis was higher in patients treated without AZT (36.0% vs. 38.9%). At the time of diagnosis, 85.5% of patients with AZT and 30.0% of patients without AZT were treated with steroids for more than 90 days ($P < 0.001$). The incidence of extrahepatic malignancy was 1.36 and 1.23 per 100 person-years in the patients treated with AZT and without AZT, respectively ($P = 0.685$). After we adjusted for confounding by age, sex, diabetes, and liver cirrhosis, the HR was 1.09 (95% confidence interval 0.79–1.51, $P = 0.600$). **Conclusion:** The national claims data of HIRA did not show that AZT significantly increases the risk of extrahepatic malignancy among AIH patients.

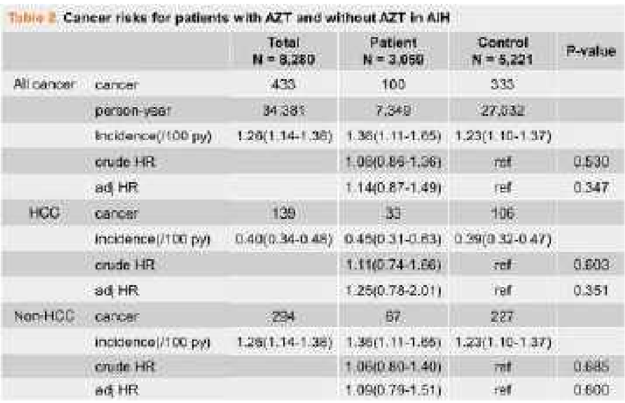

Table 2 Cancer risks for patients with AZT and without AZT in AIH

		Total N = 8,280	Patient N = 3,059	Control N = 5,221	P-value
All cancer	cancer	433	100	333	
	person-year	34,381	7,349	27,032	
	incidence(/100 py)	1.26(1.14-1.38)	1.36(1.11-1.65)	1.23(1.10-1.37)	
	crude HR		1.09(0.86-1.36)	ref	0.530
	adj HR		1.14(0.87-1.49)	ref	0.347
HCC	cancer	139	33	106	
	incidence(/100 py)	0.40(0.34-0.48)	0.45(0.31-0.63)	0.39(0.32-0.47)	
	crude HR		1.11(0.74-1.66)	ref	0.603
	adj HR		1.25(0.78-2.01)	ref	0.351
Non-HCC	cancer	294	67	227	
	incidence(/100 py)	1.26(1.14-1.38)	1.36(1.11-1.65)	1.23(1.10-1.37)	
	crude HR		1.06(0.80-1.40)	ref	0.685
	adj HR		1.09(0.79-1.51)	ref	0.600

Disclosures: The following people have nothing to disclose: Sung Hwan Yoo, Hyun Woong Lee
Disclosure information not available at the time of publication: Jung Il Lee

4502-C | BIOMARKER DISCOVERY IN PATIENTS WITH AUTOIMMUNE HEPATITIS

Claire Harrington[1], Swathi Krishnan[2], Scott Roberts[2], Allison Carroll[1], Paolo Cravedi[3], Neil Kelleher[1], James L. Boyer[2], Marina G. Silveira[2], Eleonora Forte[1], David N. Assis[2] and Josh Levitsky[1], (1)Northwestern University Feinberg School of Medicine, (2)Yale School of Medicine, New Haven, CT, (3)Icahn School of Medicine at Mount Sinai, New York, NY

Background: Autoimmune hepatitis (AIH) is a rare disease characterized by a loss of immunological tolerance and persistent hepatic immunoreactivity requiring immunosuppressive therapy (IST). Novel biomarkers are needed to better understand AIH pathogenesis, predict patients at high risk for relapse, and assess suitability for IST withdrawal. The study aim is to investigate candidate blood biomarkers of AIH activity vs. quiescence to eventually guide and personalize IST management. **Methods:** Blood samples from 38 patients were collected and segregated into three groups: active AIH at liver biopsy (AD) ($n = 11$), AIH with complete biochemical response on IST for > 1 year (RT) ($n = 16$), and AIH with complete biochemical response off IST for > 1 year (NRT) ($n = 11$) from two liver centers.

Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Healthy controls (n = 5) from a biorepository were also included. Between the groups, we compared results from a large discovery panel of 92 plasma inflammatory markers (OLINK) as well as targeted candidate biomarkers (Sandwich ELISA) identified from prior studies (Harrington et al, *Hepatology* 2022). **Results:** The mean AIH cohort age was 55.6 yo, 82.2% female, and 71.1% Caucasian. The AD group had significantly higher levels of BAFF, CDCP1, and CXCL11 vs. all other groups. AD also had a higher ferritin, sCD74 and sCD74/MIF ratio vs. the RT group. Compared to healthy controls, the NRT group had higher levels of MCP-3, CCL3, and IL-10RB and the RT group higher levels of MCP-3, CCL3, and CCL19. Interestingly, the NRT group (off IST) had higher ferritin levels and sCD74/MIF ratio vs. the RT group (*Figure 1*), despite both having normal liver enzymes and IgG levels. **Conclusion:** Our study reveals several inflammatory biomarkers associated with active vs. biochemically quiescent AIH, supporting their potential use for detecting immunoactivity. In addition, the biomarker differences between inactive AIH vs. healthy controls and, importantly, inactive AIH on vs. off IST suggest a potential role to detect immunoactivity despite normal liver tests, which may be useful when considering IST withdrawal. We are currently performing detailed PBMC immunophenotyping and proteomic analyses to identify additional biomarkers, to be presented subsequently. Further validation of these biomarkers is needed to elucidate their clinical utility above currently available tests.

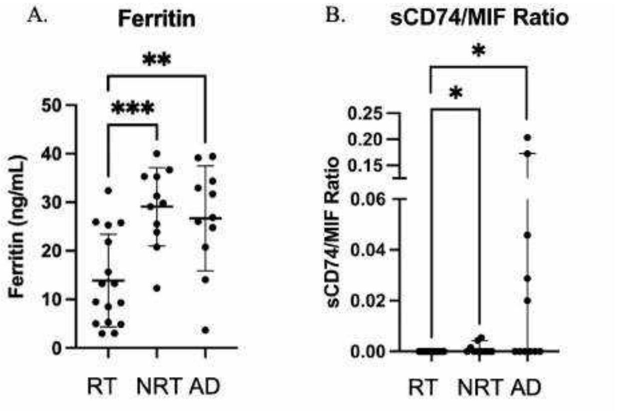

Figure 1: Using ELISA, analysis resulted in a significant finding of higher ferritin (A) and sCD74/MIF ratio (B) in the NRT group compared to the RT group.
RT (stable on IS >1 yr), NRT (stable off IS >1 yr), AD (active AIH)
***p<0.001, **p<0.01, *p<0.05

Disclosures: Josh Levitsky – Eurofins: Advisor, Yes, No; Mallinckrodt: Speaking and Teaching, No, No;
The following people have nothing to disclose: Claire Harrington, Swathi Krishnan, Allison Carroll, James L. Boyer
David N. Assis:

Disclosure information not available at the time of publication: Scott Roberts, Paolo Cravedi, Neil Kelleher, Marina G. Silveira, Eleonora Forte

4503-C | CAN LMS (LIVER MULTISCAN) BE AN ALTERNATIVE TO LIVER HISTOLOGY IN MANAGING ADULT AIH?

Abdullah Mubarak[1], Sai Priya Metla[1], Mahnoor Fatima[1], Caleb Keng[1], James Gray[1] and Liver Center of Texas, (1)Liver Center of Texas

Background: Autoimmune hepatitis (AIH) is a chronic liver disease caused by an abnormal immune response targeting the liver cells, leading to ongoing inflammation and potential liver fibrosis. While immunosuppressive therapy remains the primary treatment for AIH, monitoring disease progression and response to treatment is crucial. Liver enzymes and CBC are done routinely to monitor patients for response to treatment, relapse or flares of autoimmune hepatitis. Liver biopsy remains the mainstay to assess remission, relapse or flare of autoimmune liver disease. Unfortunately, Liver biopsy is invasive and apart from biochemical evaluation, Liver Multi Scan (LMS) can be used as an alternative to evaluate autoimmune hepatitis. **Methods:** 3 patients from our database with a diagnosis of Autoimmune liver disease who had LMS were analyzed for this study. Laboratory data, LMS (cT1), and index liver biopsy findings were reviewed. **Results:** Index liver biopsy of all three subjects were reviewed and two of them had findings consistent with autoimmune hepatitis and one had features of autoimmune cholangiopathy. All the subjects were on anti-inflammatory therapy with prednisone (one was switched from Budesonide to prednisone) along with Azathioprine (2 subjects) and Cellcept. All of the subjects were followed quarterly to biannually with close monitoring of her liver enzymes and CBC for any bone marrow suppression. The average duration of immunosuppression was 60 months (AIC), 48 months (AIH) and 12 months (AIH). All of their liver function tests were normal for > 6 months and patients were interested in dose reduction or withdrawal of therapy. Liver biopsy was suggested but two subjects wanted an alternative method to assess liver inflammation LMS scan was done as an alternative to liver biopsy to determine liver inflammation using cT1 scores. Their average cT1 score was 836 (Table 1). **Conclusion:** Biochemical and histological resolution is required to stop treatment for patients with AIH. All patients showed biochemical resolution and LMS was used to determine indirect histological resolution. Ct1 values < 875 are considered a benchmark in NASH patients as marker of reduced liver inflammation. While further research is needed and larger volume of patients need to be analyzed, LMS is a non-invasive and cost-effective tool to utilize for evaluating treatment response and optimizing therapeutic strategies in AIH management.

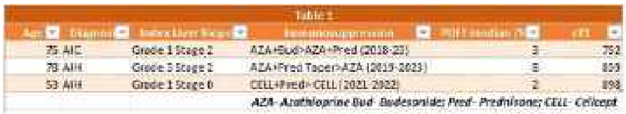

Table 1

Age	Diagnosis	[illegible]	[illegible]	[illegible]	[illegible]
75	AIC	Grade 1 Stage 2	AZA+Bud>AZA+Pred (2018-23)	3	752
78	AIH	Grade 3 Stage 2	AZA+Pred Taper>AZA (2019-2023)	8	839
53	AIH	Grade 1 Stage 0	CELL+Pred>CELL (2021-2022)	2	898
			AZA- Azathioprine Bud- Budesonide; Pred- Prednisone; CELL- Cellcept		

Disclosures: The following people have nothing to disclose: Abdullah Mubarak, Sai Priya Metla, Mahnoor Fatima, Caleb Keng, James Gray

4504-C | CHILDREN WITH AIH RECEIVING STANDARD-OF-CARE THERAPY DEMONSTRATE LONG-TERM EXCESS WEIGHT GAIN AND OBESITY: AN UNDER-RECOGNIZED COMPLICATION OF PEDIATRIC AIH THERAPY

Or Steg Saban[1], Syeda Aiman Fatima[1], Shannon M. Vandriel[2], Amrita Mundh[1], Vicky Lee Ng[3], Simon C. Ling[3], Robert H.J. Bandsma[3] and Binita M. Kamath[4], (1) The Hospital for Sick Children, Toronto, (2)The Hospital for Sick Children and the University of Toronto, (3) Division of Gastroenterology, Hepatology and Nutrition, the Hospital for Sick Children, Toronto, ON, Canada, (4)The Hospital for Sick Children, Toronto, ON, Canada

Background: The management of autoimmune hepatitis (AIH) can be challenging, given the need for chronic therapy with potential side effects. Standard-of-care (SOC) treatment in children includes induction with Prednisone 1-2mg/kg daily, combined with Azathioprine. In patients responsive to SOC, the dose of Prednisone is gradually reduced over 6 months to ≤5-10mg daily. There are limited data showing reduction in height in patients treated with high-dose prednisone, but no literature available about growth in SOC AIH treatment. We aimed to test the hypothesis that children with AIH on SOC treatment have altered growth trajectories. **Methods:** Children newly diagnosed with AIH 2000-2022 in a single tertiary center had weight and height measurements every 6 months for 2 years, then yearly for up to 5 years and Z-scores were calculated. Patients were excluded if not treated with SOC treatment or if <1 year of follow-up. Chi-squared test was applied to obesity prevalence. Wilcoxon signed-rank tests were used to compare Z-scores for weight, height, and BMI at baseline (before therapy) and 1 and 2 years (after therapy). **Results:** 43 patients (65% females, median age at diagnosis 10.4 years, IQR 7.5-13.4) were included and followed for a median of 4 years (IQR 3-5). 91% of the patients had AIH type 1. The median Z-scores for baseline weight, height, and BMI were 0.3, 0.3, and 0.4, respectively. 1 year after treatment, Z-scores for weight (1.0, $p<0.01$) and BMI (1.4, $p<0.01$) increased substantially. 2 years after treatment, Z-scores for weight and BMI remained significantly elevated ($p<0.01$ and ($p<0.01$). The prevalence of obesity *increased* significantly between baseline and Year 1 (4.6% vs. 32.6%, $p<0.01$) and remained significant in Year 2 (35.1%, $p<0.01$). 10 patients (23.2%) had excessive weight gain (increase of ≥1.0 SD in BMI Z- score) after 1 year of treatment, and 8 patients (21.6%) had excessive weight gain after 2 years. No patients had new-onset short stature (height z- score ≤-2), but 7 patients (16.2%) had new-onset growth delay (a decrease of ≥1.0 in height Z-score) during follow-up. **Conclusion:** It is well-established that excessive steroid exposure is associated with weight gain. This study demonstrates that children with AIH receiving SOC treatment demonstrate long-term excess weight gain and obesity. These data indicate the need to re-evaluate treatment algorithms for pediatric AIH in terms of steroid dosing and potential non-steroid alternatives.

Disclosures: Shannon M. Vandriel – Mirum Pharmaceuticals: Consultant, No, No;

Binita M. Kamath – Albireo, Mirum, and Audentes: Consultant, No, No; Albireo and Mirum: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Or Steg Saban, Vicky Lee Ng

Disclosure information not available at the time of publication: Syeda Aiman Fatima, Amrita Mundh, Simon C. Ling, Robert H.J. Bandsma

4505-C | GLUCOSE METABOLISM REPROGRAMMING OF NEUTROPHILS IN AUTOIMMUNE HEPATITIS

Chen Huang and Li Yang, West China Hospital, Sichuan University

Background: Autoimmune hepatitis (AIH) is an inflammatory liver disease caused by immune homeostasis imbalance. Neutrophils participate in

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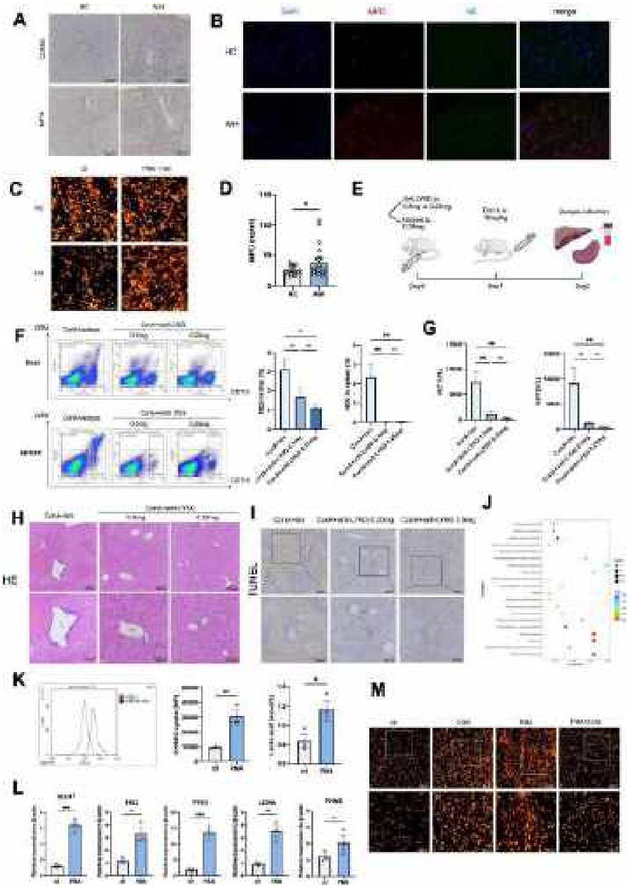
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

the pathogenesis of autoimmune disorders through neutrophil extracellular traps (NETs), degranulation, and cytokine production. Enhanced glycolysis promotes neutrophil activation, thereby leading to autoimmune disorders. However, there are limited studies reporting the function of neutrophils and the effect of neutrophil metabolic reprogramming in AIH. The aim of this study was to examine alterations in neutrophil numbers and functions in AIH while exploring associations between dysregulated neutrophils and glucose metabolism. **Methods:** Neutrophil frequency and functions were detected in AIH patients and healthy controls (HCs). Hepatic infiltration of neutrophils in AIH patients was evaluated by immunohistochemistry. Activation markers in circulating neutrophils and serum levels of MPO were assessed. In Con A-induced immune hepatitis, a Ly6G neutralizing antibody was administered to deplete neutrophils. Moreover, this study collected circulating neutrophils from AIH patients and HCs for RNA sequencing. In addition, the parameters related to glucose metabolism were assessed in PMA-treated neutrophils. Finally, the effect of the glycolytic inhibitor 2-DG on neutrophils was investigated in vitro. **Results:** The frequency of CD66b+/MPO+ neutrophils was increased in liver biopsies of AIH patients. The mRNA levels of activation markers were elevated in circulating neutrophils of AIH patients. AIH patients also had higher MPO serum levels than HCs. Moreover, NET formation was increased in liver tissues and circulating neutrophils of AIH patients. Ly6G neutralizing antibody treatment resulted in depletion of neutrophils, which was confirmed by flow cytometry. Notably, neutrophil depletion alleviated liver apoptosis and necrosis in Con A-induced immune hepatitis, suggesting a pathogenic role of neutrophils in AIH. Moreover, RNA sequencing indicated downregulation of the oxidative phosphorylation (OXPHOS) pathway in circulating neutrophils of AIH patients. Altered expression was confirmed by qPCR. After PMA stimulation, glucose uptake and lactic acid production were enhanced in primary human neutrophils. In addition, the expression of key glycolytic genes was increased in PMA-induced neutrophils. 2-DG reduced PMA-induced NETs in vitro. **Conclusion:** Neutrophils accumulated in the livers of AIH. Circulating neutrophils from AIH patients exhibited an activation phenotype, enhanced glycolysis, and reduced OXPHOS compared with those from HCs. Neutrophil depletion alleviated Con A-induced immune hepatitis, suggesting a pathogenic role of neutrophils in AIH. Glucose metabolism reprogramming in neutrophils may promote their activation, thus leading to immune disorders in AIH. Inhibiting glycolysis may reverse neutrophil dysfunction in AIH patients.



Disclosures: The following people have nothing to disclose: Chen Huang, Li Yang

f 4506-C | HIGH BURDEN OF UNMET NEEDS IN PATIENTS WITH AUTOIMMUNE HEPATITIS IS EXACERBATED BY LOW SOCIOECONOMIC STATUS

Carolyn Haugh[1], *Emma Jones*[2], *Kelsey Green*[1], *Brittany Baker*[1], *Naga P. Chalasani*[3], *Craig Lammert*[1] *and Lauren D. Nephew*[4], *(1)Indiana University School of Medicine, (2)University of Indianapolis, (3)Indiana University Medical Center, Indianapolis, IN, (4)Indiana University*

Background: Diminished quality of life has been well characterized in autoimmune hepatitis (AIH) patients, however the full spectrum of unmet needs in this population is not fully known. We hypothesized that there is a high burden of unmet needs in patients with autoimmune hepatitis and this burden differs by socioeconomic status (SES). **Methods:** Online community members of the Autoimmune Hepatitis Association were invited to complete a modified 50-item

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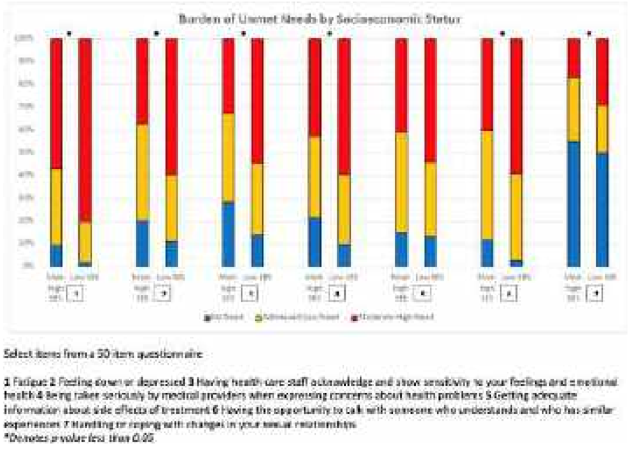
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

version of the SLE Patient Needs Questionnaire (SLENQ), a validated tool that evaluates unmet need across seven domains: physical, daily living, psychological/spiritual, health services, health information, social support and employment/financial. Demographic data, fibrosis severity, and country of residence were captured. Low-SES was defined as annual household income < 30k per year, education level less than high school, or report of moderate-high concern for lack of reliable transportation, food, or housing in the last year. Multivariable logistic regression was used to evaluate the association between unmet needs and SES. **Results:** There were 397 participants; 87.8% identified as female, 16.4% of lived outside the USA, and 26.2% were classified as low-SES. 44.3% of participants reported a moderate-high burden of unmet needs related to gaining information about treatment and side-effects. There was a significant difference in all seven physical needs questions between low-SES and moderate-high SES participants (all p-values < 0.05). Participants within the low-SES group also reported higher prevalence of unmet needs regarding healthcare providers taking them seriously (p = 0.005), addressing financial concerns (p < 0.0001), and coping with changes in their sexual relationships (p = 0.029). On multivariable logistic regression, controlling for race, gender, fibrosis stage, and USA residence, participants within the low-SES group had a higher odds of reporting unmet needs in fatigue (OR 6.73, 95% CI 1.50-30.23), depression (OR 2.87, 95% CI 1.33-6.22), health care staff sensitivity (OR 3.35, 95% CI 1.61-6.95), and lack of opportunity to speak with other people with AIH (OR 5.67, 95% CI 1/61-19.88) than those in the moderate-high-SES group. **Conclusion:** There is high burden of unmet needs in all patients with AIH that is exacerbated by low-SES. These data can help inform interventions to improve health service delivery, treatment options, and the mental health care of patients with AIH.



Select items from a 50 item questionnaire

1 Fatigue 2 Feeling down or depressed 3 Having health care staff acknowledge and show sensitivity to your feelings and emotional health 4 Being taken seriously by medical providers when expressing concerns about health problems 5 Getting adequate information about side effects of treatment 6 Having the opportunity to talk with someone who understands and who has similar experiences 7 Handling or coping with changes in your sexual relationships
*Denotes p-value less than 0.05

Disclosures: Lauren D. Nephew – Delfi diagnostic: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;

The following people have nothing to disclose: Carolyn Haugh, Naga P. Chalasani, Craig Lammert

Disclosure information not available at the time of publication: Emma Jones, Kelsey Green, Brittany Baker

4507-C | IDENTIFYING PATHOGENIC CELL POPULATIONS WITH GENETIC VARIANT PREDISPOSITION IN PRIMARY SCLEROSING CHOLANGITIS THROUGH SINGLE-CELL MULTIOME PROFILING

Zi Yang, Ramesh Kudira, Joseph Wayman, Xiaoting Chen, Anthony Bejjani, Leah Kottyan, Matthew Weirauch, Lee A. Denson, Alexander G. Miethke and Emily Miraldi, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background: Primary sclerosing cholangitis (PSC) is a slowly progressive destruction of the biliary tree which commonly requires liver transplantation for complications of biliary fibrosis and cholangiocarcinoma. The development of targeted therapies is hampered by our incomplete understanding of disease pathogenesis, driven by interactions between genetic predisposition and environmental factors. **Methods:** To understand the disease pathogenesis and identify cellular drivers and related molecular mechanisms, we performed single-cell multiome-seq, an assay that simultaneously measures gene expression and chromatin accessibility in single nuclei, on frozen explanted liver tissue and biopsy samples from patients with early PSC (n = 2), end-stage disease (n = 3), and from healthy controls (n = 2). We analyzed changes in gene expression and chromatin accessibility between patient and control groups. We performed Regulatory Element Locus Intersection (RELI) analysis to identify cell-type-resolved accessibility overlapping disease risk variants, nominating pathogenic cell populations. **Results:** 12 major liver epithelial and immune cell types were identified across 63,257 nuclei from 7 multiome-seq samples. RELI analysis revealed significant overlaps of PSC genetic risk loci in immune cell accessible chromatin regions (FDR < = 10%), suggesting T cells as the pathogenic cell population. We identified a risk locus, rs13140464, downstream of IL21 overlapping T-cell-specific accessibility, associated with higher *IL21* gene expression in the disease context. **Conclusion:** Single-cell multiome-seq analysis recovered major cell populations in the liver and identified changes in gene expression and chromatin accessibility under disease context. Association of GWAS genetic risk variants with cell-type-resolved ATAC-seq profiles provides an opportunity to nominate pathogenic cell populations, identifying potential therapeutic targets to combat immune-mediated disease pathogenesis in PSC.

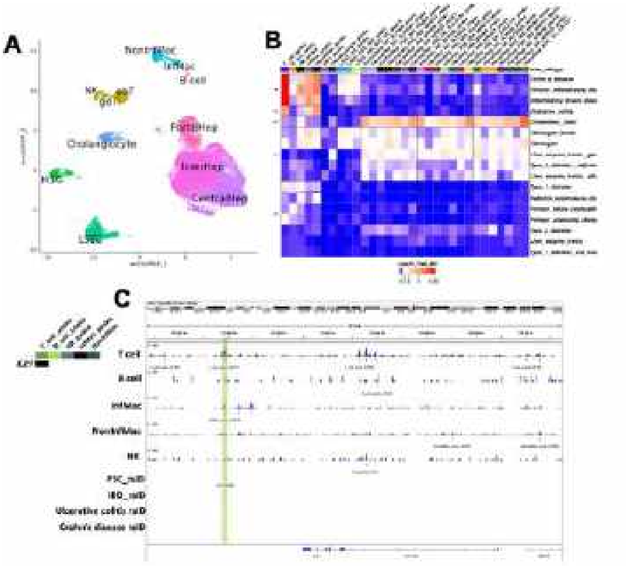


Figure 1. A) UMAP shows cell type annotations of 63,257 high quality nuclei , B) Heatmap of RELI results showing disease genetic risk variants enrichment in cell type specific ATAC peaks, C) *rs13140464* risk loci in PSC , downstream of IL21 intersects with T cell peaks.

Disclosures: Alexander G. Miethke – Mirum Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Mirum Pharmaceuticals: Consultant, Yes, No;

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Disclosure information not available at the time of publication: Ramesh Kudira, Joseph Wayman, Xiaoting Chen, Anthony Bejjani, Leah Kottyan, Matthew Weirauch, Lee A. Denson, Emily Miraldi

4508-C | IL-16 AND IL-10 AS BIOMARKERS OF DISEASE ACTIVITY AND RESPONSE TO TREATMENT IN PATIENTS WITH AUTOIMMUNE HEPATITIS

Vanessa Navalhas-Cipriano[1], Francis Dilauro[1], Valérie-Ann Raymond[1], Catherine Vincent[1,2], Fernando Alvarez[3], Marc Bilodeau[1,2] and Pascal Lapierre[1,2], (1) Centre De Recherche Du Centre Hospitalier De L'université De Montréal (CRCHUM), (2)Département De Médecine, Université De Montréal, (3)Service De Gastroentérologie, Hépatologie Et Nutrition, CHU Sainte-Justine, Université De Montréal

Background: First-line treatment achieves an adequate response in 80-90% of patients with autoimmune hepatitis (AIH). However, 10-20% of patients may progress to cirrhosis or liver transplantation. Currently, no clinical, biological, or histological parameters can predict the initial response to treatment or long-term remission. Therefore, there is a crying need for reliable biomarkers to predict disease activity and response to treatment. This study aimed to identify biomarker(s) of disease activity and treatment response in AIH patients. **Methods:** Using our AIH patient's biobank, a cross-sectional immunological profiling of cytokines linked to subtypes of CD4 T cells and flow cytometry analysis of CD4 T cells was performed on biological samples at the time of diagnosis and during treatment to identify putative biomarkers associated with disease activity and/or a favorable response to treatment. **Results:** Expression of the anti-inflammatory cytokine IL-10 by PBMCs increased significantly after treatment in AIH patients that respond to treatment (13.64 ± 2.84 Fold vs. 3.36 ± 3.1, n = 9, p = 0.017) while plasma levels of IL-16 decreased (542.3 ± 107.2 vs. 338.7 ± 22.7 pg/mL after treatment, n = 116, p = 0.0099). AIH patients with elevated ALT levels (> 40 IU/L) have significantly higher plasmatic levels of IL-16 than those with normal ALT levels (< 40 IU/L) (71.34 ± 33.85, n = 243, p = 0.0359). Patients that respond to treatment also had higher $CD3^+CD4^+FoxP3^+CD25_{high}CD127_{low}$ regulatory T cells (Tregs) levels after treatment (5.38% ± 0.42%, n = 6), similar to that of healthy controls (4.93% ± 0.55%, n = 5), compared to patients before treatment and these levels correlate with IL-10 expression ($r^2 = 0.6484$, n = 9, p = 0.0088) and plasmatic levels of IL-16 ($r^2 = 0.1864$, n = 49, p = 0.0020). Plasmatic levels of IL-16 also correlate with the levels of activated CD4 and CD8 T cells ($r^2 = 0.1469$, n = 49, p = 0.0066 and $r^2 = 0.08227$, n = 49, p = 0.0457, respectively). PCA Analysis shows that $CD4^+$ and $CD8^+$ $CXCR3^+$ T cells and Treg levels are responsible for most of the variance of ALT levels (n = 131). Using chemotaxis assays, IL-16 was found to promote the migration of $CD4^+$ but not $CD8^+$ T cells from AIH patients (CD4/CD8 ratio of 14.82 ± 7.424 (IL-16 50ng/mL) vs 2.583 ± 2.583 (Control), n = 3). **Conclusion:** IL-10 and CD4 regulatory T cells are increased in AIH patients that respond to treatment while IL-16 levels are decreased suggesting that these could be putative biomarkers for disease activity and treatment response in AIH patients. These results also suggest that IL-16 could affect both pro-inflammatory and anti-inflammatory pathways and thus influence AIH activity in these patients. The identification of reliable biomarkers could allow for the prediction of treatment response in treatment-naïve patients and the development of effective personalized therapy and could be a milestone achievement for the clinical management of difficult-to-treat AIH patients.

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Disclosure information not available at the time of publication: Francis Dilauro, Catherine Vincent, Fernando Alvarez

4509-C | INVESTIGATING MIF AS A BIOMARKER OF DISEASE SEVERITY IN AUTOIMMUNE HEPATITIS

Swathi Krishnan[1], *Scott Roberts*[2], *Yanhong Deng*[2], *Lin Leng*[2], *Marina G. Silveira*[2], *Richard Bucala*[2], *James L. Boyer*[2] *and David N. Assis*[2], *(1)Yale New Haven Hospital, Stamford, CT, (2)Yale School of Medicine, New Haven, CT*

Background: The presentation and clinical course of autoimmune hepatitis (AIH) is highly variable and immune biomarkers of disease severity are lacking. Novel biomarkers could help identify patients with more aggressive phenotypes requiring second-line immunosuppression (IS). Macrophage migration inhibitory factor (MIF), a pro-inflammatory mediator, and sCD74, the circulating MIF receptor, are implicated in AIH (Assis et al, Hepatology 2014). We studied MIF as a candidate biomarker of disease severity in AIH. **Methods:** 139 serum samples from 106 adult AIH patients were accessed from the Yale Liver Center Biorepository. Serum MIF and sCD74 expression were measured by sandwich ELISA. The high-risk *MIF* -173 C/G polymorphism was tested. Clinical and outcomes data, including AIH disease activity state (active, biochemical response on or off IS), fibrosis stage, IS requirements (first line, second/third line), and time to response were recorded. **Results:** The mean age was 55 years and 82% were female. There was no significant difference in serum levels of MIF or sCD74 between AIH disease activity states, mild vs. advanced fibrosis, or steroid use at the time of sample collection. However, significantly higher median levels of MIF (4 vs. 1.3 ng/mL, $p = 0.004$) and sCD74 (86 vs. 7.1 ng/mL, $p = 0.003$) were found in patients requiring second- and third-line IS (cyclosporine, mercaptopurine, mycophenolate, rituximab, and tacrolimus) compared to patients on first-line therapy with azathioprine. A subgroup of patients with available *MIF* -173 G/C polymorphism data were analyzed, revealing a trend toward longer time to biochemical response in patients with one or more C alleles vs. GG (36 vs. 13.9 months, p = NS). Additional *MIF* genotype data is being processed for subsequent analysis. **Conclusion:** Our study shows that circulating MIF and sCD74 levels are significantly higher in AIH patients requiring second- and third-line IS vs. standard IS with thiopurines. This suggests that these candidate immune-based biomarkers may be able to identify patients with severe disease and complex immunoreactivity requiring more aggressive IS regimens to achieve biochemical response. Ongoing analysis of high-risk *MIF* polymorphisms will clarify the possible association between the -173C allele and time to biochemical response. MIF, sCD74, and similar candidate immune-based biomarkers should be further evaluated as predictors of AIH disease severity.

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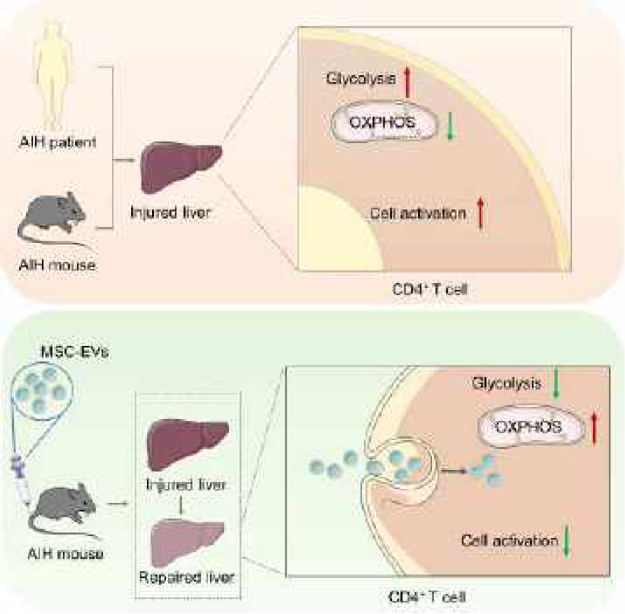
Disclosure information not available at the time of publication: Scott Roberts, Yanhong Deng, Lin Leng, Marina G. Silveira, Richard Bucala

4510-C | METABOLIC REPROGRAMMING OF CD4+ T CELLS BY MESENCHYMAL STEM CELL-DERIVED EXTRACELLULAR VESICLES ATTENUATES AUTOIMMUNE HEPATITIS THROUGH MITOCHONDRIAL CONTENT TRANSFER

Mengyi Shen and Li Yang, West China Hospital, Sichuan University

Background: Autoimmune hepatitis (AIH) is a serious liver disease characterized by immune disorders (e.g., abnormal T cell activation), and more efficient therapies for treating AIH are urgently required. However, the metabolic features of $CD4^+$ T cells in AIH and the corresponding targeted therapies have not been well-explored. This study aimed to explore the role of glucose metabolism of $CD4^+$ T cells in AIH and further elucidate the metabolic reprogramming effect and underlying mechanism of mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) in AIH. **Methods:** $CD4^+$ T cells of AIH patients were isolated from peripheral blood by immunomagnetic cell sorting, and the levels of key enzymes related to glycolysis were measured. Liver biopsy specimens from AIH patients were stained with CD4 and GLUT1 (carrier proteins responsible for glucose transport). 2-Deoxy-D-glucose (a glycolysis inhibitor) or MSC-EVs were injected into AIH mice to evaluate their therapeutic effects. RNA- sequencing was used to identify the gene profile changes in $CD4^+$ T cells subjected to MSC-EVs. We confirmed the metabolic reprogramming effect MSC-EVs on $CD4^+$ T cells and identified the functional cargos. **Results:** Enhanced glycolysis of $CD4^+$ T cells was verified as a key factor in AIH in patient samples and mouse models. More importantly, MSC-EV treatment reduced activation and induced metabolic reprogramming of $CD4^+$ T cells, ameliorating liver damage in AIH mice. Mechanistically, we found that MSC-EVs transferred functional mitochondrial electron transport chain proteins to induce metabolic switch of $CD4^+$ T cells. Conversely, disruption of mitochondrial function in donor cells attenuated the rescue effect of MSC- EVs on suppressing glycolysis and activation in $CD4^+$ T cells. **Conclusion:** This study highlights that MSC-EVs can metabolic reprogram T cell phenotype by transferring mitochondrial components, which may offer a new avenue for treating autoimmune disease, such as AIH.



Disclosures: The following people have nothing to disclose: Mengyi Shen, Li Yang

f 4511-C | NEUTROPHIL EXTRACELLULAR TRAPS PROMOTE AUTOIMMUNE HEPATITIS THROUGH INHIBITING THE SUICIDE OF CD8+ T CELLS★

Han Wang[1]*, Yu Lei*[1]*, Yu Chen*[1]*, Shuhui Wang*[1]*, Dean Tian*[1]*, Hai Huang*[2] *and Mei Liu*[1]*, (1)Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, (2)Center for Immunology and Inflammation, Feinstein Institutes for Medical Research, Manhasset, NY*

Background: Autoimmune hepatitis (AIH) is a chronic, progressive, and immune-mediated liver injury. Its prevalence has been increasing worldwide. The treatment of AIH is challenging and currently relies on corticosteroid therapy. Innate and adaptive immunity play critical roles in AIH pathogenesis. In AIH, CD8^{+}T cells actively invade hepatocytes, enter endosomal/lysosomal compartments, and are degraded (the "suicidal emperipolesis")[1]. Our most recent findings revealed neutrophil extracellular traps (NETs) link the crosstalk between innate and adaptive immunity by directly interacting with hepatic regulatory T cells[2]. However, the role of NETs in the setting of AIH remains unknown. Here we aim to elucidate the mechanisms by which AIH-induced NETs promote the development of AIH by arresting hepatic CD8^{+}T cells and preventing their suicidal emperipolesis. **Methods:** A well-established AIH model was performed by hydrodynamic transfecting with human CYP2D6 plasmid into C57Bl/6 mouse liver. DNase to inhibit NETs or peptidyl arginine deiminase 4 knockout (PAD4 KO) mice (genetically unable to form NETs) were utilized *in vivo* experiments. **Results:** AIH was successfully established as autoantibodies and characteristic pathological features of AIH were observed in the mice livers at four weeks. Utilizing 10x Genomics RNA-sequencing (RNA-seq), we uncovered the presence of a distinctive cluster of autoreactive CD8^{+}T cells that exhibited aggregation within the liver of AIH mice. Cith-H3 and MPO levels (the specific NETs markers) increased in the livers and sera of AIH mice, respectively. We confirmed a positive correlation between hepatic NETs and CD8^{+}T cells in AIH patients and mice. Using confocal microscopy, we observed NETs arresting CD8^{+}T cells. Inhibiting NETs protected liver injury in AIH mice, which was predominantly linked to the reduced quantity and functional impairment of hepatic CD8^{+}T cells. *In vitro*, the transwell experiment revealed NETs possess the ability to hinder the migration of CD8^{+}T cells towards hepatocytes. Flow cytometry indicated that NETs promoted CD8^{+}T cells function by augmenting their secretion of TNF-α and IFN-γ. Seahorse data suggested the oxidative phosphorylation of CD8^{+}T cells enhanced significantly after NETs treatment. Bulk RNA-seq confirmed that most differentially expressed genes of CD8^{+}T cells after NETs treatment enriched in the metabolic pathways. **Conclusion:** NETs capture hepatic CD8^{+}T cells and prevent their suicidal emperipolesis. NETs promote AIH progression through the crosstalk between innate and adaptive immunity and maybe the potential therapeutic targets.

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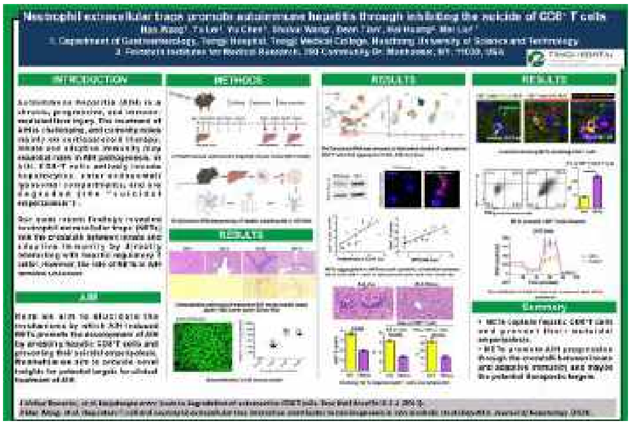
2. Han Wang, et al. Regulatory T-cell and neutrophil extracellular trap interaction contributes to carcinogenesisi in non-alcoholic steatohepatitis. *Journal of Hepatology* (2021).


Neutrophil extracellular traps promote autoimmune hepatitis through inhibiting the suicide of CD8+ T cells
INTRODUCTION
METHODS
RESULTS
RESULTS
AIM
Summary

Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Disclosures: The following people have nothing to disclose: Han Wang, Yu Lei, Yu Chen, Shuhui Wang, Dean Tian, Hai Huang, Mei Liu

4512-C | PNEUMOCYSTIS JIROVECII PNEUMONIA IN AUTOIMMUNE HEPATITIS PATIENTS: TRENDS, RISKS, AND HOSPITALIZATION OUTCOMES (2016-2020)

Chun-Wei Pan[1], Bashar M Attar[1] and Ayobami Olafimihan[2], (1)John H. Stroger, Jr. Hospital of Cook County, (2)John H Stroger Jr. Hospital of Cook County

Background: Pneumocystis jiroveci pneumonia (PCP) is an opportunistic infection that is well known for correlation with HIV infection, and it's considered as AIDs defining illness. However, with recent advancement in antiretrovirals, the epidemiology has shifted, it's becoming increasingly common in non-HIV individual's and data have suggested clinical courses can be more critical in these individual's. Limited data have been investigated on the risks and in-hospital outcomes of PCP among patients with autoimmune hepatitis. Our study aimed to analyze the contemporary trend of PCP admission rates among autoimmune hepatitis patients and investigate the associated infection risk and hospital outcomes. **Methods:** We surveyed the National Inpatient Sample Database from 2016-2020, by identifying hospitalization with corresponding international disease classification ICD-10 for PCP, and further stratified the cohort into those with autoimmune hepatitis and without. We also analyzed the prevalence of risk factors for development of PCP among autoimmune hepatitis. **Results:** From 2016 to 2020, we identified 110 hospitalizations for PCP among patients concurrently diagnosed with autoimmune hepatitis, accounting for 0.09% of total admissions. Patients in the PCP cohort had an unadjusted mortality rate of 27.3%, compared to 4.0% in the alternative reason for admission cohort. After adjusting for sex, age, and Charlson comorbidity index, the odds of mortality increased 12.2-fold in the PCP cohort ($P < 0.01$). Furthermore, the PCP cohort had a longer mean length of stay (12.0 d) compared to the autoimmune hepatitis patients without PCP infection (5.8 d), with a significant difference of 5.0 days ($P < 0.01$) after adjustments. The most notable additional risk factors for PCP were HIV (18.18% in the PCP cohort vs. 0.63% in the non-PCP cohort, $P < 0.05$), connective tissue disorder (CTD), chronic steroid use, lymphoma, and a past medical history of organ transplant. Over the study period, the annual percentage change in PCP cases among autoimmune hepatitis patients was 18.37%, whereas the national trend of PCP cases decreased from 9,410 in 2016 to 8,295 in 2020, with an annual percentage change of -2.51. **Conclusion:** Our study highlights an emerging trend of increasing PCP incidence among autoimmune hepatitis patients, contrasting with a national decrease in overall PCP cases. This elevated risk leads to greater in-hospital mortality and longer hospital stays in this population. The notable risk factors associated with PCP in autoimmune hepatitis patients include HIV, connective tissue disorders, chronic steroid use, lymphoma, and a history of organ transplantation. These findings point towards the need for identifying additional risk factors and potentially implementing preventative measures in autoimmune hepatitis patients.

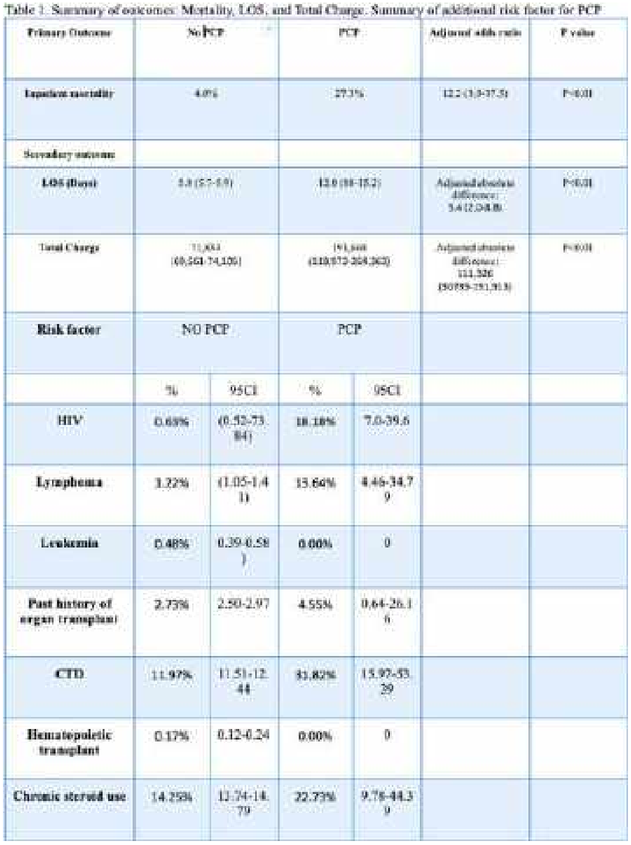


Table 1: Summary of outcomes: Mortality, LOS, and Total Charge. Summary of additional risk factor for PCP

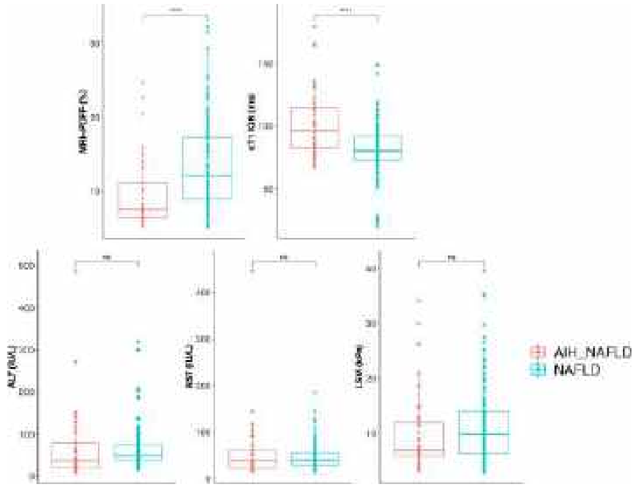
Primary Outcome	No PCP		PCP		Adjusted odds ratio	P value
Inpatient mortality	4.0%		27.3%		12.2 (3.9-37.5)	P<0.01
Secondary outcome						
LOS (Days)	5.8 (5.7-5.9)		12.0 (8.8-15.2)		Adjusted absolute difference: 5.4 (2.0-8.8)	P<0.01
Total Charge	71,[illegible] (68,561-74,105)		191,[illegible] (110,873-268,363)		Adjusted absolute difference: 111,326 (30785-191,913)	P<0.01
Risk factor	NO PCP		PCP			
	%	95CI	%	95CI		
HIV	0.63%	(0.52-73.84)	18.18%	7.0-39.6		
Lymphoma	1.22%	(1.05-1.41)	13.64%	4.46-34.79		
Leukemia	0.48%	0.39-0.58)	0.00%	0		
Past history of organ transplant	2.73%	2.50-2.97	4.55%	0.64-26.16		
CTD	11.97%	11.51-12.44	31.82%	15.97-53.29		
Hematopoietic transplant	0.17%	0.12-0.24	0.00%	0		
Chronic steroid use	14.25%	13.74-14.79	22.73%	9.78-44.39		

Disclosures: The following people have nothing to disclose: Chun-Wei Pan, Ayobami Olafimihan
Disclosure information not available at the time of publication: Bashar M Attar

4513-C | PRESENCE OF LIVER DISEASE HETEROGENEITY CAN SUPPORT DISTINGUISHING BETWEEN AUTOIMMUNE HEPATITIS OVERLAP AND NON-ALCOHOLIC FATTY LIVER DISEASE

Elizabeth Shumbayawonda, Perspectum, Gideon Hirschfield, Toronto Centre for Liver Disease, University of Toronto, Toronto, Ontario, Canada, Rajarshi Banerjee, Perspectum Ltd., Emma Culver, Oxford University Hospitals, Michael A. Heneghan, King's College Hospital, London, United Kingdom, Kento Imajo, Shin-Yurigaoka General Hospital and Mazen Noureddin, Houston Liver Institute, Houston, TX

Background: Autoimmune hepatitis (AIH) is relatively rare, while non-alcoholic fatty liver disease (NAFLD), and the more progressive form non-alcoholic steatohepatitis (NASH), is the leading cause of liver disease in the West. Given the high prevalence of NAFLD and obesity, overlap between these two conditions is also on the rise. AIH treatment can include the use of steroids which have adverse metabolic effects that can worsen NAFLD. Quantification of overall liver disease activity can be achieved using cT1 from MRI, and disease heterogeneity observed and quantified using the interquartile range (IQR) of the resulted map of the liver. Our aim was to explore the utility of imaging and blood biomarkers to stratify between AIH/NAFLD overlap and NAFLD alone. **Methods:** We retrospectively examined MRI biomarkers (cT1 IQR, MRI-PDFF), blood biomarkers (ALT, AST) and vibration controlled transient elastography liver stiffness measure (LSM) from 165 patients, N = 37 (aged 24-70) on treatment with histologically confirmed AIH and 128 with histologically confirmed NAFLD/NASH (aged 24-84). Comparisons between AIH/NAFLD and NAFLD were performed using Kruskal-Wallis rank sum test. All patients had fatty liver which was defined as MRI-PDFF ≥ 5%. **Results:** Treatment plans for patients with AIH/NAFLD require careful consideration to avoid accelerating the comorbid fatty liver disease. In this cohort, those with NAFLD alone had higher liver fat (PDFF) compared to those with AIH/NAFLD overlap (13.4% vs 9.5%, $p < 0.001$ respectively). However, conversely, those with AIH/NAFLD overlap had more heterogenous disease with higher cT1 IQR compared to those with NAFLD alone (103ms vs. 81ms, $p < 0.001$). There were no significant differences between blood markers ALT (69.9 vs 63.5, $p = 0.07$), AST (61.1 vs 47.7, $p = 0.495$) and LSM (9.9 vs. 11.5, $p = 0.061$) between those with AIH/NAFLD and those with NAFLD alone respectively. **Conclusion:** Heterogeneity in liver parenchymal fibro-inflammation is a feature of AIH in comparison to NAFLD and may reflect differences in disease pathophysiology. MRI biomarkers have utility to support patient stratification and aide management as no specific treatment guidelines are available to guide treatment goals in those with AIH/NAFLD overlap. Figure: Boxplots showing differences in MRI biomarkers (cT1 IQR, MRI-PDFF), blood biomarkers (ALT, AST) and vibration controlled transient elastography liver stiffness measure (LSM).



Disclosures: Elizabeth Shumbayawonda – Perspectum Ltd.: Employee, Yes, No;
Gideon Hirschfield – Intercept: Consultant, No, No; GSK: Consultant, Yes, No; CymaBay: Consultant, No, No; Ipsen: Consultant, No, No; Falk: Consultant, No, No; Pliant: Consultant, No, No; Morphogen: Consultant, No, No; Roche: Consultant, No, No; Mirum: Consultant, No, No;
Rajarshi Banerjee – Perspectum Ltd: Employee, Yes, No; Perspectum Ltd: Stock – privately held company (individual stocks and stock options), Yes, No;
Mazen Noureddin – ChronWell: Stock – privately held company (individual stocks and stock options), No, No; Zydus: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Viking: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Terns: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Takeda: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Shire: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Novo Nordisk: Grant/Research Support (research

funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Novartis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GSK: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genfit: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Galectin: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Enanta: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Corcept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Conatus: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Allergan: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Akero: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Terns: Advisor, No, No; Takeda: Advisor, No, No; Siemens: Advisor, No, No; Roche diagnostic: Advisor, No, No; Perspectum: Advisor, No, No; Novo Nordisk: Advisor, No, No; Merck: Advisor, No, No; Madrigal: Advisor, No, No; GSK: Advisor, No, No; EchoSens: Advisor, No, No; Cytodyn: Advisor, No, No; Boehringer Ingelheim: Advisor, No, No; Altimmune: Advisor, No, No; 89bio: Advisor, No, No; CIMA: Stock – privately held company (individual stocks and stock options), No, No; Rivus Pharma: Stock – privately held company (individual stocks and stock options), No, No;

The following people have nothing to disclose: Emma Culver, Michael A. Heneghan, Kento Imajo

4514-C | PREVALENCE OF AUTOANTIBODIES IN PATIENTS WITH AUTOIMMUNE HEPATITIS AT UNIVERSITY MEDICAL CENTER HCMC★

Huy Nguyen Huu, Suong Thi- Bang Nguyen, Phong Vi Kim, Nga Cao Minh, Thong Luu Nguyen Trung, Chi Mai Thi Bich, Khoi Le Minh and Bac Nguyen Hoang, University Medical Center Hcmc

Background: Autoimmune hepatitis (AIH) is an acute or chronic inflammatory disease of the liver caused by an immune response of unknown origin. AIH is a rare disease but with increasing incidence in Asia–Pacific area. Autoantibodies are a key diagnostic tool in AIH. This study aimed to describe the clinical, paraclinical characteristics and prevalence of autoantibodies in patients with autoimmune hepatitis at University Medical Center HCMC. **Methods:** Cross-sectional descriptive study. 72 patients diagnosed with autoimmune hepatitis according to the shortened scoring table Hennes EM 2008 in combination with the standard diagnosis scoring system of autoimmune hepatitis amended in 1999 and treated at the University Medical Centre in Ho Chi Minh City from January 2018 to April 2022. **Results:** In 72 patients with autoimmune hepatitis, mean age ± standard deviation is 56.3 ± 16.8 years; the proportion of female was 72.2% and male was 27.8%. Approximately half of patients presented with symptoms of acute hepatitis. Cirrhosis was found in 34.7% with an elevated APRI and FIB-4 scores. Biochemical analysis revealed elevated alanine transaminase (109 (49.3-499)), aspartate transaminase (105 (49-383), and gamma glutamyl transferase (127 (58-349)). Marker autoantibodies ANA (+): 62,5%, ASMA (+): 44,4%, F-Actin (+): 15,3%, AMA (+): 6,9%, LKM (+): 2,8%. **Conclusion:** AIH is characterized by female predominance, elevated liver transaminases. ANA, ASMA are the most frequent autoantibodies generated in patients with AIH.

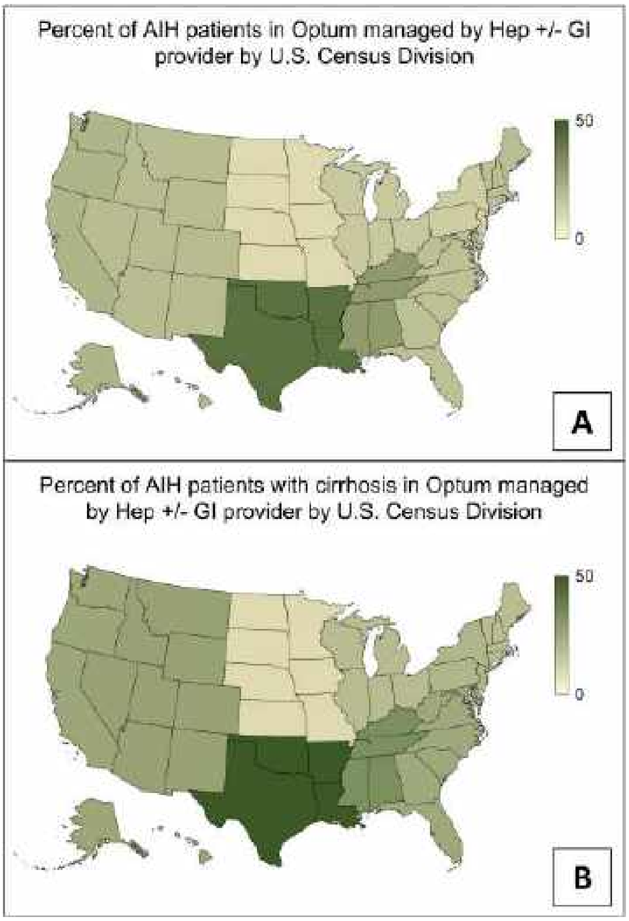
Disclosures: The following people have nothing to disclose: Huy Nguyen Huu

Disclosure information not available at the time of publication: Suong Thi- Bang Nguyen, Phong Vi Kim, Nga Cao Minh, Thong Luu Nguyen Trung, Chi Mai Thi Bich, Khoi Le Minh, Bac Nguyen Hoang

4515-C | PROVIDER SUBSPECIALTY IS NOT ASSOCIATED WITH ACHIEVING CORTICOSTEROID-SPARING MAINTENANCE THERAPY IN PATIENTS WITH AUTOIMMUNE HEPATITIS

Lina Yagan[1], Cynthia Levy[2], David Goldberg[2] and Therese Bittermann[3], (1)University of Pennsylvania Hospital, Philadelphia, Pennsylvania, USA, (2) University of Miami, (3)Hospital of the University of Pennsylvania, Philadelphia, PA

Background: Autoimmune hepatitis (AIH) is a rare liver disease that warrants experienced treatment decision-making. The optimal treatment of AIH includes avoidance of corticosteroids (CS). We aimed to evaluate whether provider subspecialty was associated with receiving corticosteroid-sparing maintenance therapy in a large AIH patient cohort. **Methods:** This was a retrospective cohort study of adults with AIH identified using a validated algorithm in the Optum® Clinformatics© Deidentified Data Mart, a U.S. health insurance database. All patients were followed 2 years from the date of their first ICD-9/10 code for AIH (first year = baseline period; second year = observation period). Dominant regimen was defined as that received > 6 months during the observation year. Using provider taxonomy codes, we classified patients according to whether they had only outpatient visits with general gastroenterology (GI) providers or ≥ 1 visit with a hepatology (Hep) provider during the baseline period. Multivariable logistic regression models evaluated the association of AIH care type with receipt of CS-sparing treatment as dominant regimen (i.e., azathioprine [AZA] or mycophenolate mofetil [MMF] monotherapy vs CS +/- AZA/MMF). **Results:** The study cohort included 3,591 patients, of whom 81.2% were female, 65.5% White, 11.1% Black, 11.8% Hispanic and with median age 61.3 (IQR: 50.4-69.9) years. During the baseline period, 6,041 outpatient visits with an associated ICD-9/10 code for AIH were identified, of which 91% were with a GI or Hep provider. Among the n = 1,489 patients with ≥ 1 outpatient AIH visit with a GI/Hep provider, 79.4% were managed by GI only. There was no difference in sex ($p = 0.976$) or race/ethnicity ($p = 0.281$) according to whether patients were managed by GI only or Hep +/- GI. However, patients managed by Hep +/- GI were younger (median 56.8 vs 61.4 years; $p < 0.001$) and more likely to have cirrhosis (47.9% vs 33.6%; $p = 0.001$). Geographic differences in the percent of AIH patients with ≥ 1 Hep provider visit were observed, from 9.5% in the West North Central to 42.3% in the West South Central divisions ($p < 0.001$ overall; Figure A). A similar pattern was observed for AIH patients with cirrhosis ($p < 0.001$; Figure B). No temporal trends were seen ($p = 0.437$). Among the patients with ≥ 1 GI or Hep AIH visit during the baseline period, dominant regimens filled during the observation period included 49.2% AZA/MMF monotherapy, 14.6% AZA/MMF with CS, and 10.4% CS monotherapy. In multivariable models, provider type was not associated with receipt of CS-sparing treatment: adjusted OR 0.98 ($p = 0.915$). No interaction was found between provider type and coexistence of cirrhosis ($p = 0.526$). **Conclusion:** The majority of AIH care in the U.S. is provided exclusively by general GI providers, though geographic heterogeneity exists. The likelihood of achieving CS-sparing maintenance therapy was not different according to AIH provider subspecialty.


Percent of AIH patients in Optum managed by Hep +/- GI provider by U.S. Census Division

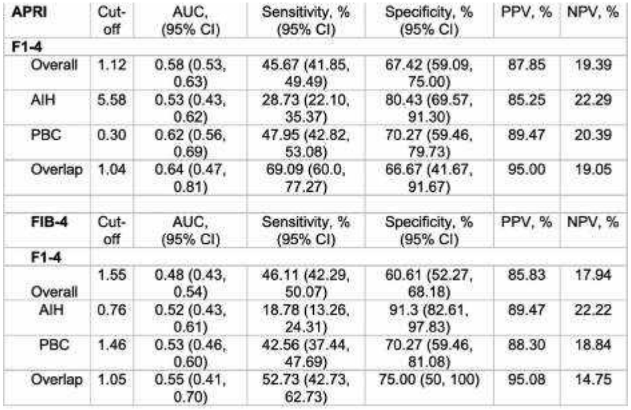
Percent of AIH patients with cirrhosis in Optum managed by Hep +/- GI provider by U.S. Census Division

Disclosures: The following people have nothing to disclose: Lina Yagan, Cynthia Levy, David Goldberg, Therese Bittermann

4516-C | ROLE OF NON-INVASIVE MARKERS IN ASSESSING THE DEGREE OF FIBROSIS IN AUTOIMMUNE HEPATITIS, PRIMARY BILIARY CHOLANGITIS, AND OVERLAP SYNDROME A CANADIAN MULTI-CENTER REVIEW

Mohammed Alsager[1], Surain B Roberts[2], Surim Son[1], Anouar Teriaky[1], Nazia Selzner[3], Madeline Cameron[1], Aliya Gulamhusein[3], Harry L. A. Janssen[4], Majed Almghrabi[5], May Alzahrani[6], Abdulwahed Alotay[7], Bishoi Aziz[8], Ellina Lytvyak[8], Aldo J. Montano-Loza[8], Lawrence Worobetz[9], Catherine Vincent[10], Jennifer A. Flemming[11], Angela Cheung[12], Mark Gordon Swain[13], Dusanka Grbic[14], Hin Hin Ko[15], Kevork M. Peltekian[16], Gideon Hirschfield[17], Andrew L. Mason[18], Bettina E. E. Hansen[19] and Karim Mohammed Qumosani[1], (1) Western University, (2)Li Ka Shing Knowledge Institute, St Michael's Hospital, Unity Health Toronto, (3) University of Toronto, (4)Toronto General Hospital Research Institute, (5)King Saud Bin Abdulaziz University for Health Sciences, (6)King Faisal Specialist Hospital and Research Centre, (7)Imam Mohammed Bin Saud Islamic University, (8)University of Alberta, AB, Canada, (9)Royal University Hospital, (10) Département De Médecine, Université De Montréal, (11)Queen's University Cancer Research Institute, Kingston, ON, Canada, (12)University of Ottawa, (13) University of Calgary, (14)Université De Sherbrooke, (15)University of British Columbia, (16)Dalhousie University, (17)Toronto Centre for Liver Disease, University of Toronto, Toronto, Ontario, Canada, (18) Univeristy of Alberta, Edmonton, AB, Canada, (19) Toronto General Hospital University Health Network, Rotterdam, Netherlands

Background: We investigate the ability of the Aspartate transaminase to Platelet Ratio Index (APRI) and Fibrosis-4 score (FIB4) to discriminate for liver fibrosis stage based on liver biopsy in patients with autoimmune liver disease. **Methods:** Using data from the Canadian Network for Autoimmune Liver Disease, Liver biopsy was compared to AST/Platelet Ratio (APRI) and Fibrosis-4 score (FIB-4) within one year from Liver biopsy date. Logistic regression was used to assess the association of APRI and FIB-4 with fibrosis stage (F0 vs. F1-4 and F0-2 vs. F3-4). Area under the curve (AUC), sensitivity, specificity, and their 95% CI are reported along with positive predictive value and negative predictive value, with cut off points defined by using Youden's index (the maximum value of sensitivity + specificity). All analyses were performed in R version 4.2.2 **Results:** A total of 815 patients were included out of which 682 (83.7%) were female. The mean age was 61 years (SD 15.5), 228 (27.9%) patients had autoimmune hepatitis (AIH), 465 (57.1%) patients had Primary Biliary Cholangitis (PBC), and the remaining 122 (15%) had overlap syndrome (OS). F0 fibrosis was present in 132 (16.2%) patients, 364 (44.6%) had F1-F2 fibrosis, and the remaining 319 (39.1%) had F3-F4 fibrosis. Median APRI was 0.65 (25th-75th 0.17-2.80) and the median FIB-4 was 1.40 (25th-75th 0.71-2.73). APRI analysis: Overall, the area under the curve for APRI to discriminate for Fibrosis stages 1-4 was 0.58 (95% CI: 0.53-0.63). For AIH, PBC, and OS respectively, the positive predictive values for F1-F4 Fibrosis were 85.2%, 89.4%, 95% and the negative predictive values for F1-F4 fibrosis were 22.2%, 20.3%, 19.0% (Table1). Overall, APRI was associated with moderate-to-severe fibrosis (F3-4) in people with PBC (OR = 1.27; 95%CI = 1.16-1.40). In addition, APRI was associated with moderate to severe fibrosis in OS with (OR = 1.19; 95%CI 1.06-1.34) while it was associated in AIH (OR = 0.99, 95%CI = 0.97-1.02). FIB-4: analysis: Overall, the area under the curve for FIB-4 to discriminate for Fibrosis stages 1-4 was 0.48 (95%CI: 0.43-0.54). For AIH, PBC, and OS respectively, the positive predictive values for F1-F4 Fibrosis were 89.4%, 88.3%, 95.0% and the negative predictive values for F1-F4 fibrosis were (22.2%, 18.8%, 14.7%) (Table1). FIB-4 was not associated with moderate to severe fibrosis in AIH, PBC or OS. (OR = 1.01,95% CI = 0.97 -1.05), (OR = 1.39, 95%CI = 1.07-1.8), (OR = 1.12, 95%CI = 0.9- 1.40) respectively. **Conclusion:** APRI score and FIB-4 score had reasonable PPV however, poor NPV, and therefore, both APRI and FIB-4 can't be used to stratify patients with or without fibrosis. In patients with PBC and OS, higher APRI score was associated with advanced fibrosis.



APRI	Cut-off	AUC, (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, %	NPV, %
F1-4						
Overall	1.12	0.58 (0.53, 0.63)	45.67 (41.85, 49.49)	67.42 (59.09, 75.00)	87.85	19.39
AIH	5.58	0.53 (0.43, 0.62)	28.73 (22.10, 35.37)	80.43 (69.57, 91.30)	85.25	22.29
PBC	0.30	0.62 (0.56, 0.69)	47.95 (42.82, 53.08)	70.27 (59.46, 79.73)	89.47	20.39
Overlap	1.04	0.64 (0.47, 0.81)	69.09 (60.0, 77.27)	66.67 (41.67, 91.67)	95.00	19.05

FIB-4	Cut-off	AUC, (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, %	NPV, %
F1-4						
Overall	1.55	0.48 (0.43, 0.54)	46.11 (42.29, 50.07)	60.61 (52.27, 68.18)	85.83	17.94
AIH	0.76	0.52 (0.43, 0.61)	18.78 (13.26, 24.31)	91.3 (82.61, 97.83)	89.47	22.22
PBC	1.46	0.53 (0.46, 0.60)	42.56 (37.44, 47.69)	70.27 (59.46, 81.08)	88.30	18.84
Overlap	1.05	0.55 (0.41, 0.70)	52.73 (42.73, 62.73)	75.00 (50, 100)	95.08	14.75

Table 1: Ability of FIB-4 and APRI to discriminate for any liver fibrosis stage F1-F4, by liver disease.

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4517-C | SIGNIFICANT SOCIOECONOMIC IMPACT ON PATIENT AND GRAFT SURVIVAL AMONG PATIENTS WITH AUTOIMMUNE LIVER DISEASES: A 20-YEAR PERSPECTIVE

Romelia Barba Bernal[1], Leandro Sierra[1], Ana Marenco-Flores[1], Daniela Goyes[2], Bryan Ferrigno[3], Wilfor Diaz Fernandez[3], John Esli Medina Morales[4], Vilas Patwardhan[1], Behnam Saberi[1] and Alan Bonder[1], (1) Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, (2)Yale University Medical Center, New Haven, CT, United States, (3)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (4) Rutgers New Jersey Medical School, Kearny, NJ

Background: Autoimmune liver diseases (ALD) including AIH, PBC, and PSC account for a significant minority of liver transplants (LT) performed in the United States. We have previously shown that certain social determinants of health have an impact on waitlist mortality amongst patients with ALD listed for LT. Less is known regarding the impact on post-LT patient and graft survival amongst this patient population. We sought to analyze the impact of social determinants of health on ALD patients post-LT, focusing on graft and patient survival. **Methods:** We used the OPTN/United Network of Organ Sharing (UNOS) database to identify adult patients with ALD listed for LT between January 2002 and December 2021. Data extracted included diagnosis, MELD score, age, gender, ethnicity, and socioeconomic variables. The primary outcome was to analyze survival for LT recipients. Chi-Square and ANOVA tests were used for comparative analysis. Kaplan-Meier analysis was used for survival calculation. To identify significant predictors of survival, we conducted forward stepwise multi-variate Cox regression analyses adjusted for recipient and donor characteristics. **Results:** 9470 LT between 2002 and 2021 were for AILD indication. Most patients were Caucasian, with female predominance among the AIH and PBC groups. Age was comparable among the three groups. Our analysis revealed that the AIH group had a higher median BMI than the PBC and PSC groups (28, 26, and 25%) and was significantly more likely to have diabetes (22%, 17%, and 11%). Regarding the socioeconomic distribution, the PSC group was likelier to have higher education, private insurance, and working for income than the AIH and PBC groups. Citizenship was comparable among the three groups. No college education (HR, 1.16; 95% CI, 1.06–1.26; $p = 0.001$), having public insurance (HR, 1.15; 95% CI, 1.06–1.25; $p = 0.001$), and no income (HR, 1.41; 95% CI, 1.24–1.60; $p = 0.000$) had a detrimental impact on post-LT patient survival. The same socioeconomic variables were associated with an increased risk of post-LT graft failure, no-college education (HR, 1.13; 95% CI, 1.05–1.23; $p = 0.002$), public insurance (HR, 1.15; 95% CI, 1.06–1.25; $p = 0.001$), and no income (HR, 1.21; 95% CI, 1.09–1.35; $p = 0.000$). (Tables 1 & 2) **Conclusion:** This analysis displays findings suggestive that social determinants of health including education, insurance status, and financial security, seem to have a detrimental impact on post-LT patient and graft survival.

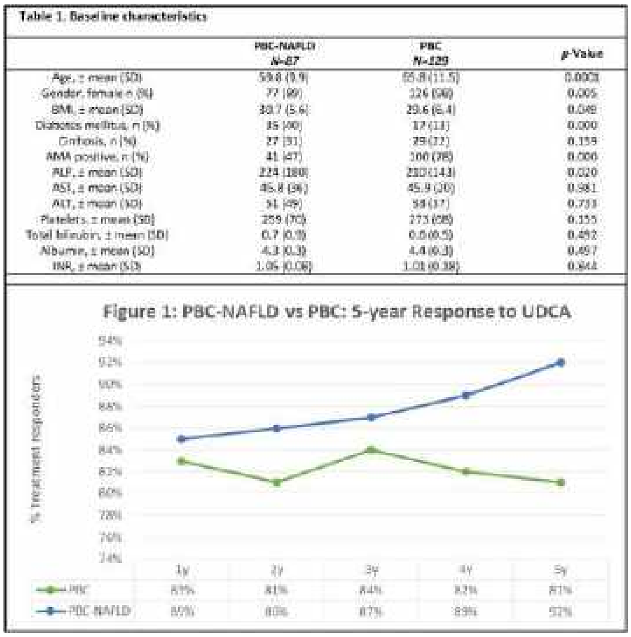

Table 1. Baseline characteristics

	PBC-NAFLD *N=87*	PBC *N=129*	*p*-Value
Age, ± mean (SD)	59.8 (9.9)	65.8 (11.5)	0.0001
Gender, female n (%)	77 (89)	126 (98)	0.005
BMI, ± mean (SD)	30.7 (5.6)	29.6 (6.4)	0.049
Diabetes mellitus, n (%)	35 (40)	17 (13)	0.000
Cirrhosis, n (%)	27 (31)	29 (22)	0.159
AMA positive, n (%)	41 (47)	100 (78)	0.000
ALP, ± mean (SD)	224 (180)	210 (143)	0.020
AST, ± mean (SD)	46.8 (36)	45.9 (20)	0.981
ALT, ± mean (SD)	51 (49)	58 (37)	0.733
Platelets, ± mean (SD)	259 (70)	273 (68)	0.155
Total bilirubin, ± mean (SD)	0.7 (0.9)	0.6 (0.5)	0.492
Albumin, ± mean (SD)	4.3 (0.3)	4.4 (0.3)	0.497
INR, ± mean (SD)	1.06 (0.08)	1.01 (0.38)	0.944

Figure 1: PBC-NAFLD vs PBC: 5-year Response to UDCA

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4518-C | SILENCING OF ARYL HYDROCARBON RECEPTOR REPRESSOR MODULATES Th17-CELL IMMUNITY IN AUTOIMMUNE HEPATITIS

Barbora Gromova[1], Li Gao[1], Wei Zhang[1], Lina Zhang[1], Silvia Nastasio[2], Alan Bonder[3], Vilas Patwardhan[3] and Maria Serena Longhi[1], (1)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (2)Boston Children's Hospital and Harvard Medical School, Boston, MA, (3)Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School

Background: Th17-cells play a key role in the pathogenesis of autoimmune hepatitis (AIH), a severe liver disease that often progresses to end-stage hepatopathy, despite immunosuppression. Aberrant Th17-cell response in AIH is linked to inability to respond to aryl-hydrocarbon-receptor (AHR) activation by endogenous or exogenous ligands. Once activated, AHR translocates to the cell nucleus where it modulates gene expression. In turn, AHR is regulated by aryl-hydrocarbon-receptor-repressor (AHRR), which inhibits AHR transcriptional activity. In this study, we investigated whether, in AIH, altered Th17-cell response to AHR activation derives from aberrant AHRR regulation. **Methods:** Th17-cells, obtained from the peripheral blood of AIH patients (n = 29) and healthy controls (n = 19) were exposed to the AHR endogenous ligand L-kynurenine (L-kyn), with or without AHRR siRNA. Therapeutic effects of AHRR silencing were tested in a model of Concanavalin-A (Con-A)-induced liver injury in humanized mice. **Results:** AHRR was markedly upregulated at both mRNA and protein levels in AIH Th17 cells, following exposure to L-kyn. In AIH, silencing of AHRR by siRNA boosted Th17-cell response to L-kyn, as reflected by increased levels of *CYP1A1*, the main gene controlled by AHR, and by decreased *IL17A* expression. Blockade of AHRR limited the differentiation of naïve CD4-cells into Th17 lymphocytes and modulated Th17-cell metabolic profile by increasing the levels of anti-inflammatory metabolites like uridine and allantoin. Treatment with 2’-deoxy-2’-fluoro-d-arabinonucleic acid (FANA) oligos to silence AHRR *in vivo*, reduced ALT levels and attenuated lymphocyte infiltration on histology in *NOD/scid/gamma* mice, pre-emptively reconstituted with human CD4 cells, and subsequently exposed to Con-A. Further, FANA-treated mice displayed increased proportions of intrahepatic IL-10^+ and FOXP3^+ CD4 lymphocytes, when compared to vehicle-treated mice. **Conclusion:** In AIH, blockade of AHRR restores Th17-cell response to AHR activation and limits Th17-cell differentiation while promoting generation of anti-inflammatory metabolites. *In vivo*, silencing of AHRR attenuates liver damage in *NOD/scid/gamma* mice, while boosting intrahepatic immunoregulatory CD4 subsets. Silencing of AHRR might represent a novel therapeutic strategy to modulate effector Th17-cell immunity and restore immune homeostasis in AIH.

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4519-C | TACROLIMUS AS A SECOND LINE THERAPY IN STEROID-TACROLIMUS-MYCOPHENOLATE-MOFETIL REFRACTORY AUTOIMMUNE HEPATITIS: EXPERIENCE FROM A TERTIARY CARE CENTER

Mithun Sharma, Anand V. Kulkarni, Manasa Alla, Sowmya T R, Padaki Nagaraja Rao, Shantan Venishetty, Rajesh Gupta and Nageshwar D Reddy, Aig Hospitals, Hyderabad, India

Background: The response of autoimmune hepatitis to a combination of steroids and azathioprine is excellent, with approximately 16-20% of patients requiring second-line medications like mycophenolate mofetil (MMF) or tacrolimus (TK). These 2nd line drugs' efficacy is considered lower than standard therapy. We report a single-center experience of using tacrolimus in the steroid, azathioprine, and MMF refractory AIH patients. To evaluate the efficacy and safety of tacrolimus as a second-line therapy in patients with AIH. **Methods:** A retrospective data analysis of AIH patients treated from 2012 to 2022 were analyzed. The clinical, immunological, and biochemical parameters were recorded. The response was defined as normalization of transaminases and IgG. **Results:** Out of 210 patients with AIH, 7 (3.34%) patients (5 female and 2 males) who were nonresponsive/intolerant to MMF received tacrolimus (TK). 6 patients were intolerant to Azathioprine and MMF, and one patient showed an inadequate response to both the drugs. Remission with TK was 71.4% with monotherapy, and two patients(28.57%) required an additional prednisolone dose to achieve disease control. The median dose of tacrolimus was 5 mg, and the median level to achieve remission was 7 ng/dl. The median time receiving tacrolimus was 20 months. Calcineurin inhibitor nephrotoxicity was seen in 2/7 (28.57%) patients, and treatment had to be discontinued in one patient. **Conclusion:** Tacrolimus is a safe and effective alternative to MMF in refractory AIH.

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4520-C | THE INFLUENCE OF ETHNICITY ON THE EPIDEMIOLOGY AND PHENOTYPES OF AUTOIMMUNE HEPATITIS IN CANTERBURY, NEW ZEALAND

Asim Abdulhamid[1], Catherine A. Stedman[1], Michael John Burt[1] and Jing Hieng Ngu[2], (1)Te Whatu Ora Waitaha Canterbury, (2)Christchurch Hospital

Background: The etiology of autoimmune hepatitis (AIH) remains unknown. There is a paucity of data on the influence of ethnicity on the epidemiology and phenotype of the disease. We aim to (i) describe the epidemiology of AIH in Europeans and non-Europeans, and (ii) compare the phenotypes of European and non-European AIH patients in Canterbury, New Zealand. **Methods:** Cases that fulfilled the Simplified Diagnostic Criteria of AIH were prospectively included in the Canterbury AIH registry. AIH patients that were diagnosed before 31st December 2021 were included for analysis. Population data were obtained for NZ Statistics. In 2021, Canterbury had a population of 650,200 and 64% identified themselves as Europeans. **Results:** A total of 312 AIH patients were included. The majority (90.4%) were of European descent. The point prevalence of AIH in European on 31st December 2021 in Canterbury is 47.6/100,000 (95% CI 41.0-54.2/100,000), whereas for non-European it is 11.1/100,000 (95% CI 6.8-15.3/100,000). The incidence of AIH in 2021 for Europeans is 1.9/100,000 (95% CI 0.6-3.3/100,000), whereas for non-Europeans it is 0.4/100,000 (95% CI 0-1.3/100,000). Interestingly, comparing European and non-European AIH patients, there was no significant difference in gender, autoantibodies, immunoglobulins, age at diagnosis, response to treatment and transplant-free survival. **Conclusion:** The prevalence of AIH is significantly higher in Europeans than non-Europeans in Canterbury, in this population-based study. However, there was no difference in the disease manifestation and outcomes between European and non-European AIH patients. Ethnicity appeared to influence disease susceptibility but not disease phenotype.

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f 4521-C | THE RELAXIN FAMILY PEPTIDE RECEPTOR 1 (RXFP1) IDENTIFIED AS A NOVEL TARGET OF AUTOANTIBODIES IN PATIENTS WITH AUTOIMMUNE HEPATITIS (AIH) BY PROTEOME-WIDE PROGRAMMABLE PHAGE DISPLAY (PHIP-SEQ)

Arielle Klepper[1], Andrew Kung[1], Sara Vasquez[1], Anthea Mitchell[1], Sabrina Mann[1], Isaac Avila-Vargas[1], Swathi Kari[1], Melawit Tekeste[1], Javier Castro[1], Briton Lee[1], Mandana Khalili[1], Jennifer Y. Chen[1], Jennifer C. Price[1], Emily J. Rothbaum Perito[2], D. Montgomery Bissell[3], Sandy Feng[1], Jacquelyn J. Maher[2], Jennifer C. Lai[4], Christina Weiler-Normann[5], Ansgar W. Lohse[5], Joseph DeRisi[6] and Michele M. Tana[1], (1)University of California, San Francisco, (2)University of California, San Francisco, San Francisco, CA, (3)University of California, San Francisco, Berkeley, CA, (4)University of California-San Francisco, San Francisco, CA, (5) University Medical Centre Hamburg-Eppendorf, (6) UCSF, Chan Zuckerberg Biohub

Background: Identification of autoantigens remains a critical challenge in understanding and treating autoimmune diseases; the role of autoantibodies in the pathophysiology of autoimmune hepatitis (AIH) is uncertain. We aimed to use Phage Immunoprecipitation-Sequencing (PhIP-Seq) to identify novel autoantibodies specific to patients with AIH. **Methods:** We performed PhIP-Seq on serum or plasma from 413 subjects to identify autoantibodies that distinguish AIH patients ($n = 115$) from healthy controls ($n = 94$) or those

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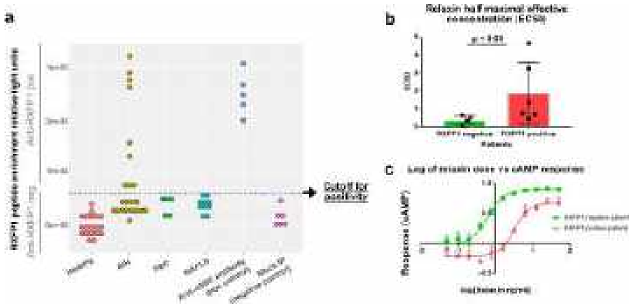
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

with other liver diseases (metabolic associated fatty liver disease, $n = 178$; primary biliary cholangitis, $n = 26$). Phage were cloned to express > 700,000 overlapping short peptides spanning the human proteome for immunoprecipitation with serum autoantibodies. Antibody-bound phage were sequenced to identify peptide-coding genes. Peptides were considered significant if they were enriched > 2.5 standard deviations from the mean of healthy controls in > 6% of AIH samples. PhIP-Seq findings were validated using a split luciferase binding assay (SLBA). Blocking assays were performed in the THP1 monocyte cell line, incubated with patient serum [1:100] prior to stimulation with relaxin (R&D systems). Signaling was quantified using the cAMP-Glo assay (Promega). **Results:** A logistic regression classifier demonstrated that we can differentiate patients with AIH from controls based on peptide-level proteome-wide PhIP-Seq autoantibody profiles (AUC = 0.84). To further investigate the autoantibodies most specific to AIH, we identified significant peptides with > 98% specificity to AIH relative to all controls. Top candidates included anti-SLA, a well-recognized autoantibody in AIH, as well as antibodies targeting a linker region of the relaxin family peptide receptor 1 (RXFP1), which is required for receptor activation. RXFP1 is a G-protein coupled receptor that binds relaxin, an anti-fibrogenic molecule shown to reduce the myofibroblastic phenotype of hepatic stellate cells. Eight of nine patients with antibodies to RXFP1 had evidence of advanced fibrosis (F3 or greater). SLBA was used to orthogonally validate antibodies targeting RXFP1 in a subset of AIH and control patients (Fig 1a). Serum from AIH patients positive for anti-RFXP1 antibody was able to block relaxin signaling in THP1 cells relative to anti-RXFP1 antibody-negative control serum ($p < 0.05$, Fig 1b, c); depletion of IgG abrogated this effect. **Conclusion:** We used the PhIP-Seq platform to discover novel autoantigens in AIH and identified RXFP1 as a highly specific disease target. Anti-RXFP1 antibodies are capable of blocking relaxin signaling via RXFP1, diminishing the anti-fibrotic properties of the molecule. Identification of anti-RXFP1 in patient serum may enable risk stratification of AIH patients for fibrosis progression and lead to the development of novel strategies for disease intervention.



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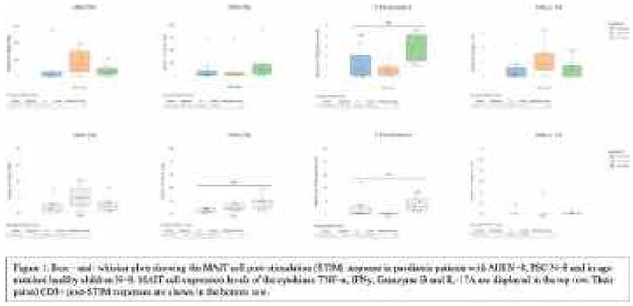
4522-C | THE ROLE OF MAIT CELLS IN CHILDREN WITH AUTOIMMUNE LIVER DISEASE

Suz Warner, University of Birmingham, Birmingham, United Kingdom; Birmingham Children's Hospital

Background: Mucosal-associated invariant T (MAIT) cells, defined as CD3+ Valpha7.2+ CD161++ T lymphocytes, are the most abundant intra-hepatic T cell population in adults. MAIT cells are increasingly recognised to play a central role in hepatic immunosurveillance, tissue maintenance and repair. In adults with autoimmune liver disease (AILD), MAIT cell frequency and cytokine production are significantly depleted due to activation-induced cell exhaustion and dysfunction. Furthermore, chronic MAIT cell activation in AILD predisposes to liver fibrosis which was shown to be interleukin-17A (IL-17A) dependent. AILD is a lifelong immune mediated liver disease which often starts in childhood but the biological characteristics and functional activity of MAIT cells in children with AILD has not been investigated. **Methods:** We performed mass cytometry by CyTOF (Cytometry by Time of Flight) on peripheral blood mononuclear cells (PBMC) from children with AILD (AIH type 1, N = 8, median age 14yrs (range 9-14), and PSC, N = 8, 14yrs (range 12-15) and in healthy children (HC) (N = 8, 12yrs (range 5-15)). PBMCs treated with CytoStim, an antibody based polylconal activator of T lymphocytes, for 4hours prior to downstream CyTOF investigation (STIM). Untreated paired PBMCs from the same patients were used as controls (UNSTIM). MAIT cell and conventional CD3+ cytokine production, measured as the median metal intensity (MMI), were recorded. **Results:** Our results show stimulated (STIM) blood MAIT cells from children with PSC had higher TNF-a production than AIH patients and healthy children (HC) (Figure 1). Reduced MAIT cell Granzyme B and IFNy expression were observed from the AIH and PSC cohorts compared to HC. IL-17A production was induced in the 4hour incubation period, an observation not previously reported in adult MAIT cells which requires prolonged activation. The patients' CD3+ T lymphocyte cytokine expression levels were also assessed and are presented for comparison. Of note, CD3+ TNF-a production was 20-fold less than observed in MAIT cells from the same patients. Furthermore, no CD3+ IL-17A production was observed in all three cohorts. **Conclusion:** In conclusion, reduced IFNγ and Granzyme production in our paediatric AILD cohort is consistent with MAIT cell dysfunction observed in adult AILD. However, higher MAIT cell TNF-a and IL-17A production in the PSC cohort following acute activation suggests TNF superfamily pathway preservation and a greater potential for early release of the chronic inflammatory and pro-fibrotic cytokine IL-17A in children, both of which could contribute to autoimmune liver disease progression.

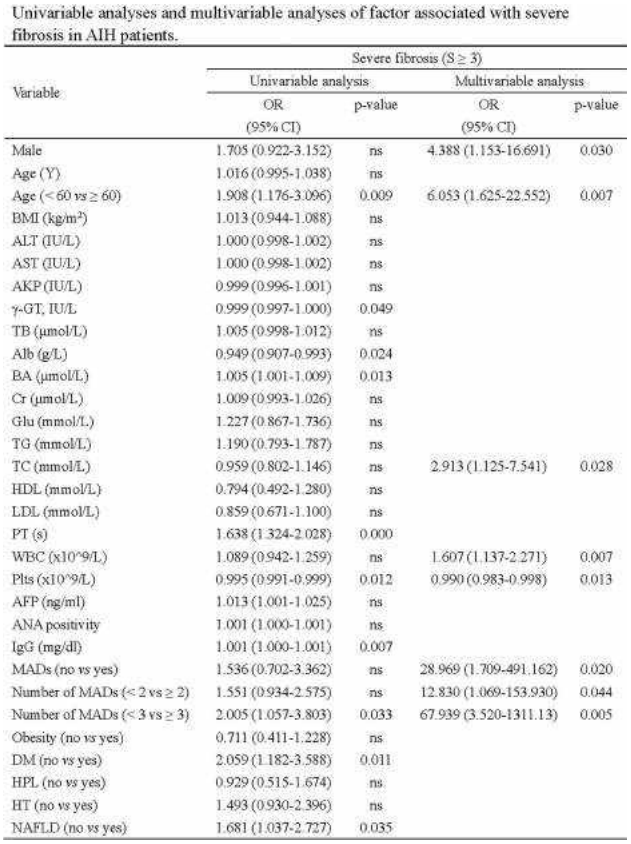


Disclosures: The following people have nothing to disclose: Suz Warner

4523-C | THE ROLE OF METABOLIC ASSOCIATED DISEASES AND LIVER STEATOSIS IN AUTOIMMUNE HEPATITIS

Kehui Liu[1], Mingyang Feng[1], Wanqing Chi[2], Xiaoyin Wang[1], Yezhou Ding[1], Shike Lou[1], Gangde Zhao[1], Li Ziqiang[1], Qing Xie[1], Lanyi Lin[1], Shisan Bao[3] and Hui Wang[1], (1)Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, (2)Yale University School of Public Health, New Haven, CT, (3)University of Sydney

Background: This study aimed to investigate the impact of metabolic associated diseases (MADs) on patients with autoimmune hepatitis (AIH). **Methods:** This cross-sectional study analysed the clinical characteristics of 283 AIH patients who underwent liver biopsy from January 2016 to February 2022. The study collected extensive clinical and histological data. **Results:** Among the enrolled AIH patients, 87.3%, 38.9% or 43.1% had MADs, NAFLD, or severe fibrosis, respectively. AIH patients with NAFLD were older and predominantly overweight/obese. Fibrosis was more severe in patients with NAFLD than in those without (50.9% vs. 38.2%, $p<0.05$). Severe liver fibrosis (stages 3 to 4) was independently associated with male gender (odds ratio, 4.388; $p=0.030$), age ≥ 60 (odds ratio, 6.053; $p=0.007$), higher TC level (odds ratio, 2.913; $p=0.028$), and combination with MADs (odds ratio, 28.969; $p=0.020$). **Conclusion:** The study findings suggest that metabolic factors aggravate hepatic fibrosis in AIH patients, highlighting the importance of screening for MADs and NAFLD among these patients. Proactive interventions should be provided to manage the progression of AIH.



Univariable analyses and multivariable analyses of factor associated with severe fibrosis in AIH patients.

Variable	Severe fibrosis (S ≥ 3)			
	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Male	1.705 (0.922-3.152)	ns	4.388 (1.153-16.691)	0.030
Age (Y)	1.016 (0.995-1.038)	ns		
Age (< 60 *vs* ≥ 60)	1.908 (1.176-3.096)	0.009	6.053 (1.625-22.552)	0.007
BMI (kg/m²)	1.013 (0.944-1.088)	ns		
ALT (IU/L)	1.000 (0.998-1.002)	ns		
AST (IU/L)	1.000 (0.998-1.002)	ns		
AKP (IU/L)	0.999 (0.996-1.001)	ns		
γ-GT, IU/L	0.999 (0.997-1.000)	0.049		
TB (μmol/L)	1.005 (0.998-1.012)	ns		
Alb (g/L)	0.949 (0.907-0.993)	0.024		
BA (μmol/L)	1.005 (1.001-1.009)	0.013		
Cr (μmol/L)	1.009 (0.993-1.026)	ns		
Glu (mmol/L)	1.227 (0.867-1.736)	ns		
TG (mmol/L)	1.190 (0.793-1.787)	ns		
TC (mmol/L)	0.959 (0.802-1.146)	ns	2.913 (1.125-7.541)	0.028
HDL (mmol/L)	0.794 (0.492-1.280)	ns		
LDL (mmol/L)	0.859 (0.671-1.100)	ns		
PT (s)	1.638 (1.324-2.028)	0.000		
WBC (x10^9/L)	1.089 (0.942-1.259)	ns	1.607 (1.137-2.271)	0.007
Plts (x10^9/L)	0.995 (0.991-0.999)	0.012	0.990 (0.983-0.998)	0.013
AFP (ng/ml)	1.013 (1.001-1.025)	ns		
ANA positivity	1.001 (1.000-1.001)	ns		
IgG (mg/dl)	1.001 (1.000-1.001)	0.007		
MADs (no *vs* yes)	1.536 (0.702-3.362)	ns	28.969 (1.709-491.162)	0.020
Number of MADs (< 2 vs ≥ 2)	1.551 (0.934-2.575)	ns	12.830 (1.069-153.930)	0.044
Number of MADs (< 3 vs ≥ 3)	2.005 (1.057-3.803)	0.033	67.939 (3.520-1311.13)	0.005
Obesity (no *vs* yes)	0.711 (0.411-1.228)	ns		
DM (no *vs* yes)	2.059 (1.182-3.588)	0.011		
HPL (no *vs* yes)	0.929 (0.515-1.674)	ns		
HT (no *vs* yes)	1.493 (0.930-2.396)	ns		
NAFLD (no *vs* yes)	1.681 (1.037-2.727)	0.035		

Disclosures: The following people have nothing to disclose: Kehui Liu, Mingyang Feng, Wanqing Chi, Xiaoyin Wang, Yezhou Ding, Shike Lou, Gangde Zhao, Li Ziqiang, Qing Xie, Lanyi Lin, Shisan Bao, Hui Wang

4524-C | THE UNUSUAL PRESENCE OF MIXED OVERLAP SYNDROME IN A SINGLE COHORT OF PATIENTS WITH AUTOIMMUNE LIVER DISEASES

Ana Marenco-Flores[1], Romelia Barba Bernal[1], Leandro Sierra[1], Bryan Ferrigno[2], Daniela Goyes[3], Wilfor Diaz Fernandez[2], John Esli Medina Morales[4], Alan Bonder[1] and Vilas Patwardhan[1], (1)Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, (2)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (3)Yale University Medical Center, New Haven, CT, United States, (4)Rutgers New Jersey Medical School, Kearny, NJ

Background: The term overlap syndrome describes variant forms of autoimmune liver disease, including autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and sclerosing cholangitis (PSC). Patients with overlap syndromes exhibit both hepatic and cholestatic liver function tests, as well as histological features of AIH, PBC, or PSC. The most prevalent presentation is the AIH-PBC overlap syndrome, which has been reported in nearly 10% of adults with AIH or PBC and may be associated with a poor prognosis. Due to their rarity, few studies have described the presence of other overlap syndrome variants. This study aimed to define the prevalence of uncommon overlap syndromes in a well-characterized prospective cohort of AIH, PBC, and PSC patients seen at a tertiary referral center and to describe their clinical characteristics. **Methods:** We conducted a single-center, observational cohort study from our autoimmune liver registry. We recorded demographics, clinic, and liver biopsies from 1131 patients from January 2018 to May 2023. Our registry is composed of patients with a primary diagnosis of AIH (n = 608), PBC (258), and PSC (265). Data included biochemical profiles, autoimmune markers, liver histology, and imaging reports. **Results:** From our cohort of 1131 patients, 20 met the criteria for uncommon overlap syndromes, representing a prevalence of 1.76%. The subjects were divided into four different groups: AIH-PSC, PBC-PSC, AIH-PBC-PSC, and AIH-IgG4 Cholangiopathy. Their mean age was 34, 62, 38, and 73, respectively. Patients were predominantly female, except for the AIH-PSC group. The white Caucasian ethnicity prevailed in all four groups. At baseline, the mean ALP was 437U/L for the AIH-PSC group and 102U/L for the PBC-PSC group. The mean AST and ALT values in the AIH-PBC-PSC group were 597U/L and 135U/L, respectively. In most cases, liver biopsy has been used to identify the AIH component of overlaps (88%); only 2% of patients were diagnosed with clinical findings. The diagnosis of PBC overlap was made based on the presence of antimitochondrial antibodies (AMA) and histopathological findings. In PSC overlaps, magnetic resonance cholangiopancreatography (MRCP) and biopsy were the most common methods of diagnosis (47% each), followed by clinical findings (6%). Only two patients were diagnosed with AIH-PBC-PSC overlap. **Conclusion:** Accurate and timely diagnosis for uncommon overlap syndrome is challenging but may improve long-term outcomes in these patients. Therefore, there is a need to develop

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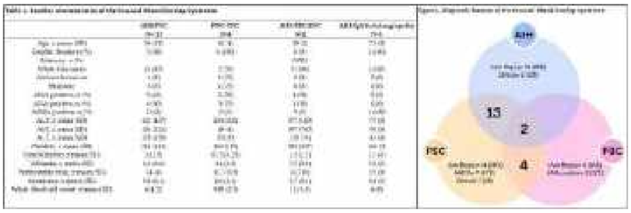
standard diagnostic criteria and therapeutic interventions for this specific group of patients.

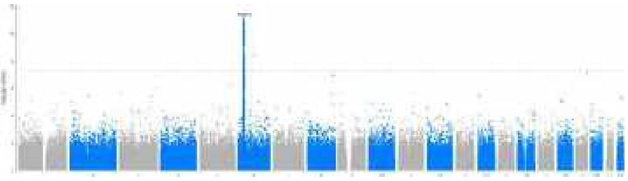

AIH
15
2
PSC
4
PBC

Disclosures: The following people have nothing to disclose: Ana Marenco-Flores, Romelia Barba Bernal, Leandro Sierra, Bryan Ferrigno, Daniela Goyes, Wilfor Diaz Fernandez, John Esli Medina Morales, Alan Bonder, Vilas Patwardhan

4525-C | TSBP1 IS ASSOCIATED WITH AUTOIMMUNE HEPATITIS RISK

Craig Lammert, Kelsey Green, Marco A Abreu and Tae-Hwi Schwantes-An, Indiana University School of Medicine

Background: The HLA class II allele associated with the DRB1 locus is the commonly described genetic risk factor for autoimmune hepatitis (AIH), yet it accounts only a small amount of AIH risk variance. In this study, we aimed to further characterize genetic contributions to AIH by identifying novel associations and genetic overlap across polygenetic risk catalog. **Methods:** AIH cases were defined per standard criteria. Cases were recruited from a well-established institutional AIH cohort consisting of patients visiting our center between 1995 and 2020. Liver disease-free controls were chosen from Indiana Biobank-Liver Cohort (IB-LC) among participants without existing ICD codes for liver diseases in their electronic medical record. GWAS (genome-wide association study) was conducted using PLINK comparing AIH cases versus liver-disease free controls adjusting for age, sex, and two principal components for ancestry stratification. PheWAS (phenome-wide association study) of polygenic risk scores (PRS) to identify diseases that share genetic risk factors with AIH was conducted in R. 3,284 PRSs from PGS Catalog v2023-01-19, were calculated in our cohort using the Michigan Imputation Server. To test association between each PRS and AIH, we used logistic regression with normalized PRS as continuous explanatory variable with age and sex as covariates. **Results:** In total, there were 420 AIH cases and 3,170 liver disease-free controls with available genotypes. In GWAS, we observed a genome-wide associated locus on chromosome 6, rs6910668, an intronic variant in *TSBP1* (Testis Expressed Basic Protein 1) with a p-value of 7.71e^{-12} (odds ratio [OR] = 1.83 for each G allele) (Figure). For PheWAS of PRS, we used a Bonferroni corrected p-value threshold of 1.52e^{-05}. Out of 3,284 PRSs tested, 25 PRS were statistically significant. Top five associated (by p-value) PRSs were for predicting the risk of celiac disease (p-values ranging between 8.23e^{-12} to 4.50e^{-11}) with increasing PRS score for celiac disease also leading to increased risk for AIH. PRSs for lung cancer, liver disease, hypothyroidism, and lupus were also associated with AIH. **Conclusion:** We identified a new genome-wide association on chromosome 6 for increasing the risk of AIH. We also observed variants that increase risk for developing celiac disease, lung cancer, hypothyroidism, and lupus also increased risk of AIH. These relationships may identify previously unknown genes/genetic variants that underlie AIH.



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Tae-Hwi Schwantes-An – Target RWE: Consultant, No, Yes;
Disclosure information not available at the time of publication: Kelsey Green, Marco A Abreu

4526-C | TTHE DIAGNOSTIC/PROGNOSTIC ROLE OF RANTES, IP-10 AND MCP-1 KYNETICS PROFILES IN AIH PATIENTS DURING IMMUNOSUPPRESSIVE TREATMNT

Giuseppe Colucci[1], Enrico Sguazzini[2], Sara Colonia Uceda Renteria[3], Riccardo Perbellini[4], Clara Dibenedetto[3], Pietro Lampertico[5] and Maria Francesca Donato[3], (1)Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico,, (2)Università Del Piemonte Orientale (UPO), (3)Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, (4)Division of Gastroenterology and Hepatology, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, (5) University of Milan

Background: The CC5, CXC3 and CC2 chemokines (CK) pathways are known to play a role in the pathogenesis of Auto Immune Hepatitis (AIH). Monitoring these CK has been previously shown to correlate with response to treatment in HCV related chronic hepatitis and cirrhosis. In his respect, we intended to assess the potential clinical utility of RANTES (CCL5), IP-10 (CXCL10) and MCP-1 (CCL2) in predicting stable disease remission in AIH patients receiving immunuppressive therapy. **Methods:** Plasma samples of 53 patients with AIH were analyzed at the time of treatment initiation and at biochemical, clinical and histological remission. RANTES, IP-10 and MCP-1 levels were determined by ELISA tests (Quantikine ELISA Kit R&D System). A group of 49 healthy donors (HD) served as controls **Results:** At baseline, while median IP-10 and MCP-1 levels were higher in AIH patients than in HD (261 pg/ml vs 101 pg/ml, $p > 0.01$ and 689 pg/ml vs 330 pg/ml, $p > 0.01$, respectively), median RANTES levels were similar in AIH patients and in HD, but differed according to the subsequent increasing or decreasing kinetics (28765 pg/ml vs 52010 pg/ml and 70960 pg/ml vs 52010 pg/ml, $p > 0.01$, respectively). At remission, both groups showed no significant differences compared to HD. IP-10 and MCP-1 values showed a significant decrease from baseline to remission approaching those of HD (501 pg/ml vs 106 pg/ml and 689 pg/ml vs 387 pg/ml, $p > 0.01$, respectively). **Conclusion:** In conclusion, monitoring plasma IP-10 and MCP-1 in levels, as well as RANTES levels may help in predicting stable AIH remission and in supporting the decision if and when to suspend immune suppressive, maintenance therapy. RANTES may also be useful in patients with low baseline levels.

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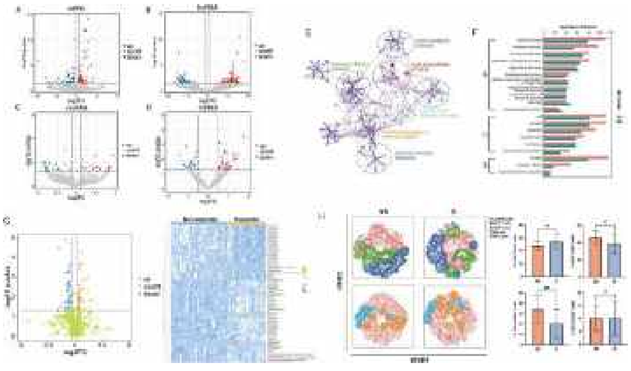
The following people have nothing to disclose: Giuseppe Colucci, Enrico Sguazzini, Sara Colonia Uceda Renteria, Riccardo Perbellini, Clara Dibenedetto, Maria Francesca Donato

4527-C | WHOLE-TRANSCRIPTOMICS, METABOLOMICS AND CYTOKINOMICS PROFILING REVEALS MOLECULAR MECHANISMS INVOLVED IN RESPONSE OF PBC/AIH OVERLAP SYNDROME

Fan Yang, West China Hospital, Sichuan University

Background: PBC/AIH overlap syndrome (OS) refers to the coexistence of features of autoimmune hepatitis (AIH) with primary biliary cholangitis (PBC), but poor understanding of its pathogenesis has limited effective clinical management of these patients. The aim of this work was to provide an overview of potential molecular mechanisms and crucial metabolic pathways underlying PBC/AIH OS by integrating whole-transcriptomics and metabolomics combined with the multiple analysis of plasma cytokines. **Methods:** We performed whole-transcriptome sequencing ($n = 5$) based on the liver tissues of responders (R) and non-responders (NR) from ten PBC/AIH OS patients. Peripheral blood metabolomics were performed on plasma from 50 PBC/AIH OS patients subdivided into R ($n = 20$) and NR ($n = 30$). A large panel of cytokines was evaluated on the same plasma using LEGENDplex™ bead-based immunoassay technology. **Results:** There were 223 differentially expressed (DE) mRNAs, 189 DE lncRNAs, 39 DE circRNAs and 63 DE miRNAs in total. Functional pathway analysis revealed transcriptional levels were mainly related to immune response, metabolic process and cytokine signaling. 71 metabolites showed significant differences between the two groups. Joint-pathway analysis showed altered pathways aberrantly expressed were mainly enriched in glutathione metabolism, primary bile acid biosynthesis, taurine and hypotaurine metabolism. Furthermore, significant differences were detected in inflammatory cytokines and peripheral blood immune cell profiles between two groups. **Conclusion:** Overall, this exploratory study provides an overview of potential molecular mechanisms and crucial metabolic pathways underlying PBC/AIH overlap syndrome, which may further assist in the development of therapeutic targets of these patients.



Disclosures: The following people have nothing to disclose: Fan Yang

4528-C | A HETEROGENEOUS SUBTYPE OF BILIARY EPITHELIAL SENESCENCE MAY BE INVOLVED IN THE PATHOGENESIS OF PRIMARY BILIARY CHOLANGITIS

Motoko Sasaki[1], Yasunori Sato[1] and Yasuni Nakanuma[2], (1)Kanazawa University Graduate School of Medical Sciences, (2)Fukui Saiseikai Hospital

Background: We disclosed an involvement of biliary epithelial senescence in the pathogenesis of primary biliary cholangitis (PBC) and other cholangiopathies. Recent studies suggest that a unique subtype of programmed death-ligand 1 (PD-L1)-positive senescent cells escape from immune-surveillance and express higher levels of senescence associated secretory phenotypes (SASPs). The expression of PD-L1 reportedly depends on cGAS (cyclic GMP-AMP synthase-STING (stimulator of interferon genes)) pathway. We hypothesized that a unique PD-L1-positive subtype of senescent biliary epithelial cells (BECs) may be related to the pathogenesis of PBC in association with cGAS-STING pathway. **Methods:** The expression of PD-L1, STING and their association with senescent markers $p16^{INK4a}$ and $p21^{WAF1/Cip1}$ were immunohistochemically determined in livers taken from the patients with PBC ($n = 87$; early stage [stages 1, 2], 54: late stage [stages 3,4], 33) and 107 control diseased and normal livers, including primary sclerosing cholangitis (PSC). Cellular senescence was induced in cultured BECs by a treatment with serum depletion or glycochenodeoxycholic acid (GCDC, 200mM) for 4-7 days. The effect of STING inhibition on mRNA and protein expression of PD-L1, STING and various SASPs including interferon (IFN)-beta and interferon induced protein with tetratricopeptide repeats 3 (Ifit3) was examined using *si*RNA in senescent BECs. Proliferation activity and cellular senescence were detected by WST-1 assay and senescence-associated ß-galactosidase (SA-ß-gal), respectively. **Results:** The increased expression of PD-L1 was seen in a part of senescent BECs with $p16^{INK4a}$ and/or $p21^{WAF1/Cip1}$ in bile duct lesions in PBC. The expression of PD-L1 was significantly increased in BECs in the damaged small bile ducts involved in cholangitis in PBC, compared to control livers ($p < 0.01$). In contrast, PD-L1 was not expressed in BECs in ductular reactions in PBC and control livers. The expression of STING was significantly increased in BECs in small bile ducts and ductular reactions in PBC, compared to control livers ($p < 0.01$). The expression of PD-L1, STING and SASPs (IFN-beta, Ifit3) was significantly increased in senescent BECs induced by a treatment with serum depletion or GCDC ($p < 0.01$) and it was significantly suppressed by a knockdown of STING using *si*RNA ($p < 0.01$). A proliferation activity and cellular senescence were not affected by STING inhibition in BECs ($p < 0.01$). **Conclusion:** A unique subtype of senescent BECs with PD-L1 expression was present in BECs involved in destructive cholangitis but not in ductular reactions in PBC. This finding suggests a heterogeneity in senescent BECs in PBC. Senescent BECs with PD-L1 expression associated with cGAS-STING pathway may be involved in the pathogenesis of PBC.

Disclosures: The following people have nothing to disclose: Motoko Sasaki, Yasunori Sato, Yasuni Nakanuma

f 4529-C | A MULTICENTER RANDOMIZED TRIAL COMPARING DENOSUMAB AND ZOLEDRONIC ACID FOR OSTEOPOROSIS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (DELTA STUDY)

Yoshitaka Arase[1], *Tatehiro Kagawa*[1], *Yusuke Mishima*[1], *Kota Tsuruya*[1], *Shunji Hirose*[1], *Koichi Shiraishi*[1], *Keisuke Kakisaka*[2], *Tadashi Namisaki*[3], *Kosuke Matsumoto*[4], *Toru Setsu*[5], *Haruki Uojima*[6], *Masanori Abe*[7], *Taeang Arai*[8], *Tomomi Okubo*[9], *Masanori Atsukawa*[8], *Akira Honda*[10], *Shuji Terai*[5], *Hitoshi Yoshiji*[3], *Atsushi Tanaka*[4] *and Ministry of Health, Labour and Welfare (Japan) Research Project, The Intractable Hepatobiliary Disease Study Group, (1)Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokai University School of Medicine, (2)Iwate Medical University, (3)Nara Medical University, (4)Teikyo University School of Medicine, (5)Graduate School of Medical and Dental Sciences, Niigata University, (6)National Center for Global Health and Medicine, (7)Ehime University Graduate School of Medicine, (8)Nippon Medical School Hospital, (9) Nippon Medical School Chibahokusoh Hospital, (10) Joint Research Center, Tokyo Medical University Ibaraki Medical Center*

Background: Osteoporosis is a major complication in patients with primary biliary cholangitis (PBC). Denosumab, a fully human monoclonal antibody against the receptor activator of nuclear factor-κB ligand (RANKL), increases bone mineral density (BMD) by inhibiting development and activity of osteoclasts and decreasing bone resorption. In this study, we compared the effects and safety of denosumab and bisphosphonates for osteoporosis in patients with PBC. **Methods:** We performed a multicenter, randomized, open-label, parallel-group trial in Japanese PBC patients with osteoporosis. Subjects were randomized 1:1 to subcutaneous denosumab 60mg every 6 months (D group) or bisphosphonate therapy with intravenous zoledronic acid (ZOL) 5 mg once-yearly (Z group). The primary end point was the mean percentage change in lumbar spine and total hip BMD between baseline and 12 months. We tested the non-inferiority of denosumab to ZOL with a non-inferiority margin of −2.4% for lumbar spine and −0.9% for total hip. Secondary endpoints were changes in laboratory parameters and the incidence of adverse events. **Results:** A total of 47 patients were enrolled and randomly assigned to the D group ($n = 25$) and the Z group ($n = 22$) between May 2018 and March 2021. Of these, 41 patients (87.2%) completed the study (D group, $n = 21$; Z group, $n = 20$). Baseline demographics and clinical characteristics were similar between the two groups. BMD at lumbar spine increased from baseline

Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

by 7.5% and 6.4% in the D and Z group, respectively, demonstrating the non-inferiority of denosumab with a difference of 1.1% (95% CI; −1.6%~3.8%). The increase in BMD at total hip was greater in the D group (5.0%) than that in the Z group (2.6%), but the difference did not meet non-inferiority (95% CI; −1.3% ~6.2%). The ratio of ALP to upper limit of normal (ULN) significantly decreased from 1.2 ± 0.9 at baseline to 0.9 ± 0.8×ULN at 12 months in the D group ($P < 0.01$) and from 1.1 ± 0.6 to 0.8 ± 0.5×ULN in the Z group ($P < 0.01$), but the rates of change in ALP did not differ between groups (−24.8% vs. −23.1%, $P = 0.75$). The bone turnover markers significantly decreased in both groups, but the rates of change were not different between groups; tartrate-resistant acid phosphatase 5b (−52.9% vs.−49.6%, $P = 0.73$) and bone-type ALP (−45.0% vs.−36.9%, $P = 0.27$). The incidence of adverse events was significantly lower in the D group compared with the Z group (14.3% [hypocalcemia 2, arthralgia 1] vs. 45.0%[fever 7, hypocalcemia 2, headache 2, nausea 1, back pain 1, myalgia 1], $P = 0.03$). In this study period, fresh vertebral fractures and osteonecrosis of the jaw were not observed. **Conclusion:** Denosumab was non-inferior to ZOL in increasing BMD at lumbar spine in 12 months and was associated with fewer adverse effects than ZOL. Denosumab is a highly useful therapeutic agent for osteoporosis in patients with PBC.

Disclosures: Yoshitaka Arase – Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Kowa Company: Speaking and Teaching, No, Yes; Gilead Sciences: Speaking and Teaching, No, Yes; Abbvie: Speaking and Teaching, No, Yes; Takeda Pharmaceutical Company: Speaking and Teaching, No, Yes; ASKA Pharmaceutical: Speaking and Teaching, No, Yes; Daiichi Sankyo Company: Speaking and Teaching, No, Yes; Chugai-pharma: Speaking and Teaching, No, Yes; Otsuka Pharmaceutical: Speaking and Teaching, No, Yes; Sumitomo Pharma: Speaking and Teaching, No, Yes;

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Kota Tsuruya – Chugai Pharmaceutical Co., Ltd.: Speaking and Teaching, No, Yes; ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, No, Yes; Eisai Co., Ltd.: Speaking and Teaching, No, Yes; Kowa Co., Ltd.: Speaking and Teaching, No, Yes; AbbVie GK: Speaking and Teaching, No, Yes;

Atsushi Tanaka – Kowa Company: Consultant, No, No; GSK: Consultant, No, No; Gilead Sciences: Advisor, No, No; Abbvie: Speaking and Teaching, No, No;

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Disclosure information not available at the time of publication: Keisuke Kakisaka, Tadashi Namisaki, Masanori Abe, Hitoshi Yoshiji

4530-C | A PILOT STUDY EXAMINING A LOW-SULFUR/LOW-PROTEIN DIET VERSUS THE SPECIFIC CARBOHYDRATE DIET IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

Gila Feinman Sasson[1], Demsina Babazadeh[1], Macie Andrews[1], Shelley Hurwitz[1], Maia Paul[1], Nadine Javier[1], Malav Dave[1], Alexandra Austin[1], Linda Gray[2], Francene Steinberg[2], Elaine Souza[2], Daniel S. Pratt[3], Christopher L. Bowlus[4] and Joshua R. Korzenik[1], (1) Brigham and Women's Hospital, (2)University of California, Davis, (3)Massachusetts General Hospital, (4)University of California Davis, Sacramento, CA

Background: Little is known about the role of diet in primary sclerosing cholangitis (PSC) despite increasing interest in diet as a therapeutic approach. An emerging dietary therapy from ulcerative colitis (UC) studies suggest high-sulfur/high-protein diet may be associated with increased disease activity. This study compares the effects of a low-protein diet (LPD) and Specific Carbohydrate Diet (SCD) on clinical, microbial and metabolomic parameters in PSC. We propose that SCD, with higher protein content, increases disease activity and LPD reduces activity, as assessed by alkaline phosphatase (ALP), through modulatory effects on the gut microbiome. **Methods:** Individual's with a diagnosis of large-duct PSC were screened for eligibility including ALP > 1.5 x upper limit of normal, and randomized 1:1 to LPD or SCD for 8 weeks under dietitian supervision, with an option to continue self-directed for 4 additional weeks. The primary outcome was within-group change in ALP. Participants attended 7 video visits with dietitians. Diet was assessed using 3-day food diaries every 2 weeks and a baseline Food Frequency Questionnaire. Blood and stool were collected every 4 weeks. Groups were compared with exact Wilcoxon-Mann-Whitney tests. **Results:** Twenty participants were enrolled. Decrease in ALP (defined by ≥ 10% reduction) in LPD was seen as early as week 4 and was sustained throughout week 8. At week 4, 60% in LPD demonstrated ≥ 10% reduction in ALP (14.72- 39.65%) compared to 22% in SCD (11.59-23.76%) (P = 0.05). Macronutrient analysis of week 4 ALP response demonstrated decreased protein consumption in responders at week 2 (P = 0.02), between weeks 0 and 2 (P = 0.03), and the average of weeks 2 and 4 compared to week 0 (P = 0.03). There was no significant difference in carbohydrate consumption between responders and non-responders. LPD reported lower protein consumption at all time points (P < 0.05) while SCD reported lower carbohydrate consumption at all time points (P < 0.05 at baseline and weeks 6-10), confirming dietary compliance in both groups. Metabolomic data submitted separately further supports an association between LPD and ALP response, particularly in the subset of individual's with PSC-UC. **Conclusion:** Our analysis demonstrates that LPD is associated with a meaningful ALP reduction that appears to be driven by protein consumption. In contrast, a high protein diet is associated with worsening ALP. Additional dietary and microbiome analyses will better understand the impact of diet on microbiome and disease activity in PSC.

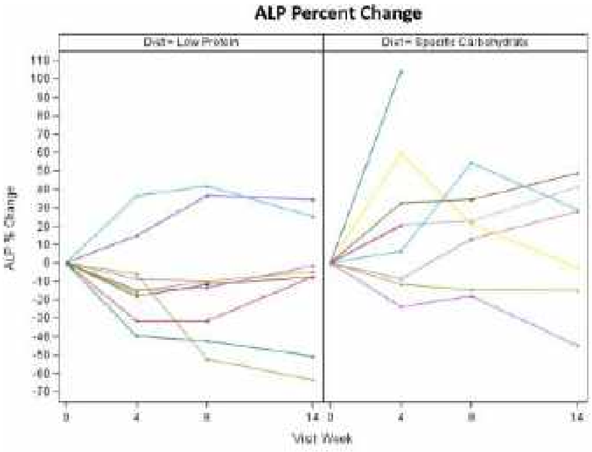

Figure 1. Percent change in ALP in the Low Protein Diet and Specific Carbohydrate Diet groups

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The following people have nothing to disclose: Gila Feinman Sasson, Demsina Babazadeh, Macie Andrews, Shelley Hurwitz, Maia Paul, Nadine Javier, Malav Dave, Alexandra Austin, Linda Gray, Francene Steinberg, Elaine Souza, Daniel S. Pratt

4531-C | ANALYSIS OF NONINVASIVE DIAGNOSTIC PREDICTORS IN PATIENTS WITH PBC-AIH OVERLAP SYNDROME BASED ON CLINICAL AND PATHOLOGICAL CHARACTERISTICS

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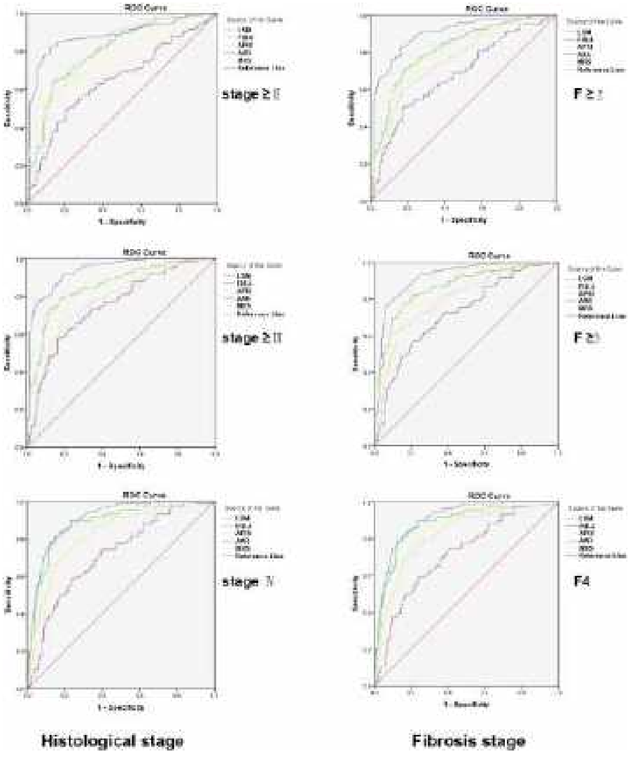
Background: Primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH) are main categories of autoimmune liver disease. Approximately 20% of PBC patients displayed overlapping features of both PBC and AIH, referred as PBC-AIH overlap syndrome (PBC-AIH OS). Early diagnosis and proper treatment of PBC-AIH OS are crucial for the prognosis of these patients. This study aimed to explore non-invasive hematological indicators for early diagnosis of PBC-AIH OS. **Methods:** By retrospective analysis, the general characteristics, clinical manifestations, biochemical tests, immunological tests, liver histological examinations, and imaging examinations in pathology suggested non-cirrhotic patients with PBC-AIH OS and PBC at the time of initial diagnosis were analyzed. The correlations between blood indexes and histopathological features were analyzed. Univariate logistic regression analysis and multiple-factors analysis via multivariate logistical regression were used to predict the diagnosis of PBC-AIH OS based on the hematological indicators. **Results:** A total of 83 pathologically non-cirrhotic AILDs patients were included in this retrospective study who underwent liver biopsy. There were no statistically significant differences in mean age, sex, or symptoms between PBC-AIH OS and PBC patients. Compared to PBC patients, PBC-AIH OS patients showed significantly high levels of serum globulin, ALT, AST, total bilirubin, direct bilirubin, ALP, GGT, total bile acid, IgG and significantly low levels of serum albumin and cholinesterase. Univariate logistic regression analysis and multiple-factors analysis via multivariate logistical regression showed that direct bilirubin (DBIL), total bilirubin (TBIL) and IgG were significant predictors of PBC-AIH OS. Histopathological analysis of liver indicated that all patients had different degrees of intrahepatic small bile duct injury, while PBC-AIH OS patients also had moderate to severe interface hepatitis. In addition, compared with PBC patients, Metavir score showed that the liver fibrosis grade of PBC-AIH OS patients was significantly higher (The degree of inflammation and fibrosis were statistically different, $P < 0.05$). In addition, in both PBC-AIH OS and PBC patients, a subset of patients who did not progress to histologically cirrhosis developed intrahepatic ductopenia (30.77% and 22.73%, respectively), and biliary enzyme and bilirubin levels were significantly elevated in these patients. **Conclusion:** The degrees of hepatocyte inflammation, cholestasis and liver fibrosis in PBC-AIH OS patients were significantly higher than that in PBC patients. No matter in PBC-AIH OS or PBC patients who have not progressed histologically to cirrhosis, a portion of them have intrahepatic loss of small bile ducts and greater cholestasis. DBIL, TBIL and IgG can be used as noninvasive diagnostic indicators to predict PBC-AIH OS.

Disclosures: The following people have nothing to disclose: Li Zhang, Hongmei Wu, Li Liu, Xiaofeng Shi, Peng Hu, Yu Lei

4532-C | ASSESSMENT OF BIOPSY-PROVEN LIVER FIBROSIS BY TRANSIENT ELASTOGRAPHY (FIBROSCAN) IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: A REAL-WORLD STUDY IN CHINA

Jialiang Chen, Yao Liu, Yufei Bi, Fangyuan Gao and Xianbo Wang, Beijing Ditan Hospital, Capital Medical University, Beijing, China

Background: Noninvasive measurement of liver stiffness with transient elastography (TE) by Fibroscan has been widely used for the assessment of liver fibrosis in various chronic liver diseases, including primary biliary cholangitis (PBC). However, previous studies using TE to diagnose liver fibrosis in PBC mainly focused on Western populations, while there is still a lack of relevant research from Asian or Chinese populations. The current study aimed to investigate the real-word diagnostic performance of liver stiffness measurement (LSM) for the determination of fibrosis stage in Chinese patients with PBC. **Methods:** A total of 277 patients (88.4% female, median age: 52 y) diagnosed with PBC who underwent liver biopsy and LSM by Fibroscan were retrospectively enrolled from January 2008 to December 2021 in a tertiary hospital in China. Histological and fibrosis stages were determined according to the Ludwig's classification and METAVIA scoring system. Spearman correlation test was used to analyze the correlation of LSM and fibrosis stage. The accuracy of LSM for the determination of histological and fibrosis stages were determined by a receiver operating characteristics (ROC) curve analysis and compared with that of other serum fibrosis models, including the aspartate aminotransferase to platelet ratio index (APRI), fibrosis-4 (FIB-4), AST/ALT ratio (AAR) and Mayo risk score (MRS). Optimal cutoff values between fibrosis categories were determined at the maximum total sensitivity and specificity. **Results:** The number of patients with fibrosis stages F0-F1, F2, F3, and F4, were 131 (47.3%), 40 (14.4%), 20 (7.2%), and 86 (31.0%), respectively. The number of patients with histological stages I, stage **a**, stage III, and stage **c** , were 89 (32.1%), 66 (23.8%), 36 (13.0%), 86 (31.0%), respectively. LSM ranged from 2.8 to 75.0 kPa (median, 10.1 kPa). LSM was correlated to both fibrosis (Spearman's $r = 0.753$, $P < 0.001$) and histological ($r = 0.778$, $P < 0.001$) stages. The areas under the ROC curves of LSM for diagnosing fibrosis stages ≥F2, ≥F3, and F4 were 0.902 (95%CI: 0.860-0.934), 0.920 (0.881-0.949), and 0.904 (0.863-0.936), respectively. The optimal cutoff values of LSM for fibrosis stages ≥F2, ≥F3, and F4 were 9.4, 14.9, and 16.1 kPa, respectively. LSM was significantly superior to FIB-4, APRI, AAR, and MRS in detecting severe fibrosis (≥F3) and advanced histological stage (stage III/**c**) (all $P < 0.05$). **Conclusion:** Liver stiffness measurement using TE in real-world setting has high accuracy in assessing fibrosis and histologic stage in Chinese PBC patients, reinforcing its role as a first-line investigation in the noninvasive assessment of patients with PBC.



Disclosures: The following people have nothing to disclose: Jialiang Chen, Yao Liu, Yufei Bi, Fangyuan Gao, Xianbo Wang

4533-C | ASSOCIATION BETWEEN ABO BLOOD TYPE AND HISTOLOGIC FIBROSIS STAGE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

Jialiang Chen, Yao Liu, Yufei Bi, Fangyuan Gao and Xianbo Wang, Beijing Ditan Hospital, Capital Medical University, Beijing, China

Background: Primary biliary cholangitis (PBC) is an immune-mediated chronic cholestatic liver disease that can progress to liver fibrosis and cirrhosis. Advanced histologic stage has been proven to be an independent predictive factor of liver transplantation or death in PBC patients. The non-O phenotype of the ABO genotype has been linked with an increased risk of liver fibrosis in hepatitis C. We aimed to investigate the association between blood group status and histological stage in patients with PBC. **Methods:** A single-center retrospective observational study were performed in a tertiary hospital in China. From January 2008 to December 2021, a total of 246 patients diagnosed with PBC who underwent liver biopsy and ABO blood type measurement were retrospectively collected. The Ludwig's classification was used to evaluate histological stages. Multivariate logistic regression was used to assess the relationship between ABO blood groups and histological stage. The adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. PBC. **Results:** In our study population, there were 218 (88.6%) women, with a mean age of 51.2 ± 9.5 years. There were 57 patients (23.2%) in histological stage I, 56 (22.7%) in stage **a**, 44 (17.9%) in stage III and 89 (36.2%) in stage **c** . The proportion of blood groups A, B, AB and O were 34.1%, 29.3%, 6.5%, and 30.1%, respectively. Patients with non-O blood groups (A, B, or AB type) had a significantly higher risk of histological advanced-stage (stage III/**c**) than those with blood group O (crude OR = 2.02, 95% CI: 1.16 - 3.51; the fully adjusted OR = 4.48, 95% CI: 1.30 - 15.37). There was a significant interactive effect of AMA antibodies, gp210 antibodies, and non-O blood groups on histological stage in patients with PBC ($P_{\text{interaction}} < 0.05$). When AMA or gp210 antibodies are negative, patients with non-O blood groups have a higher risk of advanced histological stage (crude OR = 4.52, 95% CI: 1.70 - 12.06; crude OR = 4.40, 95% CI:1.54 - 12.57). **Conclusion:** This is the first study that has evaluated the potential relationship between PBC histological stage and ABO blood groups. This study indicates that PBC patients with non-O blood group types have a higher risk for advanced histological stage compared with O blood group patients, suggesting that ABO blood group must be taken into account for accurate assessment of the risk of fibrosis severity in patients with PBC.

Disclosures: The following people have nothing to disclose: Jialiang Chen, Yao Liu, Yufei Bi, Fangyuan Gao, Xianbo Wang

f 4534-C | ASSOCIATIONS BETWEEN LIVER BIOMARKERS AND CLINICAL OUTCOMES IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: A RETROSPECTIVE REAL-WORLD STUDY

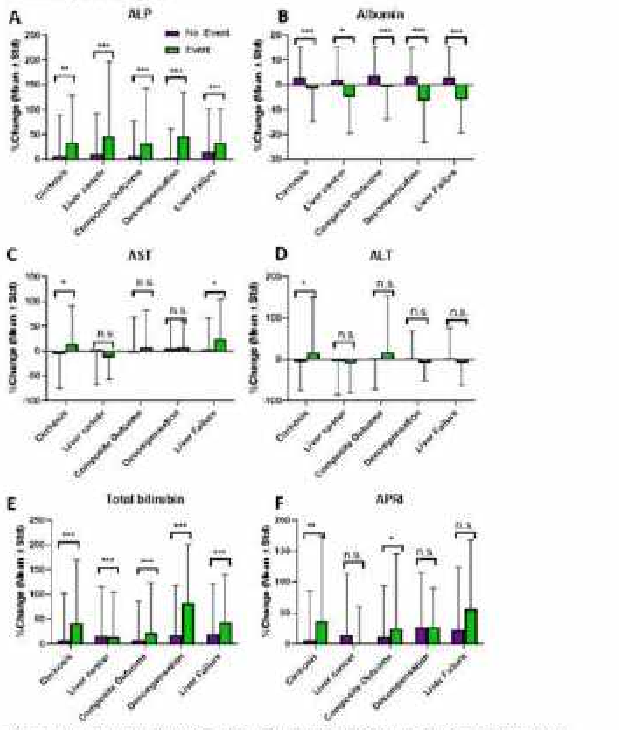
Jun Xu[1], Jessica Duchen[2], Luke Liu[1], Catherine Frenette[1], Stephanie Watkins[1], William Barchuk[1], Lisa Boyette[1] and Shahed Iqbal[1], (1)Gilead Sciences, Inc., (2)Trinetx LLC

Background: Primary sclerosing cholangitis (PSC) is a disease of inflammation and fibrosis of the bile ducts. PSC is not well characterized due to small study samples and patient heterogeneity. We explored the associations between liver biomarker levels and clinical outcomes in a large cohort of patients with PSC. **Methods**: Adult patients with ≥2 PSC ICD10 codes (K83.01) were included from the TriNetX Research Database. Liver biomarkers (albumin, total bilirubin, ALP, ALT, AST and APRI) at baseline and 6−12 months prior to an outcome were measured. Outcomes included: cirrhosis, decompensation, liver failure, liver cancer and a composite outcome (cirrhosis/liver transplant/death). Associations between biomarker levels and outcomes were assessed using Cox proportional hazard models including age, sex, region, IBD treatment, comorbidities, neutrophil, platelets and lymphocyte counts. Adjusted Hazard Ratios (aHR) with 95% confidential intervals (CI) were reported for higher quartiles (Q2−Q4) of biomarker measures vs Q1. **Results**: PSC patients (N = 2373) were mostly 35 −64 years (57%, mean: 50 ± 17 y), male (60%), and white (80%) with a mean follow-up of 4.2 years. Percent changes in biomarkers from baseline to outcomes were associated ($p < 0.05$) with most events (Figure 1). In adjusted models, baseline higher ALT was associated (Q3 vs Q1) with composite outcome [aHR (95% CI): 1.67 (1.1−2.6)] and liver failure [4.6 (1.3−16.8)]; AST (Q4 vs Q1) with decompensation [3.8 (1.2−11.6)] and liver cancer [3.7 (1.2−11.6)]; ALP (Q4 vs Q1) with liver failure [6.1 (1.7−21.7)]; and total bilirubin (Q4 vs Q1) with composite outcome [1.6 (1.0−2.4)]. However, for liver cancer, PSC patients had lower ALP (Q4 vs Q1) at baseline [0.3 (0.1−0.6)]. For biomarkers at outcomes (Q4 vs Q1) lower albumin correlated with risk of cirrhosis [aHR (95% CI): 0.5 (0.3−0.7)], composite outcome [0.4 (0.2−0.6)], decompensation, [0.2 (0.05

Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

−0.5)], liver failure [0.3 (0.1−1.0)] and liver cancer [0.3 (0.1−0.9)]; increased ALP was associated with a composite outcome [1.8 (1.0−3.2)]; total bilirubin with decompensation [4.6 (1.2−17.3)]; and increased ALT was associated with cirrhosis [2.0 (1.2−3.4)] and composite outcome [2.2 (1.2−3.8)]. **Conclusion**: Liver biomarkers at baseline and changes during follow-up were associated with PSC outcomes. Further research is needed to identify the exact clinical correlates and confirm prognostic thresholds for these biomarkers.

Figure 1: Association between clinical outcomes and percent changes in liver biomarkers from baseline to 6-12 months prior to outcomes



ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate aminotransferase; APRI: AST to platelet ratio index
*: p<0.05, **: p<0.01, ***: p<0.001, n.s.: no significance

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Luke Liu – Gilead Sciences Inc: Employee, No, No; Gilead Sciences Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
Catherine Frenette – Gilead Sciences Inc: Employee, Yes, No; Gilead Sciences Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;
Stephanie Watkins – Gilead Sciences Inc: Employee, No, No; Gilead Sciences Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;
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Shahed Iqbal – Gilead Sciences Inc: Employee, No, No; Gilead Sciences Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), No, No;

4535-C | CLINICAL CHARACTERISTICS, TREATMENT, AND OUTCOMES OF PRIMARY SCLEROSING CHOLANGITIS IN CHINESE PATIENTS

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Background: Primary sclerosing cholangitis (PSC) is a rare liver disease, and its epidemiology has not been well described in China. Our study aimed to depict the demographic and clinical profile of Chinese patients with PSC. **Methods:** The PSC cases were identified by a retrospective review of electronic medical records (EMRs) for the inpatients and outpatients from May 2009 to May 2023 in eight tertiary hospitals in China. ICD-10 and natural language, together with clinical records including biochemical, imaging (MRCP/ERCP), and/or liver biopsy were used to confirm the PSC cases. Data on demographic characteristics, clinical and biochemical profiles, treatment, and clinical outcomes were retrieved. **Results:** Finally, 108 PSC cases were enrolled with a median age of 47 (33, 57) years and 45.4% male patients. The median interval from the first onset of PSC-related symptoms to definitive diagnosis was 1.0 (IQR: < 1.0, 3.0) years. While 63 (58.3%) patients were diagnosed by imaging, 24 (22.2%) by liver biopsy, and 17 (15.7%) by a combination of histology, imaging, biochemistry, and other clinical features. The first clinical presentations were jaundice (42.7%,41/96), fatigue (31.3%, 30/96), abdominal discomfort (29.2%, 28/96), and pruritus (16.7%, 16/96). The median levels of alkaline phosphatase, glutamyl transpeptidase, total bilirubin, and total bile acid were 309.5 U/L (*IQR*: 176.8 U/L, 513.3 U/L), 251.0 U/L (*IQR*: 113.5 U/L, 543.5 U/L), 51.6 μmol/L (*IQR*: 19.1 μmol/L, 139.9 μmol/L), 60.2 μmol/L (*IQR*: 17.2 μmol/L, 135.2 μmol/L), respectively, with no statistical difference in gender ($P = 0.601$~0.896). The proportions of elevated immunoglobulin G and immunoglobulin M were 40.2% and 20.0% in PSC cases, respectively, with no statistical difference in gender. The antineutrophil cytoplasmic antibody (ANCA) positive rate was 38.6% (27/70), with a higher rate in males than in females (58.1% *vs.* 23.1%, $P = 0.006$). Totally, 23.9% (21/88) patients were concomitant with inflammatory bowel disease (IBD), and 9.1% (8/88) with other autoimmune diseases. Eighty-six patients had prescription records, with 89.5%, 62.8%, 29.1%, and 9.3% of them taking ursodeoxycholic acid, hepatoprotective agents, steroid/immunosuppressive agents, and antibiotics, respectively. The 3-year cumulative rates of decompensated cirrhosis and liver transplantation/death were 37.6 % (95% *CI*: 26.4%, 50.3%), and 26.4% (95%*CI*: 16.3%, 39.8%), respectively. The 5-year cumulative rates of decompensated cirrhosis and liver transplantation/death were 55.5% (95%*CI*: 40.0%, 70.0%), and 41.3% (95%*CI*: 26.5%, 57.9%), respectively. **Conclusion:** In China, PSC patients had a more balanced gender distribution, less concomitant IBD, and a lower ANCA-positive rate. In terms of treatment, the main focus was on symptomatic treatment to improve liver biochemistry.

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4536-C | CLINICAL COURSE OF PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

Kazuma Shinkai[1]*, Hayato Hikita*[1]*, Kazuki Maesaka*[2]*, Akira Doi*[2]*, Yuki Tahata*[2]*, Kazuhiro Murai*[1]*, Takahiro Kodama*[2]*, Tomohide Tatsumi*[2] *and Tetsuo Takehara*[2]*, (1)Osaka University, Graduate School of Medicine, (2) Osaka University Graduate School of Medicine*

Background: The clinical course of patients with primary sclerosing cholangitis (PSC) and factors associated with transplantation free prognosis have not been fully investigated in Japan. The aim of this study was to assess the clinical course of patients with PSC in our hospital and to clarify the factors related to transplantation free prognosis. **Methods:** Patients with PSC who have visited our hospital from January 2000 to March 2022 were searched from the medical record and enrolled in this study. Their characteristics at diagnosis were evaluated. The time from the date of diagnosis to liver transplantation or death was calculated as transplantation free survival. The factors associated with transplantation free survival were analyzed using Cox proportional hazards model. **Results:** Of 48 PSC patients who have visited our hospital, the characteristics at diagnosis were available in 40 patients. Twenty-eight patients were males and median age at diagnosis was 34 (6-75) years. Patients with Child-Pugh classification A, B, and C were 31, 5, 4, respectively. Patients with ALBI grade 1, 2, and 3 were 17, 18, and 5, respectively. Median MELD score was 8 (5-23). Nineteen patients were classified in the New Mayo model low-risk group, 16 were in the intermediate-risk group, and 5 were in the high-risk group. Sixteen patients were complicated by ulcerative colitis. Median transplantation free survival was 2034 (12-7990) days, and 8 patients received liver transplantation and 7 died. In univariate analysis, γ-GTP, albumin, total bilirubin, PT-INR, Child-Pugh classification, ALBI grade, MELD score, and the New Mayo model were associated with transplantation free survival. Multivariate analysis showed that albumin and total bilirubin were the independent factors associated with transplantation free survival. Transplantation free survival rate at 5 years after diagnosis was 100% in the low-risk group, 58.4% in the intermediate-risk group, 0% in the high-risk group of New Mayo model. Transplantation free survival rate at 5 years after diagnosis was 100% in ALBI grade 1, 67.8% in grade 2, and 0% in grade 3. Of 7 patients who died, 5 patients were awaiting transplantation. Of these patients, 4 patients had rapidly progressing liver failure triggered by events such as ascites exacerbation, portal vein thrombosis, spontaneous bacterial peritonitis, rupture of esophageal varices, pyogenic cholangitis. One patient, who was complicated by ulcerative colitis, died of pneumocystis carinii pneumonia. **Conclusion:** Albumin and total bilirubin at diagnosis were independent prognostic factors in patients with PSC at our hospital. The New Mayo model and ALBI grade may be useful for risk stratification for transplantation and mortality. Patients awaiting transplantation should be carefully monitored for complications of portal hypertension and infectious disease.

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4537-C | CLINICAL SUPPORT USING DEEP LEARNING TO PREDICT THE NEED FOR INTERVENTION IN ELDERLY PATIENTS WITH PRIMARY BILIARY CHOLANGITIS FROM MULTICENTER DATA

Takafumi Tonouchi[1], Hiroteru Kamimura[2], Hiroki Maruyama[1], Suguru Miida[1], Norihiro Sakai[2], Yusuke Watanabe[2], Naruhiro Kimura[2], Toru Setsu[2], Hiroyuki Abe[1], Takeshi Yokoo[2], Akira Sakamaki[2], Atsunori Tsuchiya[1], Kenya Kamimura[3] and Shuji Terai[2], (1) Niigata University, (2)Graduate School of Medical and Dental Sciences, Niigata University, (3)School of Medicine, Niigata University

Background: In Japan, a super-aging society ahead of all over the world, more than 40% of the population has six or more types of drugs called polypharmacy. Aging society caused the number of cases of elderly-onset primary cholangitis (PBC). In addition, many patients are taking multiple medications such as antihypertensive and hyperlipidemic drugs at the time of diagnosis, and even ursodeoxycholic acid (UDCA) may cause polypharmacy and poor oral compliance when the number of tablets is large, and some patients are troubled by the dosage and administration method. Disease types are divided into hepatic failure type, portal hypertensive type, and asymptomatic to slowly progressive type. Even in the slowly progressive type, the pattern of progression may not be linear due to treatment modification. In addition, ALBI score and grade have recently been reported as prognostic indicators. We aimed to demonstrate the safety of UDCA dose reduction in patients with the settled disease and low medication adherence and to improve polypharmacy by using AI tools. The predictive models were built based on algorithms set up by SONY Neural Network Console, and their accuracy was compared using statistical analysis. **Methods:** Patients enrolled in this study prior to 2018 and with 10 years of continuous data were included. Liver biopsy, stage classification, AST, ALT, Alb, T-bil, esophageal varices, itchy skin, UDCA dosage at diagnosis, and AST, ALT, Alb, T-bil one year after starting medication, and ALBI score after 10 years were incorporated into a Deep Neural Network as supervised data. Patients with onset at age 65 years or older and with 10 years of follow-up were validated as test data. **Results:** Of the 140 cases, 85% were female, age 58 (28-78) years, with the asymptomatic carrier (18%), ALBI score -2.95 (-3.75-1.05) at diagnosis and -2.85 (-3.41-1.17) at 10 years. In addition, 10 cases with onset over 60 years of age and follow-up over 10 years, age 62 (60-72) years, data at the first visit and 1 year later were entered as test data. Machine learning results showed that only 2 of the 30 cases were incorrect, and the overall accuracy rate was over 90%. Furthermore, patients whose ALBI grade changed had a correct answer rate of about 80%. **Conclusion:** In patients with asymptomatic PBC patients detected by medical checkups or promising long-term prognosis, and in routine clinical practice, deep learning can be used to predict ALBI scores at 10 years with high predictive accuracy using data from one year later as a decision-making tool for therapeutic intervention. The results also suggest deep learning can contribute to the selection of UDCA dosage and prevent polypharmacy.

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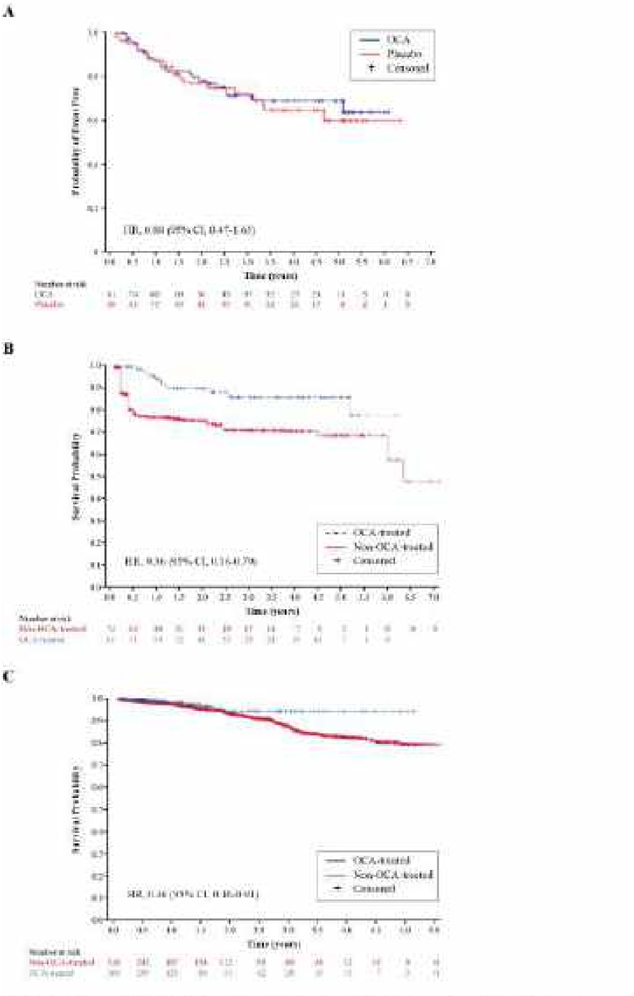
4538-C | CLINICAL TRIAL AND REAL-WORLD OUTCOMES IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS TREATED WITH OBETICHOLIC ACID PER CURRENT US LABEL

Kris V. Kowdley[1], Gideon Hirschfield[2], Tracy Mayne[3], Elizabeth S. Malecha[3], Charles Coombs[4], Erik Ness[3], John D. Seeger[5] and M. Alan Brookhart[6,7], (1)Liver Institute Northwest and Elson S. Floyd College of Medicine, Washington State University, Seattle, WA, USA, (2)Toronto Centre for Liver Disease, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada, (3)Intercept Pharmaceuticals, Inc., Morristown, NJ, (4)Real World Evidence, Syneos Health, Morrisville, NC, USA, (5)Optum Epidemiology, Boston, MA, (6) Target Rwe, Durham, NC, (7)Department of Population Health Sciences, Duke University, Durham, NC

Background: Obeticholic acid (OCA) received accelerated approval for primary biliary cholangitis (PBC) in 2016 based on significant reduction in alkaline phosphatase, a surrogate marker predictive of clinical outcomes. The label has been revised twice, excluding patients with hepatic decompensation or comorbid cirrhosis + portal hypertension (PH). Data from the COBALT phase 3b/4 outcomes trial with external control (EC) and the fully real-world HEROES study were reanalyzed, including only patients consistent with current US prescribing information (USPI) and using an expanded composite endpoint including PH. **Methods:** COBALT, a double-blind, placebo-controlled trial, randomized subjects to OCA treatment (5 mg titrated to 10 mg if tolerated) or placebo (intent-to-treat analysis). An EC group was created from the US Komodo Health database using standardized morbidity ratio (SMR) weighting (as-treated analysis). HEROES, a nested trial emulation using the Komodo Health database, compared SMR-weighted patients treated with OCA with those who were eligible for OCA but not treated with OCA (as-treated). We reanalyzed data from patients consistent with current USPI (excluding hepatic decompensation and cirrhosis + PH). In consultation with the FDA, the original endpoint of death, liver transplant, uncontrolled ascites, model for end-stage liver disease (MELD) score > 15, and hospitalization for hepatic decompensation was expanded to include additional decompensating events and PH. COBALT EC and HEROES excluded MELD. **Results:** In COBALT RCT, 21/81 (25.9%) OCA-treated and 19/68 (27.9%) placebo subjects experienced a composite event (HR, 0.88; 95% CI, 0.47–1.65). In the COBALT as-treated EC analysis, 10/81 (12.4%) OCA-treated patients and 18/74 (24.6%) non–OCA-treated weighted controls experienced an event (HR, 0.36; 95% CI, 0.16–0.79). In the HEROES trial emulation, 8/308 (2.6%) OCA-treated and 28/310 (9.0%) non–OCA-treated weighted controls experienced an event (HR, 0.46; 95% CI, 0.16–0.91). **Conclusion:** Among patients consistent with the current USPI, a composite endpoint of death, liver transplant, and progression to hepatic decompensation and/or PH was less frequent for OCA-treated patients. Despite substantial treatment crossover and informative censoring, the COBALT RCT showed a non-statistically significant efficacy signal in favor of OCA treatment, and both the COBALT EC and HEROES trial emulation studies showed statistically significant superiority of OCA vs non-treatment.

Figure. Time to composite FDA expanded endpoint for (A) COBALT intent-to-treat analysis, (B) COBALT external control as-treated analysis, and (C) HEROES trial emulation as-treated analysis.



Abbreviations: CI, confidence interval; FDA, Food and Drug Administration; HR, hazard ratio; OCA, obeticholic acid.

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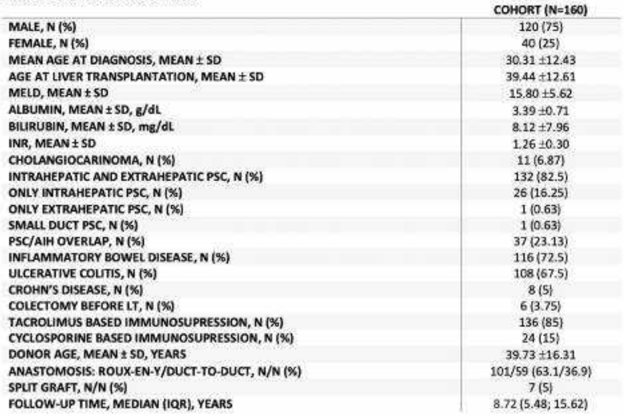
Disclosure information not available at the time of publication: Gideon Hirschfield, Charles Coombs, John D. Seeger, M. Alan Brookhart

4539-C | CMV INFECTION AND ACUTE CELLULAR REJECTION ARE ASSOCIATED WITH RISK OF RECURRENT PRIMARY SCLEROSING CHOLANGITIS AND GRAFT FAILURE AFTER LIVER TRANSPLANTATION

Mojmír Hlavatý, Lukas Bajer, Jan Brezina, Pavel Wohl, Istvan Modos, Julius Spicak and Pavel Drastich, Institute for Clinical and Experimental Medicine

Background: Primary sclerosing cholangitis (PSC) is a chronic liver disease causing inflammation of the bile ducts, forming progressive strictures and stenoses of bile ducts resulting in recurrent cholangitis, liver cirrhosis and death. Liver transplantation (LT) is necessary for most of the patients as the only curative treatment. However, about 30% of patients develop recurrence of PSC (rPSC), which negatively impacts the outcome of liver grafts and patients. The pathogenesis of recurrent disease is multifactorial, but not entirely understood. **Methods:** The aim of this study was to evaluate the risk factors for rPSC and graft failure (GF) in patients after LT for PSC and PSC/AIH overlap syndrome. Furthermore, we evaluated the patient survival, graft survival and the patient survival after post-LT. In this single-centre retrospective study (IKEM, Prague, Czech Republic), we included patients who underwent LT for PSC in our transplant centre between 1996-2019. **Results:** A total of 160 patients after LT for PSC and PSC/AIH overlap syndrome were included in the study. Biliary strictures after LT developed in 67 (41.88%) patients, of which 16 (23.88%) were anastomotic. rPSC was confirmed in totally 51 (31.87%) patients. The mean time to diagnosis of rPSC was 6.2 (CI 95% +- 1.04) years. In multivariant analysis of risk factors for rPSC: Cytomegalovirus (CMV) infection (HR 3.21; 95% CI 1.43-7.19), at least one episode of acute cellular rejection (ACR) (HR 3.00; 95%CI 1.00-9.03) and length of hospitalization after LT (HR 1.03; 95% CI 1.01-1.05) were statistically significant predictors of rPSC.
Liver retransplatation (reLT) due to GF was performed in 23 patients (15.22%). The cause of GF was as follows: rPSC in 18 patients (78.26%), hepatic artery thrombosis in 2 patients (8.69%), primary graft dysfunction in 2 patients (8.69%) and persistent biliary leak in 1 patient (4.35%). The median time to reLT due to rePSC was 8.59 (IQR 6.84,13.81) years. Furthermore, 3 patients required 2nd reLT and 1 patient 3rd reLT. In multivariant survival analysis, CMV infection after LT (HR 5.00; 95%CI 1.22-20.5), PSC/AIH overlap syndrome (HR 6.4; 95% CI 1.13-36.4) and length of hospitalization after LT (HR 1.04; 95%CI 1.01-1.07) were significant predictors for GF. Overall survival of patients in 5 years after LT was 89.5%. **Conclusion:** Based on our results, ACR, CMV infection and length of hospitalization post-LT were significant risk factors for rPSC. PSC/AIH overlap syndrome, length of hospitalisation post-LT and CMV infection were associated with worse liver graft outcome.

Table 1. Cohort characteristics



	COHORT (N=160)
MALE, N (%)	120 (75)
FEMALE, N (%)	40 (25)
MEAN AGE AT DIAGNOSIS, MEAN ± SD	30.31 ±12.43
AGE AT LIVER TRANSPLANTATION, MEAN ± SD	39.44 ±12.61
MELD, MEAN ± SD	15.80 ±5.62
ALBUMIN, MEAN ± SD, g/dL	3.39 ±0.71
BILIRUBIN, MEAN ± SD, mg/dL	8.12 ±7.96
INR, MEAN ± SD	1.26 ±0.30
CHOLANGIOCARINOMA, N (%)	11 (6.87)
INTRAHEPATIC AND EXTRAHEPATIC PSC, N (%)	132 (82.5)
ONLY INTRAHEPATIC PSC, N (%)	26 (16.25)
ONLY EXTRAHEPATIC PSC, N (%)	1 (0.63)
SMALL DUCT PSC, N (%)	1 (0.63)
PSC/AIH OVERLAP, N (%)	37 (23.13)
INFLAMMATORY BOWEL DISEASE, N (%)	116 (72.5)
ULCERATIVE COLITIS, N (%)	108 (67.5)
CROHN'S DISEASE, N (%)	8 (5)
COLECTOMY BEFORE LT, N (%)	6 (3.75)
TACROLIMUS BASED IMMUNOSUPRESSION, N (%)	136 (85)
CYCLOSPORINE BASED IMMUNOSUPRESSION, N (%)	24 (15)
DONOR AGE, MEAN ± SD, YEARS	39.73 ±16.31
ANASTOMOSIS: ROUX-EN-Y/DUCT-TO-DUCT, N/N (%)	101/59 (63.1/36.9)
SPLIT GRAFT, N/N (%)	7 (5)
FOLLOW-UP TIME, MEDIAN (IQR), YEARS	8.72 (5.48; 15.62)

IQR, interquartile range; N, number; SD, standard deviation; PSC/AIH Overlap, Primary sclerosing cholangitis/Autoimmune hepatitis overlap syndrome

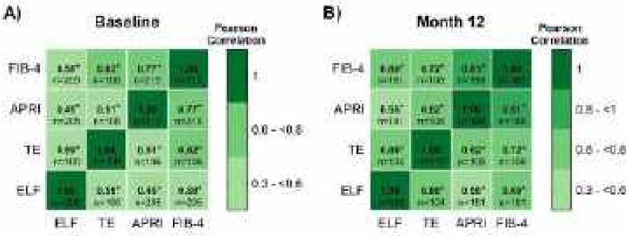
Disclosures: The following people have nothing to disclose: Mojmír Hlavatý, Lukas Bajer, Jan Brezina, Pavel Wohl, Istvan Modos, Julius Spicak, Pavel Drastich

4540-C | CORRELATIONS BETWEEN FIBROSIS SCORING SYSTEMS AND TRANSIENT ELASTOGRAPHY IN THE PHASE 3 POISE STUDY OF OBETICHOLIC ACID IN PRIMARY BILIARY CHOLANGITIS

Robert G. Gish[1], Darren Wheeler[2], Radhika Nair[2], Tracy Mayne[2], Erik Ness[2], Elizabeth S. Malecha[2], Jing Li[2] and Alan Bonder[3], (1)Robert G Gish Consultants LLC, (2) Intercept Pharmaceuticals, Inc., Morristown, NJ, (3) Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School

Background: Transient elastography (TE) is a widely used, non-invasive method of evaluating hepatic fibrosis, a key prognostic factor in primary biliary cholangitis (PBC). However, not all practice sites have access to the equipment required to perform TE. Therefore, scoring systems such as Fibrosis-4 (FIB-4) represent a more feasible approach for many clinicians. We performed a post hoc sub-analysis of the phase 3 POISE PBC study to assess the correlations of TE with fibrosis scoring systems. **Methods:** POISE was a phase 3, randomized, double-blind trial evaluating obeticholic acid in patients with PBC. TE, enhanced liver fibrosis (ELF) score, FIB-4 score, and aspartate aminotransferase to platelet ratio index (APRI) were measured at baseline and Month 12. Associations across TE, ELF score, FIB-4, and APRI at baseline and Month 12 were evaluated via Pearson correlation. **Results:** At both baseline and at Month 12, all correlations across the 4 fibrosis markers were moderate or strong and statistically significant (Figure). Notably, of the 3 scoring systems (ELF, FIB-4, and APRI), FIB-4 had the highest correlation with TE at both time points (baseline [n = 106], 0.62; Month 12 [n = 106], 0.72; $P < 0.0001$ for both time points). The correlations between ELF and TE were 0.59 and 0.66 at baseline (n = 100) and Month 12 (n = 104), respectively ($P < 0.0001$ for both time points), and correlations between APRI and TE were 0.51 and 0.62 at baseline (n = 106) and Month 12 (n = 106), respectively ($P < 0.0001$ for both time points). **Conclusion:** This post hoc sub-analysis of the phase 3 POISE trial demonstrated significant associations across all 4 fibrosis markers. At both time points, the correlation between FIB-4 and TE was stronger than the correlations between ELF and TE and APRI and TE. Although FIB-4 is not validated in PBC, the moderately strong observed correlation with TE suggests that FIB-4 may be a possible surrogate for evaluating fibrosis in patients with PBC, especially in the case of limited access to TE.

Figure. Correlation across fibrosis markers at baseline (A) and Month 12 (B).



*Indicates $P < .0001$ for a given correlation.
Abbreviations: APRI, aspartate aminotransferase to platelet ratio index; ELF, enhanced liver fibrosis; FIB-4, Fibrosis 4; TE, transient elastography.

Disclosures: Robert G. Gish – Abbott: Consultant, No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; HepQuantum: Stock – privately held company (individual stocks and stock options), No, No; Ganlantis: Stock – privately held company (individual stocks and stock options), No, No; Eiger: Stock – privately held company (individual stocks and stock options), No, No; Prodigy: Advisor, No, No; Venatorx: Consultant, No, No; Topography Health: Consultant, No, No; Pfizer: Consultant, No, No; Merck: Consultant, No, No; Janssen: Consultant, No, No; Intercept: Speaking and Teaching, No, No; HepQuant: Advisor, No, No; HepaTx: Advisor, No, No; Helios: Consultant, No, No; Gilead Sciences: Consultant, Yes, No; GLG: Consultant, No, No; Genlantis: Consultant, No, No; Genentech: Consultant, No, No; Enyo: Consultant, No, No; Eiger: Advisor, No, No; Dynavax: Consultant, No, No; Arrowhead: Consultant, No, No; Antios: Consultant, No, No; Altimmune: Consultant, No, No; Abbvie: Speaking and Teaching, No, No; Abbott: Consultant, No, No; Eisai: Consultant, No, No; Gilead Sciences: Consultant, No, No; CymaBay: Advisor, No, No; Durect: Advisor, No, No; AstraZeneca: Speaking and Teaching, No, No; BMS: Speaking and Teaching, No, No; Eisai: Speaking and Teaching, No, No; Hepquant: Stock – privately held company (individual stocks and stock options), No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; Gilead Sciences: Grant/ Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

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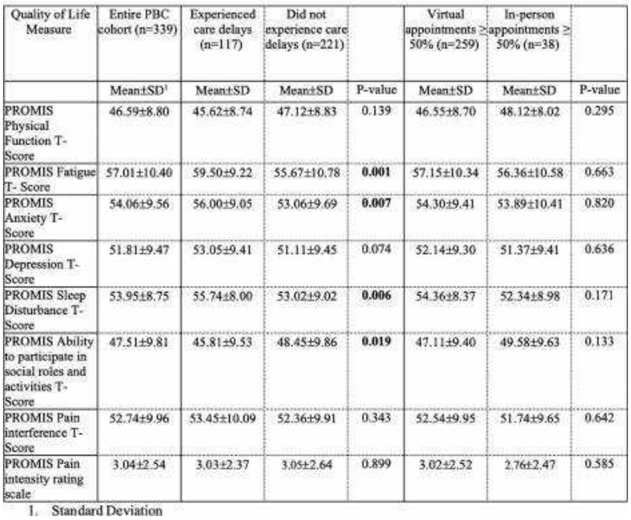
Tracy Mayne – Intercept Pharmaceuticals, Inc.: Employee, No, No;
Erik Ness – Intercept Pharmaceuticals, Inc.: Employee, No, No;
Elizabeth S. Malecha – Intercept Pharmaceuticals, Inc.: Employee, No, No;
Jing Li – Intercept Pharmaceuticals Inc.: Employee, No, No;
The following people have nothing to disclose: Alan Bonder

4541-C | COVID PANDEMIC IMPACT ON CARE DELIVERY AND QUALITY OF LIFE AMONG PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: A LARGE CANADIAN STUDY

Elizabeth Baguley[1], Madelyn Knaub[1], Gail Wright[2], Jessica VanDyke[1], Mark Gordon Swain[1], Deirdre McCaughey[1], Gideon Hirschfield[3] and Abdel-Aziz Shaheen[4], (1)University of Calgary, (2)Canadian PBC Society, (3)Toronto Centre for Liver Disease, University of Toronto, Toronto, Ontario, Canada, (4)Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

Background: The pandemic-related restrictions impacted care delivery, particularly during the first year. We assess the impact of the pandemic on care delivery for patients with primary biliary cholangitis (PBC) and describe the quality of life they experienced during this time. **Methods:** The 29-item Patient-Reported Outcomes Measurement Instrument Survey (PROMIS-29) and a PBC Care Delivery questionnaire were administered to patients with PBC ($n = 339$), followed by two focus groups for patients ($n = 14$) and stakeholders ($n = 3$) between August 2021 and June 2022. The PROMIS-29 has seven health domains measured as T-Scores, including pain interference, depression, physical function, ability to participate in social roles/activities, fatigue, anxiety, and sleep disturbance, and a single pain intensity item. PROMIS-29 scores were compared between our PBC cohort and a reference population from the 2000 General US Census. Additionally, we compared PROMIS-29 scores of our population based on experienced care delay (laboratory work and imaging) and appointment type (in person vs. virtual). **Results:** Participants were primarily females (93.5%) and Caucasian (89.1%), with a median age of 62 yrs (IQR:55-70). Median time from PBC diagnosis was 9 years (IQR: 4-18). During the pandemic, most participants (76.4%) had ≥ 50% of their hepatologist appointments virtually; however, post-pandemic only 22.4% preferred to continue with virtual appointments. Many participants (34.6%) experienced at least one delay in obtaining laboratory work, imaging, or medications. Participants scored significantly worse ($p < 0.001$) in all PROMIS-29 domains compared to the general population. Participants who experienced delays in care had higher fatigue ($p = 0.001$), anxiety ($p = 0.007$), and sleep disturbance ($p = 0.006$) scores, and more difficulty participating in social roles and activities ($p = 0.019$), compared to individual's who had no care delays (Table 1). No significant differences were found between PROMIS-29 scores and appointment type (Table 1). Focus groups indicated both patients and stakeholders agreed on the importance of in-person appointments, while recognizing that virtual care may play a role in post-pandemic care. **Conclusion:** For post-pandemic care, the majority of PBC patients and providers preferred in-person appointments. PBC patients experienced poor quality of life during the pandemic compared to the general population, particularly those with delayed care.

Table 1: Quality of life measures for entire PBC cohort, including comparisons between timing of care (delayed verse non-delayed) and type of appointment (virtual verse in-person) during the pandemic



Quality of Life Measure	Entire PBC cohort (n=339)	Experienced care delays (n=117)	Did not experience care delays (n=221)		Virtual appointments ≥ 50% (n=259)	In-person appointments ≥ 50% (n=38)	
	Mean±SD[1]	Mean±SD	Mean±SD	P-value	Mean±SD	Mean±SD	P-value
PROMIS Physical Function T-Score	46.59±8.80	45.62±8.74	47.12±8.83	0.139	46.55±8.70	48.12±8.02	0.295
PROMIS Fatigue T- Score	57.01±10.40	59.50±9.22	55.67±10.78	**0.001**	57.15±10.34	56.36±10.58	0.663
PROMIS Anxiety T-Score	54.06±9.56	56.00±9.05	53.06±9.69	**0.007**	54.30±9.41	53.89±10.41	0.820
PROMIS Depression T-Score	51.81±9.47	53.05±9.41	51.11±9.45	0.074	52.14±9.30	51.37±9.41	0.636
PROMIS Sleep Disturbance T-Score	53.95±8.75	55.74±8.00	53.02±9.02	**0.006**	54.36±8.37	52.34±8.98	0.171
PROMIS Ability to participate in social roles and activities T-Score	47.51±9.81	45.81±9.53	48.45±9.86	**0.019**	47.11±9.40	49.58±9.63	0.133
PROMIS Pain interference T-Score	52.74±9.96	53.45±10.09	52.36±9.91	0.343	52.54±9.95	51.74±9.65	0.642
PROMIS Pain intensity rating scale	3.04±2.54	3.03±2.37	3.05±2.64	0.899	3.02±2.52	2.76±2.47	0.585

1. Standard Deviation

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Gideon Hirschfield – Intercept: Consultant, No, No; GSK: Consultant, Yes, No; CymaBay: Consultant, No, No; Ipsen: Consultant, No, No; Falk: Consultant, No, No; Pliant: Consultant, No, No; Morphogen: Consultant, No, No; Roche: Consultant, No, No; Mirum: Consultant, No, No;

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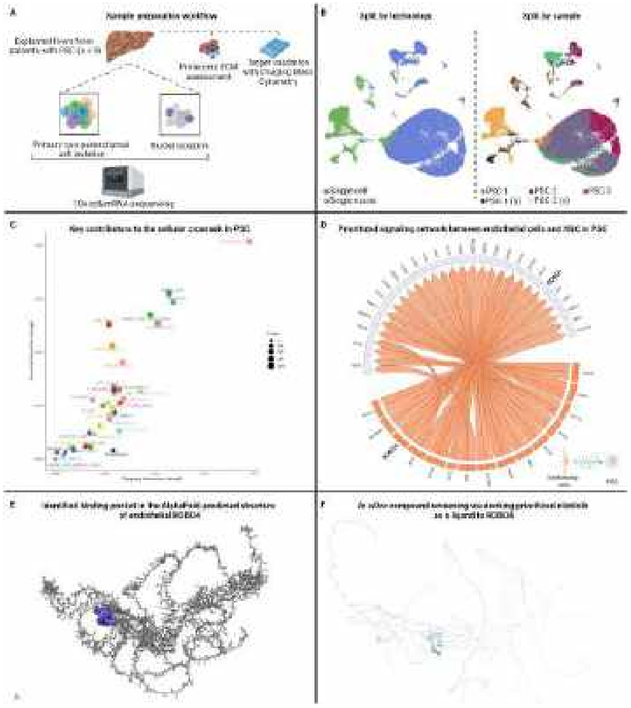
4542-C | DECIPHERING OF THE HEPATIC SINGLE-CELL INTERACTOME IN PRIMARY SCLEROSING CHOLANGITIS★

Oleksandr Petrenko[1,2,3], Carolina Mangana[3], Thomas Sorz[1,2,3], Benedikt Silvester Hofer[1,2,3], Benedikt Simbrunner[1,2,3], Kerstin Zinober[1,2], Vlad Taru[1,2], Philipp Schwabl[1,2,3], Barbara Maier[3], Claudia Daniela Fuchs[1], Michael Trauner[1] and Thomas Reiberger[1,2,3], (1) Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, (2)Christian Doppler Laboratory for Portal Hypertension and Liver Fibrosis, Medical University of Vienna, (3)Cemm Research Center for Molecular Medicine of the Austrian Academy of Sciences

Background: Primary sclerosing cholangitis (PSC) is a rare liver disease characterized by cholangitis and periportal fibrosis resulting in bile duct sclerosis. In this study, we aimed to investigate the hepatic cell-cell interactions that drive PSC progression and perform in silico ligand screening. **Methods:** We used single-cell and single-nuclei RNA sequencing of primary non-parenchymal cells isolated from explanted livers of three PSC patients. The obtained dataset was integrated into human non-diseased and cirrhotic liver scRNA-seq datasets (MacParland 2018; Ramachandran 2019) for reference-guided clustering and annotation using Harmony and Seurat. We identified key gene signatures involved in the cellular crosstalk and performed differential interaction analysis versus other aetiologies with CellChat and NicheNet. Targets specific to PSC were then subjected to *in-silico* compound screening by predicted binding probability against the library ofof FDA-approved small molecules using AutoDock Vina. **Results:** We obtained 35501 cell transcriptomes from three human PSC liver samples. We detected an abundance of activated γδ-T-cells and a depletion of tolerogenic MARCO+ Kupffer cells (KC) in PSC. Activated KC were major sources of incoming and outgoing signaling based on cell ligand-receptor analysis. KC were enriched for *MIF*, *HMGB1*, and *HMGB2* genes compared to other immune cell populations and interacted with non-parenchymal cells via ITGB2, THBS and Galectin pathways. In the cell interaction analysis, we identified 57 ligands, 77 receptors and 257 downstream targets with significant differential expression in PSC vs. other etiologies – with SLIT2-ROBO1/4, RUNX1, and RELN identified as novel targets. Molecular docking prioritized small molecules as potential ligands for such PSC targets (e.g., nilotinib and rucaparib for ROBO4). **Conclusion:** We discovered perspective molecular targets in PSC with their ligands for further *in vitro* and *in vivo* investigations aiming at the development of new therapeutic strategies. The identified targets are currently being validated by Imaging Mass Cytometry and LC-MS proteomics, and their role in biliary fibrosis is being accessed using transcriptomes of Mdr2$^{-/-}$ KO mice.



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The following people have nothing to disclose: Carolina Mangana, Benedikt Silvester Hofer, Benedikt Simbrunner, Vlad Taru, Barbara Maier, Claudia Daniela Fuchs, Michael Trauner

4543-C | DEVELOPMENT OF A PRIMARY BILIARY CHOLANGITIS (PBC)-SPECIFIC VERSION OF CHRONIC LIVER DISEASE QUESTIONNAIRE: CLDQ-PBC

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Background: Primary biliary cholangitis (PBC) is an important chronic liver disease (CLD) leading to cirrhosis and impaired patient reported outcomes (PROs). We aimed to develop PBC-specific version of CLDQ instrument. **Methods:** From our Liver Database, we included patients with PBC who had completed CLDQ, clinico-laboratory data, and other PRO instruments (Short Form-36 (SF-36) or Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)). The 29 items of CLDQ were subjected to item reduction by excluding items with a score of 6 or 7 (highest possible scores, suggesting the item was never or hardly ever a problem for patients with PBC over the recall period of 2 weeks) chosen by $>65\%$ PBC subjects; remaining items were subjected to exploratory factor analysis to explain 95% of variance. A standard instrument validation pipeline with internal consistency and validity assessments were applied to the new CLDQ-PBC. **Results:** Data were available for 108 PBC patients: 57 ± 11 years old, 7% male, 58% with cirrhosis, 24% with advanced cirrhosis (CPT class B or C), 93% on UDCA. Of the 29 CLDQ items, none met the exclusion criteria. Exploratory factor analysis suggested that 95% of variance could be explained by 7 factors. Based on evaluation of factor loadings and face validity assessment by three hepatology experts, those factors yielded the domains of Diet, Emotion, Fatigue, Itch, Symptoms, Sleep, and Worry (CLDQ-PBC). The domains of CLDQ-PBC demonstrated varying internal consistency: good to excellent Cronbach's alpha 0.85-0.93 for 5/7 domains. The item-to-own domain correlations were >0.60 for 24/26 items from the 5 internally consistent domains (Emotion, Fatigue, Symptoms, Sleep, Worry). For the two domains with lower internal consistency and/or comprehensiveness (Diet, Itch), we included additional relevant items using focus groups, expert opinions, and literature review. For the valid domains, known-groups validity tests discriminated between PBC patients with and without cirrhosis, with and without advanced cirrhosis, as well as presence or absence of history of depression ($p < 0.05$ for 3-5 domains). The highest correlated domains of SF-36 with those of CLDQ-PBC were: Mental Health for Emotional (rho = +0.88), Physical Functioning and Vitality for Fatigue (both rho $\geq$ +0.83), Vitality and Social Functioning for Sleep (both rho $\geq$ +0.60), Vitality for Symptoms (rho = +0.74), and Social Functioning for Worry (rho = +0.73) (all $p < 0.0001$). Fatigue domain of CLDQ-PBC was also highly correlated with Fatigue Scale of FACIT-F (rho = +0.85), and Worry domain of CLDQ-PBC was negatively correlated with the level of alkaline phosphatase (rho = -0.38, p = 0.0082). **Conclusion:** CLDQ-PBC was developed based on the original CLDQ. The new instrument has evidence for internal consistency and validity, and is being fully validated using an external cohort.

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The following people have nothing to disclose: Maria Stepanova

Disclosure information not available at the time of publication: Issah Younossi, Andrei Racila

4544-C | DISPARITIES EXCESS MORTALITY IN CIRRHOTIC PATIENTS WITH PRIMARY BILIARY CHOLANGITIS AND PRIMARY SCLEROSING CHOLANGITIS DURING THE COVID-19 PANDEMIC

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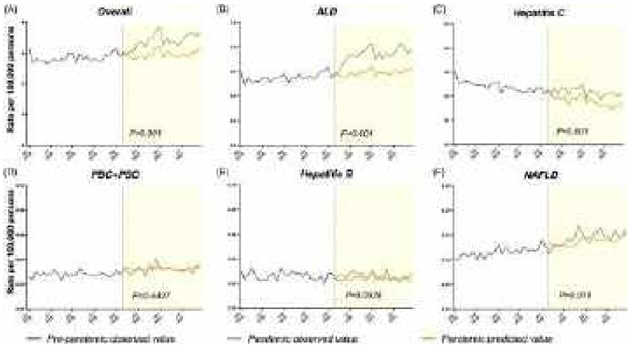
Background: The COVID-19 pandemic increased liver-related mortality and had etiology disparities. Previous study showed ursodeoxycholic acid (UDCA), commonly used in primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) treatment, was associated with both a decrease in SARS-CoV-2 infection and a reduction in severe or critical COVID-19 among patients with cirrhosis. We estimated the monthly age-standardized mortality (ASMR) with cirrhosis, further categorizing by etiologies to investigate the potential affect of UDCA on PBC/PSC-related mortality during the COVID-19 pandemic. **Methods:** Using Vital Statistics Online Data Portal of the of the National Vital Statistic System, we calculated the monthly ASMR of cirrhosis aged 25 years or older and stratified by etiology from 2012 to 2021. We conducted a Prophet model to predict mortality rates in 03/2020-12/2021 based on the trend between 01/2012 and 02/2020 to determine the impact of the pandemic on cirrhosis-related mortality. By calculating the difference between observe and predicted mortality rate, we quantified the impact of the pandemic on people with cirrhosis and stratified by etiology. **Results:** Among 878,601 cirrhosis-related deaths identified from 1/1/2012-12/31/2021, there was a significantly increasing trend in cirrhosis-related mortality during the pandemic from 3.026 to 3.680 in 03/2020 and 12/2021, with an average excess mortality of 14.46% (95%CI 11.89 to 17.02%, $p < 0.001$). The observed mortality rates were higher than the predicted values for alcohol-associated liver disease (ALD), HCV, and non-alcoholic fatty liver disease (NAFLD) (all $p < 0.05$), with an average excess mortality of 24.81% (95%CI 20.95 to 28.68%), 21.24% (95%CI 16.70 to 25.77%) and 6.11% (95% CI 2.29 to 9.92%), respectively. Notably, PBC/PSC-related cirrhosis deaths did not show this increase, with an average excess mortality of -1.69% (95%CI -5.63 to 2.25%, $p = 0.44$), similar to hepatitis B virus (HBV)-related deaths (Figure 1). Additionally, there were small to negligible proportions (less than 9 decedents) of COVID-19 among decedents in the PBC/PSC and HBV subgroups. **Conclusion:** Our study found no significant increase in mortality related to PBC/PSC during the pandemic and had a lower excess mortality when compared to the pre-pandemic period and to other etiologies of cirrhosis.



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The following people have nothing to disclose: Xinyuan He, Ning Gao, Fan Lv, Fengping Wu, Yi Liu, Lamei Li, Yee Hui Yeo, Fanpu Ji

4545-C | EFFECT OF OBETICHOLIC ACID ON PROGNOSTIC THRESHOLDS OF GAMMA-GLUTAMYL TRANSFERASE AND ALKALINE PHOSPHATASE LEVELS: SUB-ANALYSIS OF THE PHASE 3 POISE TRIAL IN PRIMARY BILIARY CHOLANGITIS

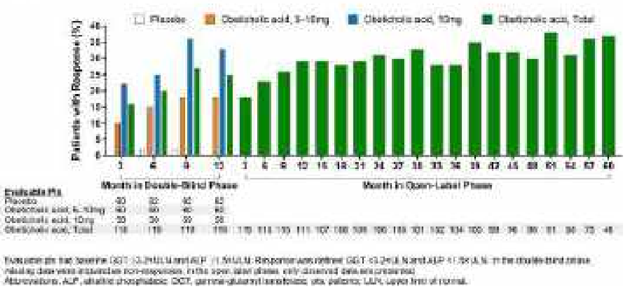
Alan Bonder[1], Darren Wheeler[2], Radhika Nair[2], Erik Ness[2], Elizabeth S. Malecha[2] and Robert G. Gish[3], (1) Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, (2)Intercept Pharmaceuticals, Inc., Morristown, NJ, (3)Robert G Gish Consultants LLC

Background: A recent study from the Global PBC study group has shown that gamma-glutamyl transferase (GGT) ≥3.2×upper limit of normal (ULN) and alkaline phosphatase (ALP) ≥1.5×ULN increases the risk of liver transplantation or death in patients (pts) with primary biliary cholangitis (PBC); GGT also increases the prognostic value of ALP (Gerussi A, et al. *Clin Gastroenterol Hepatol.* 2021). Obeticholic acid (OCA), a selective, potent farnesoid X receptor agonist, received accelerated approval in 2016 for the treatment of PBC based on biomarker improvement in POISE, a 12-month randomized, double-blind, placebo-controlled phase 3 study. Here, we evaluate the impact of OCA on achievement of GGT < 3.2×ULN and ALP < 1.5×ULN. **Methods:** Pts with PBC who were receiving a stable dose of ursodeoxycholic acid (UDCA) or who were unable to tolerate UDCA were randomized to receive placebo, OCA 5−10 mg (OCA titration), or OCA

Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

10 mg daily. POISE included a 12-month double-blind (DB) period followed by a 5-year open-label extension (OLE), in which all pts were initially treated with OCA 5 mg daily. Serum GGT and ALP levels were assessed at baseline and every 3 months. Pts with baseline GGT ≥3.2×ULN and ALP ≥1.5×ULN were included in this analysis. Responders were defined as pts with GGT < 3.2×ULN and ALP < 1.5×ULN. *P*-values for comparing treatments were obtained via Cochran-Mantel-Haenszel test. **Results:** In the DB intention-to-treat (ITT) set (N = 203), the proportion of responders increased over time in both OCA arms through DB Month 12 vs placebo, with the highest responder rates observed in the OCA 10 mg arm (Figure). In the OCA titration arm, 17% (11/66) were responders at DB Months 9 and 12. In the OCA 10 mg arm, the highest responder rate was observed at DB Month 9 (31% [21/68]), followed by DB Month 12 (26% [18/68]). One responder was observed in the placebo arm at DB Months 6 and 9; the comparisons of both OCA arms vs placebo reached significance ($P < 0.05$) at each post-baseline 3-month time point. In the OLE ITT set (N = 119), the proportion of responders generally increased over time, ranging from 16% (19/118) at DB Month 3 to 38% (35/91) at OLE Month 51 (Figure). At OLE Month 60, 37% (17/46) were responders. **Conclusion:** Among evaluable pts treated with OCA, the proportion of GGT and ALP responders generally increased over 72 months of treatment, suggesting that OCA may have the potential to reduce GGT and ALP levels below the thresholds that are prognostic for worse clinical outcomes.

Figure. GGT/ALP responders (ie, pts with GGT <3.2×ULN and ALP <1.5×ULN) at each time point.



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Robert G. Gish – Abbott: Consultant, No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; HepQuantum: Stock – privately held company (individual stocks and stock options), No, No; Ganlantis: Stock – privately held company (individual stocks and stock options), No, No; Eiger: Stock – privately held company (individual stocks and stock options), No, No; Prodigy: Advisor, No, No; Venatorx: Consultant, No, No; Topography Health: Consultant, No, No; Pfizer: Consultant, No, No; Merck: Consultant, No, No; Janssen: Consultant, No, No; Intercept: Speaking and Teaching, No, No; HepQuant: Advisor, No, No; HepaTx: Advisor, No, No; Helios: Consultant, No, No; Gilead Sciences: Consultant, Yes, No; GLG: Consultant, No, No; Genlantis: Consultant, No, No; Genentech: Consultant, No, No; Enyo: Consultant, No, No; Eiger: Advisor, No, No; Dynavax: Consultant, No, No; Arrowhead: Consultant, No, No; Antios: Consultant, No, No; Altimmune: Consultant, No, No; Abbvie: Speaking and Teaching, No, No; Abbott: Consultant, No, No; Eisai: Consultant, No, No; Gilead Sciences: Consultant, No, No; CymaBay: Advisor, No, No; Durect: Advisor, No, No; AstraZeneca: Speaking and Teaching, No, No; BMS: Speaking and Teaching, No, No; Eisai: Speaking and Teaching, No, No; Hepquant: Stock – privately held company (individual stocks and stock options), No, No; HepaTx: Stock – privately held company (individual stocks and stock options), No, No; AngioCrine: Stock – privately held company (individual stocks and stock options), No, No; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
The following people have nothing to disclose: Alan Bonder

4546-C | EFFECTS OF THE MELD EXCEPTION POINT POLICY CHANGE ON APPROVED APPLICATIONS AND WAITLIST OUTCOMES AMONG PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS AND CIRRHOSIS

Melinda Wang, University of California, San Francisco, Jennifer C. Lai, University of California-San Francisco, San Francisco, CA and Michael Li, University of California San Francisco

Background: As the risk of adverse outcomes related to bacterial cholangitis is not reflected in the MELD score for patients with primary sclerosing cholangitis (PSC), transplant centers can apply for MELD exception points for PSC patients meeting certain criteria. In June 2021, new National Liver Review Board (NLRB) guidance with more lenient criteria for PSC patients with a history of bacterial cholangitis was implemented. We sought to characterize the effect of this policy change on application acceptance rates and waitlist outcomes among patients with PSC. **Methods:** Patients with a primary diagnosis of PSC in the Standard Transplant Analysis and Research (STAR) files 20 months before and after the policy change were included in this study. MELD exception applications for cholangitis were defined as those classified as "Other" in the STAR files and petitions for other reasons such as cholangiocarcinoma or hepatocellular carcinoma were excluded. Covariates associated with MELD petition denial were identified using logistic regression, and survival analysis was used to assess time to a composite outcome of waitlist death or dropout **Results:** Overall, 1330 and 791 PSC patients were listed before and after the policy change, respectively, and 232 (11%) reached the composite outcome. There was no difference in time to waitlist death or dropout comparing pre- vs post-policy change patients (aHR 0.89, 95%CI 0.65-1.21, p = 0.44). 61 patients had exception applications submitted prior to the policy change compared to 60 after. There was no difference in number of total exception applications submitted per patient (median 1 [IQR 1, 3] vs 2 [1, 2] applications, p = 0.60), and there was no difference in time to waitlist death or dropout comparing the patients with exception applications submitted pre- vs post-policy change (HR 1.13, 95%CI 0.32-4.02, p = 0.85). However, the post-policy change period was associated with decreased odds of application denial (aOR 0.59, 95%CI 0.35-0.98, p = 0.04). **Conclusion:** Our findings suggest that the MELD exception policy change for PSC has made submitted applications more likely to be accepted. The change did not impact waitlist outcomes in patients who had exception applications submitted, though longer follow-up time is needed for further investigation. The policy change also did not affect waitlist outcomes among all listed PSC patients, likely due to the small proportion of patients who ever had a MELD exception application submitted.

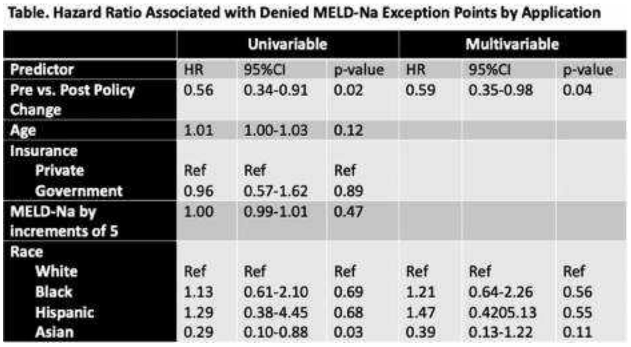
Table. Hazard Ratio Associated with Denied MELD-Na Exception Points by Application

	Univariable			Multivariable		
Predictor	HR	95%CI	p-value	HR	95%CI	p-value
Pre vs. Post Policy Change	0.56	0.34-0.91	0.02	0.59	0.35-0.98	0.04
Age	1.01	1.00-1.03	0.12			
Insurance						
Private	Ref	Ref	Ref			
Government	0.96	0.57-1.62	0.89			
MELD-Na by increments of 5	1.00	0.99-1.01	0.47			
Race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.13	0.61-2.10	0.69	1.21	0.64-2.26	0.56
Hispanic	1.29	0.38-4.45	0.68	1.47	0.4205.13	0.55
Asian	0.29	0.10-0.88	0.03	0.39	0.13-1.22	0.11

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The following people have nothing to disclose: Melinda Wang, Michael Li

4547-C | EFFICACY, SAFETY AND TOLERABILITY OF VOLIXIBAT IN PATIENTS WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY: A CASE SERIES OF 4 PATIENTS

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Background: Intrahepatic cholestasis of pregnancy (ICP) is the most common hepatic disorder that presents during pregnancy involving cholestatic pruritus, elevated serum bile acids (sBA), and increased risk of adverse perinatal outcomes. Volixibat (VLX) is a minimally absorbed ileal bile acid transporter (IBAT) inhibitor that interrupts the enterohepatic recirculation. IBAT inhibitors in patients with ICP have never been characterized. Herein, we describe 4 ICP patients treated with VLX under the OHANA trial (NCT04718961). **Methods:** Patients with ICP, sBA > ULN, and pruritus were treated with open-label VLX 20mg or 80mg BID until delivery, with dose modifications permitted for tolerability. Daily pruritus scores (Adult ItchRO 0-10 scale; 0 = no itch to 10 = worst possible itch), sBA, liver enzymes, hematology, perinatal outcomes and treatment-emergent adverse events (TEAEs) were assessed. **Results:** Over 1,000 patients were invited to participate. 26 were screened and 4 patients enrolled; small numbers were primarily due to patient reticence for trial participation in pregnancy or not meeting criteria to screen (68.2%) or withdrawal of consent (22.7%). Two patients initiated VLX at 80mg BID; the other two started at 20mg BID. Baseline pruritus scores were 2.2, 5.3, 7.0 and 7.3, with respective peak sBA levels prior to the first VLX dose of

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

8.9, 111.7, 9.1, and 41.2 μmol/L. Treatment duration varied from 1 week to 7 weeks. All patients experienced reductions in pruritus from Baseline regardless of VLX dose with intermittent relief coinciding with resumption of dosing where doses were interrupted. sBA nadir values all reached < 6 μmol/L following VLX. No clinically meaningful changes in liver enzymes or hematology parameters were observed. All patients had healthy live births (at weeks 34, 35 and two to term). The most frequent TEAEs were gastrointestinal (GI) in nature and mild to moderate in severity. Three of 4 patients experienced diarrhea and/or abdominal cramping leading to dose reduction, treatment interruption and/or early discontinuation. One patient tolerated treatment until delivery with no dose modifications due to AEs. **Conclusion:** VLX demonstrated improvements in pruritus and sBA in 4 patients with ICP, signaling proof of concept in this disease. However, studies in pregnancy are inherently difficult to enroll as shown in this trial. These data warrant further research.

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Catherine Williamson – Mirum Pharmaceuticals, Inc: Consultant, Yes, No; GSK: Consultant, No, Yes;

The following people have nothing to disclose: Sophia Stone, Baha Sibai

4548-C | HIGH RECURRENCE RATE OF PRIMARY SCLEROSING CHOLANGITIS AFTER LIVER TRANSPLANTATION IN A SYSTEMATIC EVALUATION

Lise Katrine Engesæter[1,2,3,4], Henrik Mikael Reims[5], Krzytof Grzyb[5], Andreas Abildgaard[6], Ida Bjørk[6], Tom H. Karlsen[1,2,3,4], Kristian Bjoro[1,2,4], Kirsten M. Boberg[1,2,4], Johannes R. Hov[1,2,3,4] and Espen Melum[1,2,3,4,7], (1)Norwegian PSC Research Center, (2) Institute of Clinical Medicine, (3)Research Institute of Internal Medicine, (4)Section of Gastroenterology, (5) Department of Pathology, (6)Department of Radiology, (7)Hybrid Technology Hub, Center of Excellence

Background: Primary sclerosing cholangitis (PSC) recurrence after liver transplantation (LTX) is a common clinical problem with large variation in reported rates that could be dependent on follow-up strategies. In this study, we reevaluated magnet resonance cholangiography (MRC) examinations and liver biopsies to provide accurate data up to 15 years after transplantation. **Methods:** Patients listed for LTX with PSC in Norway between 1988-2016 were identified. MRC scans and liver biopsies performed up to 2018 were re-evaluated. Between 2007-2017, routine liver biopsies and MRC were planned at 1, 3 and 5 years and then every 5 years. MRC scans were evaluated by two abdominal radiologists and liver biopsies by two liver pathologists, all blinded for clinical information except for the post-transplant state. Recurrent PSC (rPSC) was defined by cholangiographic findings or histology according to the Graziadei criteria. **Results:** Two-hundred and twenty-seven PSC patients were transplanted in the study period (76% male, 81% IBD). Median age at transplantation was 43 years (range 16-72). One-hundred and eighty (79%) had at least one available MRC scan and/or liver biopsy. Median follow-up after transplant was 3.3 years (range 0-21). During follow-up, 115 (51%) fulfilled the criteria for rPSC (median 5.1 y post-LTX) at either a routine follow-up or examination due to clinical indication. Patients with hepatic artery complications (n = 29, 13%), a sole anastomotic stricture or early bile duct strictures (n = 6, 3%) were censored in survival analyses and not given a diagnosis of rPSC. In a cross-sectional analysis of patients with at least one year follow-up without graft loss (n = 211), 27 patients (13%) fulfilled rPSC criteria on at least one routine MRC or biopsy. At three years 27% (53/194) had rPSC, at five years 43% (72/164), at 10 years 55% (56/97) and at 15 years follow up 45% (19/42). A diagnosis of rPSC before or at the 1-year follow-up was associated with an increased risk of retransplantation or death (hazard ratio [HR] 7.4, 95% CI 3.3 to 16.6), while in a similar analysis of patients reaching the 5-year follow-up without graft loss, the HR for re-LTX or death in those with rPSC was 3.9 (95% CI, 2.0-7.6). **Conclusion:** Systematic reevaluation of MRC and histology at a large single center suggests that rPSC occurs in about half of the transplanted PSC patients. An early diagnosis of rPSC has a particularly strong impact on retransplantation-free survival.

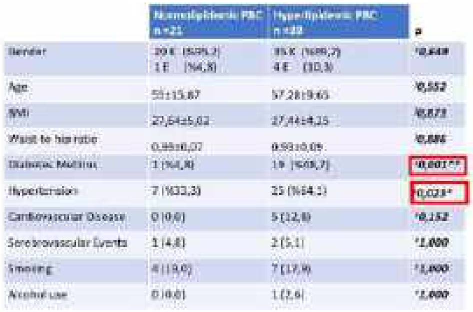
Disclosures: The following people have nothing to disclose: Lise Katrine Engesæter

Disclosure information not available at the time of publication: Henrik Mikael Reims, Krzytof Grzyb, Andreas Abildgaard, Ida Bjørk, Tom H. Karlsen, Kristian Bjoro, Kirsten M. Boberg, Johannes R. Hov, Espen Melum

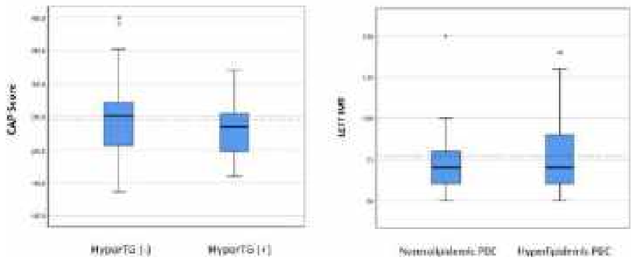
4549-C | HYPERLIPIDEMIA, ATHEROSCLEROSIS AND HEPATOSTEATOSIS IN PRIMARY BILIARY CHOLANGITIS: WHAT IS THE RISK?★

Aylin Coskun, Aslı Çifcibaşı Örmeci, Bilgen Çavuş, Ibrahim Volkan Senkal, Edanur Karapınar, Arzu Poyanlı, Filiz Akyuz, Kadir Demir, Fatih Besisik and Sabahattin Kaymakoglu, Istanbul University, Istanbul Faculty of Medicine

Background: Primary biliary cholangitis is a chronic autoimmune cholestatic liver disease that mainly affects women. Cholestasis and also PBC-specific mechanisms result in hypercholesterolemia in up to %76 of patients. Because cardiovascular diseases are the most common cause of death worldwide, hyperlipidemia in PBC has a huge importance. Additionally, mild hypertriglyceridemia may be seen in PBC and it is important to know whether this situation leads to hepatosteatosis. This study aims to establish hyperlipidemia, subclinical atherosclerosis parameters, and hepatosteatosis degrees in PBC. **Methods:** This is a single-center cross-sectional study, 160 PBC patient files have been examined in Istanbul Faculty of Medicine. Those with overlap syndrome and non-volunteers were excluded from the study. A total of 60 PBC patients and a control group of 44 over 18 years old without chronic liver disease were included. We noted demographic features, BMIs, Waist-to hip ratios, lipid profiles, UDCA responses, APRI scores, fibrosis, and CAP scores measured with Fibroscan. Radiologist measured intima-media thickness and plaque presence with bilateral carotid Doppler ultrasonography. **Results:** A total of 104 people were categorized into four groups due to their lipid status. We defined hypercholesterolemia as the use of antihyperlipidemic treatment or total cholesterol level higher than 6.2 mmol/L. Hyperlipidemic PBC (n = 39), normolipidemic PBC (n = 21), hyperlipidemic control (n = 12), and normolipidemic control (n = 32) groups were compared. IMT values (0.75 ± 0.21 vs 0.78 ± 0.23) and presence of plaques (7 (33.3%) vs 14 (35.9%)) between the matched for demographic data hyperlipidemic PBC and normolipidemic PBC groups was not found to be significant. (p = 1,00) The effect of the variables on the presence of plaque is examined; Age (p = 0,001, OR: 1,187) and presence of diabetes mellitus (p = 0,003, OR: 8,412) were independent risk factors and lipid levels had no effect on the presence of plaque. Age (p = 0.001, OR: 0,006), gender (p = 0,025, OR:0,177), and BMI (p = 0,035, OR:0,009) were seen as risk factors in the regression analyses performed on IMT, the effect of lipid levels was not observed. When hyperlipidemic and normolipidemic PBC patients were compared, no significant difference was found between Apri scores (p = 0,190), Fibrosis levels (p = 0,551), CAP scores (p = 0,099), presence of cirrhosis (p = 1,00) and UDCA responses (p = 0,694). When the PBC group was separated according to the presence of hypertriglyceridemia, there was no difference in CAP scores between the two groups.(p = 0,361) **Conclusion:** In this study, hypercholesterolemia which is frequently observed in PBC, was not associated with subclinical atherosclerosis parameters. It is also observed that hypertriglyceridemia did not cause an increase in hepatosteatosis. Patients should be followed up in terms of cardiovascular risk, taking into account additional comorbid diseases and age.



	Normolipidemic PBC n=21	Hyperlipidemic PBC n=39	p
Gender	20 K (%95,2) 1 E (%4,8)	35 K (%89,7) 4 E (10,3)	*0,648
Age	55±15,87	57,28±9,65	*0,552
BMI	27,64±5,02	27,44±4,25	*0,873
Waist to hip ratio	0,95±0,07	0,93±0,09	*0,886
Diabetes Mellitus	1 (%4,8)	19 (%48,7)	*0,001**
Hypertension	7 (%33,3)	25 (%64,1)	0,023*
Cardiovascular Disease	0 (0,0)	5 (12,8)	*0,152
Serebrovascular Events	1 (4,8)	2 (5,1)	*1,000
Smoking	4 (19,0)	7 (17,9)	*1,000
Alcohol use	0 (0,0)	1 (2,6)	*1,000



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4550-C | IDENTIFYING DRIVERS OF PATIENT (PT) PREFERENCE IN THE TREATMENT OF PRURITUS IN PRIMARY BILIARY CHOLANGITIS (PBC)

Anna Halliday[1], Helen T Smith[1], Dorothy Szinay[2], Andy Walker[1], Keila Meginnis[3], Sebastian Heidenreich[2] and Jaein Seo[4], (1)GSK, London, UK, (2)Evidera, London, United Kingdom, (3)Evidera, Glasgow, United Kingdom, (4)Evidera, Bethesda, MD

Background: Pruritus is common in PBC and can significantly impact pts' quality of life (QoL). Cholestyramine is recommended as the first-line treatment option for pruritus in PBC, but tolerability, inconvenient administration, and limited efficacy data restrict its use. Pt-focused drug development can help address this unmet need, but an understanding of pts' perspectives on pruritus and treatments is required. This study

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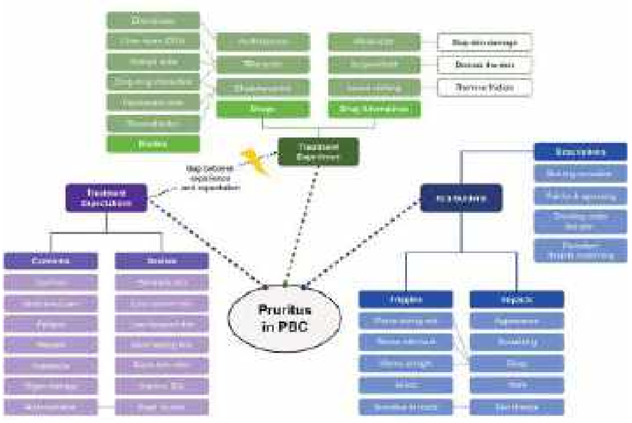
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

conducted semi-structured qualitative pt interviews to explore pts' experiences, expectations, and concerns with regards to pruritus and treatments. **Methods:** Semi-structured virtual interviews were designed following a literature review and conducted with pts from the USA, Germany, UK, and Italy. Eligible pts self-reported a PBC diagnosis and had a worst itch score of ≥ 4 on a 0–10 numerical rating scale (NRS) in the past 2 months. Interviews had four parts: 1) pruritus experience, 2) treatment desires and concerns, 3) treatment experience, 4) hypothetical choice questions that required pts to make trade-offs between two options. Responses were used in an inductive thematic analysis and visually summarized. **Results:** Ten pts per country were interviewed ($N = 40$); most were female (78%) and mean (standard deviation) age was 52.5 (15.2) years. For 53% ($n = 21$), pruritus had started within the last 3 years. On the NRS, pts rated their pruritus over the last 2 months on average as mean 5.4 (range 2–10), and worst itch as mean 7.1 (range 4–10). Key themes that emerged from pt discussions were visualized with a concept map (Figure). Pruritus was widespread over pts' bodies, persistent despite scratching, and described as 'crawling', 'burning' and 'nettles'. Pruritus impacted social interactions, sleep quality, appearance, emotional stability, and work productivity. Many pts wished for complete resolution, but primarily wanted treatment to reduce pruritus severity (60%; $n = 23$). Of those who had ever received cholestyramine ($n = 12$), 62% reported a repulsive taste and texture; 50% mentioned concerns about interactions between cholestyramine and PBC medication. From five potential pruritus medication side effects, diarrhea and nausea were of greatest concern. **Conclusion:** Pruritus impacts QoL in PBC in several ways and the limitations of existing treatments mean pts would welcome alternative options. Future research will establish the relative importance to pts of treatment aspects such as administration, benefits, and tolerability.

Funding: GSK (218705).

Figure: Concept map that summarizes the themes and concepts that emerged from discussions with pts, capturing aspects of itch burden, treatment experience, and treatment expectations



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Disclosures: Anna Halliday – GSK: Employee, Yes, No; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No; Novartis: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;
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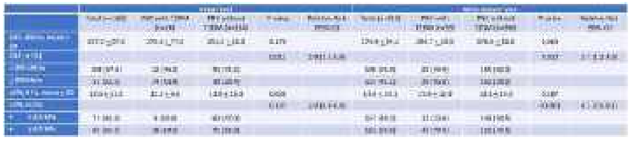
4551-C | IMPACT OF TYPE 2 DIABETES MELLITUS ON LIVER FIBROSIS AND HEPATIC STEATOSIS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: A LONGITUDINAL STUDY

Elizabeth Williams, Craig Lammert and Raj Vuppalanchi, Indiana University School of Medicine

Background: Type 2 diabetes mellitus (T2DM) is strongly associated with hepatic steatosis. However, the impact of T2DM on the progression of liver fibrosis and hepatic steatosis in patients with primary biliary cholangitis (PBC) requires further investigation. This study aims to explore the influence of T2DM on the development of hepatic steatosis and liver fibrosis in patients with PBC, both at their initial visit and during follow-up. **Methods:** A retrospective analysis was conducted to identify PBC patients at Indiana University Health using ICD9 and ICD10 codes to identify a cohort of 570 patients through electronic health record query. Data was collected through manual review of EHR after confirmation of the PBC diagnosis, as per the AASLD criteria. The median follow-up duration was 3.6 years (interquartile range: 1.6-6.6). T2DM status was determined based on a hemoglobin A1c > 6.5% or the use of anti-diabetic medications at any point during the study. FibroScan assessments were performed to evaluate the extent of hepatic steatosis and liver fibrosis. Hepatic steatosis was defined as a controlled attenuation parameter (CAP) greater than 285 dB/m, while clinically significant liver fibrosis was defined by a liver stiffness measurement (LSM) exceeding 8.5 kPa. Data comparisons were analyzed using t-tests and chi-squared tests. **Results:** Among the participants, 160 individual's had a FibroScan at their initial visit, and 319 of them had at least one FibroScan assessment during follow-up. At the initial visit, patients with both PBC and T2DM were more likely to have NAFLD (CAP > 285 dB/m) compared to those without T2DM (54% vs. 28%, p-value 0.011, relative risk [RR] 2.9, 95% confidence interval [CI] 1.3-6.9) (Table 1). The degree of liver fibrosis at the initial visit was similar between PBC patients with and without T2DM (p-value = 0.127) (Table 1). However, at the most recent follow-up, patients with both PBC and T2DM had a significantly higher prevalence of hepatic steatosis (57% vs. 38.0%, p-value 0.012, RR 2.1, 95% CI 1.2-3.9) and clinically significant liver fibrosis (77% vs. 46%, p-value < 0.001, RR 4.1, 95% CI 2.1-8.1) (Table 1). **Conclusion:** Among patients with PBC, the presence of T2DM at the initial visit is associated with an increased likelihood of hepatic steatosis, but not clinically significant liver fibrosis. However, over time, patients with PBC and T2DM have a significantly higher risk of developing both hepatic steatosis and clinically significant fibrosis compared to those without T2DM.

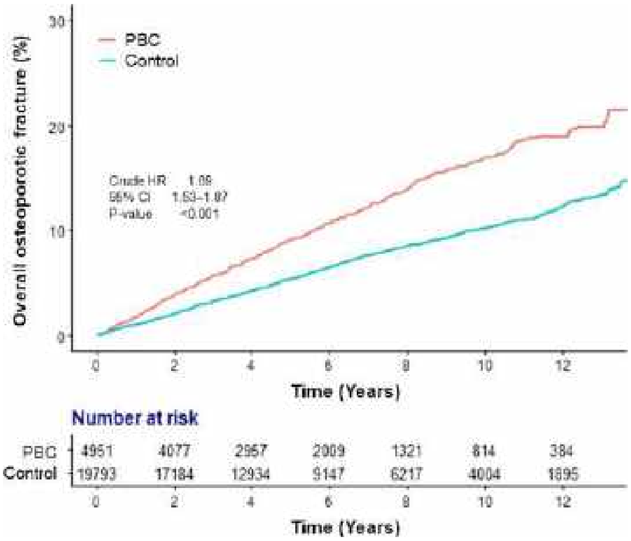


Disclosures: The following people have nothing to disclose: Elizabeth Williams, Craig Lammert, Raj Vuppalanchi

4552-C | INCREASED RISK OF OSTEOPOROTIC FRACTURE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

Jihye Lim[1], *Ye-Jee Kim*[2], *Sehee Kim*[2] *and Jonggi Choi*[2], *(1)Yeouido St. Mary's Hospital, (2)Asan Medical Center, Seoul, Korea, Republic of (South)*

Background: Patients with primary biliary cholangitis (PBC) have suspicions of having increased risk of osteoporosis and osteoporotic fracture. However, large-scale studies have been restricted due to low incidence of PBC and osteoporotic fracture. This study aimed to investigate the relationship between PBC and the likelihood of osteoporotic fracture analyzing with a long term and nationwide real-world data. **Methods:** The claims data from the Korean National Health Insurance Service (NHIS) between 2007 and 2020 had been analyzed. A total of 4,951 patients with PBC were included in the study and randomly matched with a control group of 19,793 individual's based on age, sex, and duration of follow-up, using a 1:4 ratio. Fractures of the vertebrae, hip, distal radius, and proximal humerus were defined as osteoporotic fracture. The incidence rate (IR) and hazard ratio (HR) were obtained to reveal the impact of PBC on osteoporotic fracture. **Results:** Over a median follow-up period of 5.37 years, PBC cohort experienced a total of 524 osteoporotic fractures with an IR of 18.59 per 1,000 person years which was notably higher than that of matched cohort (IR of 10.98 per 1000 person years). After adjustments with clinical factors including age, sex, socioeconomic status, comorbidities, decompensated cirrhosis, body mass index, smoking, alcohol, exercise, and health checkup, PBC elevates the risk of osteoporotic fracture by 1.63-fold (95% confidence interval [CI], 1.20–2.22, P = 0.002). Vertebrae was particularly susceptible to osteoporotic fracture in PBC patients with adjusted hazard ratio of 2.23 (95% CI, 1.04–4.76). In gender-specific analysis, the risk of osteoporotic fractures was found to be 2.53 times higher in male PBC patients (95% CI, 1.84–3.48) and 1.59 times higher in female PBC patients (95% CI, 1.41–1.79) than non-PBC male and female control, respectively. **Conclusion:** Patients diagnosed with PBC had a higher risk of experiencing osteoporotic fractures when compared to their matched controls. Considering the related morbidity and mortality of osteoporotic fracture, it is imperative to be aware of osteoporotic fracture risk and take preventive measures in PBC population.



Disclosures: The following people have nothing to disclose: Jihye Lim, Ye-Jee Kim, Sehee Kim, Jonggi Choi

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

4553-C | INCREASING INCIDENCE OF PRIMARY BILIARY CHOLANGITIS IN THE NETHERLANDS

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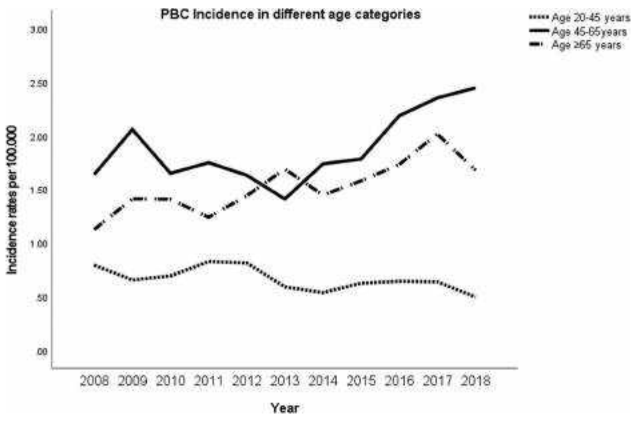
Background: Large population-based studies are needed to gain more insight in the epidemiology of primary biliary cholangitis (PBC). We assessed the incidence of PBC in the Netherlands over time through the nationwide Dutch PBC Cohort Study (DPCS). **Methods:** DPCS is a retrospective registry in all Dutch hospitals in which every identifiable patient with an established PBC-diagnosis in the Netherlands from 1990 onwards is included. Comprehensive and systematic case identification (based on diagnosis/treatment codes, antimitochondrial antibodies test results, and locally available registers based on liver disease diagnosis or outcome) was performed by two dedicated investigators of the research team according to local possibilities. The current incidence assessment was restricted to the time period between January 2008 (general introduction of electronic patient records) and December 2018 (the year prior to the start of data collection). Incidence rates (per 100.000 persons) and annual changes were estimated using Poisson regression. Incidence differences in sex and age groups (20-45, 45-65, and ≥65 y) were calculated with rate ratios. The yearly size of the general population was retrieved from the Dutch Central Bureau of Statistics. **Results:** In total, 4370 patients with a confirmed PBC diagnosis were identified in all 71 hospitals in the Netherlands, of which 2187 were diagnosed between 2008 and 2019. Mean age at diagnosis was 58.7 (SD 12.6) years and 1925 (88%) patients were female. The median yearly incidence rate was 1.33 (IQR 1.29-1.58) per 100.000 persons. The incidence rate ratio (IRR) adjusted for age and year, was 8.81 (95%CI 7.74-10.03, $p < 0.001$) for female patients compared to male patients. Patients between 45-65 years and ≥65 years showed an adjusted IRR of 3.90 (95%CI 3.43-4.42, $p < 0.001$) and 3.86 (95%CI 3.38-4.42, $p < 0.001$) compared to patients between 20-45 years (Figure). Over time, the adjusted annual IRR was 1.03 (95%CI 1.01-1.04, $p < 0.001$). Similar annual IRRs were shown for patients between 45-65 years (IRR 1.03, 95%CI 1.02-1.05, $p < 0.001$) and for patients ≥65 years (IRR 1.04, 95%CI 1.02-1.07, $p = 0.001$). The annual IRR of patients between 20-45 years was 0.97 (95%CI 0.93-1.00, $p = 0.07$). **Conclusion:** Based on this nationwide registry including every identifiable patient with PBC in the Netherlands, the overall incidence of PBC slowly increased over the recent years. However, in the Dutch population < 45 years of age the incidence of PBC remained stable.



Disclosures: Harry L. A. Janssen – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GlaxoSmithKline: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named

Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

investigator even if that individual's institution receives the research grant and manages the funds), No, No; Janssen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Vir Biotechnology Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Aligos: Consultant, No, No; Gilead Sciences: Consultant, No, No; GlaxoSmithKline: Consultant, No, No; Janssen: Consultant, No, No; Roche: Consultant, No, No; Vir Biotechnology Inc.: Consultant, No, No; Precision Biosciences: Consultant, No, No;

The following people have nothing to disclose: Rozanne C. De Veer, Ulrich H. Beuers, Michael Klemt-Kropp, Cyriel Y. Ponsioen, Gijs J. De Bruin, Bettina E. Hansen

Disclosure information not available at the time of publication: Maria C. Van Hooff, Ellen Werner, Joost P. H. Drenth, Frans J. C. Cuperus, Bart Van Hoek, Johannes T. Brouwer, Suzanne Van Meer, Robert C. Verdonk, Hajo J. Flink, Jan M. Vrolijk, Tom J. Gevers, Martijn Ter Borg, Khalida Soufidi, Femke Boersma, Henk-Marijn De Jonge, Frank H.J. Wolfhagen, Lubburtus C. Baak, Suzanne L. Onderwater, Jeroen D. Van Bergeijk, Paul G. Van Putten, Rob P. R. Adang, Maria N. Aparicio-Pages, Wink De Boer, Frank Ter Borg, Hanneke Van Soest, Nicole S. Erler, Adriaan J. Van der Meer

4554-C | INDUCED REGULATORY T CELLS VIA CYCLIN-DEPENDENT KINASE INHIBITION FROM PATIENTS WITH PRIMARY BILIARY CHOLANGITIS ARE SUPPRESSIVE AND STABLE IN AN INTERFERON ENRICHED ENVIRONMENT AND ARE EPIGENETICALLY DIFFERENT FROM NATURAL REGULATORY T CELLS.

Vincenzo Ronca[1,2,3,4], Kayani Kayani[1,2], Scott Davies[1], Masaya Arai[2], Yamami Nakamura[2], Natsumi Okamoto[2], Norisha Mikami[2], Naganari Ohkura[2], Jason White[2], Naomi Richardson[1], Pietro Invernizzi[3], Shimon Sakaguchi[2] and Ye Htun Oo[1], (1)University of Birmingham, Birmingham, United Kingdom, (2)Osaka University, (3)University of Milano-Bicocca, (4) European Reference Network on Hepatological Diseases (ERN RARE-LIVER)

Background: The use of autologous regulatory T cells (Treg) as cell therapy in autoimmune disease has been proposed. Potential limitation of such approach lies on the dysfunction and/or instability that these cells might have in patients with autoimmune conditions. Primary biliary cholangitis (PBC), is a chronic, cholestatic liver disease. A reduction in number, lineage stability and functionality of Tregs has been observed in patients with PBC. We aimed to produce stable and function induced Tregs (SFiTregs) from PBC-derived effector CD4 cells in vitro, via cyclin-dependent kinase (CDK8/19) inhibition and compare their epigenetic profile, their lineage stability and suppressive function with natural Tregs in patients with PBC **Methods:** CD4+ T cells were magnetically enriched from peripheral blood mononuclear cells (PBMCs) of PBC patients. CD4+T cells were activated through TCR stimulation by CD3+ activator beads and cultured in presence of AS2863619 (4-[1-(2-methyl-1H-benzimidazol-5-yl)-1H-imidazo[4,5-c] pyridin-2-yl]-1,2,5-oxadiazol-3-amine dihydrochloride) and IL-2. FoxP3, CTLA4 and Helios expression was assessed in SF-iTregs via flow cytometry and by bisulphite sequencing pre- and post-activation in presence of Th1 polarising cytokines. The functionality of Tregs and SF-iTregs was investigated by in vitro suppression assays using CellTrace Violet dye-labelled effector T-cells, CD3 activator beads and IL-2. For the all three cell populations, nTreg, Tnaive, SF-iTregs, Foxp3 gene locus for STAT5 binding, H3K27ac, and chromatin status was characterized by Chromatin immunoprecipitation followed by sequencing (ChIP-seq) and assay for transposase-accessible Chromatin using sequencing (ATAC-seq). **Results:** The chemical inhibition of cyclin-dependent kinase 8/19 and the deprivation of CD28 signal induced DNA hypomethylation in Treg signature genes. We obtained a 100-fold increase in the cell number and the product was suppressive and pure ($>90\%$ FOXP3 expressing cells). Furthermore, the SFiTregs were found to be more stable compared with nTreg when cultured for 6 days in Th1 polorising conditions. ATAC-seq and ChIP-seq confirmed that Treg specific epigenetic changes in the SF-iTregs were comparable to nTreg at the baseline. However, differentially accesible regions of SF-iTregs differ significantly when compared to nTreg. **Conclusion:** We applied a novel technique to generate abundant, functional regulatory T cells from peripheral T CD4+ cells in patients with PBC. This approach would allow us to overcome the potential limit of using autologous ex-vivo expanded Tregs based therapy and generate a more stable product to infuse in the inflamed envoirment typical of the liver of PBC patients.

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Pietro Invernizzi – Advanz: Consultant, Yes, Yes;

The following people have nothing to disclose: Ye Htun Oo

Disclosure information not available at the time of publication: Kayani Kayani, Scott Davies, Masaya Arai, Yamami Nakamura, Natsumi Okamoto, Norisha Mikami, Naganari Ohkura, Jason White, Naomi Richardson, Shimon Sakaguchi

4555-C | IS AMA-NEGATIVE PRIMARY BILIARY CHOLANGITIS MORE COMMON IN BLACK PATIENTS?

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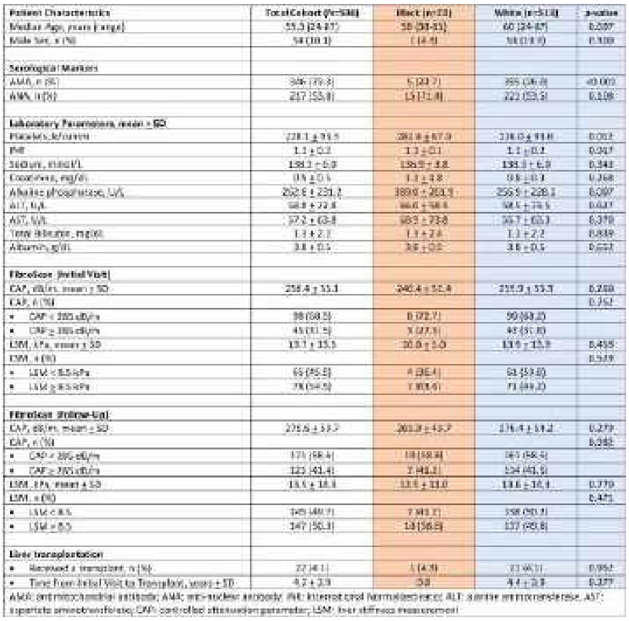
Background: Primary biliary cholangitis (PBC) is predominantly observed in middle-aged White women, with rare occurrences reported in the Black population. This study aimed to identify any disparities in clinical, biochemical, and elastography between Black and White patients diagnosed with PBC. **Methods:** A retrospective analysis was conducted through electronic health records (EHR) query using ICD 9 and ICD10 codes at Indiana University Health to identify 536 individual's with a confirmed diagnosis of PBC, as per the AASLD criteria. Laboratory data were collected from their initial visit through manual EHR. For patients who underwent vibration-controlled transient elastography using FibroScan, the presence of hepatic steatosis was defined as a controlled attenuation parameter (CAP) greater than 285 dB/m, and clinically significant liver fibrosis was determined by a liver stiffness measurement (LSM) exceeding 8.5 kPa. T-tests and chi-squared analyses were employed to compare differences between Black and White patients with PBC. **Results:** The median follow-up duration was 3.7 years (interquartile range: 1.7-6.9). Among the PBC cohort, 23 patients (4.2%) were Black. Black patients with PBC were significantly less likely to test positive for anti-mitochondrial antibody (AMA) compared to White patients with PBC (23% vs. 76%, $p\text{-value} < 0.001$) (Table 1). Additionally, Black patients exhibited significantly higher alkaline phosphatase levels than White patients (389 ± 262 U/L vs. 257 ± 228 U/L, $p\text{-value} = 0.007$) (Table 1). A FibroScan evaluation was conducted during the initial visit for 11 Black and 132 White PBC patients, while 17 Black and 275 White patients underwent FibroScan at some point during their follow-up. Black and White patients with PBC displayed similar degrees of hepatic steatosis, liver fibrosis, and rates of liver transplantation (Table 1). **Conclusion:** This study indicates that Black patients with PBC are significantly less likely to test positive for AMA. Therefore, it suggests a lower threshold for performing a liver biopsy in Black patients who exhibit elevated alkaline phosphatase levels, signs of liver disease, and suspected PBC.



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The following people have nothing to disclose: Elizabeth Williams, Craig Lammert, Raj Vuppalanchi

4556-C | LANDSCAPE OF PERIPHERAL IMMUNE CELLS AND IDENTIFICATION OF BIOMARKERS FOR PRIMARY BILIARY CHOLANGITIS

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Background: Primary biliary cholangitis (PBC) is an autoimmune liver disease caused by the immune system attacking the bile ducts. Detailed mechanisms of autoimmunity and the roles of immune cells in PBC are largely unknown. Diagnosis of PBC is based on blood tests for anti-mitochondrial antibody (AMA); however, some PBC patients are negative for AMA and invasive liver biopsy testing is required for inconclusive cases. The current study aims to

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

determine immune cell proportions in blood samples of PBC patients and to identify novel PBC biomarkers that lead to non-invasive diagnostic blood testing. **Methods:** Human transcriptomic profiling data of blood samples (GSE119600) were obtained from Gene Expression Omnibus (GEO). Immune cell proportions in blood samples were calculated by CIBERSORTx using LM22, which is a signature matrix established for peripheral immune cells. To identify novel PBC biomarkers, differentially expressed genes (DEGs) were identified using GSE119600 data. DEGs in GSE119600 were compared to those identified in other microarray data (GSE79850 and GSE159676). Identified candidate DEGs were further analyzed for function enrichment, protein-protein interaction network, and molecular complex using R studio and Cytoscape. To evaluate the diagnostic potentials of candidate biomarkers in blood testing, receiver operating characteristic (ROC) curve analysis was performed using GSE119600 data. **Results:** In blood samples, PBC patients had elevated proportions of M0 macrophages, monocytes, neutrophils, CD4$^+$ memory T cells, and Tregs, and decreased proportions of resting NK cells and CD8$^+$ T cells compared to healthy individual's. Analysis and comparison of DEGs identified 12 candidate genes that were significantly upregulated in PBC patients. Enrichment analysis identified 5 biological functions/pathways, and these pathways, such as osteoclast differentiation, were associated with autoimmunity or PBC. ROC curve analysis for blood samples showed that one of the candidate genes, ITGAL, had good diagnostic potentials to distinguish PBC status from healthy individual's, as well as from other diseases, such as primary sclerosing cholangitis, indicating that transcriptomic analysis of ITGAL using blood samples could be a novel diagnostic approach for PBC. **Conclusion:** PBC patients have unique peripheral immune cell proportions compared to healthy donors. ITGAL could be a potential diagnostic biomarker to identify PBC status by non-invasive blood testing.

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4557-C | LIVER TRANSPLANTATION FOR PRIMARY BILIARY CHOLANGITIS IN THE U.S. IN 2008-2022

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Background: Primary biliary cholangitis (PBC) is an important cause of chronic liver disease (CLD) that can lead to advanced cirrhosis requiring liver transplantation (LT). We assessed recent trends and outcomes of liver transplant recipients with PBC in the U. **Methods:** From the Scientific Registry of Transplant Recipients (SRTR 2008-2022), we selected all adult (≥ 18 y) LT candidates and recipients with PBC, with or without hepatocellular carcinoma (HCC). **Results:** Between 2008-2022, 167,919 LT candidates with a known etiology of chronic liver disease were included in this study. Of these, 3.0% had PBC. The average number of listings for PBC per year was 321 (SD 30) in the most recent 5 years. The prevalence of PBC among LT candidates without HCC was 3.5%, changed from 4.0% (2008) to 3.5% (2014) to 2.7% (2022) (decreasing trend $p < 0.0001$). In contrast, the prevalence of PBC among candidates with HCC did not change (average 1.0%, ranging from 0.7% (2007) to 1.4% (2022); $p > 0.05$). Transplant candidates with PBC were, on average, 58 (SD 10) years old, 85% female, 70% white, 7% black, 19% Hispanic, 3% Asian, 31% college-educated, 26% employed, 57% covered by private insurance, 29% Medicare, 12% Medicaid, $< 1\%$ uninsured, and 5% were re-transplants. Additionally, 28% were obese (BMI ≥ 30), 15% with type 2 diabetes, with a mean MELD score of 23 (SD 10). Excluding those listed during the most recent two years (2021-2022), 62% of PBC candidates (60% in PBC without HCC and 73% in PBC with HCC, $p = 0.0001$) received a transplant after mean 258 (SD 382) days. Furthermore, 26% died or deteriorated on the list (27% without HCC vs. 20% with HCC, $p = 0.02$), 3% were removed from the list due to improvement, and 7% were removed for other causes. Among transplant recipients with PBC, post-transplant mortality was 7.5% at 1 year, 12.5% at 3 years, 15.7% at 5 years, 28.2% at 10 years. Over time, post-transplant mortality in PBC followed a decreasing trend: 3-year mortality was 17.2% in 2008, 12.4% in 2014, and 11.9% in 2019 (trend $p = 0.06$). In a multivariate survival model, independent predictors of post-transplant mortality in PBC included older age (adjusted hazard ratio (aHR) (95% CI) = 1.020 (1.008-1.031) per year), male sex (aHR = 1.37 (1.09-1.72)), lack of college education (aHR = 0.78 (0.63-0.95)), pre-transplant type 2 diabetes (aHR = 1.50 (1.20-1.88)), cancer (aHR = 1.36 (1.04-1.78)), receiving a re-transplant (aHR = 1.75 (1.23-

2.47)), and being on life support (aHR = 1.83 (1.35-2.48)) ($p < 0.05$) while there was no significant association of post-transplant mortality with calendar year ($p = 0.11$) as well as race/ethnicity, type of insurance coverage, obesity, MELD score, and having HCC (all $p > 0.05$). **Conclusion:** The proportion of PBC among patients in need of a LT is decreasing, potentially due to available effective treatments. Regardless of the presence or absence of HCC, patients with PBC experience high post-transplant survival.

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The following people have nothing to disclose: Maria Stepanova, Saleh A Alqahtani, Linda Henry

Disclosure information not available at the time of publication: Katherine Elizabeth Eberly, Dipam Shah, Reem Al Shabeeb, Veronica Nguyen, Janus Ong

4558-C | NETWORK ANALYSIS OF SYMPTOMS EXPERIENCED BY PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS★

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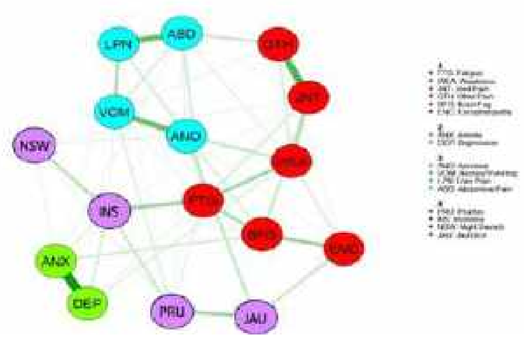
Background: Patients with primary sclerosing cholangitis (PSC) experience numerous symptoms that impact quality of life. PSC Partners Seeking a Cure developed the international "Our Voices" survey to capture the presence, severity, and impact of PSC symptoms on quality of life. We sought to identify PSC-specific symptom clusters and relationships between these symptoms to better understand the lived experience of PSC patients. **Methods:** Presence and severity of 16 symptoms potentially related to PSC were identified from the "Our Voices" survey. LASSO regularized partial correlation network analyses were performed to model unique interactions between symptoms. The primary analysis utilized symptoms reported within the past 6 months of survey completion. Secondary analyses included active symptoms and symptoms at their worst. Expected influence, which accounts for both positive and negative associations and assesses the nature and strength of a node's cumulative influence within a network, was computed for all symptoms in each network. The Spinglass algorithm was employed to identify symptom communities. **Results:** Among 970 total participants, 54% were women, most were white (70%), and 70% had inflammatory bowel disease (IBD). 88% of patients reported experiencing symptoms. Four dominant communities were identified across networks including psychological symptoms (anxiety, depression), gastrointestinal symptoms (anorexia, nausea/vomiting, liver pain, abdominal pain), cholestasis-related symptoms (pruritus, insomnia, night sweats, jaundice), and global symptoms (fatigue, weakness, joint pain, other pain, brain fog, encephalopathy) (Figure). Of the 16 PSC symptoms, fatigue and weakness consistently had the greatest expected influence across the multiple networks generated in the primary and secondary analyses. On subgroup analysis, symptoms with the strongest influence among patients with and without IBD were similar (IBD: fatigue and insomnia; no IBD: fatigue and anorexia). **Conclusion:** Our analyses suggest that the complex relationships between PSC symptoms organize into four dominant, clinically-relevant clusters. Fatigue and weakness emerged as the symptoms with the strongest influence across the primary and secondary analyses. Our data emphasize the co-occurring nature of PSC symptoms, identify highly influential symptoms, and highlight the need to develop patient-reported outcome measures to assess changes in these key symptoms in clinical trials.

Figure. LASSO regularized partial correlation network of 16 symptoms reported in the past 6 months using communities determined by Spinglass algorithm



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Jennifer C. Lai – Novo Nordisk: Advisor, No, No; Genfit: Consultant, No, No; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Vir: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gore: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Flagship Pioneering: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Melinda Wang, Amy M. Shui, Joanne Hatchett, Ruth-Anne Pai, Rachel Gomel, Mary Pressley Vyas, Sarah Curup Callif, Ricky Safer, Michael Li

4559-C | NEXT GENERATION HEPQUANT TESTS PREDICT CLINICAL OUTCOME IN PRIMARY SCLEROSING CHOLANGITIS

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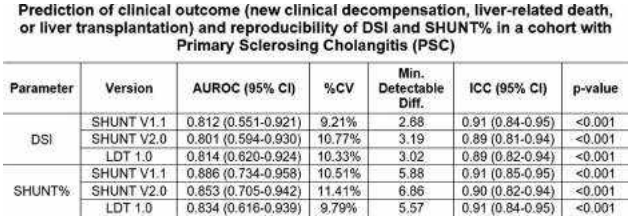
Background: We quantified liver function and portal-systemic shunting in primary sclerosing cholangitis (PSC) using V1.1 of the HepQuant SHUNT test (Everson et al. 2007) and NEXT GENERATION tests (V2.0 and LDT 1.0) based on a compartmental model (McRae et al. 2022). We compared test results to standard laboratory tests and clinical models in the prediction of clinical outcome. **Methods:** Forty-seven patients, spanning the clinical spectrum of PSC, underwent baseline tests. Forty-six were retested at baseline for reproducibility by intraclass correlation coefficient (ICC). The cohort was followed prospectively for clinical outcomes, and forty were retested after 1 year. For each test, 20 mg of [24-13C]cholate (13C-CA) was injected intravenously and [2,2,4,4-2H]cholate (d4-CA) was administered orally. Blood was sampled at 0, 5, 20, 45, 60, and 90 minutes for serum cholate concentrations. In V1.1, clearances were calculated from the measured 13C-CA and d4-CA concentrations. The clearances for

V2.0 were derived from model parameters fit to the 13C- and d4-CA concentrations at 20 and 60 minutes and for LDT 1.0, only d4-CA concentrations at 20 and 60 minutes. A disease severity index (DSI) and portal-systemic shunt (SHUNT%) were calculated. **Results:** The within-subject reproducibility was excellent and comparable across Test versions with ICCs $\geq$0.89 for DSI and SHUNT%. Three subgroups of progressors, slow (n = 28), moderate (n = 16), and rapid (n = 3), were suggested from age-related degree of hepatic impairment. Rapid progressors were characterized by high SHUNT% at relatively young age. Moderate/rapid progressors had higher DSI, SHUNT%, and lower Portal HFR and hepatic reserve, worse laboratory tests, higher levels of IL-6, IL-8, and GM-CSF, and were more likely to experience clinical outcome compared to slow progressors. In univariate analysis SHUNT% was the strongest single predictor of new clinical decompensation, liver-related death, or liver transplantation (n = 13 with clinical outcomes, AUROC 0.886 for V1.1, 0.853 for V2.0, and 0.834 for LDT 1.0) with no significant differences in operating characteristics between Test versions. **Conclusion:** HepQuant's Test parameters of liver function and physiology correlate with laboratory and clinical evidence of PSC disease severity, identify progressor groups, and predict risk for clinical outcome. All versions of the HepQuant Test had excellent reproducibility.



Prediction of clinical outcome (new clinical decompensation, liver-related death, or liver transplantation) and reproducibility of DSI and SHUNT% in a cohort with Primary Sclerosing Cholangitis (PSC)

Parameter	Version	AUROC (95% CI)	%CV	Min. Detectable Diff.	ICC (95% CI)	p-value
DSI	SHUNT V1.1	0.812 (0.551-0.921)	9.21%	2.68	0.91 (0.84-0.95)	<0.001
	SHUNT V2.0	0.801 (0.594-0.930)	10.77%	3.19	0.89 (0.81-0.94)	<0.001
	LDT 1.0	0.814 (0.620-0.924)	10.33%	3.02	0.89 (0.82-0.94)	<0.001
SHUNT%	SHUNT V1.1	0.886 (0.734-0.958)	10.51%	5.88	0.91 (0.85-0.95)	<0.001
	SHUNT V2.0	0.853 (0.705-0.942)	11.41%	6.86	0.90 (0.82-0.94)	<0.001
	LDT 1.0	0.834 (0.616-0.939)	9.79%	5.57	0.91 (0.84-0.95)	<0.001

Disclosures: Michael P. McRae – HepQuant LLC: Consultant, Yes, No;

Disclosure information not available at the time of publication: Steve M. Helmke, Gregory T Everson

4560-C | PREDICTION OF BIOCHEMICAL RESPONSE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS TREATED WITH OBETICHOLIC ACID: DERIVATION AND EXTERNAL VALIDATION OF THE OCA RESPONSE SCORE (ORS)

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Background: Obeticholic acid (OCA) is the approved second-line treatment for patients with primary biliary cholangitis (PBC). Biochemical response by POISE criteria is achieved in ~40% of patients, according to registrative and post-marketing studies. The aim of the present study was to derive the OCA response score (ORS) for predicting response to OCA therapy at 12 and 24 months. **Methods:** We used data from the Italian RECAPITULATE (N 441, women 88%, mean age 57.8, cirrhosis 34%; Italy) and the IBERIAN (N 244, women 93%, mean age 56.6, cirrhosis 23%; Spain-Portugal) OCA real-world cohorts to derive and validate a scoring system including only widely available pre-treatment variables (ORS), or also the change of alkaline phosphatase(ALP)/upper limit of normal(ULN) and total bilirubin after 6 months' therapy (ORS+). Multivariable Cox's regressions with backward selection method were applied to obtain parsimonious predictive models. The predicted outcomes were biochemical response to OCA according to either POISE (ALP/ULN < 1.67 with a reduction of at least 15%, and normal bilirubin), or ALP/ULN < 1.67, or NORMAL RANGE criteria (NR, ALP/ULN < 1 and alanine aminotransferase(ALT)/ULN < 1 and normal bilirubin). **Results:** After variable selection procedures, the ORS was derived in the RECAPITULATE cohort and included age at OCA start, pruritus, cirrhosis, ALP/ULN, ALT/ULN, GGT/ULN and total bilirubin (for predicting POISE response), pruritus, cirrhosis, ALP/ULN, GGT/ULN and total bilirubin (for ALP/ULN < 1.67 response) and pruritus, ALP/ULN and total bilirubin (for NR response). The ORS+ was also derived by including the relative changes of ALP/ULN and of total bilirubin at 6 months. Good discriminative properties for both ORS and ORS+ were observed in the RECAPITULATE cohort (c-statistics: POISE criteria $= 0.77$ and 0.84; ALP/ULN $< 1.67 = 0.79$ and 0.88; NR criteria $= 0.73$ and 0.82, respectively), and confirmed in the IBERIAN validation cohort (c-statistics: POISE criteria $= 0.70$ and 0.81; ALP/ULN $< 1.67 = 0.72$ and 0.82; NR criteria $= 0.71$ and 0.86, respectively). Bootstrap validation evidenced modest overfitting (calibration slopes > 0.90). Mean absolute errors < 0.08 were observed in the IBERIAN cohort, indicating adequate models' calibration (Figure 1). **Conclusion:** The ORS accurately predicts OCA response at 12 and

24 months, according to different biochemical criteria. This will enable to enhance allocation of second-line therapies in PBC with a personalised medicine approach.

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4561-C | PREDICTORS OF GRAFT AND PATIENT SURVIVAL IN PRIMARY BILIARY CHOLANGITIS RECIPIENTS UNDERGOING LIVING DONOR LIVER TRANSPLANTATION

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Background: Few studies have explored the effect of living donor liver transplantation (LDLT) in patients with primary biliary cholangitis (PBC). Early recurrence of PBC and poorer outcomes have been reported. However, long-term analyses comparing post-transplant outcomes among liver transplantation (LT) types are scarce. In this study, we aimed to compare deceased donor liver transplantation (DDLT) vs LDLT to determine the survival outcomes and to identify recipient and donor characteristics associated with patient mortality and graft failure. **Methods:** A retrospective cohort analysis of adult patients with PBC registered in the Organ Procurement and Transplantation Network (OPTN) database who received primary LT between 2002 and 2019 was analyzed. Recipient characteristics such as demographics, comorbidities, pre-transplant labs, along with donor demographics were included. The primary outcomes were graft and patient survival at 1-,3-, 5- and 10 years post-LT. Stepwise Cox proportional hazard regression models were used to identify significant graft and patient survival predictors. **Results:** 3,328 DDLTs and 405 LDLT recipients were identified. On unadjusted analysis, LDLT recipients showed superior survival compared to DDLT at 1-, 3-, 5-, and 10-years (92.5%, 89.3%, 87.9%, 87.0%, 77.3% vs 91.1%, 88.1%, 86.1%, 82.1%, 70%, respectively). No significance was found in graft survival in LDLT recipients compared to DDLT (88.4%, 85.3%, 82.6%, 79.3%, 70.5% vs 88.9%, 85.7%, 83.6%, 79.7%, 67.2%; respectively). On univariate analysis, recipient age at transplant, male gender, recipient weight, presence of diabetes, use of mechanical ventilation, LDLT, donor age and weight were significantly associated with graft survival ($p < 0.05$). Recipient age at transplant, male gender, recipient weight, presence of diabetes, history of previous abdominal surgery, use of mechanical ventilation, portal vein thrombosis, LDLT, donor age, donor race, and cold ischemia time were associated with patient survival ($p < 0.05$). On multivariate analysis, recipient age at transplant, male gender, recipient weight, mechanical ventilation use, diabetes, and donor age were significantly associated with poorer graft and patient survival (table 1). **Conclusion:** No difference was found in graft and patient survival in PBC recipients undergoing LDLT compared to DDLT. Recipient factors such as recipient age at transplant, male gender, recipient weight, mechanical ventilation, diabetes, and donor age were associated with poorer post-LT outcomes. Prospective analyses are required to validate these findings.

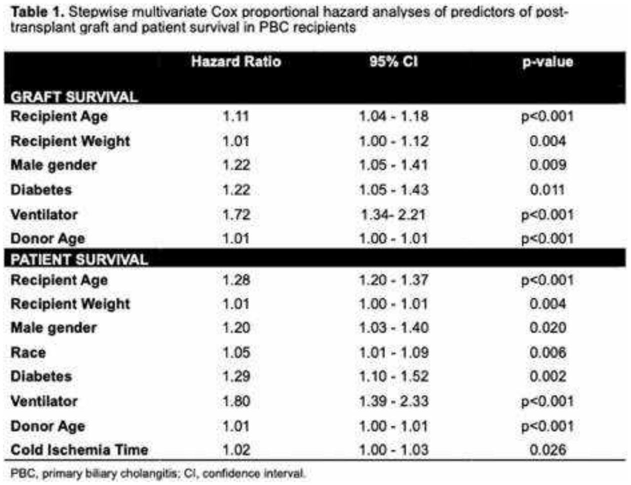

Table 1. Stepwise multivariate Cox proportional hazard analyses of predictors of post-transplant graft and patient survival in PBC recipients

	Hazard Ratio	95% CI	p-value
GRAFT SURVIVAL			
Recipient Age	1.11	1.04 - 1.18	p<0.001
Recipient Weight	1.01	1.00 - 1.12	0.004
Male gender	1.22	1.05 - 1.41	0.009
Diabetes	1.22	1.05 - 1.43	0.011
Ventilator	1.72	1.34- 2.21	p<0.001
Donor Age	1.01	1.00 - 1.01	p<0.001
PATIENT SURVIVAL			
Recipient Age	1.28	1.20 - 1.37	p<0.001
Recipient Weight	1.01	1.00 - 1.01	0.004
Male gender	1.20	1.03 - 1.40	0.020
Race	1.05	1.01 - 1.09	0.006
Diabetes	1.29	1.10 - 1.52	0.002
Ventilator	1.80	1.39 - 2.33	p<0.001
Donor Age	1.01	1.00 - 1.01	p<0.001
Cold Ischemia Time	1.02	1.00 - 1.03	0.026

PBC, primary biliary cholangitis; CI, confidence interval.

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4562-C | PREGNANCY OUTCOMES IN WOMEN WITH BILIARY TRANSPORTER GENES ABCB4 AND ABCB11 MUTATIONS

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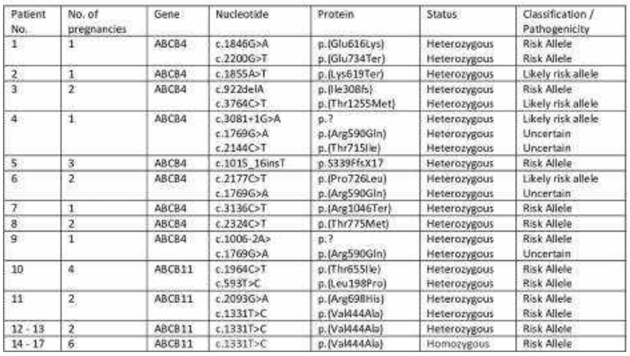
Background: Mutations in the bile acid (BA) transporter genes can result in intrahepatic cholestasis of pregnancy (ICP), cholelithiasis and progressive familial intrahepatic cholestasis. Severe ICP is associated with adverse fetal outcomes including preterm births and stillbirths whilst posing a challenge in the management of intractable pruritus for some women. **Methods:** A prospective database of self-reported pregnancies from women with liver disease was used to identify pregnancies with BA transporter gene mutations. Liver transplantation (LT) patients were excluded. Data on demographics, pregnancy outcomes and biochemical markers were gathered from medical records. **Results:** There were 28 pregnancies from 17 women with BA transporter gene mutations between 2001-2021 at King's College Hospital (Table 1). Median age at conception was 30 years (IQR 25-34). One woman with 2 pregnancies was cirrhotic at conception. Eight women with 12 pregnancies had cholecystectomy prior to conception and 1 required cholecystectomy post-partum. Median age at cholecystectomy was 21 years (IQR 18-29). ICP occurred in 22 pregnancies with median gestation at onset of 18 weeks (IQR 13-22). Median peak BA was 250 (IQR 160-400). All ICP patients received ursodeoxycholic acid and adjunct therapies included BA sequestrants ($n = 1$), rifampicin ($n = 4$), antihistamine ($n = 2$), nasobiliary drainage ($n = 1$) and plasma exchange ($n = 1$). Two patients received phototherapy post-partum. There were 26 live births with 2 terminations. Majority had spontaneous vaginal delivery ($n = 17$), 4 had planned caesarean (CS), 2 emergency CS and data missing in 3. There were 19 preterm births of which 2 were very preterm (< 32 weeks gestation) and 17 moderate (32-36 weeks). Median birthweight was 2565g (IQR 2120-3212). Five babies required admission to special care baby unit (SCBU) of which 4 were short stays and the babies were healthy. The patient with cirrhosis had preconception MELD score 10, decompensated during pregnancy and required LT within 1-year post-partum. The baby had a prolonged admission in SCBU. There were no stillbirths or miscarriages. **Conclusion:** There is a high rate of ICP and preterm births in women with BA transporter gene mutations. Despite the high BA there were no stillbirths and overall had good outcomes in this case series. Management of pruritus is difficult with often suboptimal response and requires an individualised approach.

Table 1.



Patient No.	No. of pregnancies	Gene	Nucleotide	Protein	Status	Classification / Pathogenicity
1	1	ABCB4	c.1846G>A c.2200G>T	p.(Glu616Lys) p.(Glu734Ter)	Heterozygous Heterozygous	Risk Allele Risk Allele
2	1	ABCB4	c.1855A>T	p.(Lys619Ter)	Heterozygous	Likely risk allele
3	2	ABCB4	c.922delA c.3764C>T	p.(Ile308fs) p.(Thr1255Met)	Heterozygous Heterozygous	Risk Allele Likely risk allele
4	1	ABCB4	c.3081+1G>A c.1769G>A c.2144C>T	p.? p.(Arg590Gln) p.(Thr715Ile)	Heterozygous Heterozygous Heterozygous	Likely risk allele Uncertain Uncertain
5	3	ABCB4	c.1015_16insT	p.S339FfsX17	Heterozygous	Risk Allele
6	2	ABCB4	c.2177C>T c.1769G>A	p.(Pro726Leu) p.(Arg590Gln)	Heterozygous Heterozygous	Likely risk allele Uncertain
7	1	ABCB4	c.3136C>T	p.(Arg1046Ter)	Heterozygous	Risk Allele
8	2	ABCB4	c.2324C>T	p.(Thr775Met)	Heterozygous	Risk Allele
9	1	ABCB4	c.1006-2A> c.1769G>A	p.? p.(Arg590Gln)	Heterozygous Heterozygous	Risk Allele Uncertain
10	4	ABCB11	c.1964C>T c.593T>C	p.(Thr655Ile) p.(Leu198Pro)	Heterozygous Heterozygous	Risk Allele Risk Allele
11	2	ABCB11	c.2093G>A c.1331T>C	p.(Arg698His) p.(Val444Ala)	Heterozygous Heterozygous	Risk Allele Risk Allele
12 - 13	2	ABCB11	c.1331T>C	p.(Val444Ala)	Heterozygous	Risk Allele
14 - 17	6	ABCB11	c.1331T>C	p.(Val444Ala)	Homozygous	Risk Allele

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4563-C | PREVALENCE AND TREATMENT OF PRURITUS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (PBC): RESULTS FROM THE GERMAN PBC REGISTRY

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Background: Pruritus is a major symptom of primary biliary cholangitis (PBC). Systematic data on prevalence and treatment of pruritus in patients with PBC is limited. We therefore characterized PBC patients with pruritus in the German real-world setting. **Methods:** The German PBC Registry is a nationwide database for routine clinical data of 32 centers, which recruited PBC patients between September 2019 and January 2023. Pruritus was recorded with a 4-point Lickert scale as absent, mild, moderate, or severe by the treating physician. Fisher's Exact test, Chi²-test or Mann-Whitney-U-test were used to analyze statistical differences for significance ($p < 0.05$). **Results:** Pruritus was noted in 117/496 (24%) of patients (87% female, median age at diagnosis 50 years, 15% with cirrhosis, median UDCA daily dosage 12.7 mg/kg) and classified as mild, moderate, or severe in 57 (49%), 41 (35%), and 19 (16%) cases. Patients with pruritus were younger at PBC diagnosis (50.7 ± 11.2 vs. 54.8 ± 11.8 years, $p < 0.001$) and reported more often depression (14.5% vs. 6.1%, $p = 0.006$) than individual's without pruritus. They were significantly more often treated at academic than non-academic centers (79.5% vs. 20.5%, $p < 0.0001$). The prevalence of pruritus in academic centers was 27% ($n = 93/345$) and in non-academic centers 16% ($n = 24/151$) ($p = 0.0081$), with a range of 0-86% and 0-50% at both care levels, respectively. 56/496 (11%) and 48/496 (9.7%) of patients received second line PBC therapy with bezafibrate or obeticholic acid. Prevalence of pruritus was not significantly different between both second line treatment groups (27% vs. 31%), or between UDCA responder patients and primary UDCA incomplete responders according to Paris II criteria (21% vs. 27%). Antipruritic therapies were infrequently used: bezafibrate $n = 15$, antihistamines $n = 7$, cholestyramine $n = 3$, sertraline $n = 2$, rifampicin $n = 1$, steroid-containing ointment $n = 1$, opiate-antagonists $n = 0$. **Conclusion:** Pruritus is common and inadequately treated in PBC patients. Diagnosis highly depends on the treating physician and needs harmonization. Education about antipruritic therapies should be improved.

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4564-C | PRIMARY SCLEROSING CHOLANGITIS: EXPERIENCE FROM A TERTIARY CARE CENTER IN ASIA

Mithun Sharma[1], Anand V. Kulkarni[2], Rajesh Gupta[2], Nitin Jagtap[1], Padaki Nagaraja Rao[2], Manasa Alla[2], Anuradha Sekaran[2], Shantan Venishetty[2], Sowmya T R[2] and Nageshwar D Reddy[2], (1)Asian Institute of Gastroenterology, Hyderabad, Telangana, India, (2)Aig Hospitals, Hyderabad, India

Background: The incidence of primary sclerosing cholangitis (PSC) are less in India when compared to the Western world. This study reports the clinical profile of one of the largest reported case series of PSC from India **Methods:** Retrospective data from 2012 to January 2023 were retrieved for clinical profile, development of cholangiocarcinoma, presence of concomitant autoimmune hepatitis (AIH), presence of inflammatory bowel disease, presence of dominant stricture and risks involved with endoscopic interventions **Results:** 48 patients of PSC (40 male and 8 female) were included. The mean age of presentation was 25 +_ 9 yrs. The most common presenting feature was jaundice in 68% of patients and 38% of cases had a preceding history of cholecystectomy. The median duration between the detection of PSC and cholecystectomy was 5.4 years. Large duct PSC was in 33(75%) patients as detected by MRCP while biopsy small duct in the remaining. The median duration of follow-up was 3.4 yrs (1.2 to 8.2 yrs). The dominant stricture was present in 12(25%) at presentation while an additional 4 (8.33%) developed in the follow-up period. Cholangiocarcinoma was detected in 1 patient at the time of presentation while an additional 6(12.5%) developed at a median of 2.7 yrs. Spy cholangioscopy was done in 3 patients. Endoscopic intervention was done in 8 patients but was associated with sepsis in 50% of patients. 3 patients underwent liver transplantation and all were doing fine at a median 3 years follow-up. Associated inflammatory bowel disease was present in 15(31.25%) patients and was mostly ulcerative colitis. Mortality during this follow-up period was 8(16.65) **Conclusion:** PSC is a disease that affects the young population with a high transition to cholangiocarcinoma and interventions are associated with the risk of contaminating the ductal system. There is lower incidence of IBD in Asians. Transplantation of the liver is associated with a good prognosis

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Disclosure information not available at the time of publication: Anand V. Kulkarni

4565-C | PRURITUS IS COMMON AND BURDENSOME IN PATIENTS (PTS) WITH CHRONIC LIVER DISEASE (CLD): FINDINGS FROM A CROSS-SECTIONAL NATURAL HISTORY STUDY

Usha Gungabissoon[1], Ellie McDermott[2], Andrew Lovley[3], Kristen L McCausland[3], Monica Frazer[3], Kaitlin LaGasse[3], Gideon Hirschfield[4], Jake Hunnicutt[5], *Ashleigh McGirr[6] and Helen T Smith[1], (1)GSK, London, UK, (2)GSK, Stevenage, Hertfordshire, UK, (3) Qualitymetric Incorporated, LLC, Johnston, RI, USA, (4) Toronto Centre for Liver Disease, University of Toronto, Toronto, Ontario, Canada, (5)GSK, Collegeville, PA, USA, (6)GSK, Mississauga, Ontario, Canada*

Background: Pruritus is a common condition associated with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). There are limited data reporting pruritus in other CLDs such as autoimmune hepatitis (AIH), chronic hepatitis B/C (Hep B/C), non-alcoholic steatohepatitis (NASH) and cholestatic or mixed drug-induced liver injury (DILI). We aimed to understand the severity and impact of pruritus in CLDs using screening and baseline data from our online, patient-reported outcome study. **Methods:** Adult patients (pts) with CLDs were recruited in the USA, UK, Canada, and Germany and screened online for pruritus and eligibility. Among screened pts, pruritus burden was assessed using the worst itch numerical rating scale (WI-NRS; scale 0–10) with a 3-month recall and reported for overall (score ≥1) and moderate-to severe itch (score ≥4). Eligible pts were those who reported pruritus within the prior 3 months, and had a CLD diagnosis confirmed by a third party (using documentation from healthcare providers or medical records). Pts with other pruritus causes, previous liver transplant, or end-stage liver disease were excluded. Baseline demographics and pruritus characteristics from the past 2 weeks are reported for eligible pts. **Results**: From 717 screened pts, 56% indicated some degree of pruritus, 42% reported moderate-to-severe itch (Table). Pruritus frequency was highest among pts with Hep B/C (70%/73%), and NASH (69%). Of those screened, 357 met further eligibility criteria. In eligible pts, there were notably more females in AIH, PBC, and PSC, similar proportions in Hep C, DILI, and NASH, and more males in the Hep B cohort. Pts were mostly white/Caucasian (78%, range 22–94%) and mean (SD) age was 51.1 (12.8) years (range 44.1–57.1). In eligible pts, 80% experienced pruritus for ≥2 days/week in the last 2 weeks, with the highest in pts with DILI (95%), and Hep C (91%); with one third itching every day. Similar percentages of pts in each cohort (27% overall; range 16–34%) reported scratching enough to make their skin raw on ≥2 days/week in the past 2 weeks. This was highest in pts with PBC (34%) and DILI (32%). **Conclusion**: Initial findings from this multi-country study highlight that overall and moderate-to-severe pruritus is common (>40%) and burdensome (>25% scratched enough to make their skin raw on ≥2 days/week in the last 2 weeks) in pts with CLD, emphasizing an unmet need in these pts. Funding: GSK (209971).

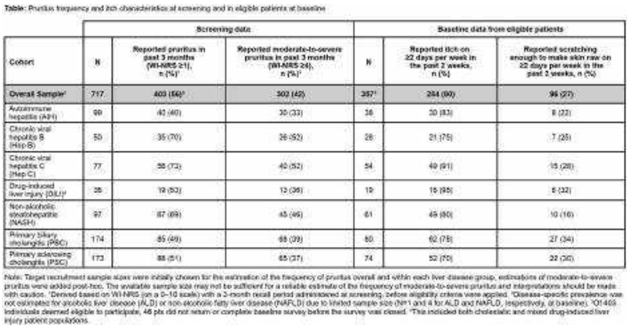

Table: Pruritus frequency and itch characteristics at screening and in eligible patients at baseline

	Screening data			Baseline data from eligible patients		
Cohort	N	Reported pruritus in past 3 months (WI-NRS ≥1), n (%)[1]	Reported moderate-to-severe pruritus in past 3 months (WI-NRS ≥4), n (%)[1]	N	Reported itch on ≥2 days per week in the past 2 weeks, n (%)	Reported scratching enough to make skin raw on ≥2 days per week in the past 2 weeks, n (%)
Overall Sample[2]	**717**	**403 (56)[3]**	**302 (42)**	**357[3]**	**284 (80)**	**96 (27)**
Autoimmune hepatitis (AIH)	99	40 (40)	30 (33)	36	30 (83)	8 (22)
Chronic viral hepatitis B (Hep B)	50	35 (70)	26 (52)	28	21 (75)	7 (25)
Chronic viral hepatitis C (Hep C)	77	56 (73)	40 (52)	54	49 (91)	15 (28)
Drug-induced liver injury (DILI)[4]	36	19 (53)	13 (36)	19	18 (95)	6 (32)
Non-alcoholic steatohepatitis (NASH)	97	67 (69)	45 (46)	61	49 (80)	10 (16)
Primary biliary cholangitis (PBC)	174	85 (49)	68 (39)	80	62 (78)	27 (34)
Primary sclerosing cholangitis (PSC)	173	88 (51)	65 (37)	74	52 (70)	22 (30)

Note: Target recruitment sample sizes were initially chosen for the estimation of the frequency of pruritus overall and within each liver disease group, estimations of moderate-to-severe pruritus were added post-hoc. The available sample size may not be sufficient for a reliable estimate of the frequency of moderate-to-severe pruritus and interpretations should be made with caution. [1]Derived based on WI-NRS (on a 0–10 scale) with a 3-month recall period administered at screening, before eligibility criteria were applied. [2]Disease-specific prevalence was not estimated for alcoholic liver disease (ALD) or non-alcoholic fatty liver disease (NAFLD) due to limited sample size (N=1 and 4 for ALD and NAFLD, respectively, at baseline). [3]Of 403 individuals deemed eligible to participate, 46 pts did not return or complete baseline survey before the survey was closed. [4]This included both cholestatic and mixed drug-induced liver injury patient populations.

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4566-C | QUANTITATIVE ASSESSMENT OF ANTI-MITOCHONDRIAL ANTIBODIES IN PRIMARY BILIARY COLANGITIS: A CROSS-SECTIONAL ANALYSIS

Lorenzo Canova[1], Elisabetta Degasperi[1], Maria Paola Anolli[1], Marta Borghi[1], Riccardo Perbellini[1], Sonia Stella[1] and Pietro Lampertico[1,2], (1)Division of Gastroenterology and Hepatology, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, (2) CRC "a. M. and a. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan

Background: In patients with primary biliary cholangitis (PBC), quantitative assessment of anti-mitochondrial antibodies (AMA)-M2 is currently available, however its clinical meaning is still unknown. Aim of our study was to analyse quantitative AMA-M2 in PBC patients and its correlation with clinical features. . **Methods:** PBC patients followed in a tertiary hepatology Italian centre with available quantitative AMA-M2 values were included in a cross-sectional analysis. PBC was diagnosed according to international recommendations, response to Ursodeoxycholic acid (UDCA) was defined according to Paris-II criteria. Demographic, clinical and biochemical features were collected ±3 months from AMA assessment. AMA was tested by chemiluminescence immunoassay (CLIA) (assay range 0-3000 AU/mL). **Results:** Overall, 92 PBC patients (87% females) were included. At the time of AMA assessment, median age was 67 (39-93) years, ALT 30 (8-258) U/L, ALP 0.7 (0.2-4.4) ULN, 38% patients with ALP > 1.5 ULN, gGT 1.44 (0.2-14.3) ULN, IgM 237 (39-1,037) mg/dl, liver stiffness measurement (LSM) 5.9 (3.9-38.6) kPa, 23% with advanced fibrosis (Stage III-IV Ludwig). Median time since PBC diagnosis was 89 (1-433) months, 91% patients were UDCA-treated, 19% under second-line therapy due to UDCA non-response. Overall, in the 49 (53%) patients with quantifiable AMA, median value was 319 (20-2500) AU/mL, while AMA-M2 tested > 3000 AU/mL in 43 (47%) patients. No statistically significant differences were observed between patients with AMA titers above *vs.* below 3000 concerning most important clinical, biochemical and disease features: age ($p = 0.18$), sex ($p = 0.31$), BMI ($p = 0.34$), advanced fibrosis stage ($p = 0.55$), LSM values ($p = 0.73$), disease duration ($p = 0.78$), UDCA response ($p = 0.45$), ALT ($p = 0.97$), ALP ($p = 0.78$) values and ALP ULN categories (< 1.5 ULN *vs.* 1.5-2.0 ULN *vs.* > 2 ULN, $p = 0.84$), gGT ($p = 0.49$) and IgM ($p = 0.84$) values. The same was true when AMA values were analyzed according to multiple thresholds (AMA < 300 *vs.* 300-1000 *vs.* 1000-3000 *vs.* > 3000). Conversely, in patients with AMA < 3000, male sex was associated with lower AMA-M2 values (56 *vs.* 426, $p = 0.02$). **Conclusion:** In UDCA-treated PBC patients, lower AMA-M2 levels were associated only with male gender, while they did not correlate with other clinical or disease features.

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The following people have nothing to disclose: Lorenzo Canova, Elisabetta Degasperi, Maria Paola Anolli, Marta Borghi, Riccardo Perbellini, Sonia Stella

4567-C | REAL-WORLD CLINICAL CHARACTERISTICS AND TREATMENT PATTERNS OF PATIENTS WITH PRIMARY BILIARY CHOLANGITIS IN THE UNITED STATES

Nisreen Shamseddine[1], Hongbo Yang[2], Su Zhang[2], Dongni Ye[2], Sonal Kumar[3] and Kris V. Kowdley[4], (1) Ipsen Biopharmaceuticals, Inc., (2)Analysis Group, Inc., (3)Weill Cornell Medical College, (4)Liver Institute Northwest

Background: Patients (pts) with primary biliary cholangitis (PBC) are at a risk of progression to end-stage liver disease. Ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) are currently approved treatments (Txs) for PBC in the United States (US). Delayed Tx can negatively impact the prognosis of PBC. This study assessed clinical characteristics and Tx patterns of pts with PBC during their Tx journey. **Methods:** This retrospective cohort study used IQVIA PharMetrics® Plus data (2016-2022). Three non-mutually exclusive pt cohorts were created: 1) pts with newly-diagnosed untreated PBC (newly-diagnosed cohort), 2) pts initiated first-line Tx (UDCA) (1L cohort), and 3) pts initiated second-line or more Tx (OCA/fibrates ± UDCA) (2L+ cohort). Index date was defined as the initial PBC diagnosis, 1L Tx initiation, or 2L Tx initiation, for each cohort, respectively. Baseline characteristics, measured 12-months before index, were summarized for each cohort. Tx sequence and time to 1L Tx initiation, based on Kaplan-Meier (KM) analysis, were described for the newly-diagnosed cohort. Time to 1L Tx discontinuation and time to 2L Tx initiation were described for the 1L cohort. Time to 2L Tx discontinuation was summarized for the 2L+ cohort. **Results:** A total of 1,549, 1,462, and 158 pts met eligibility criteria and were included in the newly-diagnosed, 1L, and 2L+ cohorts, respectively (Table 1). Baseline comorbidity burden was the highest in the 2L+ cohort, followed by the 1L and the newly-diagnosed cohort; baseline pruritus rate was also the highest in the 2L+ cohort. In the newly-diagnosed cohort, with a median follow-up of 18.3 months, 1,018 (65.8%) pts received ≥1 Tx after the initial diagnosis. While the median time from initial PBC diagnosis to 1L initiation was 1.2 months, 27.2% of pts did not initiate any Tx at 4 years after diagnosis based on the KM analysis. In the 1L cohort, with a median follow-up of 19.9 months, 440 (30.1%) pts discontinued 1L Tx (median time to 1L Tx discontinuation: 51.0 months); 121 (8.3%) pts initiated 2L Tx. In the 2L+ cohort, with a median follow-up of 15.1 months, 23 (14.6%) pts discontinued 2L Tx and the median time to 2L Tx discontinuation was not reached. **Conclusion:** This analysis suggests that pts with PBC in the 2L+ setting have the highest comorbidity burden. Additionally, despite approved Txs, a non-trivial proportion of PBC pts appear to remain untreated years after diagnosis, and 2L Tx initiation rate also appears low, highlighting an unmet need in this population.

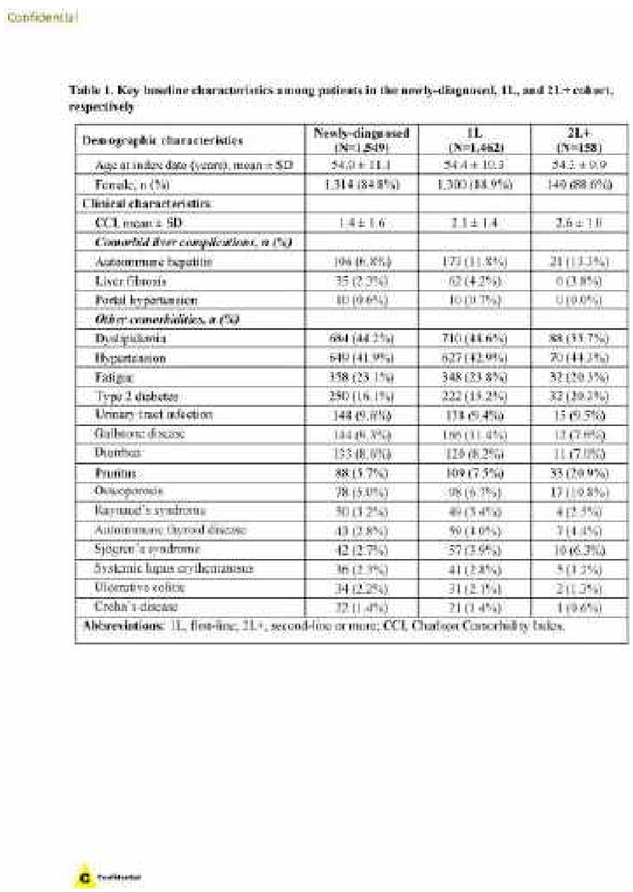
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Table 1. Key baseline characteristics among patients in the newly-diagnosed, 1L, and 2L+ cohort, respectively

Demographic characteristics	Newly-diagnosed (N=1,549)	1L (N=1,462)	2L+ (N=158)
Age at index date (years), mean ± SD	54.0 ± 11.1	54.4 ± 10.3	54.3 ± 9.9
Female, n (%)	1,314 (84.8%)	1,300 (88.9%)	140 (88.6%)
Clinical characteristics			
CCI, mean ± SD	1.4 ± 1.6	2.1 ± 1.4	2.6 ± 1.9
Comorbid liver complications, n (%)			
Autoimmune hepatitis	106 (6.8%)	173 (11.8%)	21 (13.3%)
Liver fibrosis	35 (2.3%)	62 (4.2%)	6 (3.8%)
Portal hypertension	10 (0.6%)	10 (0.7%)	0 (0.0%)
Other comorbidities, n (%)			
Dyslipidemia	684 (44.2%)	710 (48.6%)	88 (55.7%)
Hypertension	649 (41.9%)	627 (42.9%)	70 (44.3%)
Fatigue	358 (23.1%)	348 (23.8%)	32 (20.3%)
Type 2 diabetes	250 (16.1%)	222 (15.2%)	32 (20.3%)
Urinary tract infection	144 (9.3%)	138 (9.4%)	15 (9.5%)
Gallstone disease	104 (6.7%)	166 (11.4%)	12 (7.6%)
Diarrhea	133 (8.6%)	120 (8.2%)	11 (7.0%)
Pruritus	88 (5.7%)	109 (7.5%)	33 (20.9%)
Osteoporosis	78 (5.0%)	98 (6.7%)	17 (10.8%)
Raynaud's syndrome	50 (3.2%)	49 (3.4%)	4 (2.5%)
Autoimmune thyroid disease	43 (2.8%)	59 (4.0%)	7 (4.4%)
Sjogren's syndrome	42 (2.7%)	57 (3.9%)	10 (6.3%)
Systemic lupus erythematosus	36 (2.3%)	41 (2.8%)	5 (3.2%)
Ulcerative colitis	34 (2.2%)	31 (2.1%)	2 (1.3%)
Crohn's disease	22 (1.4%)	21 (1.4%)	1 (0.6%)

Abbreviations: 1L, first-line; 2L+, second-line or more; CCI, Charlson Comorbidity Index.

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4568-C | REAL-WORLD EVIDENCE, CLINICAL CHARACTERISTICS, & DISEASE PROGRESSION INSIGHTS FROM A GLOBAL COHORT OF PRIMARY BILIARY CHOLANGITIS PATIENTS DIAGNOSED BETWEEN 2015 AND 2023

Gianni Amato and Courtney Thompson, Trinetx

Background: Primary biliary cholangitis (PBC) is a rare autoimmune liver disease characterized by impaired bile flow, inflammation, & bile duct damage. Disease characteristics include elevated markers of cholestasis, along with symptoms of fatigue and pruritus. Treatment includes first-line ursodeoxycholic acid (UDCA) & second-line obeticholic acid (OCA). PPARδ agonists are under investigation. **Methods:** This study utilized TriNetX Dataworks Global Network & extracted electronic health records (EHR) from 67 global healthcare organizations (HCOs). Eligible patients were identified with ICD-10 codes K74.3 to K74.5. Descriptive statistics were reported and time to event analysis was used to explore the cohort which includes real-world evidence (RWE) of patients diagnosed between 2015 and 2023. Demographics, diagnoses, procedures, medications, serum liver tests, genomics, and time to event variables, including advanced fibrosis, cirrhosis, portal hypertension, hepatocellular carcinoma, liver transplant, or death, were measured. **Results:** The cohort includes 33,095 patients across 67 HCOs. Of these, 74% were female, 72% were white, and 65% were non-Hispanic. The mean (SD) age was 65 (14) years & mean (SD) duration of PBC was 11 (6) years. Patients had multiple comorbidities, including disorders of the endocrine, circulatory, genitourinary, blood, skin, and subcutaneous tissue systems. Baseline mean (SD) levels of ALP, ALT, AST, GGT, total bilirubin, and albumin were 184 (187), 51.4 (19.2), 84.8 (55.0), 192 (305), 2.15 (4.94), and 3.72 (0.86), respectively. Patients were stratified based on GLOBE score and UDCA response for time-to-event analysis. Approx. 45% of patients progressed to a more severe condition during the course of their disease. Approx. 17,600 received UDCA, & 1,119 received OCA. Within eight years of diagnosis, approximately 45% of high-risk patients who failed or were intolerant to UDCA or OCA progressed to more severe disease states, including liver failure, liver transplant, or hepatocellular carcinoma, and had a combined real-world Hazard Ratio (HR) of 11.2 (95% CI 9.1–21.9). **Conclusion:** This study underscores the vital role of RWE in understanding the management and progression of primary biliary cholangitis & analyzes biochemical factors of progression to more severe disease states. Insights from robust longitudinal datasets are essential for drug developers and clinical practitioners to get a comprehensive view of progression in PCB in the real-world.

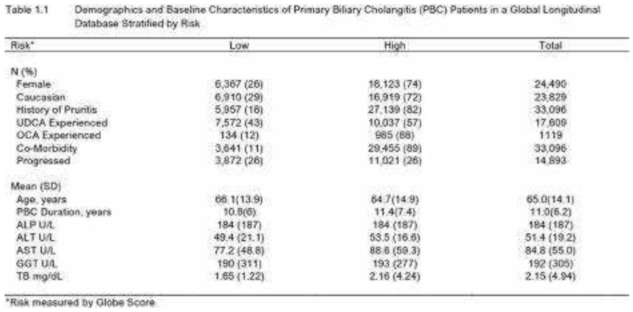

Table 1.1 Demographics and Baseline Characteristics of Primary Biliary Cholangitis (PBC) Patients in a Global Longitudinal Database Stratified by Risk

Risk*	Low	High	Total
N (%)			
Female	6,367 (26)	18,123 (74)	24,490
Caucasian	6,910 (29)	16,919 (72)	23,829
History of Pruritis	5,957 (18)	27,139 (82)	33,096
UDCA Experienced	7,572 (43)	10,037 (57)	17,609
OCA Experienced	134 (12)	985 (88)	1119
Co-Morbidity	3,641 (11)	29,455 (89)	33,096
Progressed	3,872 (26)	11,021 (26)	14,893
Mean (SD)			
Age, years	66.1(13.9)	64.7(14.9)	65.0(14.1)
PBC Duration, years	10.8(6)	11.4(7.4)	11.0(6.2)
ALP U/L	184 (187)	184 (187)	184 (187)
ALT U/L	49.4 (21.1)	53.5 (16.6)	51.4 (19.2)
AST U/L	77.2 (48.8)	88.6 (59.3)	84.8 (55.0)
GGT U/L	190 (311)	193 (277)	192 (305)
TB mg/dL	1.65 (1.22)	2.16 (4.24)	2.15 (4.94)

*Risk measured by Globe Score

Disclosures: The following people have nothing to disclose: Gianni Amato, Courtney Thompson

f 4569-C | REAL-WORLD EXPERIENCE WITH FIBRATES IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Marleen De Vree[16], Alexander C Poen[17], Philip W Friederich[18], Merel M Tielemans[19], Huseyin Aktas[20], Daphne M Hotho[21], Ulrike De Wit[22], Johan P Kuyvenhoven[23], Sunje Abraham[24], Edith M Kuiper[25], Stephan Schmittgens[26], Yasser A Alderlieste[27], Harry L. A. Janssen[1], Bettina E. Hansen[1], Nicole S. Erler[1], Adriaan J. Van der Meer[1] and Dutch PBC Study Group, (1)Erasmus MC, University Medical Center Rotterdam, (2)Amsterdam University Medical Center, Amsterdam, Netherlands, (3)Radboud University Medical Center, Nijmegen, (4)University Medical Center Groningen, Groningen, (5)Leiden University Medical Center, Leiden, (6)Reinier De Graaf Gasthuis Hospital Group, Delft, (7)Northwest Clinics (NWZ), Alkmaar, (8) University Medical Center Utrecht, Utrecht, (9)Antonius Hospital, Nieuwegein, (10)Catharina Hospital, Eindhoven, (11)Rijnstate Hospital, Arnhem, (12) Maastricht University Medical Center, Maastricht, (13) Tjongerschans Hospital, Heerenveen, (14)Medisch Spectrum Twente, Enschede, (15)Amphia Hospital, Breda, (16)Treant Hospital, Hoogeveen, (17)Isala Hospital, Zwolle, (18)Meander Medical Center, Amersfoort, Netherlands, (19)Bravis Hospital, Roosendaal/Bergen Op Zoom, (20)Hospital Group Twente (ZGT), Hengelo, (21)St Jansdal Hospital, Harderwijk, (22)Elisabeth – Tweesteden Hospital (ETZ), Tilburg, (23)Spaarne Gasthuis Hospital, Haarlem, (24) Alrijne Hospital, Leiden, (25)Maasstad Hospital, Rotterdam, (26)Nij Smellinghe Hospital, Drachten, (27) Beatrix Hospital, Gorinchem

Background: At present, fibrates can be used off-label among patients with primary biliary cholangitis (PBC). We aimed to evaluate the real-world use and effectiveness of fibrates in a nationwide cohort. **Methods:** For this analyses all patients in the Dutch PBC cohort study - a retrospective study in all Dutch hospitals including every identifiable patient with PBC from 1990 onwards - who initiated fibrates during follow-up were included. Biochemical measurements before the start of fibrates and those closest to 12 months (minimum nine months, maximum 18 months) were used. Fibrate-induced biochemical changes during the first year were assessed by median (IQR) changes (Δ) in the upper limit of normal (ULN) and dichotomously (normal ALP or bilirubin ≤0.6xULN). **Results:** In total, 318 patients (female $n = 291$; 91.5%) with PBC who initiated fibrates during follow up were included, of which 4 (1.2%) did not use ursodeoxycholic acid. Fibrates of use were bezafibrate ($n = 311$; 97.8%), ciprofibrate ($n = 5$; 1.6%) and gemfibrozil ($n = 2$; 0.6%). At start of fibrate therapy, median age was 55.3 (IQR 48.4–64.4) years, 45 (14.2%) had cirrhosis, median ALP was 2.42xULN (IQR 1.58-3.51), and median bilirubin was 0.55xULN (IQR 0.41-0.94). Fibrate therapy was discontinued within the first year in 67 (21.1%) patients, another 63 (19.8%) patients had not (yet) reached nine months of treatment. The change in ALP and bilirubin could be assessed in 165 and 148 patients, respectively. Overall, the median ΔALP and Δbilirubin were -1.03 (IQR -0.60 to -1.77) and -0.08 (IQR -0.20 to 0.06), respectively. The median ΔALP was -0.58 (IQR -0.79 to -0.14) for patients with an ALP ≤ 1.67xULN at baseline versus -1.33 (IQR -2.14 to -0.81) for those > 1.67xULN ($p < 0.01$). The median Δbilirubin was 0.00 (IQR -0.10 to 0.06) for patients ≤ 0.6xULN at baseline, versus -0.17 (IQR -0.35 to 0.00) for those > 0.6xULN ($p < 0.01$). At 12 months, 49/158 (31.0%) patients with elevated baseline ALP reached normalization and 20/72 (27.4%) with a baseline bilirubin > 0.6xULN were below this threshold. **Conclusion:** In this nation-wide real-world study, fibrate use was associated with statistically significant reductions in cholestatic surrogate markers after one year of therapy, with about a third of patients reaching the most stringent biochemical treatment goals. However, discontinuation rate was high, indicating the need to optimize fibrate treatment strategies.

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Verdonk, Hajo J. Flink, Jan M. Vrolijk, Tom J. Gevers, Janne E Van Rooij, Marjo J Kerbert-Dreteler, Jerome Sint Nicolaas, J Marleen De Vree, Alexander C Poen, Merel M Tielemans, Huseyin Aktas, Daphne M Hotho, Ulrike De Wit, Johan P Kuyvenhoven, Sunje Abraham, Edith M Kuiper, Stephan Schmittgens, Yasser A Alderlieste, Nicole S. Erler, Adriaan J. Van der Meer

4570-C | REEVALUATING THE TREATMENT INDICATIONS FOR PRIMARY BILIARY CHOLANGITIS - ANALYSIS OF A NATIONWIDE SURVEY COHORT IN JAPAN-

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Background: PBC Clinical practice guidelines state that patients with abnormal ALP values are eligible for treatment, but there is no clear evidence supporting this recommendation. In this study, we retrospectively examined the association among ALP levels at baseline, treatment, and long-term prognosis, using a large cohort of patients with PBC in Japan to reevaluate the indications for treatment of PBC. **Methods:** From patient data ($n = 9919$) enrolled in the cohort of PBC, we extracted patients in which ALP level at presentation, presence or absence of treatment during the course of the disease, and long-term prognosis were all recorded. Enrolled patients were classified into 4 groups: ALP less than the upper limit of normal (ULN) at baseline (< 1 group), ALP with 1-1.5 xULN (1-1.5 group), ALP with 1.5-2 xULN (1.5-2 group), and ALP > 2 xULN (> 2 group). The association of treatment with long-term outcome was statistically analyzed in each group. **Results:** Of the 6595 patients enrolled for the study, 1676 were in the < 1 group (male/female = 213/1463, age at diagnosis 58.5 ± 11.1 y), 1817 in the 1-1.5 group (224/1593, 58.5 ± 11.1 y), 1045 in the 1.5-2 group (146/899, 58.0 ± 11.2 y), and 2057 patients in the > 2 group (334/1723, 20.0 ± 11.2 y). In each group, 1527 (91%), 1718 (95%), 986 (94%), and 1954 (95%) were treated with ursodeoxycholic acid and/or bezafibrate, respectively. The mean observation periods were 8.0, 7.6, 7.5, and 7.2 years, and death or liver transplantation (LT) occurred in 120 (7.2%), 130 (7.2%), 103 (9.9%), and 339 (16.5%) patients, respectively. When the association between treatment and LT-free survival was examined by the Kaplan-Meier method, there was no significant difference between treatment and non-treatment in the < 1 group ($p = 0.326$), but significant difference was observed in the other groups (1-1.5 group $p = 0.049$, 1.5-2 group $p = 0.029$, > 2 group $p < 0.001$). Cox regression analysis using sex, age at diagnosis, albumin, bilirubin, symptom status, and treatment as covariates, and LT or death as the endpoint, showed that treatment status was not significant in the < 1 and 1.5-2 groups, but was a significant factor in the 1-1.5 and > 2 groups (1-1.5 group HR = 0.531, 95%CI 0.28-0.99, $p = 0.048$; > 2 group HR = 0.397, 95%CI 0.27-0.59, $p < 0.001$). **Conclusion:** For patients with ALP levels within ULN at presentation, treatment is unlikely to have any effect on long-term prognosis. In contrast, a more detailed analysis of the effect of treatment on patients with ALP levels 1-2 times higher than the baseline ALP level is warranted.

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The following people have nothing to disclose: Kosuke Matsumoto, Junko Hirohara, Toshiaki Nakano

4571-C | RESPONSE TO URSODIOL THERAPY IN REDUCING ALKALINE PHOSPHATASE TO NORMAL LEVELS IN PRIMARY BILIARY CHOLANGITIS IN A DIVERSE COMMUNITY PRACTICE

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Background: Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease that can lead to advanced fibrosis and cirrhosis. First-line treatment is ursodiol (UDCA), which decreases hepatic synthesis of cholesterol and desaturates biliary cholesterol. The objective is to assess the effectiveness of UDCA on lowering alkaline phosphatase (ALP) levels in patients diagnosed with PBC. **Methods:** A retrospective review was conducted at a diverse urban academic center to obtain UDCA dosage and ALP values at the start of UDCA therapy and at 6 and 12 month periods to correlate with long term survival. Covariants such as Fibroscan results and liver transplant status were analyzed followed by chi-squared tests and linear regression analysis. **Results:** 122 newly-presenting PBC patients were treated only with UDCA. Mean age was 61.6 years old (range 26-90). 73% ($n = 89$) of the patients were females. The mean liver stiffness by Fibroscan evaluation was 9.7 kPa with standard deviation (SD) of 6.65 (n = 47). Results were tiered based on low (< 130), medium (130-200) and high (> 200) ALP levels. At baseline, the percentage of patients in low, medium, and high ALP groups were 11%, 36%, and 53%, respectively. After 12 months of treatment, the percentage of patients in low, medium, and high ALP groups were 42%, 33%, and 21%, respectively. Treatment regimen was defined as low dose (< 10mg/kg/day, 31%), medium dose (10-15mg/kg/day, 51%) and high dose (> 15mg/kg/day, 18%). The mean UDCA dose was 11.7 mg/kg/day (SD 4.44) upon initiation of therapy. Baseline ALP levels in low, medium and high dose UDCA groups was 47%, 53%, and 59%, respectively. ALP > 200 at 12 months in low, medium and high dose UDCA groups was 21%, 18%, and 18%, respectively. Overall 20.9% of patients had ALP > 200 after 12 months. 56.5% of patients had ALP > 130 at 12 months. The chi-square test showed no significant association between categorical UDCA dose and categorical ALP at 6 and 12 months. Linear regression analysis showed no significant UDCA dose effect on change in ALP from baseline to 6 and 12 months. The 3 and 5 year survival following diagnosis was 96% (n = 117) and 95% (n = 116), respectively. Survival at 3 and 5 years was 100% in those with 12 month ALP < 130, 97.6% and 95.1% in those with 12 month ALP 130-200, and 95.7% in those with 12 month ALP > 200, respectively. In patients with ALP > 200 at baseline, 44.4% had a Fibroscan value < 8kpa vs 18.5% had a Fibroscan value > 14 kpa. In patients with ALP > 200 at 12 months, 21.7% had a Fibroscan value < 8kpA vs 0% had a Fibroscan value > 14kpa. **Conclusion:** Initiating UDCA decreased the number of patients with ALP > 200 at 6 and 12 months compared to baseline. UDCA therapy aids survival but failed to reduce ALP levels < 200 in 20% of patients. Additional therapies should be considered for these patients.

Disclosures: The following people have nothing to disclose: Austin Mueller, Syed-Mohammed Jafri

4572-C | SAFETY, TOLERABILITY, AND PHARMACOKINETIC EFFECTS OF ELAFIBRANOR CO-ADMINISTRATION WITH SIMVASTATIN: AN OPEN-LABEL PHASE I TRIAL

Costello Medical[1], Benjamin Miller[1], Sarah Mazain[1], Rémy Hanf[2] and Carol Addy[3], (1)Ipsen, (2)Genfit S.a., (3)Genfit Corp

Background: The dual peroxisome proliferator-activated receptor (PPAR)α/δ agonist elafibranor is under development for treatment of primary biliary cholangitis (PBC). *In vitro* studies have demonstrated that elafibranor and its main active metabolite, GFT1007, do not have major effects on CYP450 activity. Patients with PBC often receive concomitant antihyperlipidemic therapies such as simvastatin, a sensitive substrate of CYP3A4. **Methods:** In this phase I, open-label, drug-drug interaction (DDI) trial (EudraCT: 2009-012523-28) investigating elafibranor and simvastatin, healthy participants were randomized into two groups: Group 1 received single oral doses of simvastatin 20 mg (Days 0 and 16) and once daily oral doses of elafibranor 80 mg (Day 2–17); Group 2 received single oral doses of elafibranor 80 mg (Days 0 and 28) and once daily oral doses of simvastatin 20 mg (Day 14–41). Pharmacokinetic parameters derived for elafibranor, GFT1007, and simvastatin included maximum observed plasma drug concentration (C_{max}) and area under the concentration-time curve from time 0–24 hours ($AUC_{(0-24)}$), which were analyzed using an ANOVA model. Adverse events (AEs) were described according to MedDRA (version 12.0) classifications. Treatment-emergent AEs (TEAEs), vital signs, laboratory safety, and ECG parameters were recorded. **Results:** 31 White male participants were randomized; data are reported for 28 who completed the trial. Mean (standard deviation) age was 27.2 (6.1) years. Point estimates and 90% confidence intervals for C_{max} and AUC_{0-24} values for elafibranor, GFT1007, and simvastatin are presented in the Table; no significant differences were reported. 28 TEAEs were reported by 17 participants; 24/28 were mild/moderate, 4/28 were severe. 3 AEs were considered treatment related, 6 possibly related, and 19 not related. No TEAEs were considered co-administration related. The most common TEAEs were headaches (n = 6) and diarrhea (n = 4). 1 serious AE occurred, prior to any study treatment. No clinically relevant safety findings were linked to elafibranor and/or simvastatin intake, except for an expected decrease in lipid parameters. **Conclusion:** Simvastatin and elafibranor co-administration was well tolerated in healthy male participants. There was no clinically meaningful effect of elafibranor administration on the C_{max} or daily exposure of simvastatin or *vice versa*. Therefore, co-administration of elafibranor with substrates of CYP3A4 is not expected to result in clinically significant DDIs.

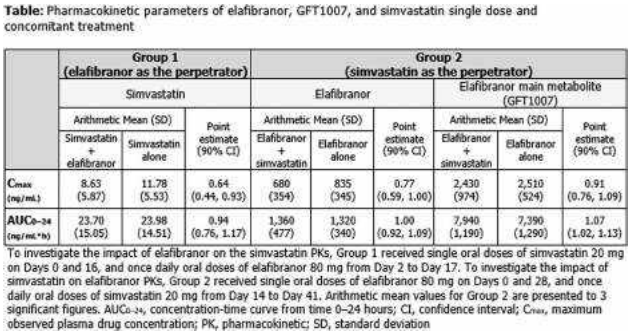

Table: Pharmacokinetic parameters of elafibranor, GFT1007, and simvastatin single dose and concomitant treatment

	Group 1 (elafibranor as the perpetrator)			Group 2 (simvastatin as the perpetrator)					
	Simvastatin			Elafibranor			Elafibranor main metabolite (GFT1007)		
	Arithmetic Mean (SD)		Point estimate (90% CI)	Arithmetic Mean (SD)		Point estimate (90% CI)	Arithmetic Mean (SD)		Point estimate (90% CI)
	Simvastatin + elafibranor	Simvastatin alone		Elafibranor + simvastatin	Elafibranor alone		Elafibranor + simvastatin	Elafibranor alone	
C_{max} (ng/mL)	8.63 (5.87)	11.78 (5.53)	0.64 (0.44, 0.93)	680 (354)	835 (345)	0.77 (0.59, 1.00)	2,430 (974)	2,510 (524)	0.91 (0.76, 1.09)
AUC_{0-24} (ng/mL*h)	23.70 (15.05)	23.98 (14.51)	0.94 (0.76, 1.17)	1,360 (477)	1,320 (340)	1.00 (0.92, 1.09)	7,940 (1,190)	7,390 (1,290)	1.07 (1.02, 1.13)

To investigate the impact of elafibranor on the simvastatin PKs, Group 1 received single oral doses of simvastatin 20 mg on Days 0 and 16, and once daily oral doses of elafibranor 80 mg from Day 2 to Day 17. To investigate the impact of simvastatin on elafibranor PKs, Group 2 received single oral doses of elafibranor 80 mg on Days 0 and 28, and once daily oral doses of simvastatin 20 mg from Day 14 to Day 41. Arithmetic mean values for Group 2 are presented to 3 significant figures. AUC_{0-24}, concentration-time curve from time 0–24 hours; CI, confidence interval; C_{max}, maximum observed plasma drug concentration; PK, pharmacokinetic; SD, standard deviation

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Benjamin Miller – Ipsen: Employee, Yes, No;
Sarah Mazain – Ipsen: Employee, Yes, No;
Rémy Hanf – GENFIT: Employee, Yes, Yes;
Carol Addy – GENFIT: Employee, Yes, No;

4573-C | SELADELPAR ACTIVITY IN A PRE-CLINICAL MODEL OF HUMAN PBC

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Background: Seladelpar, a selective peroxisome proliferator-activated receptor delta (PPARδ) agonist, has shown promising results in improving cholestasis in primary biliary cholangitis (PBC) patients in clinical trials. However, relevant pre-clinical PBC models to study possible targets and treatments are currently lacking. The human precision-cut liver slices (PCLS) model holds promise as it closely mimics the diverse liver cell types in a relevant pathological environment. In this study, we evaluate the effect of seladelpar by using PCLS from transplantation explants from PBC patients. **Methods:** The human PCLS were prepared from liver explants from PBC patients (n = 3) and subsequently cultured in William's E Medium with or without 2 μM of seladelpar up to 48 hours. The viability of the PCLS was assessed by measuring the ATP level in PCLS. The pyruvate dehydrogenase kinase 4 *(PDK4)* gene expression in the human PBC PCLS was assessed over time as a marker for PPARδ activation. Additionally, RNA-sequencing was performed on PBC PCLS after 48 hours of culture to investigate different pathways associated with PPARd activation. **Results:** The human PBC PCLS were viable with or without 2 μM seladelpar up to 48 hours of incubation, indicating that the PBC PCLS can be cultured for 48 hours. In addition, the *PDK4* expression was significantly increased, 10-fold, after 48 hours of incubation. Indicating that in PBC PCLS the marker of PPARd can be activated by 2 μM seladelpar. Furthermore, pathway enrichment analysis of the RNA-sequencing data revealed that the PPAR signaling pathway and the fatty acid degradation pathway were significantly enriched in slices that were treated with 2μM of seladelpar, which is in line with seladelpar results in other studies. **Conclusion:** By using pharmacological activity of seladelpar as proof-of-concept, PCLS obtained from end-stage PBC patients closely mimic the pathophysiological environment of PBC, and can serve as a relative inexpensive, reproducible, and valuable pre-clinical model for studying treatments.

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f 4574-C | SERUM AUTOTAXIN (ATX) AND FIBROBLAST GROWTH FACTOR-19 (FGF-19) ARE BIOMARKERS OF LINERIXIBAT TREATMENT RESPONSE IN PATIENTS (PTS) WITH CHOLESTATIC PRURITUS ASSOCIATED WITH PRIMARY BILIARY CHOLANGITIS (PBC)

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Background: Cholestatic pruritus (itch) is common in PBC and is associated with significantly impaired quality of life. Lysophosphatidic acid (LPA) and bile acids may have a pathophysiological role in pruritus. ATX is the primary enzyme that produces LPA and is a surrogate for LPA levels. ATX activity correlates with itch intensity in PBC. Linerixibat is a minimally absorbed, small-molecule ileal bile acid transporter inhibitor that improves pruritus and reduces systemic bile acid levels, ATX, and FGF-19, a downstream effector of farnesoid X receptor activation and regulator of bile acid biosynthesis.[1] Here, we analyze the association between itch response and changes in ATX and FGF-19 biomarker levels following linerixibat treatment. **Methods**: The Phase 2b, placebo-controlled, dose-ranging GLIMMER study (NCT02966834) enrolled 147 adult pts with PBC and pruritus.[1] Pts were randomized to receive linerixibat or placebo for 12 weeks (Weeks 4–16). Pts reported itch on a 0–10 numerical rating scale. As pt numbers were too low to analyze biomarkers in individual dose groups, the two twice daily (BID) dose groups, 40 and 90 mg BID which showed a greater response in pharmacodynamic biomarkers compared to once daily dosing, were combined. Serum ATX and FGF-19 levels were compared post hoc in pts receiving linerixibat 40/90 mg BID or placebo, at baseline versus Week 16, in itch responders and non-responders. Responder analysis from individual dose groups is not shown. Itch responders were defined as pts with a monthly itch score improvement of ≥2 at Week 16 compared with baseline. **Results**: Pts treated with linerixibat 40/90 mg BID (n = 45), or placebo (n = 36) were included; baseline demographics have been

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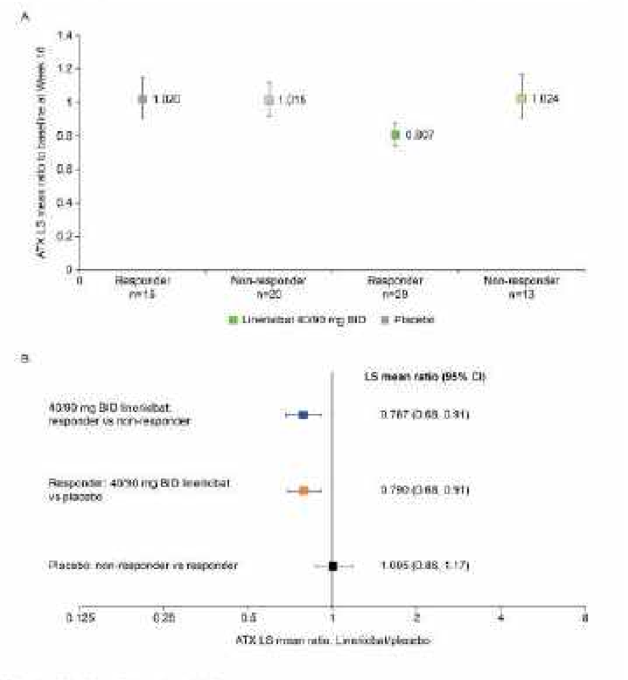
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

reported previously.[1] Itch responders in the 40/90 mg BID group, but not in the placebo group, had greater reductions in serum ATX at Week 16 compared with baseline (Figure 1A). In linerixibat -treated pts, ATX levels at Week 16 were reduced in itch responders compared to non-responders, and in comparison with placebo (Figure 1B). Similarly, FGF-19 reduction was associated with itch response in pts receiving linerixibat 40/90mg BID compared with placebo. **Conclusion**: Serum ATX and FGF-19 may function as biomarkers of itch response to linerixibat treatment. Reductions in these biomarkers are associated with clinical response in pts with PBC and pruritus. Reference: [1]Levy C, et al. *Clin Gastroenterol Hepatol*. 2022;S1542-3565(22) 01021-7. Funding: GSK (210000).

Figure 1: (A) ATX LS mean ratio to baseline at Week 16 in itch responders versus non-responders treated with 40/90 mg BID linerixibat or placebo (B) LS mean ratio of linerixibat versus placebo treatment in itch responders and non-responders



BID, twice daily; CI, confidence interval; LS, least squares

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f 4575-C | SUPPRESSING CHOLESTATIC FIBROTIC PROGRESSION BY TARGETING JCAD IN HEPATIC STELLATE CELLS

Li Xie[1], Hui Chen[1], Yuan Zhou[1], Li Zhang[1], Yongyu Yang[1], Xiuping Liu[2] and Jian Wu[1,3,4], (1)Dept. of Medical Microbiology, Fudan University School of Basic Medical Sciences, Shanghai 200032, China, (2) Department of Pathology, Shanghai Fifth People's Hospital, School of Basic Medical Sciences, Fudan University, Shanghai 200032, China, (3)Fudan University, Department of Gastroenterology and Hepatology, Zhongshan Hospital, Shanghai, China, (4) Shanghai Institute of Liver Diseases, Fudan University Shanghai Medical College, Shanghai 200032, China

Background: Activated hepatic stellate cells (HSCs) are the main cellular effectors in liver fibrosis in response to cholangiocyte damage. JCAD is a membrane conjunction protein, and was found to interact with LATS2 in the Hippo-YAP signaling pathway and to promote the transition from NASH to HCC. However, its participation in cholestatic fibrosis has not been explored yet. The present study aims to investigate the critical role of JCAD in cholestatic fibrosis in HSC-specific JCAD knock-out (HSC-JCAD-

KO) mice. **Methods:** Serial sections in the liver tissue of PBC patients were immunohistochemically stained. Hepatic fibrosis was induced by bile duct ligation (BDL) in wild-type (WT) and HSC-JCAD-KO mice. *In situ*-activated HSCs were isolated 0, 5 or 14 days after BDL. **Results:** Consistent with staining of serial sections from PBC patients, immunofluorescent staining of cholestatic liver revealed that JCAD was co-localized with smooth muscle α-actin (α-SMA) and was significantly up-regulated in activated HSCs in WT mice with BDL. Biochemical tests and H&E staining indicated that conditional inactivation of JCAD in HSCs did not significantly affect liver injury. However, hepatic fibrosis was remarkably ameliorated in HSC-JCAD-KO mice as documented by liver hydroxyproline content (0.31 ± 0.04 vs. 0.46 ± 0.06μg/mg, $p = 0.0541$) when compared to WT mice with BDL. Meanwhile, collagen deposition was dramatically reduced in HSC-JCAD-KO compared to WT mice as visualized by Trichrome staining and semi-quantitation score (2.72 ± 0.08 vs. $5.76 \pm 0.28\%$, $p < 0.01$). Second harmonic generation/two-photon excitation fluorescence microscopy with artificial intelligence analysis further revealed that fibrotic reduction was significant in the HSC-JCAD-KO mice undergone BDL, especially in the transitional and periportal areas (0.55 ± 0.10vs. 1.06 ± 0.14 %, $p < 0.05$). Liver levels of α-SMA protein in HSC-JCAD-KO mice were markedly lower than WT. Gene expression of TGF-β, CTGF, α-SMA, Col-1α1, and TIMP1 was strikingly enhanced in WT mice after BDL; whereas these markers were significantly suppressed in HSC-JCAD-KO mice. Moreover, JCAD deprivation significantly attenuated *in situ* activation of HSCs and decreased gene expression of TGF-β, CTGF, α-SMA, Col-1α1 and TIMP1, especially in 14 days after BDL. Furthermore, JCAD depletion reduced YAP/TAZ/TEAD transcriptional activity as documented by YAP/TEAD-based dual-luciferase reporter assay (54.8 ± 1.8 vs.113.0 ± 3.8 ratio, $p < 0.05$) compared to the controls; whereas, JCAD over-expression caused a significant induction of 8xGTIIC luciferase reporter activity. **Conclusion:** HSC-specific JCAD knock-out effectively halted hepatic fibrosis induced by bile duct ligation and the underlying mechanisms is attributed to suppressed Hippo-YAP signaling activity in HSCs. The elucidation of the critical role of JCAD in HSCs enables to develop molecular intervention against cholestasis-associated fibrosis.

Disclosures: The following people have nothing to disclose: Li Xie, Hui Chen, Yuan Zhou, Li Zhang, Yongyu Yang, Xiuping Liu, Jian Wu

4576-C | SURVIVAL OF PATIENTS WITH DECOMPENSATED PRIMARY BILIARY CHOLANGITIS IN THE ERA OF OBETICHOLIC ACID AND MELD 3.0

Mai Sedki[1], Nakia L Chung[1], Aparna Goel[1], Aldo J. Montano-Loza[2], Allison J. Kwong[3], Kazunari Sasaki[1], W. Ray Kim[1] and Ajitha Mannalithara[1], (1)Stanford University School of Medicine, (2)University of Alberta, AB, Canada, (3)Stanford University

Background: Since the approval of obeticholic acid (OCA) for the treatment of primary biliary cholangitis (PBC) in 2016, there have been concerns regarding hepatotoxicity, particularly in patients with advanced liver disease. In this study, we look for evidence of excess mortality among PBC patients awaiting liver transplantation (LT) following the approval of OCA, incorporating the latest version of the model for end-stage liver disease (MELD 3.0) for survival prediction. **Methods:** Data for all PBC patients with Child-Turcotte-Pugh (CTP) class B or C waitlisted for primary LT between Jan 2005 and Dec 2021 were extracted from the Organ Procurement and Transplantation Network registry. Patients were divided into two cohorts based on the date of waitlist registration: before (pre-OCA era) and after May 2016 (OCA era). We applied Cox regression to predict 90-day survival based on MELD 3.0 in a subset from the pre-OCA era and validated the prediction in the same era. We then compared observed versus predicted survival in the OCA era and calculated the standardized mortality ratios (SMRs). **Results:** There were 5,061 waitlist registrants with PBC, of whom 4,405 met the inclusion criteria, with 2,606 subjects in the pre-OCA era and 1,502 in the OCA era. The pre-OCA group was randomly divided into model training ($n = 1{,}825$) and validation sets ($n = 781$). As expected, MELD 3.0 was highly predictive of 90-day mortality among patients waitlisted for PBC with a hazard ratio of 1.220 (95% confidence interval [95%CI]: 1.196-1.245, $p < 0.001$) per 1 MELD point and Harrell's c-index of 0.860. When the survival prediction model was applied to the pre-OCA era validation subset, the observed and expected 90-day survival matched closely (Figure A, $p = 0.38$, GND test). In the OCA era, waitlist registrants were 59 years (median) and 85% were women, 65% white, 22% Hispanic, 9% black and 3% Asian. The median MELD 3.0 was 21 and the CTP score was 10 at registration. In Figure B, when the survival prediction model derived and validated from the pre-OCA era was applied to predict the number of deaths in the OCA era, the observed ($n = 124$ deaths) was nearly identical to the predicted (n = 126 deaths). The SMR was 0.82 (95%CI: 0.61-1.10) on day 15, 1.09 (95%CI: 0.87-1.36) on day 30, and gradually decreased to 0.99 (95%CI: 0.83-1.18) on day 90. **Conclusion:** MELD 3.0 is highly predictive of 90-day mortality in liver transplant waitlist registrants with PBC and hepatic decompensation. Based on the MELD 3.0-based survival prediction estimates, the survival of PBC patients in the OCA era was comparable to that in the pre-OCA era.

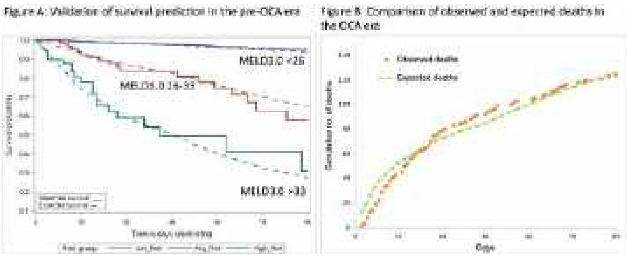


Figure A: Validation of survival prediction in the pre-OCA era
Figure B: Comparison of observed and expected deaths in the OCA era

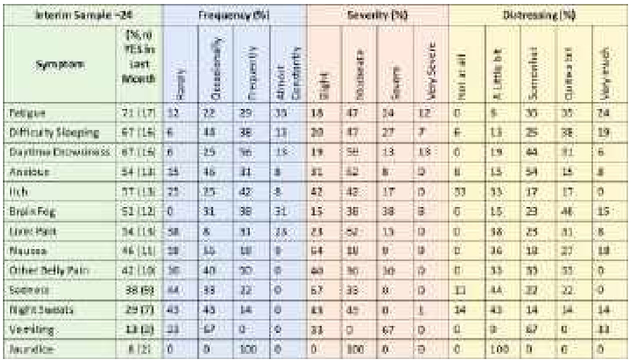
Disclosures: The following people have nothing to disclose: Mai Sedki, Nakia L Chung, Aparna Goel, Aldo J. Montano-Loza, Allison J. Kwong, Kazunari Sasaki, W. Ray Kim

Disclosure information not available at the time of publication: Ajitha Mannalithara

4577-C | SYMPTOMS OF PRIMARY SCLEROSING CHOLANGITIS (PSC) IN THE LAST MONTH: PRELIMINARY DATA FROM THE PSC-PARTNERS PATIENT REPORTED OUTCOME MEASURE PROJECT

Donna M. Evon[1], Kaya Merkler[1], Bryce Reeve[2], Chelsea Anderson[1], Ricky Safer[3], Joanne Hatchett[3], Rachel Gomel[3], Christopher L. Bowlus[4] and David N. Assis[5], (1)University of North Carolina, (2)Duke University, (3)PSC Partners Seeking a Cure, (4) University of California Davis, Sacramento, CA, (5)Yale School of Medicine, New Haven, CT

Background: Patient-reported symptoms of primary sclerosing cholangitis (PSC) are not well documented. We are studying symptoms of PSC for the comprehensive development of PSC-specific patient-reported symptom measures fit for clinical trials. **Methods:** Patients with PSC were recruited through the PSC Partners Patient Registry. Inclusion criteria were PSC diagnosis, age 18 or older, English-speaking, living in the US, symptomatic within the last 5 years, and not waitlisted nor a recipient of a liver transplant. Patients engaged in a phone survey to screen for the presence, frequency, severity, and distress of 13 symptoms associated with PSC, using a modified version of the Memorial Symptom Assessment Scale. Patients indicated if they had experienced each symptom in the last month (yes/no). If yes, they were queried about symptom frequency (How often did you experience fatigue?), severity (How severe was the fatigue?), and distress (How much did the fatigue distress or bother you?). Response options were based on a 4- or 5-point ordinal scale. Patients classified each symptom as definitely, partially, or unrelated to PSC. Sociodemographics and patient-reported medical history related to PSC were recorded. **Results:** Participants (currently N = 24 in interim sample) were 63% female, 88% white, with a mean age of 49 (SD = 12.6). 87% were college educated, 58% were working and 21% were retired. 75% had irritable bowel disease, 79% had large duct PSC, 17% had autoimmune hepatitis, 33% had cirrhosis, and two reported symptoms consistent with decompensated cirrhosis. Fatigue (71%) was the most prevalent symptom in the past month (See table below). Over 50% of patients experienced difficulty sleeping, daytime drowsiness, anxiety, pruritus, brain fog, and pain over the liver. Between 85-100% of patients indicated that these symptoms were definitely or partially related to PSC. Between 29-46% of patients experienced nausea, other belly pain, sadness, or night sweats. For symptoms that were prevalent in more than 50% of patients, 46-69% of patients rated these symptoms as “frequent” or “always constant”; 61-84% rated these symptoms as “moderate” to "very severe," and 30-94% rated these symptoms as “somewhat” to “very much” distressing. **Conclusion:** Among symptomatic adults with PSC, over 50% report issues with fatigue, sleep, anxiety, itch, brain fog, and liver pain within the last month that are frequent, moderate in severity, and distressing. Planned in-depth qualitative interviews are the critical next step towards understanding the breadth and depth of PSC symptoms to develop PSC-specific patient-reported symptom measures.



Interim Sample =24		Frequency (%)				Severity (%)				Distressing (%)				
Symptom	(%, n) YES in Last Month	Rarely	Occasionally	Frequently	Almost Constantly	Slight	Moderate	Severe	Very Severe	Not at all	A Little bit	Somewhat	Quite a bit	Very much
Fatigue	71 (17)	12	22	29	35	18	47	24	12	0	6	35	35	24
Difficulty Sleeping	67 (16)	6	44	38	13	20	47	27	7	6	13	25	38	19
Daytime Drowsiness	67 (16)	6	25	56	13	19	56	13	13	0	19	44	31	6
Anxiety	54 (13)	15	46	31	8	31	62	8	0	8	15	54	15	8
Itch	57 (13)	25	25	42	8	42	42	17	0	33	33	17	17	0
Brain Fog	51 (12)	0	31	38	31	15	38	38	8	0	15	23	46	15
Liver Pain	54 (13)	38	8	31	23	23	62	15	0	0	38	23	31	8
Nausea	46 (11)	18	55	18	9	64	18	9	9	0	36	18	27	18
Other Belly Pain	42 (10)	30	40	30	0	40	30	30	0	0	33	33	33	0
Sadness	38 (9)	44	33	22	0	67	33	0	0	11	44	22	22	0
Night Sweats	29 (7)	43	43	14	0	43	43	0	14	14	43	14	14	14
Vomiting	13 (3)	33	67	0	0	33	0	67	0	0	0	67	0	33
Jaundice	8 (2)	0	0	100	0	0	100	0	0	0	100	0	0	0

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Christopher L. Bowlus – Cymabay: Advisor, No, Yes; GSK: Advisor, No, Yes; Invea: Advisor, No, Yes; Ipsen: Advisor, No, No; Boston Scientific: Grant/Research

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David N. Assis:

Disclosure information not available at the time of publication: Kaya Merkler, Bryce Reeve, Chelsea Anderson, Rachel Gomel

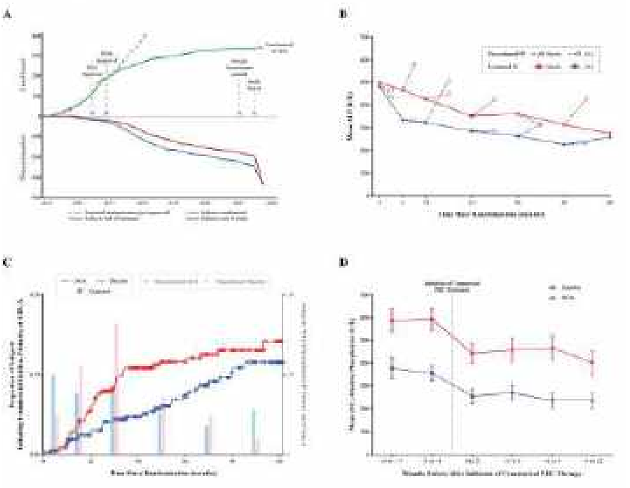
4578-C | THE CHALLENGE OF CONFIRMATORY TRIALS IN RARE DISEASE: LESSONS LEARNED FROM THE COBALT TRIAL IN PRIMARY BILIARY CHOLANGITIS

Kris V. Kowdley[1], *Tracy Mayne*[2], *Darren Wheeler*[2], *Elizabeth S. Malecha*[2], *Erik Ness*[2] *and Nora Cazzagon*[3], *(1)Liver Institute Northwest and Elson S. Floyd College of Medicine, Washington State University, Seattle, WA, USA, (2)Intercept Pharmaceuticals,*
Inc., Morristown, NJ, (3)Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy

Background: Recruitment and retention are difficult in rare disease clinical outcomes trials, particularly when a study drug is commercially available or when markers of disease progression are readily observable, which lead to functional unblinding, informative censoring, and treatment crossover.

We explore these issues in the COBALT phase 3b/4 confirmatory outcomes trial of obeticholic acid (OCA) for the treatment of primary biliary cholangitis (PBC). **Methods:** COBALT was a randomized, double-blind, placebo-controlled outcomes trial. Patients were randomized to placebo or OCA 5 mg daily, titrated to 10 mg if tolerated. We examined recruitment before and after commercial OCA availability; discontinuation of investigational product (IP); association between IP discontinuation and alkaline phosphatase (ALP) levels, a surrogate marker of disease progression in PBC; crossover to other therapies (commercial OCA, fibrates, or ursodeoxycholic acid [when not used at baseline]); and the impact of treatment crossover on ALP levels. **Results:** Recruitment met projections and dropout was negligible before OCA became commercially available. Subsequently, recruitment slowed, and dropout increased (Figure 1A). The study was terminated early with 80% targeted enrollment (OCA, n = 168; placebo, n = 166). Figure 1B shows ALP levels over time by treatment for subjects who continued IP (solid circles) and discontinued IP prior to an endpoint event (open circles). Placebo subjects who discontinued IP had consistently higher ALPs just prior to discontinuation, suggestive of functional unblinding. As shown in Figure 1C, peak discontinuation of OCA occurred during the first 6 months (blue bars) largely due to pruritus (40%), with almost no initiation of commercial treatment (blue line). Peak placebo IP discontinuation occurred in the first 24 months, when initiation of commercially available PBC therapy peaked at 27%. ALP levels of patients initiating commercial PBC therapy decreased in both treatment groups and were sustained after initiating commercial treatments, with a greater decrease in the placebo group (Figure 1D). **Conclusion:** In the COBALT trial, functional unblinding and early treatment crossover in the placebo group led to loss of balance, biasing results and compromising their interpretation. Alternative study designs (eg external controls) are needed to assess the efficacy and safety of commercially available study drugs in rare diseases.

Figure 1. (A) Enrollment and discontinuation of subjects with PBC in the COBALT study. (B) Mean ALP levels in subjects who continued or discontinued IP. (C) Number of subjects who discontinued IP and initiated commercial treatments. (D) Mean ALP levels before and after initiation of commercial therapy (includes subjects with at least one second-line therapy measurement).



Abbreviations: ALP, alkaline phosphatase; DSMB, data and safety monitoring board; EMA, European Medicines Agency; FDA, Food and Drug Administration; IP, investigational product; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

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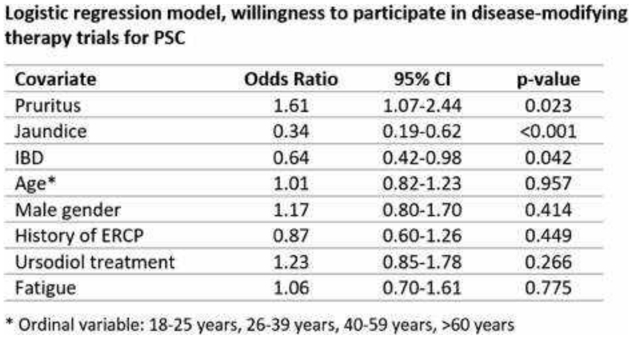
Darren Wheeler – Intercept Pharmaceuticals, Inc.: Employee, No, No;
Elizabeth S. Malecha – Intercept Pharmaceuticals, Inc.: Employee, No, No;
Erik Ness – Intercept Pharmaceuticals, Inc.: Employee, No, No;
The following people have nothing to disclose: Nora Cazzagon

4579-C | THE EXTERNALLY-LED PATIENT-FOCUSED DRUG DEVELOPMENT MEETING FOR PRIMARY SCLEROSING CHOLANGITIS: INSIGHTS ON PATIENT INVOLVEMENT IN CLINICAL TRIALS

Michael Li[1], Ruth-Anne Pai[2], Rachel Gomel[2], Mary Pressley Vyas[3], Sarah Curup Callif[2], Joanne Hatchett[2], Ricky Safer[2], Christopher L. Bowlus[4] and Jennifer C. Lai[5], (1)University of California, San Francisco, (2)PSC Partners Seeking a Cure, (3)PSC Partners Seeking a Cure Canada, (4)University of California Davis, Sacramento, CA, (5)University of California-San Francisco

Background: New AASLD guidance recommends consideration of all patients with primary sclerosing cholangitis (PSC) as potential candidates for clinical trials. However, the factors influencing patient interest and the barriers preventing inclusive and accessible participation in trials for PSC have yet to be elucidated. We investigated PSC patient interest in trial participation and identified factors associated with willingness to participate in drug trials. **Methods:** Patient-Focused Drug Development (PFDD) is an FDA initiative to ensure that patient experiences and perspectives on drug development are captured. PSC Partners developed the international "Our Voices" survey to inform the development of the Externally-Led PSC PFDD meeting. Our team of researchers and patient advocacy representatives analyzed data from this survey, which included 797 adults with PSC. **Results:** Patients identified slowing disease progression as the most important drug development outcome (67%). 89% of patients identified their hepatologist/gastroenterologist as who they would approach for advice about trials. 61% of patients reported being willing to participate in drug trials, while only 26% of patients reported ever being asked to participate. Notable frequently reported barriers to trial involvement included unknown long-term risks (71%), long travel times to study center (32%), a liver biopsy requirement (27%), and concerns about taking too much time off work (22%). On multivariable logistic regression, pruritus (aOR 1.61, 95% CI 1.07-2.44, p = 0.023), jaundice (aOR 0.34, 95% CI 0.19-0.62, p < 0.001), and inflammatory bowel disease (aOR 0.64, 95% CI 0.42-0.98, p = 0.042) were associated with willingness to participate in disease-modifying therapy trials (Figure). Pruritus (aOR 2.25, 95% CI 1.50-3.39, p < 0.001) was also independently associated with willingness to participate in symptom treatment trials. **Conclusion:** Hepatologists/gastroenterologists are trusted by PSC patients and must be responsible for closing the gap between trial interest and participation. Pruritus is one of the most influential symptoms associated with willingness to participate in drug trials and can serve as an indicator of patient interest in trial participation. Patient advocacy groups like PSC Partners can play a crucial role in further investigation to understand the gaps between clinical trial interest, referral, and participation, with an emphasis on promoting equity and diversity in clinical trials.



Logistic regression model, willingness to participate in disease-modifying therapy trials for PSC

Covariate	Odds Ratio	95% CI	p-value
Pruritus	1.61	1.07-2.44	0.023
Jaundice	0.34	0.19-0.62	<0.001
IBD	0.64	0.42-0.98	0.042
Age*	1.01	0.82-1.23	0.957
Male gender	1.17	0.80-1.70	0.414
History of ERCP	0.87	0.60-1.26	0.449
Ursodiol treatment	1.23	0.85-1.78	0.266
Fatigue	1.06	0.70-1.61	0.775

* Ordinal variable: 18-25 years, 26-39 years, 40-59 years, >60 years

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Jennifer C. Lai – Novo Nordisk: Advisor, No, No; Genfit: Consultant, No, No; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Vir: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gore: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Flagship Pioneering: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Michael Li, Ruth-Anne Pai, Rachel Gomel, Mary Pressley Vyas, Sarah Curup Callif, Joanne Hatchett, Ricky Safer

4580-C | THE IMPACT OF CONCOMITANT NON-ALCOHOLIC FATTY LIVER DISEASE ON PRIMARY SCLEROSING CHOLANGITIS

Ana Marenco-Flores[1], Leandro Sierra[1], Romelia Barba Bernal[1], Bryan Ferrigno[2], Daniela Goyes[3], Wilfor Diaz Fernandez[2], Vilas Patwardhan[1] and Alan Bonder[1], (1) Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, (2)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (3)Yale University Medical Center, New Haven, CT, United States

Background: Primary sclerosing cholangitis (PSC) is a rare chronic cholestatic liver disease characterized by inflammation and fibrosis of bile ducts. PSC is a progressive condition that can lead to fibrosis and cirrhosis, the only definitive treatment is transplant. Non-alcoholic fatty liver disease (NAFLD) is becoming one of the fastest-growing leading indications for liver transplants. There is a scarcity of studies examining the impact of PSC and concomitant NAFLD on disease progression, compared to PSC alone. Understanding the impact of concomitant NAFLD on PSC progression is crucial for patient management and prognostication. We aimed to evaluate the effect of fatty liver disease on patients with PSC. **Methods:** We conducted a single-center, observational cohort study from our prospective autoimmune liver disease registry. We compared patients with PSC alone to patients with PSC and NAFLD. NAFLD was defined as hepatic steatosis by imaging (MRI, CT scan, ultrasound, and transient elastography) or biopsy in the absence of excessive alcohol consumption (< 14 drinks/week for women, < 21 drinks/weekfor men). Patient's demographic and clinical characteristics were collected and compared among the two groups. Statistical analysis evaluating for significant differences was performed using Chi-square and t-tests. **Results:** We identified 85 patients with PSC and 71 with features of both PSC

Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

and NAFLD. Patients with PSC and concomitant NAFLD (PSC-NAFLD) were older (47 vs. 40; p = 0.008) and more likely to be men than the PSC group (58% vs. 48%; p = 0.236). The PSC group had a higher percentage of White Caucasians (82% vs. 73%; p = 0.003). Markers of liver inflammation were higher at the time of diagnosis in patients with PSC alone than in patients with PSC-NAFLD overlap (ALP: 245 vs. 211; ALT: 91 vs. 81; AST: 68 vs. 59; total bilirubin: 1.07 vs. 1.04; p > 0.05 for all). Body mass index (BMI) was significantly higher in the PSC-NAFLD group (30 vs. 27; p = 0.005). Among patients with available liver biopsies, PSC patients were more likely to have moderate to severe activity (40% vs. 15%; p = 0.026) and advanced liver fibrosis (30% vs. 18%; p = 0.081). (Table 1) **Conclusion:** NAFLD does not appear to adversely affect PSC disease progression. Surprisingly, patients with PSC alone had more active disease and advanced fibrosis compared to those with PSC-NAFLD. Further studies investigating the impact of NAFLD on PSC are warranted.

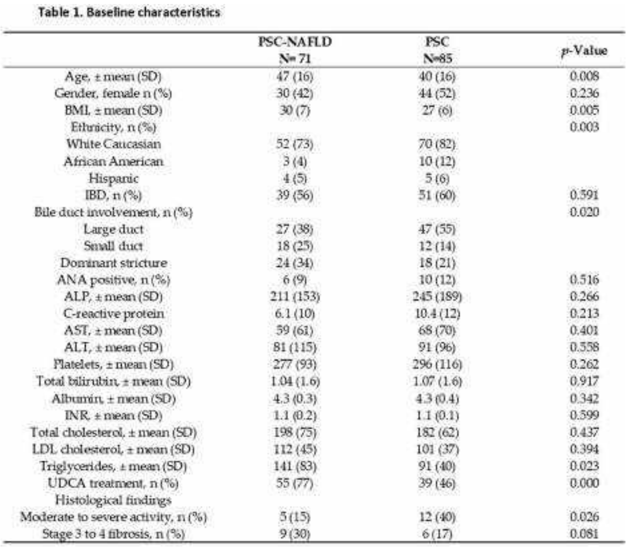

Table 1. Baseline characteristics

	PSC-NAFLD N= 71	PSC N=85	p-Value
Age, ± mean (SD)	47 (16)	40 (16)	0.008
Gender, female n (%)	30 (42)	44 (52)	0.236
BMI, ± mean (SD)	30 (7)	27 (6)	0.005
Ethnicity, n (%)			0.003
White Caucasian	52 (73)	70 (82)	
African American	3 (4)	10 (12)	
Hispanic	4 (5)	5 (6)	
IBD, n (%)	39 (56)	51 (60)	0.591
Bile duct involvement, n (%)			0.020
Large duct	27 (38)	47 (55)	
Small duct	18 (25)	12 (14)	
Dominant stricture	24 (34)	18 (21)	
ANA positive, n (%)	6 (9)	10 (12)	0.516
ALP, ± mean (SD)	211 (153)	245 (189)	0.266
C-reactive protein	6.1 (10)	10.4 (12)	0.213
AST, ± mean (SD)	59 (61)	68 (70)	0.401
ALT, ± mean (SD)	81 (115)	91 (96)	0.558
Platelets, ± mean (SD)	277 (93)	296 (116)	0.262
Total bilirubin, ± mean (SD)	1.04 (1.6)	1.07 (1.6)	0.917
Albumin, ± mean (SD)	4.3 (0.3)	4.3 (0.4)	0.342
INR, ± mean (SD)	1.1 (0.2)	1.1 (0.1)	0.599
Total cholesterol, ± mean (SD)	198 (75)	182 (62)	0.437
LDL cholesterol, ± mean (SD)	112 (45)	101 (37)	0.394
Triglycerides, ± mean (SD)	141 (83)	91 (40)	0.023
UDCA treatment, n (%)	55 (77)	39 (46)	0.000
Histological findings			
Moderate to severe activity, n (%)	5 (15)	12 (40)	0.026
Stage 3 to 4 fibrosis, n (%)	9 (30)	6 (17)	0.081

Disclosures: The following people have nothing to disclose: Ana Marenco-Flores, Leandro Sierra, Romelia Barba Bernal, Bryan Ferrigno, Daniela Goyes, Wilfor Diaz Fernandez, Vilas Patwardhan, Alan Bonder

4581-C | THE IMPACT OF DIETARY INTERVENTIONS ON METABOLOMIC PROFILE AND DISEASE PROGRESSION IN PRIMARY SCLEROSING CHOLANGITIS PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Xiaole Yin[1], Zheng Sun[1], Shanlin Ke[1], Shaikh Danish Mahmood[2], Gila Feinman Sasson[2], Demsina Babazadeh[2], Macie Andrews[2], Shelley Hurwitz[2], Maia Paul[2], Nadine Javier[2], Malav Dave[2], Alexandra Austin[2], Dan Pratt[3], Christopher L. Bowlus[4], Linda Gray[4], Francene Steinberg[5], Elaine Souza[5], Yang-Yu Liu[1] and Joshua R. Korzenik[2], (1)Channing Division of Network Medicine, Brigham and Women's Hospital, (2)Brigham and Women's Hospital, (3)Massachusetts General Hospital, (4)University of California Davis, Sacramento, CA, (5)University of California, Davis

Background: Primary sclerosing cholangitis (PSC) is a chronic liver disease often associated with inflammatory bowel disease (IBD). Diet plays an important role in the host health and disease. However, the role of diet in modifying disease progression in PSC and associated IBD remains underexplored. **Methods:** We undertook a longitudinal study involving PSC patients (n = 20), which were randomly subjected to one of the following two distinct dietary interventions for 8 weeks: Low Protein Diet (LPD, n = 10) or Specific Carbohydrate Diet (SCD, n = 10). Diet was recorded in detail and stool samples were obtained at 4 time points for whole metagenomic sequencing and global untargeted metabolomics. Alkaline Phosphatase (ALP) values were measured to reflect potential disease amelioration. **Results:** A total of 20 PSC patients were enrolled including 10 with ulcerative colitis (UC), 3 with Crohn's disease (CD) and 7 with PSC alone. The clinical results are reported in detail in a separate abstract. We report here the microbial analysis. Our results showed a significant correlation between dietary intervention and disease progression via Lasso regression indicating lower ALP values with lower protein intake compared to baseline. A total of 1428 detected metabolites were analyzed using linear multivariable models to identify key metabolite features in response to the LPD. We identified 27 elevated and 9 decreasing metabolites, which align with previously known metabolite sets associated with IBD, CD, and UC, but unreported in PSC before. Moreover, enrichment analysis highlighted *ammonia recycling* and *methionine metabolism* as key pathways influenced by LPD dietary interventions. The notable metabolites including p-cresol sulfate and methionine represent organic sulfur acids and derivatives, and L-glutamine represents nitrogen metabolism. We finally performed stratified analysis, finding that LPD to be especially beneficial in terms of high metabolomic response for PSC patients with UC (but not PSC patients with CD, or PSC alone), which is consistent with the clinical response. Longitudinal observation in this subgroup illustrated a clear reduction in sulfur and nitrogen-related metabolites under LPD. **Conclusion:** Dietary interventions, particularly LPD, significantly influence disease progression in PSC patients with UC, offering potential as a supplementary therapeutic strategy. Our study also reveals unique metabolite responses to dietary modifications, expanding our understanding of metabolic mechanisms in PSC and associated IBD. Further research is warranted to optimize dietary strategies for individual patient subgroups.

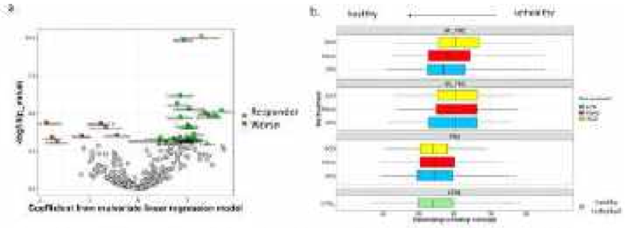

Figure 1. The metabolite profile under the dietary intervention. a. The multivariate analysis highlights the metabolites with significant changes under the LPD treatment for PSC patients. b. The stratification analysis showed LPD to be especially beneficial for PSC patients with UC.

Disclosures: Christopher L. Bowlus – Cymabay: Advisor, No, Yes; GSK: Advisor, No, Yes; Invea: Advisor, No, Yes; Ipsen: Advisor, No, No; Boston Scientific: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Calliditas: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; ChemoMab: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; COUR Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Cymabay: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; GSK: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Hanmi: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Ipsen: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Mirum: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Novo Nordisk: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pliant: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Viking: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; BMS: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;

Joshua R. Korzenik – Thetis: Consultant, No, No; ClostraBio: Consultant, No, No; Corevitas: Consultant, No, No; Promakhos: Consultant, No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; ColonaryConcepts: Executive role , No, No; Bilayer Therapeutics: Executive role , No, No;

The following people have nothing to disclose: Xiaole Yin, Zheng Sun, Shanlin Ke, Shaikh Danish Mahmood, Gila Feinman Sasson, Demsina Babazadeh, Macie Andrews, Shelley Hurwitz, Maia Paul, Nadine Javier, Malav Dave, Alexandra Austin, Dan Pratt, Linda Gray, Francene Steinberg, Elaine Souza, Yang-Yu Liu

4582-C | THE PRESENCE OF FATTY LIVER IS ASSOCIATED WITH HIGHER TREATMENT RESPONSE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

Leandro Sierra[1], Romelia Barba Bernal[1], Ana Marenco-Flores[1], Bryan Ferrigno[2], Daniela Goyes[3], Wilfor Diaz Fernandez[2], John Esli Medina Morales[4], Alan Bonder[1], Vilas Patwardhan[1] and ALD team, (1)Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, (2)Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, (3)Yale University Medical Center, New Haven, CT, United States, (4)Rutgers New Jersey Medical School, Kearny, NJ

Background: Primary biliary cholangitis (PBC) is an autoimmune, chronic cholestatic liver disease involving bile ducts. Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide and affects up to 25% of the general population. Therefore, it is not surprising that both pathologies can coexist. However, data regarding the impact of concomitant NAFLD on PBC treatment response or disease progression is scarce. Therefore, this study aimed to evaluate the relationship between coexistent fatty liver on the treatment response of PBC patients. **Methods:** We conducted a single-center, observational cohort study from our prospective autoimmune liver disease registry. We compared patients with PBC alone to patients with PBC and concomitant NAFLD who received treatment with ursodeoxycholic (UDCA). NAFLD was defined as hepatic steatosis by imaging (MRI, CT scan, ultrasound, and transient elastography) or biopsy in the absence of excessive alcohol consumption (<14 drinks/week for women, <21 drinks/week for men). Patient's demographic and clinical characteristics were collected. We used the GLOBAL-PBC score to assess treatment response. Statistical analysis evaluating for significant differences was performed with Chi-square and t-tests. **Results:** We identified 129 patients with PBC and 87 patients with both PBC and NAFLD. Patients with PBC-NAFLD were younger (59.8 vs. 65.8; $p=0.0001$). The PBC group was significantly more likely to be women than the PBC-NAFLD cohort (98% vs. 89%; $p=0.005$). At diagnosis, the ALP levels were significantly higher in PBC-NAFLD than in the PBC group (224 vs. 210; $p=0.020$). Other markers tended to be higher at diagnosis in the PBC group than in patients with PBC-NAFLD (mean ALT: 53 vs. 51, AST: 45.9 vs. 45.8; $p>0.05$ for both). Body Mass Index (BMI) was significantly higher in the PBC-NAFLD group compared to PBC alone (30.7 vs. 29.6; $p=0.049$). Patients with PBC-NAFLD were more likely to have a higher percentage of treatment response compared to the PBC group, with a trend towards higher response rates at a five-year follow-up. The rate of responders at one-year follow-up was 83% vs. 85%; $p=0.680$ and the five-year follow-up was 81 vs. 92% in the PBC groups and PBC-NAFLD, respectively; $p=0.021$. (Figure 1) **Conclusion:** The presence of NAFLD may not adversely affect the course of PBC. PBC-NAFLD patients might present earlier to physicians and treating NAFLD might improve the course of PBC. Moreover, it is possible that individual's with NAFLD are more motivated to make positive lifestyle changes, which could have indirect benefits for their overall health, including their response to PBC treatment. Further studies investigating the impact of concomitant NAFLD on PBC patients are warranted.

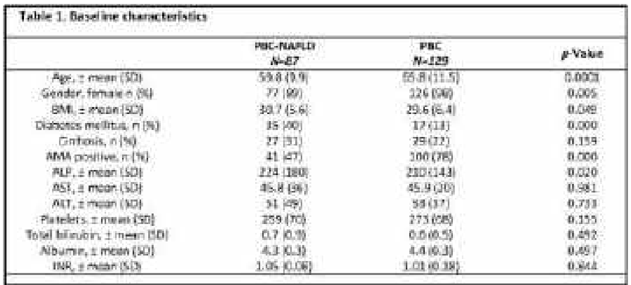

Table 1. Baseline characteristics

	PBC-NAFLD *N=87*	PBC *N=129*	*p*-Value
Age, ± mean (SD)	59.8 (9.9)	65.8 (11.5)	0.0001
Gender, female n (%)	77 (89)	126 (98)	0.005
BMI, ± mean (SD)	30.7 (5.6)	29.6 (6.4)	0.049
Diabetes mellitus, n (%)	35 (40)	17 (13)	0.000
Cirrhosis, n (%)	27 (31)	29 (22)	0.159
AMA positive, n (%)	41 (47)	100 (78)	0.000
ALP, ± mean (SD)	224 (180)	210 (143)	0.020
AST, ± mean (SD)	45.8 (36)	45.9 (20)	0.981
ALT, ± mean (SD)	51 (49)	53 (37)	0.733
Platelets, ± mean (SD)	259 (70)	273 (68)	0.155
Total bilirubin, ± mean (SD)	0.7 (0.9)	0.6 (0.5)	0.492
Albumin, ± mean (SD)	4.3 (0.3)	4.4 (0.3)	0.497
INR, ± mean (SD)	1.06 (0.08)	1.01 (0.38)	0.844

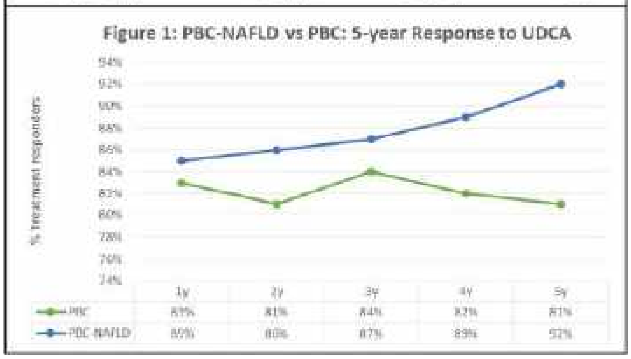

Figure 1: PBC-NAFLD vs PBC: 5-year Response to UDCA

Disclosures: The following people have nothing to disclose: Leandro Sierra, Romelia Barba Bernal, Ana Marenco-Flores, Bryan Ferrigno, Daniela Goyes, Wilfor Diaz Fernandez, John Esli Medina Morales, Alan Bonder, Vilas Patwardhan

4583-C | THE PRESENCE OF HEPATITIS B CORE ANTIBODY CORRELATES WITH RISK OF CHRONIC KIDNEY DISEASE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

Jialiang Chen, Yao Liu, Yufei Bi, Fangyuan Gao and Xianbo Wang, Beijing Ditan Hospital, Capital Medical University, Beijing, China

Background: Chronic kidney disease (CKD) is a common comorbidity in patients with chronic liver diseases, especially in chronic hepatitis B and decompensated cirrhosis. Whether the same is true for patients with primary biliary cholangitis (PBC) who have recovered from previous HBV infections remains to be determined. This study aimed to investigate the association between antibody to hepatitis B core antigen (anti-HBc) and risk of CKD in patients with PBC who test negative for hepatitis B surface antigen (HBsAg). **Methods:** A total of 1257 patients diagnosed with PBC at first admission from a tertiary hospital in China were divided into anti-HBc-positive ($n=503$) and anti-HBc-negative ($n=754$) cohorts. All patients tested negative for HBsAg. Demographic, clinical, and laboratory features were retrospectively analyzed from January 2008 to December 2021. Serum creatinine-based equations from the Chronic

Kidney Disease Epidemiology Collaboration (CKD-EPI) were used to estimate the glomerular filtration rate (eGFR). CKD was defined as an eGFR < 60 mL/min/1.73 m². Univariate and multivariate logistic regression analyses were conducted to determine the risk factors of CKD. The adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. **Results:** In our study population, there were 1080 (85.9%) women, with a median age of 57 years. Compared with the anti-HBc-negative cohort, the median age was higher in the anti-HBc-positive cohort (59 vs. 56 years, $P < 0.001$). Anti-HBc-positive cohort also had higher median levels of blood urea nitrogen (4.81 vs. 4.57 mmol/L, $P = 0.016$), serum creatinine (59.4 vs. 57.4 μmol/L, $P = 0.009$), and lower median levels of eGFR (101.1 vs. 103.0 mL/min/1.73 m², $P = 0.011$). The overall prevalence of CKD was 8.3% (104/1257), accompanied by 232 patients (18.5%) with mild renal impairment (eGFR < 90 but ≥ 60 mL/min/1.73 m^2). Anti-HBc-positive cohort had a higher prevalence of CKD than the anti-HBc-negative cohort (11.3% vs. 6.2%; OR = 1.92, 95% CI: 1.28 – 2.88, $P = 0.002$). In the multivariate analysis, anti- HBc positive (OR = 1.56, 95% CI: 0.98 – 2.46, $P = 0.057$), age (OR = 1.12, 95%CI: 1.09 – 1.15, $P < 0.001$), current smoking (OR = 2.97, 95% CI: 1.30 – 6.79, $P = 0.010$), hypertension (OR = 1.85, 95% CI: 1.15 – 2.98, $P = 0.011$) and decompensated cirrhosis (OR = 3.71, 95%CI: 2.10 – 6.57, $P < 0.001$) were independent factors associated with the presence of CKD. **Conclusion:** Previous hepatitis B virus infection was associated with chronic renal dysfunction of PBC, potentially leading to poorer outcomes. PBC patients with anti-HBc positive in clinical practice should strengthen follow-up of renal function.

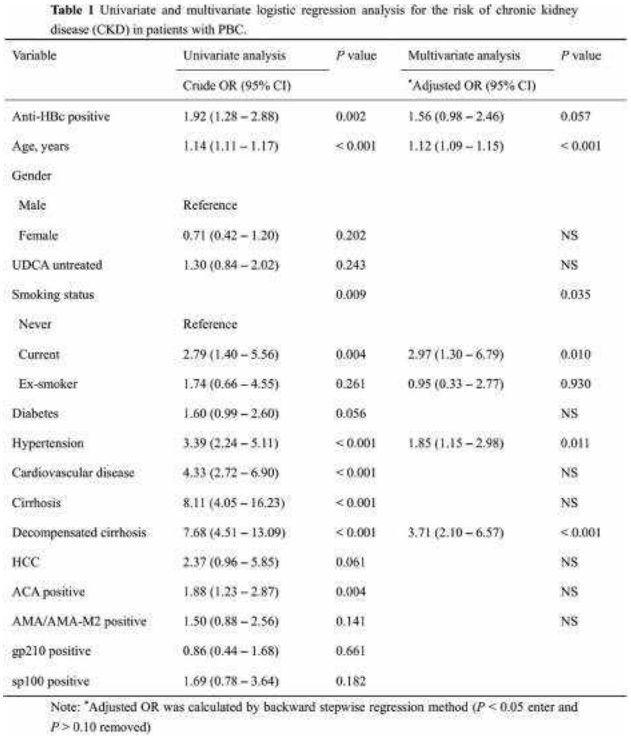

Table 1 Univariate and multivariate logistic regression analysis for the risk of chronic kidney disease (CKD) in patients with PBC.

Variable	Univariate analysis Crude OR (95% CI)	*P* value	Multivariate analysis *Adjusted OR (95% CI)	*P* value
Anti-HBc positive	1.92 (1.28 – 2.88)	0.002	1.56 (0.98 – 2.46)	0.057
Age, years	1.14 (1.11 – 1.17)	< 0.001	1.12 (1.09 – 1.15)	< 0.001
Gender				
Male	Reference			
Female	0.71 (0.42 – 1.20)	0.202		NS
UDCA untreated	1.30 (0.84 – 2.02)	0.243		NS
Smoking status		0.009		0.035
Never	Reference			
Current	2.79 (1.40 – 5.56)	0.004	2.97 (1.30 – 6.79)	0.010
Ex-smoker	1.74 (0.66 – 4.55)	0.261	0.95 (0.33 – 2.77)	0.930
Diabetes	1.60 (0.99 – 2.60)	0.056		NS
Hypertension	3.39 (2.24 – 5.11)	< 0.001	1.85 (1.15 – 2.98)	0.011
Cardiovascular disease	4.33 (2.72 – 6.90)	< 0.001		NS
Cirrhosis	8.11 (4.05 – 16.23)	< 0.001		NS
Decompensated cirrhosis	7.68 (4.51 – 13.09)	< 0.001	3.71 (2.10 – 6.57)	< 0.001
HCC	2.37 (0.96 – 5.85)	0.061		NS
ACA positive	1.88 (1.23 – 2.87)	0.004		NS
AMA/AMA-M2 positive	1.50 (0.88 – 2.56)	0.141		NS
gp210 positive	0.86 (0.44 – 1.68)	0.661		
sp100 positive	1.69 (0.78 – 3.64)	0.182		

Note: *Adjusted OR was calculated by backward stepwise regression method ($P < 0.05$ enter and $P > 0.10$ removed)

Disclosures: The following people have nothing to disclose: Jialiang Chen, Yao Liu, Yufei Bi, Fangyuan Gao, Xianbo Wang

f 4584-C | TRANSCRIPTOME ANALYSIS REVEALS ADAPTIVE RESPONSES TO HYPOXIA IN THE CEREBRAL CORTEX OF CHOLESTATIC MICE

Wagdi Almishri, Mark Gordon Swain and Charlotte D'Mello, University of Calgary

Background: We have previously shown that patients with the cholestatic liver disease primary biliary cholangitis (PBC) exhibit significant cerebral cortical hypoxia (Duszynski. Hepatology. 2020). However, the cause of cortical hypoxia in PBC remains unknown. We therefore used a mouse model to examine the impact of cholestasis on cerebral hypoxia development. **Methods:** Male C57BL/6 mice (Jackson; 10 wks old) were subjected to either bile duct ligation (BDL) or sham surgery (n = 6 mice/group). Ten days post-surgery mice were evaluated for hypoxia-associated gene expression alterations and metabolic pathway adaptations in the cerebral cortex using mRNA-seq and Ingenuity Pathway Analysis bioinformatics software (IPA; Qiagen). **Results:** Key hypoxia response-related genes were significantly dysregulated in the cerebral cortex of BDL vs sham mice, including a significant 1.5-fold increase (pŽ 1.3x10^{-3}) in Hif-1α (master regulator of hypoxia cellular responses) gene expression, a 2.8-fold decrease (pŽ4.5x10^{-2}) in gene expression of the HIF-1α- degrading enzyme (P4ha1), and a 28-fold increase (pŽ1.4x10^{-5}) in gene expression of the enzyme Pdk1 (regulates HIF-1-dependent hypoxia-induced anaerobic glycolysis) in BDL vs sham mice. IPA Pathway Analysis software was used to identify hypoxia-related biological pathway gene expression signature changes in the cerebral cortex of BDL vs sham mice. BDL was associated with enriched gene expression in the *Oxidative Phosphorylation* (pŽ3.1x10^{-2}), *Mitochondrial Function* (pŽ1.5x10^{-2}), and *Unfolded Protein Response* (pŽ1.7x10^{-5}) pathways. To delineate a possible mechanism driving these brain cortical hypoxic changes, we employed brain spinning disc confocal intravital microscopy (methods, D'Mello. Gastroenterol. 2017) and identified robust recruitment of monocytes into brain cortical blood vessels in BDL mice (none in sham mice) with associated cortical capillary 'plugging' (Fig. 1). **Conclusion:** BDL mice demonstrate gene expression changes in the cerebral cortex indicating significant tissue hypoxia – similar to findings in PBC patients. We suggest brain hypoxia-related changes in cholestatic liver disease are driven by monocyte recruitment to cerebral blood vessels and associated capillary

Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

'plugging' leading to impaired microregional blood flow. The BDL mouse model represents a valuable tool to mechanistically define this process and to develop potential therapeutic approaches to address this issue (eg. anti-cell adhesion approaches).

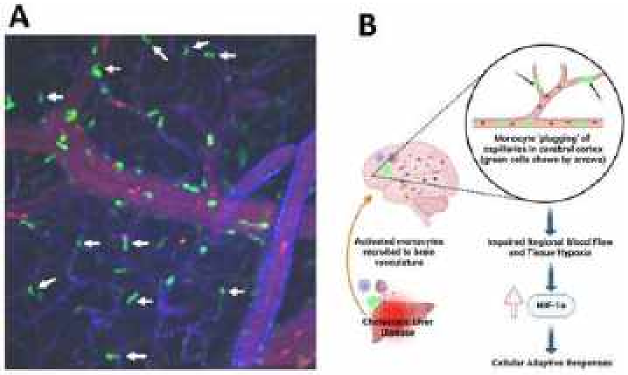
A
B
Monocyte 'plugging' of capillaries in cerebral cortex (green cells shown by arrows)
Activated monocytes recruited to brain vasculature
Impaired Regional Blood Flow and Tissue Hypoxia
HIF-1α
Cholestatic Liver Disease
Cellular Adaptive Responses

Fig.1. (A) Representative image of cerebral intravital microscopy from a LysM-GFP+ BDL mouse, showing cerebral cortical blood vessels 10 days post-surgery (methods D'Mello at al. J Neurosci 2009, and Gastroenterology 2017). LysM-GFP+ monocytes are green; platelets are red (PE-CD49b), and endothelial cells are blue (APC-CD31). White arrows indicate immobile green GFP+ monocytes 'plugging' cerebral cortical capillaries (< 30 µm diameter). (B) A schematic representation, created with BioRender.com, depicts a hypothesized mechanism whereby cholestatic liver disease activates circulating monocytes, which are subsequently recruited to roll and adhere along the cerebral endothelium, consequently causing physical 'plugging' of smaller capillaries, impairing downstream blood flow, and leading to microregional cortical hypoxia.

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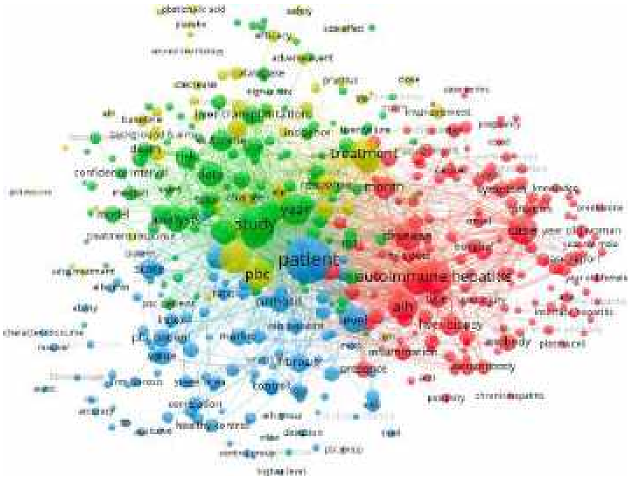
The following people have nothing to disclose: Wagdi Almishri, Charlotte D'Mello

4585-C | TRENDS IN AUTOIMMUNE LIVER DISEASE RESEARCH SINCE THE OCCURRENCE OF THE COVID-19 PANDEMIC: A BIBLIOMETRIC ANALYSIS

Taylor Beedie, Children's Hospital, London Health Sciences Centre; Lawson Health Research Institute and Andreanne N. Zizzo, Children's Hospital, London Health Sciences Centre, Western University

Background: Autoimmune liver diseases (AILDs) consist of 3 main diagnoses; autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). Much research today continues to be dedicated to the field of AILDs to understand the disease characteristics, its treatment, outcomes and modelling prognostic and diagnostic models. Bibliometric studies are helpful for providing a scope of the current publication landscape within a particular field and aid in assisting the path within which future research should direct their efforts. Since the onset of the COVID-19 pandemic, there have been no studies investigating the course of research on AILDs, and how this may influence future research endeavours. **Methods:** An expert librarian driven literature search was conducted on September 10, 2021 using multiple databases. A total of 697 included papers were then coded for type of article, subject population, area of research and publishing journal. Univariate analysis was performed to compare trends in publication between adults and paediatric studies. Data was then imported in VOSViewer for visual analysis, term occurrences and relationship mapping. **Results:** Our literature search determined that 10x as many adult papers (87.5%) were published in a two year time frame compared to paediatric papers (8.6%). Paediatric papers were more focused on AIH ($p = 0.01$), whereas adult papers were split between PBC and AIH. The majority of papers explored disease characteristics, and the most common study types across both adults and paediatrics were retrospective studies and case reports. It was surprising to discover that a low number of publications investigated COVID-19 and autoimmune liver diseases (adults = 2.6%, paediatrics = 1.7%). **Conclusion:** The publications during 2020 and 2021 on AILDs primarily used adult case presentations/reports with PBC and AIH. Authors focused on disease characteristics and diagnosis, with less emphasis on outcomes, treatment, response to therapy and novel therapy. Overall, the area not well represented was therapeutic advances, which may suggest that future studies will use these prior case presentations to report treatment options and responses. Future studies may also want to consider more research within paediatrics as the current landscape is heavily focused on adults. Only a small percentage of papers explored the interaction between COVID-19 and AILDs, which may provide an opportunity for furture investigations to explore a possible influence of the pandemic on autoimmune liver diseases.



Disclosures: The following people have nothing to disclose: Taylor Beedie
Disclosure information not available at the time of publication: Andreanne N. Zizzo

4586-C | TYPE-I INTERFERONS ARE SELECTIVELY ELEVATED IN PRIMARY SCLEROSING CHOLANGITIS AND CORRELATE WITH DISEASE ACTIVITY

Rebekka J.S. Salzmann[1], Christina Mehrfeld[2], Sophia Rottmann[1], Tudor Mocan[3], Arnulf G. Willms[4], Marcin Krawczyk[5], Piotr Milkiewicz[6,7], Miroslaw T. Kornek[1], Bettina Langhans[1], Leona Dold[1] and Veronika Lukacs-Kornek[1], (1)University Hospital Bonn, (2)Saarland University Medical Center, (3)Babeş-Bolyai University, (4)German Armed Forces Central Hospital Hamburg, (5)Saarland University Hospital, (6)Medical University of Warsaw, (7)Pomeranian Medical University

Background: The level of type-I interferons (IFNs) in primary sclerosing cholangitis (PSC) was investigated to evaluate its association with disease activity and progression. **Methods:** Bioactive type I IFNs were evaluated in murine model of PSC and in human patients' sera using a cell-based reporter assay and ELISA techniques. In total, 70 healthy participants, 81 PSC, and 24 patients with primary biliary cholangitis (PBC) as well as 9 patients with autoimmune hepatitis (AIH) were enrolled in this study. **Results:** Bioactive type-I IFNs were elevated in liver and serum of multi drug resistance protein 2 deficient (Mdr2) animals and the frequency of plasmacytoid dendritic cells, the main producers of type-I IFNs, were 3-fold increased in the livers of Mdr2 animals compared to wild types. In accordance with results in the above animal model of PSC, bioactive type-I IFNs were elevated in the sera of PSC patients as compared to healthy controls as well as patients with PBC and AIH (all $p < 0.05$). This test showed good diagnostic performance with a sensitivity of 80.56%, a specificity of 85.19% and an AUROC value of 0.89 in distinguishing PSC from healthy individual's. PBC patients did not demonstrate elevated IFN levels and remained similar to heathy individual's. Notably, PSC patients demonstrated significantly ($p = 0.039$) higher serum levels of type I IFNs compared to AIH (sensitivity of 86.7% and a specificity of 55.6% and an AUROC value of 0.778). The highest correlation of bioactive IFNs with laboratory parameters was found to be with alanine phosphatase ($r = 0.50$, $p < 0.001$) and bilirubin ($r = 0.43$, $p = 0.004$), moderate correlation with disease duration ($r = 0.42$, $p < 0.05$) but no correlation with fibrosis stage ($r = 0.18$, $p = 0.38$). Among the type-I IFN subtypes IFNα, β and IFNω could be detected in PSC patients, IFNω had the highest concentration detected (ng/mL) with a mean of 154.531 ng/mL. **Conclusion:** The selectively elevated bioactive type-I-IFNs could suggest a novel inflammatory pathway that might also have a hitherto unrecognized role in the pathomechanism of PSC

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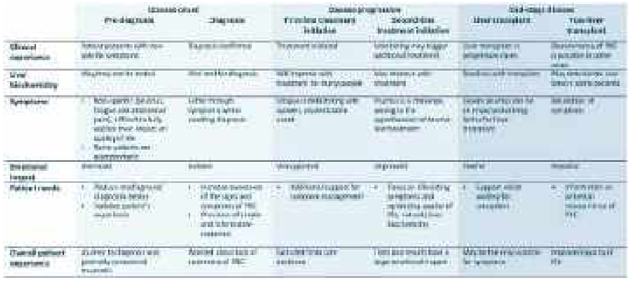
4587-C | UNDERSTANDING THE EXPERIENCE OF PEOPLE LIVING WITH PRIMARY BILIARY CHOLANGITIS: DEVELOPMENT OF AN EXPERIENCE MAP

Alexander Artyomenko[1], Abi Bowden[2], Maureen Christie[3], Robert Mitchell-Thain[4] and Marwan Sleiman[1], (1)Ipsen, (2)Health Unlimited, (3)PBC Foundation, (4) PBC Foundation, Edinburgh, United Kingdom

Background: Primary biliary cholangitis (PBC) is a rare autoimmune disease of the liver, characterized by destruction of the bile ducts[1]. People with PBC can experience non-specific symptoms such as pruritus, fatigue and joint pain[1]. The severity of symptoms and their impact on quality of life do not always correlate with liver biochemistry or disease progression[1]. This incongruence affects most of the PBC population; although many people are asymptomatic at diagnosis, 50% may develop symptoms after 5 years and 95% by 20 years post-diagnosis[2]. Nevertheless, the experience of people living with PBC is highly variable and current understanding is limited. Aims: To further understand patient experience throughout the disease course, people living with the disease were consulted to capture their thoughts, feelings and symptoms, and the overall impact of PBC on their lives. **Methods:** An initial review of online sources, including publicly available literature, medical and patient organization websites, and patient stories, was conducted to identify key themes: overall experience, symptoms, emotional impact, evolving patient needs, and medical team interactions. These themes were used to guide a meeting with a steering committee of seven PBC patient advocates. Insights were validated via 1:1 interviews and a visual experience map was created and finalized with the steering committee. **Results:** The PBC journey was divided into six distinct periods, representing diagnosis, living with PBC, and progression to end-stage liver disease (Table 1). Key clinical experiences, including representative measures for liver biochemistry, were added to provide a clinical reference point. The resulting map highlights that effective management of PBC requires a multi-factorial approach, aspiring for normal liver biochemistry whilst achieving low symptom burden and optimizing quality of life. Most importantly, people with PBC express a strong need to have their experiences acknowledged and addressed by management strategies, alongside any clinical measures. **Conclusion:** We present an initial patient experience map for PBC, a visual aid to align approaches to treatment and care with patient-reported experiences and needs. Future validation with a targeted survey in a wider group of patients will aim to strengthen these findings and ensure accurate representation of the PBC population. References: 1. Hirschfield GM et al., Gut 2018;67:1568–1594; 2. Prince MI et al Gut 2004;53:865–870



Disclosures: Alexander Artyomenko – Ipsen: Employee, Yes, No; Ipsen: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;

Abi Bowden – Health Unlimited: Employee, Yes, No;

Maureen Christie – PBC Foundation: Employee, Yes, No;

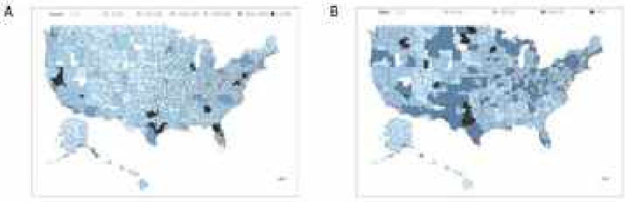
Robert Mitchell-Thain – PBC Foundation: Executive role , Yes, No; PBC Foundation: Employee, Yes, No;
Marwan Sleiman – Ipsen: Employee, Yes, No; Ipsen: Stock – privately held company (individual stocks and stock options), Yes, No;

4588-C | UNITED STATES (US) PREVALENCE OF DIAGNOSED PRIMARY BILIARY CHOLANGITIS: 41 PER 100,000 ADULTS WITH WIDE REGIONAL VARIABILITY

Keri-Ann Buchanan-Peart[1], Joanna P. MacEwan[2], Alina Levine[2], Radhika Nair[3], Darren Wheeler[3], Erik Ness[3], Tracy Mayne[3] and Cynthia Levy[1], (1)University of Miami Health System, (2)Genesis Research, (3)Intercept Pharmaceuticals, Inc., Morristown, NJ

Background: Primary biliary cholangitis (PBC) prevalence in the US has been extrapolated from small regional databases. However, environmental and genetic factors vary considerably by region, potentially influencing prevalence. Our objective was to estimate a robust national prevalence while quantifying regional variability. **Methods:** We included patients in the Komodo Health claims database in 2021 and with 1 inpatient or 2 outpatient (separated by > 1 d) claims with a PBC diagnosis [ICD9 (571.6) or ICD10 code (k74.3)] with first claim between 1/1/14 and 12/31/21. We excluded patients < 18 years old or missing a 3-digit ZIP code. We characterized patients by age, sex, and race/ethnicity, and adjusted PBC prevalence by sex, age, and census population at the 3-digit zip-code tabulation area (ZCTA3) level to calculate prevalence per 100,000 adult population. We created heat maps for absolute number and prevalence by ZCTA3. **Results:** Of the 106.8 million patients in Komodo Health database in 2021, 41,426 met PBC diagnosis criteria. Patients were predominantly female (83%) with a mean age of 61.9 years (SD = 13.2). Of the 31,806 (76.8%) patients with race/ethnicity information, 67.6% of patients were White, 16.9% Hispanic/Latino, 7.6% Black, and 3.5% Asian/Pacific Islander. The adjusted prevalence of patients with PBC in 2021 was 40.9 per 100,000 adult population, or 105,506 adult patients nationally. The absolute number of patients varied by population density, with the highest numbers in the largest metropolitan statistical areas, eg, New York, Los Angeles, Chicago, and Houston (Figure 1A). Prevalence showed a markedly different pattern, with the highest number per 100,000 in rural areas in the Midwest, with pockets in the West and along the Appalachians in the Mid-Atlantic (Figure 1B). **Conclusion:** These data, using a large nationally representative sample adjusting for population and patient demographics, provide the best estimate of diagnosed PBC patients to date. The greatest burden of PBC exists in major cities, which may be best equipped to address treatment needs given the presence of major university hospitals. The high prevalence in more rural areas leaves several unanswered questions regarding the potential presence of environmental and genetic factors which may be driving highly localized spikes in prevalence, as well as access to specialty care for treating rare disease. Further analyses are underway to address these outstanding questions.

Figure 1. (A) Absolute number of adult patients with PBC by ZCTA3. (B) PBC prevalence per 100,000 adult population by ZCTA3.



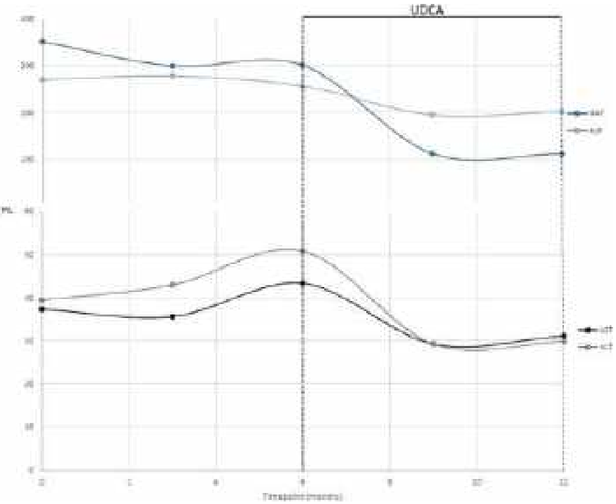
Abbreviations: PBC, primary biliary cholangitis; ZCTA3, 3-digit zip-code tabulation area.

Disclosures: Joanna P. MacEwan – Genesis Research: Employee, No, No;
Alina Levine – Genesis Research: Employee, No, No;
Radhika Nair – Intercept Pharmaceuticals, Inc.: Employee, No, No;
Darren Wheeler – Intercept Pharmaceuticals, Inc.: Employee, No, No;
Erik Ness – Intercept Pharmaceuticals, Inc.: Employee, No, No;
Tracy Mayne – Intercept Pharmaceuticals, Inc.: Employee, No, No;
The following people have nothing to disclose: Keri-Ann Buchanan-Peart, Cynthia Levy

4590-C | URSODEOXYCHOLIC ACID FOR THE TREATMENT OF HEPATIC SARCOID: A PRE-POST STUDY

Ethan M. Weinberg[1], Aimee Stonelake[1], Emily Toal[1], Kelly Borges[1], Colin Ligon[2], Milton Rossman[1] and K Rajender Rajender Reddy[1], (1)University of Pennsylvania, (2)Bon Scours

Background: Sarcoidosis is a poorly defined autoimmune disease characterized by the formation of sterile granulomas in affected organs, including the liver. The diagnosis of hepatic sarcoid is often presumed based upon an elevated liver-specific iso-enzyme of alkaline phosphatase or imaging findings suggestive of portal hypertension, hepatomegaly, or liver lesions in a patient with known sarcoidosis; a minority are diagnosed through liver biopsy. The primary treatment of sarcoidosis in those with symptoms is immunosuppression. However, given its excellent safety profile and minimal side effects, ursodeoxycholic acid (UDCA) could be a first-line treatment for hepatic sarcoid. We set out to evaluate the effects of UDCA on hepatic sarcoid in a single-center open-label, pre-post study design. **Methods:** We conducted a 12-month open-label single-arm pre-post pilot study for patients with hepatic sarcoid. After enrollment, patients were observed for 6 months followed by 6 months of weight-based UDCA (13-15mg/kg) divided into two daily doses. Key inclusion criteria were a diagnosis of systemic sarcoidosis with evidence of liver involvement as denoted by elevated liver-specific alkaline phosphatase plus any of the following: granulomas on liver biopsy, hepatomegaly on imaging, or portal Hypertension (via imaging or endoscopy) or granulomas on liver biopsy (not attributable to infection) with concomitant elevated liver-specific alkaline phosphatase. The primary endpoints were decrease in alkaline phosphatase (ALP) or gamma-glutamyl transferase (GGT) at month 6 of UDCA treatment. Key secondary endpoint included decreases in alanine aminotransferease (ALT), aspartate aminotransferease (AST), and liver stiffness (kPa) as assessed by vibration-controlled transient elastography (VCTE). **Results:** 10 patients were screened for participation in the study from August 2018 to July 2020; seven were enrolled. Target enrollment was 10 patients – the study was terminated prior to achieving target enrollment due to the COVID-19 pandemic. One patient dropped out during the first month of observation due to new diagnosis of esophageal cancer. Six completed the 6-month observation and UDCA periods. One patient stopped UDCA within the first month of active treatment due to side effect of nausea. There was a decrease in ALP and GGT at six-months of UDCA treatment (ALP - 257.6 to 202.2, $p = 0.23$; GGT – 302.5 to 111.8, $p = 0.059$, Figure 1). There was also decreases in all key secondary endpoints (ALT - 50.8 to 29.8, p = NS; AST – 40.3 to 31.2, p = NS, VCTE kPa – 8.3 to 6.3, p = NS). **Conclusion:** UDCA is safe for use in patients with sarcoidosis with liver involvement. This pilot study suggests a role for UDCA in the treatment of hepatic sarcoid, with improvements in hepatic biochemical tests and liver stiffness. Multi-centered studies of longer duration are needed to assess the impact of UDCA on hepatic sarcoid. Figure 1 – Hepatic biochemical tests, baseline to Month 12

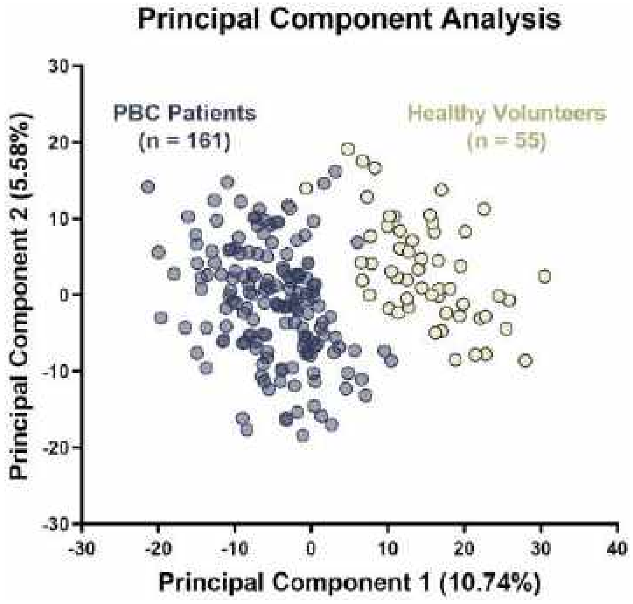


Disclosures: Ethan M. Weinberg – Mallinckrodt Pharmaceuticals: Consultant, Yes, No; Biovie: Consultant, No, No; PharmaIN: Consultant, No, No; Mallinckrodt Pharmaceuticals: Advisor, Yes, No;
K Rajender Rajender Reddy – BMS: Consultant, No, No; Intercept: Consultant, No, No; Mallinckrodt: Consultant, No, No; Sequana: Consultant, No, No; Exact Sciences: Consultant, No, No; Target-RWE: Consultant, No, No; Merck: Consultant, No, Yes; Spark Therapeutics: Consultant, No, No; Novo Nordisk: Consultant, No, No; Genfit: Consultant, No, No; BioVie: Consultant, No, No; Novartis: Consultant, No, No; Astra Zeneca: Consultant, No, No;
The following people have nothing to disclose: Aimee Stonelake, Emily Toal, Kelly Borges, Colin Ligon, Milton Rossman

4591-C | WIDESPREAD DYSREGULATION OF METABOLIC STRESS PATHWAYS IS A CHARACTERISTIC OF PRIMARY BILIARY CHOLANGITIS (PBC): COMPARISON OF THE SERUM METABOLOMES OF PBC PATIENTS TO MATCHED HEALTHY VOLUNTEERS

Yun-Jung Choi[1]*, Jeffrey D. Johnson*[1]*, Andrew J. Schwab*[2] *and Charles A. McWherter*[1]*, (1)Cymabay Therapeutics, (2)Metabolon*

Background: Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease characterized by progressive inflammation and destruction of small intrahepatic bile ducts. Current analytical methods can measure over 1000 metabolites to define a serum metabolome. Comparison of the serum metabolomes of patients with PBC to matched healthy volunteers (HV) is a comprehensive approach to discover novel disease signatures and therapeutic opportunities for this disease. **Methods:** Serum samples were collected from 161 PBC patients in a phase 3 study (ENHANCE: NCT03602560) and from 55 healthy volunteers prospectively recruited by matching age, gender and BMI to PBC patients. Serum metabolomic analyses were performed using UHPLC-MS/MS (Metabolon, Inc). The relative abundance of each identified metabolite between PBC patients and HV was evaluated. **Results:** A total of 1031 metabolites were identified from global metabolomic analysis of serum from patients with PBC and HV. Among these, 468 (45%) of the total metabolites were significantly increased in PBC and 189 (18%) were significantly decreased ($p < 0.05$). There was a clear separation between the overall metabolomic profiles of PBC patients and HV (Figure). Bile acids were broadly elevated, and the data reveal new details for less abundant, but potentially consequential differences among them. Many biochemical changes implicate metabolic stress brought about by the mitochondrial dysfunction consequent in PBC: medium- and long-chain fatty acids were elevated, and fatty acid dicarboxylates and fatty acyl carnitines were broadly increased consistent with insufficient beta-oxidation. Ceramides and lysophospholipids, markers of oxidative stress and inflammation, were also significantly elevated in PBC. PBC patients also showed non-lipid metabolomic changes that reflect perturbed energy balance and reduced metabolic capacity of the liver. **Conclusion:** PBC patients displayed broad changes in serum metabolites reflective of metabolic stress indicating mitochondrial defects and liver dysfunction associated with their cholestasis. This new detailed map of metabolomic changes in matched cohorts of significant size sheds light on the broad metabolic pathology of PBC. These results will aid in our understanding of the substantial impact of PBC on systemic metabolism and energy balance and will help guide efforts to advance therapeutics to counteract the integrated metabolic effects of cholestasis in PBC patients.



Disclosures: Yun-Jung Choi – CymaBay Therapeutics, Inc.: Employee, Yes, No;

Disclosure information not available at the time of publication: Jeffrey D. Johnson, Andrew J. Schwab, Charles A. McWherter

4600-C | FARNESOID X RECEPTOR (FXR) CONTROLS CHOLANGIOCYTE INJURY RESPONSES IN EXPERIMENTAL BILIARY ATRESIA★

Astha Malik[1], Annika Yang Vom Hofe[1], Bryan Donnelly[1], Brandee Wagner[2], Gregory M. Tiao[1] and Alexander G. Miethke[1], (1)Cincinnati Children's Hospital Medical Center, Cincinnati, OH, (2)Metacrine, Inc

Background: Biliary atresia (BA) is a fibroinflammatory obliteration of the extrahepatic biliary tree in neonates. We previously showed FXR agonist tames macrophage mediated proinflammatory cytokine production in sclerosing cholangitis and to reduce serum bile acid concentrations in experimental BA. Here we examine its effects on infection of cholangiocytes with rhesus rotavirus (RRV) and on progression of biliary fibrosis in RRV-induced neonatal bile duct obstruction. **Methods:** Newborn BALB/c mice were injected with $1.5X10^6$ FFU of RRV to induce experimental BA followed by daily orogastric gavage of 10 mg/kg of the non-steroidal FXR agonist, M044, or vehicle (corn oil) in controls. Mice were sacrificed 7 days post RRV (d7pRRV). Livers and bile ducts were micro dissected to determine viral titers by focus forming assay, to quantitate gene expression by qPCR, and to assess liver fibrosis by Sirius Red staining of liver sections. In vitro, primary neonatal cholangiocytes were infected with RRV or challenged with LPS or TCDCA while exposed to M044 or vehicle. Protein and gene expression levels were quantified using western blot, ELISA, and qPCR. **Results:** Compared with controls, treatment with FXR agonist following RRV challenge induced hepatic expression of *Shp*, target gene of FXR, and significantly repressed both proinflammatory and profibrogenic genes, including *Tnfa, Cxcl9, Cxcl10* and *Pdgfb.* FXR agonist treatment lowered viral titers in livers (average viral particles: 9,700 ± 11000 vs 280 ± 160 FFU/ml in vehicle vs M044; $p < 0.005$) and to lesser extent in extrahepatic bile ducts (11,100 ± 4,700 vs 4,400 ± 1700 FFU/ml; $p = 0.045$). FXR agonist reduced progression of periportal fibrosis (Figure 1A). FXR protein was expressed in neonatal cholangiocytes as demonstrated by western blot. Incubation of neonatal cholangiocytes with FXR agonist prior to RRV exposure lowered viral replication in dose dependent manner. Furthermore, it reduced secretion of profibrogenic TGFb1 by cholangiocytes upon stimulation with LPS or TCDCA (Figure 1B). **Conclusion:** Pharmacological activation of

FXR confers renders cholangiocytes resistant to infection with double stranded RRV and represses their proinflammatory and profibrogenic responses. Given the preclinical anti-cholestatic, anti-inflammatory, and anti-fibrogenic effects of non-steroidal FXR agonist, this class of drugs may be considered for clinical trials in infants with BA.

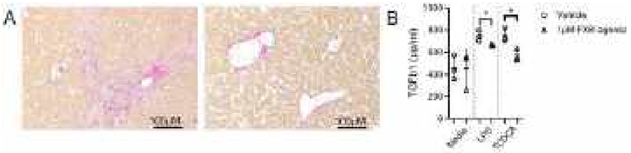


Figure 1: FXR agonist represses profibrogenic responses by cholangiocytes. A| Photomicrographs of liver sections stained with Sirius Red from neonatal mice on d7pRRV. B) TGFb1 protein concentrations measured by ELISA in supernatants from cultured neonatal cholangiocytes stimulated with 10ng/ml of LPS or 100µM of TCDCA in presence of FXR agonist (or vehicle).

Disclosures: The following people have nothing to disclose: Astha Malik, Bryan Donnelly, Gregory M. Tiao

Disclosure information not available at the time of publication: Annika Yang Vom Hofe, Brandee Wagner, Alexander G. Miethke

4601-C | GENETIC SURVEY FOR MODIFYING GENES IN KASAI PORTOENTEROSTOMY OUTCOMES

Aaron Bennett, Phoebe Wood, Bryanna Domenick and Elizabeth Rand, Children's Hospital of Philadelphia, Philadelphia, PA

Background: Biliary atresia (BA) is the most common cause of obstructive cholestasis in neonates. Primary treatment of BA is surgical correction via Kasai Portoenterostomy (KPE). Despite surgical remediation of the obstruction, approximately half of patients with BA will require liver transplantation (LT) by two years of age due to complications of persistent cholestasis, and another large group requires LT later in childhood or young adulthood due to complications of portal hypertension and hepatic cirrhosis. Multiple clinical factors have been investigated to prognosticate post-KPE outcomes, including age at KPE, the trend of conjugated bilirubin, surgical technique, center experience, and post-KPE steroid use. Genetic studies have not identified an etiology of BA, however underlying known cholestatic genes have not been studied as potential modifiers of post-KPE outcomes. **Methods:** Liver explant tissue samples were saved in an IRB approved biorepository. Explant specimens from patients with BA post-KPE were sent for genomic DNA extraction and genetic panel analysis of 77 genes implicated in disorders of cholestasis (PreventionGenetics Cholestasis Panel). Patient demographic and clinical data were collected via electronic chart review. Patients were dichotomized into early LT and late LT groups, representative of persistent cholestasis post-KPE and non-cholestatic cirrhosis respectively. The presence of genetic variants were compared between the two groups. **Results:** Fifty-three patients were included in our analysis. Both groups had a similar age at KPE (median age 2.1 months). The early LT group, as anticipated, had cholestasis at LT while the late LT group had complications related to portal hypertension. Forty-nine patients (92%) had abnormal genetic variants identified. Differences in prevalence of genetic variants are shown in Table 1. **Conclusion:** Multiple factors contribute to post-KPE outcomes in patients with BA. Underlying genetic variants associated with disorders of cholestasis may modify post-KPE outcomes. We found a higher prevalence of multiple genes implicated in disorders of cholestasis, including CFTR, in the early LT cohort. While this study is not properly powered to identify statistically significant differences in genetic variants due to its inherently small sample size, mutations in CFTR are of particular interest given the advent of CFTR modulating therapies and the potential for disease modifying intervention. Additional studies evaluating the prevalence of cholestasis related genetic variants in a larger sample of patients with BA, and the function of specific CFTR variants in this cohort, may highlight novel methods of prognostication and intervention.

Table 1: Prevalence of cholestasis related genetic variants by transplant cohort

Gene	Early Transplant (n=36)	Late Transplant (n=17)
No Mutation	2 (6%)	2 (12%)
ABCB11	1 (3%)	0 (0%)
ABCB4	3 (8%)	2 (12%)
ABCC2	2 (6%)	0 (0%)
ABCG5	1 (3%)	0 (0%)
ALDOB	1 (3%)	1 (6%)
AMACR	1 (3%)	0 (0%)
ATP8B1	2 (6%)	1 (6%)
CC2D2A	0 (0%)	1 (6%)
CFTR	8 (22%)	2 (12%)
CLDN1	1 (3%)	0 (0%)
DCDC2	1 (3%)	0 (0%)
DHCR7	0 (0%)	1 (6%)
EHHADH	0 (0%)	1 (6%)
FAH	1 (3%)	0 (0%)
GNAS	3 (8%)	0 (0%)
HNF1B	1 (3%)	0 (0%)
HSD17B4	0 (0%)	1 (6%)
JAG1	2 (6%)	1 (6%)
KMT2D	3 (8%)	3 (18%)
MYO5B	2 (6%)	1 (6%)
NOTCH2	2 (6%)	0 (0%)
NPC1	4 (11%)	0 (0%)
NPHP3	1 (3%)	1 (6%)
NPHP4	4 (11%)	2 (12%)
NR1H4	1 (3%)	0 (0%)
PEX12	1 (3%)	1 (6%)
PEX14	1 (3%)	0 (0%)
PEX26	1 (3%)	0 (0%)
PEX5	1 (3%)	0 (0%)
PEX6	1 (3%)	0 (0%)
PEX7	1 (3%)	0 (0%)
PKD1L1	6 (17%)	2 (12%)
PKHD1	2 (6%)	0 (0%)
POLG	3 (8%)	1 (6%)
SERPINA1	4 (11%)	2 (12%)
SLC10A1	1 (3%)	0 (0%)
SLC25A13	0 (0%)	2 (12%)
SLC27A5	2 (6%)	0 (0%)
SLC51A	1 (3%)	0 (0%)
SLCO1B3	2 (6%)	0 (0%)
TJP2	2 (6%)	1 (6%)
TRMU	0 (0%)	1 (6%)
UGT1A1	23 (64%)	8 (47%)

Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

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4602-C | IMPROVEMENTS IN PRURITUS WITH MARALIXIBAT ARE ASSOCIATED WITH IMPROVED QUALITY OF LIFE FOR PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS: DATA FROM THE MARCH-PFIC TRIAL

Amal A. Aqul[1], Alexander G. Miethke[2], Chuan-Hao Lin[3], Gilda Porta[4], Étienne M. Sokal[5], Douglas B. Mogul[6], Tiago Nunes[6], Marshall Baek[6], Pamela Vig[6], Ulrich Baumann[7] and Richard J. Thompson[8], (1)University of Texas Southwestern Medical Center, Dallas, Texas, (2) Cincinnati Children's Hospital Medical Center, Cincinnati, OH, (3)Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA, (4) Hospital Sirio Libanes, Sao Paulo, Brazil, (5)Cliniques Universitaires Saint-Luc, (6)Mirum Pharmaceuticals, Inc., Foster City, California, (7) Hannover Medical School, Hannover, Germany, (8) Institute of Liver Studies, King's College London, London, United Kingdom

Background: Progressive Familial Intrahepatic Cholestasis (PFIC) is a group of rare genetic disorders characterized by retention of bile acids leading to cholestatic pruritus, impaired growth and end-stage liver disease. Pruritus, the most burdensome symptom of PFIC, occurs in the majority, and leads to sleep disturbances, self-mutilation, decreased school performance, and impaired quality of life (QoL). MARCH-PFIC (MARCH) was a Phase 3 trial of maralixibat (MRX), an ileal bile acid transporter inhibitor, that demonstrated significant reductions in pruritus. Here, we analyze whether improvements in pruritus are associated with an increase in QoL for patients with PFIC. **Methods:** Participants from MARCH in the All-PFIC cohort (BSEP, FIC1, MDR3, TJP2, and MYO5B) were randomized to receive MRX 570 μg/kg BID or placebo (PBO) for 26 weeks. Change from Baseline (BL; CFB) in QoL was assessed from BLto Week 18-26 for pruritus responders [$\geq$1-point change in ItchRO (Obs)] using the PedsQL, Peds-QL Social Functioning (PedsQL-SF), Peds-QL Physical Functioning (PedsQL-SF), and the Family Impact Total Scale (FI-T); all instruments use a 0-100 scale with higher scores indicating better QoL. **Results:** 64 participants (31 BSEP, 13 FIC1, 9 MDR3, 7 TJP2, 4 MYO5B) were randomized (33 MRX, 31 PBO). BL disease characteristics were well-balanced between MRX and PBO, and participants had similar BL QoL score (e.g., PedsQL: 56 vs 63). In MRX, the CFB in PedsQL for pruritus responders was 22 ($p < 0.0001$) with no significant CFB for non-responders (-2; $p = 0.7062$) and relative change between groups was significant ($p = 0.0014$). In PBO, there was no difference between responders and non-responders ($p = 0.8192$). The PedsQL-SF, PedsQL-PF and FI-T showed similar patterns, with MRX demonstrating significant CFB for social/physical functioning and family impact among pruritus responders, but minimal CFB among non-responders, such that there was significant relative change for PedsQL-SF ($p = 0.0011$) and PedsQL-PF ($p = 0.0012$) and trend towards relative change in FI-T ($p = 0.0895$). In the PBO group, there was no significant difference between pruritus responders and non-responders for PedsQL-SF, PedsQL-PF, and FI-T. **Conclusion:** In MARCH, pruritus control among MRX recipients was associated with clinically significant improvements in QoL across several domains. These data indicate that improvements in pruritus in patients with PFIC on MRX are associated with significant improvements in social and physical functioning as well as benefit to the family.

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The following people have nothing to disclose: Gilda Porta, Étienne M. Sokal

4603-C | MANAGEMENT OF GASTROINTESTINAL HEMORRHAGE IN BILIARY ATRESIA – RECOMMENDATIONS VS CLINICAL PRACTICE

Lee Bass[1], Wen Ye[2], Kieran Hawthorne[3], Simon P. Horslen[4], Jean Pappas Molleston[5], Lisa Henn[3], Daniel H. Leung[6], Ronald J. Sokol[7], Saul Karpen[8], Philip Rosenthal[9], Kathleen M. Loomes[10], Rohit Kohli[11], Evelyn K. Hsu[12], Alexander G. Miethke[13], Vicky Lee Ng[14], Steve Guthery[15], John C. Magee[16], Benjamin L. Shneider[17] and the Childhood Liver Disease Research Network (ChiLDReN), (1)Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, (2) University of Michigan, (3)Arbor Research Collaborative for Health, (4)UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, (5)Riley Hospital for Children, (6)Texas Children's Hospital, Baylor College of Medicine, (7)Children's Hospital of Colorado and University of Colorado School of Medicine, (8)Children's Healthcare of Atlanta, (9)University of California, San Francisco, (10)The Children's Hospital of Philadelphia and the University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, (11)Children's Hospital Los Angeles, Los Angeles, CA, (12)University of Washington School of Medicine, (13)Cincinnati Children's Hospital Medical Center, Cincinnati, OH, (14) Division of Gastroenterology, Hepatology and Nutrition, the Hospital for Sick Children, Toronto, ON, Canada, (15)Primary Children's Hospital, (16)University of Michigan Hospitals and Health Centers, (17)Texas Children's Hospital, Houston, TX

Background: Secondary prophylaxis of gastroesophageal variceal hemorrhage is recommended in adults, and by corollary in pediatrics. However, there are few real-world studies of implementation. We describe the outcomes of gastrointestinal hemorrhage (GIH) in a large multi-center cohort of participants with biliary atresia (BA) and portal hypertension at hepatology centers in North America. **Methods:** Data from two prospective longitudinal studies of BA, PROBE and BASIC, in ChiLDReN, were analyzed in parallel. PROBE captures incident cases of BA < 6 months old, while BASIC includes a prevalent cohort > 6 months old. The clinical course of participants with GIH was analyzed for those with their native liver and possible or definite clinically evident portal hypertension. **Results:** A total of 180 participants were included in this analysis; 96 PROBE and 84 BASIC. The median age at the qualifying episode of GIH was 11 and 77 months in PROBE and BASIC, respectively. 32 (38%) of PROBE participants had a successful hepato-portoenterostomy (HPE) (TB < 2 mg/dL within 3 months of HPE). Following the index episode of bleeding, endoscopy was performed in 110 participants (61%). Esophageal varices were reported in 96 participants with 68 noted to have varices of grade II-III or higher. Comparison of participants undergoing endoscopy with or without intervention, to those who did not undergo an endoscopy after the index bleed are listed (TABLE). Participants who did not have endoscopy were younger, listed for transplant prior to GIH and did not have a draining HPE. 44 participants (30%) underwent liver transplant (LT) within 3 months of the index bleed. 31/44 were listed for LT prior to the index bleed and the median PELD at transplant was 24. There was no difference in transplant-free survival in those who underwent banding or sclerotherapy compared to those who did not. Secondary prophylaxis, consisting of at least two endoscopic interventions with 3 months of the index bleed, was performed in only 17 participants overall (9.4%). **Conclusion:** This real-world data from hepatology centers in North America demonstrates that BA patients with a GI bleeding episode do not typically receive conventional secondary prophylaxis. A nuanced approach appears based upon expected transplant-free survival and the endoscopic appearance of varices. Optimal approaches for management of variceal hemorrhage in biliary atresia warrant continued investigation.

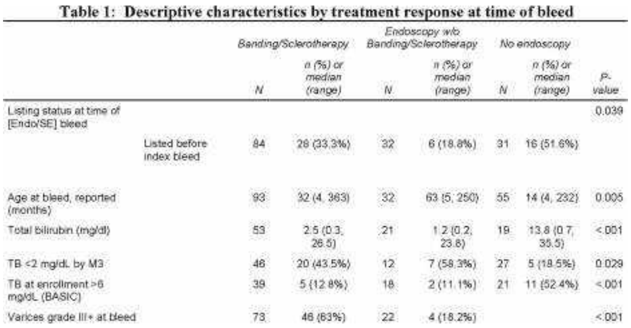

Table 1: Descriptive characteristics by treatment response at time of bleed

		Banding/Sclerotherapy		Endoscopy w/o Banding/Sclerotherapy		No endoscopy		
		N	*n (%) or median (range)*	*N*	*n (%) or median (range)*	*N*	*n (%) or median (range)*	*P-value*
Listing status at time of [Endo/SE] bleed								0.039
	Listed before index bleed	84	28 (33.3%)	32	6 (18.8%)	31	16 (51.6%)	
Age at bleed, reported (months)		93	32 (4, 363)	32	63 (5, 250)	55	14 (4, 232)	0.005
Total bilirubin (mg/dl)		53	2.5 (0.3, 26.5)	21	1.2 (0.2, 23.8)	19	13.8 (0.7, 35.5)	<.001
TB <2 mg/dL by M3		46	20 (43.5%)	12	7 (58.3%)	27	5 (18.5%)	0.029
TB at enrollment >6 mg/dL (BASIC)		39	5 (12.8%)	18	2 (11.1%)	21	11 (52.4%)	<.001
Varices grade III+ at bleed		73	46 (63%)	22	4 (18.2%)			<.001

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4604-C | MARALIXIBAT LEADS TO SIGNIFICANT IMPROVEMENT IN CHOLESTATIC PRURITUS FOR CHILDREN WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS DUE TO TJP2 OR MYO5B DEFICIENCY: DATA FROM THE MARCH-PFIC TRIAL

Alexander G. Miethke[1], Gilda Porta[2], Adib Moukarzel[3], Chuan-Hao Lin[4], Daniel D'Agostino[5], Douglas B Mogul[6], Tiago Nunes[6], Raul Aguilar[6], Pamela Vig[6], Fang Kuan Chiou[7] and Richard J. Thompson[8], (1) Cincinnati Children's Hospital Medical Center, Cincinnati, OH, (2)University of Sao Paulo School of Medicine, Sao Paulo, Brazil, (3)Hotel Dieu De France Saint Joseph University Hospital, Beirut, Lebanon, (4) Children’s Hospital Los Angeles, University of Southern California, Los Angeles, CA, (5)Hospital Italiano De Buenos Aires, Buenos Aires, Argentina, (6)Mirum Pharmaceuticals, Inc., Foster City, California, (7)Kk Women's and Children's Hospital, Singapore, (8) Institute of Liver Studies, King's College London, London, United Kingdom

Background: Progressive Familial Intrahepatic Cholestasis (PFIC) is a heterogeneous family of disorders of bile formation with the most commonly identified causes being deficiencies in BSEP, FIC1, and MDR3. Although other, rarer, causes continue to be discovered, all types share a phenotype characterized by elevated serum bile acids (sBA), cholestatic pruritus, impaired growth, and progressive liver disease. MARCH-PFIC (MARCH) was a randomized Phase 3 trial of maralixibat (MRX), an ileal bile acid transporter (IBAT) inhibitor, vs placebo (PBO), that achieved its primary and key secondary endpoints of pruritus and sBA reduction. Here we report on use of MRX in TJP2 and MYO5B deficiencies from the first trial of IBAT inhibition that included these subtypes. **Methods:** MARCH has been previously described. Data comparing change from Baseline (BL; CFB) to Weeks 15-26 for key efficacy endpoints (pruritus using 0-4 ItchRO[Obs], sBA, and bilirubin) were analyzed for individual’s with TJP2 or MYO5B deficiency. **Results:** In TJP2 deficiency (n = 6 MRX; n = 1 PBO), the median (range) of BL ItchRO(Obs) for MRX was 2.5 (1.5-3.6) with CFB of -1.9 (-0.4 to -3.4) with no change for the individual on PBO. BL sBA for MRX was 205 (96-428) µmol/L with CFB of -138 (-10 to -342) µmol/L; the individual on PBO also decreased sBA from 196 to 50 µmol/L. There were no meaningful changes in total and direct bilirubin for either group. In MYO5B deficiency (n = 2 MRX; n = 2 PBO), both individual’s on MRX had complete resolution of pruritus, with BL ItchRO(Obs) of 4 and 3 decreasing to 0; one individual on PBO had no change through end of study, and the other stopped at Week 6 for no perceived benefit. Both individual’s on MRX had complete normalization of sBA, from BL of 88 and 422 µmol/L to 4 and 2 µmol/L; one on PBO had normal BL sBA which was maintained through Week 26 and the other had elevated sBA at BL to Week 6. One individual on MRX had elevated BL bilirubin which normalized from 4.9 to 0.3 mg/dL (total) and 4.0 to 0.1 mg/dL (direct); both individual’s on PBO had normal BL bilirubin. Safety signals were consistent with other PFIC types. **Conclusion:** MARCH is the first trial of IBAT inhibition to show benefit for TJP2 and MYO5B deficiencies. All individual’s receiving MRX had large improvements in pruritus and most had large reductions in sBA. Normalization of bilirubin was observed in a MYO5B patient. Individual’s receiving PBO typically had little benefit. These data support the ongoing efficacy of MRX for PFIC across a broad range of types.

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(individual stocks and stock options), No, No; Alnylam: Consultant, No, No;
The following people have nothing to disclose: Gilda Porta, Adib Moukarzel, Daniel D'Agostino, Fang Kuan Chiou

4605-C | MARALIXIBAT LEADS TO SIGNIFICANT IMPROVEMENTS IN CHOLESTATIC PRURITUS FOR CHILDREN WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS WITHOUT A GENETIC DIAGNOSIS: DATA FROM THE MARCH-PFIC TRIAL

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Background: Progressive Familial Intrahepatic Cholestasis (PFIC) is a heterogeneous family of disorders of hepatocellular bile formation leading to cholestatic pruritus, growth deficits and liver failure. Whereas PFIC is commonly caused by mutations in *ATP8B1*, *ABCB11*, and *ABCB4*, new genes continue to be identified and other individual's have a PFIC phenotype without an identifiable cause. In the MARCH-PFIC (MARCH) Phase 3 trial, maralixibat (MRX), an ileal bile acid transporter (IBAT) inhibitor, achieved its primary and key secondary endpoints of improvement in pruritus, serum bile acids (sBA), and bilirubin for patients with BSEP deficiency and the All-PFIC cohort (i.e., with a genetic diagnosis). Here we present data on the efficacy and safety of MRX for individual's without an identified cause, the first time IBAT inhibition has been studied in this population. **Methods:** MARCH has been previously described. Participants were randomized to receive MRX 570 μg/kg BID or placebo (PBO) for 26 weeks. Data on key efficacy endpoints (pruritus, sBA, and bilirubin) were analyzed for participants with no diagnostic variants identified using a mixed effects model of repeated measurements. **Results:** 8 patients with PFIC, but without a genetic cause, were randomized ($n = 3$ MRX; $n = 5$ PBO). MRX and PBO were well-balanced with respect to Baseline pruritus score (3.4 vs 3.3 on 0-4 ItchRO[Obs] score) and sBA (140 vs 129 μmol/L). In the MRX group, significant changes from Baseline (CFB) were observed in ItchRO(Obs) response (-2.6; $p < 0.0001$), whereas no significant CFB was seen in PBO (0.05; $p = 0.8263$) and relative change between groups was significant (-2.6; $p < 0.0001$). The mean percentage of assessments with severity scores of 0 (none) or 1 (mild) was greater in the MRX group (66.8%) compared to PBO (0.4%) and the relative difference was significant ($p = 0.0007$). Large reductions of –105 μmol/L in sBA were observed in the MRX group ($p = 0.1000$) and no change in PBO. Decreases in total and direct bilirubin (-1.50 mg/dL; $p = 0.0602$; -1.23 mg/dL; $p = 0.0271$) were observed in the MRX group, while there was no improvement in PBO. One serious adverse event (UTI, unrelated) was reported in the MRX group. Diarrhea was reported in 2 (66.7%) MRX and 2 (40%) PBO, all mild in severity. No participants discontinued treatment. **Conclusion:** This is the first evidence of IBAT inhibition in patients with the PFIC phenotype without a genetic cause. MRX was associated with improvements in pruritus and sBA vs no change in PBO.

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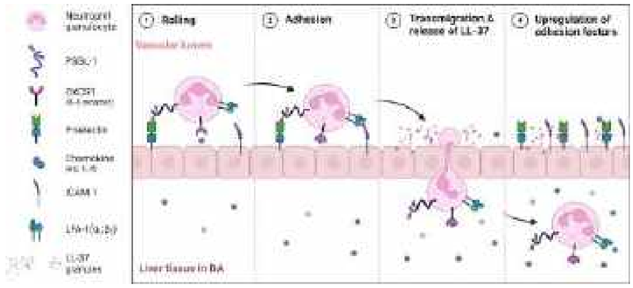
4606-C | NEUTROPHIL-DERIVED LL-37 IS INCREASED IN EARLY BILIARY ATRESIA AND CAN AFFECT LEUCOCYTE RECRUITMENT BY UPREGULATING ENDOTHELIAL ADHESION FACTORS

Christoph Slavetinsky[1], Jule Basenach[1], Franziska Ott[1], Stefan Fleischmann[1], Tobias Miserre[1], Lena Schultheis[1], Silvio Nadalin[2], Steffen Hartleif[1], Stephan Singer[2], Jörg Fuchs[1] and Ekkehard Sturm[3], (1) University Children´s Hospital Tübingen, (2)University Hospital Tübingen, (3)University Children's Hospital Tübingen

Background: Biliary atresia (BA) is a life-threatening liver disease characterized by progressive liver inflammation, fibro-obliterative obstruction of bile ducts due to an unknown trigger and major indication for liver transplantation in childhood. Liver inflammation of BA is characterized by a decrease of T regulatory and NK cells, but infiltration of cytotoxic T cells, circulating macrophages and neutrophils causing massive oxidative stress. The role of the soluble immune barrier of the biliary tree in hepatic pathophysiology in children is unknown. We planned to determine the expression profiles of common antimicrobial peptides and proteins in BA and analyze their role in hepatic/biliary damage, inflammation, and leucocyte trafficking. **Methods:** Expression of LL-37, LEAP-1, Lysozyme, and MBL was analyzed by qPCR from patient liver tissue of BA (n = 62) and familial cholestasis (PFIC, n = 18; ALGS, n = 6) at early and late disease stages expressed as proportion of age-matched normal controls (n = 19). LL-37 expression was correlated with pro-fibrotic activity (TGF-ß), adhesion factor expression (e.g., ICAM-1) and cholestasis (e.g., bile acids) by regression analysis, and localized in liver sections by immunohistochemistry and immunofluorescence (IF). Primary endothelial cells (HUVECs, LSECs) were treated with recombinant LL-37, assessed for cell viability (MTT assay), upregulation of adhesion factors (qPCR, IF), and *in vitro* adhesion of leucocytes (endothelium adhesion assay). **Results:** Liver gene expression of LL-37 but not of LEAP-1, Lysozyme and MBL is significantly upregulated 18-fold exclusively in early BA ($P = 0.001$) vs. 3-fold in familial cholestasis (ns). LL-37 expression in BA correlates with TGF-ß ($R^2 = 0.26$, $P = 0.007$) and ICAM-1 ($R^2 = 0.12$, $P = 0.006$) but not with cholestasis markers. LL-37 in BA is localized in neutrophils and on endothelial cells co-localizing with adhesion factors. Recombinant LL-37 has a dose-dependent cytotoxic effect on endothelia (HUVECs, $P = < 0.0001$; LSECs, $P = < 0.0001$) upregulating adhesion factors (ICAM-1: HUVECs, $P = 0.01$; LSECs, $P = < 0.0001$. P-selectin: HUVECs, $P = 0.0007$; LSECs, $P = < 0.0001$. E-selectin: HUVECs, $P = 0.02$; LSECs, $P = 0.001$.) and increasing *in vitro* adhesion of THP-1 cells by twofold ($P = 0.04$). **Conclusion:** LL-37 is upregulated in early BA, most likely due to neutrophil invasion which may release LL-37 on endothelia. In consequence, fibrotic activity may be induced by endothelial stress and subsequent upregulation of adhesion factors enabling increased binding of leucocytes. LL-37 may act as propagator of inflammation and leucocyte trafficking in BA.



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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

4607-C | RHESUS ROTAVIRUS INFECTION OF PLASMACYTOID DENDRITIC CELLS DRIVES NATURAL KILLER CELL ACTIVATION LEADING TO BILE DUCT OBSTRUCTION★

Stephen J. Hartman[1], Bryan Donnelly[1], Sujit K. Mohanty[2], Haley Temple[1], Rajamouli Pasula[1], Holly M Poling[1] and Gregory M. Tiao[1], (1)Cincinnati Children's Hospital Medical Center, Cincinnati, OH, (2)United States Department of Agriculture (USDA-ARS)

Background: Biliary atresia (BA) is a neonatal fibro-obliterative cholangiopathy resulting in life-threatening bile duct obstruction, which is universally fatal without early surgical intervention. BA's etiology remains unknown, but a murine model exists where infection of neonatal BALB/c mice with rhesus rotavirus (RRV) induces biliary obstruction akin to human BA. We have demonstrated that strain-specific activation of natural killer (NK) cells plays a critical role in the obstruction process. In this study we evaluated the mechanism of NK cell activation. **Methods:** BALB/c pups were injected with RRV and Ro1845 – a strain incapable of inducing murine BA – and viral titers were measured in liver NK and plasmacytoid dendritic cells (pDCs) at 7 days post infection (DPI). Flow cytometry was performed on uninfected murine pDCs to evaluate their surface receptors. Naïve pDCs at day of life (DOL) 2 and DOL10 were infected with RRV in vitro and evaluated for viral titer. Naïve NK cells were co-cultured with pDCs from RRV- and Ro1845-infected pups and evaluated for NK cell activation. *In vivo*, pDCs were selectively depleted by diphtheria toxin in mouse pups and then infected with RRV. **Results:** There was no significant difference in RRV and Ro1845 titers in NK cells at 7 DPI. PDCs from RRV-infected mice had significantly higher viral titer compared to Ro1845-infection. By flow, pDCs possessed only one known rotavirus receptor: heat shock cognate 70 protein (Hsc70), which decreased with increasing age. Naïve pDCs from DOL2 pups produced significantly higher viral titers than DOL10. Flow cytometry demonstrated pDCs from RRV-infected pups had significantly higher activation compared to saline and Ro1845-infected pups (Figure 1). Naïve NK cells co-cultured with RRV-infected pDCs exhibited higher activation compared to pDCs from saline and Ro1845-injected pups. After pDC depletion, RRV-infected pups revealed patent bile ducts and a significant reduction of NK cells on liver histology, contrasting with the obstructed control mice. **Conclusion:** RRV infection of pDCs leads to their activation and this activation potentiates activation of NK cells inducing biliary obstruction observed in the murine model of BA. We have previously demonstrated that only rotavirus strains containing an "SRL" motif on their attachment protein, such as RRV, can bind to Hsc70 and induce the murine model of BA, whereas other viruses cannot bind Hsc70, which may explain their low infectivity in pDCs and diminished NK cell activation.

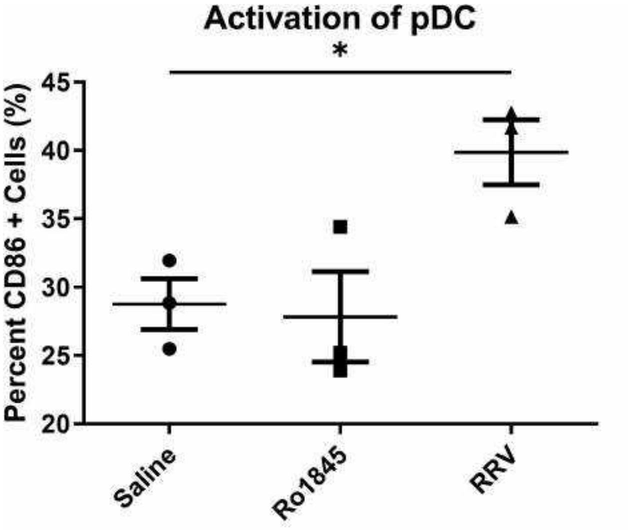

Figure 1: Flow cytometry demonstrating percentage of activated pDCs (% CD86+) isolated at 7 days post-injection.

Disclosures: The following people have nothing to disclose: Stephen J Hartman, Bryan Donnelly, Sujit K. Mohanty, Haley Temple, Rajamouli Pasula, Holly M Poling, Gregory M. Tiao

4608-C | THE ROLE OF ENDOSCOPIC RETROGRADE CHOLANGIO-PANCREATOGRAPHY IN PAEDIATRIC CHOLANGIOPATHIES

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Background: Cholangiopathies represent a significant proportion of paediatric liver disease. However, there is little information on the role and safety of endoscopic retrograde cholangiopancreatography (ERCP) in this population. We present data on safety and outcomes in paediatric patients undergoing ERCP. **Methods:** Data was collected on all paediatric patients (< 18 y old) from an electronic endoscopic database) between 2008 - 2022. Data collected included patient age, gender, diagnosis, indications and therapy. Complications were also reviewed for primary and subsequent ERCPs. **Results:** In total, 230 ERCP procedures were

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

performed for 103 patients (60 male). All ERCP cases were performed under general anaesthetic. The median age of the patient population was 11 years (range 22 d-16 y). 72% weighed above 20 kg. 19 patients had concurrent IBD. Successful cannulation was achieved in 89% of cases. All patients received prophylactic antibiotics pre and post procedure. The most common indication was for a dominant stricture (DS), 66%. Primary sclerosing cholangitis and autoimmune sclerosing cholangitis accounted for only 26% of the cases. There was no obvious difference in the rates of sphincterotomy performed between the DS and non-DS groups (22 vs 18 %). 191(83%) ERCPs were performed for DS. DS patients required more ERCPs (median 2, range 1-14 vs median 1, range 1-3, $p < 0.005$)). DS patients were more likely to require a stent (50% vs 5%), with plastic stents more frequently used. Overall, the mean change in bilirubin, alkaline phosphatase and gamma glutamyl transferase post procedure was -35.7 μmol/l, -77.3 IU/L and -34.3 IU/L, respectively. Time to liver transplantation was 4.9 years (range 0.17 – 11). At the time of follow up, 8 patients had died. Causes of death included graft dysfunction post liver transplant, disseminated malignancy and respiratory failure. The overall complication rate of ERCP in the paediatric population was 3.0%. Individual complication rates for post ERCP bleeding, pancreatitis, cholangitis and perforation were 0.9%, 1.3%, 1.3% and 0.4% respectively. **Conclusion:** ERCP appears to be safe and efficacious in paediatric patients. It plays an integral role in the management of paediatric cholangiopathies.

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Disclosure information not available at the time of publication: Marianne Samyn, David Reffitt, John Devlin, Phillip Harrison, Deepak Joshi

4609-C | TIME-COURSE RNASEQ REVEALED DYNAMIC TRANSCRIPTIONAL CHANGES IN A MOUSE MODEL OF TOXIN-INDUCED BILIARY ATRESIA

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Background: We have previously established a toxin-induced biliary atresia (BA) model in the zebrafish using biliatresone, an isoflavonoid causatively linked BA outbreaks in newborn Australian livestock. Here, we aimed to elucidate mechanisms underlying BA pathogenesis using a biliatresone-induced mouse model of biliary injury. **Methods:** We injected BALB/c mouse pups intraperitoneally with biliatresone (30μg/g) *vs* vehicle control between one and two days of age. Histopathological analyses of the extrahepatic bile ducts (EHBD) and livers were performed using H&E and immunofluorescence staining. For global gene expression profiling, EHBD and livers were harvested separately at 6 hr, 12 hr, 24 hr, 72 hr, and 7 days post exposure for RNA extraction. Sequencing was performed on the Novaseq S4 and differential gene expression analyses were obtained using DESeq2. **Results:** We found that intraperitoneal injection of biliatresone led to obstructive jaundice in selected pups secondary to extrahepatic bile duct injury, resulting in liver cholestasis, similar to the human disease. Specifically, we observed that 100% of neonatal mice would develop jaundice and significant weight loss within 72 hr of toxin injection, which would persist or progress in 48.6% of pups 7 days post injection with associated acholic stool and a maximum survival time of 18 days. The remaining neonatal mice would recover with no perceivable jaundice. Gross morphological examination of the EHBD at 72 hr post biliatresone injection revealed thickened common bile ducts (CBD). While the CBD in the recovered pups appeared indistinguishable from the controls at 7 days post exposure, they appeared narrowed in the jaundiced pups, resulting in upstream biliary dilation and inspissated bile with sludge. Subsequent histological analyses and immunofluorescence staining of Z0-1 in the EHBD of these pups showed luminal occlusion and aberrant Z0-1 patterning, suggestive of loss of cellular integrity and polarity. Ductular reaction was observed in the liver tissues at 7 days. Time-course transcriptional profiling revealed a number of differentially expressed genes (DEGs) across different timepoints post toxin exposure in the EHBD and livers. Gene ontology enrichment analyses of DEGs in the EHBD samples revealed enrichment of genes involved in stress responses early on post exposure (6hr, 12hr), consistent with prior zebrafish studies. The enriched pathways shifted to cell migration, cell adhesions and maintenance of polarity in the intermediate times points (24h, 72hr), and inflammatory signaling involving the innate immune system at the late time point (7 d). **Conclusion:** We utilized a novel mammalian BA model to identify dynamic transcriptional changes in the EHBD in response to toxic insult that may shed valuable insights into the mechanisms driving injury progression in BA and inform the rational design of therapeutic strategies.

Disclosures: The following people have nothing to disclose: Shang-Hsin Wu, Abigail Spingarn, Xiao Zhao

4610-C | TREATMENT WITH MARALIXIBAT FOR REFRACTORY PRURITUS IN PATIENT WITH ARTHROGRYPOSIS RENAL DISEASE AND CHOLESTASIS SYNDROME

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Background: Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a rare, autosomal recessive multisystemic disorder with almost universal mortality in childhood. Cholestasis is a cardinal feature of the disorder resulting in fat-soluble vitamin deficiency, growth failure and debilitating pruritus. Pruritus is often exacerbated by concurrent ichthyosis, resulting in self-mutilating behaviors and poor quality of life. Here we present a single Subject Investigational New Drug Study (sIND) using Maralixibat, an ileal bile acid transport inhibitor, to treat an 11-month old female with ARC syndrome and severe pruritus, refractory to medical therapy. **Methods:** Patient was treated with standard FDA-approved Maralixibat dosing for Alagille Syndrome of 190mcg/kg/day, followed by an increase to 380mcg/kg/day. Patient was monitored during clinic visits and with laboratory evaluations according to study protocol. During the treatment protocol, the patient continued to be closely followed by nephrology for diabetes insipidus, and by palliative/hospice care. **Results:** Prior to initiation of therapy patient's serum bile acids were notable for elevated cholic acid of > 75 umol/L, chenodeoxycholic acid of 39.3 umol/L, ursodeoxycholic acid of 18.3 umol/L (patient was on ursodiol) and total serum bile acids of > 132.9 umol/L. INR was normal (0.76), while total and conjugated bilirubin were 4 mg/dL and 1.8mg/dL respectively. After 4 weeks of treatment, pruritus and total serum bile acids were unchanged (131.8 umol/L). After 9 weeks of therapy, patient developed worsening jaundice, rise in total and conjugated bilirubin (5.3mg/dL and 2.1mg/dL, respectively), and hypopigmented stools when transitioned from infant to pediatric hydrolyzed formula. Liver ultrasound showed no signs of biliary obstruction. Formula was changed to a different pediatric hydrolyzed brand. Twelve weeks after initiation of therapy, daily dosing was increased to 380mcg/kg/day according to protocol; however, cholestasis continued to worsen with total and conjugated bilirubin rising to 9.8mg/dL and 5.1mg/dL respectively, in addition to worsening pruritus correlating with rise in total bile acids of > 166.4umol/L. Over the next 4 weeks the patient continued to have debilitating pruritus, hypopigmented stools as well as worsening diarrhea. Because of ongoing diabetes insipidus as part of her phenotype patient had worsening dehydration in the setting of worsening diarrhea. Sixteen weeks after initiation of therapy Maralixibat was discontinued due to lack of efficacy. Patient ultimately died 18 weeks after initiation of study. **Conclusion:** This is the first reported sIND trial of Maralixibat for treatment of ARC syndrome. Maralixibat was not beneficial in palliating pruritus in the severe phenotype of our patient. Further studies in larger populations with varying severity of phenotype would be beneficial to further evaluate efficacy.

Disclosures: The following people have nothing to disclose: Tamir Diamond, Elizabeth Rand

Disclosure information not available at the time of publication: Iraklis Petrof, Christa Seidman, Alanna Strong

4611-C | A PILOT STUDY USING TRANSIENT ELASTOGRAPHY FOR SCREENING IN CHILDREN WITH CYSTIC KIDNEY DISEASES

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Background: Congenital Hepatic Fibrosis (CHF) is a portobiliary anomaly with multiple associations, including cystic kidney diseases. Classically, CHF is associated with autosomal recessive polycystic kidney disease. However, there are case reports of hepatic fibrosis resulting in portal hypertension in patients with autosomal dominant polycystic kidney disease. Our study objective is to use vibration-controlled transient elastography (VCTE) to determine the baseline liver stiffness measurements (LSM) in pediatric patients with cystic kidney diseases and compare to reported normal values. **Methods:** A single-center cohort study of children with cystic kidney diseases was completed. ICD 9 and10 codes were used to identify subjects within our practice. Retrospective chart review provided demographic and clinical information. VCTE (FibroScan, Echosens, Paris, France) was performed to obtain LSM (kPa) at time of enrollment. Data was compared to published mean LSM values. **Results:** Baseline data on 28 patients with cystic kidney disease was collected: 9 (32%) autosomal recessive polycystic kidney disease (ARPKD), 9 (32%) autosomal dominant polycystic kidney disease (ADPKD), 3 (11%) nephronophthisis, and 7 (25%) other cystic kidney disease. Mean age was 10.1 years. While the mean LSM in this cohort was not above normal, 10 subjects had a LSM greater than 2 standard deviations above the mean: 7 ARPKD (7.3 kPa, 7.9 kPa, 10.2 kPa, 13.1 kPa, 13.2 kPa, 18.3 kPa, 32.7 kPa), 1 ADPKD (8 kPa), 1 bilateral cystic renal dysplasia (9.4 kPa), and 1 nephronophthisis

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(75 kPa). **Conclusion:** Data on liver stiffness and its progression in the spectrum of cystic kidney disease is rare. Although most subjects did not have elevated LSM, there were ten identified patients with ARPKD, ADPKD, bilateral cystic renal dysplasia, and nephronophthisis with increased LSM compared to normals for age. LSM may progress over time. We plan to obtain longitudinal data to provide important insight into the role of VCTE in monitoring liver stiffness in cystic kidney disease.

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Disclosure information not available at the time of publication: Wendy Morlan, Sushil Gupta

4612-C | AN UNUSUAL CAUSE OF LOW CERULOPLASMIN IN A PAIR OF AUTISTIC TWINS

Vipreet Janjua and Nanda Kerkar, University of Rochester, New York

Background: Low ceruloplasmin is often used as a screening test for Wilson disease (WD). Ceruloplasmin is an alpha-2 glycoprotein that belongs to the family of multi-copper oxidases that do not transport copper but instead contain 95% of the copper in serum. The *Ceruloplasmin gene* is located on chromosome 3 and the protein being an essential ferroxidase is responsible for oxidizing ferrous to ferric ion. Low Ceruloplasmin levels may also be found in Menke's disease, malignancy, inflammatory bowel disease, thyroid disease, neonates, heterozygotes for WD and aceruloplasminemia **Methods:** Electronic medical record review **Results:** A 12-year-old Hispanic nonverbal autistic male with history of constipation and urticaria pigmentosa was referred for elevated serum transaminases with normal bilirubin levels. Physical exam was unremarkable. Initial screening for common causes of liver disease was negative including viral hepatitis, autoimmune hepatitis and alpha-1antitrypsin deficiency. Initial ceruloplasmin level was 6 mg/dL (normal 20-35mg/dL) so a screen for WD was commenced. We repeated the ceruloplasmin level that was low again (6 mg/dL). In addition, Kayser-Fleischer ring was not noted on slit lamp exam and 24-hour urine copper level was non-contributory. He was lost to follow-up for a few years and then presented with increased tiredness and weight loss. A liver biopsy was performed and histology showed near normal liver parenchyma with no significant portal or lobular inflammation. Liver copper was reported to be below 50 mcg/g which was within normal limits. Liver copper > 250mcg/g of liver tissue is diagnostic of WD. His autistic, twin brother also had a low ceruloplasmin level and screening in him for WD was also negative, but liver biopsy was not performed. Our patient had a history of genetic testing done during investigation of autism and was found to have duplication of chromosome 22, negative fragile X testing and also had no mutation in *ATP7B* (gene for WD). On Invitae sponsored copper metabolism gene panel, he was noted to have a single pathogenic variant in the *Ceruloplasmin gene* that prevents incorporation of copper in Ceruloplasmin and disrupts iron metabolism. His serum ferritin was normal at 40ng/ml (normal 20-200 ng/ml). **Conclusion:** Our patient is a heterozygote for aceruloplasminemia, as was his twin brother. This is a rare cause of low ceruloplasmin. Aceruloplasminemia is an autosomal recessive condition that has symptom onset in the 40s to 50s and primarily presents with neurological disease (gait abnormalities, memory and speech impairments) as well as diabetes mellitus associated with iron overload. As genetic testing is becoming more available in the general clinical setting, this case illustrates the importance of considering alternative etiologies for low ceruloplasmin in addition to Wilson disease.

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The following people have nothing to disclose: Vipreet Janjua

4613-C | CLINICAL, GENETIC, AND PATHOLOGIC FEATURES, TREATMENT, AND LONG-TERM OUTCOME IN PATIENTS WITH BENIGN RECURRENT INTRAHEPATIC CHOLESTASIS: A MULTICENTER STUDY IN JAPAN

Ken Kato[1], Shuichiro Umetsu[2], Takao Togawa[3], Koichi Ito[3], Takayoshi Kawabata[4], Teruko Arinaga-Hino[1], Naoya Tsumura[1], Ryosuke Yasuda[1], Yutaro Mihara[1], Hironori Kusano[1], Shogo Ito[3], Kazuo Imagawa[5], Hisamitsu Hayashi[6], Ayano Inui[2], Yushiro Yamashita[1] and Tatsuki Mizuochi[1], (1)Kurume University School of Medicine, (2)Saiseikai Yokohamashi Tobu Hospital, (3) Nagoya City University Graduate School of Medical Sciences, (4)Ishikawa Prefectural Central Hospital, (5) University of Tsukuba, (6)The University of Tokyo

Background: There have been few reports of benign recurrent intrahepatic cholestasis (BRIC) from East Asia. We aimed to clarify clinical, genetic, and pathologic features, treatment and long-term outcome in Japanese patients with BRIC. **Methods:** We recruited patients with BRIC type 1 (BRIC-1) or type 2 (BRIC-2) who visited at 4 pediatric and 1 adult centers in Japan between April 2007 and March 2022. Demographic, clinical course, laboratory blood tests, molecular genetic results concerning *ATP8B1* or *ABCB11* gene, histopathological findings in the liver, and treatment were retrospectively examined. **Results:** Seven Japanese patients with BRIC (4 males and 3 females; 4 BRIC-1 and 3 BRIC-2) were enrolled. Median age at onset in patients with BRIC-1 was 12 years while BRIC-2 was 1 month. Number of intermittent cholestatic attacks varied from 1 to 8 during 11 years of median follow-up period. Six patients received a regular education; only 1 attended special education. No patients had developed cirrhosis. Three patients with BRIC-1 had compound heterozygous variant in the *ATP8B1* gene and 1 had heterozygous while 2 patients with BRIC-2 had compound heterozygous in the *ABCB11* gene and 1 had heterozygous. Liver biopsy specimens during the cholestatic attacks showed that fibrosis stage varied from none to moderate but inflammation grade showed none or mild. Rifampicin was administered to 3 patients for their cholestatic attacks and was effective in all of them while cholestyramine to 2 patients and was effective in both. **Conclusion:** To our knowledge, this is the first report of multicenter study for patients with BRIC from East Asia. Onset age and number of intermittent cholestatic attacks varied. Rifampicin and cholestyramine were effective for the cholestatic attacks. No patients developed cirrhosis and most patients showed normal growth and development. Long-term outcome of Japanese patients with BRIC was fairly good.

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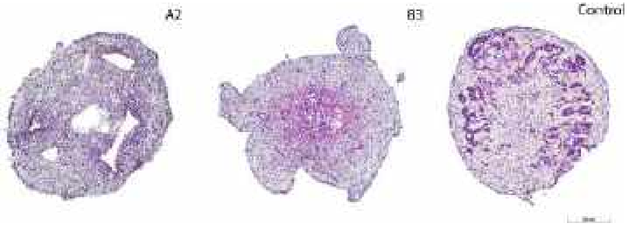
4614-C | DOWNREGULATION OF SOX9 MEDIATED BY REDUCED NOTCH AND HIPPO SIGNALING RESULTS IN BILE DUCT PAUCITY AND IMPAIRED DUCTULAR REACTION IN AN iPSC-DERIVED, HUMAN, THREE-DIMENSIONAL MODEL OF ALAGILLE SYNDROME

Marie-Agnès M'Callum, Silvia Selleri, Quang Toan Pham, Alexandre Archambault-Marsan, Kristen Vieira-Lomasney and Massimiliano Paganelli, CHU Sainte-Justine, Université De Montréal

Background: Alagille syndrome (ALGS) is an autosomal dominant multisystemic disease resulting in bile duct paucity, cholestasis and progressive fibrosis. The genes involved (JAG1, NOTCH2) belong to the Notch signalling pathway. The aim of this study was to develop a representative human model of ALGS and use it to better understand the pathophysiology of the disease. **Methods:** We developed a 3D in vitro model of ALGS by generating liver organoids from human induced pluripotent stem cells (iPSC). Two isogeneic iPSC clones with mutations in exon 23 of JAG1 gene (large deletion in A2, single base substitution in B3) were generated with CRISPR/Cas9. Mutated iPSCs and an isogeneic control were differentiated into hepatic (HPC), mesenchymal (MPC) and endothelial (EPC) progenitor cells and used to compose the liver organoids. Within the organoids, these cells interact to become hepatocytes, biliary epithelial cells, and stellate and sinusoidal cells, and form ductal plate structures and bile ducts (Raggi et al. Stem Cell Reports 2022). We studied the impact of the mutations on the different liver cell types and assessed bile duct formation and fibrogenesis in the organoids. We also generated hybrid organoids mixing mutated and control progenitors to assess the role of each cell type in determining the disease phenotype. **Results:** The different JAG1 mutations of the two clones resulted in HPCs with different hepatic and Notch pathway gene expression profiles, as expected from the known phenotypic heterogeneity of ALGS. JAG1mutation also affected mesenchymal and endothelial progenitors, with EPC showing an impaired capacity to form vessels in vitro. Organoids from the two mutated clones lacked biliary structures compared to healthy organoids (see Figure), reproducing the bile duct paucity of ALGS. Among the 18 hybrid organoid conditions generated, only organoids with healthy HPCs were able to form proper biliary structures (although JAG1 mutation in EPC and MPC resulted in dysmorphic organoids), attesting that mutation in parenchymal cells drives the disease phenotype. No significant apoptosis was detected in JAG1-mutated organoids, but profibrotic markers were overexpressed. Although YAP1 was overexpressed in mutated HPC cultured in 2D (with clear difference between the two mutated clones), YAP/TAZ and SOX9 were underexpressed in JAG1-mutated organoids, which well correlated with ductular paucity. A loss of CFTR and β-catenin resulted in increased NF-κB expression in mutated organoids, but this did not result in the expected ductular reaction. **Conclusion:** We generated a representative human developmental model of Alagille syndrome using complex liver organoids derived from iPSCs. These organoids reproduced the histological phenotype of Alagille syndrome, allowing for the study of the pathophysiology of bile duct paucity and lack of ductular reaction.



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4615-C | FAT-SOLUBLE VITAMIN LEVELS IN PATIENTS WITH ALAGILLE SYNDROME TREATED WITH ODEVIXIBAT IN THE PHASE 3 ASSERT STUDY

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Background: Alagille syndrome (ALGS) is a rare, genetic, multisystem disease that affects the liver and can lead to cholestasis, with resultant impairments in lipid absorption and subsequent fat-soluble vitamin (FSV) deficiency. In the 24-week ASSERT study, treatment with odevixibat resulted in significant improvements in pruritus and reductions in bile acids versus placebo in patients with ALGS. Here, we summarize effects related to FSVs in ASSERT. **Methods:** Patients eligible for ASSERT were those of any age with ALGS, history of significant pruritus, and elevated serum bile acids; patients were randomized 2:1 to odevixibat 120 μg/kg/day or placebo. Vitamins A, D, E, and international normalized ratio (INR; surrogate for vitamin K) were measured at screening, randomization, and 2−6 times through week 24. Treatment-emergent adverse events (TEAEs) resulting from new or worsening FSV deficiency refractory to clinically recommended vitamin supplementation and possible sequelae of FSV deficiency were evaluated. **Results:** Overall, 52 patients (mean age, 6.3 y) received odevixibat (n = 35) or placebo (n = 17); all 52 patients completed the study. At baseline, mean levels of vitamins A, D, E, and INR were generally within normal range, reflective of vitamin supplementation received by most patients. Overall, no clinically relevant changes were observed in mean FSV levels or INR in patients receiving odevixibat or placebo during the study. In total, 6 patients reported TEAEs related to FSV levels (odevixibat, n = 3 [9%]; placebo, n = 3 [18%]). Two of these (odevixibat, n = 1 [3%]; placebo, n = 1 [6%]) had TEAEs of vitamin D deficiency that were refractory to clinically recommended vitamin supplementation; both were nonserious, did not lead to treatment interruption, and were assessed as unrelated to study drug. The 4 additional patients with TEAEs related to FSV levels had increased INR (odevixibat, n = 1; placebo, n = 2) or decreased vitamin A and vitamin E serum levels (odevixibat, n = 1 each [both in the same patient]) that were not considered refractory to clinically recommended vitamin supplementation. TEAEs of possible sequelae of FSV deficiency had a similar incidence with odevixibat (n = 5 [14%]) and placebo (n = 3 [18%]; Table); the most common in the odevixibat group was hematoma, reported in 3 (9%) patients and all attributed to trauma. Most TEAEs possibly secondary to FSV deficiency were reported as Grade 1 or 2 in intensity, were nonserious, and did not lead to treatment interruption or discontinuation. Review of the Kaplan-Meier curve for time to onset of these sequelae indicated no difference between treatment groups. **Conclusion:** In the ASSERT study, treatment of patients with ALGS with odevixibat for up to 24 weeks was not associated with clinically meaningful changes in mean FSV levels or INR. Possible sequelae of FSV deficiency were reported at similar incidence with both odevixibat and placebo.

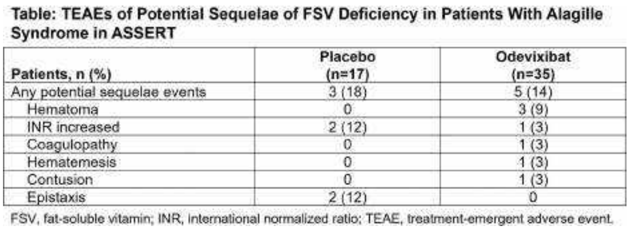

Table: TEAEs of Potential Sequelae of FSV Deficiency in Patients With Alagille Syndrome in ASSERT

Patients, n (%)	Placebo (n=17)	Odevixibat (n=35)
Any potential sequelae events	3 (18)	5 (14)
Hematoma	0	3 (9)
INR increased	2 (12)	1 (3)
Coagulopathy	0	1 (3)
Hematemesis	0	1 (3)
Contusion	0	1 (3)
Epistaxis	2 (12)	0

FSV, fat-soluble vitamin; INR, international normalized ratio; TEAE, treatment-emergent adverse event.

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4616-C | ODEVIXIBAT EFFICACY AND SAFETY ACROSS PATIENT SUBGROUPS: AN EVALUATION OF POOLED DATA FROM THE PEDFIC 1 AND PEDFIC 2 TRIALS

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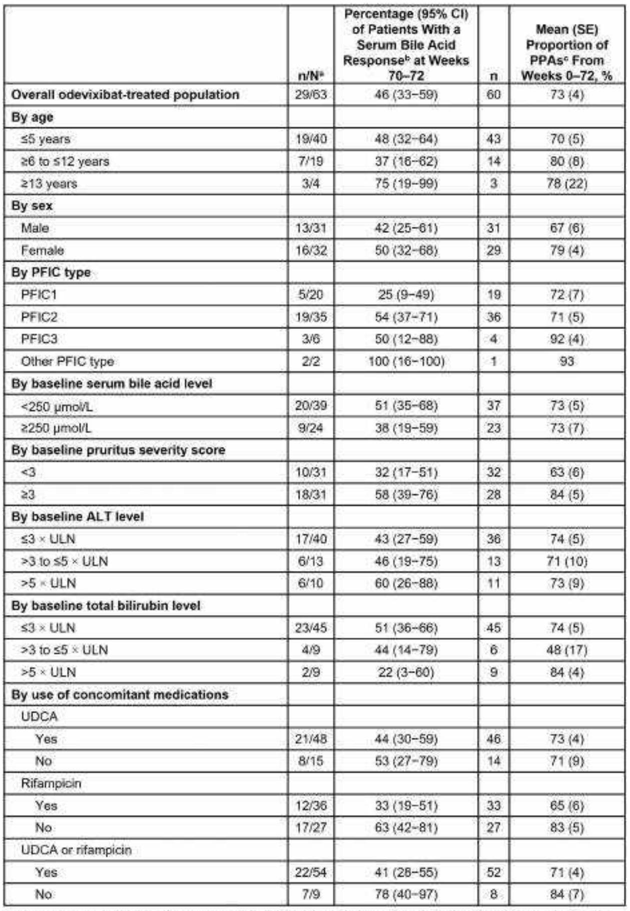
Background: Progressive familial intrahepatic cholestasis (PFIC) is a group of inherited liver diseases with clinical features that may include elevated serum bile acids and severe pruritus. The efficacy and safety of odevixibat, an ileal bile acid transporter inhibitor, were evaluated in two phase 3 trials in patients with PFIC called PEDFIC 1 and PEDFIC 2. In these studies, odevixibat treatment reduced serum bile acids and improved pruritus. Using pooled data from these trials, we assessed treatment effects in patient subgroups defined by demographic and baseline characteristics. **Methods:** Patients eligible for PEDFIC 1 (NCT03566238) and PEDFIC 2 (NCT03659916) had elevated serum bile acids and significant pruritus at screening. PEDFIC 1 was a 24-week, double-blind study in children with PFIC1 or PFIC2; patients were randomized to placebo, odevixibat 40 μg/kg/day, or odevixibat 120 μg/kg/day. PEDFIC 2 is an ongoing, open-label extension study in which patients from PEDFIC 1 or newly enrolled patients with any PFIC type receive odevixibat 120 μg/kg/day. In a pooled analysis of data from patients' first dose of odevixibat in PEDFIC 1 and/or PEDFIC 2 to a data cutoff date of July 31, 2022, we evaluated the percentage of patients with a serum bile acid response (ie, serum bile acids reduced ≥70% from baseline or levels ≤70 μmol/L) and the proportion of positive pruritus assessments (PPAs) at the patient level (ie, scratching score ≤1 or a ≥1-point drop from baseline based on the validated PRUCISION instrument [range 0–4; higher scores indicate worse symptoms]) over 72 weeks of treatment in patient subgroups defined by age, sex, PFIC type, baseline serum bile acid level, baseline pruritus score, baseline alanine aminotransferase or total bilirubin level, and concomitant use of ursodeoxycholic acid and/or rifampicin. Safety was evaluated by monitoring treatment-emergent adverse events (TEAEs). **Results:** Overall, 119 patients comprised the pooled population (median age, 5.9 y; 45% female; 29% PFIC1, 60% PFIC2, 6% PFIC3, 5% other PFIC type). Median (range) exposure to odevixibat was 82 weeks (4 to 201 weeks). In the overall odevixibat-treated group, 29 of 63 (46%) patients with data at week 72 met serum bile acid response criteria. Over the 72-week treatment period, the mean (SE) proportion of PPAs was 73% (4%). The percentage of patients with a serum bile acid response and the mean proportion of PPAs in various patient subgroups are shown in the Table. In the overall population, 108/119 (91%) of patients reported TEAEs; most were mild to moderate in severity. **Conclusion:** All patient subgroups had clinically meaningful decreases in serum bile acid levels and improvements in pruritus score from baseline, although the magnitude of efficacy response was variable in some subgroups. TEAEs with odevixibat in this pooled analysis were consistent with previously reported results.

Table. Rate of Serum Bile Acid Response and Mean Proportion of PPAs With 72 Weeks of Odevixibat Treatment: Subgroup Analyses Using Data From the PEDFIC Studies



	n/N[a]	Percentage (95% CI) of Patients With a Serum Bile Acid Response[b] at Weeks 70–72	n	Mean (SE) Proportion of PPAs[c] From Weeks 0–72, %
Overall odevixibat-treated population	29/63	46 (33–59)	60	73 (4)
By age				
≤5 years	19/40	48 (32–64)	43	70 (5)
≥6 to ≤12 years	7/19	37 (16–62)	14	80 (8)
≥13 years	3/4	75 (19–99)	3	78 (22)
By sex				
Male	13/31	42 (25–61)	31	67 (6)
Female	16/32	50 (32–68)	29	79 (4)
By PFIC type				
PFIC1	5/20	25 (9–49)	19	72 (7)
PFIC2	19/35	54 (37–71)	36	71 (5)
PFIC3	3/6	50 (12–88)	4	92 (4)
Other PFIC type	2/2	100 (16–100)	1	93
By baseline serum bile acid level				
<250 μmol/L	20/39	51 (35–68)	37	73 (5)
≥250 μmol/L	9/24	38 (19–59)	23	73 (7)
By baseline pruritus severity score				
<3	10/31	32 (17–51)	32	63 (6)
≥3	18/31	58 (39–76)	28	84 (5)
By baseline ALT level				
≤3 × ULN	17/40	43 (27–59)	36	74 (5)
>3 to ≤5 × ULN	6/13	46 (19–75)	13	71 (10)
>5 × ULN	6/10	60 (26–88)	11	73 (9)
By baseline total bilirubin level				
≤3 × ULN	23/45	51 (36–66)	45	74 (5)
>3 to ≤5 × ULN	4/9	44 (14–79)	6	48 (17)
>5 × ULN	2/9	22 (3–60)	9	84 (4)
By use of concomitant medications				
UDCA				
Yes	21/48	44 (30–59)	46	73 (4)
No	8/15	53 (27–79)	14	71 (9)
Rifampicin				
Yes	12/36	33 (19–51)	33	65 (6)
No	17/27	63 (42–81)	27	83 (5)
UDCA or rifampicin				
Yes	22/54	41 (28–55)	52	71 (4)
No	7/9	78 (40–97)	8	84 (7)

[a] Number of patients with available data at the week 72 visit. [b] Serum bile acids reduced ≥70% from baseline or levels ≤70 μmol/L. [c] Pruritus score ≤1 or a ≥1-point drop from baseline. ALT, alanine aminotransferase; PFIC, progressive familial intrahepatic cholestasis; PPA, positive pruritus assessment; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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4617-C | OUTCOMES WITH ODEVIXIBAT TREATMENT IN PATIENTS WITH ALAGILLE SYNDROME: ANALYSIS OF PRURITUS RESPONDERS FROM THE PHASE 3 ASSERT STUDY

Nadia Ovchinsky[1], Madeleine Aumar[2], Alastair J. Baker[3], Ulrich Baumann[4], Philip Bufler[5], Mara Cananzi[6], Piotr Czubkowski[7], Özlem Durmaz[8], Ryan T. Fischer[9], Giuseppe Indolfi[10], Wikrom Karnsakul[11], Florence Lacaille[12], Way Seah Lee[13], Giuseppe Maggiore[14], Philip Rosenthal[15], Mathias Ruiz[16], Etienne Sokal[17], Ekkehard Sturm[18], Wendy Van Der Woerd[19], Henkjan J. Verkade[20], Andrew Wehrman[21], Christine Clemson[22], Qifeng Yu[22], Quanhong Ni[22], Jessica Ruvido[22], Susan Manganaro[22] and Jan P. Mattsson[22], (1)Hassenfeld Children's Hospital at NYU Langone, (2) Univ Lille, CHU Lille, (3)King's College Hospital, (4) Hannover Medical School, Hannover, Germany, (5) Charité Universitätsmedizin Berlin, (6)University Hospital of Padova, (7)The Children's Memorial Health Institute, (8)Istanbul University, Istanbul Faculty of Medicine, (9)Children's Mercy Hospital, (10)Meyer Children's University Hospital of Florence, (11)Johns Hopkins University School of Medicine, (12)Hôpital Universitaire Necker-Enfants Malades, (13)University of Malaya, (14)Bambino Gesù Children's Hospital Irccs, (15)University of California San Francisco, (16) Hospices Civils De Lyon, Hôpital Femme-Mère-Enfant, (17)Université Catholique De Louvain, Cliniques St Luc, (18)University Children's Hospital Tübingen, (19) Wilhelmina Children's Hospital, University Medical Centre Utrecht, (20)University of Groningen, Beatrix Children's Hospital/University Medical Centre Groningen, Groningen, Netherlands, (21)Boston Children's Hospital and Harvard Medical School, Boston, MA, (22)Albireo Pharma, Inc.

Background: Clinical manifestations of Alagille syndrome (ALGS) include elevated levels of bile acids and severe pruritus associated with impaired sleep and quality of life. Odevixibat is a potent, selective inhibitor of the ileal bile acid transporter and effectively reduced bile acids and improved pruritus and sleep in patients with ALGS in the phase 3 ASSERT study. We examined efficacy and safety outcomes in patients who met criteria for pruritus response following 24 weeks of treatment in ASSERT. **Methods:** Patients with a confirmed diagnosis of ALGS, history of significant pruritus, and elevated serum bile acids were randomized 2:1 to odevixibat 120 μg/kg/day or placebo. Patient pruritus and daytime tiredness were rated by caregivers using the PRUCISION observer-reported outcome (ObsRO) tool (range: 0–4; higher scores indicate worse symptoms). Efficacy outcomes evaluated in pruritus responders (defined as patients achieving a ≥ 1-point decrease in ObsRO scratching score from baseline to weeks 21–24) were change from baseline in ObsRO scratching score, serum bile acids, ObsRO sleep parameters, and caregiver-reported Pediatric Quality of Life Inventory (PedsQL) scores; safety outcomes included treatment-emergent adverse events (TEAEs). **Results:** Overall, 52 patients (mean age, 6.3 y) received odevixibat (n = 35) or placebo (n = 17) in ASSERT, and all 52 patients completed the study. Six (35%) patients receiving placebo and 28 (80%) patients receiving odevixibat were pruritus responders. Pruritus responders treated with odevixibat (mean age, 7.1 y) had a mean scratching score of 2.8 at baseline and 0.9 at weeks 21−24; these pruritus responders also had mean reductions in bile acids and improvements in sleep parameters and PedsQL scores compared with baseline (Table 1). Among odevixibat-treated pruritus responders, 21 (75%) of 28 reported any TEAE; most TEAEs were mild or moderate in severity. Serious, drug-related TEAEs

(hematemesis and international normalized ratio increased) were reported in a single patient who had enteroviral gastroenteritis; the serious TEAEs resolved after 2 days, and no change was made to odevixibat dose. **Conclusion:** In the ASSERT study, patients with ALGS who had a pruritus response following treatment with odevixibat also had clinically meaningful mean reductions from baseline in bile acids and improvements in sleep and quality of life. In addition, most TEAEs in odevixibat-treated pruritus responders were mild or moderate, and none led to study discontinuation.

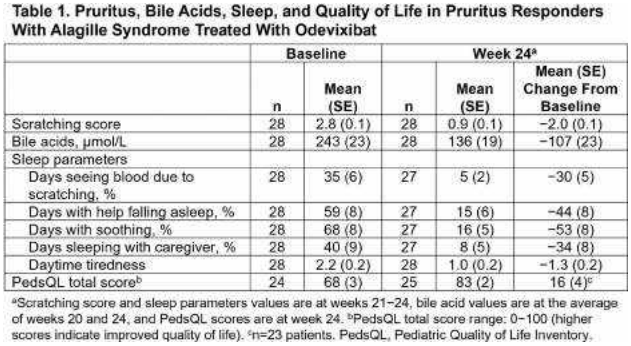
Table 1. Pruritus, Bile Acids, Sleep, and Quality of Life in Pruritus Responders With Alagille Syndrome Treated With Odevixibat

	Baseline		Week 24[a]		
	n	Mean (SE)	n	Mean (SE)	Mean (SE) Change From Baseline
Scratching score	28	2.8 (0.1)	28	0.9 (0.1)	−2.0 (0.1)
Bile acids, μmol/L	28	243 (23)	28	136 (19)	−107 (23)
Sleep parameters					
Days seeing blood due to scratching, %	28	35 (6)	27	5 (2)	−30 (5)
Days with help falling asleep, %	28	59 (8)	27	15 (6)	−44 (8)
Days with soothing, %	28	68 (8)	27	16 (5)	−53 (8)
Days sleeping with caregiver, %	28	40 (9)	27	8 (5)	−34 (8)
Daytime tiredness	28	2.2 (0.2)	28	1.0 (0.2)	−1.3 (0.2)
PedsQL total score[b]	24	68 (3)	25	83 (2)	16 (4)[c]

[a]Scratching score and sleep parameters values are at weeks 21−24, bile acid values are at the average of weeks 20 and 24, and PedsQL scores are at week 24. [b]PedsQL total score range: 0−100 (higher scores indicate improved quality of life). [c]n=23 patients. PedsQL, Pediatric Quality of Life Inventory.

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Jan P. Mattsson – Albireo: Employee, No, No;
The following people have nothing to disclose: Madeleine Aumar, Piotr Czubkowski, Özlem Durmaz, Way Seah Lee, Wendy Van Der Woerd

4618-C | PREVALENCE AND CHARACTERISTICS OF NON-ALCOHOLIC STEATOHEPATITIS (NASH) AMONG PEDIATRIC POPULATION IN THE UNITED STATES: A CROSS-SECTIONAL STUDY USING MARKETSCAN® DATABASES

Xiao Zhang[1], Tongtong Wang[1], Xinyue Liu[1], Gail Fernandes[1], Samuel S. Engel[2] and Ravi Shankar[1], (1) Merck Sharp & Dohme LLC, a Subsidiary of Merck &

Co., Inc., Rahway, NJ, USA, (2)Global Clinical Development, Merck & Co., Inc., Rahway, NJ, USA

Background: Non-Alcoholic Steatohepatitis (NASH) is the most rapidly increasing indication for liver transplantation in the United States and is associated with obesity, type 2 diabetes (T2D), and metabolic syndrome. There are limited epidemiologic data in the pediatric population (< 18 y) and its subgroups. This cross-sectional study was conducted to estimate the prevalence of NASH in the pediatric population overall and by subgroups including age, sex, obesity, T2D, and metabolic syndrome. **Methods:** IBM® MarketScan® Commercial Claims and Encounters Database (CCAE) and IBM® MarketScan® Multi-State Medicaid Database (Medicaid) were used for the analyses. Pediatric patients who had ≥ 1 medical encounter from 01-JAN-2020 to 31-DEC-2020 with ≥ 6 months of continuous enrollment before the most recent medical encounter were included. NASH was confirmed if an International Classification of Diseases, 10th Revision (ICD-10-CM) diagnosis code for NASH (K75.81) was present in patient's medical history. **Results:** As shown in Table 1, a total of 1,476 and 410 pediatric NASH patients were identified in Medicaid and CCAE databases, with a prevalence of 0.036% (95% confidence interval (CI): 0.034%-0.038%) in Medicaid, as compared to 0.011% (95% CI: 0.010%-0.012%) in CCAE. In both databases, prevalence of NASH increased by age, and NASH was more prevalent in those who were male, obese, had T2D, and had metabolic syndrome. Among all pediatric NASH patients, majority were ≥ 10 years old, male, and obese. **Conclusion:** In this cross-sectional study, we found that the pediatric population who were older, male, obese, had T2D, or had metabolic syndrome had a higher prevalence of NASH. Slightly higher prevalence was identified in Medicaid than CCAE, potentially due to the underlying different enrollee makeup in the two databases. Despite the potential underdiagnosis of NASH and the limitations of claims databases in real-world setting, the low observed prevalence may suggest a low overall NASH prevalence in the US pediatric population. Additional studies in the population are required to better quantify disease burden and subgroups that might have a higher risk of the disease.

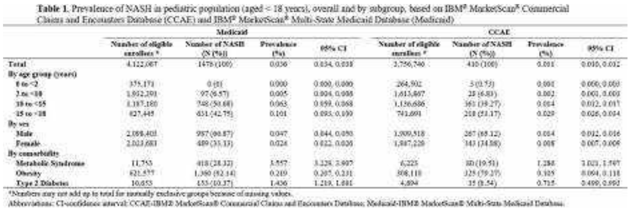

Table 1. Prevalence of NASH in pediatric population (aged < 18 years), overall and by subgroup, based on IBM® MarketScan® Commercial Claims and Encounters Database (CCAE) and IBM® MarketScan® Multi-State Medicaid Database (Medicaid)

	Medicaid				CCAE			
	Number of eligible enrollees *	Number of NASH (N (%))	Prevalence (%)	95% CI	Number of eligible enrollees *	Number of NASH (N (%))	Prevalence (%)	95% CI
Total	4,122,067	1476 (100)	0.036	0.034, 0.038	3,756,740	410 (100)	0.011	0.010, 0.012
By age group (years)								
0 to <2	375,171	0 (0)	0.000	0.000, 0.000	264,902	3 (0.73)	0.001	0.000, 0.003
2 to <10	1,932,291	97 (6.57)	0.005	0.004, 0.006	1,613,867	28 (6.83)	0.002	0.001, 0.003
10 to <15	1,187,180	748 (50.68)	0.063	0.059, 0.068	1,136,686	161 (39.27)	0.014	0.012, 0.017
15 to <18	627,445	631 (42.75)	0.101	0.093, 0.109	741,091	218 (53.17)	0.029	0.026, 0.034
By sex								
Male	2,088,403	987 (66.87)	0.047	0.044, 0.050	1,909,518	267 (65.12)	0.014	0.012, 0.016
Female	2,033,681	489 (33.13)	0.024	0.022, 0.026	1,847,220	143 (34.88)	0.008	0.007, 0.009
By comorbidity								
Metabolic Syndrome	11,753	418 (28.32)	3.557	3.228, 3.907	6,225	80 (19.51)	1.285	1.021, 1.597
Obesity	621,577	1,360 (92.14)	0.219	0.207, 0.231	308,118	325 (79.27)	0.105	0.094, 0.118
Type 2 Diabetes	10,653	153 (10.37)	1.436	1.219, 1.681	4,894	35 (8.54)	0.715	0.499, 0.993

*Numbers may not add up to total for mutually exclusive groups because of missing values.
Abbreviations: CI-confidence interval; CCAE-IBM® MarketScan® Commercial Claims and Encounters Database; Medicaid-IBM® MarketScan® Multi-State Medicaid Database.

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Gail Fernandes – Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA: Employee, No, No;
Samuel S. Engel – Merck & Co., Inc.: Employee, No, No; Merck & Co., Inc.: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;
Ravi Shankar – Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA: Employee, No, No;

f 4619-C | SARCOPENIC OBESITY CORRELATES WITH HEPATIC STEATOSIS, BUT NOT INSULIN SENSITIVITY, IN ADOLESCENTS WITH OVERWEIGHT AND OBESITY

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Background: Sarcopenic obesity (SO) is characterized by concurrent increased fat mass and decreased muscle mass and is associated with adverse cardiometabolic outcomes in adults. The incidence and implications of SO in childhood and adolescence are poorly understood. This study aimed to assess pediatric SO and determine its relationship with hepatic steatosis and insulin sensitivity. **Methods:** This is a secondary analysis of dual energy x-ray absorptiometry (DXA) data collected across 7 metabolic studies in adolescents with a range of BMI's at the University of Colorado. Appendicular lean mass (ALM) measured by DXA was used to calculate skeletal muscle mass index (SMI (%) = ALM(kg)/weight(kg)x100). Liver, visceral, and subcutaneous fat were measured with MRI and fasting laboratory assessments for insulin sensitivity (HOMA-IR, 1/fasting insulin) were collected. Spearman correlation was used to assess the relationship between SMI, fat distribution (liver, subcutaneous, and visceral fat), and insulin sensitivity. **Results:** SMI was calculated in 230 adolescents with overweight/obesity (OO, mean age 15.2 ± 2.4 y, mean BMI 18.7 kg/m^2, 88% female) and 76 with lean weight (LN, mean age 13.7 ± 2.6 years, mean BMI 34.3 kg/m^2, 59% female). Adolescents with OO had a significantly lower mean SMI than LN controls

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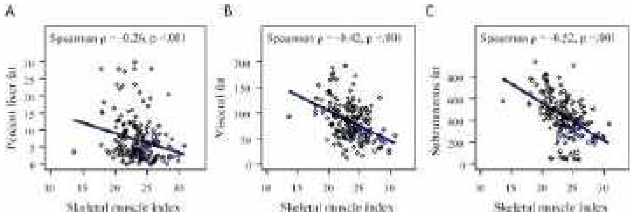
(23.7 ± 2.9% vs 31.8 ± 4.5%, $p < 0.001$). In OO, SMI inversely correlated with percent liver fat ($r = -0.26$, $p < 0.001$), visceral fat ($r = -0.42$, $p < 0.001$), and subcutaneous fat ($r = -0.52$, $p < 0.001$) (Figure 1A-C). SMI had a weak inverse correlation with fasting glucose ($r = -0.20$, $p = 0.004$) and hemoglobin a1c ($r = -0.15$, $p = 0.04$) but not with HOMA-IR or 1/fasting insulin ($r = -0.02$, $p = NS$). SMI also correlated inversely with leptin ($r = -0.65$, $p < 0.001$) and adiponectin concentrations ($r = -0.15$, $p = 0.03$). **Conclusion:** As assessed by SMI on DXA, a significantly lower proportion of body weight is made up of muscle mass in adolescents with OO as compared to LN controls, indicating that SO is already present in a young age group. SO correlates with increased hepatic steatosis and visceral and subcutaneous adiposity, but less so with markers of insulin sensitivity, in adolescents with OO. As such, interventions targeting muscle health and function starting in childhood and adolescence may be important in the management of pediatric NAFLD. Future studies using more robust measures of insulin sensitivity are needed to identify predictive cut-off values for pediatric SO.



Disclosures: Shikha S. Sundaram – Mirum: Consultant, No, No; Albireo: Consultant, No, No;

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Disclosure information not available at the time of publication: Melanie G Cree, Megan M Kelsey, Kristen J Nadeau, Alexander Chaidez, Zhaoxing Pan

4620-C | SUCCESSFUL RESOLUTION OF ACUTE NEONATAL LIVER FAILURE AND SECONDARY AKR1D1 DEFICIENCY BY ORAL CHOLIC ACID REPLACEMENT THERAPY

Kenneth David Reginald Setchell[1], Sarah Keeme[2], Kathy Campbell[1] and Amy Feldman[3], (1)Cincinnati Children's Hospital Medical Center, Cincinnati, OH, (2) University of Colorado Denver School of Medicine and Children's Hospital Colorado, Aurora, CO, (3)University of Colorado

Background: Bile acid synthesis disorders (BASD) are a well-established class of metabolic liver disease. Hepatotoxicity is caused by a lack of synthesis of the normal primary bile acids that promote bile flow and accumulation of atypical bile acids and intermediary metabolites. In the Δ^4-3-oxosteroid 5b-reductase (AKR1D1) deficiency, the second most common BASD, accumulation of hepatotoxic/cholestatic Δ^4-3-oxo bile acids that cannot be transported across the canaliculus, causes severe neonatal liver disease with rapid progression to cirrhosis. Diagnosis is complicated by the fact that Δ^4-3-oxo bile acids are often transiently elevated in the urine of healthy infants during early life and also a feature of end-stage disease. Cholic acid therapy, approved for primary BASD has not been studied as an adjunctive therapy in patients with a 'secondary' AKR1D1 deficiency from acute or advanced liver disease. **Methods:** Presented is a case of a patient with Neonatal Acute Liver Failure (NALF) with elevated atypical Δ^4-3-oxo bile acids that subsequently was proven by genetic analysis to be a 'secondary' AKR1D1 deficiency. Cholic acid (Cholbam (10 mg/kg bw/day) treatment led to a complete resolution of liver failure. The patient was a male born in NALF with extensive negative evaluation and found on urine fast atom bombardment ionization mass spectrometry (FAB-MS) to have an AKR1D1 deficiency. Due to clinical deterioration, and with this finding, cholic acid therapy was started on day of life (DOL) 8 and he was evaluated for liver transplantation on DOL 9. Rapid whole genome sequencing was pending at the time of cholic acid initiation. **Results:** Rapid whole genome sequencing did not identify a primary AKR1D1 deficiency. Despite this, his NALF rapidly improved after initiation of cholic acid, and he was discharged by DOL 38 without a need to list for transplantation. By DOL 84, his liver biochemical testing improved and cholic acid was discontinued. Subsequent urine FAB-MS analysis revealed a normal profile with a disappearance of the atypical Δ^4-3-oxo bile acids consistent with a complete resolution of his 'secondary'AKR1D1 deficiency. **Conclusion:** Neonates in NALF with a biochemically confirmed 'secondary' AKR1D1 deficiency may show a successful clinical response to cholic acid therapy.

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Disclosure information not available at the time of publication: Sarah Keeme, Kathy Campbell, Amy Feldman

4621-C | A KNOCKIN BSEPE297G MOUSE PRESENTS WITH CHOLESTASIS AND IS A NOVEL TRANSLATIONAL MODEL OF PFIC2

Eric Bell[1], Jennifer Truong[1], Patrick Stoiber[1], Youhwa Jo[1], Renata Franca[1], Eitan Hoch[1], Yong Ren[1], Alastair Garfield[1] and Jonathan Moore[2], (1)Rectify Pharmaceuticals, (2)MIT

Background: Progressive Familial Intrahepatic Cholestasis type 2 (PFIC2) is a rare pediatric liver disease caused by genetic variants in the bile salt export pump (BSEP, *ABCB11*). The E297G variant is one of the most prevalent drivers of PFIC2 (when inherited biallelically), leading to impaired bile acid efflux and consequential hepatic accumulation and toxicity. Here, we present a novel PFIC2 mouse model harboring the BSEP^{E297G} variant. Characterization of this mouse demonstrates its recapitulation of key translational aspects of the human disease and can serve as a new tool to evaluate novel therapeutics for the treatment of PFIC2. **Methods:** BSEP^{E297G} knock-in mice were generated using CRISPR/Cas9-mediated gene editing in congenic C57BL/6 zygotes. Comprehensive phenotyping of the male and female wildtype (WT), heterozygous (HET) and homozygous (HOM) mice was undertaken from 6 weeks of age to assess clinically relevant markers of progressive cholestasis, liver damage and PFIC2 pathophysiology. Including, serum, biliary and liver bile acid concentration, bile acid composition, liver enzymes, gene expression and liver histopathology. **Results:** HOM BSEP^{E297G} mice recapitulate the key clinical aspects of PFIC2. While females exhibited a more severe disease phenotype, both sexes demonstrate the hallmark presentation of cholestasis and hepatoxicity. Female HOM BSEP^{E297G} mice exhibited progressive increases in serum total bile acids (TBA), and markers of liver damage from 6 to 12 weeks of age. As predicted, no significant change in GGT was observed. At 12 weeks serum TBA was increased 92%, and ALT and ALP were increased 48% and 88%, respectively. Importantly, biliary TBA content was dramatically decreased by 82% while liver TBA increased 203%, consistent with BSEP insufficiency and cholestasis. Furthermore, *in vitro* bile acid efflux capacity of primary hepatocytes isolated from the livers of BSEP^{E297G} mice highlighted a gene dosage impact of the E297G variant. **Conclusion:** HOM BSEP^{E297G} mice are a validated translational model of PFIC2 demonstrating the expected mechanistic and pathophysiological characteristics of the human disease. This model will significantly advance an understanding of the underlying molecular BSEP deficits driving cholestasis and provides a powerful *in vivo* platform to evaluate potential disease modifying therapeutics for the treatment of PFIC2.

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Jonathan Moore – Rectify Pharmaceuticals: Employee, No, No;
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f 4622-C | CELL-SPECIFIC EXPRESSION OF HIF1α ENABLES FXR AGONIST-MEDIATED PROTECTION FROM PARENTERAL NUTRITION ASSOCIATED CHOLESTASIS

Swati Ghosh[1], Michael W Devereaux[1], Karim C. El Kasmi[1] and Ronald J. Sokol[1,2], (1)Department of Pediatrics, University of Colorado School of Medicine, (2)Digestive Health Institute, Children's Hospital Colorado

Background: Parenteral nutrition (PN)-associated cholestasis (PNAC) is caused by chronic PN in the setting of intestinal injury/failure. Suppression of hepatocyte FXR signaling contributes to PNAC pathogenesis. Intestinally absorbed LPS and PN-derived phytosterols combine to activate hepatic macrophages to produce pro-inflammatory cytokines (e.g., IL-1β) which then suppress hepatocyte FXR signaling. Recently, we reported an anti-apoptotic role of an FXR agonist, GW4064, during PNAC (*Ghosh* et al*.,Hepatology Communication 2023).*Hypoxia-inducible factor 1-α (HIF1α) is a transcription factor that plays a vital role in cell proliferation, survival and glucose metabolism in liver and macrophages. However, its role in PNAC is not known. Here we examined the interaction of HIF1α and FXR signaling in macrophages and hepatocytes in a PNAC mouse model. **Methods:** PNAC mouse model (oral DSSx4d followed by TPNx14d; DSS-PN) received GW4064 (30mg/kg/day) in PN solution (days 4-14 of PN; DSS-PN/GW4064). Macrophage specific HIF1α -knockout mice, Huh7, Raw 264.5 cells and THP-1 cells were used. **Results:** GW4064 treatment significantly reduced liver apoptosis in DSS-PN mice. Bulk RNA sequencing and qPCR showed increased *H19*, and decreased *HIF1a,* mRNA expression and its targets in DSS-PN liver. We performed RNA-immunoprecipitation and found HIF1α interacted with H19 and GW4064 treatment enhanced this interaction, which has been shown to be anti-apoptotic. GW4064 treatment induced *HIF1a* mRNA and its targets (*Slc2a2*, *Hk2* and *Vegf*a) in liver of DSS-PN mice. siRNA-HIF1α knockdown in Huh7 cells significantly reduced expression of *ABCB11*, *NR0B2 and ABCC2* with further reduced expression of

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

these genes in Huh7 cells incubated with IL-1ß + phytosterols, even in the presence of FXR agonist. HIF1α stabilization by the PHD inhibitor, DMOG, in Raw 264.5 macrophages prevented GW4064 from suppressing LPS-induced *Il-1b* expression. Macrophage specific HIF1α-knockout DSS-PN mice had decreased AST and ALT and upregulated mRNA of *Abcb11*, *Nrob2* and *Abcg5* relative to wild type mice. Moreover, in THP-1 monocytes line, GW4064 suppressed the LPS-induced increase in *IL-6* and *TNF* expression, and this inhibition was enhanced by siRNA-HIF1α. **Conclusion:** This study suggests that *inhibition* of HIF1α in macrophages may enhance FXR activation and enable its protective effects in PNAC. Conversely, *activation* of HIF1α in hepatocytes by GW4064 may also be protective in PNAC. Thus cell-specific modulation of HIF1α may have therapeutic benefit in PNAC.

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Disclosure information not available at the time of publication: Michael W Devereaux, Karim C. El Kasmi, Ronald J. Sokol

4623-C | CHARACTERISATION OF A NOVEL BILE SALT EXPORT PUMP DEFICIENCY MOUSE MODEL WITH THE P.E297G MUTATION

Antonia Felzen, Milaine V Hovingh, Rick Havinga, Niels Mulder, Martijn Koehorst, Bart Van De Sluis, Jan Freark De Boer, Folkert Kuipers and Henkjan J. Verkade, University Medical Center Groningen

Background: Bile Salt Export Pump (BSEP) deficiency, or PFIC2, is a rare genetic liver disease. It often leads to end-stage cholestatic liver disease and need for transplantation. The p.E297G missense mutation with suggested residual BSEP function is associated with a milder course of disease and delayed need for transplantation. BSEP knock-out mouse models exist, but are unfit to study interventions aiming to improve BSEP function, due to complete absence of BSEP protein. No *in vivo* models with milder mutations are available. Therefore, we aimed to generate a p. E297G BSEP knock-in (KI) mouse model. **Methods:** The KI model was generated by CRISPR-Cas9 technology. Female and male KI mice ($n = 8$, each) and WT littermates ($n = 7$, each) were fed chow diet, terminated at age 14 weeks and characterized for BSEP expression and liver pathology. The BSEP transport capacity of was determined *in vivo* by measuring bile flow during IV administration of increasing dosages of the bile acid tauroursodeoxycholic acid (TUDCA). **Results:** Western blotting showed reduced BSEP protein expression in KI vs. WT livers, due to impaired BSEP glycosylation. The capacity to induce bile flow upon TUDCA administration was strongly reduced in KI mice (Figure). Median liver weight was increased in KI vs. WT mice (Females: 2.1g vs. 1.0g; Males: 2.3g vs 1.4g; each $P < 0.001$). Median plasma AST levels were also significantly increased in KI vs. WT mice (Females: 187 vs. 50 μmol/l; Males: 198 vs. 60 μmol/l , $P = 0.01$ and $P < 0.001$; resp.), as were median plasma ALT levels (Females: 160 μmol/l vs. 25 μmol/l; Males: 248 μmol/l KI vs. 30 μmol/l; $P = 0.02$ and $P < 0.001$; resp.). Histological analysis showed mild fibrosis in KI livers. **Conclusion:** The p.E297G mouse model displays marked liver pathology and provides a new model for BSEP deficiency with suggested residual BSEP function. We anticipate its importance for future *in vivo* testing of medications that stimulate residual BSEP functionality.

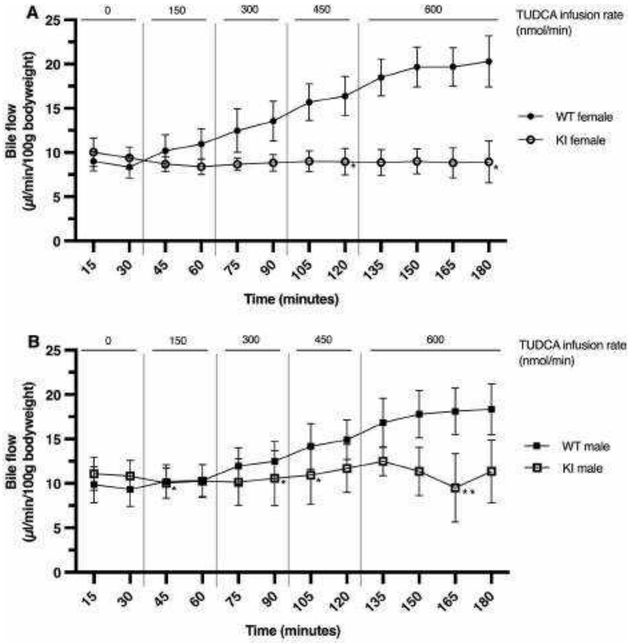

Figure. BSEP transport capacity as assessed by biliary bile flow during bile acid infusion.

Bile acid infusion was performed with TUDCA in female (A) and male (B) BSEP KI and WT mice (n=8 for all groups). The TUDCA infusion rate is depicted at the top of the graph. Bile was collected in time intervals of 15min. *Several KI mice did not survive until the end of the experiment. Data are expressed as mean ± SD. Statistics: interaction genotype-time: $P<0.0001$ in (A) and (B). *BSEP (bile salt export pump); SD (standard deviation); KI (knock-in); WT (wild-type); TUDCA (tauroursodeoxycholic acid).*

Disclosures: Henkjan J. Verkade – Ausnutria BV, Albireo, Danone Nutricia Research, Intercept, Mirum, Orphalan, and Vivet: Consultant, No, No;

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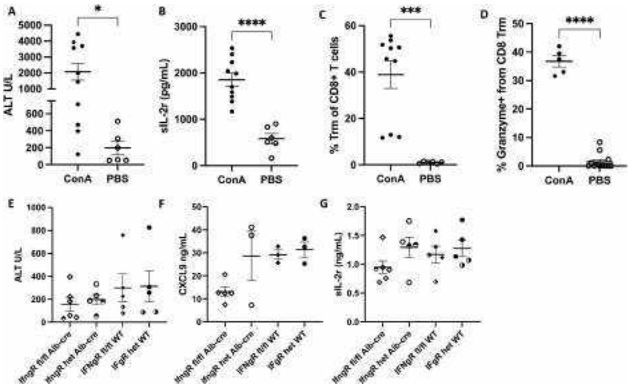
4624-C | CONCANAVALIN A MODELS THE INFLAMMATORY PHENOTYPE OF PEDIATRIC ACTIVATED T-CELL HEPATITIS/ ACUTE LIVER FAILURE

Tamir Diamond[1,2], MIchelle Lau[1], Niansheng Chu[1], Portia Kreiger[1,2] and Edward Behrens[1,2], (1)Children's Hospital of Philadelphia, Philadelphia, PA, (2)University of Pennsylvania

Background: Pediatric acute liver failure (PALF) incidence in the United States is estimated at 500-600 cases annually with most patients not having a unifying diagnosis. Over the last decade, there has been growing evidence that the liver injury in many cases of indeterminate pediatric acute liver failure (iPALF) is mediated by a hyperinflammatory response. These patients have a dense hepatic infiltrate of effector tissue resident memory (TRM) CD8 T-cells (CD8+, CD103+ and perforin+) in liver tissue specimens with a transcriptional profile of activated IFNg pathways. Subsequently, our group has labeled this entity Activated T-cell Hepatitis (TC-PALF). To date there was no animal model that mimics the pathophysiology of TC-PALF. **Methods:** WT C57BL/6 mice (WT) females were treated with low dose (10mg/kg/dose) Concanavalin A (ConA), a lectin known to induce acute immune mediated hepatitis and fulminant necrosis in high doses (15-40mg/kg/dose) with goal to stimulate CD8 T cell response without significant tissue necrosis. Measurement of serum cytokines, splenocytes and intrahepatic leukocytes were performed 12 hours post conA injection. To study the interferon gamma response in hepatocytes *infgr* flox/flox-Albumin-cre mice from both sexes were treated with 5mg/kg/dose conA, and measurement of serum cytokines, ALT and intrahepatic leukocytes were performed 12 hours post injection and compared to controls. **Results:** Mice treated with ConA replicated the TC-PALF characteristics compared to PBS controls including elevated ALT (mean 2078 U/L SEM ±530.3 vs.197.5U/L SEM ±75.65 $P < 0.05$) (Figure 1A), serum soluble IL2-r (mean 1853 pg/mL SEM ±144.5 vs. 582.3 SEM± 109.2 $P < 0.0001$) (Figure 1B), and increase in percent of hepatic CD8 T cells (mean 32.86% SEM±1.077 vs. 18.65 SEM±1.247 $P < 0.001$) with predominance of effector TRM CD8 T cells (CD69+ CD103+ Granzyme B +) (Figure 1C and D). Those that lacked the hepatic IFNg response (*infgr* flox/flox-Albumin-cre) had moderate decrease in hepatitis measured by ALT (Figure 1E) and production of the IFNg induced chemokine CXCL9 (Figure 1F). In addition, serum sIL-2r, a marker for lymphocyte activation was decreased in *infgr* flox/flox-Albumin-cre group (Figure 1G), suggestive the intrinsic hepatic IFNg response is critical for lymphocyte activation in murine TC-PALF. **Conclusion:** Low dose ConA hepatitis models many feature of the immunological milieu of TC-PALF. Hepatocytes have an intrinsic IFNg response that contributes to hepatocellular injury and hypercytokinemia in this model. This model will assist with understanding the role of hepatic and non-hepatic IFNg response in pathogenesis of TC-PALF.



Disclosures: The following people have nothing to disclose: Tamir Diamond

Disclosure information not available at the time of publication: MIchelle Lau, Niansheng Chu, Portia Kreiger, Edward Behrens

4625-C | FXR AGONIST INDUCED INTESTINAL FGF15/19 REGULATES FXR SIGNALING IN LIVER IN LITHOCHOLIC ACID DIET-INDUCED ACUTE CHOLANGIOPATHY MOUSE MODEL.

Swati Ghosh[1], Michael W Devereaux[1], Aimee Anderson[1], David J Orlicky[2] and Ronald J. Sokol[1,3], (1) Department of Pediatrics, University of Colorado School of Medicine, (2)Department of Pathology, University of Colorado, (3)Digestive Health Institute, Children's Hospital Colorado

Background: Lithocholic acid (LCA) containing diet in mice causes an acute cholangiopathy with hepatocyte necrosis. The aim of this study is to determine effects and mechanisms of FXR agonists (GW4064 and obeticholic acid [OCA]) in the acute LCA mouse model of cholestasis. **Methods:** Adult C57/B6 mice were fed either 1% LCA supplemented diet for 2 days or chow (controls). A group of mice received either i.v. GW4064 (30mg/kg/bw) or i.v. OCA (20mg/kg/bw) through central venous catheter daily for 2 days prior to and including the 2 days of the LCA diet. Huh7, THP1, and T84 human cells were also studied. **Results:** LCA mice had markedly increased serum AST, ALT and total bile acids; liver histology showed ductular reaction, macrophage infiltration and hepatocyte necrosis; and hepatocyte mRNA expression of *BSEP, Abcg8, SHP*, *LRH-1* and *MRP2* were reduced relative to chow mice. Biochemistry, histology and gene expression were all normalized by both of the FXR agonists, except *Cyp7a1* which remained suppressed. Hepatic mRNA levels of *Il-6,* and *Tnf* were elevated in the LCA mice; FXR agonist treatment markedly reduced these mRNA levels. We next determined that the i.v. FXR agonist induced ileal expression of *Fgf15*, *Nr0b2, Nr5a2,* and *Abcg5,* which were suppressed in LCA mice (except for *Fgf15).* ChIP assay showed that OCA increased the binding of FXR to the ileal *Fgf15* promoter. To determine if the protective effect of FXR agonists in this model involved the gut-liver FGF15/19 axis, a series of co-culture experiments were performed using T84 intestinal epithelial cells and Huh7 cells. Incubation of the T84 cells with LCA (100uM) in the presence or absence of OCA or GW4064 overnight was cocultured with Huh7 cells in lower insert. FXR agonist induced expression of *FGF19* and *SHP* in T84 cells which was surprisingly associated with upregulation of *Nr0b2* and *ABCB11* with downregulation of *CYP27A1* mRNA in Huh7 cells. Furthermore, treatment of Huh7 cells with FGFR4 inhibitor (H3B-6527) partially prevented OCA or GW4064 mediated upregulation of *BSEP* or *SHP* in Huh7 cells after exposure of T84 to LCA.Finally, recombinant FGF19 treated T84 cells induced *BSEP* and decreased *CYP27A1* expression in Huh7 cells, indicating hepatocyte FXR targets may also be regulated by FGF19. **Conclusion:** FXR agonists increase intestinal FGF19 by enhancing FXR binding to *FGF19* promoter, that then induces hepatocyte bile exporters to decrease bile acid levels in hepatocytes, thus alleviating LCA mediated hepatocyte injury.

Disclosures: The following people have nothing to disclose: Swati Ghosh

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4626-C | INVESTIGATION OF POLYMORPHISM IN THE GENE ENCODING MRGPRX4 AND PRURITUS SEVERITY IN CHOLESTATIC CHILDREN

Minna Rodrigo, Daphne Chien, James Limjunyawong, Xinzhong Dong and Wikrom Karnsakul, Johns Hopkins University School of Medicine

Background: Many pediatric patients who suffer from cholestatic liver disease also suffer from severe pruritus which is often refractory to antipruritic therapy. Mas-related G protein-coupled receptor X4 (MRGPRX4) is an itch receptor found in dorsal root ganglion sensory neurons that innervate the skin and is activated by bile acids. Additionally, cholic acid is a potent ligand for the MRGPRX4 receptor. However, the contribution of genetic variations in the gene encoding MRGPRX4 remains unknown. Among the single nucleotide polymorphisms (SNPs) harbored within coding regions of MRGPRX4, the most common missense SNP is Tyr54Cys (A to G mutation) with an allele frequency of 31.7%. Therefore, our study aimed to explore the potential association between Tyr54Cys and cholestatic pruritus in children. **Methods:** We conducted a case-control pilot study of children diagnosed with Alagille syndrome and Progressive Familial Intrahepatic Cholestasis (PFIC). Cases included individual's having one of these diagnoses who also experienced pruritus, while controls consisted of individual's with one of the above-mentioned diagnoses but without pruritus. Pruritus reports were obtained from both inpatient and outpatient records. The severity of pruritus was classified based on the number of prescribed antipruritic treatments (Table 1). Whole blood samples were collected from enrolled individual's and DNA was isolated and sequenced with a specific focus on Tyr54Cys. We investigated the correlation between this polymorphism and the degree of pruritus. Serum total and fractionated bile acid profiles were also performed in all cases. **Results:** We have sequenced DNA for four subjects, three of whom had Alagille syndrome and one who had PFIC3. As shown in Table 1, Patients A and B were 3-year-old males with Alagille syndrome and a history of mild/moderate pruritus. Their MRGPRX4 sequencing revealed heterozygosity for the G/A variant. Patient C, a 12-month-old male with Alagille syndrome and a history of severe pruritus, was found to be homozygous for the G/G at this site. Patient D, a 16-year-old male with PFIC, had no history of pruritus and was homozygous for the wild-type allele at this site. All subjects exhibited elevated levels of serum cholic acids, which correlated with patients' pruritus symptoms and their history of antipruritic therapy. **Conclusion:** In this cohort, the majority of patients experienced pruritus in the setting of their cholestatic liver disease. The only patient without pruritus exhibited above-baseline bile acid levels but was homozygous for the wild-type variant of MRGPRX4 at codon 54. Further investigation with a larger dataset is warranted and mechanistic studies aiming to determine if this mutation affects bile acid binding affinity or the receptor's signaling pathway are ongoing to provide a better understanding of the relevance of this SNP. Furthermore, the exploration of other SNPs in the MRGPRX4 gene is underway as well.

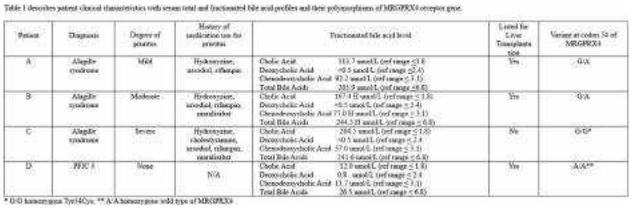

Table 1 describes patient clinical characteristics with serum total and fractionated bile acid profiles and their polymorphisms of MRGPRX4 receptor gene.

Patient	Diagnosis	Degree of pruritus	History of medication use for pruritus	Fractionated bile acid level	Listed for Liver Transplantation	Variant at codon 54 of MRGPRX4
A	Alagille syndrome	Mild	Hydroxyzine; ursodiol, rifampin	Cholic Acid 113.7 umol/L (ref range ≤1.8 Deoxycholic Acid <0.5 umol/L (ref range ≤2.4) Chenodeoxycholic Acid 92.2 umol/L (ref range ≤3.1) Total Bile Acids 205.9 umol/L (ref range ≤6.8)	Yes	G/A
B	Alagille syndrome	Moderate	Hydroxyzine, ursodiol, rifampin, maralixibat	Cholic Acid 167.4 H umol/L (ref range ≤ 1.8) Deoxycholic Acid <0.5 umol/L (ref range ≤ 2.4) Chenodeoxycholic Acid 77.0 H umol/L (ref range ≤ 3.1) Total Bile Acids 244.5 H umol/L (ref range ≤ 6.8)	Yes	G/A
C	Alagille syndrome	Severe	Hydroxyzine, cholestyramine, ursodiol, rifampin, maralixibat	Cholic Acid 204.5 umol/L (ref range ≤1.8) Deoxycholic Acid <0.5 umol/L (ref range ≤ 2.4 Chenodeoxycholic Acid 57.0 umol/L (ref range ≤ 3.1) Total Bile Acids 261.6 umol/L (ref range ≤ 6.8)	No	G/G*
D	PFIC 3	None	N/A	Cholic Acid 12.0 umol/L (ref range ≤ 1.8) Deoxycholic Acid 0.8 umol/L (ref range ≤ 2.4 Chenodeoxycholic Acid 13.7 umol/L (ref range ≤ 3.1) Total Bile Acids 26.5 umol/L (ref range ≤ 6.8)	Yes	A/A**

* G/G homozygous Tyr54Cys; ** A/A homozygous wild type of MRGPRX4

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4627-C | L-CARNITINE PROTECTS AGAINST BILE ACID-INDUCED MITOCHONDRIAL DYSFUNCTION AND IGF-1 IMPAIRMENT IN RAT HEPATOCYTE CULTURES

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Background: Bile acids play a major role in many vital functions of the liver and several extrahepatic tissues; however, their excessive amounts are known to exert hepatotoxic effects. Aim of this study was to examine the effect of Glycochenodeoxycholic acid (GCDC) on mitochondrial function and Insulin-like growth factor (IGF-1) activity in hepatocyte cultures. **Methods**: GCDC (0-100 μM) was added to primary hepatocyte cultures in the presence /absence of L- Carnitine (L-Crtn). DNA synthesis was measured by bromo-deoxyuridine (BrdU) incorporation assay. Activities of the key mitochondrial enzymes Carnitine palmitoyltransferase-1 (CPT-1), Cytochrome c oxidase (COX) and Palmitoyl CoA oxidase (PCO) were assayed in cell homogenates. Gene expression of peroxisome proliferator activated receptor gamma coactivator 1-α (PGC-1α) and IGF-1 receptor was evaluated by RT-PCR. **Results**: GCDC was observed to significantly ($p < 0.01$) decrease the enzyme activities of CPT-1, COX and PCO. GCDC also significantly ($p < 0.01$) decreased the gene expression of PGC-1α. IGF-1-induced DNA synthesis and gene expression of IGF-1 receptor were significantly decreased in hepatocytes following GCDC treatment. Addition of L-Crtn (5mM) to hepatocyte cultures restored CPT-1 enzyme activity to nearly normal levels and markedly reduced GCDC-induced impairment of COX and PGC-1α, however, no marked effect was noticed on PCO activity. In addition, the gene expression of IGF-1 receptor in GCDC treated hepatocytes was significantly increased ($p < 0.05$) by L-Crtn. **Conclusion**: This study demonstrates that GCDC-induced hepatotoxic effects are possibly mediated through mitochondrial dysfunction and impairment of growth promoting IGF-1 activity. L-carnitine has potential beneficial effects against bile acid-induced cytotoxicity through upregulation of CPT-1 activity as well as gene expression of PGC-1α and IGF-1 receptor.

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4628-C | LIVER DYSFUNCTION IN DOWN SYNDROME

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Background: Trisomy of chromosome 21 (T21) gives rise to Down syndrome (DS), a condition defined for decades by cognitive deficits, craniofacial anomalies, and a decreased lifespan. Research over the past 40 years has revealed a more complex picture of DS, characterized by an increased prevalence of numerous conditions including autoimmune disorders, heart defects, and Alzheimer's Disease. The diversity of this disease spectrum implies impacts of T21 across tissue systems. The nature of T21 and the presence of the extra chromosome in every cell type supports the hypothesis that DS is a multi-organ condition and should be studied as such. Although there are modest increases in biliary atresia and autoimmune hepatitis in DS, these conditions are extremely rare. Liver function in DS has been almost exclusively studied through the lens of transient abnormal myelopoiesis, a perturbation in fetal hematopoiesis which takes place in the liver and can be a precursor to pediatric leukemias. Several recent reports have identified widespread liver dysfunction via imaging-based methods (Valentini et al., 2017). Few studies, however, have examined the impact of T21 on liver function throughout development and into adulthood and none have aimed to elucidate the mechanisms by which this phenotype occurs. **Methods:** Here we report the results from SOMAscan proteomic and metabolomic analyses of plasma from ~400 individual's in the Human Trisome Project Biobank, including more than 300 with DS. Using a mouse model of DS, we also report histopathology and transcriptome analysis of the liver, along with plasma proteome and metabolome measurements. **Results:** Our plasma proteomic and metabolomic analyses from individual's with DS revealed the dysregulation of several pathways consistent with liver dysfunction, broadly involving the immune system, protein synthesis, and metabolism. Consistent with previous work from our group, we report that the Dp16 mouse model of DS exhibits substantial liver pathology, including periportal inflammation and ductular reaction, without elevation of ALT or AST (Tuttle et al., 2020). Transcriptome analysis of Dp16 livers revealed potential mechanisms of pathogenesis and plasma samples show alterations of key biosignatures consistent with those seen in the human population. **Conclusion:** Individual's with DS may experience widespread liver dysfunction. Further research is needed to define the mechanisms driving liver dysfunction in DS, understand the role trisomy of human chromosome 21 plays, and elucidate potential therapeutic targets.

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4629-C | NAT10-MEDIATED ac4C MODIFICATIONS PROGRAM JUVENILE NAFLD IN RESPONSE TO MATERNAL HIGH FAT DIET FEEDING

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Background: Growing evidence has shown that early life exposure to maternal high fat diet (HFD) during pregnancy and lactation increases the risk of nonalcoholic fatty liver disease (NAFLD) in juvenile offspring, which involves epigenetic machinery. As a novel epi-transcriptomic modification, ac4C could enhance the expression of target gene by increasing mRNA stability and translation efficiency. The aim of this study was to explore the involvement of ac4C and its writer protein NAT10 in maternal HFD-induced NAFLD. **Methods:** 6-week-old female C57BL/6J mice were fed either chow diet or HFD for 6 weeks before fertilization and kept on the same diet throughout gestation and lactation. Chow-fed male hepatocyte-specific *Nat10* knockout (*Nat10*^{HKO}) mice were mated with chow-fed or HFD-fed (6-week feeding before fertilization, maintained respective diets during gestation and lactation) female *Nat*10$^{\text{fl/fl}}$ mice to generate *Nat10*^{HKO} and *Nat10*$^{\text{fl/fl}}$ littermates which could be subdivided into 4 groups: chow *Nat10*$^{\text{fl/fl}}$, chow *Nat10*^{HKO}, HFD *Nat10*$^{\text{fl/fl}}$ and HFD *Nat10*^{HKO}. All pups were sacrificed at weaning to assess body weight, liver histopathology and lipid metabolism. Transcriptomic-wide mapping of ac4C modification was performed on mRNA samples isolated from primary hepatocytes of pups, with the aid of RNA-seq and acetylated RNA immunoprecipitation sequencing (acRIP-seq). **Results:** C57BL/6J offspring of HFD dams weighed more at weaning, exhibited higher hepatic triglyceride levels, had more hepatic lipid accumulation, expressed significantly higher NAT10, and presented markedly improved ac4C abundance in hepatocyte mRNAs, when compared with pups of chow C57BL/6J dams. Similarly, pups of the HFD *Nat10*$^{\text{fl/fl}}$ group exhibited more lipid droplets and triglyceride contents in livers than offspring from the chow *Nat10*$^{\text{fl/fl}}$ group. However, genetic ablation of *Nat10* in offspring hepatocytes markedly ameliorated hepatic steatosis induced by maternal HFD feeding. Moreover, hepatic expressions of lipogenesis-associated proteins, including SREBP-1c, phosphorylated ACC and FASN were also inhibited in HFD *Nat10*^{HKO} pups when compared with HFD *Nat10*$^{\text{fl/fl}}$ pups. The combined analysis of RNA-seq and acRIP-seq data showed that *Nat10* deletion led to significantly reduced ac4C abundance in *Srebp1c*, *Acc* and *Fasn* mRNAs, which was in line with suppressed transcriptional expressions and reduced half-lives of these mRNAs. Moreover, lipoprotein associated genes including *Fatp2*, *Apob*, *Mttp*, and *Apol9a* were also found downregulated in *Nat10*^{HKO} livers than *Nat10*$^{\text{fl/fl}}$ livers, due to almost diminished ac4C peaks in relevant mRNAs. *In vitro* experiments further confirmed that *Nat10* knockdown suppressed the ability of HepG2 cells to uptake and deliver lipids. **Conclusion:** NAT10-mediated ac4C modification played an important role in maternal-HFD-induced offspring NAFLD, which also serves as a potential therapeutic target.

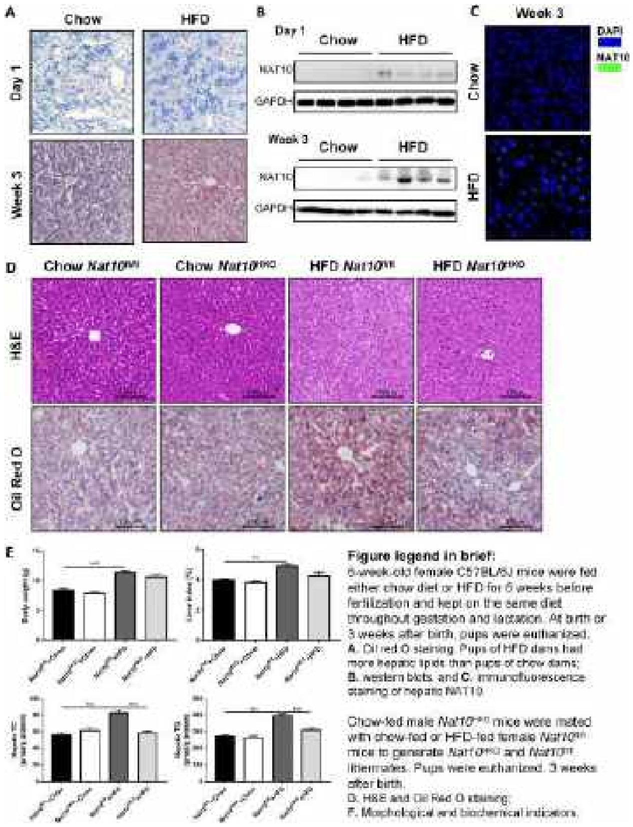

Figure legend in brief:
5-week-old female C57BL/6J mice were fed either chow diet or HFD for 6 weeks before fertilization and kept on the same diet throughout gestation and lactation. At birth or 3 weeks after birth, pups were euthanized. **A.** Oil red O staining. Pups of HFD dams had more hepatic lipids than pups of chow dams; **B.** western blots and **C.** immunofluorescence staining of hepatic NAT10

Chow-fed male *Nat10*^{HKO} mice were mated with chow-fed or HFD-fed female *Nat10*$^{fl/fl}$ mice to generate *Nat10*^{HKO} and *Nat10*$^{fl/fl}$ littermates. Pups were euthanized 3 weeks after birth.
D. H&E and Oil Red O staining;
F. Morphological and biochemical indicators.

Disclosures: The following people have nothing to disclose: Ren Tianyi, Jiangao Fan, Qianren Zhang, Rui Xue

4630-C | SINGLE-CELL ATLAS OF HUMAN PEDIATRIC LIVERS REVEALS A MYELOID SPECIFIC INFLAMMATORY SIGNATURE ENRICHED IN THE PEDIATRIC LIVER

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Background: The liver is vital for metabolism and immune function. Although it is known that the liver is composed of a heterogeneous mix of cell types, how these cell types contribute individually, and in concert, toward liver function remains poorly understood. What is known about healthy liver function, cellular heterogeneity and cell structures is primarily based on studies of the adult liver. Comparatively little is known about the pediatric liver. To better understand cellular drivers of childhood liver diseases, including many rare metabolic and immune disorders, we generated single-cell RNA-seq (scRNA-seq) maps of the normal pediatric liver and employed this map to examine disease-specific populations in biopsies from pediatric patients with Intestinal Failure-Associated Liver Disease (IFALD). **Methods:** Here we integrated 10x Genomics scRNA-seq from adult normal, pediatric normal and pediatric IFALD livers for a total of 15 profiled livers. **Results:** The normal pediatric liver map consists of 20,519 cells from caudate liver lobes of 5 pediatric transplant donors aged 2-17 years. In comparison to an adult map (25,460 cells; age 26-69) we observed differences in myeloid populations in the pediatric liver. Specifically, pediatric Kupffer-like cells (*MARCO+C1QA+VSIG4+*) exhibited higher expression of inflammatory cytokines and chemokines than adults (*CCL4*, *CCL3* and *IL1-β*). Using the normal pediatric liver map as a comparator for three IFALD biopsies (12,015 cells; age 4 mo-9 y) we were able to identify myeloid cell populations specific to IFALD as well as higher expression of profibrotic genes (*LY96*) in IFALD Kupffer-like cells. **Conclusion:** The normal pediatric liver map will allow for further comparison of adult and pediatric livers, which could establish commonalities and pediatric-specific differences—an important issue as there are clear differences in pediatric and adult liver function. In addition the map will serve as an important comparator for the study of pediatric liver diseases.

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4631-C | THE ABC TRANSPORTER MRP9 CONTROLS PROFIBROGENIC SIGNALING BY BILE DUCT EPITHELIAL CELLS

Anit Shah[1], *Ramesh Kudira*[1], *Manavi Singh*[1], *Annika Yang Vom Hofe*[1], *Zi Yang*[2], *Emily Miraldi*[1], *Wenying Zhang*[3], *Chunyue Yin*[4] *and Alexander G. Miethke*[1], *(1) Cincinnati Children's Hospital Medical Center,*

Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

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Background: We recently reported a homozygous truncating mutation in the *ABCC12* gene encoding an ABC transporter, MRP9, in a child with idiopathic low GGT cholestasis and bile duct paucity. Subsequently, additional rare variants were detected in children with chronic liver disease. In CRISPR/Cas9 gene-edited zebrafish and mouse model organisms, *Abcc12* deficiency rendered cholangiocytes susceptible to bile acid-induced apoptosis. Here we examine the impact of *Abcc12* deficiency on biliary fibrosis progression. **Methods:** 45-day-old, male WT and *Abcc12-/-* mice were treated with 0.1% 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) admixed to chow for 7 days prior to the assessment of liver fibrosis by image analysis of Sirius Red (SR) stained liver sections, serum liver biochemistries by colorimetry, and liver mononuclear cell composition by flow cytometry. Single-cell RNA-seq (scRNAseq) data from a time course study in WT mice challenged with DDC was mined for cellular crosstalk between biliary epithelial and stellate cells using CellChat. Bulk RNAseq was performed on intrahepatic cholangiocytes from neonatal WT and *Abcc12-/-* mice and from adult zebrafish of both genotypes. **Results:** Hepatocellular injury and cholestasis were aggravated in *Abcc12-/-* compared with WT mice following the DDC challenge, as indicated by higher serum ALT and total bilirubin levels (Figure A). Image analysis of Sirius Red stained liver sections revealed accelerated liver fibrosis (Figure B). Exacerbated cholestatic liver injury and fibrosis in *Abcc12-/-* mice was accompanied by expansion of hepatic Ly6C-low monocytes (3.9 ± 0.6% vs 0.6 ± 0.4%; p = 0.0015) and reduced number of CD4 lymphocytes (1.3 ± 0.3% vs 12.9 ± 1.0%, p = 0.0003) compared to WT. CellChat analysis of scRNAseq data from WT mice challenged with DDC predicted profibrogenic signaling from cholangiocytes to hepatic stellate cells involving the ligands - *Sema3/4*, Laminin (*Lam a1, Lam b2, Lam c2, Lam c3*), and *Gdf* (*Gdf9, Gdf15*). These genes were upregulated in cultured cholangiocytes from neonatal *Abcc12-/-* vs WT mice. Pathway enrichment analysis of RNAseq data of freshly isolated biliary cells showed upregulation of pathways indicative of defective maturation, tight junction formation, and epithelial-to-mesenchymal transition in *abcc12-/-* vs wt zebrafish. Expression of profibrogenic genes such as *tgfb3, fzd2*, andi*ltgb3*was upregulated in mutant zebrafish cholangiocytes. **Conclusion:** Loss of *Abcc12*/MRP9 predisposes to profibrogenic gene expression leading to accelerated fibrosis in a mouse model of xenobiotic sclerosing cholangitis.

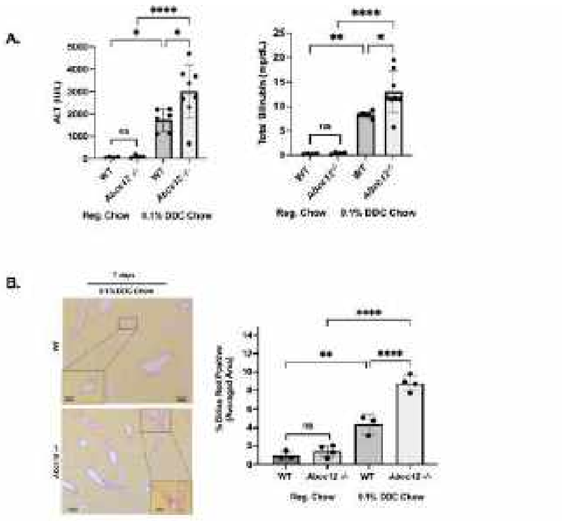

Fig1. *Abcc12-/-* deficiency contributes to liver injury. (A) Serum liver biochemistries after exposure to 7 days of 0.1% DDC or regular chow in controls. **(B)** Representative photomicrographs of Sirius Red stained liver sections and results of image analysis/. Unpaired t test with * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

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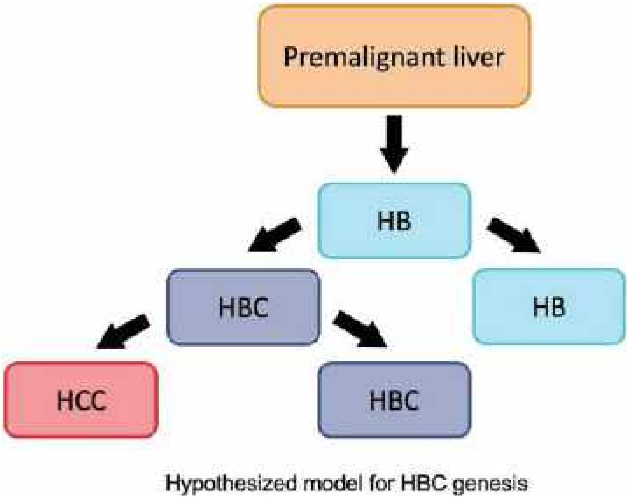
4632-C | THE PROGRESSION AND COMPOSITION OF HEPATOBLASTOMAS WITH CARCINOMA FEATURES

Xinjian Yu, Stephen F Sarabia, Martin Urbicain, Dolores Lopez-Terrada and Pavel Sumazin, Baylor College of Medicine, Texas Children's Hospital, Houston, TX

Background: Liver cancer is a leading cause of cancer-related deaths, and its incidence in children is rising. Childhood liver cancers are commonly classified as either hepatoblastoma (HB) or hepatocellular carcinoma (HCC). HBs have an 80% overall survival rate and predominantly affect young children, while HCCs have an overall survival rate of 30% and predominantly affect older children and young adults. Interestingly, some studies pointed to hepatocellular cancers with shared HB and HCC histological and molecular features that are almost always associated with clinically aggressive features and poor outcomes (Prokurat et al., 2002; Eichenmüller et al., 2014; Ranganathan et al., 2020).

Methods: We investigated neoplasms that display a combination of HB and HCC histological features, either across large tumor areas or focally using bulk RNA and DNA profiling in multiple tumor regions in search of recurring alterations and dysregulated genes and pathways. We also profiled RNA and DNA in select tumors and their models at single-cell resolutions. We compared molecular and clinical profiles across subclasses of these cancers and contrasted them with features of HBs and HCCs. **Results:** We showed that cancers with combined HB and HCC features are genetically heterogeneous and may be composed of subclones with features of fetal or embryonal HBs, features of HCCs, and other subclones that are distinct from both HBs and HCCs. Because of their overall shared histological, molecular, and clinical features, we designated these cancers HBs with HCC features (*HBC*s) and showed that HBCs have poor outcomes. In our single-institution study, high-dosage chemotherapy followed by complete resection or transplantation at early treatment stages significantly improved (hazard ratio 2.5X-4.3X at 95% confidence) outcomes. HBC patients that were treated with standard therapy had a 5-year survival rate of 30% (Sumazin et al., 2022). Our single-cell resolution profiles suggested that HBCs contain cells with both HB and HCC molecular features and that these cells exhibit common genetic alterations with HB-like and HCC-like cells found in the same tumors. Moreover, we proposed a diagnostic algorithm to classify patients into HBs, HBCs, and HCCs using a combination of molecular and histological features at diagnosis. **Conclusion:** Our analyses suggested that HBCs are molecularly, histologically, and clinically distinct from HBs and HCCs and that they include cancer cells with both HB and HCC features. Phylogeny analyses suggested that HBCs are derived from HB-like cells and may be precursors to HCC-like progenies, suggesting that HBCs are intermediate liver cancers. We proposed a model for HBC progression, as shown in the figure.



Disclosures: The following people have nothing to disclose: Xinjian Yu

Disclosure information not available at the time of publication: Stephen F Sarabia, Martin Urbicain, Dolores Lopez-Terrada, Pavel Sumazin

4633-C | ALPHA FETOPROTEIN (AFP) LEVELS AND THE LIVER INJURY UNIT (LIU) SCORE PREDICT OUTCOME IN NEONATAL ACUTE LIVER FAILURE

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Background: Neonatal acute liver failure (NALF) is a rare disease for which there are currently no reliable prognostic indicators. Alpha fetoprotein (AFP) is an established biomarker for hepatic regeneration and is used in the diagnosis of gestational alloimmune liver disease (GALD), a leading cause of NALF. The Liver Injury Unit (LIU) score has previously been shown to predict outcomes in pediatric ALF, with higher scores predicting death or need for liver transplant (LT). We aimed to determine if there is an association between AFP level or the LIU score and outcome in patients with NALF. **Methods:** A single-center retrospective chart review from Jan. 2005 to Dec. 2022 was conducted on neonates $</=30$ days of life with NALF, as defined by an INR $>/=2$ and liver dysfunction. Comparisons were made by outcome of survival with native liver (SNL) versus LT or death using the Mann-Whitney U test and Kaplan Meier Survival analysis. The predictive ability of lab tests was evaluated by receiver operating characteristic (ROC) analysis. **Results:** 54 patients (50% F) met inclusion criteria. Etiologies of NALF included viral infection (20%), GALD (20%), ischemic/cardiac (20%), genetic (13%), Trisomy 21-associated myelodysplasia (9.3%), hemophagocytic lymphohistiocytosis (3.7%), unidentified (9.3%), multiple diagnoses (1.9%), or other (1.9%). Median age at presentation was 5.5 days (IQR 1.0-11 d) and overall SNL was 44% (n = 24). There were no differences in age at presentation, gestational age, or birthweight between patients with or without SNL ($p > 0.05$ for all). AFP levels were available for 31/54 (57%) patients and were significantly higher in SNL patients ($p = 0.034$). AFP levels differed more significantly by SNL outcome among the 22 non-GALD patients ($p = 0.001$, Fig. 1A). Non-GALD patients with an AFP < 4775 ng/mL had 89% sensitivity and 100% specificity to predict death or transplant with an area under the ROC curve of 0.89. Among the full cohort with complete lab data (n = 47), LIU score differed

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significantly with a median score of 145 in SNL and 241 in non-SNL patients (p < 0.001). Stratification of patients by previously established LIU score quartiles showed significantly different rates of SNL (p = 0.002, Fig. 1B). **Conclusion:** AFP and LIU score may be useful prognostic indicators in NALF. Given that patients with GALD have very high AFP values (often > 100,000 ng/mL), the prognostic value of AFP is likely greater in NALF patients without GALD and may be helpful in transplant decision making.

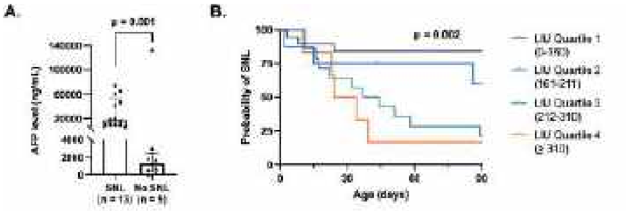

Figure 1. **A.** AFP values are significantly higher among non-GALD patients that survive without death or transplant. **B.** Kaplan Meier Survival analysis until death/transplant or age at last follow-up shows significant differences by LUI score quartile (data shown up to 90 days). LIU = 3.584 * peak total bilirubin (mg/dl) + 1.809 * peak PT (seconds) + 0.307 * peak ammonia (umol/L).

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Disclosure information not available at the time of publication: Ronald J. Sokol, Sarah A. Taylor

4634-C | EARLY EXTUBATION AS A PATHWAY TO RECOVERY AFTER PEDIATRIC LIVER TRANSPLANTATION.

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Background: Successful early extubation (EE) after liver transplantation (LT) has been shown to reduce ICU and hospital length of stay, infectious and vascular complications, sedation use, and has improved graft and patient survival. Though ideal, EE may not always be feasible in many recipients. Failed extubations and emergent reintubations can be catastrophic and can increase patient morbidity and mortality reversing any gains achieved from EE. Thus, it is important to identify those children who can benefit from EE so that failure rates can be minimized. Recent Early Recovery After Surgery guidelines in adults recommend all patients be screened for EE but no such guidelines currently exist for pediatrics, since little is known about predictors associated with EE after pediatric LT. Aim: We investigated the predictive factors associated with successful EE (within 24 hours of LT) in infants and children after orthotopic LT. **Methods:** We conducted a retrospective cohort analysis of children listed for LT (2011-2020) at a quaternary, free-standing children's hospital. Subjects with clinical (lab and ventilator parameters) and left ventricular mass indexed to height$^{2.7}$ and relative heart wall thickness (RWT) obtained on pre-LT 2D echocardiogram (2DE) were included Statistics: Fisher's Exact and Mann-Whitney tests to measure strength of univariate associations. **Results:** Median [IQR]. Results: Out of 338 (184;54% were female, 167; 49% with cirrhosis), 246 (73%) children successfully extubated on post operative day 0. When compared between early and delayed extubation; median age (months) 60 (20,142) vs 13 (8, 43), p < 0.001, weight 18 kg (11,38) vs 10 (8,15) p < 0.0001, PELD was 26 (12, 30) vs 26 (17,33) p ns, Total OR time (mins) 350 (321,391) vs 383 (341, 426) p < 0.0001, intraoperative blood loss (ml/kg) 7 (4,13) vs 18 (8,39) p < 0.0001, ICU LOS (days) was 3 (2,5) vs 22 (10,43) p < 0.0001, Hospital LOS (days) 13 (8,22) vs 51 (26,108); p < 0.0001. Of those patients not extubated on post operative day 0 (n = 67) median respiratory rate 28 (24, 32), V_t (ml/kg) 8 (7, 9), Peak Inspiratory Pressure (cmH_2O) was 22 (19,28), Peak End Expiratory Pressure (cmH_2O) 5 (5,7), Mean Airway Pressure (cmH_2O) 11 (9,13), inspiratory time (sec) 0.7 (0.6, 0.9), PaO_2 (mmHg) 195 (143, 251), LVMI (g/m2.7) 50 (39, 70) vs 72 (49, 97) p < 0.0001, and RWT 0.35 (0.31, 0.4) vs 0.37 (0.33, 0.42) p = 0.003. See table 1 for predictors of successful early extubation. **Conclusion:** Majority of patients in our cohort were successfully extubated within 24 hours post-LT. Several factors such as older age, normal LV geometry on 2DE, absence of cirrhosis, lower intra-operative blood loss and lower operative time are associated with successful EE. Early screening for eligibility and protocolized pathways are needed to accelerate liberation from mechanical ventilation and decrease overall morbidity in this population.

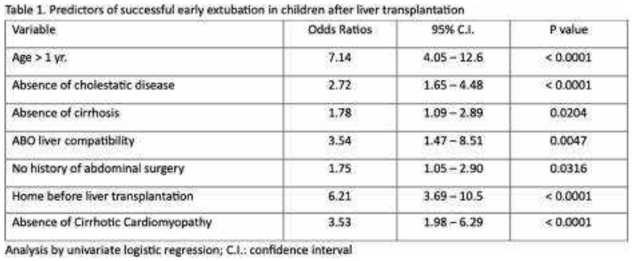

Table 1. Predictors of successful early extubation in children after liver transplantation

Variable	Odds Ratios	95% C.I.	P value
Age > 1 yr.	7.14	4.05 – 12.6	< 0.0001
Absence of cholestatic disease	2.72	1.65 – 4.48	< 0.0001
Absence of cirrhosis	1.78	1.09 – 2.89	0.0204
ABO liver compatibility	3.54	1.47 – 8.51	0.0047
No history of abdominal surgery	1.75	1.05 – 2.90	0.0316
Home before liver transplantation	6.21	3.69 – 10.5	< 0.0001
Absence of Cirrhotic Cardiomyopathy	3.53	1.98 – 6.29	< 0.0001

Analysis by univariate logistic regression; C.I.: confidence interval

Disclosures: The following people have nothing to disclose: Manpreet Kaur Virk, Moreshwar S Desai
Disclosure information not available at the time of publication: Muhammad Umair Mukhtar Mian, Thomas Fogarty, N. Thao N. Galván, Sanjiv Harpavat, Jorge Antonio Coss-Bu

f 4635-C | IDENTIFYING DRIVERS OF COST IN PEDIATRIC LIVER TRANSPLANTATION

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Background: Pediatric liver transplant (LT) is a resource-intensive intervention with center-specific variation in practice and outcomes. Under the same regulatory purview as adult LT centers, pediatric centers face intense pressure to optimize outcomes and finances across a lower patient volume. Thus, there is need to characterize unnecessary variations in care, and identify actionable targets for performance improvement. We examined national resource utilization, and outcome patterns in pediatric LT to test the *hypothesis that there are unique hospital factors and modifiable drivers of cost associated with greater total cost of care.* **Methods:** We reviewed children (age < 21 y) receiving a LT from 2010-2020 in the Pediatric Health Information System. Repeat and dual-organ transplants were excluded. All Patient Refined Diagnosis Related Group (APR-DRG) classifications were used as a proxy for patient severity of illness (SOI) and risk of mortality (ROM). Primary outcomes of interest were total cost, both per LT and by service-line (Clinical, Pharmacy, Supply, Imaging, Lab, and Other). Secondary outcomes were: mortality, care complications, and key metrics of resource utilization, including total parenteral nutrition (TPN), and mechanical ventilation (MV). To facilitate comparisons, patients were stratified into high-, intermediate-, or low-cost hospital tertiles based on LT cost. Data were analyzed with summary statistics, and multivariable linear regression. **Results:** We identified 3295 patients from 30 hospitals. While the median cost per LT was $150,836 [IQR $104,481, $250,129], there was marked variance in cost within, and between, hospital tertiles (Figure 1). High-cost hospitals (HCH) cared for more patients with the highest SOI and ROM levels (67% and 29%, respectively), compared to intermediate (60%, 21%; $p < 0.001$), and low (51%,16%; $p < 0.001$) cost hospitals. There was a higher prevalence of MV, TPN use, renal comorbidities and surgical complications at HCH than other tertiles. Service-lines contributing most to total cost were: Other 37.3%, Clinical 26.1%, and Pharmacy 11.3% (Figure 2). Admission to a HCH was the largest, independent contributor to total cost ($154,003), followed by renal comorbidities ($67,798), and TPN use ($39,903). **Conclusion:** There exists significant variation in the cost of pediatric LT care. Future studies are planned to examine drivers of cost and associated clinical outcomes at a more granular level, with the goal of standardizing care. Such efforts may uniquely benefit the sicker patient cohort that require the strategic resources located within high-cost hospitals to achieve the best outcomes.

Figure 1: Total Cost per Liver Transplant by Hospital Tertile

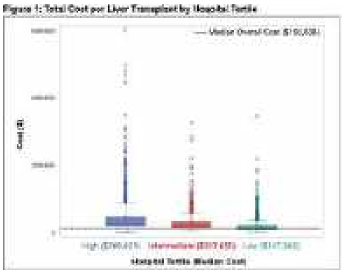
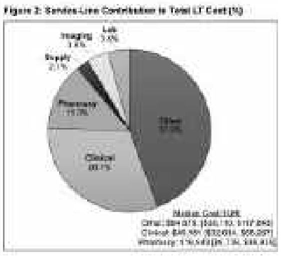


Figure 2: Service-Line Contribution to Total LT Cost (%)



Disclosures: The following people have nothing to disclose: Divya Sabapathy, Moreshwar S Desai
Disclosure information not available at the time of publication: Kathleen Hosek, Fong Lam, Eric Williams, John A. Goss, Jean Raphael, Michelle Lopez

4636-C | Immediate Post-operative Infections After Liver Transplantation in Children

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Background: Post-operative Infections (POI) are a leading cause of morbidity and mortality after liver transplantation. Single-center studies have identified risk factors for early infections, but large-scale studies are lacking. **Methods:** We performed a retrospective, multicenter cohort study of pediatric liver transplant recipients from 2017-2018 at 12 US liver transplant centers. We assessed the association of pre- and peri-operative variables with POI that occurred while in the pediatric intensive care unit. Continuous data was compared using the Wilcoxon rank-sum test and categorical data with the chi-squared test. In addition, multivariable logistic regression was used to identify independent predictors of infection using stepwise backward

elimination for p-value > 0.3. **Results:** In the immediate post-operative period, 76/327 (23%) patients developed POI (49% bacterial, 9% viral, 13% fungal, 17% culture negative, and 12% polymicrobial). Abdominal/surgical site and bloodstream infections were most common at 29% and 26%, respectively. Compared to children without POI, POI patients were younger (median 1.0y [IQR 0.6-3.5] vs 3y [IQR 0.8–11], p < 0.001), more likely to have an underlying immunodeficiency (5% vs 0.4%, p = 0.011), and be hospitalized prior to transplant (49% vs 31%, p = 0.004). Further, POI patients were more likely to have open fascia (42% vs 20%, p < 0.001), longer duration of mechanical ventilation (median 2.4d [IQR 0.5-8.5] vs 0.6d [IQR 0.0-2.1], p < 0.001), allograft thrombotic complications (49% vs 18%, p < 0.001), and receive blood products (74% vs 46%, p < 0.001). In addition, patients with POI had longer hospital length of stay (median 23d [IQR 17-34] vs 13d [IQR 9-20], p < 0.001), more graft loss (9% vs 0.4%, p < 0.001), and mortality (5% vs 0.4%, p = 0.002). On multivariable analysis, independent predictors of POI included younger age (OR = 0.92 (95%CI 0.87-0.98), p = 0.006), history of immunodeficiency (OR = 12.6 (95%CI 1.3-122.9), p = 0.03), open fascia (OR = 3.3 (95%CI 1.8-5.9), p < 0.001), and hospitalization before transplant (OR = 2.0 (95%CI 1.1-3.5), p = 0.02). **Conclusion:** One in five patients developed POI in the immediate postoperative period. Predictors of POI included younger age, history of immunodeficiency, open fascia, and hospitalization prior to transplant. POI were associated with significant morbidity, including prolonged length of stay, graft loss, and mortality. These data support the need for prospective studies to better characterize POI risk factors and develop protocols to prevent POI to ultimately optimize graft and patient survival.

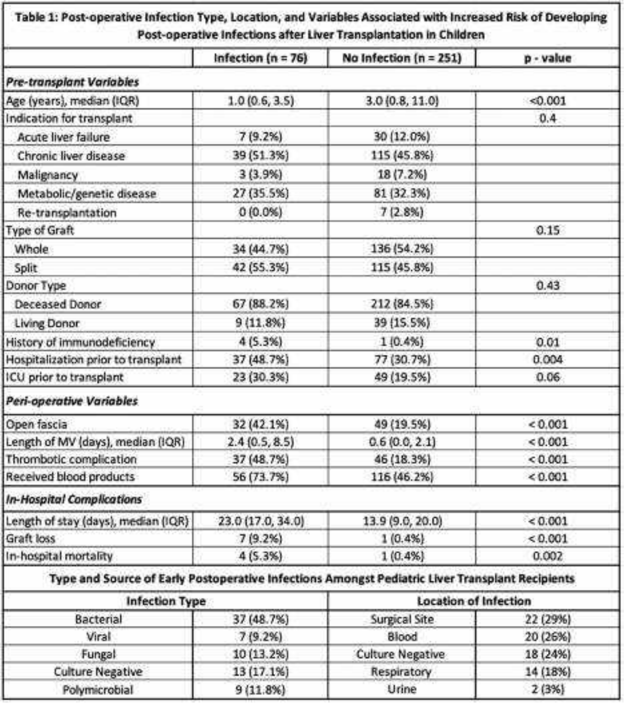

Table 1: Post-operative Infection Type, Location, and Variables Associated with Increased Risk of Developing Post-operative Infections after Liver Transplantation in Children

	Infection (n = 76)	No Infection (n = 251)	p - value
Pre-transplant Variables			
Age (years), median (IQR)	1.0 (0.6, 3.5)	3.0 (0.8, 11.0)	<0.001
Indication for transplant			0.4
Acute liver failure	7 (9.2%)	30 (12.0%)	
Chronic liver disease	39 (51.3%)	115 (45.8%)	
Malignancy	3 (3.9%)	18 (7.2%)	
Metabolic/genetic disease	27 (35.5%)	81 (32.3%)	
Re-transplantation	0 (0.0%)	7 (2.8%)	
Type of Graft			0.15
Whole	34 (44.7%)	136 (54.2%)	
Split	42 (55.3%)	115 (45.8%)	
Donor Type			0.43
Deceased Donor	67 (88.2%)	212 (84.5%)	
Living Donor	9 (11.8%)	39 (15.5%)	
History of immunodeficiency	4 (5.3%)	1 (0.4%)	0.01
Hospitalization prior to transplant	37 (48.7%)	77 (30.7%)	0.004
ICU prior to transplant	23 (30.3%)	49 (19.5%)	0.06
Peri-operative Variables			
Open fascia	32 (42.1%)	49 (19.5%)	< 0.001
Length of MV (days), median (IQR)	2.4 (0.5, 8.5)	0.6 (0.0, 2.1)	< 0.001
Thrombotic complication	37 (48.7%)	46 (18.3%)	< 0.001
Received blood products	56 (73.7%)	116 (46.2%)	< 0.001
In-Hospital Complications			
Length of stay (days), median (IQR)	23.0 (17.0, 34.0)	13.9 (9.0, 20.0)	< 0.001
Graft loss	7 (9.2%)	1 (0.4%)	< 0.001
In-hospital mortality	4 (5.3%)	1 (0.4%)	0.002

Type and Source of Early Postoperative Infections Amongst Pediatric Liver Transplant Recipients

Infection Type		Location of Infection	
Bacterial	37 (48.7%)	Surgical Site	22 (29%)
Viral	7 (9.2%)	Blood	20 (26%)
Fungal	10 (13.2%)	Culture Negative	18 (24%)
Culture Negative	13 (17.1%)	Respiratory	14 (18%)
Polymicrobial	9 (11.8%)	Urine	2 (3%)

Disclosures: The following people have nothing to disclose: Elise Kang, Mercedes Martinez

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4637-C | INVASIVE FUNGAL INFECTIONS IN CHILDREN ON LIVER TRANSPLANT WAITLIST: A LARGE SINGLE CENTER EXPERIENCE

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Background: Invasive fungal infections (IFIs) are associated with high morbidity and mortality in patients awaiting liver transplant (LT), and can often result in being delisted. Although well described in adults, the incidence and outcomes of IFI's in children awaiting LT is largely undefined. We aimed to assess the incidence, clinical manifestations, and outcomes of IFI in children on LT waitlist. **Methods:** Medical records of children listed for LT between January 2012 and December 2022 were retrospectively reviewed. IFI was defined as having histopathological evidence of fungal tissue invasion, isolation of fungal pathogen in blood culture or from a normally sterile body fluid or site, or imaging and clinical course consistent with IFI. Patients listed for multiple-organ transplantation, or who previously received LT were excluded. Statistical analyses were done on GraphPad Prism 9.3 **Results:** Twenty-four of 507 children (4.7%) listed for LT over an 11-year period had IFI; 12 (50%) were female, median age at listing was 7.6 yrs (IQR 0.7, 13.7 yrs). Median native PELD score at listing was 14 (IQR:8, 22). The most common infection was blood stream (12/24, 50%), followed by UTI (4/24, 17%) and peritonitis (2/24, 8%). Candida species were isolated in 20 (83%) cases, 2 had a mold. Biliary atresia (7/24, 29%) and other cholestatic liver disease (7/24, 29%) were major indications for LT. The median time to infection from listing was 28 days (IQR: 6, 171) overall. 11 (46%) patients with IFI died. Among patients who died, median age at listing was 9.1 yrs compared to 1.2 yrs in children who survived (p = 0.09). The median time from listing to IFI was 28 days in children who died and 9.5 days among survivors. The median time from infection to death was 11 days. The median time from infection to LT among survivors was 91 days. The number of children with decompensated cirrhosis (symptomatic ascites and/or a history of variceal hemorrhage) at listing was similar amongst the groups. There were no significant differences between baseline laboratory values at time of listing in both groups including total bilirubin, INR, albumin, WBC, absolute lymphocyte count, platelets and renal function. The incidence of bacterial and viral infections, and antibiotic exposure in the month preceding IFI was similar amongst the groups. **Conclusion:** The incidence of IFI in children awaiting LT at our institution was 4.7%, and mortality was very high, approaching 50%, in patients with IFIs. Children who died of IFI were older and were infected later after listing, but otherwise had similar indications for LT, PELD scores, and liver laboratory indices at the time of listing. Candida species were the most common cause of IFI. In contrast to adults, the incidence of bacterial and viral infections was similar in both groups, suggesting that death may actually be associated with IFI in these children. Multicenter studies are needed to identify risk factors for IFI's in children on LT waitlist.

Disclosures: The following people have nothing to disclose: Madelyn Cohen

Disclosure information not available at the time of publication: Flor Munoz, Krupa Mysore

4638-C | MAKING THE INVISIBLE VISIBLE - UNCOVERING DISCREPANCIES BETWEEN PARENT AND CHILD/YOUTH REPORTS ON A PEDIATRIC LIVER TRANSPLANT PROM

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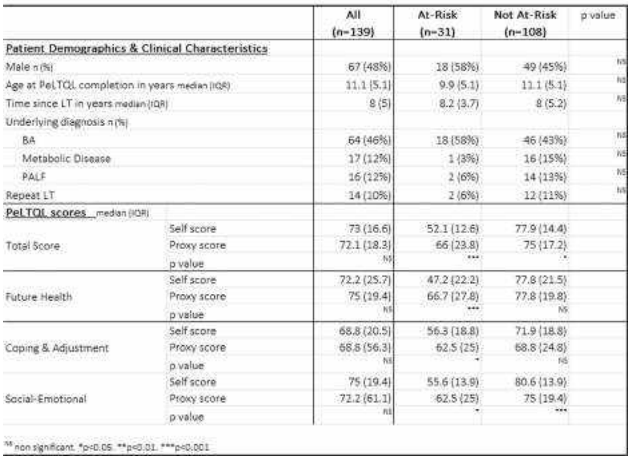
Background: Research on discrepancies between self- and proxy-reported patient-reported outcomes in children who have undergone liver transplantation (LT) is limited. The PeLTQL® is a validated disease-specific self- and proxy-reported HRQOL tool for children post LT, and is a non-stigmatizing option to screen for anxiety and depression. This study aimed to 1) evaluate and compare subjects identified as at risk of anxiety and depression and 2) describe discrepancies between self- and proxy-reported PeLTQL scores. **Methods:** PeLTQL completed by patient-parent dyads at LT clinic between 03/13-05/22 were reviewed. Each question is answered using a Likert scale from 1-5 (best to worst) and reversed scored to a 0-100 point scale (Likert 1 = 100 to Likert 5 = 0). PeLTQL scoring generates 4 scores (total score (PeLTQL-TS) and 3 subdomain scores (Future Health (FH), Coping & Adjustment (C&A) & Social-Emotional (SE)) with higher values indicative of better HRQOL. PeLTQL-TS $\leq$ 62.5 indicates risk for anxiety or depression ("at-risk"). Discrepancy was defined for each question as self response-proxy response. We targeted identification of specific questions with discrepant results of -100 (self response of 0 - proxy response of 100). **Results:** PeLTQL data from 139 patient-parent dyads were reviewed. Demographics, PeLTQL scores & discrepancies are provided in the table. Median self and proxy-reported PeLTQL-TS and subdomain scores were not statistically different. Questions about their surgical scar (20%), overly protective parents (16.5%) & hurting their allograft (14%) were most frequently of concern for patients. 22% patients were identified as "at-risk" with self report total and subdomain scores significantly lower than proxy scores. At-risk patients scored lowest in FH subdomain and the majority of questions with a "-100" discrepant result were related to FH (58%). At risk patients had increased concerns about their surgical scar (42%), overly protective parents (45%) and hurting their transplanted graft (29%). **Conclusion:** Parents of LT recipients identified to be at risk of anxiety or depression on disease-specific HRQOL questionnaires score their HRQOL significantly higher than their children, underscoring the importance of hearing the patient voice. Worries about future health and their scar are of particular concern for at-risk patients. These important mental health findings highlight opportunities for anticipatory guidance and targeted education by pediatric LT care teams.

Table: Patient demographics, clinical characteristics, PeLTQL scores & discrepancies of children post LT



		All (n=139)	At-Risk (n=31)	Not At-Risk (n=108)	p value
Patient Demographics & Clinical Characteristics					
Male n (%)		67 (48%)	18 (58%)	49 (45%)	NS
Age at PeLTQL completion in years median (IQR)		11.1 (5.1)	9.9 (5.1)	11.1 (5.1)	NS
Time since LT in years median (IQR)		8 (5)	8.2 (3.7)	8 (5.2)	NS
Underlying diagnosis n (%)					
BA		64 (46%)	18 (58%)	46 (43%)	NS
Metabolic Disease		17 (12%)	1 (3%)	16 (15%)	NS
PALF		16 (12%)	2 (6%)	14 (13%)	NS
Repeat LT		14 (10%)	2 (6%)	12 (11%)	NS
PeLTQL scores median (IQR)					
Total Score	Self score	73 (16.6)	52.1 (12.6)	77.9 (14.4)	
	Proxy score	72.1 (18.3)	66 (23.8)	75 (17.2)	
	p value	NS	***	*	
Future Health	Self score	72.2 (25.7)	47.2 (22.2)	77.8 (21.5)	
	Proxy score	75 (19.4)	66.7 (27.8)	77.8 (19.8)	
	p value	NS	***	NS	
Coping & Adjustment	Self score	68.8 (20.5)	56.3 (18.8)	71.9 (18.8)	
	Proxy score	68.8 (56.3)	62.5 (25)	68.8 (24.8)	
	p value	NS	*	NS	
Social-Emotional	Self score	75 (19.4)	55.6 (13.9)	80.6 (13.9)	
	Proxy score	72.2 (61.1)	62.5 (25)	75 (19.4)	
	p value	NS	*	***	

NS non significant. *p<0.05. **p<0.01. ***p<0.001

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Disclosure information not available at the time of publication: Tomisin John, Anthony Otley

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

4639-C | Prophylactic Antimicrobial Usage Following Pediatric Liver Transplantation

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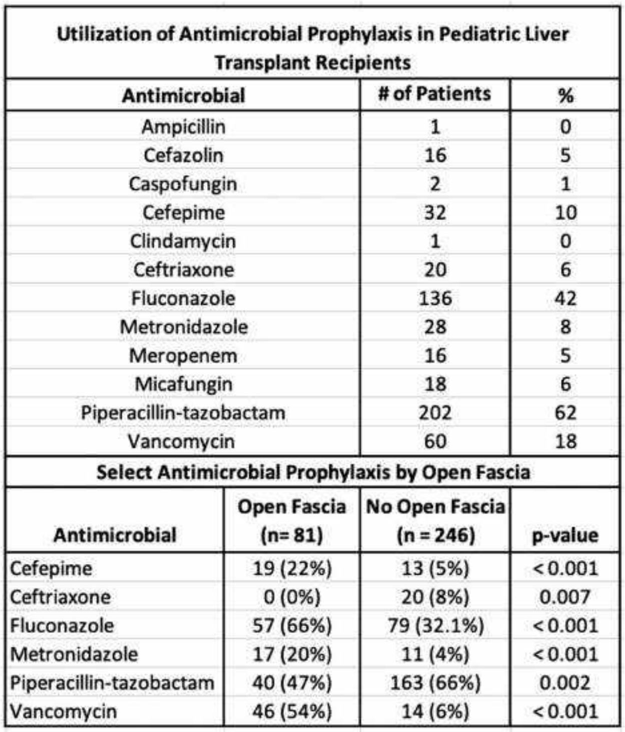
Background: Although clinical guidelines exist for antimicrobial prophylaxis following adult liver transplantation, consensus on pediatric-specific prophylaxis has not been established. Few single-center studies have assessed antibiotic utilization, but large-scale studies are lacking. **Methods:** We performed a retrospective, multicenter cohort study of pediatric liver transplant recipients admitted to the pediatric intensive care unit (PICU) from 2017-2018 at 12 US liver transplant centers. We assessed the utilization of prophylactic antimicrobials following transplantation. In addition, we examined differences in rates of post-operative infections in the PICU with antimicrobial prophylaxis usage as well as differences in antimicrobial usage if fascia remained opened post-operatively using chi-square tests. A p-value < 0.05 was considered significant. **Results:** Following transplantation, 91% (299/327) of patients received prophylactic antimicrobials. There was no significant difference in the post-operative infection rate between those with and without antimicrobial prophylaxis (29% vs 23%, $\chi^2 = 0.54$, $p = 0.46$). Significant variability existed in the utilization of various antimicrobials amongst different transplant centers. The most common antimicrobials included piperacillin-tazobactam (62%), fluconazole (42%), vancomycin (18%), and cefepime (10%). Patients with open fascia had higher rates of cefepime (22% vs 5%, $p < 0.001$), fluconazole (66% vs 32%, $p < 0.001$), metronidazole (20% vs 4%, $p < 0.001$), and vancomycin (54% vs 6%, $p < 0.001$) usage and lower rates of ceftriaxone (0% vs 8%, $p = 0.007$) and piperacillin-tazobactam (47% vs 66%, $p = 0.002$) usage compared to those without open fascia. Open fascia was associated with lower rates of prophylactic antibiotic usage (82.5% vs 94.3%, $\chi^2 = 10.80$, p-value $= 0.001$). 75% ($n = 21$) of patients without antimicrobial prophylaxis were limited to one center. Of the 76 children with post-operative infections, 65% were bacteria. The most common bacteria identified were *Escherichia coli* and *Staphylococcus epidermis*. 17% of post-operative infections were viral, all of which were respiratory infections. 13% were fungal, most commonly *Candida* species. **Conclusion:** Significant variability exists in antimicrobial utilization amongst pediatric liver transplant centers. Open fascia patients received broader spectrum antibiotics. Open fascia was also associated with lower rates of prophylactic antibiotic usage, likely reflective of infrequent antimicrobial prophylaxis use at certain centers. These data support the need for prospective studies to optimize antimicrobial regimens to reduce the risk of post-operative infections and develop protocols to ultimately optimize graft and patient survival.



Utilization of Antimicrobial Prophylaxis in Pediatric Liver Transplant Recipients

Antimicrobial	# of Patients	%
Ampicillin	1	0
Cefazolin	16	5
Caspofungin	2	1
Cefepime	32	10
Clindamycin	1	0
Ceftriaxone	20	6
Fluconazole	136	42
Metronidazole	28	8
Meropenem	16	5
Micafungin	18	6
Piperacillin-tazobactam	202	62
Vancomycin	60	18

Select Antimicrobial Prophylaxis by Open Fascia

Antimicrobial	Open Fascia (n= 81)	No Open Fascia (n = 246)	p-value
Cefepime	19 (22%)	13 (5%)	< 0.001
Ceftriaxone	0 (0%)	20 (8%)	0.007
Fluconazole	57 (66%)	79 (32.1%)	< 0.001
Metronidazole	17 (20%)	11 (4%)	< 0.001
Piperacillin-tazobactam	40 (47%)	163 (66%)	0.002
Vancomycin	46 (54%)	14 (6%)	< 0.001

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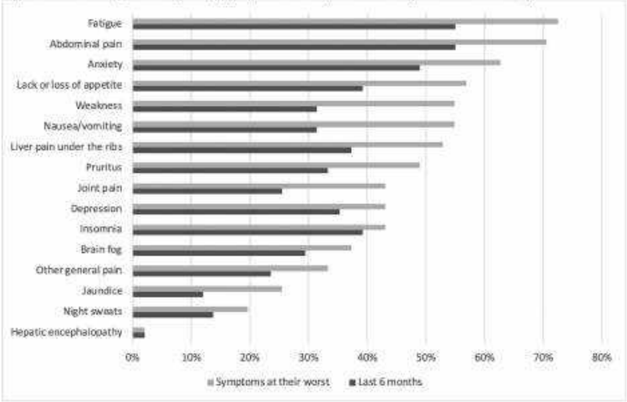
Disclosure information not available at the time of publication: Alicia M Alcamo, Danielle Maue, Fernando Beltramo, Asumthia Jeyapalan, Michael Nares, Alexandra Monde, Leslie Ridall, Sameer Kamath, Courtney M Rowan, Richard Mangus, Shubhi Kaushik, Matt S Zinter, Joseph Resch, Kristina Betters

4640-C | CAREGIVER-REPORTED SYMPTOM BURDEN AND PREFERENCES FOR THERAPEUTIC GOALS IN PEDIATRIC PRIMARY SCLEROSING CHOLANGITIS

Holly Payton Shifman[1], Joanne Hatchett[2], Ruth-Anne Pai[2], Ricky Safer[2], Rachel Gomel[2], Mary Pressley Vyas[3], Susan O'Dell[2], Sarah Curup Callif[2], Michael Li[4], Jennifer C. Lai[5] and Sharad Wadhwani[6], (1)Oakland University William Beaumont School of Medicine, (2) PSC Partners Seeking a Cure, (3)PSC Partners Seeking a Cure Canada, (4)University of California San Francisco, (5)University of California-San Francisco, San Francisco, CA, (6)University of California, San Francisco

Background: Primary sclerosing cholangitis (PSC) is a rare, chronic, cholestatic liver disease with no FDA-approved treatments available. Research focusing on pediatric patients with PSC is limited. We sought to characterize symptom burden and barriers to clinical trial enrollment for pediatric PSC patients and their caregivers. **Methods:** We analyzed survey responses from pediatric PSC patients and their caregivers using the PSC Partners Patient Registry 'Our Voices' survey. This registry, created in 2014, collects data on patient demographics, disease status, concurrent diagnoses, medications, clinical trial enrollment, and quality-of-life measures with the goal of incorporating patient experiences and priorities into drug development and clinical trial design. **Results:** Our analysis included 51 surveys (28M/23F) from pediatric PSC patients and their caregivers (90% caregivers, 10% patients). Most children were between 13 and 17 years old at the time of survey completion (67%), and the majority self-identified as White (88%) and non-Hispanic/non-Latino (88%). The most common symptoms reported by children include: fatigue (71%), abdominal pain (69%), anxiety (59%), loss of appetite (51%), insomnia (49%), and pruritis (45%). When experiencing symptoms at their worst, over half of the patients reported limitations in physically demanding activities (67%), work/school duties (63%), social life activities (55%), and less physically demanding activities for fun or exercise (53%). While more than 50% of patients/caregivers expressed willingness to participate in clinical trials, none of these patients reported current or previous enrollment in trials for new or investigational PSC drugs. Only one patient reported ever being asked to participate in a trial for investigational treatment of PSC. **Conclusion:** This study revealed substantial symptom burden among pediatric PSC patients and impact on daily activities and quality of life, as reported by both patients and caregivers. Despite the majority expressing willingness to participate in clinical trials, none had done so, indicating unmet needs in trial availability and accessibility for this population. Future efforts should focus on developing patient-centered clinical endpoints, increasing trial availability for pediatric PSC patients, and reducing logistical barriers to trial involvement.

Figure 1. Percent of patients reporting symptoms that impact their daily feel and functioning



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Disclosure information not available at the time of publication: Susan O'Dell

f 4641-C | COMBINATION IMMUNOSUPPRESSION IS ASSOCIATED WITH BETTER NATIVE LIVER SURVIVAL IN CHILDREN WITH AUTOIMMUNE HEPATITIS PRESENTING IN ACUTE LIVER FAILURE: AN INDIVIDUAL PATIENT DATA META-ANALYSIS

Harry Sutton, Toronto Hospital for Sick Children, Aly Fawzy, University of Toronto, Shannon M. Vandriel, Hospital for Sick Children and Binita M. Kamath, The Hospital for Sick Children, Toronto, ON, Canada

Background: Autoimmune hepatitis (AIH) in children has diverse presentations, however when presenting in acute liver failure (ALF) it can be fatal and often requires liver transplantation (LT). LT may be avoided with immunosuppressive therapy (IS). Large cohort studies on paediatric AIH presenting in ALF are lacking and management of these patients varies. This Individual Patient Data Meta-Analysis (IPD) was conducted to characterize and examine management and outcomes in this population. **Methods:** This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) statement. Database searches were conducted in PubMed and Embase. English studies published between 2000-2020 were included. Included patients were those <21 years of age presenting for the first time in PALF, defined by their local institution, diagnosed with type 1 or 2 AIH based on serum immunoglobulin levels, autoantibodies and liver histopathology. Exclusion criteria included positive hepatitis A-E serology, evidence of drug-induced liver injury, MDR3 deficiency or Wilson Disease, previous corticosteroid treatment, and LT not readily available at the reporting institution. Data extracted included clinical and biochemical characteristics, medical therapies and outcomes. **Results:** 325 patients from 61 identified studies, an additional five patients from our institution who met eligibility criteria were included for a total of 330 patients (Figure 1), 67% female, with a median age of 10 (range 6-14). Overall, 60% ($n=197/330$) had native liver survival (NLS), 35% underwent LT ($n=116/330$) and 5% ($n=17/330$) died. The use of corticosteroids (CS) with a secondary IS conferred a 2.5-fold increase in the chance of NLS compared to CS alone (95% CI 1.3 – 5.1, $p=0.008$). Patients with AIH-2 made up over one third ($n=25/68$) of our cohort and were significantly younger at presentation in comparison to those with AIH-1 (6.9 y vs. 11.0 y; $p=0.044$). AIH-2 was associated with a 3.3-fold increase in risk of LT or death compared to those with AIH-1 (95% CI 1.1- 10.0, $p=0.03$). **Conclusion:** Children presenting for the first time with AIH in ALF have a good chance at native liver survival with IS therapy. The combination of two or more IS agents is associated with better NLS. AIH-2 is associated with worse outcomes in AIH-ALF. These data offer hope for NLS in AIH-ALF and suggest a need to identify biomarkers which predict which children require combination IS in order to avoid LT.

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The following people have nothing to disclose: Harry Sutton

Disclosure information not available at the time of publication: Aly Fawzy

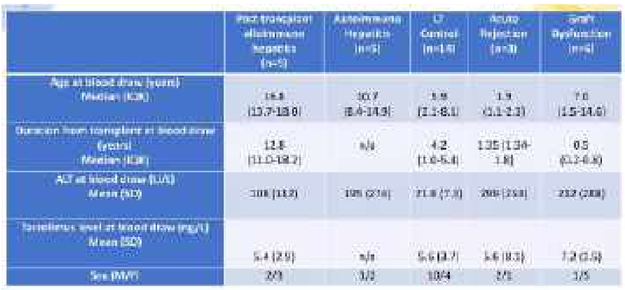
4642-C | INTRAHEPATIC TREGS IN POST-TRANSPLANT ALLOIMMUNE HEPATITIS DISPLAY AN ACTIVATED PHENOTYPE WITH ALTERED SUSCEPTIBILITY TO APOPTOSIS

Kumar Subramanian[1], Jhalen Ascue[2], Vinona Muralidaran[2], Nada A. Yazigi[3], Khalid M Khan[2], Bernadette E. Vitola[2], Stuart S. Kaufman[2], Alexander Kroemer[2], Thomas Fishbein[2], Eric Haas[4] and Udeme Ekong[1], (1)Medstar Georgetown Transplant Institute, (2)Medstar Georgetown University Hospital, (3)Medstar Georgetown University Hospital, Washington, DC, (4) Ionic Cytometry Solutions

Background: Post-transplant alloimmune hepatitis (DAIH) shares overlapping histologic and biochemical features with autoimmune hepatitis (AIH). Critical immune events that discriminate the two diseases remain unknown. We hypothesized that these immune events may occur in the regulatory T cell (Treg) compartment. We used mass cytometry & unsupervised clustering algorithm Flow self-organizing map (FlowSOM) to interrogate the distribution of subsets within *ex-vivo* $CD25^{hi}CD127^{lo/neg}FoxP3^{+}$ Treg in peripheral blood (PB) & liver (IH) of children with DAIH & non-transplanted children with AIH. **Methods:** Enriched $CD4^{+}$ T cells from peripheral blood mononuclear cells (PBMC) & intrahepatic lymphocytes (IHL) of children with DAIH ($n=5$), AIH ($n=5$), biopsy proven acute rejection (AR) ($n=3$), liver transplanted children with graft dysfunction ($n=6$), & liver transplanted children with normal graft function (LTC) ($n=14$) were expanded in culture with Dyna beads CD3/CD28, rIL-2 & TGF-b for 5-days prior to FACS sorting of Tregs. For FACS sorting, Tregs were identified by high expression of CD25 & low expression of CD127. *Ex-vivo* sorted PB

Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

and IH Tregs were then stained for mass cytometry with metal-conjugated monoclonal antibodies (CD49D, CD4, CCR4, CD45RA, CD3, CD39, FoxP3, CD95, CD45RO, CD25, CD152, HLA-DR, CD127, CD73, NRP1, Helios, LAP, CD45). Cells were acquired using a CyTOF Helios mass cytometer. CyTOF data was time-based bead normalized using standard procedures. The data were then uploaded to OMIQ (Omiq.ai), manually gated using Gaussian parameters to resolve live, intact, single cells for further analysis. Expression levels were arcsinh transformed with a cofactor of 5 and compared across disease groups within the Treg population. To further investigate the differences between disease states, clustering was performed using FlowSOM (Van Gassen, et al. 2015) & visualized using dimensionality reduction using UMAP (McInnes & Healy, et al. 2018). All statistical analyses were performed in GraphPad Prism v9 (Dotmatics). **Results:** Demographics reported in Table 1. 10 clusters identified within PB & liver Tregs that were different between DAIH and AIH patients, as well as between patients with DAIH and LTC subjects. Specifically, IH Tregs of DAIH patients were characterized by a higher expression of CCR4, Helios, CD95, and CD25 compared to IH Tregs of AIH patients ($p = 0.0037$; < 0.0001; 0.0004; 0.002 respectively) & IH Tregs of LTC subjects ($p = 0.0093$; < 0.0001; 0.0003; 0.004 respectively). PB Tregs of DAIH patients were characterized by a higher expression of Helios, CD25, FoxP3 compared to PB Tregs of AIH patients ($p = 0.0006$; 0.0021; 0.01 respectively). **Conclusion:** Intrahepatic Tregs of patients with DAIH are characterized by a more activated phenotype with altered susceptibility to apoptosis when compared to AIH patients. Improvement of Treg survival may hold a promising new therapeutic approach for patients with autoimmune liver disease.



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4643-C | PEDIATRIC HEPATITIS C PATIENT CASCADE OF CARE IN A TERTIARY ACADEMIC MEDICAL CENTER UTILIZING AN INTEGRATED HEALTH SYSTEM SPECIALTY PHARMACY MODEL

Alicia B. Carver, Cori Edmonds, Kristen Whelchel, Ryan Moore, Leena Choi and Lynette A. Gillis, *Vanderbilt University Medical Center*

Background: Direct-acting antivirals (DAAs) received FDA-approval for treatment of hepatitis C virus (HCV) in ages 12-17 years in 2017 and ages ≥ 3 years in 2019. Pediatric hepatologists at the Monroe Carrell Jr. Children's Hospital Pediatric Hepatology Clinic at Vanderbilt began utilizing an integrated Health System Specialty Pharmacy (HSSP) model in 2017 to assist with DAA selection, insurance approval, dosage form administration practice, and treatment monitoring from medication initiation to sustained virologic response (SVR). The purpose of this study was to examine the cascade of care (CoC), describe barriers to successful CoC advancement and identify factors associated with the time from HSSP referral to medication initiation in this patient population. **Methods:** This was a single-center, retrospective cohort study of hepatitis C patients < 18 years old evaluated by a pediatric hepatologist at the Monroe Carrell Jr. Children's Hospital Pediatric Hepatology Clinic at Vanderbilt between January 2017 and September 2022. **Results:** 119 patients (male, 53%; white, 73%; median [interquartile range (IQR)] age, 5 years [5-8 y]; median [IQR] weight 22.1kg [15.05-32.95kg]) were included. In the CoC (Figure 1), 119 patients were evaluated in clinic, 73 (61%) were referred to the integrated HSSP, 69 (58%) successfully administered the practice dosage form, 64 (54%) received insurance approval, 64 (54%) initiated treatment, 64 (54%) completed treatment, 60 (50%) completed SVR labs, and 58 (49%) achieved SVR. Reasons for patient non-advancement through the CoC are included in Figure 1. In patients aged 3-5 years, 57% (35/61) failed to advance beyond clinic evaluation, whereas fewer patients aged 6-11 (21%; 9/42) and 12-17 (13%; 2/16) failed to advance beyond clinic evaluation to referral to the integrated HSSP. Overall, the most common reasons for non-referral were loss to follow-up (18%; 22/119) and negative confirmatory HCV testing (12%; 14/119). The time from integrated HSSP referral to medication initiation was impacted by DAA availability [$OR = 41.47$; $p < 0.001$] and successful administration of the practice dosage form at the initial clinic visit [$OR = 3.94$; $p = 0.004$]. **Conclusion:** Utilization of an integrated HSSP was effective in navigating pediatric HCV patients

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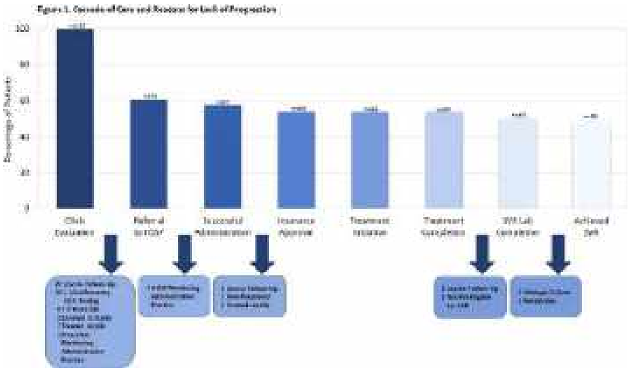
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

through the treatment cascade to achievement of SVR. Ongoing efforts should focus on linkage to care following initial clinic evaluation, as it remains a challenge in this population. Delayed DAA availability lengthened time from HSSP referral to medication initiation, however, this was due to time period of the study. Although the ability to administer the practice dosage form also delayed time to treatment initiation, all patients able to administer practice dosage form at home successfully completed prescribed treatment course.



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Disclosure information not available at the time of publication: Kristen Whelchel, Ryan Moore, Leena Choi, Lynette A. Gillis

4644-C | PEDIATRIC HEPATITIS C PATIENT OUTCOMES IN A TERTIARY ACADEMIC MEDICAL CENTER UTILIZING AN INTEGRATED HEALTH SYSTEM SPECIALTY PHARMACY MODEL

Alicia B. Carver, Cori Edmonds, Kristen Whelchel, Ryan Moore, Leena Choi and Lynette A. Gillis, Vanderbilt University Medical Center

Background: Direct-acting antivirals (DAAs) received FDA-approval for treatment of hepatitis C virus (HCV) in ages 12-17 years in 2017 and ages ≥3 years in 2019. Pediatric hepatologists at the Monroe Carrell Jr. Children's Hospital Pediatric Hepatology Clinic at Vanderbilt began utilizing an integrated Health System Specialty Pharmacy (HSSP) model in 2017 to assist with DAA selection, insurance approval, dosage form administration practice, and treatment monitoring from medication initiation to sustained virologic response (SVR). The purpose of this study was to evaluate efficacy of DAAs in pediatric hepatitis C patients utilizing an integrated HSSP model. **Methods:** This was a single-center, retrospective cohort study of hepatitis C patients < 18 years old evaluated and referred to the integrated HSSP for DAA treatment consideration by pediatric hepatologists at the at the Monroe Carrell Jr. Children's Hospital Pediatric Hepatology Clinic at Vanderbilt between January 2017 and September 2022. **Results:** Of the 73 patients referred to the integrated HSSP, 64 (86%) successfully initiated DAA treatment. Reasons for not initiating treatment included: ongoing dosage form administration practice (5.5%; 4/73), loss to follow-up (4.1%; 3/73), treatment by outside provider (1.4%; 1/73) and pregnancy (1.4%; 4/73). Baseline characteristics of the 64 patients who initiated treatment are included in Table 1. Most patients (67%; 43/64) were prescribed a 12-week course of ledipasvir/sofosbuvir (LDV/SOF). All 64 patients who initiated treatment successfully completed the prescribed course. Fifty-eight patients (91%) achieved SVR; 2 (3%) were lost to follow-up, 2 (3%) are not yet eligible for SVR, 1 (1.6%) was reinfected, and 1 (1.6%) was a true failure. Just over half (53%; 34/64) of patients experienced at least one side effect, with nausea/vomiting (25%; 16/64), headache (20%; 13/64), fatigue (20%; 13/64), and sleep disturbances (8%; 5/64) being the most common. Less than half (31%; 20/64) of patients reported any missed doses. Most missed doses were due to vomiting (9%; 6/64) followed by medication administration difficulty (6%; 4/64). The patient who failed to achieve SVR reported 13 missed doses. Drug interactions were minimal (17%; 11/64) and all were managed by the pharmacist; most frequently by holding the interacting medication (9%; 6/64) followed by adjusting the timing of administration of the non-DAA medication (6%; 4/64). **Conclusion:** Utilization of an integrated HSSP model for insurance approval, initiation, and management of all-oral DAAs in pediatric hepatitis C patients yielded high rates of therapy completion and SVR.

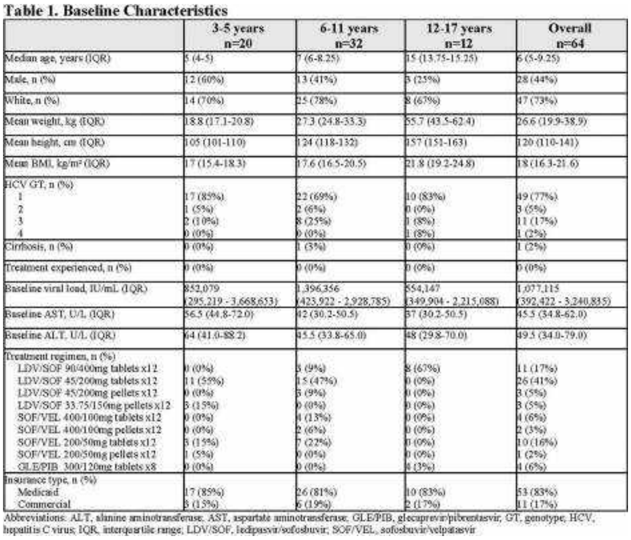

Table 1. Baseline Characteristics

	3-5 years n=20	6-11 years n=32	12-17 years n=12	Overall n=64
Median age, years (IQR)	5 (4-5)	7 (6-8.25)	15 (13.75-15.25)	6 (5-9.25)
Male, n (%)	12 (60%)	13 (41%)	3 (25%)	28 (44%)
White, n (%)	14 (70%)	25 (78%)	8 (67%)	47 (73%)
Mean weight, kg (IQR)	18.8 (17.1-20.8)	27.3 (24.8-33.3)	55.7 (43.5-62.4)	26.6 (19.9-38.9)
Mean height, cm (IQR)	105 (101-110)	124 (118-132)	157 (151-163)	120 (110-141)
Mean BMI, kg/m² (IQR)	17 (15.4-18.3)	17.6 (16.5-20.5)	21.8 (19.2-24.8)	18 (16.3-21.6)
HCV GT, n (%)				
1	17 (85%)	22 (69%)	10 (83%)	49 (77%)
2	1 (5%)	2 (6%)	0 (0%)	3 (5%)
3	2 (10%)	8 (25%)	1 (8%)	11 (17%)
4	0 (0%)	0 (0%)	1 (8%)	1 (2%)
Cirrhosis, n (%)	0 (0%)	1 (3%)	0 (0%)	1 (2%)
Treatment experienced, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Baseline viral load, IU/mL (IQR)	852,079 (295,219 - 3,668,653)	1,396,356 (423,922 - 2,928,785)	554,147 (349,904 - 2,215,088)	1,077,115 (392,422 - 3,240,835)
Baseline AST, U/L (IQR)	56.5 (44.8-72.0)	42 (30.2-50.5)	37 (30.2-50.5)	45.5 (34.8-62.0)
Baseline ALT, U/L (IQR)	64 (41.0-88.2)	45.5 (33.8-65.0)	48 (29.8-70.0)	49.5 (34.0-79.0)
Treatment regimen, n (%)				
LDV/SOF 90/400mg tablets x12	0 (0%)	3 (9%)	8 (67%)	11 (17%)
LDV/SOF 45/200mg tablets x12	11 (55%)	15 (47%)	0 (0%)	26 (41%)
LDV/SOF 45/200mg pellets x12	0 (0%)	3 (9%)	0 (0%)	3 (5%)
LDV/SOF 33.75/150mg pellets x12	3 (15%)	0 (0%)	0 (0%)	3 (5%)
SOF/VEL 400/100mg tablets x12	0 (0%)	4 (13%)	0 (0%)	4 (6%)
SOF/VEL 400/100mg pellets x12	0 (0%)	2 (6%)	0 (0%)	2 (3%)
SOF/VEL 200/50mg tablets x12	3 (15%)	7 (22%)	0 (0%)	10 (16%)
SOF/VEL 200/50mg pellets x12	1 (5%)	0 (0%)	0 (0%)	1 (2%)
GLE/PIB 300/120mg tablets x8	0 (0%)	0 (0%)	4 (3%)	4 (6%)
Insurance type, n (%)				
Medicaid	17 (85%)	26 (81%)	10 (83%)	53 (83%)
Commercial	3 (15%)	6 (19%)	2 (17%)	11 (17%)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLE/PIB, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; IQR, interquartile range; LDV/SOF, ledipasvir/sofosbuvir; SOF/VEL, sofosbuvir/velpatasvir

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Disclosure information not available at the time of publication: Kristen Whelchel, Ryan Moore, Leena Choi, Lynette A. Gillis

4645-C | SCREENING FOR LIVER FIBROSIS IN PEDIATRIC/YOUNG ADULT PATIENTS WITH IBD ON METHOTREXATE: A SINGLE CENTER EXPERIENCE

Anne Lyon[1], Elif Ozdogan[1], Enju Liu[2], Nan Du[1] and Christine K. Lee[2], (1)Boston Children's Hospital, Boston, MA, (2)Boston Children's Hospital and Harvard Medical School, Boston, MA

Background: Methotrexate (MTX), an immunomodulator used to treat inflammatory bowel disease (IBD) has been reported to cause liver fibrosis and steatosis with long term use. There are limited adult studies assessing the prevalence of liver fibrosis in patients on MTX, with disparate results regarding association between MTX cumulative dose and risk of fibrosis. There have been no pediatric studies to date. Transient elastography (TE, FibroScanχ) is a non-invasive, ultrasound-based imaging study which can predict liver fibrosis by liver stiffness measurement (LSM) and steatosis by controlled attenuation parameter (CAP). Understanding the prevalence of MTX-associated liver side effects in children will be important to inform best practices for care of children with IBD. This study aimed to describe the LSM and CAP measurements for pediatric and young adult patients with IBD on MTX who underwent TE at Boston Children's Hospital (BCH). **Methods:** Patients seen in a BCH GI clinic with an IBD diagnosis, on MTX and who underwent TE study for clinical indications from 1/2015- 1/2023 were eligible for retrospective review. LSM with > 60% success and interquartile/median ratio < 30% were valid. Abnormal LSM was any measurement > 6kPa and clinically significant fibrosis with an LSM > 8.6kPa. Abnormal steatosis was defined as a CAP > 215. **Results:** A total of 43 patients (median age 18.1y, 6.4-24.5 y, 65% males) met eligibility criteria with a diagnosis of Crohn disease in 39 (93%). The median ALT was 15 (IQR, 12-22) and MTX cumulative dose was 1950 mg (IQR, 1220-3310 mg). Median LSM was 4.5 kPa (2.8-7.8 kPa) with 5 patients (11.6%) with LSM ≥ 6 kPa and predicted fibrosis score of F1-2. Median CAP was 200 (102-361). Fifteen patients (34%) had a CAP score ≥ 215 (217-361) with a median BMI Z-score of 0.52 (N = 13, -1.2 to 1.88). MTX cumulative dose, MTX duration, age, BMI, ALT did not have a significant association with LSM or CAP. **Conclusion:** This is the first study using TE to assess liver fibrosis and steatosis in children/ young adult patients with IBD on long term MTX therapy. In this cohort of patients at a large quaternary pediatric hospital, there were 11.6% of patients with liver fibrosis and greater than 1/3 of patients (34%) with steatosis. While adult studies have had conflicting results regarding the significance of MTX on liver fibrosis/ steatosis, this may be due to a greater degree of metabolic factors in adults. In this pediatric population, the impact of MTX on liver fibrosis and steatosis was considerable enough to warrant future prospective, non-invasive investigation.

Disclosures: Christine K. Lee – Echosens: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Anne Lyon

Disclosure information not available at the time of publication: Elif Ozdogan, Enju Liu, Nan Du

4646-C | SINGLE CENTER SURVEY OF PREVALENCE OF VIRUSES IN PEDIATRIC LIVER EXPLANTS

Adriana Perez, Phoebe Wood, Zachary J Savage, Olivia Vaccaro and Elizabeth Rand, Children's Hospital of Philadelphia, Philadelphia, PA

Background: Adenovirus has been implicated as a cause of acute liver failure (ALF) following a global outbreak of adenovirus associated ALF in 2021. In order to understand the association between adenovirus and ALF it is important to know the baseline prevalence of adenovirus (and other childhood viruses) in the population of children undergoing liver transplant for acute and chronic liver disease. Various viruses are known to cause acute hepatitis with or without synthetic liver dysfunction. In 2021 clustered cases of “acute severe hepatitis” and ALF in young children were reported in association with adenovirus infection. For this reason, we have performed viral PCR for adenovirus, EBV, CMV, and HHV-6 on stored liver explant tissue collected as part of an IRB approved liver repository at the Children's Hospital of Philadelphia. Our objective was to perform retrospective evaluation of prevalence of hepatotropic viruses among children who underwent liver transplant at our center. **Methods:** We studied 33 frozen hepatic explant samples (originally collected between 2004 and 2021 and stored at -80 degrees) which fell into 3 categories; acute liver failure (ALF, n = 18; 13 indeterminate, 5 with specific diagnoses), acute on chronic liver failure (ACLF, n = 7), and chronic liver disease (CLD, n = 8). DNA was extracted via the Qiagen EZ system and accompanying EZ virus mini kit. Viral PCR testing was done using ThermoFischer QuantStudio Real Time PCR using commercially available primers with appropriate positive and negative controls. **Results:** Adenovirus was detected by PCR in a single case of indeterminate ALF transplanted in 2019 (1/18) and in none of the ACLF or CLD cases. CMV was detected in two ALF cases, one indeterminate (not the same as the adenovirus case) and one with bile acid synthesis defect, CMV was not detected in any other group. There were no EBV positive specimens in any group. As expected, HHV-6 was more prevalent, 21 of 33 specimens were positive including 12/13 indeterminate ALF cases; 2/5 specific ALF cases; 2/7 ACL; and 5/8 CLD. **Conclusion:** This retrospective study of the prevalence of common childhood viruses in liver explants provides important baseline information for those studying potential viral etiologies of acute liver failure. HHV-6 was observed in 21/33 (64%) of all liver explants even in stable outpatients with CLD underscoring the high prevalence but non-specific association with acute disease. HHV-6 prevalence did not statistically differ among our study groups.

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Disclosure information not available at the time of publication: Zachary J Savage, Olivia Vaccaro

4700-C | A HIGH-PERFORMANCE COMPUTING ANALYSIS OF CHOLESTASIS-ASSOCIATED GENE VARIANTS IN PATIENTS WITH CHOLESTASIS PHENOTYPE OF UNCLEAR ETIOLOGY

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Background: Heterozygous pathogenic mutations or common polymorphisms in genes encoding the hepatocanalicular transporters *ATP8B1*, *ABCB11* and *ABCB4*, or the bile acid ligand farnesoid X receptor (*FXR*) might contribute to liver injury in patients with an otherwise unexplained cholestasis phenotype. We aimed to determine the extent to which individual genetic variants of these transporters or their combinations play an etiopathogenetic role in patients with chronic unexplained cholestasis. **Methods:** Retrospective screening of patients of the University Medical Centre Leipzig identified a cohort of 234 patients with chronic unexplained cholestasis. Genotyping was performed using TaqMan assays, and the frequencies of *ABCB4* rs1202283 (c.504 T > C), *ABCB4* rs2109505 (p.711A > T), *ABCB4* rs2230028 (p.R652G), *ABCB4* rs2302387 (p.L59L), *ABCB4* rs45575636 (p.R590Q), *ABCB11* rs2287622 (p.A444V), *ABCB11* rs497692 (c.3084A > G), *ABCB11* rs11568367 (p.N591S), *ABCB11* rs58238559 (p.T175A), *ABCB11* rs11568372 (p.E297G), *ABCB11* rs72549402 (p.D482G), *ATP8B1* rs12968116 (p.R952Q), *ATP8B1* rs146599962 (p.N45T), *ATP8B1* rs34018205 (p.E429A), *ATP8B1* rs121909100 (p.I661T) and *FXR* rs56163822 (c.-1G > T) variants of the patient cohort were compared to a cohort of 254 healthy controls. High performance computing analysis was applied to correlate combinations of homo- or heterozygous genetic variants in *ATP8B1*, *ABCB11*, *ABCB4* and *FXR* with elevated liver enzymes in the patient cohort. **Results:** Heterozygous pathogenic mutations or any common polymorphisms in *ATP8B1*, *ABCB11*, *ABCB4* or *FXR* were similarly frequent in patients and controls (8.97% vs. 9.05%; 100% vs. 100%). Heterozygosity for the common polymorphism *ATP8B1* p.R952Q correlated with elevated serum bilirubin levels in the patient cohort ($p = 0.02$), and was more frequently found in patients as compared to controls (12.8% vs. 1.6%, $p < 0.0001$). No other single variant correlated with elevated liver enzyme activities. We next evaluated whether any combination of common variants showed an association with patients phenotype. Here the combination of heterozygous *ATP8B1* p.N45T (pathogenic) and the common homozygous SNP *ABCB4* c.504 T > C correlated with levels of serum alanine transaminase ($p = 0.009$), aspartate transaminase ($p = 0.006$), and gamma-glutamyltransferase ($p = 0.033$). This combination tended to be more frequent in patients than controls (2.16% vs. 0.4%, $p = 0.09$). The combination of homozygous *ATP8B1* p.R952Q and heterozygous *ABCB11* p.A444V correlated with serum alkaline phosphatase levels ($p = 0.001$). and was more frequent in patients as compared to controls (10.23% vs. 1.2%, $p = 0.0001$). **Conclusion:** Certain combinations of common genetic variants in cholestasis-associated genes show an association with cholestatic enzyme profiles and may be causally involved in the development of previously unexplained cholestatic liver injury.

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

4701-C | DEVELOPING A NATURAL LANGUAGE PROCESSING ALGORITHM TO IDENTIFY A HISTOLOGICALLY DEFINED NAFLD-NASH COHORT IN THE MILLION VETERAN PROGRAM BIOBANK

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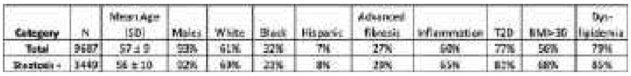
Background: Nonalcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease. GWAS studies identified multiple NAFLD-associated genetic variants in large cohorts with NAFLD phenotypes based on clinical and radiological data. However, non-invasive assessments of NAFLD have limitations, and histopathologic evidence of inflammation and fibrosis remains the gold standard to diagnose and stage NAFLD-NASH. Thus, we aimed to isolate a biopsy-proven NAFLD cohort in the VA Million Veteran Program (MVP) mega-biobank using natural language processing (NLP) of liver biopsy reports for downstream genomic analysis. **Methods:** Using CPT codes for liver biopsy results (4700, 47001, 47100), the MVP database was searched via the VA informatics and computing infrastructure (VINCI) studymart tool. An annotation guideline was developed to extract labels such as steatosis, fibrosis and inflammation. Using this, 3 annotators independently reviewed 400 biopsy reports, with weekly adjudication based on overall concordance (Inter-annotator agreement or IAA) until achieving an IAA of > 90% for Steatosis and > 80% for Fibrosis and Inflammation. The finalized guideline was validated by 2 clinicians to confirm the NLP logic. These reports were then split into training and testing set of data which were used for the development of a rule-based NLP system. **Results:** We identified 9,687 MVP participants with liver biopsy reports between 2002-2020, with broad use of histologic scoring systems consistent with Kleiner, Knodell HAI, Scheuer, Ishak and Metavir. Our NLP approach identified hepatic steatosis in 3,449 participants including 29% with advanced fibrosis and 65% with inflammation, consisting largely of males (92%) with mean age of 56, diverse ancestry (69% white, 23% black, 7% hispanic) and enriched for obesity (68%), dyslipidemia (85%) and diabetes (81%). NLP performance scores were: Precision 0.922 (Steatosis)/ 0.969 (Fibrosis)/ 0.793 (Inflammation); Recall 0.972 (Steatosis)/ 0.714 (Fibrosis)/0.809 (Inflammation) and F1(harmonic mean of precision and recall): 0.946 (Steatosis)/ 0.822 (Fibrosis)/0.801 (Inflammation). **Conclusion:** We identified a diverse cohort of 3449 Veterans with biopsy-defined hepatic steatosis, fibrosis, and inflammation using an NLP algorithm with high scores for precision, recall, and F1 (> 0.8 for most domains). Further efforts are ongoing to confirm and optimize our method to uncover genetic associations with biopsy-proven NAFLD and NASH.



Category	N	Mean Age (SD)	Males	White	Black	Hispanic	Advanced fibrosis	Inflammation	T2D	BMI>30	Dys-lipidemia
Total	9687	57 ± 9	93%	61%	32%	7%	27%	60%	77%	56%	79%
Steatosis +	3449	56 ± 10	92%	69%	23%	8%	29%	65%	81%	68%	85%

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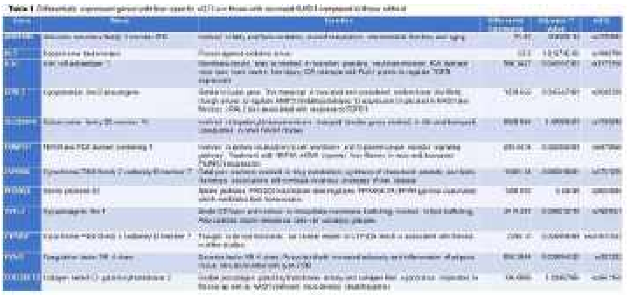
4702-C | DIFFERENTIAL RNA EXPRESSION AND EXPRESSION QUANTITATIVE TRAIT LOCI ANALYSIS IDENTIFIES NOVEL GENETIC VARIANTS ASSOCIATED WITH RECURRENT NONALCOHOLIC STEATOHEPATITIS (NASH) AFTER LIVER TRANSPLANTATION FOR NASH CIRRHOSIS

Christopher Danford[1], Richard Gilroy[2], Nephi Walton[2] and Bryce Christensen[2], (1)Intermountain Health, Millcreek, UT, (2)Intermountain Health

Background: Despite identical recipient genetics and similar recipient environmental exposures, only a minority (10-40%) of patients transplanted for NASH cirrhosis develop recurrent NASH post-transplant.[1] We hypothesize that the genetic profile of the donor liver may account for some degree of protection from recurrent NASH post-transplant. **Methods:** We included all patients who had previously undergone liver transplantation at Intermountain Medical Center for the indication of NASH cirrhosis who had at least one liver biopsy ≥ 6 months post-transplant with sufficient tissue for genotyping and RNA sequencing. The primary outcome was recurrent NASH on post-transplant biopsy. Secondary outcomes included hepatic steatosis without NASH and NASH with fibrosis on post-transplant biopsy. **Results:** We identified 8 patients with sufficient tissue for RNA sequencing in the Intermountain Biorepository. Four of 8 patients (50%) developed recurrent NASH and 3/8 (37.5%) developed recurrent NASH with fibrosis by a mean of 5.3 years post-transplant. Thirteen genes were found to be differentially expressed in those with recurrent NASH compared to those without. KEGG analysis identified "fatty acid metabolism", "biosynthesis of unsaturated fatty acids", "steroid biosynthesis", "retinol metabolism", and "PPAR signaling pathway" as those pathways most associated with differential RNA expression in recurrent NASH. Of these genes, four had liver-specific expression quantitative trait loci (eQTLs) meaning differential expression could be due to variants acquired from the donor liver (Table 1). Thirty-eight genes were differentially expressed in those with recurrent NASH and fibrosis compared to those without. Of these, eight had liver-specific eQTLs (Table 1). **Conclusion:** Studies evaluating the genetic underpinnings of NASH and cirrhosis have been limited by small patient population and inadequate patient phenotyping. In this study we demonstrate that by controlling environmental exposure and recipient genetics, we can identify several biologically plausible variants that modulate risk of recurrent NASH post-transplant despite small population. These results likely have implications for NASH outside the post-transplant population.



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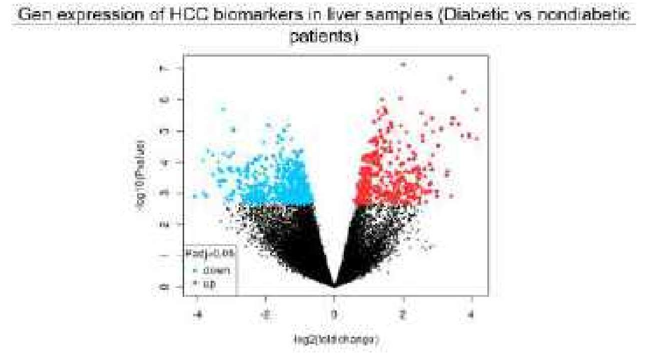
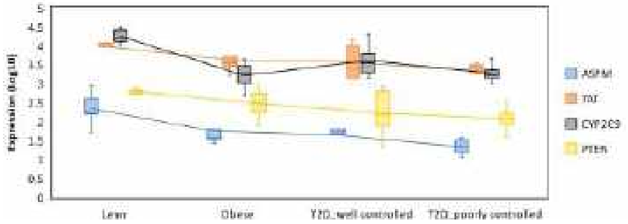
4703-C | GENE EXPRESSION OF HEPATOCELLULAR CARCINOMA BIOMARKERS ON LIVER TISSUE OF TYPE-2 DIABETES PATIENTS

Evelyn Calderon Martinez[1], *Adalberto Guzman*[2], *Wern Lynn Ng*[3], *Fatma Yilmaz*[1], *Maria Joseph*[1] *and Christian Zevallos-Delgado*[4], *(1)Umpc Central PA, (2)University of Pittsburgh, Harrisburg, PA, (3)UPMC, (4)University of Houston*

Background: Diabetes is one of the most common diseases in the world and it is projected to affect 693 million people in 2045. Obesity is a known risk factor for cardiovascular diseases, cancers, and diabetes. The liver is one of the many organs affected by diabetes and obesity. Diabetes can increase by 2 to 3-fold the risk of Hepatocellular Carcinoma (HCC) and exacerbate the progression of fibrosis in Non-Alcoholic Steatosis Hepatica (NASH). **Methods:** For this study, gene expression data uploaded by Pihlajamaki, J., et. al. was obtained from the Gene Expression Omnibus (GEO ID: GSE15653). This data was obtained from patients with Type 2 Diabetes (well and poorly controlled) and non-diabetic patients (lean and obese). The differential expression of genes (DEG) was assessed using GEO2R tool using the list of HCC gene biomarkers proposed by Zhou, Z. et al, Wang, X. et. al., and Gholizadeh, M. et al. **Results:** The results have shown that genes that have been found to be downregulated in HCC such as TAT (Tyrosine Aminotransferase)(p. adjs = 0.01363, logFC = 2.15), CYP2C9 (Cytochrome P450 family 2 subfamily C member 9) (p. adj = 0.0049, logFC = 3.23), and PTEN (Phosphatase and tensin homolog) (p. adj = 0.000575 and log FC = 2.39) genes are upregulated on liver samples from lean patients compared with poorly controlled diabetic obese patients. ASPM (Assembly Factor For Spindle Microtubules) (p. adjs = 0.02562, logFC = 3.37) which is normally is upregulated in HCC was found to be upregulated in on liver samples from lean patients. When comparing the above genes' expression between nondiabetic obese patients vs well-controlled diabetics, or well-controlled vs uncontrolled diabetics, or lean patients vs well-controlled diabetics, there was not a significant differential in expression. **Conclusion:** The dysregulated expression of HCC biomarkers on liver samples from obese poorly controlled T2D patients represents the importance of the hepatic damage due to uncontrolled-diabetes and obesity. In addition, a well-controlled diabetic patient has similar HCC-gene expression than a healthy lean patient.





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4704-C | GENOMIC CHARACTERISTICS OF HEPATOCELLULAR CARCINOMA PATIENTS WITH RESPONSE TO SORAFENIB

Yim Sun Young[1], *Ji Hoon Kim*[1], *Hyung Joon Yim*[2], *Yeon Seok Seo*[1], *Jong Eun Yeon*[1], *Young-Sun Lee*[1], *Taehyung Kim*[3], *Seong Hee Kang*[4], *Yoonseok Lee*[1], *Jong Su Kim*[1], *Chang Hee Jung*[1] *and Korea University Hospital, (1)Korea University Hospital, (2)Korea University Ansan Hospital, Ansan, Republic of Korea, (3)Korea University Ansan Hospital, (4)4 Seasons Granwell Corp.*

Background: Sorafenib is a multiple receptor tyrosine kinase inhibitor which is the standard systemic therapy for advanced hepatocellular carcinoma (HCC). However, the objective response rate is low only reaching 10%. We implemented RNA sequencing (RNA-seq) in HCC tumors to identify potential biomarkers that would predict response to sorafenib and uncover underlying biological features associated with better response. **Methods:** A total of 33 patients who had undergone liver resection prior to sorafenib treatment were enrolled. Matched tumor/surrounding tumor tissues were obtained and RNA-seq was performed. Cluster analysis was performed and gene signature associated

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with sorafenib response was identified. The gene signature was validated in independent STORM cohort. Gene network analysis by Ingenuity Pathway Analysis (IPA) was performed to uncover activated pathways and key upstream regulators associated with response to sorafenib. The composition of infiltrated immune cells in tumors was investigated using the CIBERSORTx algorithm. **Results:** The mean age was 58 ± 11 years with male predominance (81.8%), median CTP score was 5 (range, 5-8) and 57.6% of the patients switched to second-line chemotherapy mostly due to progression. The best response among 33 patients was complete response observed in 1 patient, partial response in two patients, stable disease in 12 patients while 18 patients showed disease progression. Gene signature (721 genes) associated with disease control (SD, PR, CR vs. no response) was derived using cluster analysis and was named as Korea University Sorafenib Response (KUSOR) gene signature. When applied on STORM cohort, KUSOR gene signature was able to predict patients who do not recur on adjuvant setting of sorafenib treatment after HCC resection or ablation with sensitivity of 91% and specificity of 74%. Gene network analysis by IPA revealed that patients who showed disease control were characterized by IL-6 and IL-1ß activation. In contrast, MYC was more activated in HCC tumors showing no benefit of the treatment, suggesting that MYC may trigger resistance of HCC cells to sorafenib. In addition, regulatory T cells (Treg cells) and M2 macrophage fractions were significantly higher in poor response group while the fraction of activated NK cells and CD4 cells were substantially higher in disease control group. **Conclusion:** Our study reveals that KUSOR gene signature identified patients who would show disease control when treated with sorafenib. MYC promotes hepatocarcinogenesis in chronic liver disease and overexpression is associated with poor response. It can also be inferred that poor response to sorafenib could be related immune evasion through overexpression of Treg cells and M2 macrophages in tumor microenvironment. Our study is in accord with previous studies where MYC activation was related to poor response to sorafenib indicating that combination therapy should be recommended in these patients.

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The following people have nothing to disclose: Yim Sun Young, Ji Hoon Kim, Yeon Seok Seo, Jong Eun Yeon, Young-Sun Lee, Taehyung Kim, Seong Hee Kang, Yoonseok Lee, Jong Su Kim, Chang Hee Jung

4705-C | GENOMICS REVEALS MOLECULAR CLASSES OF MICROVASCULAR INVASION IN HEPATOCELLULAR CARCINOMA

Jingwei Wei[1], Xue Yang[2], Hongjun Li[2] and Jie Tian[1], (1) Chinese Academy of Sciences, Institute of Automation, (2)Beijing Youan Hospital Capital Medical University, Beijing, China

Background: HCC is a prevalent malignancy with dismal prognosis. Microvascular invasion (MVI) is a crucial independent risk factor for early postoperative HCC recurrence. Identifying genetic subtypes of MVI could aid in developing targeted therapies to reduce recurrence risk. This study aimed to analyze genomics data to elucidate the molecular mechanism underlying MVI. **Methods:** This study enrolled 83 HCC patients from Beijing Youan Hospital. Paraffin-embedded tissue specimens (tumor and peritumoral tissue) underwent quality control and pathological interpretation. Whole exome sequencing (WES) involved DNA extraction, quality evaluation, library preparation, hybridization capture-based sequencing, and subsequent bioinformatics analysis (data preprocessing, mapping, evaluation, variant detection, somatic mutation calling, filtering, and annotation). **Results:** Among the 83 patients, 40 (48.19%) were MVI-positive, while 43 (51.81%) were MVI-negative. A total of 12,394 nonsynonymous somatic mutations were identified, predominantly missense mutations. The frequency of T > C transitions differed significantly between the MVI-positive and MVI-negative groups (20.64 ± 5.46 vs. 23.91 ± 6.39, p = 0.015). Notably, the gene FLG showed a significant difference in mutation frequency between the MVI-positive and MVI-negative groups (p = 0.017). Six driver genes were identified in the MVI-positive group: four tumor suppressor genes (TP53, ALB, TSC2, and BRD7) and two oncogenes (CTNNB1 and MMP17). The mutation frequency of TSC2 was significantly higher in the MVI-positive group (40%) than the MVI-negative group (16.3%) (p = 0.016). Similarly, BRD7 exhibited a significantly higher mutation frequency in the MVI-positive group (47.5%) compared to the MVI-negative group (23.3%) (p = 0.021). Additionally, significant differences were observed in the copy number deletions of AXIN1 and CDH1 between the MVI-positive and MVI-negative groups (p = 0.011 and 0.017). Univariate logistic regression analysis indicated that gene variations in BRD7, TSC2, AXIN1, and CDH1 were associated with MVI grouping. In multivariate logistic regression analysis, only gene variations in CDH1 remained significantly associated with MVI grouping (p = 0.007). **Conclusion:** This whole-exome analysis provides insights into the genetic characteristics of

MVI in HCC patients, contributing to the understanding of the underlying molecular and physiological mechanisms and serving as a basis for targeted treatments for MVI.

Disclosures: The following people have nothing to disclose: Jingwei Wei, Xue Yang, Hongjun Li, Jie Tian

4706-C | HIGHER PRE-TREATMENT HCV VIRAL LOAD RESETS POST-CURE INTERFERON-STIMULATED GENE (ISG) EXPRESSION IN THE PERIPHERAL BLOOD AND LIVER: EVIDENCE FOR INNATE IMMUNE TRAINING

Ang Cui[1,2], Bo Li[1,2], Jacinta A. Holmes[3,4], Michael S. Wallace[4], Anna L.K. Gonye[2,4], Christopher Oetheimer[4], Pierre Tonnerre[4], David Lieb[2], Aileen Ma[2], Kela Roberts[2], Marcos Damasio[4], Joelle Brown[4], Moshe Sade-Feldman[4], Jasneet Aneja[4], Eliana T. Epstein[4], Shadi Salloum[4], Arthur Y Kim[4], Georg M. Lauer[4], Nir Hacohen[2,4], Raymond T. Chung[4] and Nadia Alatrakchi[4], (1)Harvard University, (2)Broad Institute of MIT and Harvard, (3)St.Vincent's Hospital Melbourne, (4)Massachusetts General Hospital and Harvard Medical School

Background: Chronic viral infections, including HCV, involve a prolonged immune response and can potentially have a lasting effect on the host immune system even after the virus has been eliminated. While incomplete recovery of T cell functions has been characterized, less is known about alterations in innate immune architecture after HCV cure. Curative direct-acting antiviral (DAA) regimens, coupled with the availability of paired liver fine-needle aspirates (FNAs) and longitudinal peripheral blood mononuclear cells (PBMCs), provide a unique opportunity to assess the alteration of innate immune cell programs after the cure of chronic HCV infection. **Methods:** We studied 23 HCV patients before and after uniformly curative DAA treatment. ISG expression was quantified in liver myeloid cells using plate-based single-cell RNA-seq (scRNA-seq). ISG expression is also quantified in PBMCs using the NanoString technology (74 ISGs), with data being analyzed for gene expression relative to housekeeping genes. **Results:** Dynamic alterations in innate immune profiles were observed in both liver and blood after virus antigen removal, including an anticipated decrease in baseline elevated interferon-stimulated gene (ISG) expression during chronic HCV infection. We did not observe a direct correlation between ISG expression and viral load (VL) pre-treatment. However, we observed a directly inverse relationship between pre-treatment VL and post-cure ISG expression in myeloid cell types in the liver. This inverse relationship was reflected in the periphery as well, and patients with HCV VL > 800,000 IU/mL pre-DAA had significantly lower PBMC ISG levels 3 months post-DAA compared to patients with low pretreatment VL. **Conclusion:** Chronic high HCV viral load is strongly associated with a lower absolute level of basal ISG expression in the host post-cure. These findings support a resetting or training of innate immunity during chronic infection, which has implications for innate immune responses to future infections or disease development.

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4707-C | INCREASED ELECTROSTATIC COMPLEMENTARITY BETWEEN PRIMARY TUMOR ADAPTIVE IMMUNE RECEPTOR CDR3 AND HEPATITIS C VIRUS EPITOPES CORRELATES WITH IMPROVED PATIENT SURVIVAL AND DIFFERENTIAL GENE EXPRESSION IN HEPATOCELLULAR CARCINOMA

Joanna Song[1], Andrea Chobrutskiy[2], Boris Chobrutskiy[2], Konrad Cios[1], Taha Huda[1], Rachel Eakins[1] and George Blanck[1,3], (1)University of South Florida Morsani of Medicine, (2)Oregon Health and Science University Hospital, (3)H. Lee Moffitt Cancer Center and Research Institute

Background: Adaptive immune receptors (AIRs), e.g., immunoglobulins (IGs) and T-cell receptors (TCRs), have been identified in the tumor environment of many cancers. However, their features, such as the complementarity determining region-3 (CDR3), are not well studied in hepatocellular carcinoma (HCC), especially in the context of established contributors of HCC, such as chronic hepatitis C virus (HCV) infection. This project aims to better understand AIRs present in the HCC microenvironment and how CDR3s specificity to HCV antigens correlates with clinical features, including patient survival and gene expression. **Methods:** AIR recombination reads were recovered from primary tumor sample whole exome sequences (WXS) and RNA sequences (RNAseq) of 377 HCC cases in The Cancer Genome Atlas Liver Hepatocellular Carcinoma (TCGA-LIHC) dataset and WXS of 89 HCC cases in the Human Genome Sequencing Center at Baylor College of Medicine (HGSC-BCM) HCC dataset. Corresponding TCGA-LIHC TCR beta chain (TRB) and IG heavy chain (IGH) CDR3s were identified and used to compute electrostatic-based complementarity scores (CSs) with known HCV epitopes from the Immune Epitope Database. Cases were stratified by CSs to study association with overall (OS) and disease-free (DFS) survival distinctions via Kaplan-Meier analyses and gene expression distinctions via Pearson's correlation. CS calculation algorithm was benchmarked by comparing CSs produced from HCV-positive and HCV-negative cases in HGSC-BCM. **Results:** A 3:1 ratio of IG:TCR was observed in both the 189 and 106 recombination reads recovered from TCGA-LIHC and HGSC-BCM, respectively. Higher CSs between TCGA-LIHC TRB CDR3s and HCV epitope HCV*71871 correlated with increased DFS probabilities for CDR3s derived from WXS ($p = 0.0296$) and RNAseq ($p = 0.0327$). CSs from these two sets of CDR3s were also inversely associated with the expression of proliferation-related gene b-related factor 2 (BFR2) (WXS $p = 0.00718$, $R = -0.595$; RNAseq $p = 0.00466$, $R = -0.190$). Greater expression of BRF2 was linked to decreased DFS probabilities via KM analysis in HCC cases independent of CS ($p = 0.0316$). Higher CSs between TCGA-LIHC HCC IGH CDR3s and HCV epitope HCV*13458 as well as increased OS probabilities were observed for both WXS ($p = 0.0127$) and RNAseq ($p = 0.0189$) sources of CDR3s. HCV-positive HCC patients in HGSC-BCM showed greater CSs TRB CDR3s and HCV*71871 ($p = 0.0488$) as well as IGH CDR3s and HCV*13458 ($p = 0.0599$). These results indicated a predominantly humoral immune response to HCC from AIR recombination reads obtained from two independent sources. Increased complementarity of HCC-resident AIR CDR3s with two HCV epitopes were in correlation with better survival probabilities in HCC cases. **Conclusion:** This study demonstrates the potential use of CDR3 sequences as biomarkers for HCC patient stratification and as guides for therapeutic development.

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4708-C | LONG-TERM PROGNOSTIC MODEL OF DECOMPENSATED CIRRHOSIS BASED ON MULTIMODAL CT IMAGING DYNAMIC LIVER VOLUME CHANGES

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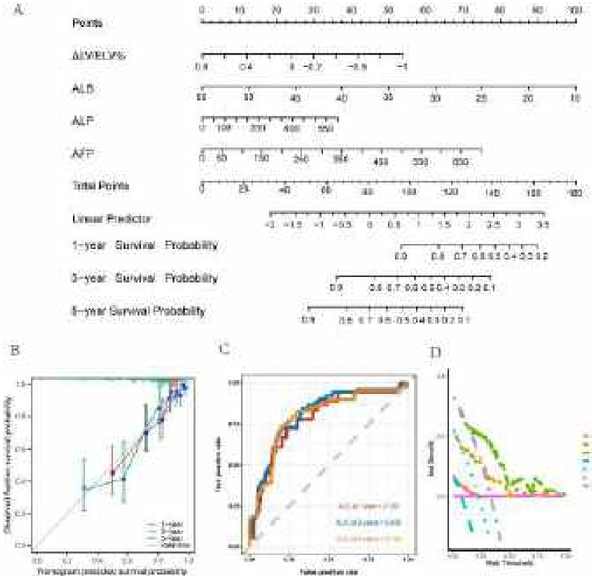
Background: Liver volume directly reflects liver capacity and the number of liver cells macroscopically and is an essential quantitative index to evaluate liver reserve function. During the progression of cirrhosis, alterations occur in the morphology and dimensions of the liver, with the liver volume remaining stable or exhibiting a relatively increase in early stages, followed by a reduction in volume during advanced stages, and a gradual decline in the liver's reserve function. Nevertheless, clinical implications of the dynamic changes in liver volume remains indeterminate. The objective of this study is to clarify the role of liver volume changes in the long-term prognosis of patients with decompensated cirrhosis. **Methods:** This retrospective study involved the analysis of 282 patients diagnosed with decompensated cirrhosis, with a median age of 54 years. The study utilized two abdominal computed tomography (CT) scans, conducted at baseline and at a 1-2-year follow-up, to measure liver volume and chest width, respectively, in order to calculate standard liver volume (ELV) and the rate of change of liver volume ratio (ΔLV/ELV%) over the course of 1 to 2 years. A COX regression analysis was employed to construct a prognosis model, and a normogram was established to further evaluate the results. The prognostic model's predictive efficacy was evaluated using the area under the subject operating characteristic curve (AUC), sensitivity, and specificity. The model's accuracy was assessed using the calibration curve, while the clinical practicability was evaluated through decision curve analysis (DCA). **Results:** The results of the multivariate COX regression analysis indicate that ΔLV/ELV% (OR:0.318,95% CI: 0.111-0.909) and albumin(ALB) (OR:0.931, 95% CI: 0.891-0.973) exhibit a protective effect on the prognosis of patients with decompensated cirrhosis, whereas alkaline phosphatase(AFP) (OR:1.004, 95% CI: 1.001-1.007) and alpha-fetoprotein(AFP) (OR:1.005, 95% CI: 1.001-1.009) are associated with an increased risk of poor prognosis in such patients, suggesting the possibility of death competition in HCC. Prognostic models were developed based on the aforementioned factors, namely ΔLV/ELV %, ALB, ALP, and AFP, with corresponding C-indexes of 0.786(95%CI :0.761-0.810) and 0.752(95%CI 0.725-0.780). The LAAA method was employed to predict the AUC for 1-year, 3-year, and 5-year survival rates of decompensated patients, yielding values of 0.783, 0.806, and 0.796, respectively. The correction curve exhibits proximity to the ideal reference line, and the DCA curve demonstrates a significant improvement in the net benefit of the model. **Conclusion:** Dynamic liver volume change is closely related to the long-term prognosis of decompensated cirrhosis patients. The LAAA model, which is based on the Δ LV/ELV%, is deemed a reliable predictor of the long-term prognosis of patients with decompensated cirrhosis.



Disclosures: The following people have nothing to disclose: Qijuan Zang, Chengbin Zhu, Juan Li, Siyi Liu, Yingren Zhao, Yingli He

4709-C | MAXIMIZING INSIGHTS FROM WHOLE EXOME SEQUENCING TO ADVANCE DIAGNOSIS OF LIVER DISEASE

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Background: Chronic liver disease (CLD) is the 11th leading cause of death worldwide. Up to 25% of patients with CLD have an unknown cause, and our group has previously shown that whole exome sequencing (WES) can provide a diagnosis in over 25% of these cases. Hence, approximately two-thirds of these patients remain undiagnosed. Thus, we hypothesized that annual re-analysis of undiagnosed cases, alongside modernizing of our WES pipeline would increase diagnostic rate. **Methods:** A new WES pipeline was developed by aligning individual sequences to the Human Pangenome Reference Consortium v1 pangenome and surjected to the linear GRCh38. Genetic variants were called with DeepVariant, and annotated with Annovar, Variant Effect Predictor, and SnpEff, incorporating novel pathogenicity prediction tools. In addition, we include annotation for liver cell type-specific gene expression extracted from our group's liver cell atlas. This WES pipeline also incorporates rare-variant phasing with SHAPEIT5, so allele-specific inheritance patterns for candidate compound heterozygous variants can be predicted. This pipeline was benchmarked against our standard GATK-based pipeline using a subset of WES samples from patients with liver disease, with a diverse set of causative genes and inheritance patterns. **Results:** This new WES pipeline recapitulated all previously identified disease-causing variants. New pathogenicity scoring tools allowed for better characterization of genetic variants. Specifically, SpliceAI identified cryptic splicing variants previously annotated as synonymous. Additionally, rare-variant phasing reliably predicted compound heterozygous variants in individual's for whom parental sequences are unavailable. This pipeline also recurrently identified a few homozygous variants in multiple patients, the majority of which appear in regions poorly covered in large databases, suggesting that these variants are systematically missed when using older analytical tools. Lastly, our re-analysis approach also uncovered a patient with a novel disease caused by recessive mutations in *TULP3*. **Conclusion:** An ancestrally-diverse pangenomic reference successfully identifies liver disease-causing variants. Re-analysis of WES data from patients with undiagnosed liver disease curtails the number of idiopathic cases, and its

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

consideration should be incorporated in the practice of genomic medicine in hepatology.

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Disclosure information not available at the time of publication: Silvia M. Vilarinho

f 4710-C | PNPLA3 GENOTYPE IS ASSOCIATED WITH RISK OF HCC BUT NOT DECOMPENSATION IN PATIENTS WITH COMPENSATED CIRRHOSIS

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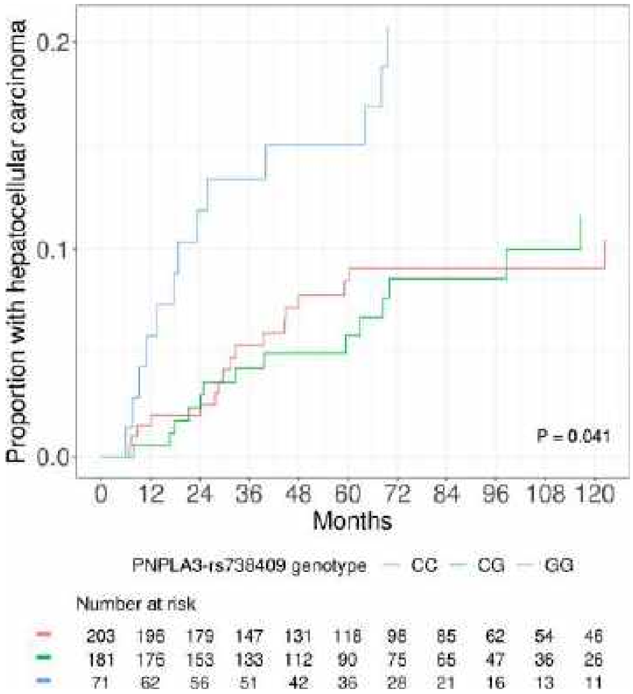
Background: The *PNPLA3*-rs738409-G, *TM6SF2*-rs58542926-T, and *HSD17B13*-rs6834314-A polymorphisms have been associated with cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). However, whether they remain associated with HCC and decompensation in people who already have cirrhosis remains unclear, which limits clinical utility of genetics in risk stratification as HCC is uncommon in the absence of cirrhosis. We aimed to characterize the effects of PNPLA*3*, *TM6SF2*, and *HSD17B13* genotype on hepatic decompensation, hepatic cellular carcinoma (HCC), and transplant-free survival in patients with baseline compensated cirrhosis. **Methods:** We conducted a single-center retrospective study of patients in the Michigan Genomics Initiative. Participants underwent genotyping on an Illumina HumanCoreExome v.12.1 array. Patients were screened for cirrhosis based on diagnosis codes, transient elastography, imaging, endoscopic evidence of varices, or liver biopsy, followed by manual chart review to verify diagnosis of cirrhosis and determine development of decompensation, HCC, death, and liver transplant. The primary predictors were *PNPLA3*, *TM6SF2*, and *HSD17B13* genotypes. Primary outcomes were either decompensation, HCC, or the combined endpoint of liver transplant or death. We conducted competing-risk Fine-Gray analyses with age, sex, etiology, and genetic principal components as covariates with a 180 day landmark to evaluate effects of the predictors and calculate cumulative incidence. **Results:** We identified 655 patients with baseline compensated cirrhosis. Median age was 58 years, 43% were female, and 93% were Caucasian. Mean follow-up time was 4.5 years. 16% had viral hepatitis, 17% had alcoholic liver disease, and 57% had non-viral non-alcoholic liver disease, and the remaining had mixed etiologies. During follow-up, 49% of patients developed decompensation, 10% developed HCC, 8% underwent liver transplant, and 28% died. *PNPLA3*-rs738409-G genotype was associated with risk of incident HCC: adjusted hazard ratio (aHR) 2.92 [1.42-5.99], $p = 0.0035$ for GG vs. CC genotype. Five-year cumulative incidence of HCC was higher in *PNPLA3*-rs738409-GG carriers than -CC/-CG carriers: 14.1% (7.2-23.3%) vs. 6.3% (4.1-9.0%), $p = 0.0097$. *PNPLA3* genotype was not associated with decompensation or the combined endpoint of liver transplant or death. *TM6SF2* and *HSD17B13* genotypes were not associated with decompensation or HCC in this cohort ($p > 0.05$ for both). **Conclusion:** The *PNPLA3*-rs738409-G allele is associated with increased risk of HCC among patients with baseline compensated cirrhosis. People with cirrhosis and *PNPLA3*-rs738409-GG genotype may warrant more intensive HCC surveillance.



Disclosures: Vincent Chen – KOWA: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AstraZeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;

The following people have nothing to disclose: Esteban Urias, Karn Wijarnpreecha

Disclosure information not available at the time of publication: Nicholas Tedesco

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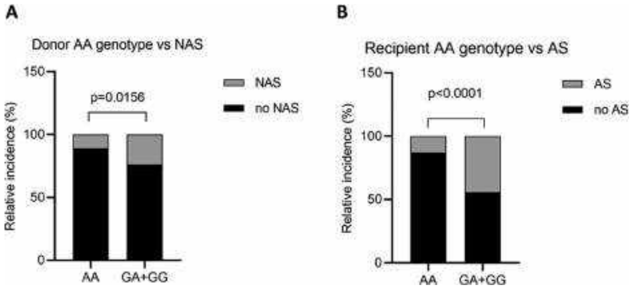
Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

4711-C | PROTECTIVE ROLE OF A GLYPICAN-6 POLYMORPHISM IN BILE DUCT STRICTURE FORMATION AFTER LIVER TRANSPLANTATION

Ruslan A. Mammadov, Jasmijn W. Selten, Monique M.A. Verstegen, Floris J.M. Roos, Henk P. Roest, Cornelia J. Verhoeven, Herold J. Metselaar, Maikel P. Peppelenbosch, Jan N.M. IJzermans and Luc J.W. Van Der Laan, Erasmus MC

Background: Bile duct strictures both non-anastomotic and anastomotic are one of the most common complications after liver transplantation, with an incidence of approximately 30%. The origin of these strictures seems multi-factorial, but damage to the bile duct stem cell niche is found to play an important role. Glypican-6 (*GPC-6*) has recently been identified as an stem cell niche factor important for stimulation of the Wnt-signaling pathway. However, the role of GPC-6 has not been established in bile duct strictures post transplantation. **Methods:** A retrospective, PCR-based, SNP analysis was performed for GPC-6 status on sequential collected blood samples from donors and recipients of a liver transplantation between 1989 and 2011. PSC patients were excluded from the analysis. Statistical analysis was performed using SPSS statistics 25 (SPSS Inc., Chicago, IL, USA). Prediction analyses were performed through backward stepwise Cox proportional hazards regression and expressed as the hazard ratio (HR). **Results:** GPC-6 status could be identified in 299 recipients, 291 donors and 197 paired donor-recipient combinations. Of the 299 transplantation recipients, biliary strictures occurred in 101 grafts (33%). Distribution of the *GPC-6* polymorphism did not differ between the recipient (AA (n = 47) vs AG/GG (n = 252)) and donor (AA (n = 46) vs AG/GG (n = 245)) (p = 0.818). However, donor *GPC-6* AA genotype was identified as a protective factor for non-anastomotic biliary strictures (p = 0.016) but not for anastomotic strictures (Figure 1A). Interestingly, *GPC-6* AA genotype also played a strong protective role against anastomotic strictures but only for recipients (p < 0.0001), and was not significant in patients with non-anastomotic strictures (Figure 1B). Cumulative incidence of overall biliary complications was significantly lower in the recipients who received a graft from donor AA genotype vs on time (p = 0.001; Cox reg = 0.004) as well as the effect of GPC6 AA genotype on graft survival (p = 0.045; Cox reg = 0.04). Multivariate analysis with other known risk factors for bile duct strictures showed *GPC-6* AG/GG genotype as an independent risk factor for biliary strictures (p = 0.049). **Conclusion:** The *GPC-6* rs9524260 AA genotype is a protective factor for the development of bile duct strictures after liver transplantation in non-PSC patients.



Disclosures: The following people have nothing to disclose: Ruslan A. Mammadov, Jasmijn W. Selten, Monique M.A. Verstegen, Floris J.M. Roos, Henk P. Roest, Cornelia J. Verhoeven, Herold J. Metselaar, Maikel P. Peppelenbosch, Jan N.M. IJzermans, Luc J.W. Van Der Laan

f 4712-C | RECAPITULATING HEPATOCELLULAR CARCINOMA'S COMPLEX BIOLOGY AND DIVERSE TREATMENT RESPONSE IN A PATIENT-DERIVED MICROFLUIDIC MODEL

Orsola Mocellin[1], Abbie Robinson[1], Aleksandra Olczyk[1], Stephane Treillard[1], Thomas Olivier[1], Chee P. Ng[1], Jeroen Heijmans[1], Arthur Stok[1], Gilles Van Tinderen[2], Monique M.A. Verstegen[2], Flavio Bonanini[1], Sebastian J. Trietsch[1], Henriëtte L. Lanz[1], Paul Vulto[1], Jos Joore[1] and Karla Queiroz[1], (1)Mimetas, (2)Erasmus MC

Background: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and is closely associated with progressive stages of liver diseases. Its transformation, survival, progression and metastasis have been associated with regulation mechanisms orchestrated by the tumor stroma. Patient differences in tumor composition and cellular signaling are reflected in the diversity of therapy response. Hence, comprehensive in vitro models that capture patient-specific tumor and stromal components are necessary to elucidate and evaluate anticancer therapy. **Methods:** Patient-derived dissociated HCC cells from eight different patients were combined with tumor-derived fibroblasts and endothelial cells within a microfluidic setup comprising 64 parallel chips in a microtiter plate format. Cultures were challenged with an individual or combinatorial treatment from a panel of tool compounds for 72 hours in an automated setup. We used immunofluorescence and high content confocal imaging to assess the structural and biological interaction between cancer cells and the associated stroma. Viability assessment, artificial intelligence-based vascular morphology characterization and multiplexed chemokine/cytokine release measurements were used to elucidate patient and drug-dependent effects of single or combinatorial treatments. **Results:**

Cellular interaction within the microfluidic platform led to a vascularized tumor construct, with hepatocellular carcinoma aggregates being enveloped and traversed by a lumenized and interconnected vascular plexus, in association with tumor-derived fibroblasts. Compound treatment led to profound differences across the tested parameters, indicating different anticancer effects in conjunction with the biological diversity of the patient material. Finally, morphological assessment revealed distinct compound-induced effects on the tumor's vascular organization. **Conclusion:** We present a vascularized patient-derived HCC model that includes relevant cellular players of the tumor microenvironment found in vivo. These co-cultures are highly suitable for studying specific cell types as well as patient-specific responses. We envision that this system has the potential to provide a platform for understanding the interplay between different cell types present in hepatocellular carcinomas, with sufficient scalability ease of use for industrial and clinical implementation.

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Paul Vulto – Mimetas: Executive role , Yes, No;

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4713-C | TARGETING FGFR2-FUSIONS WITH ANTIBODY THERAPEUTICS IN INTRAHEPATIC CHOLANGIOCARCINOMA

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Background: Translocations involving the Fibroblast Growth Factor Receptor 2 (FGFR2) are found in 10-15% of intrahepatic cholangiocarcinoma. Treatment of these patients with FGFR1-3 kinase inhibitors, induces tumor regressions, though response rate appears limited due to the acquired resistance or to suboptimal dosing which is limited by drug adverse effects. Therefore, therapeutics that drive activity specifically towards FGFR2, such as antibody drugs, are needed to enhance drug efficacy and reduce adverse effects. To this end, we first 1) ask whether the extracellular domain (ECD) of FGFR2-fusion is functional, and then 2) we sought to investigate if antibodies against the ECD could perturb the growth of FGFR2 fusion transformed cells. **Methods:** To determine whether the ECD is functional and important for transformation of FGFR2-BICC1 fusion, D1, D2, D3, and D2-3 deletion FGFR2-BICC1 constructs were generated. To evaluate the roles of ECD in transformation capacity and growth of FGFR2-BICC1, we utilized focus formation and viability assays respectively in FGFR2-BICC1 expressing NIH3T3 cell line. To investigate the roles of ECD in FGFR2-fusion receptor dimerization, we developed a NanoBiT assay, in which the ECD deletion FGFR2-BICC1 constructs were coupled to LgBiT or SmBiT fragments and luminescence can be detected upon receptor dimerization. FGFR2 downstream signaling was investigated via immunoblotting for phosphorylated FGFR, FRS, AKT, MEK, and ERK. Six FGFR2 specific antibodies were selected and produced in the Expi293T system. We validated the antibody binding affinities and cell viability assays were performed using CellTiter-Glo to determine the impact of antibodies on FGFR2 fusion transformed cells. **Results:** We have shown that D1, D2, D3, and D2-3 deleted FGFR2-BICC1 ECD decreased growth and transformation of FGFR2 fusion driven cells. Proliferation of FGFR-BICC1 expressing cells was further stimulated by FGF10 ligand. Using NanoBiT assay, we have shown that D2, D3, and D2-3 deletions decreased dimerization as compared to the FL FGFR2-BICC1. Interestingly, D1 deletion increased receptor dimerization. Consistent with dimerization results, D1 deleted FGFR2-BICC1 showed increased downstream signaling while D2, D3, and D2-3 deleted FGFR2-BICC1 had decreased phosphorylation of FGFR2 downstream effectors. Importantly, antibodies against FGFR2 ECD inhibited FGFR2-fusion driven growth and transformation. **Conclusion:** Here, we have shown that ECD of FGFR2 plays important roles in cellular growth and survival of FGFR2-fusion driven cells and is necessary for full transformation of FGFR2 fusions. Moreover, antibodies against FGFR2 ECD had activities in FGFR2-fusion driven growth, demonstrating that the antibody-based therapeutics may form the basis for a new treatment strategy that is more specific, has less side effects, and improves ICC treatment outcome.

Disclosures: The following people have nothing to disclose: Saireudee Chaturantabut, Sydney Oliver

Disclosure information not available at the time of publication: Dennie T. Federick, John Kim, Foxy Robinson, William R. Sellers

f 4714-C | TARGETING NASH AND HCC THROUGH DIVERSION OF TGF-BETA SIGNALING★

Xiaochun Yang[1], Xiyan Xiang[1], Krishanu Bhowmick[1], Kazufumi Ohshiro[1], Kirti Shetty[2], Nancy R. Gough[1],

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

Herbert Yu[3], Linda L. Wong[4], Chuong T Tran[5], Xianghong Jasmine Zhou[6], Sobia Zaidi[7], Nyasha Chambwe[8], Sanjaya Kumar Satapathy[9], James M. Crawford[10], Gregory M Grimaldi[11], Vikas Kundra[12], Patricia S. Latham[13], Richard Dima[14], Fellanza Cacaj[1], Anil K Vegesna[1], Sun Jung Kim[8], Christina Brennan[14], Kevin J Tracey[15], Sangeeta Chavan[16], Gulru Sharifova[17], Hai Huang[18], Srinivasan Dasarathy[19], Richard L Amdur[20] and Lopa Mishra[1], (1)The Institute for Bioelectronic Medicine, Feinstein Institutes for Medical Research, & Cold Spring Harbor Laboratory, Department of Medicine, Division of Gastroenterology and Hepatology, Northwell Health, Manhasset, New York, USA., (2) Department of Hepatology and Liver Transplantation, the University of Maryland, School of Medicine, Baltimore, MD, USA., (3)Department of Epidemiology, the University of Hawaii Cancer Center, Honolulu, HI, USA, (4) Department of Surgery, University of Hawaii, Honolulu, HI, USA., (5)Department of Medicine, University of Hawaii, Honolulu, HI, USA., (6)Department of Pathology and Laboratory Medicine, Ronald Reagan Medical Center, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA., (7) Department of Biomedical Sciences, Heritage College of Osteopathic Medicine, Ohio University, Athens, OH, USA, (8)The Institute of Molecular Medicine, Feinstein Institutes for Medical Research, Manhasset, NY, USA., (9)Division of Hepatology, Northwell Health, and Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA., (10)Department of Pathology and Laboratory Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA., (11)Department of Radiology, Northwell Health System, the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Manhasset, NY, USA., (12)Oncologic Imaging, University of Maryland and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA, (13) Department of Pathology, George Washington University, Washington, DC, USA., (14)Office of Clinical Research, Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, USA., (15)Center for Biomedical Science and Bioelectronic Medicine, Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, (16)Laboratory of Biomedical Science, Institute of Bioelectronic Medicine, Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, USA., (17) Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, (18)Center for Immunology and Inflammation, Feinstein Institutes for Medical Research, Manhasset, NY, (19) Cleveland Clinic Foundation, (20)Quantitative Intelligence Unit, the Institutes for Health Systems Science & Bioelectronic Medicine, the Feinstein Institutes for Medical Research, Northwell Health, NY, USA.

Background: Hepatocellular carcinoma (HCC) remains lethal rising in parallel with risk factors such as alcohol-induced cirrhosis and non-alcoholic steatohepatitis (NASH). Nearly 40% of HCCs have alterations in the TGF-β pathway. Yet, context dependent TGF-β tumor suppression or tumor promotion remain poorly understood. ALDH2, a key enzyme that metabolizes and clears both lipid end products (e.g., 4-Hydroxynonenal) and alcohol (e.g., Acetaldehyde) activity is markedly reduced in HCC and ~560 million people globally. We reported that TGF-β/SPTBN1/SMAD3 mutant mice develop HCC with high ALDH2 levels and altered microbiomes (*JCI 2016, 126(2):527-542*). Recently, we found that liver-specific knockout of a TGF-β/SMAD adaptor βII-spectrin ($SPTBN1^{LSKO)}$, blocks NASH and HCC, and βII-spectrin siRNA reverses NASH in human NASH 3D cultures (*Sci Transl Med 2021, 13:624*). We therefore sought to first identify new biomarkers that predicted HCC in NASH-cirrhotic patients, by capturing ongoing biology in the liver through the TGF-β pathway and next examined whether βII-spectrin modulates ALDH2 in NASH and HCC. **Methods:** We examined 7,000 serum proteins in 427 patients with cirrhosis, conducted human genomic studies, analyzed animal models targeting a SMAD3 adaptor SPTBN1 intercrossed with ALDH2 knockouts, performed mechanistic analyses, microbiome, and snRNA-seq analyses. **Results:** 1. We identified a TGF-β regulated serum protein biomarker panel that could potentially predict progression of cirrhosis to cancer. 2. SPTBN1intercrosses with a key enzyme in ALDH2 deficient mice (ASKO) develop NASH, metabolic syndrome (MetS) and cancer. ASKO mice showed sex difference-based decreases in anti-inflammatory species microbiome patterns and significantly decreased colonic Tregs. snRNA-seq analysis revealed disrupted TGF-β signaling in ASKO mice. 3. SPTBN1 siRNA blocked NASH and diet/chemical induced HCC in the mutant mice with restoration to tumor suppressor TGF-β signaling. In addition, SPTBN1 siRNA-mediated therapy in the mouse model and in a 3D human NASH coculture system restored disrupted TGF-β signaling observed in ASKO mice to a normal phenotype. **Conclusion:** Our work provides an important platform from large-scale genomic studies to animal models to signaling studies for analyzing MetS and NASH-liver conditions that are linked to altered gut health. Furthermore, our data suggest that SPTBN1, an intrinsically disordered protein is a potential therapeutic target for preventing or reversing NASH.

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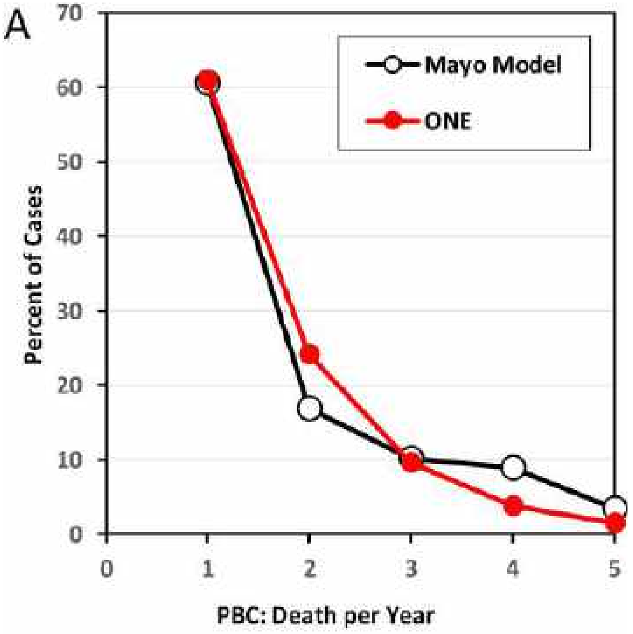
Disclosure information not available at the time of publication: Xianghong Jasmine Zhou, James M.

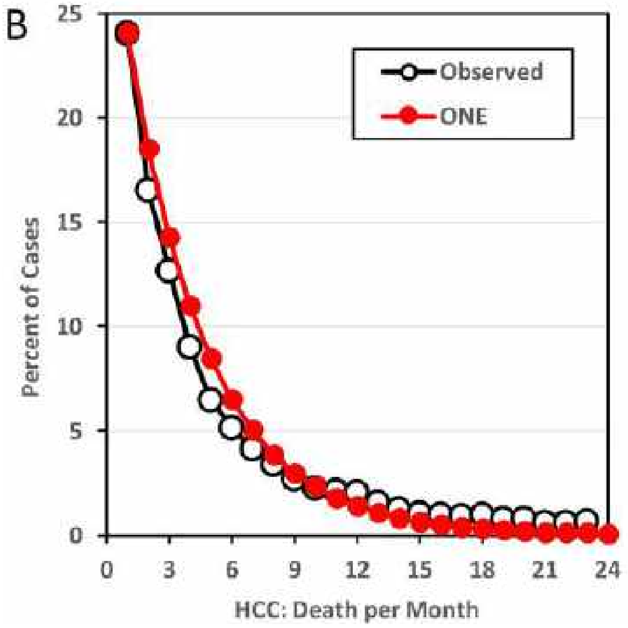
Crawford, Gregory M Grimaldi, Vikas Kundra, Christina Brennan, Kevin J Tracey, Sangeeta Chavan

4715-C | THE POINT OF NO RETURN IN CHRONIC LIVER DISEASES: WHEN RECOVERY OR CURE ARE IMPOSSIBLE

Piet De Groen, University of Minnesota

Background: Despite an unusual ability to regenerate, at some point in time a chronic, progressive liver disease becomes irreversible. At this stage recovery or cure is impossible and death is inevitable. Recent publications pose that a constant rate of somatic mutations is the cause of all intrinsic human diseases, including Primary Biliary Cholangitis (PBC) and Hepatocellular Cancer (HCC; Front Astron Space Sci 9:1067491). Diseases characterized by multiple somatic mutations show a tapering exponential population distribution where one disease event, e.g., one polyp, is common and many events, e.g., 10 polyps, are rare. Hypothesis: A defined period of survival can be regarded as a disease event representing cumulative germline and somatic mutations. Therefore, when advanced PBC and HCC are not or ineffectively treated, survival adheres to an exponential model as previously described for colorectal and pancreas cancer (Am J Gastroenterol 2020;115:s43). The same exponential model was shown to predict distribution of additional autoimmune diseases in PBC (Hepatology 2022;76:S1493). Aim: To determine whether mortality of advanced PBC and HCC adheres to an exponential model. **Methods**: To estimate untreated PBC mortality, the original Mayo Model from 1989 based on 418 patients (NEJM 1989;30:1709) was used; less than half of the patients had been treated with d-penicillamine which had no effect on survival. To estimate untreated HCC survival, SEER Medicare data from either untreated (73%) or sorafenib treated (23%) patients (N = 1532) were used; sorafenib did not alter mortality in this patient cohort (Oncologist 2016;21:1113). The exponential model consisted of the omnipresent neoplasia equations (ONE) as published. Mayo model and observed HCC data were matched at the first observation event, 1 year for the Mayo Model and 1 month for the HCC observed data. Averages over 3-5 months for each 1-month mortality estimate were applied to observed HCC data to eliminate outliers and short-term fluctuation. The Pearson correlation coefficient (PCC) was determined. **Results**: The ONE model agreed with the Mayo Model matched at the 1-year mortality time point at year 1, 3 and 5 (see Fig 1A; PCC = 0.97). The match between ONE and HCC observed data was nearly perfect (see Fig 1B; PCC = 0.99). **Conclusion**: ONE-modeled data, matched to early mortality, closely predicts observed mortality data of untreated liver diseases. As ONE assumes a constant rate of somatic mutations in all cells, a specific liver prediction model based on a limited panel of liver-derived markers such as the MELD, especially in the presence of attempts at treatment, can never apply to all types of liver disease. Moreover, the ONE model suggests that a single point of no return, i.e., the threshold beyond which recovery or cure are impossible, can never be identified as any combination of germline and somatic mutations can lead to death.





Disclosures: The following people have nothing to disclose: Piet De Groen

1259-C | BULEVIRTIDE MONOTHERAPY IN PATIENTS WITH NON-COMPENSATED LIVER CIRRHOSIS DUE TO HEPATITIS D

Natalia Alexandrovna Barsukova[1], Pavel Bogomolov[2], Alexey O. Buyeverov[1,3], Sergei Koblov[1], Ekaterina Isaeva[1], Michail Vladislavovich Kalashnikov[1], Nadezhda Anatolyevna Shub[4] and Maria Valeryevna Arapova[4], (1)Moscow Regional Research and Clinical Institute of M. F. Vladimirsky, (2)State Budgetary Institution of Health Care of Moscow Region "Moscow Regional Research Clinical Institute after M.F. Vladimirsky", (3)Sechenov First Moscow State Medical University (Sechenov university), (4)Center Targetnoy Therapii LLC

Background: Bulevirtide (BLV) is a first-in-class entry inhibitor approved as therapy for patients with chronic hepatitis D (CHD). Efficacy and safety of BLV in patients with non-compensated HDV liver cirrhosis has not been explored. **Methods:** Patients received antiviral therapy with Bulevirtide 2 mg per day subcutaneously for 24 weeks. 4 patients with non-compensated liver cirrhosis (1 man, 3 women) underwent clinical, laboratory and instrumental examination. The average age of patients was 42.5 years (from 32 to 52 y). During the objective examination the presence of ascites and hemorrhagic syndrome and encephalopathy was assessed. The laboratory and instrumental examination included routine blood tests, PCR of HBV DNA and HDV RNA, ultrasound examination and GI endoscopy. **Results:** None of the patients had previously received antiviral therapy for hepatitis D. All patients had been treated with nucleot(s)ide analogues for at least 12 months (3 patients tenofovir, 1 patient entecavir). Initially, non-compensated HDV-liver cirrhosis was diagnosed in all patients. 2 patients were treated BLV monotherapy in low accelerated dose regimen (LADR) mode (2 mg x 3 times a week subcutaneously). The remaining patients were treated BLV in full dose (2 mg per day subcutaneously). After 24 weeks of BLV monotherapy improvement were seen of Child-Pugh scores in all patients, while liver function was compensated in two. Two patients had a decrease from 9 to 7 points on the Child Pugh scale. Two had an improvement to recompensation from 7 to 6 points on the Child Pugh scale. ALT activity decreased to normal in 2 patients. In one patient decrease the level of HDV RNA more than 2 lg from the baseline was registered. Three patients had a stable platelet count or an increase from the initial level, only one had a slightly decreased platelet count. No one was found to have focal liver formations and an increase in the level of alphafetoprotein. In all patients, the control GI endoscopy revealed a decrease in the diameter of the esophageal veins, but one required endoscopic ligation. One patient was found to have non-occlusive portal vein thrombosis during BLV treatment, which required oral anticoagulants. Bulevirtide treatment was well tolerated, no serious adverse events were registrated. **Conclusion:** BLV monotherapy, including LADR, can use in patients with non-compensated HDV liver cirrhosis and may improves liver function despite the absence of viral response.

Disclosures: The following people have nothing to disclose: Natalia Alexandrovna Barsukova, Pavel Bogomolov, Alexey O. Buyeverov, Sergei Koblov, Ekaterina Isaeva, Michail Vladislavovich Kalashnikov, Nadezhda Anatolyevna Shub, Maria Valeryevna Arapova

1526-C | A COMPOSITE SCORE CONSISTING OF BOTH CCCDNA TRANSCRIPTIONAL ACTIVITY AND IMMUNOLOGICAL MARKERS ACCURATELY REFINES HBEAG-NEGATIVE CHRONIC HEPATITIS B PHASES

Ivana Carey[1], Mark Anderson[2], James Lok[1], Christiana Moigboi[1], Gavin A. Cloherty[2], Geoffrey M. Dusheiko[1] and K. Agarwal[1], (1)King's College Hospital, (2)Abbott Laboratories, IL

Background: HBeAg-negative chronic hepatitis B (CHB) is a variable disease with phases determined by HBV DNA and ALT levels: 'infection' phase (HBV DNA <2000 IU/ml & normal ALT) vs. 'hepatitis' phase (HBV DNA >20000 IU/ml & elevated ALT). Over 30% HBeAg-negative patients fall within a 'grey zone' (HBV DNA 2000–20000 IU/ml & normal ALT). Novel serological markers of cccDNA transcriptional activity: hepatitis B core-related antigens (HBcrAg) and pre-genomic HBV RNA (pgRNA) are relevant in separating HBeAg-negative patients ('infection' vs. 'hepatitis') and so reducing the number of indeterminate 'grey zone' patients. As CHB is an immune-mediated disease, the pro-inflammatory chemokine CXCL10 and soluble (s) PD-1 (exhaustion marker) levels may refine HBeAg-negative phases further. Combining these serum markers to create a composite score may increase our ability to stratify HBeAg-negative phases. **Aim:** To compare serological, virological and immunological markers in HBeAg-negative patients and determine whether these markers are able to refine HBeAg-negative CHB phases based on HBV DNA & ALT levels ('infection', 'grey zone' & 'hepatitis') and create a composite score. **Methods:** Serum samples from a cross-sectional cohort of 562 untreated HBeAg-negative patients (median age 38 y, 204 males) were tested for routine diagnostic markers: HBV DNA (Roche TaqMan, IU/ml), quantHBsAg (Abbott Architect, IU/ml), biochemical (ALT, IU/L) and further tests were performed for the biomarkers: HBcrAg (CLEIA Fujirebio, $\log_{10}$U/ml), pgRNA (Abbott Diagnostics dual-target real-time-PCR assay, LLQD = 0.4 $\log_{10}$U/ml), CXCL10 and sPD-1 serum levels by ELISA [pg/ml]. Patients were divided into 3 groups based on HBV DNA levels: 'infection' (< 2000 IU/ml), 'grey zone' (2000-20000 IU/ml) and 'hepatitis' (> 20000 IU/ml) phases. The results were compared by AUC-ROC, univariate and multivariate analysis. The scoring system for the composite score was calculated using only markers with AUC-ROC > 0.7. **Results:** Patients in 'infection' phase (n = 293) have lowest levels in all markers in contrast to 'grey zone' (n = 215) and 'hepatitis' (n = 54) phase patients by univariate analysis (Figure). However, only HBV DNA, HBcrAg, pgRNA, CXCL10 and sPD-1 levels differed between groups by multivariate and AUC-ROC analysis (Figure). The cut offs for the composite score were: HBcrAg (< 3 $\log_{10}$U/ml), pgRNA (< 0.4 $\log_{10}$U/ml), CXCL10 (< 150 pg/ml) and sPD-1 <150 pg/ml). The composite score was able to stratify 'grey zone' phase patients with greater accuracy than individual markers (AUC-ROC = 0.81). **Conclusion:** The combination of novel cccDNA transcriptional activity biomarkers (HBcrAg and pgRNA), with immunological markers (CXCL10 and sPD-1), refined delineation betwen 'active' vs. 'inactive' HBeAg-negative phases. Larger studies validating these markers to confirm their prognostic clinical significance are needed to reduce the uncertainty of 'grey zone' patients.

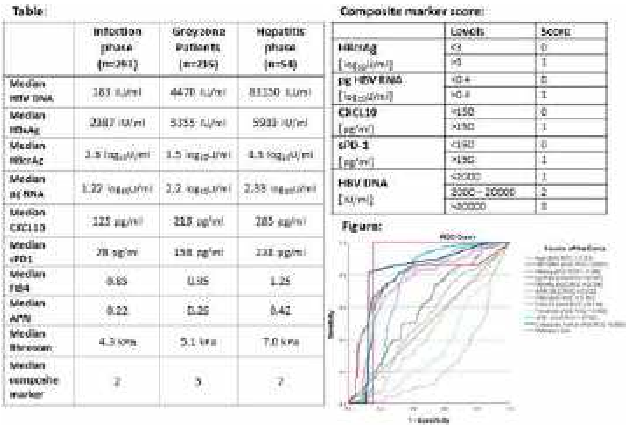


Table:

	Infection phase (n=293)	Grey zone Patients (n=215)	Hepatitis phase (n=54)
Median HBV DNA	183 IU/ml	4470 IU/ml	83150 IU/ml
Median HBsAg	2287 IU/ml	5355 IU/ml	5983 IU/ml
Median HBcrAg	2.8 $\log_{10}$U/ml	3.5 $\log_{10}$U/ml	4.5 $\log_{10}$U/ml
Median pgRNA	1.22 $\log_{10}$U/ml	2.2 $\log_{10}$U/ml	2.33 $\log_{10}$U/ml
Median CXCL10	123 pg/ml	218 pg/ml	285 pg/ml
Median sPD1	78 pg/ml	158 pg/ml	228 pg/ml
Median FIB4	0.85	0.95	1.25
Median APRI	0.22	0.25	0.42
Median fibroscan	4.3 kPa	5.1 kPa	7.0 kPa
Median composite marker	2	5	7

Composite marker score:

	Levels	Score
HBcrAg [$\log_{10}$U/ml]	<3	0
	>3	1
pg HBV RNA [$\log_{10}$U/ml]	<0.4	0
	>0.4	1
CXCL10 [pg/ml]	<150	0
	>150	1
sPD-1 [pg/ml]	<150	0
	>150	1
HBV DNA [IU/ml]	<2000	1
	2000 - 20000	2
	>20000	3

Figure:

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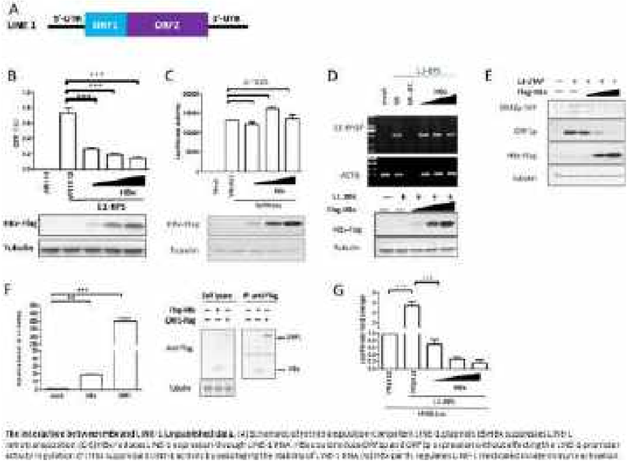
Mark Anderson – Abbott Diagnostics: Employee, Yes, No;
Gavin A. Cloherty – Abbott Diagnostics: Employee, Yes, No;

The following people have nothing to disclose: James Lok, Christiana Moigboi, Geoffrey M. Dusheiko, K. Agarwal

1527-C | MECHANISM RESEARCH ON THE INTERACTION BETWEEN HEPATITIS B VIRUS X PROTEIN AND LINE-1

Zhao Xu, Pujun Gao, Ke Zhao, Juan Du and Qiang Zhou, The First Hospital of Jilin University

Background: Long interspersed element type 1 (LINE-1), as the only active non-LTR endogenous retroelements that can replicate autonomously in human genome, has impact on genome evolution and triggering innate immune system. Little research focus on the interaction between LINE-1 and the HBV. HBV regulates natural immune responses through various pathways during its infection and replication while LINE-1 can activate the interferon signal system, indicating HBV is likely to interact with LINE-1. HBx protein is a multifunctional regulator with the ability to bind RNA and DNA, suggesting that HBx protein may interact with LINE-1. The research investigates whether there is interaction between HBx and LINE-1 and further explore the mechanisms of the interaction. **Methods:** we use Flow cytometry and LINE-1 retrotransposition assay to confirm the interaction between HBx and LINE-1. In order to explore the mechanisms of the interaction between HBx and LINE-1, we take different assays, such as Western blotting, Luciferase, co-IP, RT-qPCR to confirm whether HBx regulate LINE1 promoter activity, LINE-1 RNA, LINE-1 protein, LINE-1 RNP or the ability of integration. Finally, to explore the interplay among HBx, LINE-1 and the innate immune system by using ELISA, Western blotting, Luciferase, RT-qPCR etc. **Results:** 1.HBx suppresses LINE-1 retrotransposition. By using LINE-1 retrotransposition assay and Flow cytometry, we find that HBx could significantly reduce the replication activity of LINE-1 retrotransposition. 2. HBx reduces LINE-1 expression through LINE-1 RNA regulation. By using different assays, we find that HBx could reduce ORF1p and ORF2p expression without affecting the LINE-1 promoter activity, HBx suppressed LINE-1 activity by sabotaging the stability of LINE-1 RNA. 3.By suppressing LINE-1 activity, HBx partly regulates innate immune activation. **Conclusion:** The results reveal the new functions of HBx and provide new information on the intricate interaction between HBx, LINE-1, and innate immune systems. The results may also highlight the potential of designing novel HBx-targeting anti-HBV drugs and optimize anti-HBV treatment strategies.



Disclosures: The following people have nothing to disclose: Zhao Xu, Pujun Gao, Ke Zhao, Juan Du, Qiang Zhou

f 1739-A | DIFFERENTIAL DRUG RESPONSES AMONGST 4 IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY PATIENT-DERIVED HUMAN LIVER ORGANOIDS

Charles Zhang[1], *Sophia Meyer*[1], *Max Garcia*[1], *Megan Procario*[1], *Andrew Tucker*[1], *Robert J. Fontana*[2] *and Jonathan Sexton*[3], *(1)University of Michigan, (2) University of Michigan Medical Center, Ann Arbor, MI, (3)University of Michigan Medical Center*

Background: Idiosyncratic drug-induced liver injury (iDILI) is a rare but important cause of liver injury believed to arise, in part, from aberrant host immunity. Most in vitro models of DILI focus on primary human hepatocytes or cell lines and do not account for the potential role of non-parenchymal cells or inflammatory stimuli in iDILI susceptibility. This study reports the differential response between iPSC-derived human liver organoids (HLOs) obtained from 4 well characterized iDILI patients with and without proinflammatory cytokine priming before drug exposure. **Methods:** 4 patients with iDILI due to a single agent and a high causality score enrolled in the DILIN Prospective Study provided a blood sample for PBMC isolation. PBMCs were reprogrammed to iPSCs and differentiated into HLOs containing hepatocyte-like, stellate-like, and Kupffer-like cells over 28 days. HLOs were dispersed into a high-throughput 384-well system and treated with a library of 64 intrinsic and idiosyncratic hepatotoxins (including amoxicillin/clavulanate, sulfamethoxazole/trimethoprim, and green tea extract) in 10-point, 2-fold dose-response. HLOs were also primed with proinflammatory cytokines prior to drug exposure to mimic in vivo conditions. Hepatotoxicity was measured by loss of cell viability and phenotypic profiling using high-content imaging. Cellpose was used for nuclei segmentation followed by feature extraction using CellProfiler generating $>1{,}000$ morphological and intensity features per cell. HLO drug response was determined through a combination of loss of viability and phenotypic distance scoring vs vehicle control. **Results:** The 4 patients presented differential hepatotoxicity across a panel of 64 DILI-associated drugs, with 11 drugs responding in all patients, 24 in three patients, 17 in two, 8 in only one, and sulindac in no patients (Fig 1). A subset of active drugs is shown in Fig 1A and UpSet analysis showing differential drug response is shown in Fig 1B with the most reactive patient (patient 1) responding to 44 drugs and the least reactive (patient 2) responding to 38 out of 64 drugs. Prominent differences were observed with acetaminophen, fialuridine, isoniazid, and atorvastatin. Results of treatment with the panel of 64 drugs and variable concentrations of the specific implicated agent in the presence and absence of the proinflammatory cytokines TNF-α and IFN-γ will be presented. **Conclusion:** Our study introduces a unique method to assess personalized DILI risk. By expanding our panel of iDILI patient HLOs, we have the potential to create a more sensitive and specific *in vitro* test system that incorporates immune signaling. In addition to assessing personalized DILI risk, and potentiation by cytokine stress, our in vitro multicellular HLO model may provide novel mechanistic insights into the pathogenesis of iDILI.

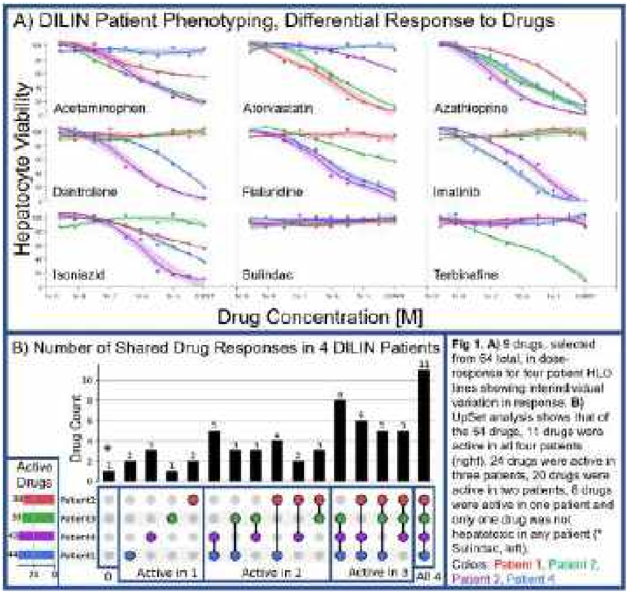


Fig 1. A) 9 drugs, selected from 64 total, in dose-response for four patient HLO lines showing interindividual variation in response. **B)** UpSet analysis shows that of the 64 drugs, 11 drugs were active in all four patients (right), 24 drugs were active in three patients, 20 drugs were active in two patients, 8 drugs were active in one patient and only one drug was not hepatotoxic in any patient (* Sulindac, left).
Colors: Patient 1, Patient 2, Patient 3, Patient 4

Disclosures: The following people have nothing to disclose: Charles Zhang, Robert J. Fontana
Disclosure information not available at the time of publication: Sophia Meyer, Max Garcia, Megan Procario, Andrew Tucker, Jonathan Sexton

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

1740-A | A HIGH THROUGHPUT AUTOMATABLE MICROFLUIDIC LIVER ORGANOID CHIP FOR LONG-TERM DILI MODELLING

Charles Zhang[1], Sumin Kim[2], Sophia Meyer[1], Amber Jolly[2], Byungjun Lee[2], Jiho Kim[2], Sanghee Yoo[2], Tsung-Li Liu[2], Kyusuk Baek[2], Robert J. Fontana[3] and Jonathan Sexton[4], (1)University of Michigan, (2) Qureator, (3)University of Michigan Medical Center, Ann Arbor, MI, (4)University of Michigan Medical Center

Background: Recent research has demonstrated the superiority of iPSC-derived human liver organoids (HLOs) and microfluidic liver chips over established hepatocyte cultures in terms of cell maintenance and physiologic relevance for various liver diseases including drug-induced liver injury (DILI). However, limitations include cost, scalability, and reproducibility. Herein, we describe a long-term high-throughput microfluidic liver chip for studying chronic liver diseases compatible with standard laboratory automation technologies. **Methods:** iPSC-derived HLO cells were embedded in hydrogel on 16-well Qureator Curio-Barrier microfluidic devices and cultured in a standard incubator. Media was collected to monitor albumin production over 28 days. Chips at days 7, 14, 21, and 28 were assessed for CYP450 expression by qPCR and activity through substrate metabolism, and immunostained for hepatocyte markers. Day 7, 14, and 21 chips were treated with acetaminophen, fialuridine, or vehicle control for an additional week to assess hepatotoxicity response by ALT release and reduction in albumin production. After the 1-week treatment, chips were fixed and stained for nuclei, cell region, and lipid content followed by automated water-immersion confocal microscopy and image-based morphological characterization. **Results:** HLOs consistently released albumin across 21 days of culture with a slight reduction in the last 7 days. CYP450 expression levels remained consistent across chips of all timepoints and HLOs maintained hepatocyte marker expression. Day 7, 14, and 21 chips treated with acetaminophen and fialuridine released ALT and had reduced albumin production consistent with DILI. **Conclusion:** Our findings establish that the Curio-Barrier devices successively maintained HLOs over 28 days in a high-throughput format. In addition to future DILI research, this platform may prove useful for other chronic liver diseases such as Hepatitis B and NAFLD.

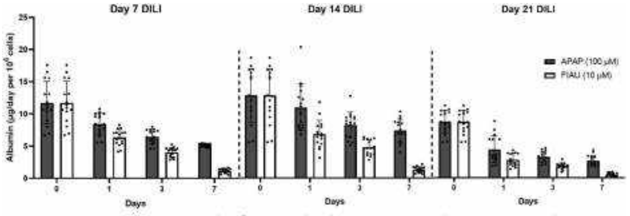


Figure: HLOs grown on Curio-Barrier chips for 7, 14, and 21 days are responsive to known DILI compounds

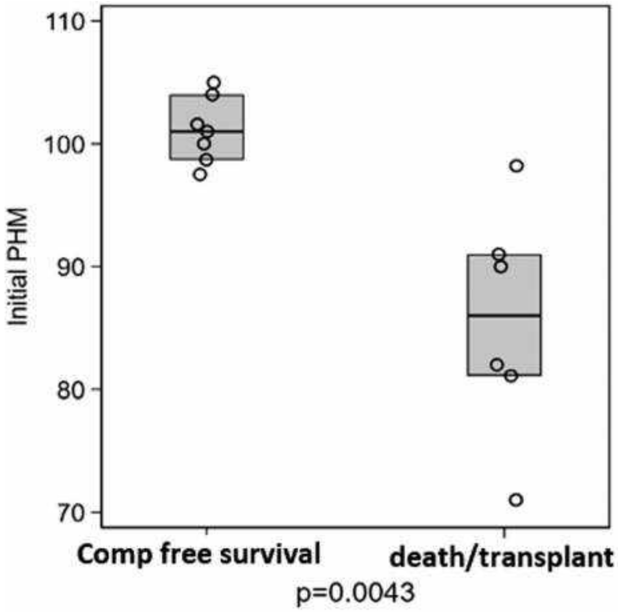
Disclosures: The following people have nothing to disclose: Charles Zhang, Robert J. Fontana

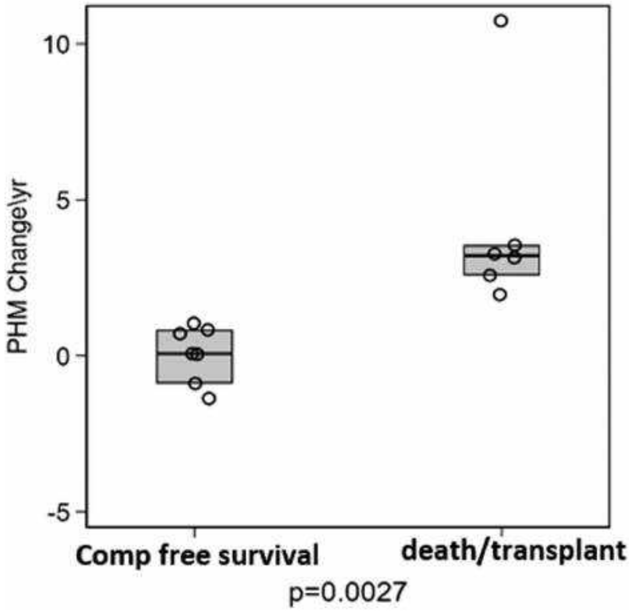
Disclosure information not available at the time of publication: Sumin Kim, Sophia Meyer, Amber Jolly, Byungjun Lee, Jiho Kim, Sanghee Yoo, Tsung-Li Liu, Kyusuk Baek, Jonathan Sexton

2495-A | NASH CIRRHOSIS: THE INTRA-HEPATIC HEMODYNAMIC ABNORMALITY (IHHA) OF CIRRHOSIS MEASURED BASELINE AND CHANGE OVER TIME PREDICTS CLINICAL OUTCOMES AND SURVIVAL

John C. Hoefs, University of California Irvine

Background: The intra-hepatic hemodynamic abnormality (IHHA) of cirrhosis determines quantitative hepatic function and correlates with clinical outcomes. In hepatitis C (investigated in the HALT-C trial), the IHHA was measured on the Quantitative liver-spleen scan (QLSS) as PHM (perfused hepatic mass) and out-performed any combination of histology and routine LFT in correlation with clinical outcomes over 8 years (*Hep, 55;1019-1029, 2012.*) Early studies showed that patients with CLD have the IHHA regardless of cause and correlates with the functional hepatic mass (Am J Gastro, 92:2054-2058, 1997). We hypothesize the outcomes of NASH cirrhosis are will be related to IHHA as measured by PHM. **Methods:** 13 patients with NASH cirrhosis were identified based on liver biopsy or nodularity of liver surface with collaterals by CT/MRI/US and followed for up to 13 years. Sulfur colloid liver-spleen scan as processed by Hepatiq for measurement of PHM (n = 100-110), functional spleen volume (fSV) (N = < 2.5 cc/lb IBW), and functional liver volume (fLV) (n = 7-12 cc/lb IBW). Data was obtained from a clinical database for clinical complications (death, ascites, encephalopathy, VB), ultrasound and routine blood tests. Statistics: Change over time was measured as delta (delta = PHM initial – last scan), delta/time observed and by the linear regression slope of change over time. A linear regression r2 of > 0.4 was considered significant for description of slope. Results are presented as box plots w/observed data overlays and tested using a Kruskal-Wallis rank test (ie, nonparametric t test). **Results:** The mean number of scans per patient was (7.5+/-2.5) over the mean number of years (8.1+/-3.2) of follow-up. 6 patients had complications and 1 had VB and Ascites prior to the first scan with no problems thereafter. 1 patient had a gastric bypass and lost 30 lb prior to the first scan. The main therapy was by control of predisposing factors of DM (11), hyperlipidemia (10), and obesity (3 patients had lean body NASH). Vitamin E was given for all patients and was taken some of the time by most. We divided patients into 2 groups based on progression to clinical complications including death: 1) 8 patients with no clinical problems and 2) 5 who progressed to clinical problems 5 of which died, had a LT or were accepted on the LT list. One death was from HCC. All 5 patients in group B who died had a PHM < 95 at baseline (figure) and had progression in PHM by linear regression slope (−0.0139 +/- 0.011 vs -.0013 +/- 0.0032; $p < 0.001$) and delta initial to final PHM (figure). Routine blood tests, MELD, Fib4 and US were not significantly different. **Conclusion:**1. Many patients with NASH cirrhosis do not progress over time to clinical problems or death. 2. IHAA as measured by PHM could identify patients at baseline or by deterioration during f/u who would progress to clinical problems and death. 3. The presence of NASH cirrhosis is not sufficient to predict a bad outcome and IHAA should be measured by PHM.





Disclosures: John C. Hoefs – Hepatiq_inc: Stock – privately held company (individual stocks and stock options), Yes, No;

2496-A | UNDERSTANDING RISK FOR NON-ALCOHOLIC STEATOHEPATITIS AND NON-ALCOHOLIC FATTY LIVER DISEASE IN MEDICARE AND MEDICAID CLAIMS

Katherine Nelson[1], Jonathan Gellar[2], Ryan Taylor Anderson[2], Patrick Campbell[1] and Arnold Chen[2], (1) Merck & Co., Inc., (2)Mathematica

Background: To build models using Medicaid and Medicare claims data to quantify the relationship between patient characteristics and diagnoses of NAFLD and NASH. **Methods:** Patients with a NAFLD or NASH diagnosis were identified in Medicare and Medicaid claims from 2018-2019 for all U.S. counties using criteria adapted from the methodology used in the CMS Chronic Conditions Warehouse. Diagnosis flags for NASH or NAFLD were given to patients who have ≥ 1 inpatient/skilled nursing facility /home health agency claim or 2 health options program (HOP)/carrier claims with diagnosis codes associated with the NASH or NAFLD. We considered any beneficiary diagnosed with NASH to also have NAFLD even in the absence of a NAFLD diagnosis. We built random forest models to assess the relationship between predictors (patient demographics and clinical risk factors: glucose intolerance, type 2 diabetes, metabolic syndrome, hypertension, and dyslipidemia) and diagnosed NAFLD or NASH. We fit one model to estimate risk of NAFLD among all patients, and another to estimate risk of NASH among patients with NAFLD ("NASH|NAFLD") in each target population. We calculated adjusted odds ratios for all binary or categorical predictors as marginal effects. **Results:** Sample sizes were 31,056,598 of Medicaid beneficiaries, 42,810,168 Medicare, and 10,151,582 dually eligible beneficiaries. All clinical risk factors had strong adjusted associations with NAFLD diagnosis (see Table 1). Risk factors were strongly associated with a diagnosis of NASH|NAFLD, with the strongest adjusted associations for metabolic syndrome and type 2 diabetes. Females had higher odds of both NAFLD and NASH|NAFLD than similar males. Hispanic and Asian beneficiaries had higher adjusted odds of NAFLD compared to white beneficiaries, but there were smaller differences between these three race/ethnicity groups for NASH|NAFLD. Black beneficiaries had lower odds of NAFLD and NASH|NAFLD than white beneficiaries. **Conclusion:** Specific patient demographic and clinical factors might help identify patients at high risk for NAFLD or NASH|NAFLD. These models may be useful for identifying undiagnosed individual's at high risk for developing NAFLD or NASH. Some observed differences between predictors may be due to under-diagnosis or failure to include diagnoses on claims for certain populations. This potential bias should be accounted when applying the models for health care planning.

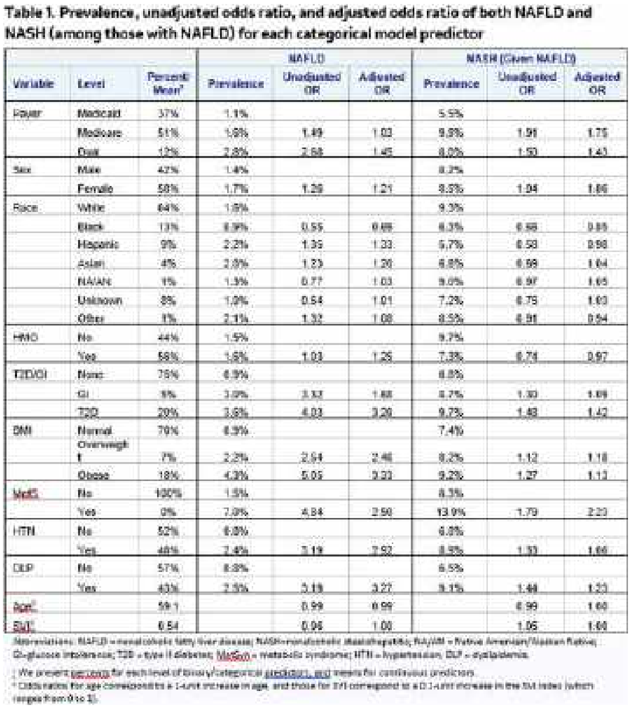


Table 1. Prevalence, unadjusted odds ratio, and adjusted odds ratio of both NAFLD and NASH (among those with NAFLD) for each categorical model predictor

			NAFLD			NASH (Given NAFLD)		
Variable	Level	Percent/ Mean†	Prevalence	Unadjusted OR	Adjusted OR	Prevalence	Unadjusted OR	Adjusted OR
Payer	Medicaid	37%	1.1%			5.5%		
	Medicare	51%	1.6%	1.49	1.03	9.9%	1.91	1.75
	Dual	12%	2.8%	2.68	1.45	8.0%	1.50	1.40
Sex	Male	42%	1.4%			8.2%		
	Female	58%	1.7%	1.29	1.21	8.5%	1.04	1.06
Race	White	64%	1.6%			9.3%		
	Black	13%	0.9%	0.55	0.69	6.3%	0.66	0.85
	Hispanic	9%	2.2%	1.36	1.33	5.7%	0.58	0.98
	Asian	4%	2.0%	1.23	1.20	6.8%	0.59	1.04
	NA/AN	1%	1.3%	0.77	1.03	9.0%	0.97	1.05
	Unknown	8%	1.0%	0.54	1.01	7.2%	0.75	1.03
	Other	1%	2.1%	1.32	1.08	8.5%	0.91	0.94
HMO	No	44%	1.5%			9.7%		
	Yes	56%	1.6%	1.03	1.25	7.3%	0.74	0.97
T2D/GI	None	75%	0.9%			8.8%		
	GI	5%	3.0%	3.32	1.88	8.7%	1.30	1.09
	T2D	20%	3.6%	4.03	3.20	9.7%	1.48	1.42
BMI	Normal	79%	0.9%			7.4%		
	Overweight	7%	2.2%	2.64	2.46	8.2%	1.12	1.18
	Obese	18%	4.3%	5.05	3.33	9.2%	1.27	1.13
MetS	No	100%	1.5%			8.3%		
	Yes	0%	7.0%	4.84	2.50	13.9%	1.79	2.20
HTN	No	52%	0.8%			6.8%		
	Yes	48%	2.4%	3.19	2.92	8.9%	1.33	1.06
DLP	No	57%	0.8%			6.5%		
	Yes	43%	2.5%	3.18	3.27	9.1%	1.48	1.23
Age‡		59.1		0.99	0.99		0.99	1.00
SVI‡		0.54		0.96	1.00		1.06	1.00

Abbreviations: NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; NA/AN = Native American/Alaskan Native; GI = glucose intolerance; T2D = type II diabetes; MetSyn = metabolic syndrome; HTN = hypertension; DLP = dyslipidemia.

† We present percents for each level of binary/categorical predictors, and means for continuous predictors.

‡ Odds ratios for age correspond to a 1-unit increase in age, and those for SVI correspond to a 0.1-unit increase in the SVI index (which ranges from 0 to 1).

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Jonathan Gellar – Merck & Co, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;
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2497-A | HEPATIC IMMUNE CELL PROFILING OF THE GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF NASH WITH ADVANCED FIBROSIS AND HCC

Kristoffer Voldum-Clausen[1], Jacob Nøhr-Meldgaard[2], Alex Frias Hernandez[1], Michael Feigh[2] and Henrik B. Hansen[2], (1)Gubra a/S, (2)Gubra

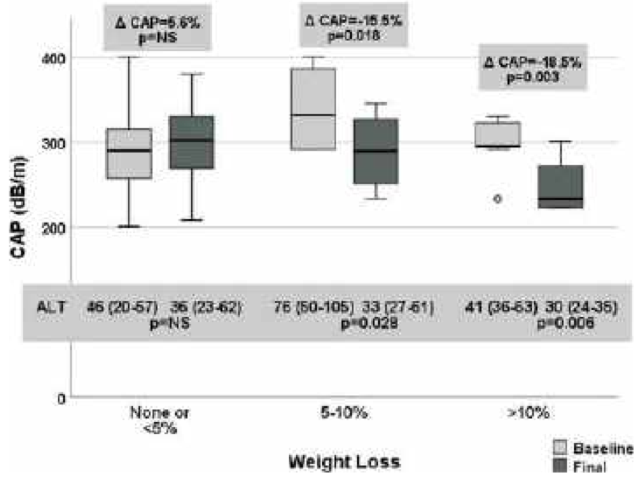
Background: Non-alcoholic steatohepatitis (NASH) has become an emerging risk factor for the development of liver fibrosis and hepatocellular carcinoma (HCC). Recent data suggest that NASH–HCC patients are less responsive to HCC-targeted immunotherapies, likely owing to NASH-related aberrant immune cell regulation. To gain further insight into immune cell regulations in NASH-driven HCC, we profiled liver leukocyte populations in the translational Gubra Amylin NASH (GAN) diet-induced obese (DIO) and biopsy-confirmed mouse model of advanced fibrosing NASH and HCC. **Methods:** C57BL/6JRj male mice were fed the GAN diet (40 kcal-% fat, 22% fructose, 10% sucrose, 2% cholesterol) or chow diet for 58 weeks before randomization. Prior to randomization all animals underwent liver biopsy for histological confirmation (fibrosis stage 3, steatosis score 3, inflammation score ≥ 2) using the non-alcoholic fatty liver disease activity scoring (NAS) and fibrosis staging system. Animals were terminated at 70 weeks on diet. Liver single-cell samples were stained using two distinct panels (lymphoid and myeloid panel). These panels targeted specific cell-surface markers to detect and quantify leukocyte subsets, including monocytes/macrophages, neutrophils, T-cells, B-cells, Natural killer (NK) and NK T-cells. Flow cytometry was employed for data analysis, enabling detailed characterization of liver immune infiltrated cell populations. **Results:** The GAN DIO-NASH-HCC mouse is a translational model of HCC development on the background of severe NASH and fibrosis here we show that DIO-NASH-HCC mice demonstrate marked expansion of hepatic resident and infiltrating monocyte/macrophage (Infiltrating monocytes, Ly6C^{++}cells, Kupffer, F4/80^{high} CD11c^{low} cells, and dendritic-like, F4/80^{low} CD11c^{high} cells) and specific T-cell populations, particularly CD8^{+} T cells. Moreover, CD8^{+} T cells have recently been implicated in NASH–driven HCC and have been linked to reduced efficacy to HCC-targeted immunotherapies in NASH patients. **Conclusion:** This study highlights the significance of understanding the interactions between immune cells and the development of HCC in the context of NASH. This knowledge can help guide the development of new and innovative anti-cancer drug concepts specifically targeting NASH-driven HCC.

Disclosures: Michael Feigh – Gubra: Employee, Yes, No; Gubra: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No; Gubra: Executive role, Yes, No;
The following people have nothing to disclose: Kristoffer Voldum-Clausen, Jacob Nøhr-Meldgaard, Alex Frias Hernandez, Henrik B. Hansen

2498-A | SEMAGLUTIDE-INDUCED WEIGHT LOSS LEADS TO SIGNIFICANT IMPROVEMENT OF HEPATIC STEATOSIS ASSESSED BY FIBROSCAN® CONTROLLED ATTENUATION PARAMETER (CAP) IN PATIENTS WITH BIOPSY-PROVEN NON-ALCOHOLIC STEATOHEPATITIS (NASH)

Savvoula Savvidou[1], Polyxeni Agorastou[1], Ioanna Papagiouvanni[1], Efrosyni Tsirogianni[1], Pavlina Pantelidou[2], Prodromos Hytiroglou[2] and Ioannis Goulis[1], (1)Hippocration University Hospital of Thessaloniki Greece, (2)Medical School of Aristotle University of Thessaloniki, Greece

Background: Improving hepatic steatosis, the "first hit" in the development of non-alcoholic steatohepatitis (NASH), is a feasible target achieved by weight loss, either with diet, bariatric surgery or pharmacotherapy such as the newly introduced glucagon-like peptide-1 agonist, semaglutide. Moreover, Controlled Attenuation Parameter (CAP) assessed by FibroScan® was shown to accurately estimate the degree of underlying steatosis. Primary aim of this study was to prospectively investigate non-invasively the effect of semaglutide-induced weight loss in patients with biopsy-proven NASH. **Methods**: Consecutive patients with biopsy-proven non-cirrhotic NASH were evaluated with somatometrics, blood tests and transient elastography with FibroScan® mini 430+ (M/XL probes). Liver Stiffness Measurement (LSM) and CAP were simultaneously measured in kPa and dB/m, respectively, by a single operator. Fibrosis-4 (FIB-4) and Fibroscan-AST (FAST) scores were calculated. Histologic assessments were performed by a single expert pathologist according to Kleiner´s classification [4 grades for steatosis (S0 to S3), 5 stages for fibrosis (F0 to F4)]. A subgroup of patients, not different in baseline characteristics, was treated with subcutaneously 2.4mg/week semaglutide for approximately six months, beginning with a 16-week escalation period (0.25->0.5->1->1.7->2.4 mg). Repeated elastography was performed by the same operator, and statistical comparisons were tested with Wilcoxon-rank test for paired samples. **Results**: Forty-six pts were recorded: 16 males/30 females, age 52.6 ± 13.1, BMI 29.7 ± 4.7 kg/m^2, diabetes in 16 pts (34.8%). Baseline laboratory tests [medians with interquartile range (IQR)]: AST 37U/L (25-60), ALT 50U/L (36-75), γGT 51U/L (25-177), PLT 221x10^9/μL (212-270), and 39.1% of patients with FIB-4 ≥1.3. Baseline elastography: median LSM 10.4kPa (IQR 7.5-15.4), CAP 295dB/m (IQR 258-345), while high FAST was recorded in 32.6% of patients. Histology revealed 16 patients (34.7%) with definite severe NASH. High diagnostic accuracy of elastography in identifying advanced fibrosis (F3-F4) with LSM and high-grade steatosis (S3) with CAP was shown with AUROCs 0.898 (95% CI 0.795-1, $p = 0.001$) and 0.841 (95% CI 0.716-0.967, $p = 0.001$), respectively. Repeated elastography was performed after a median of 6.5 months (IQR 3-11.2). The entire subgroup of patients administered semaglutide (n = 25) exhibited significant weight loss (range 6.8% to 27.3%) while presenting only minor side effects (primarily nausea). Reductions in CAP correlated to the degree of weight loss, and were accompanied by similar reductions (down to normal) in ALT levels. [GRAPH] LSM reductions did not reach the level of statistical significance. **Conclusion**: Semaglutide-induced weight loss was shown to improve both aminotransferases and hepatic steatosis. FibroScan® with CAP is a useful tool that can reliably assess non-invasively treatment of NASH.



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Disclosure information not available at the time of publication: Polyxeni Agorastou, Ioanna Papagiouvanni, Efrosyni Tsirogianni, Pavlina Pantelidou, Prodromos Hytiroglou, Ioannis Goulis

2499-A | HEPATOPROTECTIVE EFFECTS OF SEMAGLUTIDE IN THE CDAA-HFD MOUSE MODEL OF ADVANCED NASH WITH PROGRESSIVE FIBROSIS

Kristoffer Voldum-Clausen[1], Jacob Nøhr-Meldgaard[2], Denise Oró Bozzini[2], Michael Feigh[3] and Henrik B. Hansen[2], (1)Gubra a/S, (2)Gubra, (3)Gubra Aps

Background: The glucagon-like-peptide (GLP)-1 analogue semaglutide is currently approved for the treatment of type 2 diabetes and obesity. Semaglutide has recently been reported to promote NASH resolution (Newsome et al., NEJM, 2020) and is currently in phase 3 clinical trial (ESSENCE) for NASH. The present study aimed to evaluate early vs. late-stage treatment intervention with semaglutide in the non-obese choline-deficient

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

L-amino-acid defined high-fat diet (CDAA-HFD) mouse model of advanced NASH with progressive fibrosis. **Methods:** C57BL/6JRj mice were fed chow or CDAA-HFD (45 kcal% fat, 0.1% methionine, 1% cholesterol, 28 kcal% fructose) for 3 or 6 weeks prior to treatment start (i.e. before or after onset of fibrosis, respectively). Animals were randomized into treatment groups based on body weight. A baseline group (n = 12) was terminated at study start (3 and 6 weeks). CDAA-HFD fed mice (n = 12 per group) received treatment (SC) with vehicle or semaglutide (30 nmol/kg) for 8 or 9 weeks. Chow-fed mice (n = 8) served as normal controls. Terminal endpoints included plasma biomarkers alanine/aspartate aminotransferase (ALT/AST), metallopeptidase inhibitor 1 (TIMP-1) and amino terminal peptide of type III procollagen (PIIINP), liver biochemistry, NAFLD Activity Score (NAS), fibrosis stage and quantitative liver histology. **Results:** Both early and late-stage intervention with semaglutide reduced body weight and liver weight in CDAA-HFD mice. While neither intervention improved NAS, early treatment start with semaglutide improved fibrosis stage. Notably, both interventions equally reduced liver hydroxyproline concentrations and quantitative levels of fibrosis (% area of PSR) as well as reduced levels of the fibrosis biomarkers TIMP-1 and PIIINP. Irrespectively of intervention timing, semaglutide did not influence plasma ALT/AST. **Conclusion:** Semaglutide demonstrates limited therapeutic efficacy in the non-obese CDAA-HFD mouse model of NASH with progressive fibrosis. In this model, the modest anti-fibrotic effects of semaglutide are not accompanied by improved hallmarks of NASH, suggesting complex hepatoprotective effects of semaglutide.

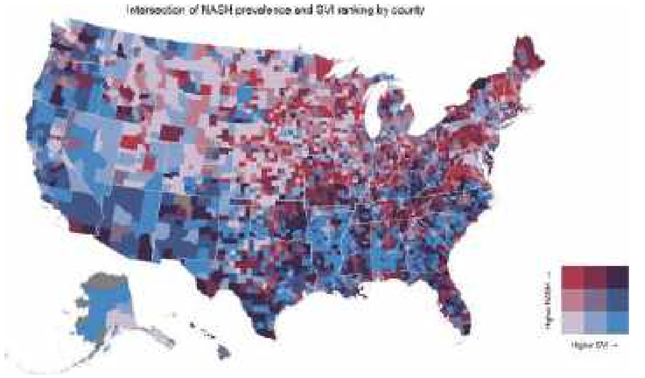
Disclosures: Michael Feigh – Gubra: Employee, Yes, No; Gubra: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No; Gubra: Executive role, Yes, No;

The following people have nothing to disclose: Kristoffer Voldum-Clausen, Jacob Nøhr-Meldgaard, Denise Oró Bozzini, Henrik B. Hansen

2855-C | NATIONAL, STATE AND COUNTY PREVALENCE OF DIAGNOSES OF NON-ALCOHOLIC FATTY LIVER DISEASE AND NON-ALCOHOLIC STEATOHEPATITIS IN THE UNITED STATES MEDICAID AND MEDICARE POPULATIONS

Katherine Nelson[1], Ryan Taylor Anderson[2], Jonathan Gellar[2], Patrick Campbell[1] and Arnold Chen[2], (1)Merck & Co., Inc., (2)Mathematica

Background: To produce geographic estimates of Medicare and Medicaid patients diagnosed with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), and to assess the geographic association with where access to care measured by the social vulnerability index (SVI). **Methods:** Patients with a NAFLD or NASH diagnosis were identified in Medicare and Medicaid claims from 2018-2019 for all U.S. counties using criteria adapted from the methodology used in the CMS Chronic Conditions Warehouse. Diagnosis flags for NASH or NAFLD were given to patients who have ≥ 1 inpatient/skilled nursing facility/home health agency claim or 2 health options program (HOP)/carrier claims with diagnosis codes associated with the NASH or NAFLD. Social determinants of health were measured at the county-level using the SVI (high SVI = greater social vulnerability) developed by the CDC. Terciles were calculated for disease prevalence and SVI scores. The relative national prevalence of disease and SVI ranges were mapped at the county-level using the ArcGIS software platform in a multi-variate analysis of geographic distribution. **Results:** Nationally, 1.43% and 0.13% of Medicare and Medicaid beneficiaries, respectively had claims with NAFLD and NASH diagnoses. Dual beneficiaries had the highest proportion of claims with a NASH and NAFLD diagnoses. At the state level NASH diagnoses were associated with 0.06 – 0.25%, 0.00 – 0.10% and 0.09 – 0.42% of claims for Medicare, Medicaid, and dual beneficiaries, respectively. NAFLD diagnoses were associated with 0.58 – 2.50%, 0.39 – 1.80% and 1.42 – 3.48% for Medicare, Medicaid and dual beneficiaries, respectively. Counties with a high prevalence of diagnosed NAFLD and NASH and a high SVI were primarily located in southeast and southwest states (Figure 1). Counties with low prevalence of diagnosed NAFLD and NASH and low SVI were mostly located in midwestern states. **Conclusion:** This is the first study to calculate state and county-level NASH and NAFLD prevalence using Medicaid and Medicare claims. Estimates may underestimate the population prevalence due underdiagnosis and low claim volume. Results show a clustering of high NASH prevalence and high social vulnerability across the southwest and southeast states. This information identifies NASH patient populations at the highest risk of experiencing disparities across the US and identifies patient populations that could most benefit from an improved patient care pathway.



Disclosures: Katherine Nelson – Merck & Co, Inc.: Employee, Yes, No;
Ryan Taylor Anderson – Merck & Co, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;
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Patrick Campbell – Merck & Co, Inc.: Employee, Yes, No;
Arnold Chen – Merck & Co, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;

3169-A | OUTCOMES OF LAPAROSCOPIC APPENDECTOMY AMONG ADULTS WITH AND WITHOUT CIRRHOSIS; ANALYSIS UTILIZING LATEST 2016-2020 NATIONAL INPATIENT SAMPLE

Tejas Vijay Joshi, Marshall University, Renuka Verma, Guru Gobind Singh Medical School, Kamleshun Ramphul, Independent Researcher and Hemamalini Sakthivel, One Brooklyn Health System/Interfaith Medical Center Program

Background: The use of laparoscopic appendectomy instead of open approach has risen drastically over the last decades. As there is a paucity of recent data among cirrhosis patients, we aim to conduct a retrospective study via a large national hospitalization database. **Methods:** Adults requiring endoscopic percutaneous appendectomy between 2016- 2020 were studied via hospital records from the National Inpatient Sample provided by HCUP, AHRQ, and collaborators. We compared cohorts with and without cirrhosis for different patient and hospitalization characteristics and outcomes. **Results:** A total of 531665 cases of laparoscopic appendectomy were performed in the United States between 1st January 2016 to 31st December 2020. Our sample further identified 2365 (0.4%) cases with a diagnosis of cirrhosis, with a higher mean age (58.27 years) than the non-cirrhosis group (45.51 years, $p < 0.01$). Most cirrhosis patients were Males (61.7%) while in the non-cirrhosis group it was almost equally balanced between the two sexes. Both cohorts had many patients racially classified as White. While Private insurances covered a higher portion of non-cirrhosis patients, Medicare was the preferred form of insurance among those with cirrhosis. Most procedures were conducted in the southern region of the United States and involved urban teaching centers and centers classified as large bed size. Cirrhosis patients reported higher prevalence of diabetes, hypertension, peripheral vascular disease, smoking, obesity, chronic kidney disease, prior stroke, prior myocardial infarction, depression, drug abuse, alcohol abuse, lipid disorder, and a higher mean Charleston Comorbidity Index score. They were also at higher risk of acute kidney injury, septicemia, use of mechanical ventilation, and death. Their hospitalization was longer (mean Length of stay 5.37 vs. 2.86) with a higher mean hospital charge ($84358 vs. $55510). **Conclusion:** Patients with cirrhosis undergoing laparoscopic appendectomy were older with more comorbidities. They also experienced more complications and had a longer. This correlated to a higher healthcare cost burden. As their existed a paucity of information on cirrhosis severity, we utilized this national data base to complete a large population-based analysis. Our findings mirror other smaller studies and retrospective analyses, but this is the first study to report this data from the latest information provided by the 2016-2020 national inpatient sample.

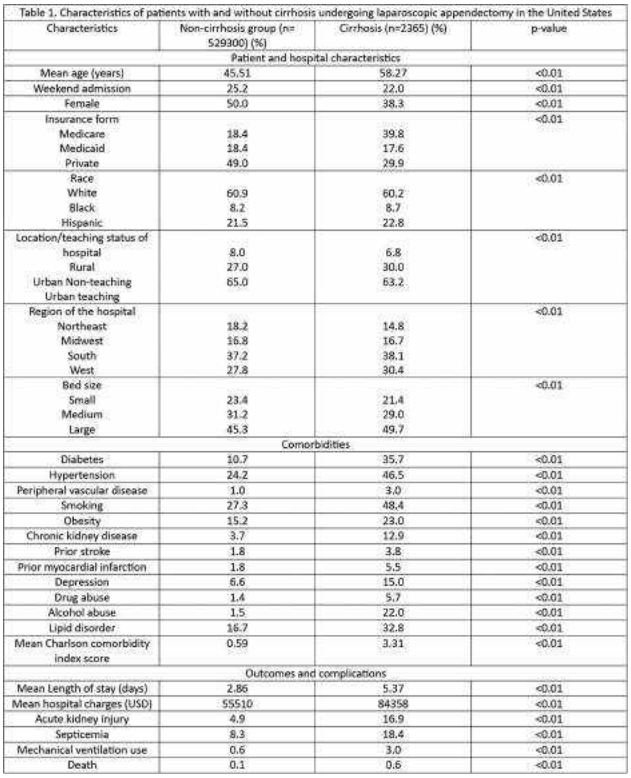


Table 1. Characteristics of patients with and without cirrhosis undergoing laparoscopic appendectomy in the United States

Characteristics	Non-cirrhosis group (n= 529300) (%)	Cirrhosis (n=2365) (%)	p-value
Patient and hospital characteristics			
Mean age (years)	45.51	58.27	<0.01
Weekend admission	25.2	22.0	<0.01
Female	50.0	38.3	<0.01
Insurance form			<0.01
Medicare	18.4	39.8	
Medicaid	18.4	17.6	
Private	49.0	29.9	
Race			<0.01
White	60.9	60.2	
Black	8.2	8.7	
Hispanic	21.5	22.8	
Location/teaching status of			<0.01
hospital	8.0	6.8	
Rural	27.0	30.0	
Urban Non-teaching	65.0	63.2	
Urban teaching			
Region of the hospital			<0.01
Northeast	18.2	14.8	
Midwest	16.8	16.7	
South	37.2	38.1	
West	27.8	30.4	
Bed size			<0.01
Small	23.4	21.4	
Medium	31.2	29.0	
Large	45.3	49.7	
Comorbidities			
Diabetes	10.7	35.7	<0.01
Hypertension	24.2	46.5	<0.01
Peripheral vascular disease	1.0	3.0	<0.01
Smoking	27.3	48.4	<0.01
Obesity	15.2	23.0	<0.01
Chronic kidney disease	3.7	12.9	<0.01
Prior stroke	1.8	3.8	<0.01
Prior myocardial infarction	1.8	5.5	<0.01
Depression	6.6	15.0	<0.01
Drug abuse	1.4	5.7	<0.01
Alcohol abuse	1.5	22.0	<0.01
Lipid disorder	16.7	32.8	<0.01
Mean Charlson comorbidity index score	0.59	3.31	<0.01
Outcomes and complications			
Mean Length of stay (days)	2.86	5.37	<0.01
Mean hospital charges (USD)	55510	84358	<0.01
Acute kidney injury	4.9	16.9	<0.01
Septicemia	8.3	18.4	<0.01
Mechanical ventilation use	0.6	3.0	<0.01
Death	0.1	0.6	<0.01

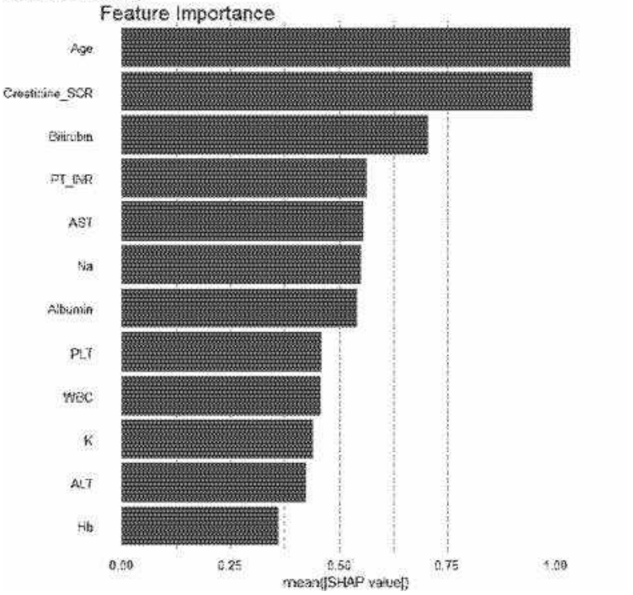
Disclosures: Tejas Vijay Joshi – Fibroscan: Consultant, No, No; Novo Nordisk: Speaking and Teaching, No, No;
The following people have nothing to disclose: Renuka Verma, Kamleshun Ramphul, Hemamalini Sakthivel

3170-A | PREDICTORS OF 30-DAY MORTALITY IN ACUTE HEPATIC DECOMPENSATION: A NATIONWIDE COHORT STUDY WITH LABORATORY DATA OF ICU ADMISSIONS

Yee Hui Yeo[1], Yi-Hsian Lin[2], Hsiu J. Ho[2], Yao-Chun Hsu[3] and Chun-Ying Wu[2], (1)Cedars-Sinai Medical Center, Culver City, CA, (2)Institute of Biomedical Informatics, Institute of Public Health, National Yang-Ming University, Taipei, Taiwan., (3)E-Da Cancer Hospital, I-Shou University

Background: Acute decompensation of cirrhosis portends a dire prognosis, frequently requiring intensive care unit (ICU) admission for vigilant management. Despite unmet needs, prior studies have been limited by cohorts with limited size or selection bias. We presented a nationwide cohort of ICU admissions with laboratory data due to hepatic decompensation and showed the predictors of mortality. **Methods:** Data were sourced from Taiwan's National Health Insurance Research Database, which comprised all ICU admissions in Taiwan from 1/1/2015 to 12/31/2018 due to acute decompensation of cirrhosis. Acute decompensation was defined using ICD-9 (2015) and ICD-10 (2016-2018) codes and included spontaneous bacterial peritonitis, gastric/esophageal variceal hemorrhage, hepatic encephalopathy, and ascites (≥ 3 outpatient or 1 inpatient diagnosis of chronic liver diseases or cirrhosis). Available data comprised demographic, clinical, and laboratory parameters. The study endpoint was 30-day mortality. The cohort was divided into training (70%) and validation (30%) cohorts. Predictors of mortality were determined using the Xgboost machine learning model. The SHAP score was assessed to ascertain each variable's contribution to the model. **Results:** We identified 10,855 ICU admissions due to acute decompensation, with a mean age of 61.1 years (SE 14.4), and were predominantly male (70.2%). The majority of patients had a diagnosis of alcohol-associated liver disease (46.3%), followed by hepatitis B (31.7%) and hepatitis C (24.7%) infection. Comorbidities were prevalent, with diabetes (40.1%), COPD (21.3%), coronary artery disease (18.2%), and malignancy (20.5%) featuring prominently. Laboratory data included median ALT 33 U/L (interquartile range [IQR] 21-59), AST 64 U/L (IQR 38-130), total bilirubin 2.27 mg/dL (IQR 1.2-5.0), platelet count 107*10^9/L (IQR 66-168), WBC count 9.7*10^9/L (IQR 6.3-15.3), and creatinine 1.26 mg/dL (IQR 0.88-2.17). Using the Xgboost model, we attained high values of accuracy, precision, F1 score, and recall in both training and validation cohorts (all above 0.995). Age, creatinine, and total bilirubin emerged as the top three predictors of 30-day mortality, followed by INR, AST, sodium, and albumin levels. **Conclusion:** We showed the 30-day mortality predictors in a nationwide ICU cohort of patients with acute hepatic decompensation using a sophisticated machine learning model. This can inform more nuanced patient monitoring and management strategies.

Figure 1. The contribution of each variable to the predictive model (Xgboost: eXtreme Gradient Boosting)



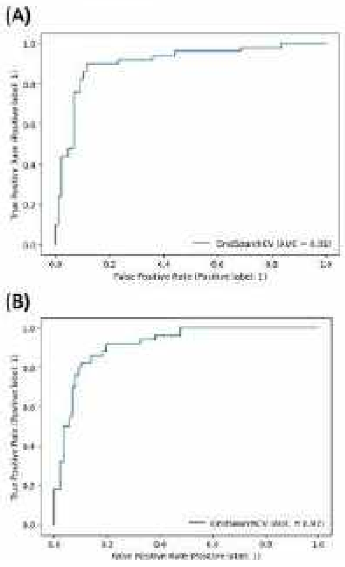
Disclosures: The following people have nothing to disclose: Yee Hui Yeo, Yi-Hsian Lin, Hsiu J. Ho, Yao-Chun Hsu, Chun-Ying Wu

3226-A | PREDICTIVE MACHINE LEARNING MODELS FOR SHORT-TERM MORTALITY IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

Yee Hui Yeo[1], Mengyi Zhang[2], Jian Zu[2], Jeff Liang[3] and Fanpu Ji[4], (1)Cedars-Sinai Medical Center, Culver City, CA, (2)School of Mathematics and Statistics, Xi'an Jiaotong University, Xi'an, Shaanxi, China, (3)Cedars-Sinai Medical Center, Los Angeles, CA, (4)The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Background: Acute-on-chronic liver failure (ACLF), characterized by rapid progression and high short-term mortality, requires better predictive mortality factors. In this study, we aimed to investigate the influencing factors and short-term mortality risk in patients with ACLF. **Methods:** We utilized the MIMIC-IV database, an extensive dataset containing over 40,000 patients admitted to ICU at the BIDMC. The dataset includes demographic information, comorbidity data, treatment details, laboratory variables, vital signs, and clinical outcomes for each admission. Using the North American Consortium for End-Stage Liver Disease diagnostic criteria, we identified ACLF patients and determined the 30-day mortality rate. We then applied Pearson's correlation analysis to identify variables with significant mortality associations. We developed and compared nine machine learning prediction models for short-term mortality forecasting and examined key influencing factors. **Results:** Our study identified 5994 cirrhosis patients. After excluding patients with a history of HIV, transplantation, and malignancies, and including patients who met the criteria for organ failure, a total of 1996 patients with two organ failures were included. The average age was 58.5 years (SE 12.1), with 65.5% of patients being male. Renal failure was the most prevalent organ failure (74.9%), followed by circulation (57.2%), respiration (24.3%), and brain (23.9%). The 30-day mortality rates in patients with 2, 3, and 4 organ failures were 35.2%, 62.5%, and 96.8%, respectively. Correlation analysis identified age, INR, total bilirubin, ventilation necessity, renal replacement therapy, WBC count, and creatinine level as variables with significant correlation coefficients. CatBoost and LightGBM models emerged as the most accurate models, with AUROC values of 0.91 and 0.92, respectively (Figure). The F-test further demonstrated that these variables significantly contributed to the predictive value. **Conclusion:** We established a large ACLF cohort and determined the 30-day mortality rate. Our models with high predictive accuracy suggest that age, INR, total bilirubin, ventilation necessity, renal replacement therapy, WBC count, and creatinine level are potential predictive factors for short-term mortality. Further validation of these models is warranted.

Figure. AUROC to denote the predictive accuracy of two machine learning models (a) CatBoost AUROC = 0.91 (b) LightGBM, AUROC = 0.92



Disclosures: The following people have nothing to disclose: Yee Hui Yeo, Mengyi Zhang, Jian Zu, Jeff Liang, Fanpu Ji

3636-C | PORPHYROMONAS GINGIVALIS STRAIN W83 INFECTION INDUCES LIVER INJURY IN EXPERIMENTAL ALCOHOL-ASSOCIATED LIVER DISEASE (ALD) IN MICE

Yun Zhou[1], Wenke Feng[1,2] and Craig J. McClain[1], (1) University of Louisville, Louisville, KY, (2)Tulane University, New Orleans, LA

Background: The liver plays a crucial role in defending against infections. *Porphyromonas gingivalis (P. gingivalis*) is a dominant oral bacterium in chronic periodontitis and is associated with multiple systemic diseases. Our previous study revealed an association between *P. gingivalis* and the development/severity of alcohol-associated liver disease (ALD) in patients. This study aims to investigate the potential causal role of *P. gingivalis in* the development of experimental ALD using mice. **Methods:** C57BL6 mice were fed a Lieber-DeCarli liquid diet containing 5% ethanol for 10 days. Two days before tissue sample collection, mice were administered *P. gingivalis* strain W83 (*Pg*) via intraperitoneal injection. The control group consisted of isocaloric pair-fed mice. Liver injury and inflammation were assessed. **Results:** Pair-fed mice with *Pg* infection (PF+*Pg)* exhibited an immune response to combat infections. However, alcohol-fed mice with *Pg* infection (AF+*Pg*) displayed noticeable abscess lesions in the liver and elevated serum ALT levels. These mice also showed significant downregulation of proinflammatory cytokine gene expression which may have played a role in decreased clearance of *Pg* from the liver. Furthermore, alcohol-fed mice with *Pg* infection (AF +*Pg)* demonstrated increased neutrophil infiltration, as confirmed by chloroacetate esterase (CAE) staining, and elevated gene expression levels of neutrophil cytosol factor 1 (Ncf1), lipocalin 2 (Lcn2), and Complement component C5a receptor C5ar1, which are associated with neutrophil-associated inflammation. Compared to PF+*Pg* mice, AF+*Pg* mice exhibited downregulation of NADPH oxidase 2 (Cybb) gene expression, leukocyte adhesion molecule Cd18, and Toll-like receptor adaptor Myd88. This resulted in impaired clearance of *Pg* and other bacteria in the liver, increased susceptibility to infections, and inflammation-associated hepatic necrotic cell death, which likely contributed to liver injury through the priming of immune cell infiltration. **Conclusion:** Our study suggests that systemic *Pg* infection exacerbates alcohol-induced liver injury. Alcohol consumption impairs the liver's ability to clear periodontal bacteria originating from periodontitis pathogenesis. The accumulation of oral pathogenic bacteria further contributes to liver injury and promotes liver lipogenesis. These findings provide additional

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Symbols: f , Poster of Distinction; ★, Foundation Award Recipient

evidence for the role of *P. gingivalis* infection as a "second hit" in the development and progression of ALD (Supported by NIH grants).

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3637-C | DRAMATIC INCREASE IN ADMISSIONS FOR ALCOHOLIC HEPATITIS DURING THE COVID-19 PANDEMIC YEARS IN VICTORIA, AUSTRALIA: UNINTENDED CONSEQUENCES OF COMMUNITY LOCKDOWNS?

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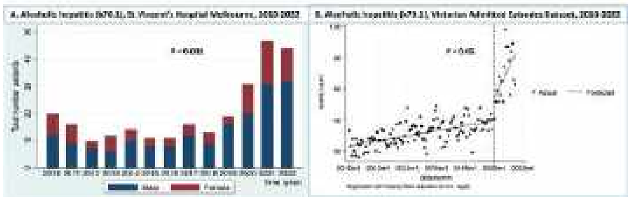
Background: The coronavirus disease 2019 (COVID-19) pandemic was associated with direct excess of morbidity and mortality related to respiratory disease. In addition, emerging data suggests indirect health consequences related to the pandemic and community lockdowns, including increased alcohol consumption and alcohol-related harm. We have observed an anecdotal increase in the number of admissions for alcoholic hepatitis (AH) since the start of 2020. In this study we have evaluated temporal trends in hospital admissions for AH, comparing the pandemic years (2020 – 2022) with the preceding decade (2010 – 2019). **Methods:** In this retrospective cohort study, we analysed the patient database at St. Vincent's Hospital Melbourne for admissions with AH (ICD code k70.1) between January 2010 and December 2022. The medical records of a representative sample of the extracted patients were reviewed to confirm the accuracy of AH ICD coding. AH was defined as at least three of the following criteria: (1) elevated alanine amino transferase (ALT) or aspartate aminotransferase (AST) > 50 IU/L, (2) AST:ALT ratio > 2, (3) an elevated international normalised ratio (INR) > 1.2, or (4) elevated total bilirubin > 30 µmol/L. We then analysed admissions for AH recorded in the Victorian Admitted Episodes Dataset (VAED) maintained by the Victorian Department of Health. Interrupted time-series and Poisson linear regression analyses were used to compare trends in number of patients admitted with AH between the two time periods (2010 – 2019 vs. 2020 – 2022). **Results:** A total of 367 admissions with AH among 264 unique patients were identified during this time period at our institution. The median age of patients was 48 years (IQR 40, 57) and 68.6% were male. There was a significant increase in the number of admissions with AH during the years 2020-2022 compared to the years 2010 – 2019 (Figure 1A, $p < 0.001$). There was an increase in AH admissions among both males and females, but the relative increase was greater in females ($p < 0.001$, figure 1A). A similar phenomenon was observed in the VAED dataset; interrupted time-series analysis confirmed a significant increase in AH cases from the beginning of 2020 (Figure 1B, $p < 0.05$). Extraction of detailed clinical data is ongoing. **Conclusion:** Admissions with alcoholic hepatitis have increased dramatically since the start of the COVID-19 pandemic, with relative greater increases in females. There is an urgent need for funding to develop and prioritise public health strategies to address the harms of excess alcohol consumption.

Figure 1: A. Admissions to St Vincent's Hospital Melbourne with alcoholic hepatitis (k70.1), 2010-2022. B. Admissions with alcoholic hepatitis (k70.1) registered in the VAE, 2010 - 2022



Disclosures: Alexander J. Thompson – Gilead Sciences: Consultant, Yes, No; AbbVie: Consultant, Yes, No; Roche: Consultant, Yes, No; BMS: Consultant, Yes, No; Assembly Biosciences: Consultant, Yes, No; Gilead Sciences: Speaking and Teaching, Yes, No; AbbVie: Speaking and Teaching, Yes, No; Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Roche Molecular Systems: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;

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3817-C | CAREGIVER BURDEN AMONG INFORMAL CAREGIVERS OF PATIENTS AWAITING LIVER TRANSPLANTATION

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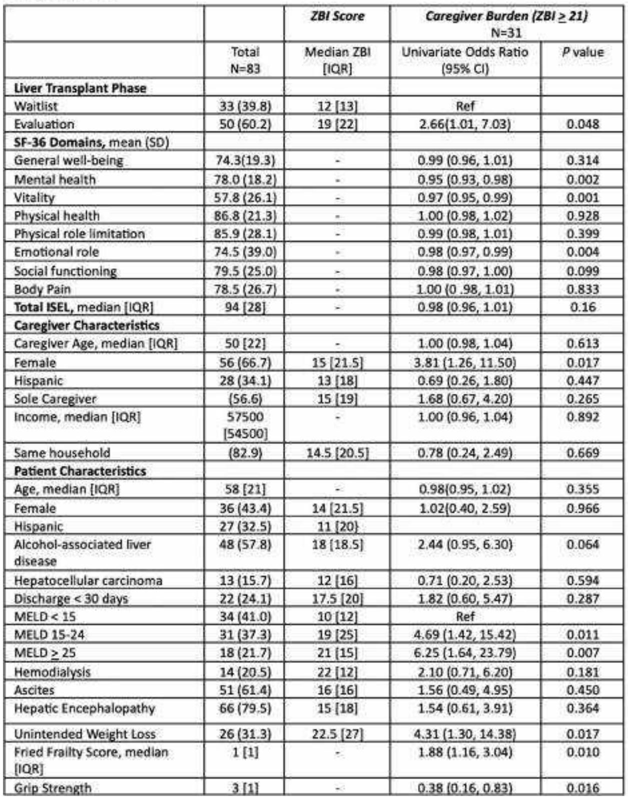
Background: Informal caregivers of patients with chronic liver disease could experience significant burden from caregiving with negative consequences for caregivers' and patients' outcomes. However, this burden is poorly understood in caregivers of patients undergoing liver transplant (LT) evaluation, which is the period of heightened vulnerability for patients and their caregivers. **Methods:** We conducted a prospective study in informal caregivers of LT candidates between January 2023 and May 2023 to examine the magnitude of and factors associated with caregiver burden. Coordinator assisted Zarit Burden Interview (ZBI) questionnaire (22-item) was used to assess perceived caregiver burden, with ZBI score ≥21 indicating high caregiver burden. We also collected data on caregiver's health-related quality of life (Short form, SF-36), perception of social support (Interpersonal Support Evaluation List, ISEL), as well as caregiver and patient characteristics. We used generalized linear regression models to evaluate associations with ZBI score and logistic regression to identify factors that were independently associated with high caregiver burden (ZBI ≥21). **Results:** In total, 83 primary caregivers participated in the study, with 60.2% caring for patients undergoing evaluation and 39.8% caring for patients on the liver transplant waitlist. Median age of caregivers was 50 years [IQR, 22], 66.7% were female, 51.2% White, 34.1% Hispanic, and 56.5% were sole caregivers. Overall, 37.6% (n = 31) reported some degree of caregiver burden, and 9.6% (n = 8) experienced moderate to severe caregiver burden. Significantly higher (worse) ZBI scores were seen in caregivers who were women, older in age, non-Hispanic, and sole caregivers (Table 1). Lower levels of caregiver perceived social support (ISEL), general well-being (SF-36), mental health, and vitality were associated with higher ZBI scores. Caregivers of patients in the evaluation phase had higher odds of experiencing burden than patients on the waitlist. In multivariable analyses, higher patient frailty (OR, 1.92, 95% CI, 1.03-3.62) and MELD (OR, 1.12, 95% CI, 1.01-1.25), as well as lower caregiver vitality (OR, 1.08, 95% CI, 1.01-1.18), were associated with increased burden. **Conclusion:** Informal caregivers of LT candidates experience high burden during the evaluation and waitlist phases. It is crucial to provide support and resources to caregivers to mitigate their burden and improve their well-being throughout the transplant process.

Table. Characteristics of informal caregivers of liver transplant candidates and predictors for caregiver burden



		ZBI Score	*Caregiver Burden (ZBI ≥ 21)* N=31	
	Total N=83	Median ZBI [IQR]	Univariate Odds Ratio (95% CI)	*P* value
Liver Transplant Phase				
Waitlist	33 (39.8)	12 [13]	Ref	
Evaluation	50 (60.2)	19 [22]	2.66(1.01, 7.03)	0.048
SF-36 Domains, mean (SD)				
General well-being	74.3(19.3)	-	0.99 (0.96, 1.01)	0.314
Mental health	78.0 (18.2)	-	0.95 (0.93, 0.98)	0.002
Vitality	57.8 (26.1)	-	0.97 (0.95, 0.99)	0.001
Physical health	86.8 (21.3)	-	1.00 (0.98, 1.02)	0.928
Physical role limitation	85.9 (28.1)	-	0.99 (0.98, 1.01)	0.399
Emotional role	74.5 (39.0)	-	0.98 (0.97, 0.99)	0.004
Social functioning	79.5 (25.0)	-	0.98 (0.97, 1.00)	0.099
Body Pain	78.5 (26.7)	-	1.00 (0 .98, 1.01)	0.833
Total ISEL, median [IQR]	94 [28]	-	0.98 (0.96, 1.01)	0.16
Caregiver Characteristics				
Caregiver Age, median [IQR]	50 [22]	-	1.00 (0.98, 1.04)	0.613
Female	56 (66.7)	15 [21.5]	3.81 (1.26, 11.50)	0.017
Hispanic	28 (34.1)	13 [18]	0.69 (0.26, 1.80)	0.447
Sole Caregiver	(56.6)	15 [19]	1.68 (0.67, 4.20)	0.265
Income, median [IQR]	57500 [54500]	-	1.00 (0.96, 1.04)	0.892
Same household	(82.9)	14.5 [20.5]	0.78 (0.24, 2.49)	0.669
Patient Characteristics				
Age, median [IQR]	58 [21]	-	0.98(0.95, 1.02)	0.355
Female	36 (43.4)	14 [21.5]	1.02(0.40, 2.59)	0.966
Hispanic	27 (32.5)	11 [20]		
Alcohol-associated liver disease	48 (57.8)	18 [18.5]	2.44 (0.95, 6.30)	0.064
Hepatocellular carcinoma	13 (15.7)	12 [16]	0.71 (0.20, 2.53)	0.594
Discharge < 30 days	22 (24.1)	17.5 [20]	1.82 (0.60, 5.47)	0.287
MELD < 15	34 (41.0)	10 [12]	Ref	
MELD 15-24	31 (37.3)	19 [25]	4.69 (1.42, 15.42)	0.011
MELD ≥ 25	18 (21.7)	21 [15]	6.25 (1.64, 23.79)	0.007
Hemodialysis	14 (20.5)	22 [12]	2.10 (0.71, 6.20)	0.181
Ascites	51 (61.4)	16 [16]	1.56 (0.49, 4.95)	0.450
Hepatic Encephalopathy	66 (79.5)	15 [18]	1.54 (0.61, 3.91)	0.364
Unintended Weight Loss	26 (31.3)	22.5 [27]	4.31 (1.30, 14.38)	0.017
Fried Frailty Score, median [IQR]	1 [1]	-	1.88 (1.16, 3.04)	0.010
Grip Strength	3 [1]	-	0.38 (0.16, 0.83)	0.016

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